Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease

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OVER A DECADE AGO, I CO-AUTHORED A REVIEW in Cardiology in the Young regarding neurological outcomes following surgery for congenital cardiac disease.[1] In that review, I placed much emphasis on the conduct of cardiopulmonary bypass, and its role in neurodevelopmental disabilities. Much has been learned in the intervening years regarding the multifactorial causes of abnormal school-age development, in particular, the role of prenatal, perioperative, socioeconomic, and genetic influences. In this update, I will highlight some of the recent advances in our understanding of the protean causes of neurological, behavioral, and developmental abnormalities in children and young adults with complex forms of congenital cardiac disease. In addition, I will summarize the current data on patients at particular high-risk for adverse neurodevelopmental outcomes, specifically those with a functionally univentricular heart who have had staged reconstruction with ultimate conversion to the Fontan circulation.

Scope of the problem

Prior to the early 1980s, it was uncommon for children with complex congenital cardiac malformations to survive into later childhood. The nearly simultaneous advances in congenital cardiac surgery, echocardiography, and intensive care were coupled with the availability of prostaglandin and the developing discipline of interventional cardiology. Together these factors resulted in a dramatic fall in surgical mortality, with complex repairs taking place at increasingly younger ages. At many large centers, palliative surgery followed by later repair was replaced by primary repair in infancy, and staged reconstructive surgery for various forms of functionally univentricular heart, including those with hypoplastic left heart syndrome, was improving with steadily falling surgical mortality rates.[2–5] As a result, the last decade has seen an increasing number of children entering primary and secondary schooling. Research into their academic and behavioral outcomes has revealed some sobering realizations about the outcomes in these surgical survivors.

As a group, patients with complex congenital cardiac malformations, and for the remainder of this review I will restrict myself to children who require cardiac surgery as neonates or young infants, have a significantly higher incidence of academic difficulties, behavioral abnormalities, fine and gross motor delays, problems with visual-motor integration and executive planning, speech delays, inattention, and hyperactivity.[6–21] Injury to the central nervous system in infants with congenital cardiac disease is characterized by abnormalities of tone, feeding difficulties, delays in major motor milestones, and abnormalities in speech. As these children get older, the need for special services in school is significantly increased compared to the general population.[6,9,20,22] As children progress through school, low academic achievement scores, learning disabilities, behavioral problems and attention deficit/hyperactivity disorder may result in academic failure, poor classroom and social skills, low self-esteem, behavioral disinhibition, and ultimate delinquency.

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Depending upon a number of factors, including the underlying congenital lesion and the associated surgical management, genetic contributions, additional perinatal events such as profound hypoxia–ischemia from a delayed diagnosis, or postoperative events such as low cardiac output syndrome,[23,24] the incidence of abnormalities may range from infrequent to ubiquitous. For example, in cohort studies of children with transposition, a small fraction may have severe developmental impairment, perhaps one-half are normal in all respects, and nearly one-half will have a combination of speech, motor, behavior, or learning issues.[9,25] The percentage of children with more "significant" cardiac disease, for example, totally anomalous pulmonary venous return with obstruction, hypoplastic left heart syndrome, or interruption of the aortic arch, who are developmentally "normal" is significantly decreased, with perhaps only one-third of those tested having no dysfunction in any domain.[16,20] While most of these abnormalities are relatively mild, and may only be determined by formal testing, they result in a so-called "high-prevalence, low-severity" developmental "signature". A schematic representation is shown in Figure 1.
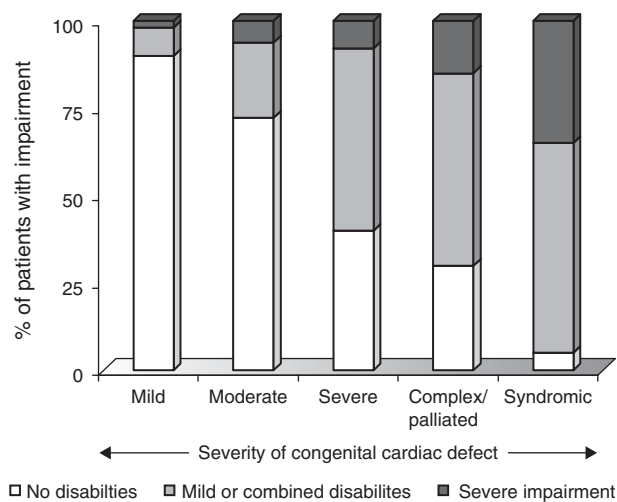
Figure 1.

Schematic representation of developmental abnormalities in children with congenital heart disease. Children with milder forms of congenital heart disease (e.g., ventricular septal defect without an associated genetic syndrome), as a group, have a low incidence of developmental abnormalities, and more than mild abnormalities are rare. Increasingly complex forms of congenital heart disease (e.g., transposition or totally anomalous pulmonary venous connection) are associated with increasing numbers of children with developmental deficits, and only the minority of children with extremely complex heart disease (e.g., functionally univentricular heart, hypoplastic left heart syndrome) are completely normal in all respects. Congenital heart disease associated with chromosomal abnormalities (e.g., Down's and DiGeorge Syndromes) or multiple congenital anomalies are nearly always associated with developmental abnormalities, in many cases, severe.

Importantly, the combined outcomes of developmental delay, academic difficulties, and behavioral abnormalities, in combination, represents the single most common morbidity affecting the quality of life in school-age survivors with congenital cardiac disease. This complication is more common than late mortality, severe exercise impairment, unplanned reoperations, bacterial endocarditis, or significant arrhythmias. The later implications of these findings through adulthood are uncertain, and must continue to be a robust area of research. Our current understanding of the etiology of these findings is discussed below.

