Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 19, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.01.061

Pre-Operative Brain Injury in Newborn Infants With Transposition of the Great Arteries Occurs at Rates Similar to Other Complex Congenital Heart Disease and Is Not Related to Balloon Atrial Septostomy

John Beca, MB, ChB,* Julia Gunn, MBBS,** Lee Coleman, MB, ChB,¶ Ayton Hope, MB, ChB,‡ Laura-Clare Whelan, BNurs,* Thomas Gentles, MB, ChB,† Terrie Inder, MD,§ Rod Hunt, MMed, PhD,# Lara Shekerdemian, MD‖**

Auckland, New Zealand; St. Louis, Missouri; and Melbourne, Australia

Objectives The goal of this study was to determine the prevalence and pattern of pre-operative brain injury in infants with transposition of the great arteries (TGA) compared with other complex congenital heart disease (CHD) and to define the risk of balloon atrial septostomy (BAS) for the development of brain injury.

Background It has recently been suggested that infants with TGA are at increased risk of pre-operative brain injury, in particular, stroke, and that this is strongly associated with having a BAS.

Methods Sixty-four newborn infants with TGA (n = 44), hypoplastic left heart syndrome (n = 13), or pulmonary atresia (n = 7) had magnetic resonance imaging (MRI) scans performed before surgery.

Results Thirty-three (75%) of the infants with TGA had a BAS. Brain injury occurred in 19 (30%) infants: white matter injury (WMI) in 17 (27%), and stroke in 3 (5%). There was no difference in the prevalence or pattern of brain injury between diagnostic groups. There was no association between BAS and brain injury in infants with TGA. There was a trend toward increased brain injury in TGA with an intact interventricular septum compared with TGA with a ventricular septal defect (38% vs. 8%, p = 0.075). There was no association between brain injury and any clinical variables.

Conclusions Pre-operative brain injury on MRI scan was present in 30% of infants with CHD. The predominant pattern was WMI. The rates and patterns of pre-operative brain injury are similar in infants with TGA compared with other complex CHD, and BAS does not increase the risk of pre-operative brain injury. (J Am Coll Cardiol 2009;53:1807–11) © 2009 by the American College of Cardiology Foundation

Neurodevelopmental impairment is common in children who have had surgery for congenital heart disease (CHD). Many studies have focused on children with d-transposition of the great arteries (TGA) because this condition is common, it has relatively standard anatomy and surgical repair, and is rarely associated with genetic syndromes. Despite the fact that repair has a low mortality and is usually straightforward, longitudinal follow-up studies of historical cohorts have demonstrated neurodevelopmental and learning difficulties in school-aged children who underwent the arterial switch operation (ASO) in infancy. Approximately one-half have deficits in at least 1 domain and one-third require remedial academic assistance (1,2).

See page 1812

Multiple factors are likely to contribute to brain injury in children with CHD. In the past, attention has largely been focused on operative factors, such as surgical and perfusion strategies and early post-operative problems including reduced systemic oxygen delivery and organ dysfunction, as well as genetic, familial, and social influences (3–6). More recently the focus has expanded to include pre-operative events and pre-natal brain development. Pre-operative cerebral magnetic resonance imaging (MRI) abnormalities have been demonstrated in 25% to 40% of neonates with

From the Departments of *Paediatric Intensive Care, †Paediatric Cardiology, and ‡Radiology, Starship Children's Hospital, Auckland, New Zealand; §Departments of Pediatrics, Radiology and Neurology, Washington University School of Medicine, St. Louis, Missouri; Departments of ‖Paediatric Intensive Care, ¶Radiology, and #Neonatology, The Royal Children's Hospital, Melbourne, Australia; and **The Murdoch Children's Research Institute, Melbourne, Australia. Supported by grants from The National Heart Foundation of New Zealand, The National Heart Foundation of Australia, Auckland Medical Research Foundation, The Murdoch Children's Research Institute, and the Green Lane Research and Education Fund.

Manuscript received November 17, 2008; revised manuscript received January 7, 2009, accepted January 19, 2009.

