Neonatal Brain Injury and Timing of Neurodevelopmental Assessment in Patients With Congenital Heart Disease

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ABSTRACT

BACKGROUND Brain injury (BI) is reported in 60% of newborns with critical congenital heart disease as white matter injury (WMI) or stroke. Neurodevelopmental (ND) impairments are reported in these patients. The relationship between neonatal BI and ND outcome has not been established.

OBJECTIVES This study sought to determine the association between peri-operative BI and ND outcomes in infants with single ventricle physiology (SVP) and d-transposition of the great arteries (d-TGA).

METHODS Term newborns with d-TGA and SVP had pre-operative and post-operative brain magnetic resonance imaging and ND outcomes assessed at 12 and 30 months with the Bayley Scales of Infant Development-II. BI was categorized by the brain injury severity score and WMI was quantified by volumetric analysis.

RESULTS A total of 104 infants had follow-up at 12 months and 70 had follow-up at 30 months. At 12 months, only clinical variables were associated with ND outcome. At 30 months, subjects with moderate-to-severe WMI had significantly lower Psychomotor Development Index (PDI) scores (13 points lower) as compared with those with none or minimal WMI for d-TGA and SVP (p = 0.03 and p = 0.05, respectively) after adjusting for various factors. Quantitative WMI volume was likewise associated. Stroke was not associated with outcome. The Bland-Altman limits of agreement for PDI scores at 12 and 30 months were wide (−40.3 to 31.2) across the range of mean PDI values.

CONCLUSIONS Increasing burden of WMI is associated with worse motor outcomes at 30 months for infants with critical congenital heart disease, whereas no adverse association was seen between small strokes and outcome. These results support the utility of neonatal brain magnetic resonance imaging in this population to aid in predicting later outcomes and the importance of ND follow-up beyond 1 year of age. (J Am Coll Cardiol 2018;71:1986–96) © 2018 by the American College of Cardiology Foundation.
Advances in peri-operative care have led to improved survival of newborns with critical congenital heart disease (CHD) (1,2). Although there has been a decline in overt neurologic insults in these children, many experience behavioral, emotional, cognitive, and motor impairment, suggesting widespread brain dysfunction that continues into adulthood (3–5). Despite significant improvements over time in survival, surgical strategies, and peri-operative care, neurodevelopmental (ND) outcomes have only modestly improved (6). These findings suggest that patient specific risk factors and brain health may be key determinants of ND outcome.

Studies have documented a high prevalence of peri-operative brain injury and delayed brain development in neonates with CHD (7–10). However, few studies have identified a strong correlation between peri-operative brain injury and ND outcome. The largest study in infants with CHD found no association between neonatal peri-operative brain injury and outcome (11), whereas other studies reported divergent results (12,13). In contrast, several important clinical variables are known to influence ND outcomes in children with CHD through mechanisms that do not involve brain injury, including maternal education, socioeconomic status, and presence of a genetic abnormality (14–16).

Given the high rates of brain injury in neonates with CHD, the use of peri-operative brain imaging in their clinical care is increasing. We hypothesize that the presence of peri-operative brain injury is associated with ND deficits in infancy. The aim of this study was to prospectively determine the association between neonatal brain injury and ND outcome at 12 and 30 months of age among patients with d-transposition of the great arteries (d-TGA) and single-ventricle physiology (SVP).

METHODS

Between 2001 and 2013, newborns with critical CHD at the University of California-San Francisco Benioff Children’s Hospital (UCSF) and University of British Columbia (UBC) were consecutively invited to participate in a prospective protocol obtaining pre-operative and post-operative MRI and ND follow-up at 12 and 30 months of age. Brain imaging findings from earlier versions of this cohort were previously reported (7,8). Patients who were born before 36 weeks’ gestation, had a suspected congenital infection, had clinical evidence of a congenital malformation or syndrome, or had a suspected or confirmed genetic or chromosomal anomaly were excluded. Informed consent was obtained. The institutional committee on human research approved the study protocol at each site.

