Deep hypothermic circulatory arrest and the effects on the brain

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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 circulatory arrest with one of predominantly low-flow cardiopulmonary bypass (CPB). Of the 129 patients with D-TGA and intact ventricular septum, 66 were randomized 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 neurobehavioral 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 2.5 years and an increased risk of both brain magnetic resonance imaging (MRI) and neurological abnormalities at one year[4,5].

- 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 oromotor 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 1993 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 an 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 is not associated with worse neurobehavioral outcome at one year of age.

PH STAT OR ALPHA STAT?

Based on the theoretical advantages of maintaining electrochemical neutrality during hypothermia, 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 choreoathetosis was noted to increase markedly following procedures performed under DHCA[15,16]. Retrospective analysis demonstrated that the presence of aortopulmonary collaterals (APCs), age beyond infancy and a shorter duration of cooling prior to DHCA, in combination with alpha-stat management, were associated risk factors[15,16]. The depth and duration of hypothermia may also be a risk factor independent of circulatory arrest[17]. Given current practice and knowledge, it is very unlikely that these connections will ever be fully substantiated.

Following these observations, a more definitive answer as to the role of acid-base management in neurological outcome following procedures utilising DHCA was sought. This search led to the initiation and completion of the only randomized clinical trial of pH-stat versus alpha-stat management in neonates and infants exposed to DHCA. Over a four-year period commencing in 1992, 182 infants and neonates undergoing two-ventricle complete repair procedures involving deep hypothermic CPB were enrolled in a prospective randomized trial of alpha-stat *versus* pH-stat management[18,19]. The number of patients (92 *vs* 90), their age (7 *vs* 9 days), weight (3.38 *vs* 3.33 kg), duration of DHCA (21 ± 17 *vs* 22 ± 16 minutes), duration of CPB (103 *vs* 107 minutes), and distribution of diagnoses (D-TGA with VSD, D-TGA with intact ventricular septum, TOF, TOF and pulmonary atresia, complete AV canal, truncus arteriosus, totally anomalous pulmonary venous return) were similar in the pH-stat and alpha-stat groups. Immediate postoperative evaluation revealed an earlier return of first EEG activity in the pH-stat group. For the entire study cohort there was a trend toward reduced 1) clinical seizures, 2) median duration of intubation, ICU stay and postoperative hospital stay and 3) early deaths in the pH-stat group, although none of these variables reached statistical significance. In the more homogenous D-TGA subgroup, patients in the pH-stat group had less frequent postoperative acidosis and hypotension, a higher cardiac index coupled with a reduced requirement for inotropic agents, and a shorter duration of mechanical ventilation and ICU stay.

Developmental follow-up evaluations were performed at one year in 111 (54 alpha-stat, 57 pH-stat) of the original cohort. The parents of 121 children (58 alpha-stat, 63 pH-stat) completed questionnaires on behaviour and development when the children were two to four years of age. For the entire study cohort at one year there were no significant differences in the psychomotor development index or the mental development index scores between the alpha-stat and pH-stat groups, nor were any neurological examination or EEG abnormalities consistently related to either group. In addition, there was no association of parental assessment

of development or behaviour at two to four years with assignment to either the alpha-stat or pH-stat groups. For the small subgroup of patients with complete AV canal or VSD (nine alpha-stat, seven pH-stat), the psychomotor development index and mental development index scores at one year were significantly lower in the pH-stat group.

In summary, the subtle differences between the alpha-stat and pH-stat groups that are evident in the immediate postoperative period did not consistently correlate with either improved or impaired neurodevelopmental outcome at one or two to four years of age. The question as to whether pH-stat management would offer any short- or long-term neurobehavioral advantage over alpha-stat management in the setting of a longer arrest interval, the presence of extensive APCs, or a more rapid rate of cooling to target temperature remains unanswered. It is important to point out that 26% of patients in this study did not undergo DHCA, that the average duration of DHCA was 22 ± 16 minutes, and that only 33% of patients had a DHCA interval greater than 30 minutes. It is not unreasonable to speculate that pH-stat management might be superior to alpha-stat management in neonates and infants undergoing Stage 1 palliation for complex single ventricle lesions or in those undergoing extensive aortic arch reconstruction, where longer DHCA intervals are the norm.

DOES HAEMATOCRIT MATTER?

There is abundant laboratory evidence demonstrating that a haematocrit of greater than 30% is associated with improved neurobehavioral and brain histological outcomes after DHCA[20,21]. 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[23]. Once DHCA commences, the cerebral oxyhaemoglobin 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 oxygenat-

ed haemoglobin signal nadir time is shorter in the higher haematocrit group[23]. This is of particular importance, given the fact that an increased oxygenated haemoglobin signal nadir time correlates strongly with adverse neurobehavioral and brain histological assessments.

There has been only one clinical trial to date investigating the effect of haematocrit during CPB on neurobehavioral outcome in infants undergoing cardiac surgery[24]. This study randomized 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/m^2) 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 utilized. However, it is important to point out that 65% of the patients in this trial did not undergo DHCA and only 16% of the patients had a DHCA interval of 30 minutes or more.

IS DHCA SOLELY TO BLAME FOR ADVERSE NEUROBEHAVIORAL OUTCOME?

Adverse neurobehavioral outcomes following neonatal and infant heart surgery are related to both fixed and modifiable factors[25]. 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 CPB and DHCA) 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 ε2 allele were associated with worse neurobehavioral outcome at one year[26]. The use of DHCA with alpha-stat management, which in this study was used in 35% of patients for a mean duration of 34 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%)[27].

At present, DHCA is used selectively and preferably 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 optimization 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 syndromic and have been demonstrated to have a high incidence of microcephaly[28]. The observation that microcephaly is associated with a small ascending aorta strongly suggests that altered *in utero* distribution of cerebral blood flow is an important factor[29]. 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 heart transplantation, staged palliation utilizing DHCA, or staged palliation avoiding DHCA[30-32].

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 CO_2 cerebral vascular reactivity was present in the subset of patients with cerebral ischemic lesions[33]. Mild cerebral ischemic injuries (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 with severe congenital heart disease[34-37]. In these same series, the postoperative incidence of ischemic and stroke lesions is 36 to 75%. Ongoing fetal brain MRI studies will be necessary to determine whether these preoperative lesions are the result of a fixed factor, such as altered *in utero* blood patterns, or the result of a modifiable factor, such as suboptimal preoperative management.

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