JACC Vol. 53, No. 19, 2009
May 12, 2009:1807–11

Abbreviations and Acronyms

ASO = arterial switch operation
BAS = balloon atrial septostomy
CHD = congenital heart disease
CI = confidence interval
HLHS = hypoplastic left heart syndrome
MRI = magnetic resonance imaging
PA = pulmonary atresia
TGA = transposition of the great arteries
VSD = ventricular septal defect
WMI = white matter injury

CHD. The predominant abnormality is white matter injury (WMI), with infarction, hemorrhage, and abnormalities of maturation also seen (7–10).

Findings differ as to the etiology of brain injury in newborns with TGA before surgery, with particular reference to the pattern of injury and the possible contribution of balloon atrial septostomy (BAS) as a risk factor. McQuillen et al. (11) reported pre-operative MRI abnormalities in 40% of infants with TGA, with the predominant injury—in contrast to other groups with CHD—being arterial ischemic stroke (75%). In these infants, brain injury was strongly associated with BAS. Those infants who had a BAS were more hypoxemic than those without, although this would not typically explain the presence of arterial ischemic stroke, which is more consistent with embolism.

As part of a large, 2-center prospective study of brain injury in newborns with CHD, we performed pre-operative MRI scans on infants with TGA, as well as other diagnostic groups including hypoplastic left heart syndrome (HLHS) and pulmonary atresia (PA) with ventricular septal defect. In both of our institutions, it has been standard practice to perform BAS on infants with TGA who do not have a generous intracardiac shunt at atrial or ventricular level. Typically, infants with TGA undergo BAS within 1 day of admission to our hospitals, after which prostaglandin infusion is discontinued and medical therapy is rapidly de-intensified. An ASO is performed several days to a week later. The existing controversy regarding the nature of brain injury in infants with TGA before surgery, and the possible risk presented by BAS, may have important implications for our practice, given the frequency with which BAS is performed. Therefore, we sought to define the prevalence of brain injury, its nature (stroke or WMI), and the impact of BAS in our population, and to compare the risk of brain injury in TGA to other subgroups with complex CHD.

Methods

Patients. This study formed part of a larger prospective longitudinal investigation of brain injury in infants with CHD conducted at Starship Children's Hospital, Auckland, New Zealand, and The Royal Children's Hospital, Melbourne, Australia. The study population included infants with TGA, HLHS, and PA. Infants were excluded if they were <36 weeks gestational age or they had a recognized genetic or malformation syndrome. The study was approved by the local ethics committees and informed consent was obtained from all parents. Clinical and demographic data were collected prospectively by either a research fellow or research nurse. Three additional data fields were recorded retrospectively for the children with TGA to assess their relationship with brain injury. These included oxygen saturation measured by pulse oximetry (SpO_2) from observation charts before MRI, vascular access route for BAS, and administration of heparin for BAS.

MRI studies. Pre-operative MRI scans were performed once the infants were clinically stable and before surgery. For infants who required BAS, MRI was undertaken after this procedure. The majority of infants were spontaneously breathing for their MRI scans. Before undergoing MRI, each infant was fed (where appropriate), wrapped, and placed in a vacuum fixation bean-bag designed to keep the infant still and supported. MRI studies were performed using a 1.5- or 3-T Magnetom Avanto (Siemens, Erlangen, Germany) Scanner. Standardized sequences were used for all studies including T1- (1-mm thickness) and T2-weighted (2-mm thickness) coronal and axial images and multidirectional axial diffusion weighted imaging (20 directions, 4-mm thickness).

MRI scans were reported independently by 1 of 2 neuroradiologists (L.C., A.H.) who were not aware of the clinical details or treatment of any of the infants. For the purpose of this analysis, brain injury was defined as the presence or absence of focal infarction (stroke), WMI, or hemorrhage (intraventricular or parenchymal). Stroke referred to discrete areas of hyperintensity on diffusion weighted imaging, with hypointensity on the corresponding apparent diffusion coefficient scan and/or hyperintensity on T2-weighted images. Size was reported by the extent of the vascular territory involved. WMI referred to discrete, usually punctate, foci of T1 hyperintensity and/or T2 hypointensity. This was classified as normal (no white matter lesions), minimal (≤3 areas of WMI measuring <2 mm), moderate (>3 areas of WMI or those areas measured >2 mm but <5% of the hemisphere involved), or severe (>5% of the hemisphere involved) (11). There were no adverse events related to MRI studies.