Congenital cerebral disease

Given that the central nervous and cardiovascular systems form nearly simultaneously in early gestation, it is not surprising that there is an increased incidence of structural abnormalities of the brain in children with structural cardiac abnormalities. Many children with multiple congenital anomalies or chromosomal abnormalities, many of whom have coexisting congenital heart disease, will have developmental delay as a significant component of late morbidity. In addition to genetic factors which may affect both systems from a macroscopic perspective, congenital heart disease may alter cerebral blood flow, oxygen delivery, or both, and result in secondary effects of the vulnerable fetal central nervous system.

In some respects, the brain of the full term neonate with congenital cardiac disease structurally resembles that of a preterm neonate, and interestingly, school-age survivors of complex heart surgery have developmental findings which are very similar to survivors of premature birth, suggesting a similar pathological response to injury. Serial studies of the fetal brain, utilizing ultrasound and magnetic resonance imaging, are currently underway and are increasing our understanding of the interactions between the abnormal fetal cardiovascular system and cerebral development.

Microcephaly

Head circumference at birth is a marker for brain development, and in neonates without congenital heart disease, microcephaly is independently associated with later developmental delays and academic difficulties. Multiple cohort studies have shown the incidence of microcephaly at birth is increased in children with congenital heart disease, approaching one-fourth of children in some reports,[11,26] and persists into later infancy.[10,13,14] In a group of 318 neonates with various forms of congenital cardiac disease evaluated at our institution between 1992 and 1997, the incidence of congenital microcephaly was

nearly one in ten.[32] More complex lesions have a higher incidence. In a 5-year study of consecutive neonatal autopsies at our institution, approximately one-third of infants with hypoplastic left heart syndrome were noted to have congenital central nervous system anomalies, and/or were microcephalic.[27] While the causes are speculative, and most certainly multifactorial, a recent report from Shillingford et al. in children with hypoplastic left heart syndrome – where the median head circumference at birth is only at the 18th percentile – revealed that patients with microcephaly had significantly smaller ascending aortas than those without, suggesting that reduced flow to the brain secondary to anatomic hypoplasia of the ascending aorta may result in diminished brain growth.[28]
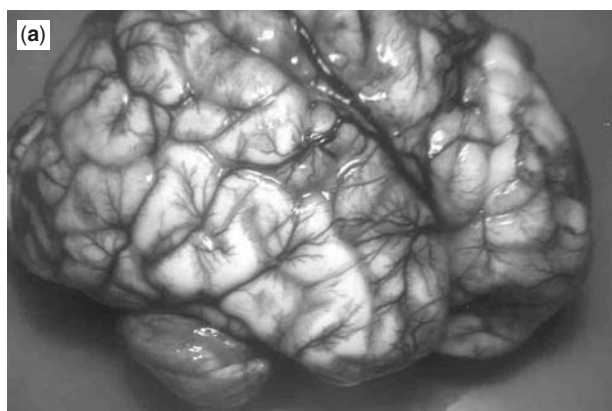
The "open operculum"

The term "operculum insulae" denotes the region that covers the insulae Relie, and is made up of frontal, temporal, and parietal cortical convolutions. In magnetic resonance and computer tomographic imaging studies of neonates with complex congenital cardiac disease, underdevelopment of the operculum may be seen in nearly one-quarter of the patients, and is a marker for functional immaturity of the brain.[29–31] This may be a unilateral or bilateral finding, and has been termed "underoperculinization" or an "open operculum" (Fig. 2). The operculum is thought to be related to oral-motor coordination, taste and speech, particularly expressive language. In adult patients who develop a stroke in this area of the brain, the so-called Foix–Chavany–Marie syndrome, deficits include impairment of voluntary movements such as chewing and deglutition, dysarthria, and taste abnormalities.[32] In macaque monkeys, receptive fields on the tongue, lips, and palate have been mapped to the operculum.[33] Given the high prevalence of feeding problems,[34] expressive language delay and oral-motor apraxia in children with complex cardiac disease,[25,35,36] as well as the increasing recognition of a high prevalence of an open operculum, one can speculate that some patients with these developmental disabilities may have a structural underdevelopment of the operculum as the etiology. Further research into this hypothesis is ongoing.

Periventricular leukomalacia

White matter injury – a common finding in premature infants – has been increasingly recognized in full term neonates with congenital cardiac disease. Mahle et al. studied 24 neonates preoperatively with magnetic resonance imaging of the brain, and found periventricular leukomalacia in four, a number by which nearly tripled after cardiac surgery.[30] Spectroscopy in this cohort revealed elevated brain lactate in slightly over half of the patients. Licht et al. have recently suggested that decreased cerebral blood flow (Fig. 2) preoperatively was significantly associated with lesions in the white matter, affecting slightly over one-quarter of the neonates.[29] In a larger study, reviewing 105 studies of the brain with magnetic resonance imaging in children with congenital cardiac disease in the early postoperative period, periventricular leukomalacia was found in slightly over half of the neonates in the study, but rarely in older children.[37]

Periventricular leukomalacia is believed to arise from several factors, including the high susceptibility of the immature oligodendrocyte to hypoxic ischemic injury, as well as the watershed distribution of cerebral blood flow to this area between the small arteries that penetrate from the cortex, and those that arise centrally and run radially outward. This watershed area is particularly prone to ischemia during decreases in cerebral perfusion pressure. In premature infants,

Figure 2.
(a) Normal external appearance of the brain; (b) underdevelopment of the operculum.

severe degrees of periventricular leukomalacia have been associated with cerebral palsy, while mild degrees of injury have been associated with developmental delay,[38] motor difficulties, and behavioral disorders;[39] a developmental signature remarkably similar to school-age children with congenital cardiac disease.

