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**COGNITIVE AND PSYCHOMOTOR DEVELOPMENT AFTER
OPERATIVE TREATMENT OF HYPOPLASTIC LEFT HEART
SYNDROME USING DEEP HYPOTHERMIC
CIRCULATORY ARREST**

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I. ABSTRACT

OBJECTIVES: Children with hypoplastic left heart syndrome (HLHS) often demonstrate lower cognitive and visual-motor skills compared to healthy children. The study at hand tests this hypothesis and focuses on potential inherent or operative risk factors that affect the intellectual, psychomotor, behavioral and quality of life outcome in children who have undergone palliative surgical treatment for HLHS.

METHODS: School-aged children born with HLHS between January 1996 and December 1999 who were operatively treated at our Institute without the use of antegrade selective cerebral perfusion (ASCP) were invited to undergo psychological testing. All children had completed the three palliative surgical steps at the time of testing. Their intellectual and visual-motor abilities were evaluated using a battery of standardized tests. Parents completed questionnaires regarding behavioral development, quality of life and socioeconomic status. Patient history and details from each operation, hospital stay and follow-up examination were obtained from patient files and a HLHS computer database. A cohort of healthy children was tested in the same manner as the control group. All tests, questionnaires and patient data were compared and statistically analyzed for significant associations.

RESULTS: 22 children with HLHS (6.9 ± 1.4 years old) and 21 healthy control children (6.9 ± 1.5 years old) participated in the study. All parents in the study and control groups completed the questionnaires. The HLHS patients had an average combined intelligence quotient (IQ) score of 72.6 ± 17.4 and a visual-motor integration score of 73.5 ± 13.7 , whereas the control children scored a combined average of 106.3 ± 8.4 on the IQ test and 105.7 ± 9.1 on the visual-motor test. Children with HLHS scored significantly worse ($p \leq 0.001$) than the control children on all administered intellectual functioning tests. The two groups scored similarly on questionnaires of behavior and quality of life ($p > 0.05$). Cumulative and individual intraoperative exposure to deep hypothermic circulatory arrest (DHCA) significantly affected IQ outcome. The visual-motor integration (VMI) of tested patients was also associated with prolonged DHCA exposure during the Norwood Operation ($p < 0.001$) and cumulative DHCA time. A later operation date positively affected the intelligence quotient and visual-motor skills for all three operative steps.

The cumulative number of pre-, post- or intraoperative complications, including neurological complications, had a significant negative effect on intellectual and psychomotor development.

CONCLUSIONS: Children operatively treated for HLHS without ASCP at our Institute between January 1996 and January 2000 have lower scores on tests of intellect and psychomotor skills as determined by objective testing methods. However, subjective questionnaires regarding general behavior and quality of life indicate that these children are no different from healthy children. Etiological causes of cognitive deficiencies among test groups are multifactorial. Early operative correction at our Institute as well as the prolonged use of DHCA was associated with worse cognitive and visual-motor outcome. Other factors such as altered fetal circulation and cerebral development, genetic abnormalities or other disease-related characteristics could influence cognitive outcome and should be studied carefully in this population.

ABBREVIATIONS:

AS	Achievement Scale
ASCP	Antegrade Selective Cerebral Perfusion
CBCL	Child Behavior Checklist
CBF	Cerebral Blood Flow
CHD	Congenital Heart Disease
CPB	Cardiopulmonary Bypass
DHCA	Deep Hypothermic Circulatory Arrest
HLHS	Hypoplastic Left Heart Syndrome
K-ABC	Kaufmann Assessment Battery for Children
KINDL	Children Quality of Life-Questionnaire
MP	Mental Processing
QL	Quality of Life
SES	Socioeconomic Status
TCPC	Total Cavopulmonary Connection or Fontan operation
VABS	Vineland Adaptive Behavior Scale
VMI	Visual-Motor Integration

II. INTRODUCTION

Until 1980 when a description of the first operative treatment was published (Norwood 1980), hypoplastic left heart syndrome (HLHS) was known as a uniformly fatal heart condition. HLHS affects approximately one in 5000 newborns and is the most common cause of death in the first month of life (Fyler 1980, Marino 1998). Today, with staged surgical reconstruction or heart transplantation, cardiac function and survival rate among these patients has improved greatly and some children with HLHS are now reaching their early 20s. Because this population continues to grow in numbers and age, the focus of current research has shifted from life-saving surgical techniques to postoperative psychological and neurodevelopmental health.

Neurodevelopmental deficiencies among children with congenital heart disease (CHD) are well established and have been researched since the 1950s (Navratil 1955). Among HLHS patients treated with palliative surgery, behavioral, psychomotor, intellectual and neurological problems have been documented since 1995 (Rogers). A more detailed assessment of these problems as well as their causal associations (operative, congenital, physiological or psychosocial) have been the focus of research since this time. Examples of such associations include congenital central nervous system (CNS) abnormalities, chronic cyanosis, seizures, poor nutrition, excessive emotional stress and decreased physical endurance.