Patients diagnosed as having d-TGA or SVP were included in the study. d-TGA was defined as great vessel malposition with the aorta arising from the right ventricle and pulmonary artery arising from the left ventricle with or without a ventricular septal defect. SVP was defined as the absence of 1 of 2 functioning ventricles requiring a palliative surgical intervention for survival in the newborn period.

MAGNETIC RESONANCE IMAGING STUDY.

Pre-operative magnetic resonance imaging (MRI) studies were performed as soon as the baby could be safely transported to the MRI scanner as determined by the clinical team. Post-operative studies were performed after completion of peri-operative care and before discharge from the hospital. Imaging time points were separated by an average of 15 days in the entire cohort. Detailed methods are listed in the Online Appendix. A neuroradiologist at each site reviewed each MRI for focal, multifocal, or global changes (A.J.B. and K.P.), blinded to clinical variables. Brain injury was characterized as stroke, white matter injury (WMI), intraventricular hemorrhage (IVH), or global hypoxic ischemic injury, as previously described (8). The description of post-operative brain injuries was limited to newly acquired lesions not evident on the pre-operative scan. WMI was further classified as mild (1 to 3 foci each <2 mm), moderate (>3 foci or any foci >2 mm), or severe (>5% of WM volume). IVH was characterized as grade I, II, III, or periventricular hemorrhagic infarct using the system of Papile et al. (17). No subjects were found to have IVH grade >II. Brain injury severity (BIS) was categorized for each subject as previously described in an ordinal scale (18): 0 = none or minimal injury (mild WMI and IVH grade I to II; no stroke); 1 = stroke (any size stroke without moderate-to-severe WMI); and 2 = moderate-to-severe injury (moderate and severe WMI). BIS score was assigned to the pre-operative MRI and to the post-operative MRI for newly acquired lesions. The BIS score was assigned based on the worst injury observed. For example, if a subject had stroke and moderate-to-severe WMI a BIS score of 2 was assigned. To account for multiple injuries in a single subject at both time points, a maximal BIS score was determined, which was the highest score between the pre-operative and post-operative BIS scores. The quantitative assessment of WMI was performed by a trained rater (T.G.) and

ABBREVIATIONS AND ACRONYMS

BAS = balloon atrial septostomy
BIS = brain injury severity
CHD = congenital heart disease
CI = confidence interval
d-TGA = d-transposition of the great arteries
FA = fractional anisotropy
IVH = intraventricular hemorrhage
MDI = Mental Development Index
MRI = magnetic resonance imaging
ND = neurodevelopmental
PDI = Psychomotor Development Index
SVP = single-ventricle physiology
UBC = University of British Columbia
UCSF = University of California-San Francisco Benioff Children’s Hospital
WMI = white matter injury
reviewed by an experienced neonatal neurologist (S.M.). Punctate WMI was characterized by areas of T1 hyperintensity and was manually delineated on all available pre-operative and post-operative scans. The total WMI volume was determined by manual segmentation, as previously described (19). If WMI was identified on both the pre-operative and post-operative T1-weighted images, the largest total WMI volume was included in the statistical analysis (maximal WMI volume).

**DIFFUSION TENSOR IMAGING.** Diffusion tensor imaging was performed using a sequence optimized at each site for neonatal brain imaging to measure microstructural brain development. For the purposes of this analysis, we focused on the regional directionality of water motion in the WM, defined as fractional anisotropy (FA). With increasing microstructural brain development, the regional directionality of water motion increases thus FA increases (20). The FA was calculated for 5 voxels in the WM bilaterally using pre-specified anatomical references (7): 1) anterior WM; 2) central WM; 3) posterior WM; 4) posterior limb of the internal capsule; and 5) optic radiations. Correct region-of-interest placements were confirmed by neuroradiologists at each site (A.J.B. and K.P.). The values from the left and right hemispheres were averaged and a mean value was used for analysis.

**CLINICAL VARIABLES.** Clinical data were prospectively collected from the medical records by a team of trained neonatal research nurses and reviewed by a pediatric intensivist and cardiologist (P.M. and S.P.) blinded to all neuroimaging findings. Maternal education was recorded as a surrogate of socioeconomic status using the Hollingshead scale of educational status (from 1 to 7) in the Four-Factor Index of Social Status.