Additional anatomical findings at birth

Congenital anomalies of the central nervous system are known to be coincident with congenital heart disease.[27,40–42] In a prospective study by Miller et al., head ultrasound examinations were performed on full term infants with congenital heart disease before and after surgical interventions. Abnormalities of the brain were noted in one-quarter of the infants, and nearly half of the anomalies were present before surgery, such as holoprosencephaly and agenesis of the corpus callosum.[43]

Fetal cerebrovascular physiology and oxygen delivery

Recent ultrasound studies have revealed that cerebral vascular resistance is altered in the presence of congenital cardiac disease. Using Doppler interrogation of middle cerebral artery flow, both Donofrio et al.,[44] and Kaltman et al.,[45] have shown that fetuses with left sided cardiac disease, for example, hypoplastic left heart syndrome, had decreased cerebral vascular resistance compared to normal. In patients with aortic atresia, for example, the fetal cardiac output through the arterial duct must deliver blood cephalad to the brain, as well as caudad to the low resistance placenta. It is speculated that cerebral vascular resistance must therefore be lower than normal to allow adequate flow to the central nervous system. Kaltman et al.,[30] also showed that fetuses with right-sided lesion, for example, tetralogy of Fallot, had increased fetal cerebral vascular resistance. The impact of these alterations in fetal cerebral vascular resistance is unclear, but almost certainly plays a role in subsequent neurological development.[45]

In the normal fetus, the intracirculatory patterns created by the normal fetal connections result in preferential streaming of the most highly oxygenated fetal blood to the developing brain, and the most desaturated blood to the placenta. When significant structural cardiac disease exists, these beneficial patterns of flow are likely to be altered. Although not yet confirmed by fetal magnetic resonance spectroscopy, albeit that studies are currently underway, fetuses with transposition are likely to have the blood with the lowest saturation of oxygen returning to the ascending aorta and brain, while blood with the highest saturation will return to the abdominal organs and placenta. Speculation concerning this "transposed" fetal circulation was put forward by Naeye nearly 40 years ago as an explanation for the high incidence of macrosomia in these infants.[46] Lesions producing complete mixing, such as seen in functionally univentricular hearts, will have intermediate values of fetal cerebral saturation of oxygen, but lower than that seen in the normal fetus (Fig. 3).

Perioperative contributors

Preoperative factors

Neonates with complex congenital cardiac disease frequently require hospitalization immediately after birth, many to receive intravenous prostaglandin infusion, some requiring intubation, mechanical ventilation, or invasive interventions such as balloon atrial septostomy. All of these interventions carry risks to the central nervous system, especially the potential for paradoxical embolus to the brain of air or particulate matter in children with intracardiac right-to-left shunts. These patients also have saturations of oxygen that are below normal, potentially compromising the delivery of oxygen to the brain.

Licht et al. recently reported that, in addition to diminished content of oxygen, neonates with critical congenital cardiac disease also suffered from diminished flow to the brain.[29] Under conditions of general anesthesia and mechanical ventilation with normocapnia, cerebral blood flow was, on average, less than half that seen in normal term newborns. The cerebral vascular response to increased inspired carbon dioxide was preserved, suggesting normal autoregulation of cerebral blood flow, at least over the short term. The finding of reduced cerebral blood flow and abnormal vascular reactivity has recently been confirmed in a neonatal piglet model of functionally univentricular physiology by Ricci et al.[47]

Intraoperative factors

The conduct of cardiopulmonary bypass, and other support techniques used during open-heart surgery, has received considerable attention, and has been the subject of active and gratifying research. As opposed to all of the risk factors for abnormal neurological development discussed thus far, variation in intraoperative support, such as the conduct of cardiopulmonary bypass, is one of the few modifiable risk factors which may be altered to improve long-term neurological outcomes. Potential modifiable technical features of cardiopulmonary bypass are shown in Table 1, three of which are reviewed below.

