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The Influence of the Method of Cerebral Protection During Neonatal Cardiac Surgery on The Development of Attention Deficit/Hyperactivity Disorder

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THE INFLUENCE OF THE METHOD OF CEREBRAL PROTECTION DURING NEONATAL CARDIAC SURGERY ON THE DEVELOPMENT OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER

BY

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I would like to dedicate this manuscript to the parents of the children who completed the surveys and devote so much of their time and energy to raising children with complex congenital cardiac defects.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-IA	Attention Deficit Hyperactivity Disorder- Inattention Type
ADHD-H	Attention Deficit Hyperactivity Disorder- Hyperactivity Type
ADHD-C	Attention Deficit Hyperactivity Disorder –Combined Type
ADHD-IV	Attention Deficit Hyperactivity Disorder IV Survey
DHCA	Deep Hypothermic Circulatory Arrest
CHD	Congenital Heart Disease
CHQ-50	Child Health Questionnaire- 50 questions
CPB	Cardiopulmonary Bypass
$CMRO_2$	Cerebral Metabolic Rate
DHCA	Deep Hypothermic Circulatory Arrest
DMN	Default Mode Network
EEG	Electroencephalogram
GlutTP	Glutamate Transporter Proteins
HLHS	Hypoplastic Left Heart Syndrome
ICF	International Classification of Functioning
ICF-CY	International Classification of Functioning- Child Youth Version
IQ	Intelligence Quotient
MAP	Mean Arterial Pressure
MDI	Bayley Mental Development Index
MMP	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
NMDA	N-Methyl-D-aspartate pCO2 Partial Pressure of Carbon Dioxide
PDI	Bayley Psychomotor Development Index
PVL	Periventricular Leukomalacia
RLFP	Regional low flow perfusion
SPECT	Single-Photon Emission Computed Tomography
VSD	Ventricular Septal Defect

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ABSTRACT

Complex congenital heart disease is a common birth defect requiring surgery soon after birth. Surgery can use a complete interruption of cerebral blood flow (DHCA) or it can be performed using regional low flow perfusion (RLFP). Either approach places the neonate at risk for oxygen deprivation resulting in neurodevelopmental impairment and Attention Deficit/Hyperactivity Disorder (ADHD). RLFP has been widely adopted but its effect on ADHD has not been elucidated.

We extracted surgical records data and surveyed parents of 5-16 year old children who had neonatal surgery using DHCA or RLFP in 1995-2006 to determine the prevalence of ADHD after DHCA vs. RLFP. ADHD was negatively associated with increased RLFP time ($p < .05$) when controlling for DHCA time, and a primary diagnosis of interrupted aortic arch. This finding confirms that use of RLFP is associated with a reduced incidence of ADHD.

1.0 BACKGROUND AND INTRODUCTION

Congenital heart disease is the most common birth defect and is present in about one percent of all newborns (NIH News May 27, 2010). Without surgical correction of many types of complex congenital heart malformations, babies usually die within the first few months. Use of deep hypothermia to cool the body temperature to less than 20 degrees Centigrade, is commonly used in the reconstruction of the aorta. Deep hypothermia techniques include either circulatory arrest (DHCA) with complete interruption of cerebral blood flow (CBF), or it can be performed using regional low flow perfusion (RLFP). Either approach places the baby at risk for oxygen deprivation of the brain with the attendant risk of neurodevelopmental impairment. Evidence from animal studies and clinical trials with DHCA has shown improvements in short term neurodevelopmental outcomes when pH stat blood gas strategy (Bellinger, 2003) and increased hematocrit are used during the cooling process (Wypij, 2008). Consequently, the neuroprotective approach used in congenital cardiac surgery has evolved over the past decade from DHCA (the primary method of cerebral protection in the early years of surgery) to use of RLFP (Ohye, 2009). Modifications in surgical, perfusion, anesthetic, and postoperative care over the past two decades have improved short-term neurodevelopmental outcomes, as measured with the Bayley Mental Development Index (MDI) and Psychomotor Index (PDI).

Despite improvements in neuroprotection during surgery, neurodevelopmental scores in children who have had congenital heart surgery are still well below the mean

values for the general population, especially in the area of motor development. Furthermore, the short-term neurodevelopmental outcomes documented with the MDI and PDI may not correlate well with long-term outcomes that are important to children and their families, such as attention deficit hyperactivity disorder (ADHD)

ADHD may be a particular risk for those who have undergone surgery in which cerebral blood flow has been compromised. For example, Mahle (2000) reported an increased incidence of ADHD of more than 50% in a population of children who had congenital heart surgery. In 2008, Shillingford completed an in depth study of 5-10 year olds who had undergone infant (< 1 year of age) cardiac surgery. Thirty percent were at high risk for ADHD according to the ADHD-IV rating scale (Anastopoulos, 1998) and nearly half (49%) were receiving remedial school services. This ADHD prevalence rate is 3-4 times higher than exists in the normal population. However, the neurodevelopmental outcomes reported in the literature are relatively short term so there is no clear understanding of the association between changes in surgical approached to neuroprotection and the risk of long-term neurodevelopmental morbidity, such as ADHD.

It is important that we understand both short and long term effects of changes in surgical approaches to optimize subsequent quality of life for children. The report of the Pediatric Heart Network and National Heart Lung and Blood Institute Working Group on Perioperative Management of Congenital Heart Disease (CHD) in 2010 (Kaltman, 2010) stated that:

The effects of cardiopulmonary bypass on early recovery and long-term sequelae such as neurodevelopmental deficits remain significant issues for neonates undergoing surgery for CHD. (p. 2766)

As the survival after complex neonatal cardiac surgery has steadily increased, the concentration on improving outcomes has shifted to quality of life in this high risk population, and ADHD may have a profound effect on both children and their families. ADHD may affect family dynamics, reduce scholastic achievement, and ultimately limit success in the workplace. While many factors other than the surgical approach used for neurological protection may be expected to affect long term neurodevelopmental outcomes and ADHD, we need to understand the association between cerebral injury during the surgical procedure and the long-term outcomes that children care about, such as the risk of ADHD.

The widespread adoption of RLFP over the past decade has not been evaluated in terms of its impact on the incidence of ADHD. Therefore, this study will investigate the association between the methods of cerebral protection used during neonatal aortic arch surgery and parental reports of ADHD in children 5-16 years of age in a single-center cohort of neonatal cardiac surgery children.

2.0 LITERATURE REVIEW

An examination of the association between the surgical approach used for neuroprotection in surgery for congenital cardiac defects and ADHD must be based on previous findings from a large number of different scientific fields. We reviewed the common surgical procedures for repair of the aortic arch in neonates and discuss the issues to consider using a conceptual model of neurodevelopmental outcomes in congenital heart surgery children as a frame work. The model includes the fetal, preoperative, intraoperative, and postoperative factors that influence outcomes. We reviewed mechanisms of cerebral injury during neonatal cardiac surgery, and the currently known associations between ADHD and the effects of cardiopulmonary bypass, deep hypothermia circulatory arrest, regional low flow perfusion, and the mechanisms related to hypoperfusion. The body of knowledge of the basic science of ADHD was primarily developed from research in preterm infants. However, oxygen deprivation in premature infants and mechanisms of injury in neonatal cardiac surgery children may be expected to have similar outcomes. Thus, the premature infant literature was expected to be relevant to this study. We also examined the pathophysiology of ADHD, its effect on the striatum and new information related to the Default Mode Network and the thickness and folding of the cerebral cortex in ADHD children. The information from this review was used to inform the selection of the data points to be abstracted from the surgical records. Finally, we reviewed the literature on the instruments available for measuring the

presence of ADHD, and elected to use the two most commonly used instruments, the ADHD IV and the Child Health Questionnaire (CHQ) surveys based on the detail the validation studies for these instruments. The key issues of importance to this study that were identified in the literature are discussed in detail below.

2.1 Hypoplastic Heart Syndrome and Aortic Arch Abnormalities

Congenital heart disease is the most common birth defect and is present in about one percent of all newborns (NIH News may 27, 2010). Without surgical correction of congenital heart malformations babies usually die. A common procedure used in heart surgery for congenital defects in the reconstruction of the aortic ascending aorta or aortic arch. This surgical procedure is performed early in the neonatal period. The requirement for corrective cardiac surgery in the neonatal period is due to the complexity of the congenital malformations that involve both pulmonary and systemic blood supply and compromise both oxygenation and tissue perfusion leading to death within the first year of life. The congenital malformations that are the focus of this study include hypoplastic left heart syndrome (HLHS), interrupted aortic arch (IAA), and the combination of a ventricular septal defect (VSD) with coarctation of the aorta.

The diagnosis of hypoplastic left heart syndrome (HLHS) encompasses varying degrees of a diminutive left ventricle with mitral and aortic valve atresia. Lack of systemic blood flow through the aortic valve diminishes the size of the ascending aorta in utero and the majority of systemic fetal blood flow is derived from the patent ductus arteriosus. The operative procedure known as the Norwood Stage I involves augmenting the size of the ascending aorta and arch with homograft tissue and anastomosing it to the pulmonary artery. The right ventricle then functions as the single primary systemic

ventricle. Pulmonary blood flow is achieved through a prosthetic shunt from either the innominate artery to the pulmonary artery or from the right ventricle to the pulmonary artery. Since the major blood vessels that arise from the aortic arch supply the cerebral circulation, augmentation of the aortic arch requires interruption of cerebral blood flow unless alternative methods for cerebral perfusion are provided.

Interrupted aortic arch is another common congenital cardiac abnormality that involves the aortic arch. Surgical repair includes reattachment of the aorta above and below the interruption. Since the repair involves the aortic arch, interruption of cerebral blood flow must occur unless provision is made for regional cerebral perfusion.

Finally, the other major procedure requiring aortic arch repair is the combination of a ventricular septal defect (VSD) with coarctation of the aorta. A coarctation is a severe narrowing of the aorta and it can be repaired through a left thoracotomy without interruption of cerebral blood flow. The VSD is repaired through a median sternotomy which previously required that the patient undergo two separate operations. In order to repair the coarctation through median sternotomy, circulatory arrest is required unless there is some method of regional cerebral perfusion.

The circulatory arrest required by these procedures and selection of the neuroprotective method applied during surgery may result in differences in both short and long term neurodevelopmental outcomes. The relationships between brain function and long term neurodevelopmental outcomes are complex. However, recent work by Wernovsky (2006) clearly describes the main important factors.

2.2 Model of Long Term Neurodevelopmental Outcomes

The Model of Neurodevelopmental Outcomes in Pediatric Cardiac Surgery Children (Wernovsky, 2006) describes the timeline for the major factors that influence long-term neurological and developmental outcomes in pediatric children undergoing complex cardiac surgery. The model is an important contribution to the field because it emphasizes the complexity of the interactions between preoperative, intraoperative, and postoperative factors in these children. Because of the multiplicity of factors affecting neurological development, the model clearly demonstrates the many issues that must be considered when examining long-term outcomes from changes in neuroprotective approaches used in congenital cardiac surgery.

The primary factors in this model that relate to our research include genetic and surgical. The most important genetic factor is in the children with IAA who have an increased risk of 22q11.1 deletion syndrome, which is associated with an increased risk of ADHD. The modifiable surgical factors in our study include DHCA, RLFP and increased hematocrit and pH stat blood gas management during cooling. A previous study has shown these surgical factors were not related to the incidence of ADHD (Shillingford, 2008), however DHCA was the only method of neuroprotection in the study.

The influence of other relevant factors is outlined in the following sections which includes the neonatal and preoperative factors such as head circumference and periventricular leukomalacia, and postoperative factors such as prolonged systemic oxygen desaturation. Low oxygen tension is a risk factor for neurological injury in all these children and is present in many of the stages of development until the corrective

surgery is completed. Periods of significant hypoxemia are one of the most difficult modifiers to quantify, but it is an important contributor to outcomes. Therefore, in this study we will evaluate primarily the surgical factors represented in this model that can be modified.

2.3 Neonatal and Preoperative Factors Affecting Neurodevelopmental Outcomes

The long term neourodevelopmental deficits reported for children who have had cardiac surgery for congenital heart defects are not solely due to the surgery. There is significant evidence of delayed cerebral development in utero among neonates who undergo cardiac surgery. Magnetic resonance imaging (MRI) has shown that brain immaturity is often present in infants with complex cardiac disease (Licht, 2009). Structural changes associated with brain immaturity in this population include the following: PVL 21%, incomplete closure of the opercular space (86%), and reduced head circumference (Licht, 2009). Thus, the quality of fetal development plays a key role in determining long-term neurodevelopmental outcomes after neonatal cardiac surgery, and a prenatal diagnosis of HLHS is associated with improved short term neurologic status and a reduction in acidosis and seizures due to early surgical intervention (Mahle, 2001).

Brain immaturity has been shown to be the greatest predictor for PVL following surgery (Licht, 2009). Measurement of the head is predictive of central nervous system development and small head circumference is indicative of reduced brain size and immaturity of the brain. Occipital frontal circumference below the 2nd percentile is considered microcephaly. In one study of HLHS children, 8% had microcephaly and there was an overall microcephaly rate of 9% in neonates undergoing heart surgery (Shillingford, 2007). Studies have shown the brain size that is 1 month delayed in

development may exhibit reductions in the number and size of fissures present. There is also increased susceptibility to PVL. This susceptibility is thought to be due to premylinating oligodendrocyte precursor cells being more vulnerable to hypoxia/ischemia between 23 and 36 weeks of gestation (Licht, 2009). Periventricular leukomalacia was found in 16% of neonates prior to surgery (Mahle, 2002). Periods of hypoxia or low venous saturation prior to surgery may induce injury due to loss of autoregulation with reperfusion injury causing localized cerebral hemorrhage. Periventriclar leukomalacia was demonstrated in 36% of children after neonatal heart surgery with MRI (Andopoulous, 2010). These studies have demonstrated that structural changes due to brain immaturity are present preoperatively in the neonatal surgical population and problems with inattention, executive functioning, language, fine and gross motor coordination and visual motor integration may be associated with these structural changes. The presence of undeveloped cerebral operculum is associated with significant feeding and swallowing disorders, thus postnatal growth may also be impaired and exacerbate the morbidity for these babies (Guerreiro, 2000).