BAS. The decision to perform BAS was made independently by the on-service pediatric cardiologist. The decision was based on the echocardiographic assessment—in particular, the size of any intracardiac communications and the presence of any restriction to interatrial mixing—and clinical criteria including hypoxemia and/or acidosis. BAS was performed either at the bedside in intensive care or in the catheterization laboratory. Echocardiographic guidance was used in all infants. Children who were not already intubated were anesthetized for the procedure. A 5-F Miller-Edwards (Edwards Lifesciences, Irvine, California) (Royal Children's Hospital) or a 6-F Rashkind (Medtronic Inc., Minneapolis, Minnesota) (Starship Children's Hospital) balloon catheter was introduced either directly to the umbilical vein or via a 6.3-F (Starship Children's Hospital) or 7-F (Royal Children's Hospital) sheath introduced to the femoral vein. Bolus heparin was not routinely given, although when a sheath was used, this was flushed with heparinized saline.

No complications of the procedure were observed in any infants.

Data collection and analysis. Clinical variables in infants with and without brain injury were compared using the *t* test for continuous parametric data, the Wilcoxon rank-sum test for continuous nonparametric data, and the Fisher exact test for categorical data (Stata version 10, Stata Corp., College Station, Texas). Confidence intervals (CIs), where presented, are 95% CI.

Results

Sixty-four infants were included in the study: 44 with TGA, 13 with HLHS, and 7 with PA. Of the infants with TGA, 32 had an intact interventricular septum and 12 had a ventricular septal defect (VSD). Thirty-three infants with TGA (25 with an intact interventricular septum and 8 with VSD) underwent BAS.

MRI findings. There were no intraventricular or parenchymal hemorrhages. Therefore, the analysis focused on stroke and WMI as significant brain injury. Brain injury was present in 19 (30%, 95% CI: 19% to 42%) infants overall. The most common abnormality was WMI, which occurred in 17 infants (27%, 95% CI: 16% to 39%). WMI injury was mild in 16 infants (94%) and moderate in 1 infant (6%). Stroke was present in 3 infants (5%, 95% CI: 1% to 13%). The 3 strokes were of middle cerebral artery distribution and as follows: a 2- to 3-mm lesion in the right middle temporal gyrus in an infant with TGA who did not have a BAS, an infarction of the left caudate head with involvement of the adjacent white matter in an infant with TGA who did have a BAS, and infarctions in the right frontal cortex (10 mm) and right caudate head (3 mm) in an infant with HLHS. There were no strokes involving significant proportions of any single vascular territory. The infant with TGA who had a BAS and caudate head infarct also had WMI.

Brain injury occurred at similar rates in infants with TGA, HLHS, and PA. WMI was present in 27%, 23%, and 29% ($p = 1.0$); stroke occurred in 5%, 8%, and 0% ($p = 0.68$) for TGA, HLHS, and PA, respectively.

BAS and brain injury in infants with TGA. There was no association between BAS and any brain injury, or with either WMI or stroke in infants with TGA (Table 1). WMI was present in 30% of infants who had a BAS and 18% of infants who did not ($p = 0.70$). Stroke occurred in 3% of those with a BAS and 9% of those without ($p = 0.44$). The absolute risk difference for infants having a BAS compared with those who did not was 3% (95% CI: −27% to 33%) for brain injury, 12% (95% CI: −16% to 40%) for WMI, and −6% (95% CI: −24% to 12%) for stroke. In a retrospective power analysis, assuming a base rate of 5% for stroke (the rate in this series for all infants and also for those with TGA), this study had 84% power to detect a difference of 10% and 99% power to detect a difference of 15%.