**NEURODEVELOPMENTAL ASSESSMENT.** The Bayley Scales of Infant Development-II (BSID-II) was administered at 12 and 30 months of age to obtain the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). Testing was administered by a single qualified individual (licensed psychologist or experienced psychometrician) at each site, blinded to the subject’s cardiac diagnosis, clinical factors, and brain imaging findings.

**STATISTICAL ANALYSIS.** Clinical and MRI characteristics were compared between subjects that had follow-up at 12 and 30 months and those that did not (due to death or loss to follow-up). Our primary outcome was prospectively defined as the cognitive (MDI) and motor (PDI) scores of the BSID-II at 12 and 30 months of age. Our primary exposure was peri-operative brain injury as measured by the BIS score. To assess the relationship between brain injury and ND outcome, linear regression was used with maximal BIS or maximal WMI volume as the independent variable and either the PDI or MDI score as the dependent variable at each time point (12 and 30 months). A univariable linear regression was performed assessing known or biologically plausible predictors of ND outcome or confounders in the relationship between brain injury and ND outcome. Variables with an association of $p < 0.10$ were included in the final model. The final multivariable linear regression model was stratified by cardiac lesion and adjusted for all significant variables in the univariable analysis. Bland-Altman limits of agreement were calculated to assess the concordance of BSID-II scores at 12 and 30 months. All analyses were performed on Stata 14.0 software (StataCorp, College, Texas).

**RESULTS**

A total of 165 neonates were enrolled at birth and obtained peri-operative (pre-operative and post-operative) brain MRIs: 98 at UCSF and 67 at UBC. By 12 months, 28 subjects had died and 33 subjects were lost to follow-up and by 30 months, 2 additional subjects had died and an additional 32 subjects were lost to follow-up (Figure 1). At each time point, baseline demographics did not differ between those that
achieved follow-up versus those that did not, except for site and cardiac diagnosis (Online Tables 1A and 1B). At each time point, there was no difference in the prevalence of neonatal brain injury (either pre-operative or post-operative) based on follow-up status (Online Tables 2A and 2B).

A total of 104 infants had peri-operative imaging and ND follow-up at 12 months (d-TGA = 84; SVP = 20). At 30 months, 70 children had peri-operative imaging and ND follow-up (d-TGA = 54; SVP = 16). At each time point (12 and 30 months), baseline demographics were not different between those with peri-operative brain injury and those without (Tables 1 and 2). The prevalence and type of brain injury among subjects with follow-up is demonstrated in Table 3.

Approximately 55% of subjects had some type of peri-operative brain injury in the neonatal period, with WMI being the most common type of injury (Figure 2). Two subjects had hypoxic-ischemic brain injury, both of which primarily involved the WM, thus they were characterized as having severe WMI. Although stroke was also highly prevalent, 25 of 29 subjects with ND outcome data (86%) had small strokes (less than one-third of the arterial territory). Four subjects had larger strokes (one-third to two-thirds of the arterial territory), all of whom had MDI and PDI scores below 90. For this study, we assessed the maximal BIS score. Among the subjects with follow-up data, all BIS scores either stayed the same or were worse on the post-operative scan as compared with the pre-operative scan. As expected, mean PDI and MDI scores were lower than the normative mean (100 ± 15) at each time point (Online Table 3).

In the univariable analyses at 12 months, only clinical factors were significantly associated with the MDI or PDI (Online Table 4). In particular, cardiac lesion, balloon atrial septostomy (BAS), and maternal education were associated with the MDI. Similarly, only birth weight, pre-operative saturations, cardiac lesion, and BAS were associated with the PDI. Those with pre-operative or any stroke (BIS = 1) had significantly higher MDI and PDI values at 12 months. No other relationship was noted between BIS and outcome at 12 months.