pH management. In one very important trial at Children's Hospital, Boston, developmental and neurological outcomes were evaluated in infants undergoing repair of a variety of cardiac defects at less than
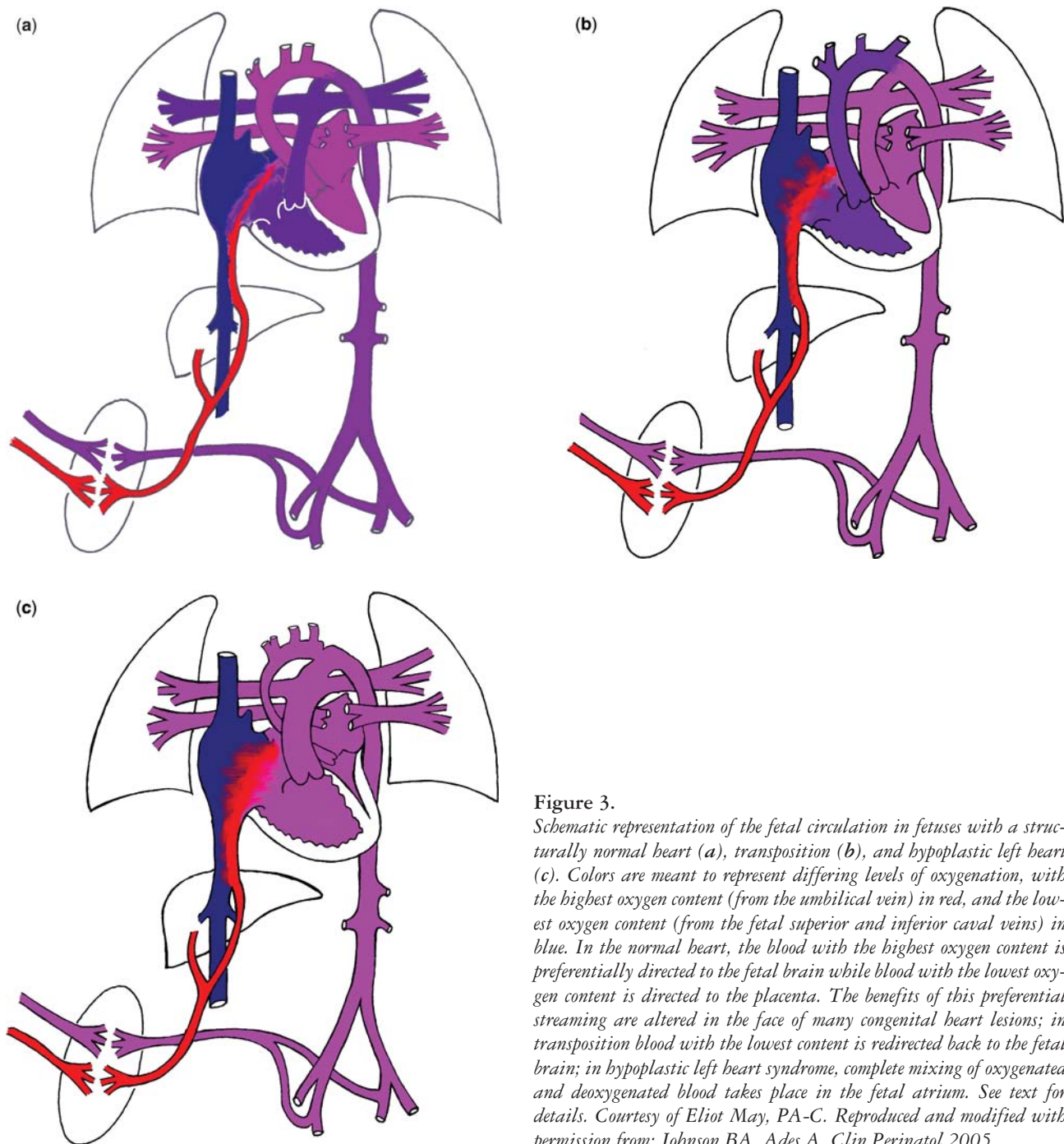
Figure 3.
*Schematic representation of the fetal circulation in fetuses with a structurally normal heart (**a**), transposition (**b**), and hypoplastic left heart (**c**). Colors are meant to represent differing levels of oxygenation, with the highest oxygen content (from the umbilical vein) in red, and the lowest oxygen content (from the fetal superior and inferior caval veins) in blue. In the normal heart, the blood with the highest oxygen content is preferentially directed to the fetal brain while blood with the lowest oxygen content is directed to the placenta. The benefits of this preferential streaming are altered in the face of many congenital heart lesions; in transposition blood with the lowest content is redirected back to the fetal brain; in hypoplastic left heart syndrome, complete mixing of oxygenated and deoxygenated blood takes place in the fetal atrium. See text for details. Courtesy of Eliot May, PA-C. Reproduced and modified with permission from: Johnson BA, Ades A. Clin Perinatol 2005.*

Table 1. Potentially modifiable intraoperative risk factors of cerebral injury.

Air or particulate embolus
Rate and depth of core cooling (if utilized)
Deep hypothermic circulatory arrest (if utilized)
Reperfusion injury and inflammation
Rate of core rewarming/hyperthermia
Hyperglycemia
Hyperoxia
pH management during cardiopulmonary bypass
Hematocrit management during cardiopulmonary bypass

9 months of age who were randomized to either alpha- or pH-stat blood gas management strategy during deep hypothermic bypass. Eligibility was limited to children undergoing various forms of biventricular repair in the first 9 months of life. Although there were some benefits reported with the use of pH-stat management for outcomes in the immediate perioperative period,[48] the use of either the alpha- or pH-stat strategies was not consistently related to either improved or impaired neurodevelopmental outcomes at short-term follow-up.[49] On the Bayley Scales of

Infant Development, there was no effect of treatment assignment on the Psychomotor Development Index, The Index of Mental Developmental, in contrast, varied significantly depending on the underlying anatomical diagnosis. For patients with transposition and tetralogy of Fallot, use of pH-stat resulted in a slightly higher mental developmental index, although the difference was not statistically significant. Interestingly, in patients with a ventricular septal defect, the treatment effect was opposite, with use of alpha-stat management resulting in significantly improved scores. There was a significant effect of cardiac diagnosis on outcomes. Both scores of the Bayley examinations were significantly higher in the patients with transposition compared to the other cardiac defects. Despite the equivocal data in this early report, with no longer-term follow-up yet available, many centers are currently utilizing pH-stat management during core cooling in all neonatal and infant operations. Further research in this area, based upon additional potential patient-related modifiers, for example, cardiac diagnosis, age, preoperative hypoxemia, and presence of major aorto-pulmonary collateral arteries, should continue.

