Brain Injury and Neurodevelopmental Outcome in Congenital Heart Disease: A Systematic Review

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 abstract

CONTEXT: Brain injury during prenatal and preoperative postnatal life might play a major role in neurodevelopmental impairment in infants with congenital heart disease (CHD) who require corrective or palliative surgery during infancy. A systematic review of cerebral findings during this period in relation to neurodevelopmental outcome (NDO), however, is lacking.

OBJECTIVE: To assess the association between prenatal and postnatal preoperative cerebral findings and NDO in infants with CHD who require corrective or palliative surgery during infancy.


STUDY SELECTION: We conducted 3 different searches for English literature between 2000 and 2016; 1 for prenatal cerebral findings, 1 for postnatal preoperative cerebral findings, and 1 for the association between brain injury and NDO.

DATA EXTRACTION: Two reviewers independently screened sources and extracted data on cerebral findings and neurodevelopmental outcome. Quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.

RESULTS: Abnormal cerebral findings are common during the prenatal and postnatal preoperative periods. Prenatally, a delay of cerebral development was most common; postnatally, white matter injury, periventricular leukomalacia, and stroke were frequently observed. Abnormal Doppler measurements, brain immaturity, cerebral oxygenation, and abnormal EEG or amplitude-integrated EEG were all associated with NDO.

LIMITATIONS: Observational studies, different types of CHD with different pathophysiological effects, and different reference values.

CONCLUSIONS: Prenatal and postnatal preoperative abnormal cerebral findings might play an important role in neurodevelopmental impairment in infants with CHD. Increased awareness of the vulnerability of the young developing brain of an infant with CHD among caregivers is essential.
It has been well established that infants with congenital heart disease (CHD) are at risk for neurodevelopmental impairments. Reports have been published that indicate that in complex CHD, up to 50% of the infants have neurodevelopmental impairments. Impairments can manifest themselves variably, involving different aspects such as (mild) impairments in cognition, fine and gross motor skills, executive functioning, visual construction and perception, attention, social interaction, and core communication skills.

Threats for the young developing brain can arise at different stages during pre- and postnatal life. Research used to focus on the intraoperative and postoperative period, but we now know that brain injury in infants with CHD may already occur before cardiac surgery. Furthermore, there is increasing evidence that suggests that brain injury in infants with CHD already occurs during intrauterine life.

The exact mechanism responsible for brain injury in CHD is not yet fully understood. There are 2 main theories. First, the brain could primarily develop differently in infants with CHD because of intrinsic (epi)genetic factors. A large part of heart and brain development occurs simultaneously in the human fetus and involves shared genetic pathways. A discrepancy in one of these pathways could lead to abnormal development of both organs and may thus cause neurodevelopmental impairments. Second, the heart defect may entail changes in oxygen saturation because of intracardiac or extracardiac mixing, which could in turn lead to circulatory alterations that affect oxygen and nutrient supply to the brain and could therefore disturb normal cerebral development.

Although several studies have reported on prenatal brain injury, preoperative brain injury, or neurodevelopmental outcome (NDO) in CHD, a systematic review of brain injury during both prenatal and postnatal preoperative life in relation to NDO is currently not available. The aim of this study was, therefore, to systematically review existing evidence for prenatal and postnatal preoperative brain injury in relation to NDO in infants with complex CHD.

METHODS

Search Strategy

This systematic review was performed according to the PRISMA guidelines for systematic reviews. There was no registered protocol available. A systematic search was conducted in PubMed and Embase independently by 2 researchers (M.J.M. and E.M.W.K.) on July 1, 2016. Publications from January 2000 to July 2016 that contained data on prenatal and/or postnatal preoperative cerebral findings and neurodevelopmental outcome in infants with congenital heart disease were selected for this review.

To assess all available literature on prenatal and postnatal preoperative brain injury in relation to NDO, we conducted 3 different searches. We started with a search on cerebral findings in fetuses with congenital heart disease. For this search, we selected all original research articles that were written in English and contained different combinations or synonyms of congenital heart disease, fetus, Doppler, MRI, sonography, and brain. Articles that exclusively focused on head biometry were excluded. For the second search, we used combinations or synonyms of congenital heart disease, neonate, infant, Doppler, MRI, near-infrared spectroscopy, EEG, and brain. Articles were selected if they were written in English, if participants were <3 months of age at the first examination, and if at least part of the study group was diagnosed prenatally with CHD. Articles that focused on infants with chromosomal or syndromal disorders were excluded because we were interested in the effect of the congenital heart defect on NDO in infants with complex CHD. For the purpose of the current review, we were not interested in developmental problems because of chromosomal disorders. In addition, we excluded articles with an interventional study design tailored to evaluate the direct impact of an experimental intervention on cerebral outcome variables. For the third search, we combined the first 2 searches and complemented it with neurodevelopmental outcome and word variants. Articles were selected only if they combined prenatal and/or postnatal preoperative cerebral findings with NDO in infants with CHD. Furthermore, NDO had to be assessed with validated tools such as the Bayley Scales of Infant Development II (BSID II) or the Bayley Scales of Infant and Toddler Development III (Bayley III). The complete search string is available online in Supplemental Information.

In addition to the database search, we screened the reference lists of all retrieved articles for additional relevant publications.

Quality Assessment

We assessed the quality of the selected articles using the Newcastle-Ottawa Quality Assessment Scale for case-control studies and cohort studies. This scale consists of 3 parts: selection, comparability, and exposure for case-control studies and selection,
comparability, and outcome for cohort studies. Each part consists of a different number of items and a different amount of points that can be acquired per item. Selection consists of 4 items with a maximum of 4 points, comparability consists of 1 item with a maximum of 2 points, and exposure or outcome consists of 3 items with a maximum of 3 points. Therefore, the total score ranges from 0 to 9, with 9 being an article of the highest quality. The quality scores of selected articles are presented online in Supplemental Tables 4 and 5.

RESULTS
Our initial search resulted in 503 articles. After removing duplicates, we assessed titles and abstracts of 260 articles, of which 40 were relevant. The main reasons for exclusion were chromosomal or syndromal disorders, not original research, and study being out of scope. From the reference lists, we found 7 additional articles. After reading the full text, 30 articles were included in the prenatal part of the review (Fig 1). Prenatal cerebral findings are presented in Table 1.

The second search resulted in 1347 articles. We assessed titles and abstract of 734 articles after removing duplicates. Reasons for exclusion at this stage were chromosomal or syndromal disorders, not original research, intraoperative or postoperative data, and study being out of scope. From the reference lists, we found another 3 articles. Eventually, we read 68 full-text articles, from which 51 were included in the postnatal part of the review (Fig 2). Postnatal cerebral findings are presented in Table 2.

The final search resulted in 882 articles. Many articles on neurodevelopmental outcome were not eligible because they did not combine prenatal or postnatal preoperative cerebral findings with neurodevelopmental outcome. Four additional relevant articles were found and added to either the prenatal or the postnatal preoperative part of the review. Results on the association between prenatal or postnatal preoperative cerebral findings and neurodevelopmental outcome are presented in Table 3.

Prenatally, 1 study included a small percentage of infants with nonisolated CHD, 13% of the studies did not report on whether they included infants with nonisolated CHD, and 84% focused exclusively on infants with isolated CHD. Postnatally, 32% of the studies did not report on including or excluding infants with nonisolated CHD and 1 study included a small percentage of infants with nonisolated CHD. When possible, only the results of infants with isolated CHD were presented.

Prenatal Cerebral Ultrasound
Twenty-two articles reported on Doppler parameters (Table 1). In general, these studies were case-control studies or cohort studies that compared Doppler parameters of fetuses with CHD with either healthy controls or reference values from the literature. Almost all studies used z scores to adjust for gestational age (the amount of SDs from the mean for a given gestational age).