One mechanism for cerebral underdevelopment is altered cerebral blood flow. Cerebral blood flow in HLHS is primarily though the patent ductus arteriosus (PDA) with retrograde flow through the hypoplastic aortic arch. Larger size ascending aorta is associated with increased head circumference due to increased cerebral blood flow (Shillngford, 2007). Thus, the long term neurodevelopmental effects may be affected by the physical characteristics of the cardiac malformation.

2.3.1 The Influence of Genetic Syndromes on Neurodevelopmental Outcomes

Some children with congenital cardiac defects also have known genetic syndromes which are associated with neurocognitive impairment. In one study of HLHS children, 28% had a confirmed or suspected genetic syndrome, and at one year follow-up, such syndromes were confirmed in 35% of patents. Both mean mental development and psychomotor development scores were lower for the children with the genetic syndromes (Tabbutt, 2008). A review of the STS database from 2002-2006 in children revealed that 8% of HLHS children had genetic syndromes and Turner Syndrome and 22q11.1 deletion syndrome (Velocardiofacial Syndrome) were associated with a decreased 10-year survival (Patel, 2010).

22q11.1 deletion syndrome is commonly associated with cardiac defects. The rate of 22q11.1 deletion syndrome in a population based study was reported to be 1.7/10,000 births, with IAA present in 23% of these children (Botto, 2003). In the neonate population with the 22q11.1 deletion syndrome and a cardiac defect, Type B interrupted aortic arch was the most common cardiac defect, occurring in 89% of the children (Momma, 2010). In another study of 22q11.1 deletion syndrome, 40% percent of children 5-17 years of age with 22q11.1 deletion syndrome also had a diagnosis of ADHD (Niklasson, 2009).

Neuroanatomy in 22q11.1 deletion syndrome shows an increase in size of the midsaggital corpus callosum and Sylvian fissures, and a decrease in size of in the posterior fossa, cerebellum, and the caudate nucleus (Momma, 2010). The change in white matter in these regions especially the caudate nucleus is associated with impairments in attention and executive function. The COMT gene has been identified as

a factor in the neurological manifestations of this disease. The COMT codes an enzyme which is involved in the breakdown of the neurotransmitters dopamine, epinephrine and norepinephrine. Abnormalities of this gene are associated with poor performance on cognitive tasks of executive function (Antshel, 2005).

Another genetic risk factor for impaired neurodevelopment is the presence of apolipoprotein E2 or E4 genotype. Apolipoprotein E is important in the transport of cholesterol and phospholipids in neuronal membranes and is associated with smaller head circumference and abnormal brain development. This genotype has been associated with increased behavior problems after infant cardiac surgery (Gaynor, 2009). The importance of these genetic syndromes on the long term outcome of ADHD needs to be further studied.

2.4 Surgical Factors Affecting Neurodevelopmental Outcomes

2.4.1 Effects of Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) subjects the cerebral circulation to sources of injury that may potentiate the development of ADHD. The key injurious factors associated with the use of cardiopulmonary bypass include hemodilution (decreased hematocrit and oxygen carrying capacity), non-pulsatile blood flow, gaseous and particulate microemboli, and alterations in cerebral blood flow related to carbon dioxide management strategies. Surface contact within the extracorporeal circuit during CPB activates major cascade systems, such as the complement, coagulation and fibrinolytic pathways, which trigger a whole body inflammatory response including cytokine production, neutrophil activation, and endothelial activation. Proinflammatory cytokines that are expressed by surface activation and ischemia may contribute to the development

of PVL. In 88% of cases of PVL, tumor necrosis factor and interleukin-6, were increased (Yoon, 1997). Therefore, these factors which increase as the length of time on CPB increases, may be associated with development of ADHD due to the increase risk of PVL from the inflammatory response to CPB and increased microemboli load in the cerebral circulation.

2.4.2 Deep Hypothermic Circulatory Arrest (DHCA)

Deep Hypothermic Circulatory Arrest (DHCA) is the technique used to cool the body temperature to 18° Centigrade to allow for a bloodless surgical field during cardiac surgical repairs in neonates. Hypothermia reduces oxygen demand for a limited period of time so extended periods are associated with neurological injury. In a study of adolescents that underwent neonatal heart surgery before 1992, 17% had cerebral palsy, 18% had an IQ in the mental retardation range, and over one half had signs of ADHD (Mahle, 2000). Longer DHCA time is associated with an increased incidence of seizures as measured by EEG (Gaynor, 2005). Postoperative seizures are associated with a decrease in the Bayley Psychomotor Index at 1 year of age (Gaynor, 2006). Moreover, a circulatory arrest time of more than 33 minutes is associated with a decrease in IQ scores at 5 years of age (Forbess, 2002).

Low systemic blood flow during hypothermia is sometimes used instead of DHCA. In a randomized trial at Boston Children's Hospital in children with transposition of the great vessels, 8-year follow-up revealed that DHCA was associated with worse performance on psychomotor tests and an increased incidence of speech apraxia (Bellinger 2003).

DHCA was also associated with a new postoperative stroke as detected by MRI in 10% of children following cardiac surgery (Chen, 2009). In this study, predictors for postoperative stroke after DHCA included lower birth weight, preoperative intubation, lower intraoperative hematocrit, and higher blood pressure at admission into the cardiac intensive care unit.

The pathophysiology of stroke after DHCA may also be related to a "no reflow" phenomenon. This response to ischemia is initiated by leukocyte adhesion receptor expression, which is promoted by cytokines released from the neutrophils and activated monocytes. Injury to basal lamina causes a collapse of the microvasculature reducing blood flow through the vessel. This collapse is exaggerated by external compression from edema. Structures that are particularly vulnerable include the striatum which has a limited blood supply under normal conditions (del Zoppo, 2000). In animal models of ischemic stroke due to hypotension, injury was greater in the striatum than in the cortex (Hamann, 2002). This mechanism of basal cellular injury is related the activation of proteolytic systems including matrix metalloproteinases (MMP) (Wang, 2007). Injury related to DHCA has been well documented, and efforts to minimize DCHA times are warranted to minimize ischemic injury. Therefore, ADHD in this population may be related to the length of DHCA and minimizing the time of DHCA or providing some cerebral perfusion during the surgical procedure may reduce the incidence of ADHD as well as other neurological injury.

2.4.3 Regional Low Flow Perfusion

Regional low flow perfusion (RLFP) has the potential to improve outcomes by providing continuous cerebral blood flow in place of ischemic arrest. Because of this

potential, RLFP was adopted in a majority of pediatric heart centers before any randomized controlled studies had been done to confirm the superiority of this technique (Ohye, 2009) Clinical adoption of RLFP began approximately the same time that cerebral oximetry with near infrared spectroscopy became commercially available. Wernovsky in 2007 reported in a survey of surgical methods that the percentage of centers using RLFP was 56% and cerebral oximetry was 64%. Ohye in 2009 reported the use of RLFP by 83% of pediatric cardiac surgeons in 2007 with only 20% routinely or exclusively using DHCA.

2.4.4 Animal Studies of Regional Low Flow Perfusion

Animal studies have been used to establish the best methods for cerebral perfusion. Cerebral oxygen metabolism during cerebral perfusion at deep hypothermia was evaluated in a neonatal piglet model (Sasaki, 2010). Cooling was accomplished at a flow rate of 200 ml/min with pH stat strategy. Following cooling to deep hypothermia, blood flow was reduced to 100 ml/min for 15 min in one group and RLFP was begun at 40 ml/min for 45 min in the other group. Microspheres were used to measure the cerebral blood flow. At 18^0 C, the cerebral blood flow at half systemic blood flow was the equal to full systemic blood flow during cooling, and after CPB, the cerebral blood flow the RLFP group matched the baseline blood flow. Researchers were unable to show any difference in the cerebral metabolic rate between half flow and RLFP at deep hypothermia.

Salazar (2009) used microdialysis in an 8-10 kilogram piglet model, and randomized two groups to either 60 min DHCA or 60 min RLFP after cooling to 18^0C with a flow rate of 100 ml/kg. The DHCA group had increased lactate, glycerol, and

lactate pyruvate ratios, along with a decrease in brain oxygen level to 0 mm Hg after 30 min of DHCA. The RLFP group was perfused with a flow rate of 10 ml/kg/min. They concluded that limiting DHCA to less than 30 min may not be injurious.

In another study, 20-30 kilogram juvenile pigs were used to compare cerebral blood flow using florescent microspheres under the varying conditions of hypothermic circulatory arrest (Straugh, 2003). Pigs were randomized to one of three groups: 30 min DHCA; 30 min of DHCA followed by 60 min of RLFP; or 90 min of RLFP. Full systemic blood flow was 80-100 kg/min, and RLFP flow rate was 10-20 ml/kg to maintain a pressure of 50 mm Hg in the axillary artery. Behavioral scores were significantly better with RLFP than DHCA. Lactate levels were also lower in the RLFP group.

The optimal pH strategy for RLFP was investigated in juvenile pigs (mean 26kg) that were randomized to either pH stat or alpha stat and cooled to 20^0 C and had 90 min of RLFP. CBF was higher in the pH stat group with a higher $CMRO_2$. Researchers suggested that alpha stat is a better strategy due to reduced blood flow and less risk of embolization (Halstead, 2004).

Another study used a juvenile pig model to determine the difference between pH stat and alpha stat during 45 min of RLFP at 25 degrees. Intravitral microscopy and microdialysis was used. Flow rates for cooling were 110 ml/kg, and RLFP was 10 ml/kg with aortic arch pressure of 50 mm Hg. Lactate levels were higher with alpha stat, and at the end of cooling, oxygen delivery was higher in the pH stat group. After re-warming, oxygen delivery was higher in the alpha stat group (Dahlbacka, 2007).

In these animal studies, researchers reported contradictory results regarding pH and alpha stat blood gas strategies. Studies using larger animals favored alpha stat, while in the smaller and younger animal studies, pH stat had better outcomes. However, in all studies regardless of the age and size, RLFP was superior to DHCA.

2.4.5 Human Studies of Regional Low Flow Perfusion

Soon after animal studies demonstrated improved metabolism and behavioral scores with RLFP, clinical studies on human subjects were done to assess the differences in short term outcomes. The first comparison of DHCA and RLFP (Visconti, 2006) did not demonstrate a difference between the two techniques in Bayley II Neurodevelopmental Indexes at one year of age. However, the RLFP group had an average DHCA time of 23.5 minutes. In the DHCA group, the DHCA time was 44.3 minutes. This study was not a clear comparison of the two techniques and shows the problem of evaluating RLFP when it is usually associated with a short DHCA time.

A retrospective study (Hannon, 2006) compared RLFP to DHCA. Children in the RLFP group had a shorter period of CA (10 min vs. 65 minutes). The conclusion of this study was that survival is significantly increased with the use of RLFP. Survival in the RLFP group was 2.25 times greater than the DHCA group. This improvement with RLFP is probably due to the capability of handling unexpected technical problems should they occur. RLFP allows for better management of such problems without increasing the DHCA time.

Only one randomized trial has been published to compare the effectiveness of DHCA vs. RLFP; the trial was completed in single ventricle children (Goldberg, 2007). Children were randomized to either DHCA or RLFP. The CA time in the RLFP group

averaged 5.7 min and the RLFP time was 41.1 ± 9.0 minutes vs. CA time of 41.0 ± 10 minutes. There was no significant difference found between Bayley II scores at one year of age between the two groups. However, both Bayley scores tended to be lower in the RLFP group, especially for psychomotor development (p=.07) (Goldberg, 2007). The average CA time in this study was uniformly short and may not reflect clinical practice in other less experienced centers.

A recent study using MRI to evaluate brain structures after RLFP has shown that RLFP using high flow rates is not associated with periventricular leukomalacia. Although the study included only 11 children and there was no comparison group, the normal incidence of 50% PVL was not seen in these children when high flow RLFP was used. Brain edema was not present as measured with brain sonography (Kwak, 2010). Although there is some evidence for improved outcomes with RLFP, the only randomized study was not conclusive and did not look at ADHD as a primary outcome. Therefore there is a need for research to determine whether ADHD is reduced with the use of RLFP compared to DHCA.

2.5 Postoperative Factors Affecting Neurodevelopmental Outcomes

The immediate post bypass time in the operating room is an especially vulnerable period. Increased cerebral vascular resistance combined with low systemic arterial oxygen saturation increases the risk of PVL (Hoffman, 2004). Continuous monitoring of venous oxygen saturation and cerebral oxygen saturation in the postoperative period is important to minimize any periods of cerebral hypoxia. Low venous oxygen saturation was associated with worse neurodevelopmental outcomes. The time below 40% venous oxygenation saturation was related directly to the extent of neurological impairment

(Hoffman, 2005). Although they did not measure the incidence of ADHD, postoperative hypoxia and hypotension may increase the risk for the of the development of ADHD.

HLHS children undergo three operations, the Stage I Norwood, Bidirectional Glenn, and then the Modified Fontan. The Modified Fontan increases the pulmonary blood flow by connecting the venous return from the lower circulation to the pulmonary artery. Until the third operation, arterial oxygen saturation is usually below 90% for their first few years of their life. The effect of chronic hypoxia on academic success has been reviewed, and even mild levels of hypoxia have been shown to have an adverse effect on development, behavior, and academic achievement (Bass, 2004). Therefore, low arterial oxygen saturation during the first few years may contribute to the development of ADHD in this population.