Table 1 Characteristics of Infants With TGA With and Without Brain Injury

Characteristic	No Brain Injury (n = 31)	Brain Injury (n = 13)	p Value
Gestational age (weeks)	39 (1.4)	39 (1.5)	0.89
Male sex	22 (71%)	9 (69%)	1.0
Birth weight (kg)	3.4 (0.4)	3.3 (0.5)	0.47
Head circumference (cm)	35.0 (2.4)	34.6 (1.2)	0.56
Antenatal diagnosis	9 (29%)	5 (38%)	0.72
Apgar 1 min	8 (5–9)	8 (4–9)	0.68
Apgar 5 min	9 (6–10)	9 (6–10)	0.91
Intact septum	20 (65%)	12 (92%)	0.075
BAS performed	23 (74%)	10 (76%)	1.0
Age at septostomy (days)	1 (0–21)	0 (0–2)	0.23
Umbilical access for BAS	12 (52%)	6 (67%)	0.69
Age at MRI scan (days)	7 (3–31)	7 (5–9)	0.73
Inotropes required	8 (26%)	1 (8%)	0.24
MAP <35 mm Hg for >30 min	4 (13%)	1 (8%)	1.0
Lowest MAP (mm Hg)	38 (7)	39 (5)	0.64
Highest lactate (mmol/l)	3.9 (1.2–18)	2.7 (1–6)	0.35
Lowest pH	7.26 (0.12)	7.29 (0.09)	0.48
Lowest PaO_2 (mm Hg)	29 (17–56)	31 (26–42)	0.45
Average SpO_2 (%)	84 (5)	82 (6)	0.23
Lowest SpO_2 (%)	58 (18)	60 (12)	0.17

Categorical data are shown as n (frequency), parametric data as mean (SD), and nonparametric data as median (range).

BAS = balloon atrial septostomy; MAP = mean systemic arterial blood pressure; MRI = magnetic resonance imaging; PaO_2 = arterial partial pressure of oxygen; SpO_2 = oxygen saturation measured by pulse oximetry.

Potential risk factors for brain injury. For the group as a whole (TGA, HLHS, and PA) Apgar scores, measures of hypoxemia (average and lowest SpO_2, lowest PaO_2), measures of cardiovascular dysfunction, and highest lactate levels were similar in patients with and without brain injury (Table 2). Similarly, when considering only patients with TGA, there was no association between any of these clinical variables and brain injury (Table 1). The route for BAS was umbilical in 19 patients (58%) and femoral in 14 (42%). BAS was performed on the day of birth or the next day in 85% and by day 2 in 94%. There was no association between either route or timing of BAS and brain injury. One child was given a bolus of heparin before BAS, and no other infants received bolus heparin for BAS. There was a trend toward increased brain injury in infants with an intact interventricular septum compared with those with a VSD (38% and 8%, respectively, $p = 0.075$), regardless of BAS.

Discussion

This study has 5 important findings relating to brain injury in newborn infants with CHD before surgery. First, we showed that brain injury was present in 30% of our patients. Second, when considering diagnostic subgroups, brain injury occurred at similar rates in infants with TGA, HLHS, and PA. Third, the pattern of brain injury was characteristically limited to WMI, with stroke being uncommon. Fourth, there were no risk factors for brain injury for the group as a whole, including markers of birth asphyxia, cardiovascular instability,

JACC Vol. 53, No. 19, 2009
May 12, 2009:1807–11

Table 2 Characteristics of All Infants With and Without Brain Injury

Characteristic	No Brain Injury (n = 45)	Brain Injury (n = 19)	p Value
Gestational age (weeks)	39 (1.6)	39 (1.4)	0.49
Male sex	26 (58%)	15 (79%)	0.15
Birth weight (kg)	3.3 (0.6)	3.3 (0.5)	0.97
Head circumference (cm)	34.6 (2.4)	34.7 (1.2)	0.93
Antenatal diagnosis	23 (51%)	10 (53%)	1.0
Apgar 1 min	8 (1–9)	8 (1–9)	0.53
Apgar 5 min	9 (5–10)	9 (5–10)	0.42
Inotropes required	13 (29%)	4 (21%)	0.76
MAP <35 mm Hg for >30 min	9 (20%)	3 (16%)	1.0
Lowest MAP (mm Hg)	37 (7)	37 (6)	0.90
Highest lactate (mmol/l)	3.4 (0.8–18)	2.6 (1–6)	0.39
Lowest pH	7.27 (0.11)	7.29 (0.09)	0.61
Lowest PaO_2 (mm Hg)	34 (17–71)	30 (26–37)	0.46