The vast majority (86%) of the 22 studies that reported on Doppler parameters found the pulsatility index (PI) of the middle cerebral
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<td>Ruiz et al, Ultrasound Obstet Gynecol, 2016</td>
<td>Retrospective study, N = 119</td>
<td>Mixed</td>
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<td>Hahn et al, Ultrasound Obstet Gynecol, 2016</td>
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<td>Zeng et al, Ultrasound Obstet Gynecol, 2015</td>
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<td>Zeng et al, Ultrasound Obstet Gynecol, 2015</td>
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<td>Masoller et al, Ultrasound Obstet Gynecol, 2014</td>
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<td>Williams et al, Am Heart J, 2013</td>
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<td>Yamamoto et al, Ultrasound Obstet Gynecol, 2013</td>
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<td>Williams et al, Ultrasound Obstet Gynecol, 2012</td>
<td>Pilot study, N = 13</td>
<td>Mixed</td>
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<td>Ardini et al, J Matern Fetal Neonatal Med, 2011</td>
<td>Case-control study, N = 60/65</td>
<td>Mixed</td>
<td>30–38 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
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<td>Itsukachi et al, Fetal Diagn Ther, 2011B</td>
<td>Retrospective study, N = 44/140</td>
<td>Mixed</td>
<td>28–34 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
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<td>McElhinney et al, Ultrasound Med Biol, 2010</td>
<td>Cohort study, N = 52</td>
<td>HLHS</td>
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<td>Ultrasound (Doppler)</td>
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<td>Beng et al, Ultrasound Obstet Gynecol, 2009</td>
<td>Case-control study, N = 113/1378</td>
<td>Mixed</td>
<td>19–41 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
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<th>Methods</th>
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<tr>
<td>Guorong et al, Fetal Diagn Ther, 2009</td>
<td>Case-control study, (N = 45/275)</td>
<td>Mixed</td>
<td>20–40 wk</td>
<td>Ultrasound (Doppler)</td>
<td>Normal MCA-PI&lt;br&gt; MCA-PI tended to be lower in LSOL and was lower in congestive heart failure&lt;br&gt; Higher UA-PI and higher U/C PI ratios&lt;br&gt; No traditional “brain sparing” as MCA-PI was normal, whereas U/C PI was higher</td>
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<td>Chen et al, Am J Perinatol, 2009</td>
<td>Case-control study, (N = 11/44)</td>
<td>Ebstein anomaly</td>
<td>23–37 wk</td>
<td>Ultrasound (Doppler)</td>
<td>Lower MCA-PI and CPR (no z scores)&lt;br&gt; Higher UA-PI and left ventricular myocardial performance index&lt;br&gt; Lower fetal cardiac profile score (median 1 point lower)&lt;br&gt; MCA-PI positive correlation with cardiovascular profile score and negative correlation with left ventricular myocardial performance index</td>
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<td>Modena et al, Am J Obstet Gynecol, 2006</td>
<td>Case-control study, (N = 71/71)</td>
<td>Mixed</td>
<td>24–28 wk</td>
<td>Ultrasound (Doppler)</td>
<td>Normal MCA-PI, UA-PI, and CPR&lt;br&gt; MCA-PI more often less than fifth percentile ((S/71 vs O/71))&lt;br&gt; CPR more often less than fifth percentile ((B/71 vs 2/71))&lt;br&gt; No difference in UA-PI &gt; 95th percentile ((B/71 vs 3/71))</td>
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<td>Kaltman et al, Ultrasound Obstet Gynecol, 2005</td>
<td>Case-control study, (N = 58/114)</td>
<td>Mixed</td>
<td>20–40 wk</td>
<td>Ultrasound (Doppler)</td>
<td>Lower MCA-PI in HLHS&lt;br&gt; Higher MCA-PI in RSOL compared with HLHS&lt;br&gt; Higher UA-PI in RSOL&lt;br&gt; U/C PI-ratio similar between diagnostic groups&lt;br&gt; Lower MCA-RI and CPR</td>
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<td>Donofrio et al, Pediatr Cardiol, 2003</td>
<td>Case-control study, (N = 35/21)</td>
<td>Mixed</td>
<td>Second and third trimester</td>
<td>Ultrasound (Doppler)</td>
<td>Normal UA-RI&lt;br&gt; HLHS and HRHS infants had highest incidence of abnormally low CPR ((58% and 80%))</td>
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<td>Jouannic et al, Ultrasound Obstet Gynecol, 2002</td>
<td>Case-control study, (N = 23/40)</td>
<td>TGA</td>
<td>36–38 wk</td>
<td>Ultrasound (Doppler)</td>
<td>Lower MCA-PI&lt;br&gt; Normal UA-PI, DV-PI, and Ao-PI (no z scores)</td>
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<td>Meise et al, Ultrasound Obstet Gynecol, 2001</td>
<td>Case-control study, (N = 115/100)</td>
<td>Mixed</td>
<td>19–41 wk</td>
<td>Ultrasound (Doppler)</td>
<td>Normal MCA-PI&lt;br&gt; Higher UA-PI&lt;br&gt; No difference in UA-PI &gt; 95th percentile</td>
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<td>Brossard-Racine et al, Am J Neuroradiol, 2016</td>
<td>Cohort study, (N = 103)</td>
<td>Mixed</td>
<td>Second and third trimester</td>
<td>MRI (structural)</td>
<td>16% fetal brain abnormalities ((6) mild ventriculomegaly, 4 increased extra-axial spaces, 2 white matter cysts, 2 inferior vermis hypoplasia, 1 white matter signal hyperintensity)&lt;br&gt; 32% neonatal brain abnormalities, 27% acquired brain injury&lt;br&gt; Postnataally, a predominance of punctate white matter injury&lt;br&gt; 23% brain injury compared with 1.5% for controls&lt;br&gt; Most common: mild unilateral ventriculomegaly and increased extra-axial CSF spaces&lt;br&gt; No association between type of brain injury and CHD diagnosis&lt;br&gt; 35% brain injury ((7) malformation, 5 acquired lesion, 9 asymmetry of the ventricles/wider CSF spaces)&lt;br&gt; Fetuses with similar PA and Ao size had higher prevalence of brain injury compared with fetuses with PA &lt; Ao or Ao &lt; PA&lt;br&gt; Lower total brain volume and cortical and subcortical volumes from 20 wk GA&lt;br&gt; Higher ventricular volumes and cerebrospinal fluid spaces&lt;br&gt; Normal intracranial cavity volume and cerebellar volume&lt;br&gt; 6 fetuses brain weights less than fifth percentile, 0 controls brain weights &lt;25th percentile&lt;br&gt; 19% lower combined ventricular output</td>
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<td>Brossard-Racine et al, Am J Neuroradiol, 2014</td>
<td>Case-control study, (N = 144/194)</td>
<td>Mixed</td>
<td>18–39 wk</td>
<td>MRI (structural)</td>
<td>Lower total brain volume and cortical and subcortical volumes from 20 wk GA&lt;br&gt; Higher ventricular volumes and cerebrospinal fluid spaces&lt;br&gt; Normal intracranial cavity volume and cerebellar volume&lt;br&gt; 6 fetuses brain weights less than fifth percentile, 0 controls brain weights &lt;25th percentile&lt;br&gt; 19% lower combined ventricular output</td>
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<td>Miczoch et al(^2), Eur J Paediatr Neurol, 2013</td>
<td>Retrospective study, (N = 53)</td>
<td>Mixed</td>
<td>20–37 wk</td>
<td>MRI (structural)</td>
<td>39% brain injury ((7) malformation, 5 acquired lesion, 9 asymmetry of the ventricles/wider CSF spaces)&lt;br&gt; Fetuses with similar PA and Ao size had higher prevalence of brain injury compared with fetuses with PA &lt; Ao or Ao &lt; PA&lt;br&gt; Lower total brain volume and cortical and subcortical volumes from 20 wk GA&lt;br&gt; Higher ventricular volumes and cerebrospinal fluid spaces&lt;br&gt; Normal intracranial cavity volume and cerebellar volume&lt;br&gt; 6 fetuses brain weights less than fifth percentile, 0 controls brain weights &lt;25th percentile&lt;br&gt; 19% lower combined ventricular output</td>
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<td>Schellen et al, Am J Obstet Gynecol, 2015</td>
<td>Retrospective study, (N = 24/24)</td>
<td>T0F</td>
<td>25 wk</td>
<td>MRI, volume</td>
<td>Lower total brain volume and cortical and subcortical volumes from 20 wk GA&lt;br&gt; Higher ventricular volumes and cerebrospinal fluid spaces&lt;br&gt; Normal intracranial cavity volume and cerebellar volume&lt;br&gt; 6 fetuses brain weights less than fifth percentile, 0 controls brain weights &lt;25th percentile&lt;br&gt; 19% lower combined ventricular output</td>
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<tr>
<td>Al Nafisi et al, J Cardiovasc Magn Reson, 2013(^3)</td>
<td>Case-control study, (N = 22/12) controls</td>
<td>Mixed</td>
<td>30–38 wk</td>
<td>MRI, volume</td>
<td>No association between type of brain injury and CHD diagnosis&lt;br&gt; 35% brain injury ((7) malformation, 5 acquired lesion, 9 asymmetry of the ventricles/wider CSF spaces)&lt;br&gt; Fetuses with similar PA and Ao size had higher prevalence of brain injury compared with fetuses with PA &lt; Ao or Ao &lt; PA&lt;br&gt; Lower total brain volume and cortical and subcortical volumes from 20 wk GA&lt;br&gt; Higher ventricular volumes and cerebrospinal fluid spaces&lt;br&gt; Normal intracranial cavity volume and cerebellar volume&lt;br&gt; 6 fetuses brain weights less than fifth percentile, 0 controls brain weights &lt;25th percentile&lt;br&gt; 19% lower combined ventricular output</td>
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<tr>
<td>Sun et al, Circulation, 2015</td>
<td>Case-control study, (N = 30/30)</td>
<td>Mixed</td>
<td>36 wk</td>
<td>MRI (volume, (O_2) saturation)</td>
<td>Smaller brain volume&lt;br&gt; 10% lower aorta oxygen saturation with cerebral blood flow and extraction being normal. As a result, 15% reduction in cerebral oxygen delivery and 32% reduction in oxygen consumption&lt;br&gt; Reduced cerebral oxygen consumption associated with a mean 13% reduction in brain volume or 1 SD reduction in estimated brain weight z score</td>
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artery (MCA) to be lower in the entire study group (13 articles) or in selected CHD diagnoses (6 articles). In particular, fetuses with hypoplastic left heart syndrome (HLHS) or cardiac lesions that are associated with impaired cerebral oxygen supply had a lower pulsatility index of the middle cerebral artery (MCA-PI) compared with healthy controls.\textsuperscript{13–21} Fetuses with right-sided obstructive lesions\textsuperscript{14,15,19,20} often had a MCA-PI similar to healthy controls. Contradictory results were reported concerning MCA-PI in fetuses with transposition of the great arteries (TGA). On the one hand, TGA is one of the lesions associated with impaired cerebral oxygen supply because venous blood from the brain is redirected to the heart. This may lead to brain sparing, as suggested by the lower MCA-PI found by some studies.\textsuperscript{13,21,22} On the other hand, 3 studies specifically looking into the MCA-PI of fetuses with TGA found values similar to healthy controls.\textsuperscript{14,15,19} None of the studies on Doppler parameters in fetuses with CHD reported higher MCA-PI compared with healthy controls. Abnormally low MCA-PI was present from the second trimester onwards\textsuperscript{23} and tended to decrease more than would be expected for gestational age.\textsuperscript{24} Cerebroplacental ratio (CPR) was also reported to be lower in the majority of fetuses with CHD (75% of the selected articles). Again, fetuses with HLHS tended to have a lower CPR than fetuses with right-sided obstructive lesions and TGA.\textsuperscript{15,19} Two articles that did not use z scores found CPR values of <1.0 in 37% to 56% of the cases.\textsuperscript{16,18} Concerning PI of the umbilical artery (UA), which reflects intraplacental resistance to flow, 11 articles reported contradictory results. Five studies reported a higher pulsatility index of the umbilical artery (UA-PI).\textsuperscript{13,20,25–27} whereas another 5 studies reported similar UA-PI\textsuperscript{18,22,28–30} in fetuses with...
CHD compared with healthy controls. One study reported both higher UA-PI (coarctation of the aorta and HLHS) as well as normal UA-PI (right-sided obstructive lesions and TGA) in different parts of the study group.\textsuperscript{15}