At 30 months, maximal BIS score was significantly associated with PDI. Those with BIS = 2 (moderate-to-severe WMI) had PDI scores on average of 13.000 (95% confidence interval [CI]: –2.520 to –3.260) points lower as compared with those with none or minimal injury. Additional variables associated with PDI included maternal education, cardiac lesion, BAS, and site. No association was seen between WMI and MDI (Online Table 5). Of note, on univariable analyses

**TABLE 1**  
Baseline Characteristics of Subjects With 12-Month Outcome by Injury Status (N = 104)

<table>
<thead>
<tr>
<th></th>
<th>No Injury (n = 48)</th>
<th>Injury (n = 56)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10 (20.8)</td>
<td>23 (41.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>26 (39.4)</td>
<td>40 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (57.9)</td>
<td>8 (42.1)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (60.0)</td>
<td>4 (40.0)</td>
<td></td>
</tr>
<tr>
<td>GA at birth, weeks</td>
<td>39.3 (38.9-39.6)</td>
<td>38.8 (38.3-39.2)</td>
<td>0.055</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.3 (3.2-3.5)</td>
<td>3.3 (3.2-3.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>Birth HC, cm</td>
<td>34.0 (33.6-34.4)</td>
<td>34.0 (33.6-34.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Weight at 12 months, kg</td>
<td>10.9 (9.3-12.6)</td>
<td>9.6 (9.3-10.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>HC at 12 months, cm</td>
<td>46.6 (46.1-47.0)</td>
<td>46.0 (45.5-46.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Lowest pre-operative oxygen saturation</td>
<td>64.8 (58.6-71.0)</td>
<td>65.9 (60.9-70.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>d-TGA</td>
<td>40 (47.6)</td>
<td>44 (52.4)</td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td>8 (40.0)</td>
<td>12 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>UCSF</td>
<td>24 (45.3)</td>
<td>29 (54.7)</td>
<td></td>
</tr>
<tr>
<td>UBC</td>
<td>24 (47.1)</td>
<td>27 (52.9)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) or median (range).

d-TGA = d-transposition of the great arteries; GA = gestational age; HC = head circumference; SVP = single-ventricle physiology; UCSF = University of California-San Francisco Benioff Children’s Hospital.

**TABLE 2**  
Baseline Characteristics of Subjects With 30 Month Outcome by Injury Status (N = 70)

<table>
<thead>
<tr>
<th></th>
<th>No Injury (n = 30)</th>
<th>Injury (n = 40)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9 (30.0)</td>
<td>16 (40.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>19 (39.6)</td>
<td>29 (60.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (50.0)</td>
<td>4 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (40.0)</td>
<td>3 (60.0)</td>
<td></td>
</tr>
<tr>
<td>GA at birth, weeks</td>
<td>39.0 (38.6-39.5)</td>
<td>39.9 (38.5-39.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>Birth HC, cm</td>
<td>33.7 (33.1-34.3)</td>
<td>34.1 (33.5-34.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.3 (3.1-3.5)</td>
<td>3.4 (3.2-3.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Weight at 30 months, kg</td>
<td>13.7 (13.1-14.3)</td>
<td>13.8 (13.1-14.5)</td>
<td>0.75</td>
</tr>
<tr>
<td>HC at 30 months, cm</td>
<td>48.7 (48.0-49.3)</td>
<td>47.5 (45.9-49.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Lowest pre-operative oxygen saturation</td>
<td>65.9 (57.9-73.9)</td>
<td>68.2 (62.7-73.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>d-TGA</td>
<td>26 (48.2)</td>
<td>28 (51.8)</td>
<td></td>
</tr>
<tr>
<td>SVP</td>
<td>4 (25.0)</td>
<td>12 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>UCSF</td>
<td>11 (42.3)</td>
<td>15 (57.7)</td>
<td></td>
</tr>
<tr>
<td>UBC</td>
<td>19 (43.2)</td>
<td>25 (56.8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) or median (range).

Abbreviations as in Table 1.
BAS was associated with significantly higher PDI and MDI scores at 30 months as compared with those that did not have a BAS. Those with stroke (BIS = 1) had significantly higher MDI scores as compared with those with none or minimal injury (similar findings were seen with PDI and MDI at 12 months). The associations among BAS, stroke, and outcome were not significant in the multivariable analysis stratified by cardiac lesion.