Categorical data are shown as n (frequency), parametric data as mean (SD), and nonparametric data as median (range).
Abbreviations as in Table 1.

hypoxemia, and impaired systemic oxygen delivery. Finally, and of most relevance to clinical practice, we found no association between BAS and brain injury in infants with TGA, with brain injury after BAS occurring at similar rates to those in other diagnostic groups.

This study presents the largest cohort to date of pre-operative MRI in infants with TGA. We chose to compare infants with TGA to infants with HLHS and PA because the latter two are representative of lesions with a high risk of brain injury that may be ischemic injury (HLHS) or hypoxemic and/or ischemic injury (PA). It has been suggested that pre-operative brain injury is more common in the biventricular circulation and post-operative injury more frequent in the functionally univentricular circulation, especially in HLHS (8). This may be due in part to a preponderance of pre-operative injury in some series with TGA and the fact that infants with a functionally univentricular heart may be less stable in the early post-operative period. In our study, there was no difference between groups in the rate of brain injury before surgery. Furthermore, the overall rate of brain injury in our cohort was similar to that reported by other groups (7,8,10,11).

The nature of injury in our population was predominantly WMI. WMI is the most common type of injury after surgery in young infants with CHD and has been associated with hypoxemia and hypotension (3). WMI has also been described before surgery and is sometimes labeled periventricular leukomalacia (3,7). We have chosen not to apply this term in our cohort because it is traditionally used to describe a pattern of injury seen on cranial ultrasound scans of pre-term infants that may evolve into cystic lesions over time. The WMI described before and after surgery in term infants with CHD does not appear to undergo the same radiologic and clinical evolution as periventricular leukomalacia in premature infants. It most likely relates to the vulnerability of immature oligodendrocytes to injury during the first 4 weeks of life (3,12). The etiology and timing of WMI is unclear and very likely multifactorial. Recent MRI studies have shown that term newborns with CHD have widespread abnormalities in brain maturation that are similar to those in premature infants and might render them particularly vulnerable to WMI (9).

Stroke affected only 2 infants with TGA, was small in both cases, and was not associated with BAS. This prevalence and severity of stroke contrasted with that in the series by McQuillen et al. (11), in which strokes affected nearly one-half of infants after BAS, and a proportion involved significant arterial territories. They found a risk difference of 63% for brain injury with BAS. For stroke in particular, our study has high power to exclude a risk difference of more than 10% to 15%. In order to further investigate the difference between the 2 series, we considered a number of potential contributory factors. The BAS catheters used in this series were similar to those described in the McQuillen et al. (11) study (without an end-hole), and in both studies bolus heparin was not routinely administered during BAS. In our institutions, at the end of the procedure the catheter and sheath (where applicable) were always removed; this practice is not detailed in the McQuillen et al. (11) series. It is unlikely that the MRI technique could have given rise to "false negative" findings with regard to stroke because the MRI sequences were very similar using either the same or a finer slice thickness. We also considered the time from BAS to MRI scan, which was slightly longer in our study, but is still well within an acceptable time frame for detecting stroke on either diffusion weighted imaging or T2-weighted scans. Moreover, arterial strokes would be expected to evolve rather than disappear within such a time frame.