2.6 Improvements in Survival and Neurodevelopmental Outcomes

Numerous individual institutional studies have shown progressive improvements in the outcomes of Hypoplastic Left Heart Syndrome through the Norwood Stage I operation. In order to quantify all these individual reports, a meta-analysis was completed for survival and neurodevelopmental outcomes in this population (Sistino, 2012, accepted for publication). Meta regression analysis was used to analyze the relationship between the year of Stage 1 Norwood surgery and survival, Wechsler standardized IQ, and the Bayley II Scales of Mental and Psychomotor Development. Peer reviewed studies included in the meta-analysis were identified by searching Ovid MEDLINE® from January 1980-December 2010. The mean weighted survival for Stage 1Norwood from 1996 to 2007 was 80.5%, 95% CI: [76.4%, 84.0%] and increased significantly during this time period ($p<0.05$). The mean Wechsler IQ from 1989 to 1999 was 85.9, 95% CI:

[82.3, 89.5] and also increased significantly during this time period ($p < 0.05$). The Bayley II Index for Mental Development (MDI) overall mean MDI from 1998 to 2005 was 86.9, 95% CI: [83.5, 90.2] and increased significantly during this time period as well ($p < 0.05$). Finally, the Bayley II Index for Psychomotor Development (PDI) overall mean PDI from 1998 to 2005 was 73.8, 95% CI: [70.7, 76.8] and increased significantly ($p < 0.05$). Although survival has improved and short term neurodevelopmental outcomes have improved, there is no evidence on any reduction on the incidence of ADHD with newer surgical strategies such as RLFP.

2.7 Pathophysiology of ADHD and Outcomes

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common problems treated in school age children. A diagnosis of ADHD is made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). If during an examination by a physician trained in making the diagnosis, the patient exhibits at least six of the behavioral criteria listed, then ADHD is confirmed. There are several subtypes of ADHD, including primary inattention disorder ADHD-I, primary hyperactivity disorder, and the combined subtype ADHD-C, which includes both inattention and hyperactivity. Within each subtype, there is a wide spectrum of behavioral patterns.

Medical treatment modalities for ADHD include pharmacologic and behavior modification. Pharmacological treatment primarily includes stimulants to reduce the symptoms and improve task accomplishment. However, pharmacological treatment has not been successful in improving reading abilities or long term academic achievement. Behavior modification therapy primarily helps in reducing defiant behavior and

improving child-parent interactions. So far, combination treatment using both modalities, although successful in reducing symptoms, still does not improve long term educational outcomes. Therefore, the importance of preventing ADHD is paramount because treatment is not always successful.

Research has primarily focused on the striatum as the key anatomic structure associated with ADHD. Injury to the striatum may occur during circulatory arrest as the oxygen supply is depleted. Onset of cardiopulmonary bypass also may potentate glutamate release during an initial period of hypotension, and then again during circulatory arrest, when absence of cerebral blood flow stimulates glutamate release. Glutamate activation increases metabolic activity and further decreases the limited oxygen supply. Although hypothermia has a protective effect, the cooling of the striatum may be limited by its location in a watershed area of the brain, which is furthest from the arterial blood supply. Therefore, neuronal protection afforded by hypothermia may not be fully achieved prior to DHCA.

Injury as manifested by periventricular leukomalacia (PVL) has been documented at 6-14 days after surgery by MRI. According to Galli and colleagues, 54% of the neonates studied had PVL, compared to 4% of infants after cardiac surgery (Galli, 2004). The mechanism of PVL appears to be similar to that diagnosed in preterm infants who have not had bypass surgery. Myelination of the oligodendrocyte occurs in this early developmental stage and appears to be more sensitive to hypoxia and/or ischemic injury. The primary risk factors for PVL include: age less than 1 month, low diastolic blood pressure, low oxygen saturation, and prolonged support time (CPB + DHCA).

Neurodevelopmental outcomes in children with PVL are poor including cerebral palsy, mental retardation, learning disabilities, visual-motor defects and ADHD (Galli, 2004).

In a study of adolescents that underwent neonatal heart surgery before 1992, more than 50% had signs of ADHD (Mahle, 2000). In 2008, Shillingford reviewed the incidence of ADHD in 5-10 year olds who had undergone infant cardiac surgery (< 1 year of age). Nearly half (49%) were receiving remedial school services, and 30% were at high risk for ADHD using the ADHD-IV rating scale. This rate is 3-4 times higher than exists in the normal population. Another study demonstrated that, after infant cardiac surgery at an average age of 0.7 +/- 0.3 years, children with Tetralogy of Fallot had an increased incidence of attention dysfunction compared with a control group of VSD children. The presence of preoperative cyanosis in this study was associated with an increased the risk of ADHD (Hovels-Gurich, 2007).

2.7.1. Neural and Biochemical Basis for ADHD

ADHD is a serious health issue in the normal population, affecting an estimated 5-10% of children and 4% of adults. Genetic disposition for ADHD has been confirmed in studies of families and twins. A 2-8 fold increased rate of ADHD was found in parents and siblings of children with ADHD. Environmental factors such as food additives, lead contamination, cigarette/alcohol exposure, and maternal smoking during pregnancy are also associated with some forms of ADHD (Banerjee, 2007).

The neural and biochemical basis for ADHD following cardiac surgery appears to be similar to the mechanisms for ADHD associated with low birth weight and intrauterine growth retardation (IUGR) due to fetal hypoxia and/or ischemia. The pathophysiological model of ADHD centers on the striatum, which includes the putamen

and the caudate body and the cortico-striato-thalamo cortical loops, which are the connections between these major centers. The striatum synthesizes information from the pre frontal cortex regarding organization and planning behavior and is important for controlling signaling from those areas. Lack of activity in the striatum is associated with ADHD (Lou, 1996).

In the fetus, loss of autoregulation and susceptibility to hypoxia places the striatum particularly at risk for ischemic injury and the development of periventricular leukomalacia (PVL). The normal fetal arterial oxygen saturation is approximately 60%. A decrease in oxygen saturation to 50% for only 10 minutes is associated with the loss of cerebral autoregulation for several hours (Tweed, 1986). The striatum is located in a watershed area; therefore, it is more susceptible to reduced cerebral blood flow. The major arterial blood supply to this area is the thalamo-striate arteries and the superficial cerebral arteries. The striatum is composed primarily (90%) of medium spiny neurons, each with approximately 10,000 glutamatergic synapses. Response to hypoxia includes increased firing of the glutamate neurons, and this massive presynaptic glutamate release results in excessive depolarization with sodium and calcium ion influx followed by neuronal swelling. In the presence of hypoxia, this results in acute cell death in this region. Dopamine is the primary neurotransmitter in the striatum and the dopamine receptors are no longer viable (Lou, 1996).

A number of additional research studies have confirmed this pathophysiology. Following ablation studies in the striatum, animals exhibited ADHD-like behavior (Lou, 1984). Additionally, dopamine receptor mutant mouse models expressed ADHD characteristics (Xu, 1994). In rat pups, intermittent hypoxia impaired dopamine

signaling, which reduced the binding affinity of dopamine receptors as measured by neurochemical analysis. Reduced dopaminergic activity in the striatum has been documented (Decker, 2002). These experiments identified the location and the role of dopamine transmission in the disease, providing the basis for treatment with stimulant therapy in ADHD children to increase the release of dopamine. D-amphetamine releases dopamine and norepinephrine, while methylphenidate specifically releases dopamine. The therapeutic benefits of these medications confirm the role of catecholamines including dopamine in ADHD (Lou, 1996).

The next series of experiments revealed the impact of hypoperfusion and hypoxia to the striatum. In children with ADHD, SPECT measured decreased blood flow to the striatum (Lou, 1984). In fetuses, hypoxia reduced cardiac output and decreased blood flow to the striatum, which manifested as periventricular leukomalacia (PVL) (Strang-Karlsson, 2008). In preterm infants with arterial blood pressure below 29 mm Hg, decreased cerebral blood flow to the white matter was measured by SPECT and was associated with development of PVL (Borch, 2010). Measurement of low cerebral blood flow by xenon in preterm infants was associated with a low dopamine receptor-binding activity by PET scan during their adolescence (Lou 2004). In a rat model of repeated hypoxia vs. normoxia, diffuse periventricular leukomalacia and ADHD like behavior was produced in the hypoxic group similar to that seen in premature infants with repeated periods of hypoxia (Oorschot, 2007). This has been confirmed by near-infrared spectroscopy, which was used to monitor cerebral blood volume changes and the oxygenation index in children with ADHD vs. controls and demonstrated areas of

lowered oxygen uptake in the ADHD children during performance of an extended attention task (Weber, 2005).

MRI mapping at 10 years of age has confirmed the anatomical changes in the striatum (Qiu, 2009). Boys with ADHD had significantly smaller basal ganglia shapes and volumes compared with the control group of typically developing boys. The caudate head and body, and the anterior putamen were reduced in size.

New information on the widespread effects of ADHD within the brain is emerging. These include interruption of networks that were previously unknown and profound anatomic changes that occur in this population. ADHD is a complex disease involving many areas of the brain and has long term implications in development with structural and functional implications.

Until recently, the primary pathophysiological models for ADHD have focused on the prefrontal striatal circuits. Newer models of ADHD based on resting functional MRI (fMRI) include abnormalities in the frontoparietal, dorsal attentional, motor visual and default mode networks (DMN). This has been shown using the Blood Oxygen Level-Dependent signal (BOLD), which demonstrates the pathways and activities of the resting state networks (RSN) The DMN is active during the resting state and is deactivated when a task is begun. DMN resting state frequencies are 10-100 times slower than the normal EEG frequencies (Castellanos, 2012).

In ADHD children, there is decreased suppression of the DMN during tasks. Deactivation of the DMN increases attention, and suppresses extraneous stimuli in the occipital cortex (Castellanos, 2012). Mapping of the early development of the RSN is important to understanding of the pathways and how they could be interrupted. One study

examined these networks in preterm infants starting at 28 weeks (Fransson, 2007). They showed that RSN were present in the full term infant brain, but they were unable to map a DMN in in premature infants. In a longitudinal analysis of RSN development in infants by Smyser (2010), the precursors of the DMN were also detected in term infants but not in preterm infants. Emergence of the anterior-posterior connectivity was seen in about half of the full term infants as myelination of white matter. Another fMIR study looked at infants born between 29 and 43 weeks and showed that growth of the RSN occurred during the period of rapid neural growth in the third trimester and paralleled development of the thalamic-cortical pathways (Doria V 2010).

Resting state networks (RSN) have been compared in both full term infants and adults. In infants, the networks and their hubs are more centrally located in the motor, sensory, auditory, and visual areas. In adults, the networks and hubs are located in areas associated with more complex adaptive behavior (Fransson 2010).

Dopamine has been shown to be important in the modulation of the DMN. Several studies have shown that increased dopamine levels are associated with deactivation of the DMN during task initiation. Treatment with methylphenidate in ADHD children has been shown to normalize DMN deactivation in the occipital cortex (Peterson, 2009). Increase in dopamine transporters (DAT) are associated with lower dopamine levels in the striatum and decreased suppression of the DMN (Tomasi D 2009) when measured with positron emission tomography (PET), a DAT radioactive tracer, and fMRI. They concluded that dopamine modulates attention in the posterior parietal cortex. Simulant medicines that block DAT increase attention by deactivating the DMN.

Another study confirmed this with cerebral blood flow measurements using PET during performance of task. The task of planning and problem solving involved fronto-striato activation and deactivation of the DMN. The study was conducted before and after a dopamine antagonist administration in both healthy volunteers and Parkinson Disease (PD) children. Cerebral blood flow changed as the task was initiated and the DMN was deactivated. PD children had abnormal suppression of the DMN, except when given Apomorphine, a D1 and D2 dopamine agonist. Therefore, they concluded that dopamine signaling is related to the suppression of the DMN (Nagano-Saito, 2009).

During DMN deactivation, there is reduced cortical function in the medial prefontal cortex and the posterior cingulate cortex as demonstrated by Delaveau P (2010). In PD children, Levodopa and a placebo were administered in a crossover trial and activation of dopamine was associated with deactivation of the ventral medial prefrontal cortex but not the posterior midline and lateral parts of the DMN.

Further evidence of widespread cortex involvement in ADHD can be observed via measurement of the cerebral volumes, thickness of the cortex, and the degree of cortical folding in ADHD vs. normal individuals. In a 33 year longitudinal follow up of ADHD children (Proal, 2011), the cortex was significantly thinner in ADHD children and grey matter was decreased in right caudate, thalamus, bilateral cerebral hemispheres. There was evidence of decreased size in the dorsal attention network with thinning of occipital region and the occipital gyrus.

ADHD children had reduced grey matter volume (> 6%) and decreased mean cortical thickness (20%) in both anterior and posterior cortices including primary motor cortex

but not in the primary sensory regions (Narr ,2009). These studies demonstrate that ADHD extends beyond the striatal and prefrontal cortical circuits.

Decreased cortical folding is another primary morphologic feature associated with ADHD (Wolosin, 2009). Folding is a way to increase surface area and this is associated with increased functioning. Previous studies have shown that cortical folding begins at 16 weeks and reaches a peak at 18 months of age (Armstrong, 1995). Children with ADHD had a reduced surface area of more than 8% in each hemisphere, and this was due to reduced cortical folding and not reduced cortical thickness (Wolosin, 2009).

Since development of the DMN occurs in the third trimester, children with HLHS have delayed cerebral development and they may be continuing to form these circuits after birth during the surgical period. Interruption of cerebral blood flow during surgery with circulatory arrest may contribute to a decrease in function of these these neural pathways. Likewise, folding of the cerebral cortex may also be delayed due to exposure to hypoxia and ischemia during prolonged circulatory arrest. The role of dopamine receptors in the modulation of the DMN is well established and hypoxic injury to these receptors also contribute to the development of ADHD.