Deep hypothermic circulatory arrest.   Much has been written on the potentially deleterious effects of prolonged circulatory arrest with profound hypothermia in neonatal and infant cardiac surgery. It is generally agreed that very prolonged periods of uninterrupted circulatory arrest may have adverse neurological outcomes. However, upon close inspection of the data, it is increasingly clear that the effects of short durations of circulatory arrest are inconsistently related to adverse outcomes, that the effect of circulatory arrest is not a linear phenomenon with a cut-off point in the range of 40 minutes,[50,51] and that the effects are most likely modified by other patient-related, preoperative and postoperative factors. Some reports, most in an earlier era of cardiac surgery, demonstrate a detrimental effect of circulatory arrest on a variety of outcomes regarding the central nervous system,[6,7,15,52–54] while some demonstrate either an inconsistent effect or no effect.[16,20,55] Some have taken the stance that, since the majority of studies suggest a negative effect of circulatory arrest, it should be avoided "at all costs". Innovative and challenging strategies have been designed to provide continuous cerebral perfusion during complex reconstruction of the aortic arch or intracardiac repair. It must be emphasized that the avoidance of circulatory arrest by necessity requires an increased duration of cardiopulmonary bypass, which has consistently been shown to have an adverse effect on both short- and long-term outcomes.[24,56] A randomized trial of circulatory arrest and continuous cerebral perfusion has recently been completed at the University of Michigan, with short-term studies soon to be reported

in the literature (Ohye R, personal communication), and long-term studies in the planning stages.

It seems imprudent to change practice based upon studies with only short-term developmental assessment, as it is clear that developmental studies in infants have very limited predictive validity for long-term outcomes, both in patients with[57] and without[58] congenital cardiac disease. Perhaps the best conducted study in this regard – which emphasizes this point – is the Boston Circulatory Arrest Study, with multiple reports from Bellinger, Newburger, Jonas et al.

In this cohort, 171 children with transposition were randomly assigned an intraoperative support strategy of predominantly deep hypothermic circulatory arrest or predominantly low-flow cardiopulmonary bypass during the arterial switch operation. Earlier reports suggested that the group as a whole was performing below expectations in many aspects of evaluation, with worse outcomes for the circulatory arrest group in the areas of postoperative seizures,[59] motor skills at 1 year of age,[60] as well as behavior, speech and language at age 4 years.[17,35] Mean intelligence quotient at age 4 was lower than expected at 93, with no difference across treatment assignment. Many centers began avoiding even short periods of circulatory arrest based upon these and other reports.

In 2003, detailed standardized testing was reported for this group.[9] Neurodevelopmental analyses of this cohort at 8 years of age revealed that the scores for Intelligence Quotient for the cohort as a whole are now closer to normal, at 98 versus the population mean of 100. The group did demonstrate significant deficits in visual-spatial and visual-memory skills, as well as in components of executive functioning such as working memory, hypothesis generation, sustained attention, and higher-order language skills. In other words, the children had difficulty coordinating skills in order to perform complex operations. Those assigned to circulatory arrest scored worse on motor and speech functioning, while the patients submitted to low-flow bypass demonstrated worse scores for impulsivity and behavior. When compared to a normative sample, parents of the entire cohort reported significantly higher frequencies of attention problems, developmental delay, learning problems, and speech problems. More than a third of the population received remedial school services, and one in ten had repeated a grade. Thus, in this population of patients who underwent the arterial switch operation between 1988 and 1992, there appears to be a correlation between congenital cardiac disease and its surgical repair with later speech and language difficulty, behavioral difficulties and execution planning in childhood.[8,9,18,50,57] Whether current modifications of support techniques will improve

the long-term outcomes remains the subject of ongoing study.

This well-designed trial, with superb follow-up compliance, enrolled neonates with transposition, with or without a ventricular septal defect, who were planned to undergo an arterial switch operation between 1988 and 1992. The results reflect the perioperative care delivered in that era, and thus may not be generalizable to the current era, or other congenital cardiac lesions. In addition, those patients randomized to predominantly continuous bypass did undergo a brief period of circulatory arrest. The study does not compare use of circulatory arrest to no circulatory arrest. Nonetheless, the results serve to show the multiple factors which influence developmental outcome at school age, and that factors related to poorer outcome such as deep hypothermic circulatory arrest, which seem apparent and significant on early testing, may be attenuated or even abolished during longer-term follow-up, as other factors assume a more important role.[57]

Hematocrit during bypass. During cardiopulmonary bypass, hemodilution has been widely applied based upon the notion that increased viscosity would be detrimental during periods of profound or even moderate hypothermia. Shinoka et al. have demonstrated the detrimental effects of extreme hemodilution, with the hematocrit decreased to less than 10% in the laboratory setting, and that higher levels above 30% resulted in improved cerebral recovery after circulatory arrest.[61] This work in animals suggesting higher hematocrit levels confirmed better cerebral protection was recently confirmed in a randomized clinical trial in infants.[62] In this study, neonates randomized to maintain an intraoperative hematocrit of close to 20% had significantly worse developmental scores at 1 year of age compared to those randomized to a hematocrit of close to 30%.