**MRI**

**Prenatal MRI**

The main findings on MRI in fetuses with different types of CHD (majority TGA, HLHS, tetralogy of Fallot, single ventricle anomaly) were features of developmental delay of the cerebrum. In 16\% to 39\% of the cases, lesions such as (unilateral) mild ventriculomegaly and increased extra-axial cerebrospinal fluid spaces were present. These abnormalities are both thought to be markers of delay of cerebral development.\textsuperscript{31–33}

In addition to these lesions, other signs of developmental delay of the cerebrum such as a smaller head circumference (HC) and biparietal diameter, lower total brain weight, lower total brain volumes, higher ventricular volumes, and higher cerebrospinal fluid volumes were also common in fetuses with CHD.\textsuperscript{21,31–38}

Another feature of developmental delay was an impaired sulcation with a delay of \(\sim 3\) to \(4\) weeks.\textsuperscript{21,36–38}

Furthermore, cerebral metabolism was altered in fetuses with CHD and included an increased myo-inositol/choline (Ino/Cho), decreased n-acetylaspartate/choline (NAA/Cho), and decreased choline/creatinine (Cho/Cr) ratio.\textsuperscript{21,31,33,37} These metabolic alterations are also in accordance with cerebral developmental delay.

Fetuses with CHD associated with impaired oxygen supply to the cerebrum (HLHS, critical aortic stenosis, interrupted aortic arch, and TGA) showed more pronounced developmental delay in comparison with fetuses with CHD associated with sufficient blood flow to the cerebrum.\textsuperscript{21,34,37} Infants with HLHS showed a progressive decline in volumetric growth of the cortical and subcortical gray matter in comparison with healthy controls. These differences in brain volumes became significant from a gestational age of 30 weeks.\textsuperscript{38} Because of the study design of most studies, a further differentiation according to the type of CHD was impossible.

