Deep hypothermic circulatory arrest and the effects on the brain

DiNardo JA
Associate Professor of Anaesthesia, Harvard Medical School, Senior Associate in Cardiac Anaesthesia
Children's Hospital Boston

Correspondence to: Prof JA DiNardo, e-mail: james.dinardo@childrens.harvard.edu

SAJAA 2008; 14(1): 70-72

Overview of deep hypothermic circulatory arrest in children

The effect of deep hypothermic circulatory arrest (DHCA) in children with congenital heart disease on subsequent cognitive and motor performance is of great importance, and a number of case reports and patient series document neurological impairment associated with DHCA.1,2 However, only one large, controlled investigation of this issue has been conducted. Between 1988 and 1992, 171 infants with dextro transposition of the great arteries (D-TGA) undergoing the arterial switch procedure at a single institution were enrolled in The Boston Circulatory Arrest Trial with the intention of comparing a strategy of predominantly low-flow circulatory arrest with one of predominantly low-flow cardiopulmonary bypass (CPB). Of the 129 patients with D-TGA and intact ventricular septum, 66 were randomised to the DHCA group and 63 to the low-flow CPB group. Of the 42 with D-TGA and ventricular septal defect (VSD), 21 were assigned to the DHCA group and 21 to the low-flow CPB group 3. In keeping with institutional practice at the time, alpha-stat management was used in all the patients. Comprehensive neurobehavioural assessment of this cohort was performed immediately postoperatively and has continued at intervals until the present. The results of these assessments can be summarised as follows:

- Immediately postoperatively, children in the DHCA half of the cohort had a higher risk of clinical seizures and a greater release of brain creatine kinase. In addition, the probability of clinical seizures, the probability of electroencephalographic (EEG) ictal activity, and the time to return of first EEG activity following DHCA were all positively correlated with the duration of DHCA.3
- At one year of age, children in the DHCA half of the cohort had significantly worse psychomotor development scores than children in the low-flow half of the cohort. In addition, psychomotor development is inversely related to the duration of DHCA and the risk of neurological abnormalities increased with the duration of DHCA. Perioperative seizures were associated with worse neurodevelopmental outcomes at ages one and two and a half years and an increased risk of both brain magnetic resonance imaging (MRI) and neurological abnormalities at one year.5,5
- At the age of four years, scores for the entire cohort were significantly lower than the population mean for IQ, expressive language, visual-motor integration, motor function, and otoromotor control. Children in the DHCA half of the cohort had significantly worse motor coordination and motor planning than children in the low-flow half of the cohort. There was no difference in IQ or overall neurological status between the two groups. Perioperative seizures were associated with lower mean IQ scores and an increased risk of neurological abnormalities.6
- At the age of eight years, the children in the cohort were reported by their parents to have more problems with attention, learning, and speech, and with the frequency of developmental delay than was reported by the parents of children in a normative sample. Despite this, children in the cohort had an overall physical and psychosocial health status similar to the general population. Furthermore, there was no association between physical and psychosocial scores and the presence or absence of a VSD or the use of low-flow CPB versus DHCA.7 Children assigned to the DHCA group performed worse on tests of motor function, apraxia of speech, visual motor tracking, and phonetic awareness, while children assigned to the low-flow CPB group exhibited a more impulsive response style and worse behaviour as rated by teachers.8
- The effect of the duration of DHCA on subsequent neurodevelopmental outcomes in this trial was nonlinear, such that neurodevelopmental outcomes were generally not adversely affected unless the duration of DHCA exceeded a threshold of 41 minutes (95% lower confidence limit 32 minutes).9

More recent data are available from The Children’s Hospital Boston Neurodevelopment Outcome Registry, which was established in 1998. All children who have undergone cardiac surgery at the institution are invited back at age five years to undergo a comprehensive neuropsychological evaluation.10 Consequently, children who have undergone cardiac surgery at the institution from 1995 until the present are eligible to become part of the database. Data relating to a group of 243 children of which 209 had undergone biventricular repair and 34 had undergone single ventricle repair between 1998 and 2001 strongly suggest that a circulatory arrest period of longer than 33 minutes is associated with a lower full-scale IQ score.11 In a smaller group of 69 patients who had undergone biventricular repair between 1993 and 1998 there was a significant reduction in full-scale IQ scores as well as visual-motor and fine-motor scores when the circulatory arrest period exceeded 39 minutes.12