2.7.2 Cellular Mechanism of Ischemic Injury Following Glutamate Activation.

Glutamate is synthesized, stored, and released from presynaptic nerve terminals. The ischemic cascade is triggered by a severe reduction in cerebral blood flow. During ischemia, neurons release large amounts of glutamate that activates glutamate receptors, especially the NMDA type (N-methyl-D-aspartate). The NMDA receptor is located in the postsynaptic membrane.This ligand-gated, ion channel ionotrophic receptor requires both glutamate and glycine.

High affinity glutamate transporter proteins (GluTP) located on the neurons and surrounding glial cells rapidly remove glutamate from the synaptic cleft to prevent cell death. This activity helps maintain a low intrasynapic concentration in order to maximize the signal-to-noise ratio and the risk of excitotoxicity (Rousseaux, 2008). Stimulation of the NMDA receptor causes increased intracellular calcium. Intracellular calcium produces DNA degradation, breakdown of the cytoskeleton by calcium sensitive proteases and production of arachidonic acid, free radicals, release of nitric oxide, and cell death (Girouard, 2009; Coleman, 2010). This mechanism of injury may be responsible for injury in several diseases, including stroke, Alzheinmer, Parkinsons, Huntingtons, and Amyotrophic Lateral Sclerosis (ALS) (Aleyasin, 2007). Blocking NMDA glutamate receptors may be one mechanism to prevent this injury. However, such blockage would also impair crucial brain functions, such as learning and memory, so this treatment will require the use of selective NMDA inhibitors. Although ADHD is the focus of this study, there may be opportunities to research long-term neurological outcomes in the adult population that may have similar mechanisms of injury. DHCA is used in adults for repair of aortic arch aneurysms and the use of RLFP instead of DHCA may also improve long-term outcomes in the adult population.

2.7.3 Cellular Mechanism of Ischemic Injury Following Dopamine Activation

Dopamine neurons are sensitive to hypoxic conditions and undergo rapid degeneration. Repeated hyperpolarization during hypoxia and hypoglycemia results in silencing of the neurons. Five minutes of oxygen-glucose deprivation (OGD) causes long-term pre-synaptic ischemic depression of glutamate transmission. Researchers attempted to reduce ischemic injury to the striatum by using receptor blockers for D1 and

D2 type dopamine receptors (Yang, 2007). They subjected newborn piglets to two periods of ischemia. After the less severe hypoxic exposure, the D1 receptor blockage produced almost complete neuron recovery vs. 60% recovery in the control group. With more severe hypoxia, D1 blockage reduced injury to 50% vs. 18% in the control group. Microdialysis samples revealed elevated dopamine levels. Degeneration of dopamine neurons in the substantia nigra plays an important role in the pathophysiology of neurodegenerative diseases like Parkinsonism and vascular dementia in adults (Singh, 2007). A study on the incidence of Parkinsons Disease (PD) following heart surgery in adults revealed that PD began shortly after heart surgery in 3 adult children out of 800 surgical cases. The normal prevalence rate of PD in the overall population over the age of 60 is 1%, so the incidence in this surgical group represents a 10-fold increase. Their conclusion was that cardiopulmonary bypass may be damaging to mesostriatal dopaminergic neurons (Hagglund, 1996). The mechanism of injury to the striatum with the resultant loss of dopamine receptors may exist in the adult population and be similar to the injury that is occurring in neonates. This is a related area that needs further study and may help understand the role of these receptors in the ADHD population.

2.8 ICF Model Overview

In order to fully understand a disease process, measuring outcomes after treatment is essential. In the area of disability, the treatment process involves more than medical treatment, so the rehabilitation models that have evolved over the past 50 years have recognized the social and environmental impact on disability. The ICF Model is an international classification that records impairment of body structure and function, limitation of activities, and restriction of participation as a function of a health disorder or

disease. This model also includes environmental factors and personal factors as they relate to the "enabling-disabling" process.

The important clinical application of this model is the ability to describe the functional status and its relationship to diagnosis. In many disorders, functioning has a diverse spectrum and the ability to describe in a uniform manner each of these areas is a valuable tool for documenting changes due to treatment modalities. The ability to describe the impact of patient's setting or environment in treatment plans will be a significant factor in developing further research to improve these factors. Health care policy will be influenced by the data generated by the ICF and priorities for treatment and environmental modifications will be identified. (Lollar, 2005)

The ICF-CY is an extension of the ICF but adds additional factors that pertain to children. The major difference between adults and children is that children are undergoing a developmental process so their body structure and function, activities, and participation are changing. The ICF –CY includes the recording of these age appropriate factors so functioning can be interpreted in the context of the developmental age.

2.8.1 ICF Model for ADHD

An ICF model for ADHD (Loe, 2007) has been developed and categorizes the various impairments of body functions, limitations in activities and restrictions in participation associated with ADHD, and includes environmental and personal factors. Limited improvements have been associated with current treatment modalities for ADHD, so there is a need for prospective, controlled, large scale studies to investigate treatment options that improve long term outcomes. Medical treatments do not include

environmental reforms which would be included in ICF-CY research. Examples of environmental reforms include small class size, reducing distractions, and planned increased physical activity (Loe, 2007).

With respect to "body structure", children with ADHD have significant alterations in cerebral blood flow, dopamine receptor activity, and size of structures in their striatum. In terms of "body function", children have lower than normal full scale IQ, but scores still fall within the normal range. Their activities and participation are strongly influenced by academic and educational achievements. In terms of activity, they score significantly lower on reading and arithmetic achievement tests, and with respect to participation, they repeat grades more often, are placed in special education classes and more likely to be expelled or suspended. Children with ADHD are 4-5 times more likely to use special educational services and other services such as remedial pull out classes, after school programs, tutoring and special accommodations. Within the ICF framework, these activities would be coded under environmental factors.

Using the ICF framework, one can visualize how quantification of ADHD in both individuals and population data can improve the overall treatment of this disease. Improvements in "body function", such as attention, memory and executive function, influence "activities and participation" and this affects schoolwork and success in the workplace following school. The ability to measure changes in outcomes allows for treatment to all children and avoids withholding treatment from a group in order to conduct research. Advanced statistical modeling methods can be used to analyze these changes and document treatment outcomes. These models could be applied to the various

subtypes of ADHD so that evidence-based treatment can be defined for these subgroups (Loe, 2007).

2.9 Child Health Outcomes in Fontan Children

The Child Health Questionnaire has been used to assess the impact on many of the factors outlined above in the ICF model in pediatric cardiac surgery children. The Pediatric Heart Network completed a cross-sectional study of 537 children from 7 pediatric centers (Anderson 2008). The ages of the children were between 6-16 years, with a mean of 11.9 years. The average length of time since the Fontan procedure was 8.7 +/-3.4 years. The Child Health Questionnaire (CHQ-50) was completed by parents and used to measure physical and psychosocial functioning. The results were converted to Z scores based on published normative data. The physical functioning score was Z = -0.47 +/-1.19 and the psychosocial functioning score was Z = -.028 +/-1.08. Both these scores were significantly below the normal population ($p < 0.001$). Both scores were significantly decreased in families with lower family income. Other deficits noted were vision problems (33%), speech problems (27%), hearing problems (7%), attention problems (46%), learning problems (43%), developmental problems (24%), behavior problems (23%), problems with anxiety (17%), and depression (8%). The independent factors associated with lower physical functioning scores were greater weight, no fenestration, other surgical procedures at the time of the Fontan, arrhythmias, and the number of current medications. The independent factors associated with decreased psychosocial functioning included behavior problems, learning problems, and problems with either anxiety, attention, or depression.

2.9 Survey Instrument Validation Studies

The clinical diagnosis of ADHD is made in individuals with symptoms starting before the age of seven. They must meet at least 6 out of 9 symptoms as outlined in the DSM-IV criteria at two separate times more than 6 months apart.

2.9.1 ADHD IV

ADHD-IV has been used in the pediatric cardiac surgical population (Shillingford, 2008). The ADHD-IV rating scale estimates the "risk" of ADHD and is used as a screening tool for referral to a clinician for a diagnosis.

Normative data was collected for standardization of the test scores. This included parents/guardians and teachers throughout the US roughly equivalent to the population distribution. The ethnic diversity of the normative sample was similar to the population distribution except African-Americans were over represented and white non-Latinos were under represented by about 7%. The prevalence of ADHD was 9.1% among those 5-7 years, 6.4% (8-10 years), 8.3% (11-13 years) and 5.8% (14-17 years), with an overall total prevalence of 7.5%. Since the ADHD-IV is a screening test and includes children who have not been diagnosed with ADHD, it is expected to yield more positives than the reported ADHD prevalence rates of 3-5% in children and the adult rate of 4.2% (Kessler, 2005).

ADHD-IV Reliability: Coefficient alpha was used to test for internal consistency. The results were a total score 0.92, inattention 0.86, and hyperactivity-impulsivity 0.88. Correlation coefficients for test-retest reliability for parent ratings occurring 4 weeks apart were 0.85, inattention 0.78, and hyperactivity-impulsivity 0.86.

Predictive Validity: The ADHD-IV was compared to a diagnostic interview conducted by doctoral level psychology clinicians. Classroom behavior observed by these clinicians correlated with the teacher scores. In this study, a score of the 93rd percentile on the ADHD IV inattention scale was recommended as a cutoff for diagnosing ADHD.

Discriminate validity: Subscales for inattention and hyperactivity-impulsivity were found to have high levels of internal consistency and reliability and significantly correlated with common survey instruments commonly used in assessment of ADHD, the Connors Parent and Teachers Rating Scales.

2.9.2 Child Health Questionnaire CHQ-50

The Child Health Questionnaire quality of life instruments have been normed for children 5-18 years of age. The CHQ Summary Scores combine results to derive an overall physical and psychosocial score. The questions relate to the child's health status and whether their activities or participation in school and normal social events are limited. The survey inquires about pain, discomfort, problems paying attention, and other behavioral issues. The survey asks about the child's satisfaction with school and friendships and if there has been a change over time due to a change in their health status. Also, the emotional concerns of parents are assessed as are the impacts of such concerns on the other children and the parent activities. The CHQ-50 identified a high prevalence of attention and learning problems in children after the Fontan procedure (Anderson, 2008).

The CHQ-50 was validated in a population of ADHD children (Rentz, 2005). A baseline evaluation survey of 921 children with ADHD was compared to national norms for the CHQ-50. There was a decrease in scores in the following areas compared with the

normal population: role/societal limitations- emotional/behavioral, behavior, parental impact-emotional, parental impact-time, family activities, family cohesion, and the overall psychosocial summary score. There was a clear impact in multiple areas related to behavioral health, clearly impacting the family dynamics.

Reliability as measured with Cronbach's alpha for the subscales ranged from 0.56 to 0.91. Construct validity was determined by correlation with the behavior and family activities of the CHQ-50. Psychosocial subscales summary scores were more correlated with the symptom measures.

The CHQ-50 has been used in both the cardiac surgical population and the ADHD population. Studies with ADHD children show a typical pattern in CHQ-50. They have below normal psychosocial scores.

2.10 Summary

The scientific issues related to the investigation of whether RLFP vs. DHCA reduces the incidence of ADHD in the neonatal surgical population span the surgical and neurodevelopmental literature, as well as the literature related to the measurements of ADHD. Although long-term neurodevelopmental outcomes in the population who have surgery for congenital cardiac defects may be due to a multitude of factors which may not be modifiable, it is important to understand if the adoption of a new technique, such as RFLP may be expected to have long term neurological impacts. The effects of ADHD in multiple areas of the brain and its impact on quality of life are well established, and this study is important to establish a superior method for improving cerebral protection during surgery. Although the increased prevalence of ADHD in this population is well established, no study has specifically looked at the surgical options to reduce the

incidence of ADHD. This study is novel, not only because it establishes the prevalence of ADHD in this population, but because it also associates the outcomes with the primary surgical methods of cerebral protection such as DHCA and RLFP, and modifications of pH and hematocrit during CPB. The outcome of this study will be extremely useful in determining which of these procedures should become a standard of care in this population in the future.

3.0 STUDY DESIGN AND METHODOLOGY

3.1 Research Problem

For two decades, deep hypothermia and circulatory arrest (DHCA) without regional low flow perfusion (RLFP) was the primary method of cerebral protection during neonatal cardiac surgery. The adoption of RLFP has increased over the past decade, but the neurological outcomes reported in the literature are relatively unexplained. Evidence in animal studies and clinical trials has shown the benefits of both pH stat and higher hematocrit during circulatory arrest in short term neurological outcomes. These strategies, although adopted almost a decade ago, have not been evaluated in terms of their impact on the incidence of ADHD.

3.2 Specific Aims

The objectives of this research are:

1. To determine the prevalence of ADHD in a population of children following neonatal surgery with aortic arch repair.
2. To determine the association between the method of cerebral perfusion and the incidence of ADHD as measured by the ADHD IV rating scale and/or reported diagnosis of ADHD, and the CHQ-50 psychosocial composite sco

3. To determine the association between the perfusion strategies of pH stat and hematocrit level during cooling on the incidence of ADHD as measured by the ADHD IV rating scale and/or reported diagnosis of ADHD, and the CHQ-50 psychosocial composite score.

3.3 Hypotheses

Hypothesis 1 The rate of ADHD among those who undergo neonatal heart surgery is significantly increased compared to the norms for the general population on the ADHD IV rating scale and/or reported diagnosis of ADHD.