**Postnatal Preoperative MRI**

Forty studies used MRI to examine preoperative cerebral findings in infants with different types of CHD (Table 2). Signs of delayed development of the cerebrum were also common during this period. Infants with CHD had an overall reduction of 21\% in total brain volume,\textsuperscript{39} with all brain regions being affected.\textsuperscript{39–42} The largest regional difference between neonates with CHD and healthy controls seemed to be in the corpus callosum (31\% smaller), cortical gray matter (29.5\% smaller), and the occipital lobes (28.5\% smaller).\textsuperscript{39–41,43} These differences in brain volumes persisted to an age of 3 months. Brain growth rate, however, did not seem to differ between neonates with CHD and healthy controls in 1 study.\textsuperscript{40}

Brain metabolism and microstructural development were also in accordance with delayed cerebral development. White matter fractional anisotropy\textsuperscript{44–47} and NAA/Cho\textsuperscript{45–47} were lower, and mean average diffusivity,\textsuperscript{45–47} lactate/choline (Lac/Cho),\textsuperscript{45–47} Cho/Cr,\textsuperscript{48} and myo-inositol/creatinine\textsuperscript{48} were higher. The mean total maturation scores were significantly lower than reported normative data in neonates without CHD and corresponded to a delay of \(\sim 4\) weeks in structural brain development.\textsuperscript{49} In infants with TGA, the altered metabolism was...
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<td>Brossard-Racine et al, ANJR Am J Neuroradiol, 2016</td>
<td>Cohort study, N = 103</td>
<td>Mixed 100% MRI (structural)</td>
<td>32% brain injury (28% acquired)</td>
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<td>McCarthy et al, Pediatr Res, 2015</td>
<td>Retrospective study, N = 72</td>
<td>Mixed U MRI (structural)</td>
<td>MRI located in the periventricular white matter; centrum semiovale, and frontal white matter</td>
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<td>Bertholdt et al, Eur J Cardiothorac Surg, 2014</td>
<td>Case-control study, N = 30/20</td>
<td>Mixed 17% MRI (structural)</td>
<td>Second most common injury: nonhemorrhagic parenchymal injury</td>
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<td>Owen et al, J Pediatr, 2014</td>
<td>Cohort study, N = 55</td>
<td>Mixed 51% MRI (structural)</td>
<td>The majority of PVL classified as moderate</td>
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<td>Goff et al, J Thorac Cardiovasc Surg, 2010</td>
<td>Cohort study, N = 57</td>
<td>HLHS 86% MRI (structural)</td>
<td>23% WMI or stroke, 47% intracranial hemorrhage (subdural hematoma or choroid plexus)</td>
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<td>Andropoulos et al, Paediatr Anaesth, 2014</td>
<td>Retrospective study, N = 39</td>
<td>Mixed U MRI (structural)</td>
<td>Low Spo2 risk factor for brain injury; BAS not associated with brain injury</td>
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<tr>
<td>Beca et al, Circulation, 2013</td>
<td>Cohort study, N = 153</td>
<td>Mixed 59% MRI (structural)</td>
<td>Brain injury associated with poorer neurologic functioning (82% abnormal assessment)</td>
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<tr>
<td>Mulkey et al, Pediatr Cardiol, 2013</td>
<td>Retrospective study, N = 73</td>
<td>Mixed 32% MRI (structural)</td>
<td>26% brain injury (20% WMI, 5% stroke, 4% hemorrhage)</td>
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<td>Ortinau et al, J Pediatr, 2013</td>
<td>Case-control study, N = 15/12</td>
<td>Mixed U MRI (structural)</td>
<td>WMI associated with brain immaturity but not with BAS, diagnostic group, or GA at birth</td>
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<td>Glass et al, Cardiol Young, 2011</td>
<td>Cohort study, N = 127</td>
<td>Mixed U MRI (structural)</td>
<td>WMI and stroke not associated with postoperative brain injury</td>
<td></td>
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<tr>
<td>Block et al, J Thorac Cardiovasc Surg, 2010</td>
<td>Cohort study, N = 92</td>
<td>TGA U MRI (structural)</td>
<td>47% ≥1 type of brain injury, 26% 2–4 injury types</td>
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<tr>
<td>Andropoulos et al, J Thorac Cardiovasc Surg, 2010</td>
<td>Cohort study, N = 67</td>
<td>Mixed 44% MRI (structural)</td>
<td>25% brain injury if hemorrhage was excluded</td>
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<tr>
<td>Beca et al, J Am Coll Cardiol, 2009</td>
<td>Cohort study, N = 64</td>
<td>Mixed 32% MRI (structural)</td>
<td>Lower Apgar score at 5 min associated with brain injury</td>
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<tr>
<td>Petit et al, Circulation, 2009</td>
<td>Retrospective study, N = 26</td>
<td>TGA U MRI (structural)</td>
<td>Reduced cortical surface area and gyriﬁcation index for left and right hemispheres</td>
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<tr>
<td>Licht et al, J Thorac Cardiovasc Surg, 2009</td>
<td>Cohort study, N = 42</td>
<td>TGA SVA MRI (structural)</td>
<td>44% focal signal abnormalities in the white matter</td>
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<td>McQuillen et al, Circulation, 2006</td>
<td>Cohort study, N = 29</td>
<td>TGA U MRI (structural)</td>
<td>WMI and stroke most common injury (5 mild and 10 moderate or severe)</td>
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<tr>
<td>Durandy et al, Artif Organs, 2011</td>
<td>Cohort study, N = 21</td>
<td>TGA U MRI (structural)</td>
<td>Brain immaturity associated with preoperative WMI and late death</td>
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</tbody>
</table>

Infants with TGA and blood stream infection might have a higher risk of developing WMI (not significant in the whole group but significant when stroke was excluded)

WMI most common injury (14 BAS)

43% brain injury (23 stroke, 21 WMI, and 7 IVH)

BAS doubled the risk for brain injury

Higher Spo2 protective factor for brain injury (OR = 0.96)

28% brain injury (single ventricle and 2 ventricles)

Brain immaturity associated with postoperative WMI and late death

58% of lesions partially or completely resolved at late MRI scan (3–6 mo)

3% WMI, 0 strokes

21% PVL, 9.5% stroke, 86% incomplete closure of the opercular space (brain immaturity)

Lower total maturation scores (10.15, −1 mo younger than their actual GA)

41% brain injury (5 stroke, 2 WMIs, 1 IIVH, 4 combination of lesions)

5 min Apgar score, lowest Spo2, and BAS (12 of 19 infants with BAS had brain injury, 0 of 10 without BAS had brain injury) are risk factors for brain injury

Brain injury associated with poorer neurologic functioning (42% abnormal assessment)

WMI most common injury (5 mild and 10 moderate or severe)

18% PVL

26% brain injury (20% WMI, 5% stroke, 4% hemorrhage)

WMI associated with brain immaturity but not with BAS, diagnostic group, or GA at birth

WMI and stroke not associated with postoperative brain injury

47% ≥1 type of brain injury, 26% 2–4 injury types

25% brain injury if hemorrhage was excluded

Reduced cortical surface area and gyriﬁcation index for left and right hemispheres

46% focal signal abnormalities in the white matter

24% white matter injury

Infants with TGA and blood stream infection might have a higher risk of developing WMI (not significant in the whole group but significant when stroke was excluded)

0% of lesions partially or completely resolved at late MRI scan (3–6 mo)

38% PVL, 0 strokes

21% PVL, 9.5% stroke, 86% incomplete closure of the opercular space (brain immaturity)

Lower total maturation scores (10.15, −1 mo younger than their actual GA)

41% brain injury (5 stroke, 2 WMIs, 1 IIVH, 4 combination of lesions)

5 min Apgar score, lowest Spo2, and BAS (12 of 19 infants with BAS had brain injury, 0 of 10 without BAS had brain injury) are risk factors for brain injury

Brain immaturity associated with preoperative WMI and late death

58% of lesions partially or completely resolved at late MRI scan (3–6 mo)

IPPV, 0 strokes

21% PVL, 9.5% stroke, 86% incomplete closure of the opercular space (brain immaturity)

Lower total maturation scores (10.15, −1 mo younger than their actual GA)

41% brain injury (5 stroke, 2 WMIs, 1 IIVH, 4 combination of lesions)

5 min Apgar score, lowest Spo2, and BAS (12 of 19 infants with BAS had brain injury, 0 of 10 without BAS had brain injury) are risk factors for brain injury