Postoperative factors

It has long been recognized that systemic blood flow is reduced in the first 24–48 hours following cardiac surgery, typically reaching a nadir in the first night after cardiac surgery.[23,24,62–64] At this time, the central nervous system may be especially vulnerable to secondary insults of decreased oxygen delivery, particularly after circulatory arrest. To minimize the potential effects of low cardiac output following intraoperative ischemia-reperfusion, Ungerleider and colleagues have suggested the routine use of extracorporeal membrane oxygenation in neonates at particularly high-risk, such as those with hypoplastic left heart syndrome.[65] Postoperative mechanical support itself has the potential for multiple deleterious effects, and the relative risks and benefits of this

approach, as well as short- and long-term outcomes, are currently under investigation (Ungerleider R, personal communication). Currently, close attention to cardiac output, and delivery and consumption of oxygen, seems warranted from a central nervous system perspective. Bedside techniques for quantitative assessment of these parameters, however, are limited, particularly if there are residual intracardiac shunts.

Using xenon washout techniques, Greeley et al. have shown that, following cardiopulmonary bypass, with or without circulatory arrest, autoregulation of cerebral blood flow may be impaired, making the neonate and infant particularly vulnerable to periods of low cardiac output and/or hypoxemia.[66–68] Recently, Bassan et al.[69] utilized transcranial Doppler and cerebral near-infrared spectroscopy to study cerebral blood flow in the cardiac intensive care unit in 43 neonates and infants following biventricular repair. In their cohort, approximately one in six patients demonstrated abnormalities of cerebrovascular pressure autoregulation, with risk factors including hypercapnia higher mean arterial pressure during the time of the measurements. To date, the potentially deleterious effects of significant hypocapnia, which decreases total cerebral blood flow, and hypotension, the latter for ethical reasons, have not been reported in postoperative neonates. Further research is mandatory to determine the interactions between cardiac output, positive pressure mechanical ventilation, and cerebral blood flow, especially in the immediate postoperative period.

Seizures occur in the immediate postoperative period in up to one-fifth of neonates, depending upon the method used for detection. Clinical seizures are significantly less prevalent than those detected on continuous electroencephalographic monitoring.[26,59,70] The etiology is most-likely multifactorial, but postoperative seizures are likely to be more prevalent in younger patients, those with prolonged periods of circulatory arrest, or those with coexisting abnormalities of the central nervous system. Perioperative seizures are a marker for early central nervous system injury, and have previously been reported to be associated with worse scores on developmental testing in children with transposition studied in the Boston Circulatory Arrest Trial,[35,60,71] although more recent data may show less of an impact than previously identified.[70]

In addition to the factors identified above, the immediate postoperative period typically requires invasive monitoring, mechanical ventilation, and significant medical support, especially in the neonate and young infant. While these therapies have resulted in significant improvements in mortality, they increase the risk of factors which may adversely affect the central nervous system, including paradoxical embolus of

air or particulate matter from peripheral or central intravenous access, fever, hyperglycemia, and swings in cerebral blood flow brought on by acute changes in mechanical ventilation. Newburger et al. have recently demonstrated in the Boston Circulatory Arrest cohort that longer hospital and intensive care unit length of stay in the newborn period was associated with worse developmental outcomes at age 8 years. These effects were significant, even when controlling for other factors known to adversely affect long-term outcome, such as seizures, intraoperative support duration, reoperations and other postoperative events. Children with transposition whose length of stay was in the fourth quartile had mean intelligence quotients 7.6 points lower than those in the first quartile.[72] Further investigation into the multiple potential mechanisms of central nervous system injury in the intensive care environment must continue.

Following discharge from hospital, some neonates remain at risk for ongoing injury to the central nervous system. Chronic hypoxemia, as a result of ongoing palliation and/or intentional intracardiac right-to-left shunting, may result in neurodevelopmental impairment. In children with transposition, older age at repair, as a surrogate for duration of hypoxemia, has been associated with worse outcomes during follow-up.[73] Cohort studies, many from a much earlier era of cardiac surgery when delayed repair was common, consistently show lower scores in children with "cyanotic" lesions compared to "acyanotic" lesions.[74–82] Simple comparisons of cardiac disease with and without associated hypoxemia, however, are confounded by the multiple factors present in children with "cyanotic" cardiac disease, including earlier age at repair and exposure to bypass, more complex surgical procedures, abnormal fetal flow patterns, and many of the factors mentioned in this review. In children with structurally normal hearts and hypoxemia from other causes, for example, chronic lung disease, sleep disordered breathing, or high altitude, chronic or intermittent hypoxemia has been associated with adverse effects on development, behavior and academic achievement.[83] The presence of hypoxemia undoubtedly plays some role in patients with congenital cardiac disease, but is most likely modified by other factors and is difficult to measure the effect of hypoxemia in isolation.

Genetic and environmental factors

Socioeconomic status is perhaps the strongest predictor of eventual neurodevelopmental outcome, and is a reflection of both the environment of the child and the genetic factors for development inherited from his or her parents. Multiple studies have shown the relationship between socioeconomic status and/or parental intelligence and outcome in children with congenital cardiac disease.[6,7,51,60,] In a study of 133 children, adolescents, and young adults who have undergone the Fontan procedure, socioeconomic status explained one-sixth of the variability in scores for intelligence quotient, whereas the variability explained by circulatory arrest and all other surgical variables was only 6.1%.[6] Curiously, this effect was not seen in a small cohort of teenagers with hypoplastic left heart syndrome.[16] The authors speculated that other, more overwhelming factors, such as preoperative cardiopulmonary collapse, were more predictive of outcome in this small sample of children with ductal-dependant cardiac disease in the era before prenatal diagnosis.