In the final model, the relationship between maximal BIS and PDI was assessed at 30 months. The analysis was stratified by cardiac lesion. After adjustment for site, BAS, and maternal education, those with moderate-to-severe WMI (BIS = 2) had significantly lower PDI scores as compared with those with none or minimal injury (BIS = 0) for both d-TGA and SVP: for d-TGA, PDI scores were 14.000 (95% CI: −26.800 to −1.100) points lower for those with BIS = 2 compared with those with BIS = 0 (p = 0.03); for SVP, PDI scores were 14.000 (95% CI: −27.700 to 0.130) points lower for those with BIS = 2 compared with those with BIS = 0 (p = 0.05) (Central Illustration, Table 4). The effects of other variables in the multivariable analysis are listed in Table 5. To address the possibility of misclassification of severity of WMI using the qualitative scale (21), the same analysis was performed using the maximal WMI volume as the predictor. In line with the qualitative scale, larger WMI volumes were associated with lower PDI scores at 30 months after adjusting for site, cardiac group, maternal education, and BAS; for every mm³ increase in WMI volume, the PDI score was on average 0.060 points lower (95% CI: −0.110 to −0.009; p = 0.02).

Given the lack of significant association between brain injury and 12-month ND testing, we examined the concordance of 12- and 30-month testing. The Bland-Altman limits of agreement for PDI scores at 12 and 30 months were wide (−40.3 to 31.2) across the range of mean PDI values (Pitman’s test of difference in variance, p = 0.27) (Figure 3). To examine whether the limits of agreement were modified by site, we stratified this analysis by site finding no appreciable difference: UCSF limits of agreement were −31.0 to 23.6 and UBC limits of agreement were −44.5 to 34.6.

### DISCUSSION

In this prospective, longitudinal study we demonstrate an association between brain injury in neonates with critical CHD and ND outcomes at 30 months of age. Specifically, those with moderate-to-severe WMI score on average 1 SD below the normative mean for motor development at 30 months. In contrast, we find no significant association at 12 months. Finally, we see no deleterious association between small strokes (less than one-third of the arterial territory) and outcome. Our results support the utility of neonatal brain MRI for predicting outcome in this high-risk population and underscore the importance of ND follow-up beyond 1 year of age.

The literature is rich with observational papers demonstrating a high prevalence of pre-operative and post-operative brain injury and delayed brain development in those with critical CHD (7-10,22). However, there are few reports of the predictive value of neonatal brain imaging for subsequent ND outcomes in this population. In the largest study to date, Beca et al. (11) reported no association between neonatal WMI or combined brain injury and outcomes at 2 years of age in a large cohort of subjects with mixed CHD. Their analysis considered brain injury as a dichotomous predictor. Furthermore, very few subjects that had more severe brain injury survived until the ND assessment at 2 years of age, limiting the conclusions regarding different severities of injury and their impact on outcome. In a well-characterized cohort of neonates with d-TGA, Andropoulos et al. (12) demonstrated an association between pre-operative, but not post-operative brain injury and motor and language deficits at 12 months of age; however, in a follow-up paper with a larger cohort and varying types of CHD, the same group found only an association with post-operative brain injury and cognitive outcome at 2 years of age (13). Similar to Beca et al. (11), the analysis was focused on injury as a dichotomous predictor, which may mask important associations between more severe types of brain injury and outcome. To address the possibility of misclassification of severity of WMI using the qualitative scale (21), the same analysis was performed using the maximal WMI volume as the predictor. In line with the qualitative scale, larger WMI volumes were associated with lower PDI scores at 30 months after adjusting for site, cardiac group, maternal education, and BAS; for every mm³ increase in WMI volume, the PDI score was on average 0.060 points lower (95% CI: −0.110 to −0.009; p = 0.02).
injury and outcome. In our study, brain injury was assessed both with a clinically applicable categorical predictor (BIS score) and quantitative WMI volumes, with similar findings using both approaches. First, the BIS category prevents comparisons that group different types of brain injury (i.e., WMI vs. stroke) with uninjured subjects. Second, maximal BIS (taking into account both pre-operative and new post-operative injuries) was assessed to represent the total burden of injury rather than focusing on individual time points. At both 12 and 30 months, approximately 16% of subjects had brain injury on the severe end of the spectrum (i.e., moderate-to-severe WMI), allowing for an adequate representation of varying degrees of brain injury. Importantly, the relationship between peri-operative brain injury and ND outcome remains significant after adjustment for factors such as maternal education, site, and BAS. Although the BIS score allows comparisons across different injury categories (i.e., stroke vs. WMI), it only crudely categorizes injury severity. To address the possibility of misclassification of WMI using this qualitative scale, we utilized a quantitative measure of brain injury, namely a volumetric assessment of WM volume. Using this measurement, which has been found to have high inter-rater reliability, we found similar results in that larger WMI volumes were associated with worse PDI scores at 30 months, even after adjusting for the same variables. Given that we measured the maximal WMI volume on either the
pre-operative or post-operative MRI, there is a small possibility of underestimating overall WMI for subjects in which the pre-operative WMI lesion disappears on the post-operative scan. However, this is a rare occurrence based on our prior publication (23).