Brain immaturity associated with preoperative WMI and late death

58% of lesions partially or completely resolved at late MRI scan (3–6 mo)
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<td>Tavani et al, <em>Neuroradiology</em>, 2003&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Cohort study, <em>N</em> = 24</td>
<td>Mixed U MRI (structural)</td>
<td>82% of infants delivered vaginally had hemorrhage on MRI  11 subdural hematomas  6 blood in the subdural space along the tentorium and falx or more laterally  7 blood in the choroid plexus  No relation between intracranial hemorrhage and abnormal neurologic examination</td>
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<td>von Rhein et al, <em>J Pediatr</em>, 2015</td>
<td>Case-control study, <em>N</em> = 19/19</td>
<td>Mixed U MRI, volume</td>
<td>21% total brain volume reduction, all regions affected  Smallest difference: mesencephalon 7.7% smaller  Biggest difference: cortical gray matter 29.5% smaller and occipital lobes 28.5% smaller</td>
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<td>Ortinau et al, <em>Pediatr Cardiol</em>, 2012</td>
<td>Cohort study, <em>N</em> = 57/36</td>
<td>Mixed U MRI, volume</td>
<td>Smaller frontal, parietal, cerebellar, and brain stem measures  Brain growth rate not different  Differences in volume persisted at 3 mo, except for cerebellar measures  Somatic growth the greatest predictor of brain growth</td>
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<td>Hagmann et al, <em>J Child Neurol</em>, 2016</td>
<td>Case-control study, <em>N</em> = 22/22</td>
<td>Mixed U MRI (volume, DTI)</td>
<td>Corpus callosum 25% (splenium) to 35% (genu) smaller  Total corpus callosum and splenium significantly smaller  Splenium lower FA, higher radial diffusion, diffusion coefficient not significant</td>
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<td>Mulkey et al, <em>Pediatr Neurol</em>, 2014</td>
<td>Pilot study, <em>N</em> = 19</td>
<td>Mixed U MRI (structural, DTI)</td>
<td>No differences in other substructures of the corpus callosum  52% brain injury (WMI or stroke)  Lower FA in multiple major white matter tracts in infants with brain injury compared with infants without brain injury  28% brain injury (focal or multifocal)</td>
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<td>Partridge et al, <em>Ann Neurol</em>, 2006</td>
<td>Cohort study, <em>N</em> = 25</td>
<td>Mixed U MRI (structural, DTI)</td>
<td>Brain injury associated with less change in FA over time in the pyramidal tract compared with newborns with 2 normal MRI scans  Infants with brain injury had the least dramatic changes with age detected by DTI  Trend in FA maturation rates across the 3 injury groups: newborns with normal scans had the most rapid changes, those with postoperative injury had intermediate maturation rates, and those with preoperative injury had the least rapid changes  No differences in directionally averaged diffusion coefficients</td>
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<td>Sethi et al, <em>Pediatr Res</em>, 2013</td>
<td>Cohort study, <em>N</em> = 36 CHD</td>
<td>SVA 61% MRI (structural, MRS)</td>
<td>36% brain injury (4 mild WMI, 4 moderate WMI, 2 severe WMI, 6 focal strokes, 5 IVH)  Higher mean average diffusivity for gray matter and lower FA in the white matter regions  Lower mean NAA/Cho ratios and higher mean Lac/Cho ratios  Delayed microstructural brain development  No abnormal findings on preoperative MRI  Altered metabolism in parietal white matter (increased Cho/Cr) and occipital gray matter (increased Cho/Cr and Ino/Cr)  Altered metabolism persisted 1 y after ASO in parietal white matter and normalized for occipital gray matter</td>
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<td>Park et al&lt;sup&gt;2&lt;/sup&gt;, <em>Pediatr Cardiol</em>, 2006</td>
<td>Case-control study, <em>N</em> = 18/15</td>
<td>TGA U MRI (structural, MRS)</td>
<td>40% brain injury (stroke or hemorrhage)  Higher Lac/Cho  Similar NAA/Cho between TGA and healthy controls, but those with brain injury on MRI had lower NAA/Cho  0% focal deficits on neurologic examination  Abnormalities in tone or reflexes common in newborns with and without brain injury</td>
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<td>Study (First Author, Journal, Year of Publication)</td>
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<td>Mahle et al, <em>Circulation</em>, 2002</td>
<td>Cohort study, N = 24</td>
<td>Mixed 83% MRI (structural, MRS)</td>
<td>25% ischemic lesions (small cortical watershed infarct, small infarct of the caudate, PVL) 4% hemorrhagic injury 16% elevated lactate with diffuse distribution, 25% lactate localized to the basal ganglia, 4% lactate in the peri-insular region Elevation of brain lactate associated with brain injury</td>
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<tr>
<td>Dimitropoulos et al, <em>Neurology</em>, 2013</td>
<td>Cohort study, N = 120</td>
<td>Mixed 33% MRI (structural, DTI, MRS)</td>
<td>41% brain injury Lower WM FA and lower NAA/Cho associated with higher injury severity preoperatively Higher SNAP-PE, lower SpO2, hypotension, and BAS predictive for higher injury severity</td>
<td></td>
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<tr>
<td>Shedeed and Elfaytouri, <em>Pediatr Cardiol</em>, 2011</td>
<td>Case-control study, N = 38/20</td>
<td>Mixed U MRI (structural, DTI, MRS)</td>
<td>24% white matter injury (PVL and stroke) Lower NAA/Cho ratio (0.55 vs 0.67) Higher Lac/Cho ratio (0.14 vs 0.09) Higher average diffusivity (1.41 vs 1.27) Lower white matter FA (0.19 vs 0.25)</td>
<td></td>
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<tr>
<td>Miller et al, <em>N Engl J Med</em>, 2007</td>
<td>Case-control study, N = 41/18</td>
<td>SVA 17% MRI (structural, DTI, MRS)</td>
<td>Decreased NAA/Cho (10%), increased average diffusivity (4%), decreased FA (12%), increased Lac/Cho (28%)</td>
<td></td>
</tr>
<tr>
<td>Nagaraj et al, <em>J Pediatr</em>, 2015</td>
<td>Case-control study, N = 43/58</td>
<td>Mixed 100% MRI (structural, ASL)</td>
<td>32.6% brain injury (64.3% WMI) compared with 0.6% in controls All cerebral blood flow parameters lower but not significantly different Lower global cerebral blood flow and regional cerebral blood flow in SVA Lower regional thalamic cerebral blood flow in cyanotic CHD and lower cerebral blood flow in thalami, occipital white matter, and basal ganglia compared with acyanotic CHD</td>
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<tr>
<td>Licht et al, <em>J Thorac Cardiovasc Surg</em>, 2004</td>
<td>Cohort study, N = 25</td>
<td>Mixed U MRI (volume, ASL)</td>
<td>Mean cerebral blood flow 19.7 ± 9.1 mL/100 g per min compared with 30 ± 3.4 mL/100 g per min in controls 5 neonates cerebral blood flow &lt;10 mL/100 g per min (moderate ischemic changes in piglets) 24% microcephaly Low Hb associated with higher baseline cerebral blood flow 28% PVL, associated with lower cerebral blood flow and less reactivity to hypercarbia</td>
<td></td>
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<tr>
<td>Van der Laan et al, <em>Pediatr Res</em>, 2013</td>
<td>Retrospective study, N = 21 (12 BAS)</td>
<td>TGA U NIRS</td>
<td>Preductal SpO2 increased immediately after BAS (72%–85%) and stabilized afterward (86%) rSO2 increased immediately after BAS and continued increasing during 24 h after BAS (42%–48% 2 h after BAS to 64% 24 h after BAS) Lower baseline rSO2 in the BAS group, whereas post-BAS rSO2 was higher compared with infants who did not undergo BAS (64% vs 58%) 10 h before surgery, HLHS infants had higher rSO2 than TGA infants (61% vs 56%) In HLHS infants, rSO2 decreased after CPB and recovered to preoperative values within 48 h after CPB In TGA infants, rSO2 decreased after CPB and increased ~20% above preoperative values within 48 h after CPB Infants with PA had lowest rSO2 values (38% ± 8%)</td>
<td></td>
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<tr>
<td>Uebing et al, <em>J Thorac Cardiovasc Surg</em>, 2011</td>
<td>Cohort study, N = 53</td>
<td>HLHS, TGA U NIRS</td>
<td>29% brain injury (16% brain edema, 6% PVL, 4% ventricular dilatation, 3% IVH grade I) Clinical variables not associated with brain injury BAS associated with brain edema (52% vs 6%)</td>
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<tr>
<td>Kurth et al, <em>Ann Thorac Surg</em>, 2001</td>
<td>Case-control study, N = 91/19</td>
<td>Mixed U NIRS</td>
<td>Lower rSO2 (immediately before surgery in the operating room, 1 min recordings) Infants with PA had lowest rSO2 values (38% ± 8%)</td>
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<tr>
<td>Latal et al, <em>Dev Med Child Neurol</em>, 2015</td>
<td>Cohort study, N = 77</td>
<td>Mixed 27% CUS</td>
<td>29% brain injury (16% brain edema, 6% PVL, 4% ventricular dilatation, 3% IVH grade I) Clinical variables not associated with brain injury BAS associated with brain edema (52% vs 6%)</td>
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<tr>
<td>Gunn et al, <em>Ann Thorac Surg</em>, 2012</td>
<td>Cohort study, N = 39</td>
<td>SVA 95% aEEG</td>
<td>33% EA, commonly left-sided, predominantly occurring during CPB 0% preoperative EA 3% preoperative EA</td>
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<tr>
<td>Gunn et al, <em>Intensive Care Med</em>, 2012</td>
<td>Cohort study, N = 150</td>
<td>Mixed U aEEG</td>
<td>33% EA, commonly left-sided, predominantly occurring during CPB 0% preoperative EA 3% preoperative EA</td>
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### TABLE 2 Continued