Children with identified genetic syndromes with known chromosomal abnormalities, for example, Down's, Williams' and DiGeorge syndromes, Trisomy 13 and 18, as well as associations of multiple congenital anomaly associations such as CHARGE and VACTERL syndromes, frequently have coexisting congenital cardiac disease. In total, perhaps one-third of all children with congenital cardiac disease have additional abnormalities besides their cardiac disease. Sub-chromosomal gene abnormalities are being discovered with increasing frequency in this population, and most studies report worse outcome in children with associated congenital anomalies compared to children with the same lesion without additional anomalies.

Trisomy 21 is universally associated with mental retardation and other neurological impairments,[84] and is associated with a variety of cardiac defects, some associated with hypoxemia, and many of which require cardiopulmonary bypass for repair.

Microdeletion of the 22nd chromosome, so-called 22q11 deletion, has been shown to result in the phenotype of DiGeorge or velo-cardio-facial syndrome, with many of these children having abnormalities of the ventricular outflow tracts, such as tetralogy of Fallot, interruption of the aortic arch, and common arterial trunk, along with isolated ventricular septal defects or abnormalities of branching of the aortic arch. While some of the developmental delay and behavioral problems seen in these patients may be related to the underlying congenital cardiac disease and/or its treatment (see above), and some of the speech delay may be related to the associated palatal abnormalities, recent reports suggest that there is an increased incidence of abnormalities of the white matter,[85] as well as a predisposition to psychiatric abnormalities such as schizophrenia.[86] Studies are currently underway to determine the relationship of these findings to the haploinsufficiency of genes on chromosome 22q11.[7]

Apolipoprotein E is important in the regulation of cholesterol metabolism is thought to effect neurological recovery following a variety of central nervous

system injuries. Gaynor et al. have recently reported that genetic polymorphisms of apolipoprotein E were related to abnormal neurological development and a small head circumference in children aged 1 year who underwent open heart surgery as neonates or young infants.[10] The effect of the genotype was independent of ethnicity, socioeconomic status, cardiac defect, and the use of deep hypothermic circulatory arrest.

Current outcomes in children following the Fontan procedure

Children with a functionally univentricular heart manifest many, if not all, of the risk factors for adverse long-term neurological and developmental outcomes. Most have abnormal fetal cerebral physiology as well as a ductal-dependant circulation at birth, require intensive care, early cardiac surgery with cardiopulmonary bypass, with or without circulatory arrest, have prolonged and multiple hospitalizations, and a prolonged period of hypoxemia. Thromboembolic complications and stroke may occur at any stage of surgical reconstruction and during follow-up.[87,88] Studies investigating the risk factors for adverse long-term outcomes in these patients are hampered by the interrelationship of most of the risk factors, and the frequent changes in surgical management. Studies of teenage children and young adults with the Fontan circulation have shown a higher than expected incidence of neurological problems. It is impossible to know if these outcomes represent sequels of management in the late 1980s and early 1990s, if they are inherent to the central nervous system of children with a functionally univentricular heart, or because of a combination of multiple factors. More recent studies have suggested better results,[19] but the predictive validity of pre-school testing is limited.

In 1998, Uzark et al. from Children's Hospital and Health Center in San Diego reported neurodevelopmental outcomes in 32 children with various forms of functionally univentricular heart who underwent the Fontan operation between 1986 and 1994.[53] The median age at testing was 30 months, the mean intelligence quotient for the group was in the normal range, with only one child falling below the lower limit of normal. As reported in children with transposition, deficits in visual-motor integration were common. Also in 1998, Kern and colleagues at Columbia University studied 14 children with hypoplastic left heart syndrome at an average age of 4.4 years who had undergone the Fontan procedure. As a group, the patients had low-normal intelligence and difficulties with adaptive behavior.[52]

In the largest series of children and young adults with a Fontan circulation to be studied to date,[6] we obtained health-related questionnaire data on 363 patients and 133 of these underwent formal testing at Children's Hospital in Boston. It is important to emphasize that the results in these patients reflect the management approach of the 1970s and 1980s, with an average age at the Fontan of 7.3 years. Intermediate superior cavopulmonary connections were performed in only a minority of the patients, as were baffle fenestrations. Over the duration of the study period, a number of different surgical modifications were undertaken, hospital mortality was high, and prolonged pleural effusions were common in the survivors.[89,90] Thus, the generalizability of these outcomes to current patients may be questioned. Only five patients with hypoplastic left heart syndrome were in the study group. Nonetheless, given these limitations, the majority of these patients had intelligence quotients and achievement testing scores in the normal range, although the group performed lower than expected compared to population norms. Risk factors for adverse outcomes in cognitive function included lower socioeconomic status, anatomic diagnosis and the prior use of circulatory arrest. The strong association of diagnosis, for example, hypoplastic left heart syndrome, and the use of circulatory arrest precluded identification of which was a stronger risk factor. The risk factors for worse performance on achievement testing included lower socioeconomic status, diagnosis and circulatory arrest, as in intelligence testing, as well as a number of postoperative factors, such as the need for an early reoperation, longer length of stay in the hospital, and higher right atrial pressures on the first postoperative day. Interestingly, duration of hypoxemia was not associated with adverse outcomes.

Forbess et al. expanded on this study, including patients from a more recent era, specifically with more patients who had undergone an interim superior cavopulmonary connection, as well as more patients with hypoplastic left heart syndrome.[91] These patients were considerably younger at the time of the Fontan procedure (Forbess JM, personal communication) and had scores slightly lower than the previously reported cohort, approximately three points lower in full-scale measurements, one point lower in verbal, and four and a half points lower in performance intelligence quotient. Longer total duration of circulatory arrest was significantly associated with lower scores. If the one patient with a cumulative duration of 158 minutes was excluded from the analysis, however, the relationship was no longer significant. Interestingly, socioeconomic status was not associated with intelligence scores. The authors concluded that the current approach to children with a functionally univentricular heart, with increasingly complex patients and a planned three stage approach in most patients, has not significantly adversely affected outcomes compared to the historical cohort.