Data from The Children’s Hospital of Philadelphia indicate that seizures or coma occurred in 19% of 164 non-hypoplastic left heart syndrome (HLHS) survivors who underwent neonatal heart surgery between 1992 and 1997. Risk factors for the development...
of these acute neurologic events were associated non-cardiac genetic conditions, aortic arch obstruction, and a DHCA interval of greater than or equal to 60 minutes.13 More recent data from a cohort of 178 patients younger than six months of age undergoing heart surgery between 2001 and 2003 revealed that the incidence of postoperative seizures was 24% in patients where the DHCA duration was more than 40 minutes and 6.8% in patients where the DHCA duration was 40 minutes or less.14 The incidence of postoperative seizures in patients where the DHCA duration was 40 minutes or less was not significantly different than that observed in patients where DHCA was not used.14 In this series, the occurrence of postoperative seizures was not associated with worse neurobehavioural outcome at one year of age.

**pH stat or alpha-stat?**

Based on the theoretical advantages of maintaining electrochemical significance, the group at Children’s Hospital, Boston switched from pH-stat management to alpha-stat management in the early 1980s. Within a short period of time, the incidence of severe neurological injury in the form of neurobehavioural and brain histological outcomes after DHCA.20,21 There has been only one clinical trial to date investigating the effect of haematocrit during CPB on neurobehavioural outcome in infants undergoing cardiac surgery.24 This study randomised 74 infants to a low haematocrit group (21.5%) and 73 infants to a high haematocrit group (27.8%) at the onset of low-flow CPB (750 mL/min/m²) utilising pH-stat management. The average interval of low-flow CPB was 45 minutes. At age one year, the low haematocrit group had worse scores on the Psychomotor Development Index or in the frequency of an abnormal neurological exam versus the high haematocrit group.25 This is of particular importance, given the fact that an increased oxygenated haemoglobin signal nadir time correlates strongly with adverse neurobehavioural and brain histological assessments.

Prediction of the safe duration of DHCA in a neonatal pig model can be accomplished using the oxygenated haemoglobin signal nadir time.26 Once DHCA commences, the cerebral oxymyoglobin signal measured by NIRS begins to decay, ultimately reaching a nadir or plateau value. The time from this nadir value to the recommencement of flow (termination of DHCA) is the oxygenated haemoglobin signal nadir time. The time to nadir at a given temperature is prolonged with a haematocrit of 30% compared to 20%. As a result, for a given period of DHCA the oxygenated haemoglobin signal nadir time is shorter in the higher haematocrit group.27 This was confirmed in the Neonatal Heart Transplant Study.28 It has long been assumed that haemodilution is an essential component of DHCA. Haemodilution is felt to offset the viscosity and rheologic changes that compromise microcirculatory flow during low-temperature CPB. A recent study utilising intravital microscopy demonstrates that a haematocrit of 30% does not impair cerebral microcirculation during or after DHCA.22 Furthermore, this study confirms that a haematocrit of 10% severely compromises cerebral oxygen delivery during cooling because the brain is still warm and oxygen delivery is limited by the low haematocrit.

Prediction of the safe duration of DHCA in a neonatal pig model can be accomplished using the oxygenated haemoglobin signal nadir time.26 Once DHCA commences, the cerebral oxymyoglobin signal measured by NIRS begins to decay, ultimately reaching a nadir or plateau value. The time from this nadir value to the recommencement of flow (termination of DHCA) is the oxygenated haemoglobin signal nadir time. The time to nadir at a given temperature is prolonged with a haematocrit of 30% compared to 20%. As a result, for a given period of DHCA the oxygenated haemoglobin signal nadir time is shorter in the higher haematocrit group.27 This is of particular importance, given the fact that an increased oxygenated haemoglobin signal nadir time correlates strongly with adverse neurobehavioural and brain histological assessments.

