Mortality rates for virtually all forms of congenital heart disease have declined with dramatic advances in medical, transcatheter, and surgical therapies. As the population of congenital heart disease survivors has burgeoned, however, their long-term functional morbidities have become the focus of increasing concern. Among the foremost morbidities are adverse neurodevelopmental outcomes, with their profound personal and societal costs.

Neurological and developmental outcomes of congenital heart patients are influenced by many factors, both innate and acquired, with cumulative effects. Genetic syndromes such as trisomy 21 or 22q11 microdeletion3–5 may affect both the heart and the brain. Cerebral dysgenesis is reported to occur in 10% to 29% of children with congenital heart disease in autopsy series, with the incidence varying by lesion6–8; findings may range from microdysgenesis to gross abnormalities such as agenesis of the corpus callosum, incomplete operculization, and microcephaly. During fetal life, congenital heart lesions may be associated with changes in cerebrovascular blood flow distribution and resistance. For example, fetuses with hypoplastic left heart syndrome, whose cerebral perfusion is supplied retrograde through the ductus arteriosus, have lower cerebrovascular resistance than normal.9

Postnatal neurodevelopmental risk factors may derive from the sequelae of congenital heart disease itself—eg, chronic severe hypoxemia, failure to thrive, arrhythmias with cardiac arrest or hypotension—or from the procedures used for cardiac correction or palliation.10 Neuropathological studies have revealed both focal and diffuse infarction. Focal infarction has been ascribed to thromboembolic events, whereas a diffuse pattern of cerebral injury has been attributed to hypotension and hypoperfusion.11 More recent neuropathological data in infants who underwent reparative or palliative cardiac surgery reveals that not only are these children at increased risk of gray matter injury but also nascent white matter is at risk. For instance, in a series of infants who died after cardiac surgery, cerebral white matter damage (periventricular leukomalacia or diffuse white matter gliosis) was the most significant lesion in terms of severity and incidence.12

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Brain Injury in Congenital Heart Disease

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Similarly, MRI performed in patients with congenital heart disease after surgery has revealed findings consistent with both gray matter injury and widely distributed white matter injury.13

Risk factors for brain injury during infant heart surgery have been particularly well studied. Cardiopulmonary bypass carries the risks of particulate and gaseous microemboli, macroemboli, and hypoperfusion with accompanying diffuse ischemia/reperfusion injury. In neonates and infants undergoing surgery with use of hypothermic bypass techniques, the risk of brain injury may be influenced by perfusion variables such as the duration of total circulation arrest,14 the depth of hypothermia,15 the rate and duration of core cooling,16 pH management during core cooling (alpha-stat versus pH stat),17,18 and the level of hemodilution.19 Disruption of cerebral vasoregulation in the early postoperative period renders the brain more vulnerable to hemodynamic instability.20–22 After infant heart surgery, longer length of stay in the intensive care unit or hospital is associated with worse neurodevelopmental outcome on mid-term follow-up.23,24 Indeed, among infants undergoing the arterial switch operation for D-transposition of the great arteries (D-TGA), full-scale IQ at age 8 years differed by a half standard deviation between children whose hospital length of stay was in the lowest compared with the highest quartile,24 a magnitude of effect similar to that of lead poisoning.25–28 Finally, genetic polymorphisms may affect the inflammatory response to cardiopulmonary bypass or susceptibility to cerebral ischemia reperfusion injury during cardiac surgery.29 For example, Gaynor et al30 recently reported that apolipoprotein E ε2 allele carriers undergoing infant heart surgery had lower Psychomotor Development Index scores at 1 year of age, hypothetically related to decreased neuroresiliency and impaired neuronal repair after central nervous system injury.