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<tr>
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<tr>
<td>Te Pas et al, <em>Acta Paediatr</em>, 2005</td>
<td>Retrospective study, N = 50</td>
<td>Mixed</td>
<td>U CUS</td>
<td>42% abnormal CUS (26% widening ventricles or subarachnoid space, 8% ischemic changes, 6% lenticulostriate vasculopathy) Abnormalities on CUS tended to occur more frequently in HLHS or CoA (63%) than TGA (14%)</td>
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<tr>
<td>Combination of techniques</td>
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<tr>
<td>Mulkey et al, <em>Pediatr Neurol</em>, 2015</td>
<td>Cohort study, N = 24</td>
<td>Mixed</td>
<td>100% aEEG MRI (structural)</td>
<td>63% abnormal aEEG (42% mildly abnormal, 21% severely abnormal) Abnormal aEEG associated with lower Apgar score at 5 min, CHD surgery at an older age, and male sex 50% brain injury (infarct and/or white matter injury) Infants with brain injury higher odds of having abnormal aEEG (OR = 3.0) 33% brain atrophy Severely abnormal aEEG background pattern associated with brain atrophy (OR = 15.0)</td>
</tr>
<tr>
<td>Dehaes et al, <em>Biomed Opt Express</em>, 2015</td>
<td>Case-control study, N = 11/13</td>
<td>SVA</td>
<td>U NIRS</td>
<td>Lower cerebral oxygen metabolism index, cerebral blood flow index, cerebral oxygen saturation index, and hemoglobin Higher cerebral oxygen extraction</td>
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<td>Lynch et al, <em>J Thorac Cardiovasc Surg</em>, 2014</td>
<td>Cohort study, N = 37</td>
<td>HLHS</td>
<td>U MRI (structural) DCS (NIRS) DCS</td>
<td>22% PVL</td>
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<td>Andropoulos et al, <em>Ann Thorac Surg</em>, 2012</td>
<td>Cohort study, N = 30</td>
<td>Mixed</td>
<td>43% MRI (structural) NIRS Ultrasound (Doppler) EEG</td>
<td>Lower time to surgery associated with postoperative PVL Lower r_{So2} and higher blood flow index associated with postoperative PVL Longer time to surgery associated with lower r_{So2} and higher FTOE 3% brain injury ultrasound (4 hemorrhage, 1 PVL) 26% brain injury MRI (WMI most common) 4 infants with hemorrhage on CUS had normal MRI suggesting 80% false positives and a positive predictive value for brain injury of only 20% for HUS before surgery 33% brain injury Mean preoperative r_{So2} 56.5% (53.0%–61.9%) r_{So2} &lt; 45% area under the curve 9 (0–191) min MCA-PI &lt; 0.75 TGA, −2.01 TOF, −2.4 HLHS CPR &lt; 1 40% TGA, 67% TOF, 60% HLHS MCA-PI positive correlation with neonatal EEG left frontal polar and left frontal β power CPR &lt; 1 associated with lower left frontal polar en left frontal β power 40% normal aEEG, 45% mildly abnormal (DNV), 15% severely abnormal (BS, CLV, FT) Similar rate of severely abnormal aEEG in cyanotic and acyanotic CHD (13% vs 16%) 19% EA, more frequently observed in acyanotic CHD (OR 9.37) 58% SWC within 72 h In acyanotic CHD, SWC more frequent in CoA than in HLHS (92% vs 48%) 9% ischemia on HUS Trend for more severely abnormal background patterns in abnormal HUS (OR 5.4) Severely abnormal background pattern and EA associated with more profound acidosis (low pH, more negative base excess, higher lactate) 39% preoperative brain injury (18% WMI, 21% stroke, 8% IVH) Risk factors for preoperative brain injury: BAS and 5 min Apgar score Preoperative brain injury more common in 2 ventricle anomalies Lower r_{So2} (27%–52%) 12 h before CPB 100% normal aEEG, 0% EA No difference in duration to normalization in aEEG after surgery between preoperative low or high r_{So2}</td>
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</table>
still present in the white matter and disappeared in the gray matter 1 year after the arterial switch operation.48

Apart from delayed cerebral development, the most commonly observed lesions in MRI were (punctate) white matter injury, periventricular leukomalacia, and stroke. Such brain lesions were reported in 19% to 52% of the cases.31,46,50–69 Although the type of CHD was associated with the occurrence of developmental delay or brain injury on MRI, most studies did not specify these differences.39–41,65

There were multiple clinical factors associated with preoperative brain injury. Risk factors for preoperative brain injury included brain immaturity,53,54,59,64,70 lower arterial oxygen saturation values,53,63,71,72 lower Apgar scores at 5 minutes,56,61,70 abnormal amplitude-integrated electroencephalography (aEEG) background pattern,65 longer time to surgery,72 male sex,73 and presence of brain lactate.74 A higher Score for Neonatal Acute Physiology–Perinatal Extension, hypotension, lower white matter fractional anisotropy, and lower NAA/Cho were associated with higher brain injury severity.53 Balloon atrial septostomy (BAS) was found to be an independent risk factor for brain injury in 4 studies,53,58,61,70 whereas 4 other studies did not find an association between BAS and brain injury.54,60,71,72

**Near-Infrared Spectroscopy**

Only a few studies examined regional cerebral oxygen saturation (rSo2) by means of near-infrared spectroscopy (NIRS) before surgery. Neonates with CHD had significantly lower preoperative rSo2 compared with healthy controls.75–77 Neonates with HLHS had higher rSo2 than neonates with TGA,78 and neonates with a pulmonary atresia (PA) had the lowest rSo2.75 In HLHS, neonates in whom cerebral oxygen saturation was monitored by NIRS had higher arterial oxygen saturation, were less often mechanically ventilated, and were less often intubated for a presumed circulatory mismatch.79 In TGA, rSo2 increased immediately after BAS and continued increasing during the 24 hours after BAS. Neonates in need of BAS had lower baseline rSo2 but higher post-BAS rSo2 compared with neonates who did not undergo BAS.80