There has been only one clinical trial to date investigating the effect of haematocrit during CPB on neurobehavioural outcome in infants undergoing cardiac surgery.24 This study randomised 74 infants to a low haematocrit group (21.5%) and 73 infants to a high haematocrit group (27.8%) at the onset of low-flow CPB (750 mL/min/m²) utilising pH-stat management. The average interval of low-flow CPB was 45 minutes. At age one year, the low haematocrit group had worse scores on the Psychomotor Development Index than the high haematocrit group. There were no differences between the groups in the Mental Development Index or in the frequency of an abnormal neurological exam (60% of patients in both groups). The results of this trial are commonly used to advocate a strategy of high haematocrit when DHCA is utilised. However, it is important to point out that 65%
of the patients in this trial did not undergo DHCA and only 10% of the patients had a DHCA interval of 30 minutes or more. Is DHCA solely to blame for adverse neurobehavioural outcome? Adverse neurobehavioural outcomes following neonatal and infant heart surgery are related to both fixed and modifiable factors. Fixed factors are patient specific and include genetic predisposition, gender, race, socioeconomic status and in utero central nervous system development. Modifiable factors include preoperative, intraoperative (such as duration and conduct of ischaemic injuries and postoperative care) and postoperative management. Both types of factors have been implicated in brain injury. A recent investigation involving 247 infants undergoing repair of two ventricle lesions concluded that a confirmed or suspected genetic syndrome, lower birth weight, and the apolipoprotein E e2 allele were associated with worse neurobehavioural outcome at one year.20

The use of DHCA with alpha-stat management, which in this series was a factor in 25% of patients for a mean duration of 9 minutes, was not implicated. On the other hand, in a study of 29 neonates with D-TGA, 12 patients (41%) had focal brain injury detected by preoperative MRI. Brain injury was identified only in neonates who had undergone preoperative balloon atrial septostomy (12/19, relative risk 63%).24

At present, DHCA is used selectively and preferentially for short intervals. The population of patients most likely to be exposed to an appreciable interval of DHCA is those undergoing Stage I palliation for HLHS. One would anticipate that these neonates would benefit most from the optimisation of modifiable factors. However, this subset of patients is also likely to have multiple patient-specific risk factors. Infants with HLHS are likely to be sick infants and have been demonstrated to have a high incidence of microcephaly.25 The observation that microcephaly is associated with a small ascending aorta strongly suggests that altered in utero blood flow patterns is a modifiable factor, such as altered in utero blood flow patterns rather than suboptimal preoperative care may also be important.26

The interplay of fixed and modifiable factors is complex. In a series of 25 patients with severe congenital cardiac defects, cerebral blood flow was found to be less than half of normal; impaired CO2 cerebral vascular reactivity was present in the subset of patients with cerebral ischaemic lesions.27 Mild cerebral ischaemia and primarily white matter injury in the form of periventricular leukomalacia and stroke have been detected preoperatively by MRI in approximately 25 to 37% of neonates (periventricular leukomalacia) and stroke have been detected with a small ascending aorta strongly suggests that altered intracardiac blood flow is an important factor.28 It is not surprising that this subset of patients is particularly at risk for both short-term and long-term impairment of neurobehavioural performance, regardless of whether they are treated with neonatal blood flow to brain transplantation, staged palliation utilising DHCA, or staged palliation avoiding DHCA.30,31,32