Studies have shown that WMI is the most frequent pattern of injury in subjects with critical CHD (8,10,23). Various risk factors in the pre-, intra-, and post-operative time period contribute to neonatal brain injury (8,24–28). Our findings increase the urgency to identify and minimize modifiable risk factors for WMI. The variable relationship between early and later ND testing may complicate neuroprotective trial design given the long interval between neonatal interventions and meaningful outcomes. However, the present findings demonstrate the predictive value of neonatal imaging for later outcomes and may facilitate design of such clinical trials by using peri-operative imaging as a surrogate outcome variable (29).

One of the first associations we reported in this prospective cohort study was a tight relationship between the need for BAS and pre-operative brain injury, especially stroke (24) in d-TGA. This relationship was not observed in other cohorts without pre-operative stroke (26) or with a very low prevalence of pre-operative stroke (11). Despite the lack of consensus among imaging studies, the association of BAS with stroke was both biologically plausible and concerning. The present findings offer important information regarding this relationship. Consistent with our prior report, the vast majority of strokes (25 of 29, 86%) were small in size (less than one-third of arterial territory) and remarkably, we demonstrate that BAS and stroke are associated with better ND outcomes on the univariable analysis. This does not suggest that stroke or BAS is protective per se because these associations were no longer seen on the multivariable analyses, but rather reflects the impact of BAS on cardiovascular physiology. Thus, although the
procedure is associated with small embolic strokes, it improves oxygen delivery and hence may contribute to better ND outcomes, though this conjecture warrants further scrutiny with more sophisticated testing based on stroke location and specific brain functions at later ages. Not surprisingly, larger strokes do seem to result in adverse outcomes, although our sample size for this injury precluded statistical testing.

Previous studies have suggested an association between measures of brain development and outcome in this population. The Total Maturation Score at 3 months of age in a mixed cohort of subjects with critical CHD was reported to be with deficits in multiple ND domains at 2 years of age (11). We assessed brain development as measured by diffusion tensor imaging (FA in WM) and found no association between isolated pre-operative or post-operative WM FA values with outcomes at 30 months of age. Although this does not exclude the possibility of a relationship between brain development and ND outcomes in this patient population, it does not appear to impact the relationship between brain injury and outcome.

ND outcomes for subjects with SVP were systematically lower at both 12 and 30 months as compared with those with d-TGA. Although both subjects with SVP and d-TGA demonstrate a similar prevalence of pre-operative brain injury and delays in brain development, they differ significantly from a physiologic perspective in addition to operative strategies and post-operative management all of which can influence ND outcomes. Recently, we demonstrated slower peri-operative brain growth in patients with hypoplastic
The limits of agreement range from -40.3 (bottom line) to 31.2 (top line), suggesting wide variability between Psychomotor Development Index (PDI) scores at the 2 time points (middle line represents no difference) for the entire cohort. Similar limits of agreement were obtained for each site (University of California-San Francisco Benioff Children’s Hospital [UCSF] and University of British Columbia [UBC]). Pitman’s test of variance ($p = 0.28$) suggests no difference in agreement across the range of PDI values.