**Other Techniques**

Brain injury on transcranial ultrasound was reported in up to 42% of the cases. The positive predictive value of transcranial ultrasound for the presence of brain injury, however, was very low with a value of 20%.81–84

Up to 63% of the neonates had an abnormal preoperative aEEG recording (42%–45% mildly abnormal and 15%–21% severely abnormal).85–87 In 0% to 19% of the cases, epileptic activity (EA) was registered85–87 before surgery. EA was more frequently observed in neonates with acyanotic CHD.85 An abnormal aEEG recording was associated with lower Apgar scores at 5 minutes, surgery at an older age, and male sex.65 Furthermore, neonates with brain injury had higher odds of having abnormal aEEG recordings.65

**Neurodevelopmental Outcome in Infants With CHD**

Sixteen prenatal or preoperative postnatal studies reported on NDO in infants with CHD. Fourteen of these studies used the BSID II or Bayley III at an age of 6 to 48 months. Thirteen studies assessed the association between prenatal or preoperative postnatal cerebral findings and NDO and were included in Table 3. Although scores were frequently within the normal range reported in healthy term infants (mean, SD 100 ± 15), almost all studies reported poorer NDO scores in infants with CHD compared with healthy controls or normative data. For the BSID II, the psychomotor developmental index (MDI) was more affected than the mental developmental index (MDI). Mean composite scores for the PDI ranged from 69.0 to 103.0 in infants with CHD14,24,81,88,89 and for the MDI from 85.2 to 103.5,14,24,81,88,89 The mean composite scores for the Bayley III were slightly higher compared with the composite scores for the BSID II. Mean cognitive scores ranged from 91.0 to 104.8, mean language scores ranged from 87.8 to 97.0, and mean motor scores ranged from 86.0 to 97.0,37,52,54,62,85,86

There were many prenatal and postnatal preoperative factors

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<td>Robertson et al42, Cardiol Young, 2004</td>
<td>Cohort study, N = 47</td>
<td>Mixed</td>
<td>EE</td>
<td>CUS</td>
<td>11% preoperative abnormal EEG (2.8% clinical seizure) Nadir CBF velocity 2 h post CPB No association between CBF velocity and EEG</td>
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ASL, arterial spin labeling; ASD, arterial switch operation; BS, burst suppression; CLV, continuous low voltage; CCA, coarctation of the aorta; CPB, cardiopulmonary bypass; CUS, cranial ultrasound; DCS, diffuse correlation spectroscopy; DNV, discontinuous normal voltage; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; FA, fractional anisotropy; FT, flat trace; FTGE, fractional tissue oxygen extraction; GA, gestational age; IHV, intraventricular hemorrhage; Ino/Dr, myo-inositol/creatinine; MRS, magnetic resonance spectroscopy; OR, odds ratio; PVL, periventricular leukomalacia; SNAP-PE, Score for Neonatal Acute Physiology–Perinatal Extension; SpO2, pulse oxygen saturation; SVA, single ventricle anomaly; SWC, sleep-wake cycling; TDF, tetralogy of Fallot; U, unknown; VMI, white matter injury.

* Articles that also address neurodevelopmental outcome.
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<th>Study (First Author, Journal, Year of Publication)</th>
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<td>Ultrasound Hahn et al, <em>Ultrasound Obstet Gynecol</em>, 2016</td>
<td>Retrospective study, <em>N</em> = 133</td>
<td>SVA 14</td>
<td>Ultrasound (Doppler and biometry)</td>
<td>BSID II</td>
<td>MCI 88.5 ± 16.6 and PDI 76.4 ± 19.8 First MCA-PI negatively associated with PDI HC/AC negatively associated with PDI</td>
<td>±</td>
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<tr>
<td>Ultrasound Zeng et al, <em>Ultrasound Obstet Gynecol</em>, 2015</td>
<td>Case-control study, <em>N</em> = 112/112</td>
<td>Mixed 12</td>
<td>Ultrasound (three dimensional, Doppler)</td>
<td>BSID II</td>
<td>Lower MCI (85.2 vs 99.1) and PDI (72.8 vs 99.4) No correlation between MCA-PI and NDO Total intracranial flow index positively correlated with PDI and MCI</td>
<td>±</td>
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<tr>
<td>Williams et al, <em>Am Heart J</em>, 2013</td>
<td>Cohort study, <em>N</em> = 134</td>
<td>SVA 14</td>
<td>Ultrasound (Doppler)</td>
<td>BSID II</td>
<td>MDI 88.5 ± 16.5 and PDI 76.4 ± 19.8 62% PDI &lt; 85 and 35% MDI &lt; 85 MCA-PI correlated negatively with PDI but not with MDI MCA-PI &lt; −2.0, on average, with 11-point-higher PDI scores compared with MCA-PI &gt; −2.0 (84.7 vs 73.6)</td>
<td>+</td>
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<tr>
<td>Latal et al, <em>Dev Med Child Neurol</em>, 2015</td>
<td>Cohort study, <em>N</em> = 77</td>
<td>Mixed 12</td>
<td>HUS</td>
<td>BSID II</td>
<td>MDI 89 (49–107) and PDI 69 (49–113) Isolated CHD: MDI 91 (50–107) and PDI 70 (49–113) No association between brain injury on ultrasound and NDO</td>
<td>−</td>
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<tr>
<td>MRI Masoller et al, <em>Ultrasound Obstet Gynecol</em>, 2016</td>
<td>Case-control study, <em>N</em> = 58/58</td>
<td>Mixed 6</td>
<td>MRI</td>
<td>Bayley III</td>
<td>Lower cognitive (91 vs 103), language (97 vs 108), motor (86 vs 100), social-emotional (85 vs 106), and adaptive (89 vs 97) score Average Bayley III score associated with total blood volume, left and right singulate depth, frontal Ino/Cho ratio, and NAA/Cho ratio</td>
<td>+</td>
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<tr>
<td>Study (First Author, Journal, Year of Publication)</td>
<td>Study Design, No. Infants</td>
<td>CHD Age at NDO Testing, Mo</td>
<td>Methods</td>
<td>Outcome</td>
<td>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</td>
<td>Relation</td>
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<td>Bece et al., <em>Circulation</em>, 2013</td>
<td>Cohort study, <em>N</em> = 153</td>
<td>Mixed</td>
<td>MRI</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 94 ± 15, language 94 ± 16, motor 97 ± 12&lt;br&gt;Delay in maturation of the posterior limb of the internal capsule on the first MRI associated with lower motor scores&lt;br&gt;Lower brain maturity associated with reduced performance on all domains</td>
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<td>Amplitude-integrated EEG</td>
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<td>Gunn et al., <em>Ann Thorac Surg</em>, 2012</td>
<td>Cohort study, <em>N</em> = 39</td>
<td>SVA</td>
<td>aEEG</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 92.4 ± 13.5, language 94.3 ± 17.7, motor 93.8 ± 10.6&lt;br&gt;Seizures associated with mortality but not associated with NDO&lt;br&gt;Recovery of background pattern within 48 h: 14 points increase in motor score</td>
<td>−</td>
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<tr>
<td>Combination of techniques</td>
<td>Cohort study, <em>N</em> = 30</td>
<td>TGA</td>
<td>NIRS</td>
<td>MRI</td>
<td>Composite scores: cognitive 104.8 ± 15, language 90.0 (83.0–94.0), motor 92.3 ± 14.2&lt;br&gt;Lower preoperative r_So2 associated with lower cognitive score&lt;br&gt;Preoperative brain injury associated with lower language score&lt;br&gt;Preoperative brain injury, lower preoperative r_So2 associated with lower motor score</td>
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associated with neurodevelopmental outcome in infants with CHD. Two articles found a negative correlation between MCA-PI and NDO.24,88 MCA-PI < 2.0 was associated with an increase of PDI of 11 points.88 One article found a positive correlation between MCA-PI and Bayley III cognitive scores16 and with lower BSID II scores.76