Recently, the role of preoperative events in neurological injury of the newborn has come into increasing focus. In children undergoing diverse palliative or corrective open heart operations before 2 years of age, preoperative neurological status was a significant risk factor for persistent developmental deficits 12 to 18 months later.23 Mahle et al31 conducted a prospective MRI study of neonates before and after surgical correction of congenital heart defects. Preoperatively, white matter injury was present in >15% and gray matter injury in 8% of neonates. Moreover, preoperative elevation of cerebral lactate peaks was noted in more than half of the infants. McConnell et al32 reported ventriculomegaly and enlarged subarachnoid spaces consistent with cerebral atrophy on preoperative MRI in one third of their study sample.

In the current issue of Circulation, McQuillen and colleagues33 describe the results of preoperative brain MRI in neonates with D-TGA before reparative open heart surgery.
with the arterial switch operation. Children with D-TGA have an extremely low incidence of coexisting intracardiac or extracardiac anomalies, have infrequent residual significant hemodynamic problems after surgery, and are repaired at a relatively uniform age. Thus, they provide an optimal group for studying the effects of procedural events on neurological and developmental outcome. Of 29 neonates with D-TGA undergoing preoperative MRI, 19 underwent preoperative balloon atrial septostomy (BAS), and 10 did not. In total, 12 neonates (41%) had focal or multifocal lesions consistent with embolic stroke. Remarkably, all 12 had undergone preoperative BAS, rendering a risk of embolic stroke in this group of 61%. In contrast, no child in the group that did not undergo BAS had an embolic stroke before surgery. As expected on the basis of the clinical indication for BAS in this series, neonates with embolic stroke also had lower systemic arterial hemoglobin saturation. The risk of injury could not be explained by any other potential risk factor.

Several methodological issues bear on the inferences that can be drawn from these findings. Because younger, sicker, and bluer infants were most likely to undergo BAS, “confounding by indication” remains a potential explanation for the increased risk of stroke. Comparing MRIs before and after BAS would be helpful in evaluating this hypothesis, but pre-BAS studies would not be feasible in at least a subset of the sickest neonates. A randomized trial evaluating the neurological outcomes associated with BAS would answer the scientific question but present a potential ethical dilemma. Although embolic events resulting from BAS are certainly undesirable, the alternative strategy of taking a severely cyanotic child without a good atrial communication directly to the operating room could result in diffuse brain injury, portending a worse outcome. The consequences of the observed small focal strokes are unknown; longer follow-up and functional testing will help elucidate this question. Furthermore, we do not know whether the observed association between BAS and embolic events can be generalized to other centers. In the Boston Circulatory Arrest Study, 142 patients with D-TGA undergoing the arterial switch operation were studied with brain MRIs at 1 year of age. Although all underwent preoperative BAS, only 20 (14%) had evidence of focal or multifocal abnormalities consistent with embolic events. It is possible that this lower incidence of focal and multifocal abnormalities in a population of D-TGA patients who had been exposed both to BAS and to cardiopulmonary bypass could be attributable to technical differences in MRI studies performed a decade earlier or to resolution of some types of embolic brain injury over the year postoperatively?

In the series in the McQuillen et al study, most children underwent BAS in the intensive care unit without administration of heparin. Could the shift away from performing BAS in a cardiac catheterization laboratory, where heparin is routinely administered, have increased the risk of embolic stroke?

In many ways, the use of BAS in children with D-TGA is a paradigm for progress in the field of congenital heart disease. First described almost 40 years ago by Rashkind and Miller, BAS has been a life-saving procedure for patients with D-TGA by ensuring mixing of parallel circulations. With this procedure, children with D-TGA can be stabilized so that they go into open heart surgery in the best possible condition. We now discover that this vital procedure might be associated with embolic strokes, providing a potential reason that the D-TGA population has performed below that of the normal population on many neurodevelopmental parameters. The work of McQuillen et al, like all important studies, has generated a series of questions about new ways to improve outcomes. It behooves us to better understand the risk factors for stroke associated with BAS, to study methods for making this procedure safer, and to design ethically sound and scientifically valid trials regarding its use.

Disclosures

None.

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