We did not find any association between any physiological or other clinical variables and brain injury. A limitation of this study is that data relating to oxygen saturation was collected retrospectively and the frequency of measurements varied widely between patients, depending on their clinical status and the age at which they presented and at which the MRI scan was performed. With this caveat in mind, we were unable to find any association between brain injury and any objective marker of hypoxemia. Only 75% of our infants had arterial blood gas or lactate measurement performed before the BAS. This might introduce a bias in that infants who had these blood tests are more likely to be sicker and therefore potentially more likely to have brain injury. But there was no difference in the rate of brain injury between those who had blood tests and those who did not. The trend toward greater WMI in infants with TGA and intact ventricular septum may support a relationship between anatomy and brain development, or at least vulnerability to injury. It is likely that the fetal circulation is more abnormal in those with TGA and intact ventricular septum compared with TGA and VSD or other forms of congenital heart disease, as there is less intracardiac mixing with a greater risk of chronic in utero cerebral hypoxemia.

Very few infants had evidence of birth asphyxia as evidenced by low 5-min Apgar scores. In addition, as observed by others, the typical pattern of brain injury seen with global hypoxic-ischemic encephalopathy (injury to the deep grey nuclei and parasagittal watershed cortex) (12) was not seen in any infants. This reinforces the notion that other factors such as fetal brain development and maturity may play a role. Relative immaturity of the brain in term infants with CHD has been described, but the relationship to injury is still unclear (9). In addition, the neurodevelopmental significance of WMI in infants with CHD is unknown. Abnormal findings on MRI scan at term in very premature infants strongly predict adverse neurodevelopmental outcomes at 2 years of age (13). Further studies of large numbers of infants with CHD are required to clarify these issues.

Conclusions

Brain injury is present on MRI scan in 30% of infants with complex CHD before surgery. Brain injury occurs at a similar rate in infants with TGA compared with infants with either HLHS or PA and predominantly affects the white matter. Arterial ischemic strokes are uncommon in this population. There is no association between brain injury and BAS. Therefore, we would advise caution before recommending widespread changes in clinical practice.

Acknowledgments

The authors thank Peter Reed (Statistician, Children's Research Centre, Starship Children's Hospital, Auckland); the cardiologists and cardiac surgeons at Starship Children's Hospital, Auckland, and Royal Children's Hospital, Melbourne; and Michael Kean (Senior MRI Technician, Royal Children's Hospital, Melbourne).

Reprint requests and correspondence: Dr. John Beca, Paediatric Intensive Care Unit, Starship Children's Hospital, Private Bag 92024, Auckland, New Zealand. E-mail: johnbeca@adhb.govt.nz.

REFERENCES

1. Bellinger DC, Wypij D, duDuplessis AJ, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1385–96.
2. Hovels-Gurich HH, Seghaye MC, Schnitker R, et al. Long-term neurodevelopmental outcomes in school-aged children after neonatal arterial switch operation. J Thorac Cardiovasc Surg 2002;124:448–58.
3. Galli KK, Zimmerman RA, Jarvik GP, et al. Periventricular leukomalacia is common after neonatal cardiac surgery. J Thorac Cardiovasc Surg 2004;127:692–704.
4. Gaynor JW, Gerdes M, Zackai EH, et al. Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. J Thorac Cardiovasc Surg 2003;126:1736–45.
5. Gaynor JW, Wernovsky G, Jarvik GP, et al. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. J Thorac Cardiovasc Surg 2007;133:1344–53.e3.
6. Wypij D, Newburger JW, Rappaport LA, et al. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1397–403.
7. Mahle WT, Tavani F, Zimmerman RA, et al. An MRI study of neurological injury before and after congenital heart surgery. Circulation 2002;106:I109–14.
8. McQuillen PS, Barkovich AJ, Hamrick SE, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke 2007;38:736–41.
9. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. N Engl J Med 2007;357:1928–38.
10. Miller SP, McQuillen PS, Vigneron DB, et al. Pre-operative brain injury in newborns with transposition of the great arteries. Ann Thorac Surg 2004;77:1698–706.
11. McQuillen PS, Hamrick SE, Perez MJ, et al. Balloon atrial septostomy is associated with pre-operative stroke in neonates with transposition of the great arteries. Circulation 2006;113:280–5.
12. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr 2005;146:453–60.
13. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685–94.

Key Words: transposition of the great vessels ■ heart defects congenital ■ brain injuries ■ magnetic resonance imaging ■ balloon septostomy.