References

1. Bellinger DC, Wernovsky G, Rappaport LA, et al. Cognitive development of children following early repair of the great arteries using deep hypothermic circulatory arrest. Pediatrics 1991;87:701–6.
2. Danss RA, Simpson JM, Turnbull JA, et al. The relationship between intelligence and duration of circulatory arrest with deep hypothermia. J Thorac Cardiovasc Surg 1995;109:819–22.
3. Newburger JW, Jonas RA, Rappaport LA, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med 1993;329:1057–64.
4. Bellinger DC, Jonas RA, Rappaport LA, et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med 1995;332:549–55.
5. Rappaport LA, Wypij D, Bellinger DC, et al. Relation of seizures after cardiac surgery in early infancy to neurodevelopmental outcome. Boston Circulatory Arrest Study Group. Circulation 1998;97:773–9.
6. Bellinger DC, Wypij D, Kuban KC, et al. Developmental and neurologic status of children after repair of the great arteries using deep hypothermic circulatory arrest or low-flow cardiopulmonary bypass. Circulation 1999;100:526–32.
7. Durrani-Master son C, Wypij D, Bellinger DC, et al. General health status of children with D-transposition of the great arteries after the arterial switch operation. Circulation 2002;105:1336–42.
8. Bellinger DC, Wypij D, Du Plessis AJ, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Toronto Circulatory Arrest Study Group. J Thorac Cardiovasc Surg 2005;129:1385–96.
9. Wypij D, Newburger JW, Rappaport LA, et al. The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopmental outcome. Circulation 2005;111:397–403.
10. Forbes JM, Visconti KJ, Bellinger DC, et al. Neurodevelopmental outcomes in children after the Fontan operation. Circulation 2003;107:117–25.
11. Forbes JM, Visconti KJ, Bellinger DC, et al. Neurodevelopmental outcomes after biventricular repair of congenital heart defects. J Thorac Cardiovasc Surg 2002;123:631–9.
12. Forbes JM, Visconti KJ, Hancock-Friessen C, et al. Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. Circulation 2002;106:1816–22.
13. Clancy RR, McGaun SA, Wernovsky G, et al. Risk of seizures in survivors of newborn heart surgery using deep hypothermic circulatory arrest. Pediatrics 2003;111:592–601.
14. Gaynor JW, Nicolson SC, Jarvik GP, et al. Increasing duration of deep hypothermic circulatory arrest is associated with an increased incidence of postoperative electroencephalographic seizures. J Thorac Cardiovasc Surg 2005;130:1278–86.
15. Jonas RA, Bellinger DC, Rappaport LA, et al. Relation of pH strategy and developmental outcome after hypothermic circulatory arrest. J Thorac Cardiovasc Surg 2005;130:962–9.
16. Wong PC, Batiow CF, Hickey PR, et al. Factors associated with choreoathetosis after cardiopulmonary bypass in children with congenital heart disease. Circulation 1999;99:8116–20.
17. Delaun D, Bhati A, Arcilla R, et al. Cerebrovascular accidents after deep hypotherma without circulatory arrest. Ann Thorac Surg 1999;50:714–9.
18. Du Plessis AJ, Jonas RA, Wypij D, et al. Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg 1997;114:991–1000; discussion 981–2.
19. Bellinger DC, Wypij D, Du Plessis AJ, et al. Developmental and neurologic effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg 2001;121:374–83.
20. Shin’oka T, Shum-Tian D, Jonas RA, et al. Higher hematocrit improves cerebral outcome after deep hypothermic circulatory arrest. J Thorac Cardiovasc Surg 1996;112:1610–20; discussion 1620–1.
21. Shin’oka T, Shum-Tian D, Laussou PC, et al. Effects of onocit pressure and hematocrit on outcome after hypothermic circulatory arrest. Ann Thorac Surg 1998;65:155–64.
22. Duerloerle FE, Sakamoto T, Hutsouka S, et al. Effects of hematocrit on cerebral microcirculation and tissue oxygenation during deep hypothermic bypass. Circulation 2001;104:1206–4.
23. Sakamoto T, Hutsouka S, Rock OA, et al. Prediction of safe duration of hypothermic circulatory arrest by near-infrared spectroscopy. J Thorac Cardiovasc Surg 2001;122:359–60.
24. Jonas RA, Wypij D, Roth SJ, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. J Thorac Cardiovasc Surg 2003;126:1705–7.
25. Ballweg JA, Wernovsky G, Gaynor JW. Neurodevelopmental outcomes following congenital heart surgery. Pediatr Cardiol 2007;28:126–33.
26. Gaynor JW, Wernovsky G. Developmental and neurologic status of children following early repair of the arterial switch procedure. Circulation 2005;111:1345–51, 1355c1–3.
27. McQuillen PS, Harris W, Perez M, et al. Baltino results of the Boston Circulatory Arrest Study Group. Circulation 1998;97:773–9.
28. McQuillen PS, Barkovich AJ, MacDonald NE, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke 2007;38:756–61.