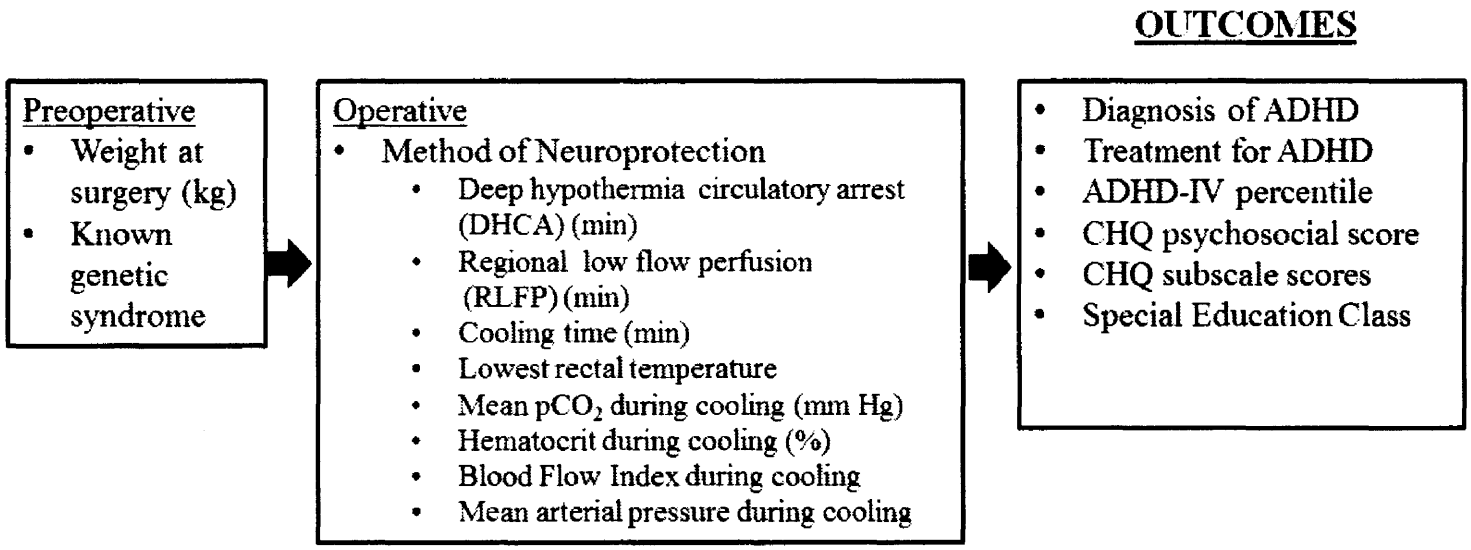
Hypothesis 2 Regional low flow perfusion (RLFP) is associated with a lower rate of ADHD than the patients who underwent deep hypothermic circulatory arrest (DHCA) when controlling for other significant surgical variables.

Hypothesis 3 Perfusion strategies of pH stat and increased hematocrit during cooling are associated with a lower rate of ADHD when controlling for other significant surgical variables.

3.4 Conceptual Model

The following conceptual model (Figure 1) illustrates the variables that will be included in this study. The model includes the preoperative and operative factors, and the outcome measures and assessments that will be completed in this study.

Figure 1. Conceptual Model



3.5 Study Design

This study is a cross sectional observational study of the prevalence of ADHD in a single center surgical cohort of children who underwent neonatal heart surgery between July 1, 1995 and June 30, 2006. A review of the surgical records of the Medical University of South Carolina during this time period identified 220 children who underwent neonatal heart surgery that required either DHCA and/or RLFP.

3.5.1 Inclusion Criteria

Surgical procedures included Norwood Stage I, Repair of Interrupted Aortic Arch (IAA), and combined Coarctation VSD repairs. A review of records of the Pediatric Heart Network of South Carolina established a list of 138 children who underwent surgery during this time period and could be located in the Children's Heart Program of South Carolina database

3.5.2 Exclusion Criteria

Children who died, had a cardiac transplant, or who did not have contact information in the Pediatric Heart Network of South Carolina database were excluded.

3.6 Questionnaires and Rating Scales

In order to avoid sending surveys to any family member of a deceased patient, reviews of medical records were performed by a pediatric cardiologist. After approval by the Institutional Review Board, a recruitment letter from the Children' Heart Program of South Carolina was sent with the surveys. The recruitment letter described the purpose of the study, the time involved, and contact information for questions about the research. The letter included a statement that participation in the survey was voluntary, and that participants implied consent by completing the survey. The parent completed both the CHQ-50 and the ADHD-IV survey (home version) and returned them in a self-addressed, stamped return envelope. After three weeks, if the surveys were not received by the study team, a member of the study team attempted to contact the parent by mail and/or by telephone.

Parents completed a questionnaire to determine whether a diagnosis and treatment of ADHD had been made and also surveys to assess the severity of inattention, hyperactivity and general health. Follow up postcards and phone calls were made to increase the survey response rate.

3.7 Scoring

The ADHD Rating Scale-IV is a validated instrument for assessing risk of ADHD in boys and girls aged 5-17. The scale is linked directly to DSM-IV diagnostic criteria for ADHD. The ADHD-IV rating scale has eighteen scale items which are based on the DSM-IV criteria. Inattention symptoms comprise the odd number items and the Hyperactive-Impulsive items are the even number items. Alternating questions reduce response bias. The answers use a 4 point Likert scale. If an item is not scored, then it is not included in the analysis. If more than 3 items are not scored, then the test is not valid. The tests results in three final scores: one for Inattention, one for Hyperactivity-Impulsivity, and one combined score, which is the total of the other two scores. Raw scores are converted to percentiles using a table.

The Child Health Questionnaire quality of life instrument has been validated and normed for children 5-to-18 years of age and measures 14 psychosocial and physical concepts. The CHQ Summary Scores combine results to derive an overall physical and psychosocial score and identifies key health conditions related to ADHD, such as attention problems, learning, and behavioral problems. The CHQ-50 has been validated in a population of diagnosed ADHD children.

3.8 Outcome Measures

The primary outcome measure was the parent reported diagnosis of ADHD and the ADHD-IV inattention score. There were two methods used for the classification of ADHD. The first method was a reported diagnosis of ADHD by the parent. Secondly, an ADHD-IV inattention score of $\geq$ 93 percentile was classified as ADHD based on the optimal cutoff scores reported for diagnosis of ADHD in the manual for the ADHD survey instrument (Anastopoulos, 1998). DHCA time and RFLP time was extracted from the medical records and neonates having DHCA and/or RFLP as the primary method of neuroprotection were compared based on ADHD classification.

3.9 Data Abstraction

Patient medical records were reviewed by the primary investigator to determine the method of cerebral protection and perioperative risk factors. These included: operative weight, age at time of first operation, known genetic syndromes, circulatory arrest time, regional low flow perfusion time, lowest hematocrit during surgery, and mean pCO_2 during cooling and period of time. Regional low flow perfusion time was measured from the time of distal aortic cross clamping with loss of the peripheral arterial pressure and ended with release of the aortic cross clamp and reinstitution of peripheral arterial blood pressure readings. Data was collected from the medical records for all children surveyed to determine whether the characteristics of the returned survey sample were similar to the characteristics of the total survey population.

3.10 Statistical Methodology

3.10.1 Sample Size and Power Analysis

Since the survey data was not normally distributed, non-parametric tests were included in the analysis. These included Mann-Whitney U, Spearman correlation, and ranked linear regression for the primary outcomes. The final study sample size depended on the ability to contact families.

During the 12-year time period, approximately 150 neonates had the Norwood operation for hypoplastic left heart syndrome, and another 40 neonates had aortic arch repair either primarily or as part of another cardiac procedure. Based on a 70% five-year survival rate, we estimated 140 children were alive and that 75% could be contacted (105 children). If there were 46 children in each group of cerebral protection DCHA vs. RLFP, then the Power for the study to detect a reduction the incidence of ADHD (primary outcome) from 50% to 10% would 80% at an alpha of 0.10.

With multiple linear regression, the rule of 10 was which specifies a minimum of 10 samples for each covariate for adequate statistical Power. This has been questioned by Green (1991) and Maxwell (2000), however the rule of 10s is still commonly used to determine Power in multiple regression studi

4.0 RESULTS

The results of this investigation are organized according to the three hypotheses. First, the survey response rate is reported and then the prevalence rate based on the study criteria for ADHD in this population is presented. The returned patient sample was compared to the demographics of all surveyed children with respect to year of surgery, type, and key surgical variables. Next, the ADHDIV and the CHQ-50 survey scores were compared to the results for children designated as ADHD by the study criteria. Correlations with the survey scores for the children designated as ADHD are then presented to demonstrate congruence with the survey responses. The domains for the CHQ-50 survey results are presented and the patterns of the significant domains for ADHD are reviewed with respect to the CHQ-50 ADHD validation study (Rentz , 2005).

In the following section, the outcome of ADHD is related to the surgical and perfusion variables that were changed during the time period under study. First, these changes in perfusion and surgical techniques are described according to the surgical years and the patterns of these changes are incorporated into the final analysis. The outcomes of both the study classification for ADHD (categorical variable), and the ADHD IV and CHQ-50 percentiles (continuous variables) are tested for associations with the surgical

variables (Hypothesis 2) and the perfusion variables (Hypothesis 3). Significant covariates related to the hypothesis are included in the final linear regression model with the ADHD-IV inattention score as the continuous outcome.

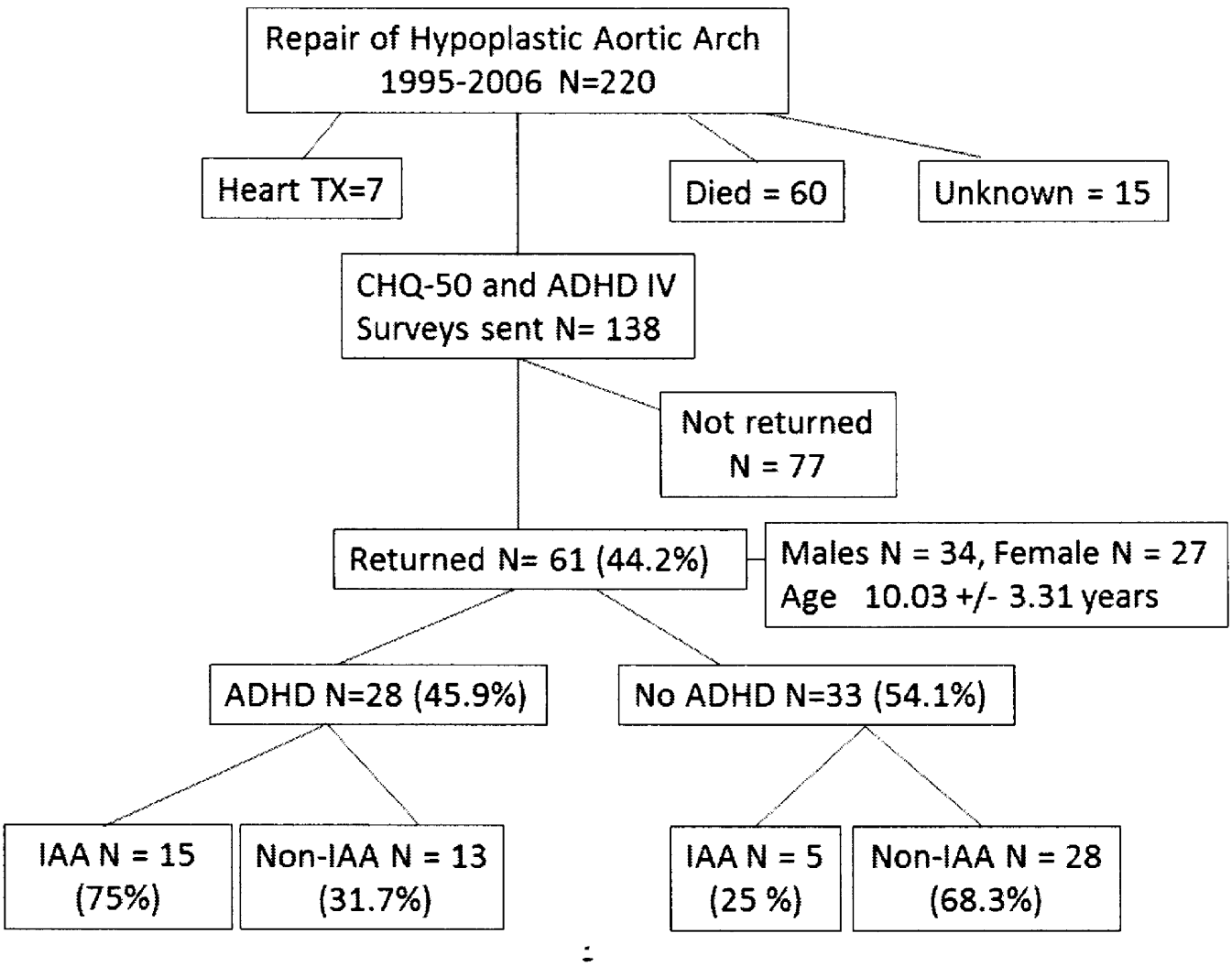
4.1 Hypothesis 1

To determine the prevalence of ADHD in a population of children following neonatal surgery with aortic arch repair.

4.1.1 Survey Response Rate -

Two hundred twenty children were identified that had circulatory arrest or selective cerebral perfusion between July 1, 1995, and June 30, 2006. Sixty children who had died since the date of surgery were identified. Fourteen children whose outcome were unknown and 7 heart transplant recipients were excluded. One hundred thirty eight were identified as still alive and had contact information in the Pediatric Heart Network of South Carolina database. Sixty one surveys were returned completed for a response rate of 44.2%. The medical records for cardiopulmonary bypass of 134 children were available for data abstraction. Missing data for cooling time, mean arterial pressure, cardiac index, DHCA time, RLFP time, lowest temperature, pCO_2, and hematocrit from 4 perfusion records were imputed from the mean for the 57 remaining children. The survey response rate is shown in Figure 2 below.