The increasing number of survivors of children with hypoplastic left heart syndrome undergoing staged reconstruction is one of the significant advances in pediatric cardiology and cardiac surgery in the past two decades. The oldest survivors have been studied by Mahle et al. at The Children's Hospital of Philadelphia.[16] Mean scores on standardized testing were significantly lower than that in normative populations, two-thirds were thought to have attention deficit–hyperactivity, and one in five had clinically important scores for anxiety and depression. On multivariate analysis, it was the preoperative status of the patient that most strongly predicted outcome, and intraoperative variables such as duration of cardiopulmonary bypass or circulatory arrest were not found to be associated with poorer scores. It was emphasized by the authors that this study group represented the earliest experience with the Norwood procedure, and with prenatal, intraoperative and postoperative advances, current results were likely to be better. This speculation was confirmed by a recent study by Goldberg et al. at the University of Michigan, were the average intelligence quotient was 98 in a more recent cohort of children with hypoplastic left heart.[19]

It is interesting to examine the developmental abnormalities seen in groups of children with hypoplastic left heart syndrome, and compare them to the findings following transplantation of the heart in infancy for the same disease.[55,92] The patterns of dysfunction are remarkably similar, despite the markedly different strategies for treatment, suggesting that factors other than the surgical approach and techniques used for intraoperative support, such as congenital cerebral disease and abnormal fetal physiology, may play a significant role in long-term outcome in these patients.

Future directions

While advances in the medical and surgical fields have allowed the ability to "mend" children born with congenital cardiac disease, the increasing number of survivors has created a growing cohort of children with potential academic difficulties. The causes are clearly multifactorial, additive and incompletely understood. Much has been learned about cardiopulmonary bypass and the short period of time these children spend in surgery, much more work needs to be done to understand the modifiable risk factors in the perioperative period, the influences of the timing of surgery and whether or not improved monitoring of the central nervous system in the intensive care unit setting will improve neurological and developmental outcomes.[93]

Summary

Figure 4 represents some of the current understanding regarding the multiple factors which may adversely affect the central nervous system in children with complex congenital cardiac disease. There is a growing body of literature showing suboptimal outcomes in school-age children, particularly with respect to attention, behavior, higher-order executive function, handwriting and school performance. Many of the risk factors for adverse outcomes are strongly interrelated,
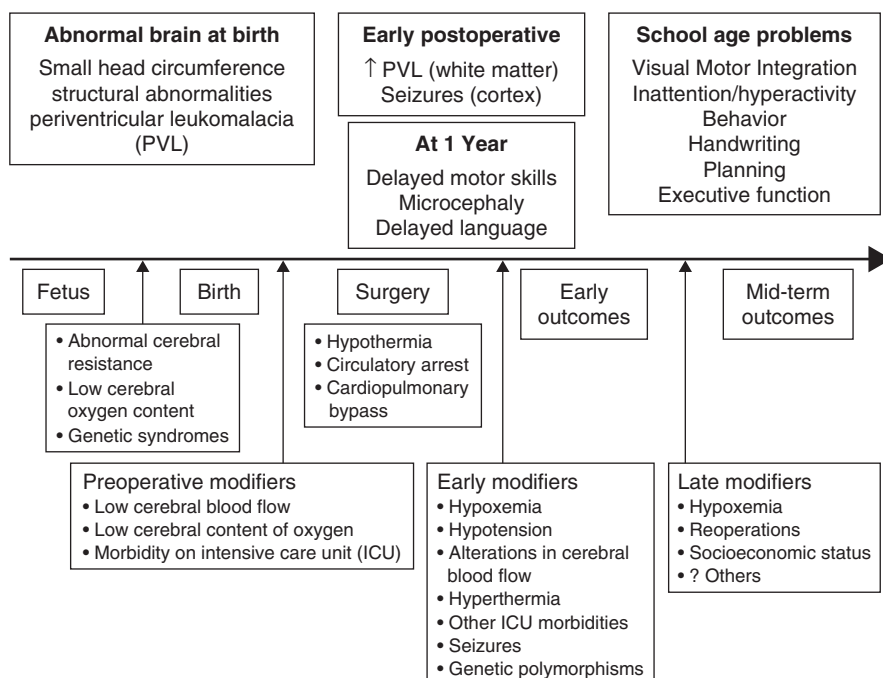
Figure 4.
Currently identified factors which, in total, adversely affect long-term neurological and developmental outcomes in children with complex congenital heart disease.

such as anatomic diagnosis, abnormalities of the fetal circulation, the need for prolonged intensive care, complex operations with cardiopulmonary bypass with or without deep hypothermia and circulatory arrest, prolonged hypoxemia, and multiple reoperations. Thus, it is difficult to conclude which, if any, are most explanatory. Many of the reports on the effects of cerebral consequences of cardiopulmonary bypass, in particular, are conflicting, and there is a need for ongoing laboratory experiments and controlled clinical trials before sweeping changes to intraoperative management are undertaken, with particular attention to long-term outcomes in school-age children. Neurodevelopmental abnormalities are widely prevalent, and are major contributors to adverse health-related quality of life outcomes. Further research must continue, in the laboratory, inpatient, and outpatient settings.

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