Figure 3

Bland-Altman Plot of PDI at 12 Months and at 30 Months by Site

left heart syndrome as compared with d-TGA, independent of BIS (30). The distribution of PDI and MDI scores for SVP subjects is consistent with prior literature (3). Although moderate-to-severe WMI appears to predict even worse outcome for SVP subjects, all patients with SVP warrant frequent and ongoing surveillance for developmental impairments as recommended by current guidelines (31), with additional vigilance for those with moderate-to-severe WMI; early intervention should be offered to these patients routinely.

Although d-TGA subjects with minimal injury or stroke had PDI and MDI scores near the normative mean, these patients have ongoing deficits in childhood and adolescent years that may not be apparent in infancy (4,32). In addition, some studies have suggested that earlier measures of ND are only modestly associated with later measures of ND in childhood for the CHD population (33). Relevant to this concept, we found that PDI scores at 12 months did not reliably predict PDI scores at 30 months, even though the same testing tool was used. This finding has 2 important implications. First, given the evidence of ongoing developmental deficits in both subjects with SVP and TGA, surveillance should begin in infancy to establish interventions as soon as possible and must continue into teenage and adulthood years. Second, our results suggest that for the purposes of clinical trials in this area, outcome needs to be measured at least at 2.5 years or later.

**STUDY LIMITATIONS.** There was a high percentage of loss to follow-up either due to death or lack of return to a study visit. Although this may potentially bias the results toward the healthier patients in the cohort (i.e., sicker children died or did not return for follow-up), we found that there was no difference in prevalence of neonatal brain injury between those that remained in the study and those that were lost to follow-up. There was a significant difference in ND outcome at both 12 and 30 months by site. The subjects evaluated at UCSF had significantly lower MDI and PDI scores as compared with the Canadian UBC cohort. Site remained a significant predictor of PDI at 30 months in the multivariable model in subjects with d-TGA. This may be secondary to multiple factors including differences in socioeconomic status, different testing operators, or environmental influences. Prior literature has suggested an attrition bias in the rate of ND impairments that varies by country in preterm-born children (34). In particular, when comparing Canada with the United States, attrition rates were much lower and the rates of ND impairments were lower at 18 to 24 months in Canada. This may be secondary to different health care systems and perhaps easier accessibility to screening and early intervention services in Canada. In our study the rate of follow-up at both 12 and 30 months was lower in the UCSF cohort as compared with the Canadian cohort, which may have influenced the PDI and MDI scores. Similarly, differences in MRI technique, acquisition and interpretation can exist by site as each site optimized their acquisitions for their local scanner. Given this, we accounted for site in the analyses in both the quantitative and qualitative MRI measures and found that the association between moderate-to-severe WMI and PDI at 30 months remained even after this adjustment. Finally, maternal education remained a significant predictor of PDI at 30 months in the multivariable model for SVP subjects. Studies have shown that maternal education can predict both short- and long-term health outcomes in offspring (35). Higher maternal education may reflect increased advocacy and receipt of services for children resulting in better outcomes. This finding deserves further study as a potential environmental influence on ND outcome.
CONCLUSIONS

Moderate-to-severe WMI is associated with worse motor outcomes at 30 months of age. In contrast, small strokes and the use of BAS are not associated with significant impairment. Although all patients with critical CHD such as d-TGA and SVP are at increased risk of ND impairments throughout the lifespan, extra vigilance is needed for those with moderate-to-severe WMI. These findings suggest that peri-operative neonatal brain MRI is a useful tool to help further risk stratify patients for ND impairments later in life and that ND follow-up should begin early with continued surveillance.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with critical CHD, clinically silent peri-operative WM brain injury detected by MRI is associated with ND impairment at 30 months of age.

TRANSLATIONAL OUTLOOK: Future studies should focus on the relationship between neonatal brain imaging findings and ND outcomes beyond infancy, in childhood and adolescence.

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KEY WORDS brain injury, congenital heart disease, neurodevelopmental outcomes

APPENDIX For expanded Methods, Results, and References sections as well as supplemental tables, please see the online version of this paper.