Figure 2. Survey Response Rate



4.1.2 ADHD as Determined by Parent Reporting and Surveys

The parents of 61 of the 138 children returned the surveys. Based on the returned surveys, 28 children had either a diagnosis of ADHD and/or ADHD IV inattention $\geq$ 93 percentile. Therefore, the prevalence rate of ADHD as classified in this study is 45.9 %. Twelve children (19.7%) had a medical diagnosis of ADHD, with 9 (14.8%) of them receiving medical treatment. Twenty five (41.0%) children met the criteria of the 93th percentile on the ADHD IV inattention score. Sixteen (26.2%) reported enrollment in Special Education classes. The results are summarized in Table 1 below.

Table 1. ADHD as Determined by Parent Reporting and Surveys

Total Surveys	(n=61)
Study ADHD (diagnosis and/or ADHD IV inattention $\geq$ 93 percentile)	45.8% (28)
Parent reported ADHD diagnosis	19.7% (12)
Parent reported ADHD diagnosis and treatment	14.8% (9)
ADHD IV Inattention $\geq$ 93 percentile	41.0% (25)
ADHD IV Inattention $\geq$ 93 percentile and ADHD Diagnosis	14.8% (9)
ADHD IV $\geq$ 93 percentile and ADHD diagnosis and treatment	9.8% (6)
Enrolled in Special Education classes	26.2% (16)

4.1.3 Comparison of Responders and Non-responders

With a response rate of less than 50 percent, it is important to determine if the responding population may be substantially different from non-responders. We compared the surgical characteristics of responders and non-responders in Table 2.

Table 2. Surgical Data from Responders and Non-Responders

Surgical Variable	Returned survey (n=61)	Not Returned Survey (n= 77)	p Value
Year of surgery	2000.1 ± 3.1	2001.4 ± 2.8	NS
Primary Diagnosis IAA	32.8%	30.8%	NS
Weight (kg)	3.17 ± 0.6	3.16 ± 0.6	NS
CPB time (min)	169.7 ± 35.9	176.5 ± 53.0	NS
Circulatory arrest (min)	22.8 ± 22.7	21.6 ± 21.2	NS
Regional low flow perfusion (min)	35.7 ± 37.3	34.8 ± 33.5	NS
Lowest temperature (^{0}C)	20.0 ± 1.8	19.1 ± 1.8	NS
Hematocrit during cooling (%)	25.6 ± 4.9	24.6 ± 6.0	NS
pCO2 during cooling (mm Hg)	29.3 + 11.6	29.7 + 11.7	NS

There was no significant difference in any of the primary surgical variables as shown in Table 2 between the completed and non-completed surveys – year of surgery. percentage of primary Interrupted Aortic Arch (IAA), weight at time of surgery, cardiopulmonary bypass time, DHCA time, RLFP time, lowest temperature before circulatory arrest, hematocrit before circulatory arrest, or pCO2 prior to circulatory arrest. The lack of differences observed in the comparison of responders and non-responders increases our confidence that the findings observed in this study are representative of all the survivors in the surgical cohort, and not simply due to selection bias.

4.1.4 ADHD-IV and CHQ-50 scores for children designated as ADHD vs. No ADHD

The primary outcome of interest in this study was the ADHD designation based on parents' report of their child's diagnosis of ADHD and/or the > 93 percentile on the ADHD-IV inattention scale. The relationship between this primary outcome variable (ADHD study classification) and the overall survey scores are provided in Table 3 below. The ADHD-IV scores and the CHQ-50 psychosocial scores for children classified as ADHD were compared to the children not classified as ADHD.

Table 3. ADHD-IV and ChQ-50 Composite Scores for Children ADHD and No ADHD

Median ADHD-IV and CHQ-50 Scores	ADHD (n=28)	No ADHD (n=33)	p Value
ADHD-IV Inattention	97	50	< .01
ADHD-IV Hyperactivity	95	25	< .01
ADHD-IV Combined	96.5	50	< .01
CHQ-50 Physical Score	46.2	50.1	NS
CHQ-50 Psychosocial Score	35.9	51.5	< .01

There was a significant difference for all three ADHD-IV scores and the CHQ-50 psychosocial score between the children designated as ADHD and No ADHD. These findings provide support for our assumption that parental report of ADHD diagnosis and/or ADHD IV inattention >93% is a valid proxy for the presence of this condition. Note the scores for CHQ-50 are in the opposite direction as the ADHD-IV percentiles. Validation studies for the CHQ-50 have shown that ADHD is associated with a psychosocial score below 37 (Rentz, 2005).

4.1.5 Correlation of ADHD-IV scores with CHQ-50 Psychosocial Score

The classification of ADHD for the purpose of this study is based on either a diagnosis and or a ≥93 percentile on the ADHD-IV inattention scale. The purpose of Table 4 is to show the association between the ADHD-IV inattention percentile and the ADHD-IV hyperactivity and combined scores and the CHQ-50 Psychosocial Score

Table 4. Correlation of ADHD-IV Inattention Scores with the CHQ-50 Psychosocial Scores

		ADHD-IV-inattention
ADHD-IV hyperactivity	Spearman Correlation	.788**
	Sig. (2-tailed)	.000
	N	61
ADHD-IV combined	Spearman Correlation	.904**
	Sig. (2-tailed)	.000
	N	61
CHQ-50 Psychosocial Score	Spearman Correlation	-.688**
	Sig. (2-tailed)	.000
	N	61

** Correlation is significant at the 0.01 level (2-tailed).

The ADHD-IV inattention scores were significantly associated with the ADHD-IV hyperactivity and combined scores and the CHQ-50 psychosocial scores ($p<.000$) for all returned surveys. This also supports the ADHD-IV inattention >93% scale as a valid proxy for the presence of this condition.

4.1.6 Results of the CHQ-50 scores for the Domains for ADHD and NO ADHD

The Child Health Questionnaire reports the child's health status in 10 different domains which include pain, discomfort, problems paying attention, and other behavioral issues. The survey also asks about the child's satisfaction with school and friendships and if there has been a change over time due to a change in their health status. Emotional concerns of parents are assessed as are the impacts of such concerns on the other children and the parent activities. The CHQ-50 domain scores are in Table 5.

Table 5. CHQ Domain Scores for ADHD and No ADHD

CHQ-50 Domains	ADHD (n=28) median	No ADHD (n=33) median	P Value
physical functioning	91.7	94.4	NS
role emotional behavior	66.6	100.0	< .05
role social physical	100.0	100.0	NS
body pain	90	100.0	NS
general behavior	52.9	76.6	< .05
mental health	70.0	85.0	< .05
self-esteem	70.8	87.5	< .05
general health perception	52.9	55.8	NS
parent impact emotional	45.8	75.0	< .05
parent impact time	58.3	75.0	< .05

There were significant differences between the children classified as ADHD vs. No ADHD in the CHQ-50 domains for role emotional behavior, general behavior, mental health, self-esteem, and both parent emotional impact and time The CHQ-50 domains that are significantly lower for ADHD children in this study are also the same domains reported in the CHQ-50 validation study in ADHD when compared to a normal population (Rentz, 2005). This is further evidence of the validity of the classification of ADHD used in our study.

4.2 Hypothesis 2

Regional low flow perfusion is associated with a lower rate of ADHD than DHCA when controlling for other significant surgical variables.

4.2.1 Time Related Surgical Changes 1995-2006

Since the children were not randomized to treatment in this study, there is bias introduced when a treatment is associated with time period. Not only was RLFP instituted in 2000, there were other concurrent changes related to perfusion practices that occurred around the same time. In order to document these specific changes, correlation with the year of surgery in shown in Table 6.

Table 6. Correlation between Year of Initial Surgical Procedure and Surgical Variables

		Year of Initial Surgical Procedure
Surgical weight (kg)	Spearman Correlation	-.009
	Sig. (2-tailed)	.452
	N	61
Surgical age (days)	Spearman Correlation	-.179
	Sig. (2-tailed)	.167
	N	61
CPB time (min)	Spearman Correlation	-.028
	Sig. (2-tailed)	.842
	N	61
Circulatory Arrest time (min)	Spearman Correlation	-.451**
	Sig. (2-tailed)	.01
	N	61
Regional low flow perfusion time (min)	Spearman Correlation	.672**
	Sig. (2-tailed)	.00
	N	61
Cooling time (min)	Spearman Correlation	.027
	Sig. (2-tailed)	.838
	N	61
Blood flow index during cooling ($l/min/m^2$)	Spearman Correlation	-.390**
	Sig. (2-tailed)	.002
	N	61
Hematocrit during cooling (%)	Spearman Correlation	.682**
	Sig. (2-tailed)	.000
	N	61
pCO_2 during cooling (mm Hg)	Spearman Correlation	.684**
	Sig. (2-tailed)	.000
	N	61

** Correlation is significant at the 0.01 level (2-tailed).

During the time period 1995-2006, there were significant changes in the following: circulatory arrest time, RLFP time, hematocrit during cooling, and pCO_2 during cooling. There was also a significant decrease in recorded blood flow rate.

4.2.2 DHCA and RLFP Times

Table 7 compares the DHCA times for patients when RLFP was used.

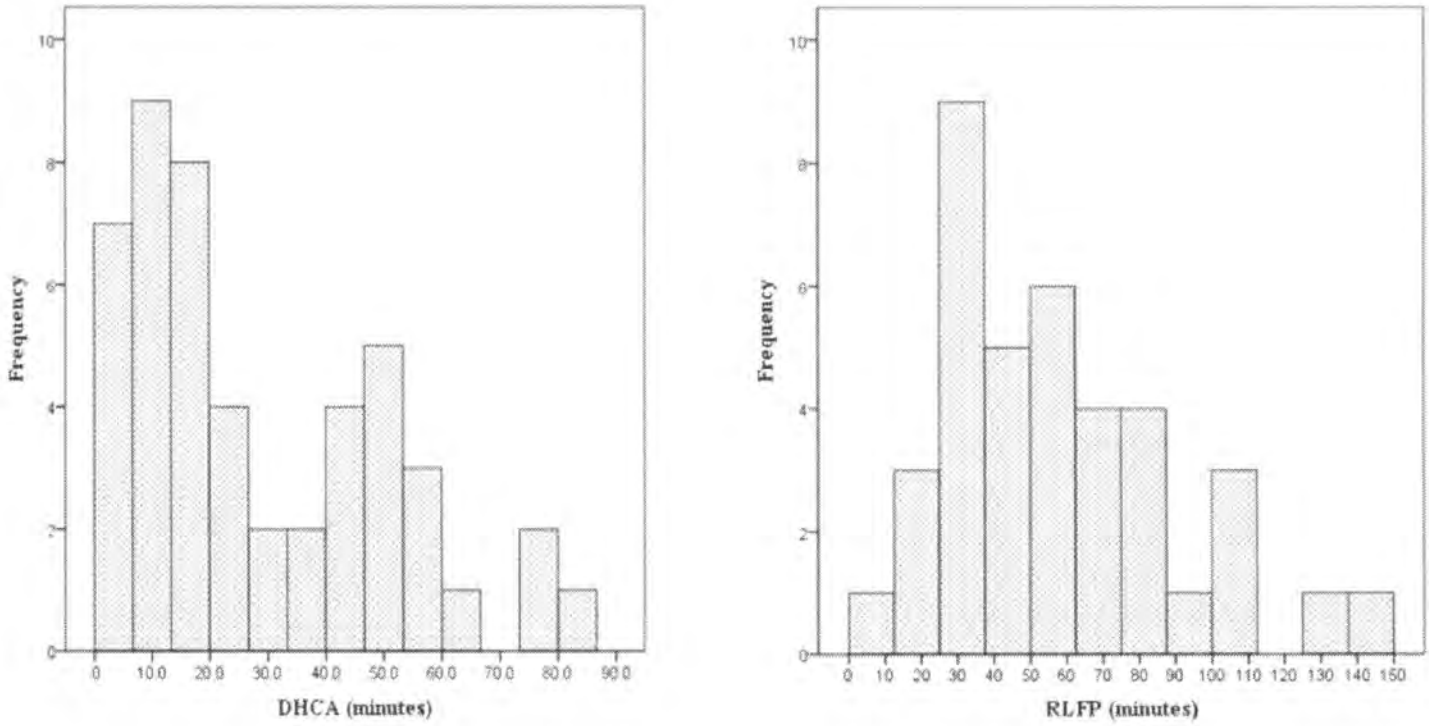
Table 7. DHCA Times for RLFP and No RLFP

	RLFP (min) (N = 38)	DHCA(min) with RLFP (N-38)	DHCA only (no RLFP) N=23
Mean	57.3	11.4	41.6
S.D.	31.4	14.7	21.1
Median	50	7	45
Range	131	75	81
Minimum	11	0	0
Maximum	142	75	81

DHCA time was significantly reduced when RLFP was used.

Figure 3. Distributions of DHCA and RLFP Times

The following graphs in Figure 3 show the DHCA and RLFP times for the 61 surveys that were returned.