There was little evidence on the association between preoperative EEG or aEEG and NDO. One study found a positive association between preoperative left frontal polar and left frontal β power and cognitive scores.16 Three other studies did find an association between intraoperative or postoperative aEEG and NDO, but not between preoperative aEEG and NDO outcome.85,86,88

**DISCUSSION**

This systematic review demonstrates that prenatal and postnatal preoperative brain injury are common in infants with CHD. More importantly, this review demonstrates that abnormal cerebral findings during these periods might be associated with poorer neurodevelopmental outcomes in later life.
One major finding of this review was the presence of cerebral developmental delay in many infants with CHD during both the prenatal as well as the postnatal preoperative period. All cerebral regions were affected and a delay of up to 4 weeks compared with healthy controls was described. Moreover, signs of cerebral developmental delay are associated with adverse NDO in preterm infants. In infants with CHD, cerebral developmental delay was associated with the occurrence of brain injury on preoperative MRI and also with the severity of brain injury. We speculate, therefore, that cerebral developmental delay might lead to an increased vulnerability of the brain and could therefore be an important contributor to brain injury in infants with CHD.

Another major finding was that many fetuses with CHD had abnormal Doppler parameters. PI of the middle cerebral artery and CPR were low, whereas UA-PI was high compared with healthy fetuses in the majority of studies that reported on Doppler parameters. These findings are in accordance with redistribution of blood flow to enhance cerebral perfusion, also called the brain-sparing effect. Brain sparing might be a consequence of low cerebral oxygen content (hypoxemia) or low cerebral blood volume (ischemia). In fetuses with intrauterine growth restriction, brain sparing is a sign of severely impaired oxygen and/or nutrient supply and is associated with mortality and poor outcome. In fetuses with CHD, this association seems to be less clear and might even be a protective factor. Moreover, it has been reported that up to 23.8% of fetuses with CHD are also growth restricted, and variable degrees of impaired placental function may concurrently modulate cerebral vascular resistance. Brain sparing in fetuses with CHD could be an adaptive mechanism to compensate for either hypoxemia (low \( \text{PO}_2 \) because of placental insufficiency), hypoxia (low oxygen saturation because of intra- and extracardiac mixing), or ischemia. In all 3 situations, changes in cerebral vascular resistance may occur to compensate for poor oxygenation and to meet cerebral metabolic demands.

Unfortunately, to date there are no studies looking systematically at uteroplacental (UA) and fetal (MCA, ductus venosus) flow to clarify if and to what extent brain sparing is determined by the effect of the cardiac lesion on oxygen saturation in fetuses with CHD.

Postnatally, brain injury was frequently reported (up to 52%) before cardiac surgery in infants with CHD. The most commonly observed lesions were all associated with decreased cerebral blood flow (ischemia) and included (punctate) white matter injury, periventricular leukomalacia, and stroke. Another indicator of an ischemic state was the presence of cerebral lactate in some infants with CHD. In addition to ischemia, hypoxia might also play a role in the development of early acquired brain injury in infants with CHD. Multiple studies found low arterial oxygen saturation values to be an independent risk factor for preoperative brain injury and high arterial oxygen saturation values to be a protective factor for preoperative brain injury.

In general, infants with CHD scored lower on neurodevelopmental tests compared with healthy infants. Their mean scores, however, were frequently within the normal ranges reported in healthy term infants (mean, SD 100 ± 15). A possible explanation for these normal scores might be that most infants were examined during early childhood (6–48 months). Certain capacities and skills such as memory function and abstract-logic thinking mature during the course of childhood, and problems might only become apparent at an older age. Children with CHD at school age on average score lower on motor skills, higher-order language, visual-spatial skills, vigilance, and sustained attention. These deficits often persist through adolescence into adulthood. Furthermore, children and adolescents with complex CHD often have difficulties with social cognition and executive functioning, which might lead to psychosocial disorders and a lower quality of life.

We found numerous associations between prenatal and postnatal preoperative cerebral findings and neurodevelopmental outcome in infants with CHD. Both prenatally as well as postnatally we were unable to identify specific cerebral findings that were responsible for poorer neurodevelopmental functioning in infants with CHD. We speculate, therefore, that neurodevelopmental impairment in CHD is the cumulative effect of delayed microstructural development in combination with multiple hypoxic and/or ischemic events during prenatal and postnatal preoperative life rather than being caused by a single independent factor.

Research to further clarify the actual mechanisms responsible for neurodevelopmental impairment in infants with CHD is essential. Nowadays, the adult population with CHD is larger than the pediatric population with CHD. Many adults with CHD still experience psychosocial and cognitive challenges that may impact emotional functioning, academic achievement, and even...
quality of life. To explore pathophysiological mechanisms and to optimize treatment protocols, large (multicenter) prospective trials should be conducted that include the prenatal to the postoperative period with an adequate duration of follow-up. Furthermore, increasing awareness of the vulnerability of the young developing brain of an infant with CHD is also essential among physicians and other caregivers that are involved in the treatment to prevent neurodevelopmental impairment later in life.

This systematic review has several limitations. First, most studies included in this review were observational studies. This type of study is unequivocally associated with a risk of bias of under- or overestimating outcome measures. The vast majority of studies, however, were of reasonable to very good quality according to the Newcastle-Ottawa Quality Assessment Scale. Second, comparisons between studies were difficult because various techniques and methods were used to assess cerebral abnormalities in infants with complex CHD. Reference values for antenatal Doppler parameters, for example, were different from one study to another. In addition to various techniques and methods, numerous different types of CHD were included with different pathophysiology, circulatory effects, and treatment protocols. This also made comparisons between studies more difficult. Future studies should differentiate between cardiac lesions to make risk stratification of infants with CHD possible and counseling perhaps a little more specific. Finally, an effect of chromosomal abnormalities on cerebral development and NDO cannot be ruled out completely since not all studies stated whether they included infants with chromosomal abnormalities with CHD. For future studies, it would also be interesting to assess differences in cerebral abnormalities and NDO between infants with isolated CHD and infants with nonisolated CHD.

CONCLUSIONS
The current systematic review suggests that prenatal and postnatal preoperative abnormal cerebral findings may play an important role in neurodevelopmental impairment in infants with CHD. Physicians and other caregivers should be more aware of this vulnerability of the brain and of the possible effect repeated episodes of hypoxia and/or ischemia during early life may have in infants with CHD. Prenatal and postnatal counseling remains challenging when CHD is diagnosed. Targeted investigation in each individual case may help clarify which injuries are already present prenatally and which are due to the postnatal course of the condition.

Prof Dr Bilardo and Prof Dr Bos conceptualized and designed the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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ABBREVIATIONS
aEEG: amplitude-integrated electroencephalography
BAS: balloon atrial septostomy
Bayley III: Bayley Scales of Infant and Toddler Development III
BSID II: Bayley Scales of Infant Development II
CHD: congenital heart disease
Cho/Cr: choline/creatine
CPR: cerebroplacental ratio
EA: epileptic activity
HC: head circumference
HLHS: hypoplastic left heart syndrome
Ino/Cho: myo-inositol/choline
Lac/Cho: lactate/choline
MCA: middle cerebral artery
MCA-PI: pulsatility index of the middle cerebral artery
MDI: mental developmental index
NAA/Cho: n-acetylaspartate/choline
NDO: neurodevelopmental outcome
NIRS: near-infrared spectroscopy
PA: pulmonary atresia
PDI: psychomotor developmental index
Pl: pulsatility index
r_SO2: cerebral oxygen saturation
TGA: transposition of the great arteries
UA: umbilical artery
UA-PI: pulsatility index of the umbilical artery
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