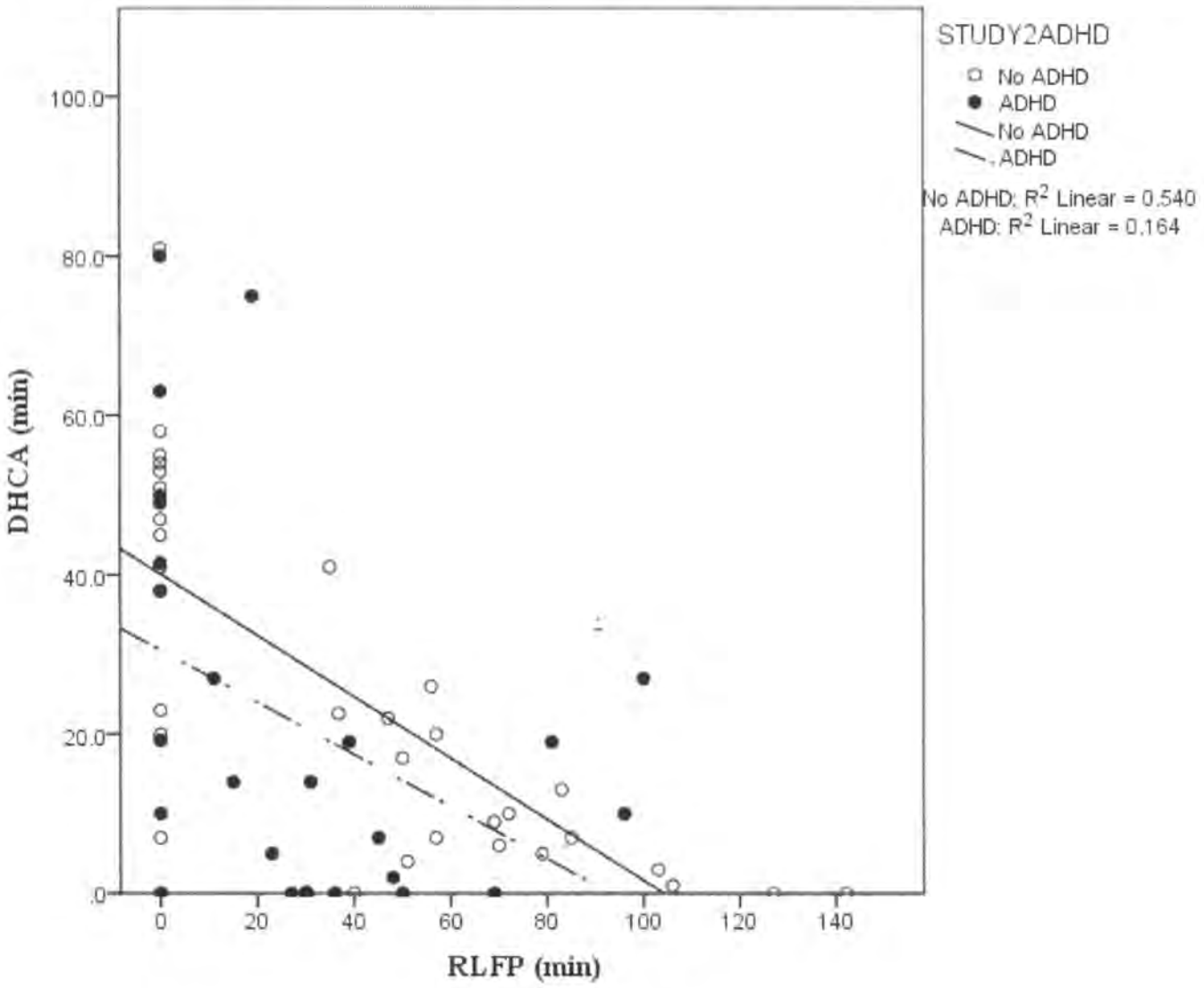


Both DHCA and RLFP times were not normally distributed (Kolmogorov-Smirnov p=.001 for DHCA and p=.000 for RLFP).

4.2.3 Correlation of DHCA and RLFP Times

Since _DHCA and RLFP were associated with the year of surgery, a Spearman correlation was completed between DHCA and RLFP in order to determine if RLFP was associated with a decrease in DHCA time. This is illustrated below in Figure 4.

Figure 4. DHCA vs. RLFP Times 1995-2006



Increase in RLFP time (min) is significantly correlated with a decrease in DHCA time (min) ($r = -.574$, $p = .00$). This negative association illustrates the effect of using RLFP, which significantly decreases circulatory arrest times. The children classified as ADHD are identified in the scatterplot as closed circles.

4.2.4 Surgical Variables for ADHD and No ADHD

The primary surgical variables were compared for the children classified as ADHD vs. no ADHD are shown in Table 8. Since IAA is associated with 22q11.1 syndrome, it was included in the analysis.

Table 8. Surgical Variables for ADHD and No ADHD

Variables	ADHD (n=28)	No ADHD (n=33)	P Value
Surgical weight (kg) (mean +/- SD)	3.3 + 0.6	3.1 + 0.6	NS
Surgical age (days) (mean +/- SD)	16.6 + 23.1	10.3 + 7.4	NS
Primary diagnosis IAA	53.5% (15)	15.2% (5)	< .01
Regional low flow perfusion (min) (median)	25	40	NS
Circulatory arrest time (min) (median)	14	20	NS

Children with a primary diagnosis of IAA had a significantly higher percentage of ADHD ($p < .01$). There was insufficient evidence to show a significant difference for any of the other surgical variables. The univariate analysis does not demonstrate a difference between DCHA and RLFP on the primary outcome.

4.3.5 Genetic Testing in IAA Patients

Table 9 shows the testing for q11.1 deletion syndrome (DiGeorge Syndrome).

Table 9. Testing for Primary Diagnosis of IAA

N=61 surveys	% tested	Tested positive FISH
DiGeorge testing	28 (45.9%)	6 (18.5%)
IAA positive (N=20)	11(55%)	4 (20%)

FISH testing was completed in 45.9% of the children and 18.5 % were positive. The percentage of positive results was increased in the children with a primary diagnosis of IAA.

4.2.6 Correlations of ADHD Surveys with Surgical Variables

Survey scores were evaluated using the Kolmogorov-Smirnov test for normality and the significance. A p value < .01 was found for ADHD-IV inattention, ADHD-IV hyperactivity, ADHD-IV combined and the CHQ-50 psychosocial score, therefore non-parametric statistics were used. The association between the scores for the surveys and the use of various intraoperative techniques was tested with Spearman correlations with the results shown in Table 10.

Table 10. Correlations of ADHD and CHQ-50 Surveys with Surgical Variables

		ADHD IV Inattention (Percentile)	ADHD IV Hyperactivity (Percentile)	ADHD IV Combined (Percentile)	CHQ-50 Psychosocial Score
Surgical Weight (kg)	Spearman Correlation	.146	.139	.145	-.245
	Sig. (2-tailed)	.26	.28	.26	.06
	N	61	61	61	61
Surgical Age (days)	Spearman Correlation	-.140	.082	-.061	.078
	Sig. (2-tailed)	.28	.53	.64	.55
	N	61	61	61	61
Circulatory Arrest Time (min)	Spearman Correlation	.067	-.107	-.077	.146
	Sig. (2-tailed)	.61	.41	.57	.26
	N	61	61	61	61
Regional Low Flow Perfusion Time (min)	Spearman Correlation	-.207	-.070	-.071	-.043
	Sig. (2-tailed)	.11	.59	.59	.75
	N	61	61	61	61

There was no independent significant association between any of the surgical variables and the ADHD-IV or CHQ-50 scores.

Table 11 compares the primary outcome of ADHD with DHCA time less than 20 minutes.

Table 11. Effect of circulatory Arrest Greater or Less Than 20 Minutes on ADHD

	N	ADHD	p Value
Circulatory arrest < 20 minutes	34	18 (52.9%)	.31 (NS)
Circulatory arrest ≥ 20 minutes	27	10 (37.0%)	

There insufficient evidence to show a difference in the primary outcome of ADHD independently with DHCA time greater or less than 20 minutes.

4.3.7 Ranked Linear Regression Model for ADHD

Since the distribution of the ADHD-IV inattention score is non-parametric, the ranks of the score were used as the primary outcome. The multiple linear regression model (Table 12) includes RLFP time, DHCA time, primary IAA, and an interaction variable for DHCA and RLFP.

Table 12. Ranked Linear Regression Model for ADHD

Parameter	Coefficient	p Value
Intercept	31.39	.000
RLFP	-0.190	0.03
DHCA	-0.050	0.69
IAA primary diagnosis	12.24	0.01
interaction DHCA*RLFP	0.01	0.03

R^2 =.22

This ranked linear regression model was significant (p=.02), showing that regional cerebral perfusion decreased the risk of ADHD, but that longer combined regional perfusion and circulatory arrest time (the interaction variable) increased the risk of ADHD.

Table 13. Using The Ranked Linear Regression Model to Predict ADHD-IV Scores

In order to validate the ranked linear regression model, it was tested using high and low ranked patients from the surveys with both no IAA and IAA as the primary diagnosis.

No IAA	Low Rank ADHD-IV Score	High Rank ADHD-IV Score
DHCA (min)	10	75
RCP (min)	72	19
RCP*DHCA	720	1425
RANK	**24.6**	**39.0**

IAA Primary Diagnosis	Low Rank ADHD-IV Score	High Rank ADHD-IV Score
DHCA (min)	22	27
RCP (min)	37	100
IAA	1	1
RCP*DHCA	814	2700
RANK	**44.1**	**52.1**

This model predicts that a low rank based on shorter DHCA and longer RLFP without a primary diagnosis of IAA reduces the risk of ADHD. Since the rate of ADHD-IV inattention score $\geq$ 93 percentile in this study is 41%, then a rank of 36 out of 61 is predictive of ADHD.

4.3 Hypothesis 3

Perfusion strategies of pH stat and increased hematocrit during cooling are associated with a lower rate of ADHD when controlling for other significant surgical variables.

Changes in pH management to increase cerebral blood flow occurred during the surgical time period of this study. Increased hematocrit was also introduced based on animal studies that showed improved cerebral metabolism and function after DHCA. In Table 14 perfusion related variables were tested for their association with the classification of ADHD in this study

4.3.1 Perfusion Variables for ADHD and No ADHD

Table 14. Perfusion Variables for ADHD and No ADHD

All values Mean +/- SD except where noted	ADHD (n=27)	No ADHD (n=33)	p value
Cardiopulmonary bypass (min)	166.4 ± 31.4	172.5 ± 40.67	NS
Lowest temperature (°C)	20.1 ± 2.3	19.9 ±3.7	NS
Hematocrit (%) during cooling (median)	25.5	26.0	NS
pCO_2 during cooling (median)	33.9	35.0	NS
Cooling time (min)	43.1 ± 15.3	38.5 ± 10.7	NS
Blood flow index (l/min/m^2)	2.39 ± 0.5	2.43 ± 0.5	NS
Mean arterial pressure (mm Hg)	34.6 ± 8.9	32.8 ± 7.7	NS

There was insufficient evidence to show a significant difference in any of the perfusion variables in the children classified as ADHD vs. No ADHD (Table 12).

4.3.2 Correlation of Perfusion Variables with ADHD

The purpose of Table 15 is to determine whether there is an association between perfusion variables the ADHD IV and CHQ-50 survey scores.

Table 15. Correlation of ADHD Surveys with Perfusion Variables

		ADHD-IV inattention (percentile)	ADHD-IV hyperactivity (percentile)	ADHD-IV combined (percentile)	CHQ-50 Psychosocial Score
Lowest temperature (^{0}C)	Spearman Correlation	-.177	-.096	-.168	.075
	Sig. (2-tailed)	.172	.462	.195	.567
	N	61	61	61	61
Hematocrit during cooling (%)	Spearman Correlation	-.088	.051	.027	-.154
	Sig. (2-tailed)	.499	..695	.834	.235
	N	61	61	61	61
pCO_2 during cooling (mm Hg)	Spearman Correlation	-.001	.114	.121	-.085
	Sig. (2-tailed)	.349	.992	.813	.592
	N	61	61	61	61
Cooling time (min)	Spearman Correlation	.093	.000	.032	-.008
	Sig. (2-tailed)	.476	.999	.807	.948
	N	61	61	61	61
Blood flow index during cooling (l/min/m^2)	Spearman Correlation	.026	-.016	-.036	.087
	Sig. (2-tailed)	.844	.903	.783	.504
	N	49	49	49	49
Mean arterial pressure (mm Hg)	Spearman Correlation	.065	.017	.033	.085
	Sig. (2-tailed)	.620	.895	.799	.514
	N	61	61	61	61

There is no significant association between any of the individual perfusion variables and the ADHD-IV and CHQ-50 scores.

4.4 Summary of Findings

4.4.1 Summary of Findings for Hypothesis 1

The rate of ADHD among those who undergo neonatal heart surgery is significantly increased compared to the norms for the general population on the ADHD IV rating scale and/or reported diagnosis of ADHD.

Twelve children (20%) had a diagnosis of ADHD, with 9 (15%) of them receiving medical treatment. Twenty five (41%) children met the criteria for ADHD classification by $\geq 93^{th}$ percentile on the ADHD IV inattention score. Based on the 61surveys returned, 28 children had either a diagnosis of ADHD and/or ADHD IV inattention $\geq$ 93 percentile. Therefore, the prevalence rate of ADHD as classified in this study is 45.6%, which is almost 10 times the normal population. Only 9/28 (32.1%) of the children classified as ADHD were receiving treatment for ADHD. CHQ-50 scores revealed a significant impact on their quality of life due to low behavioral health scores and also their parent's quality of life.

In order to validate the classification, the results of children classified as ADHD were compared to those not classified as ADHD. There was strong evidence for this classification by significant association with the other ADHD IV scores and also the pattern of the domain scores for the CHQ-50 surveys that are similar to validated ADHD CHQ-50 patterns.

4.4.2 Summary of Findings for Hypothesis 2

Regional low flow perfusion is associated with a lower rate of ADHD than the patients who underwent deep hypothermic circulatory arrest (DHCA) when controlling for other significant surgical variables.

Changes in the primary method of neuroprotection occurred during the surgical time period with a shift from DHCA to RLFP. Multivariate analysis using ranked linear regression identified that increased regional low flow perfusion (RLFP) time is significantly associated with a decrease in the incidence of ADHD ($p < .05$) when controlling for IAA as the primary diagnosis and the interaction of DHCA and RLFP ($R^2 = 0.22$). Due ot the interaction of DHCA and RFLP, longer combined regional perfusion and circulatory arrest time increased the risk of ADHD.

4.4.3 Summary of Findings for Hypothesis 3

Perfusion strategies of pH stat and increased hematocrit during cooling are associated with a lower rate of ADHD.

There was insufficient evidence to show a significant difference in any of the perfusion variables in the children classified as ADHD vs. no ADHD. There is no significant association between any of the individual perfusion variables and the ADHD IV and CHQ-50 scores.

5.0 DISCUSSION

ADHD is a serious problem following neonatal cardiac surgery. In this cross sectional study of children 5-16 years of age who underwent neonatal surgery with aortic arch repair, the proportion of patients classified as ADHD based on parent reported diagnosis and parent ADHD-IV surveys was 45.9%. ADHD IV inattention, hyperactivity and combined scores were significantly higher in the children classified as ADHD. This represents a tenfold increase in ADHD in this surgical cohort over the general pediatric population (Kessler, 2005). As a result of these behavioral problems, 26% of the parents reported that their children attend special education classes. The CHQ-50 scores reveal the significant health impact of ADHD on the children and their families. The CHQ-50 overall psychosocial score was significantly lower for children classified as ADHD, indicating an increase in behavioral problems. Children classified as ADHD had significantly lower scores in the CHQ-50 domains of role emotional behavior, role social behavior, general behavior, mental health, self-esteem, parent emotional impact and parent time.

The primary diagnosis of IAA in this surgical cohort was found to be a significant risk factor for ADHD in the multivariate model. Several key intraoperative variables in this surgical cohort were tested for their association with ADHD-IV scores. In the multivariate model, ADHD is significantly reduced when RLFP time is increased and DHCA is reduced. This improved outcome may be due to reduced ischemic time. There

was no association between the use of pH stat or increased hematocrit during cooling on the primary outcome of ADHD.

The first hypothesis for our study was that the rate of ADHD among those who undergo neonatal heart surgery is significantly increased compared to the norms for the general population based on the ADHD-IV rating scale and/or reported diagnosis of ADHD. This was supported by our data and the prevalence rate of 45.9% was established. The rate of ADHD in our study for non-IAA primary diagnosis children was 31.7% which is similar to a recent study in 5-10 year olds who underwent circulatory arrest before 45 days of age (Shillingford, 2008). The study by Shillingford used both parent and teacher ADHD-IV surveys. Parents identified 30% of the children as high risk for ADHD and teachers only 15%. In contrast to our study which included patients with q22.1 deletion syndrome, Shillingford excluded children with known genetic disorders, multiple congenital abnormalities, or evidence of end organ damage.

One reason that they suggested for the discrepancy between parent and teacher results was that teachers give lower scores because they are in an environment where behavior problems are prevalent, and therefore they may not notice the less severe problems. The authors state that using both parent and teacher surveys was conservative and may have underestimated the prevalence of ADHD. In our study 26.6% of the children were in special education classes and that is also higher than the 15% reported by Shillingford (2008). Earlier studies reported higher prevalence rates for ADHD. In a study by Mahle (2004), 67% of adolescents who had undergone surgery for HLHS had evidence of ADHD on neurological examination. After repair of total anomalous pulmonary venous return in the neonatal period,

neurological examination of school age children revealed inattention in 47% of the children (Kirshborn, 2002).

In patients with confirmed 22q11.1 deletion syndrome, the reported rate of ADHD is 42% (Gothelf, 2004). In our study the rate of ADHD in children diagnosed with IAA was 75%. There may be discrepancies in the reported rate of ADHD due to the methodology used for classification. Formal diagnosis of ADHD may be a function of health care access, and may not include all patients with symptoms. Therefore, using diagnosis of ADHD alone may underestimate the prevalence. Combined parent and teacher scores on ADHD rating scales yield a lower prevalence than parent scores alone. Examination by a neurologist in formal studies had the highest rate of identifying inattention and hyperactivity. The critical issue is that the prevalence of ADHD is significantly higher after the neonatal cardiac surgery than in the general population, and is significantly under diagnosed and treated. These abnormal behavioral patterns in this surgical population have been validated with rating scales of children's health such as the Basic Assessment System for Children (BASC) (Shillingford, 2008) and the CHQ-50 in the present study.

Participation in Special Education also confirms the increased behavioral problems in this population. Classification of ADHD in our study was based partially on the reported clinical diagnosis. Parents were questioned to determine whether their child had been diagnosed with ADHD and were receiving medication. Parent surveys revealed that a clinical diagnosis of ADHD was made in only 20% of the children, while 40% were classified as ADHD based on

the elevated ADHD-IV inattention scores. Although the specificity of parent only reported ADHD-IV scores is low, an ADHD-IV inattention score of 93% as a cutoff for diagnosis of ADHD has been validated in a clinical study (Anastopoulos, 1998). The CHQ-50 psychosocial score and the individual CHQ-50 domain scores in our study confirmed the classification of ADHD.

The impact on the parents of raising a child with ADHD was clearly seen in the CHQ-50 scores. Children classified as ADHD had significantly lower CHQ-50 scores for parent time and emotional involvement. Our findings are consistent with the daily challenges highlighted in "Safeguarding Precarious Survival: Parenting Children Who Have Life-Threatening Heart Disease" (Rempel, 2007). This study described the process of parenting a child with life threatening heart disease. Researchers examined the impact on the family, the management of home care, and the emotional stress and risk of death that remains present in their lives on a daily basis. Behaviors associated with ADHD increases the demands on parents, and extend health care concerns well into adolescence. Our study confirmed that the primary diagnosis of IAA as a significant predictor risk factor for ADHD. Interrupted aortic arch has a 40% association with velocardiofacial (22q11.1 deletion) syndrome which has a high rate of ADHD (Botto, 2003). This is related to changes in the basal ganglia and impairments of dopamine transmission (Momma, 2010). Our finding of an 80% rate of ADHD in children that tested FISH positive is consistent with this. Since the prevalence of genetic syndromes is greater in children undergoing heart surgery than the normal population, the incidence of ADHD in the neonatal surgical population will unfortunately always be higher than the normal population.

The second hypothesis that RFLP is associated with a lower rate of ADHD than DHCA when controlling for other significant surgical variables was supported by our findings. This is important because RLFP has been widely adopted without any evidence for improvement in long term outcomes. A randomized control trial comparing DHCA to RLFP was barely able to distinguish differences in short term outcomes (Goldberg, 2007), and did not address the incidence of ADHD. Because of our findings, increased circulatory arrest time is now confirmed as a risk factor for ADHD during this critical time of neurodevelopment. Reduction in cerebral blood flow during DHCA negatively affects cognitive function subsequently resulting in the development of a cognitive disorder (ADHD). Longer DHCA time has been associated with poorer neurodevelopmental outcomes (Forbess, 2002), Interruption of blood flow to the watershed areas of the striatum may be the primary mechanism for this injury. The striatum is perfused from the middle cerebral artery which branches into the lenticulostriate arteries and is extremely sensitive to ischemia and hypoxia (delZoppo, 2000). The striatal region has been shown to be highly susceptible to injury in animal models of shock (Hamann, 2002). Massive release of glutamate in the striatum activates dopaminergic receptors until cell death occurs (Yang, 2007). Both the striatum and the DMN are highly dependent on dopamine transmission and continuous blood supply. Regional low flow perfusion has shown to be critical in animal models to reduce cerebral injury (Straugh, 2003) (Dahlbacka, 2007) (Salazar 2009). Although not measured directly in this study, RFLP may provide continuous perfusion to the striatum and the developing neural networks which are necessary for DMN functioning.

The third hypothesis that perfusion strategies of pH stat and increased hematocrit during cooling are associated with a lower rate of ADHD was not supported by our data. Many simultaneous changes occurred in surgical and perfusion techniques in this surgical cohort between 1995 and 2006. In 2000, RLFP was instituted to reduce DHCA time. In 2002, pH stat blood gas strategy was implemented to improve cerebral blood flow during cooling. Increase in hematocrit prior to circulatory arrest was also introduced shortly thereafter due to new evidence of improved outcomes after DHCA. These last two changes were based on studies that demonstrated improved neurodevelopmental outcomes with pH stat and higher hematocrit (Kirshbom, 1996, Shin'oka 2006). Subsequent clinical studies supported the use of high hematocrit with evidence of increased Bayley PSI and MDI scores at one year of age. The first trial compared 20% to 30% hematocrit in children < 9 months of age undergoing heart surgery and demonstrated improved 1-year neurodevelopmental testing in the higher hematocrit group (Jonas, 2003). A subsequent comparison study of 25% vs. 35% hematocrit was completed which showed no benefit to the higher hematocrit of 35% (Newburger, 2008). Combined data from the previous two studies showed that Bayley PDI at 1 year of age was directly related to increasing hematocrit up to 23.5% (Wypij, 2008). During our study time period, the target hematocrit on CPB was increased and pH stat was instituted. Both were not shown to be independently associated with the primary outcome of ADHD. One reason for this result may be because our study was inadequately powered to detect a significant difference. Another possibility is because these techniques which are important for DHCA, do not affect the outcome after RFLP.

Marshall Jacobs wrote an invited commentary in 2007 that emphasized the importance of studying the physiological effects of RLFP just as DHCA was studied in the past. He suggested that we need to look at the impact of the specific technical details of blood flow rates, degree of hypothermia, hematocrit and pH stat during RLFP perfusion. Our study has addressed some of these factors on the long term impact of ADHD. Additional studies to determine the optimal strategies for RLFP will be very important in improving long term outcomes. Cerebral microdialysis is a new tool that is available to measure the cellular level changes that occur during RFLP and can used in animal studies to study the biochemical, vascular, cellular and functional effects of RLFP in the future. This new approach also requires assessment for its effect on ADHD.

5.1 Limitations

Sample Size

The present study is somewhat limited due to the response rate of 44.2.%. Sixty one parents out of 138 children who met the inclusion criteria returned the surveys. Since there is significant risk of selection bias based on the return rate of less than 50%, the key surgical variables on the medical record of all 138 children that were mailed surveys were included in the analysis and compared to the same variables in the returned survey group. The lack of differences observed in the comparison of responders and non-responders increases our confidence that the findings observed in this study are representative of all the survivors in the surgical cohort, and not simply due to selection bias.

Survey Methodology

The validity of the ADHD-IV survey is greatly improved with both parent and teacher reporting (Anastopoulos, 1998). Due to the number of school districts involved

with this sample and the requirement of the IRB for each school board approval, using teacher surveys was prohibitive. The best option was to use the parent-reported ADHD-IV inattention cutoff of 93% as the primary indicator for ADHD and correlate that with CHQ-50 psychosocial scores and the pattern of CHQ-50 domains that have been reported in the ADHD validation study (Rentz, 2005). However, it is possible that there may we may have misclassified some of the respondents in our study.

Treatment Time Periods

The institution of RLPF in 2000 introduces bias due to the time difference in treatment periods. Children that had DHCA as the primary method of neurological protection are older (10-17 years) while those that had RLFP (5-10 years) are significantly younger. In order to account for this, the rating scales are referenced to the general population of children based on age. The ADHD-IV percentile score is determined based on age and gender categories. The Child Health Questionnaire is normed for children 5-18 years of age.

Changes in pH management during cooling occurred during the study time period. The potential impact of this change was independently tested and there was insufficient evidence to show an association between pH stat with the primary outcome of ADHD. Increase in CPB hematocrit was also instituted during this time period. The potential impact of this change was tested independently. There was insufficient evidence to show an association between hematocrit and the primary outcome of ADHD.

In our study, the blood flow rate index was extrapolated from the perfusion record, and the decrease noted over the years may be a measurement issue rather than actual decrease in blood flow. In the middle of this surgical

study time period, ultrasonic blood flow meter technology was adopted, and the recording of the flowmeter was used rather than the arterial pump head display. The recorded flow meter reading did not include shunting in the perfusion circuit and would read lower than the arterial pump head display.

There was no significant correlation found between the year of surgery and the outcome of ADHD or the ADHD survey scores. This lack of correlation could be due to changes in survival rates and risk factors over the 12-year time period. One method to control for this may have been to use propensity scores. A propensity score is the probability of being in the treatment group. This probability is calculated by logistic regression using all the other covariates in the model and a dichotomous outcome variable. This probability of the propensity score includes all background covariates that are not included in the primary model. The use of the propensity scores requires larger populations in order to assure a sufficient number of matches. This study could be expanded in the future to a multi institutional study in order to increase the sample size to allow for propensity score matching.

Combined Treatments

Neonates that had RLFP had a median of 7 minutes of DHCA vs. 45 minutes in the group without RLFP. Increase in RLFP time was associated with a significant decrease in DHCA time. Based on the evidence in animal models and with neurodevelopmental testing, shorter DHCA times is associated with reduced neurological injury. In study by Visconti (2006), patients in the RLFP group had 23 min DHCA vs. 44 min DHCA in the non RLFP group. One of the criticisms of this study was that substantial DHCA in RLFP group may obscure the differences between the two

treatments. Neurological injury during DHCA is time related, and the risk of injury has been shown to increase exponentially (Treasure, 1983).

6.0 CONCLUSIONS

ADHD is a common disease in the neonatal cardiac surgical population and is related to both genetic predisposition and the methods of cerebral protection during neonatal cardiac surgery. The significance of our findings is that this is the first study to model long term outcome of ADHD in this high risk population and demonstrate that it can be reduced with the increased use of RFLP and an associated decrease in DHCA.

There was insufficient evidence to show that perfusion techniques of pH stat and increased hematocrit prior to DHCA were associated with a reduction in the incidence of ADHD. Further studies are needed to determine optimal methods for RLFP.

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