In this study, a patient cohort treated in the first operative era at our Institute (January 1996 –January 2000) was assessed at school age for their cognitive abilities, behavior and quality of life. This benchmark study was designed to help assess one aspect of the operative success of our HLHS patient collective and is the first in a series of psychomotor and cognitive projects at this Institute. This study is also, to our knowledge, the first among European pediatric cardiology institutions to analyze the cognitive outcome in children with HLHS. Determining the effects of operative treatment on the neurodevelopmental/psychomotor outcome of the HLHS population is of utmost importance for hospital caretakers and parents alike. It will give clinicians a broader understanding of this disease, its immediate and long-term consequences and may affect the way parents of future patients are counseled.

HLHS Anatomy and Surgical Treatment

Morphological characteristics of classic HLHS consist of an underdeveloped left ventricle with aortic atresia or stenosis and of mitral valve atresia or stenosis. Until its closure several days after birth, systemic blood is pumped from the right ventricle through the ductus arteriosus (Figure 1, Number 2) to the descending aorta and supplies the ascending and transverse aorta via retrograde perfusion. If left untreated, a decrease in pulmonary vascular resistance and closure of the ductus leads to circulatory collapse and death within the first week of life.

After pre- or postnatal diagnosis, parents are informed of the comfort care option or life-saving surgical treatment for their children. The three-step surgical treatment was first offered in 1996 at the Pediatric Cardiology Center in Kiel, Germany, which has since become one of the largest HLHS treatment locations in the nation. This Institute currently reports a one-year survival rate of 73.5% and a five-year survival of 68.4% (Furck 2010).

After birth, ductal closure is forestalled using prostaglandins, which maintains hemodynamic stability. The first operation or Norwood procedure is performed approximately one week after birth (Norwood 1980). During this procedure, the aorta is widened with a patch and then anastomosed to the right ventricle above the pulmonary valve. The main pulmonary trunk is then attached to the aorta, allowing the right ventricle to power the systemic blood circulation. An atrial septum defect (ASD) enabling unrestricted interatrial communication is established, and a Gore-Tex Blalock-Taussig shunt (BT shunt) is placed between the subclavian and pulmonary artery to supply pulmonary perfusion (Figure 2). To alleviate volume overload in the right ventricle and maintain adequate oxygen saturation by separating venous and arterial circulation as the child grows, the Hemi-Fontan and Fontan (or Total Cavopulmonary Connection, TCPC) operations are completed at this Institute on average at 5.9 and 25.9 months of age, respectively. These operations enable passive venous blood flow from the superior (Hemi-Fontan, Figure 3) and inferior (TCPC, Figure 4) vena cava directly into the pulmonary arteries (Bove 1998). The tunnel fenestration between the tunnel and left atrium is mostly closed approximately 1-2 years after the Fontan operation.

In order to create a motionless operating field, the movement of the heart and lungs must be temporarily suspended using cardiac support techniques such as cardiopulmonary bypass

(CPB) or deep hypothermic circulatory arrest (DHCA). CPB diverts the systemic and pulmonary blood flow from the heart and oxygenates and heparinizes the blood without disrupting cerebral perfusion. DHCA is necessary for aortic reconstruction primarily during the Norwood Operation. Before the severe neurological consequences of DHCA became known, it was frequently used during the Hemi-Fontan and Fontan operations. For this procedure, the blood flow to the carotid arteries must be interrupted. In order to reduce neuronal oxygen and nutrient requirements, the core body temperature is decreased to 18°C and the head is further cooled using ice.

Many neuroprotective surgical advances have improved the aforementioned techniques in past years. These include optimization of hematocrit circulation and heparin dosage during CPB, as well as the minimization of DHCA duration and the establishment of a safe cooling and total support time (de Plessis 1999). Additionally, a method of antegrade selective cerebral perfusion (ASCP) was implemented in 1996, which enables blood flow via the right carotid artery to the brain during DHCA (Asou, T 1996).

Previous Studies

Neurodevelopmental problems in the postoperative period are prominent in children with HLHS. Due to the multifactorial constitution of neurodevelopment, determining a straightforward etiological explanation in this cohort is highly unlikely. Studies of HLHS populations to date have investigated aberrations ranging from genetic mutations and *in utero* conditions to operative treatment and postoperative complications. A compilation of the most revealing studies is reviewed below.

Postoperative follow-up

Although dependent on the type of disorder, era of operative correction, underlying genetic makeup and socioeconomic status, children who have undergone surgical repair for complex cyanotic CHDs generally have lower scores on IQ tests, an increased incidence of learning disabilities, feeding problems and neurological, speech and language abnormalities compared to control children (Limperopoulos 2002, Wernovsky 2003, Delamater 2003, Forbess

2006). Many patients demonstrated emotional difficulties such as feelings of inferiority and anxiety as well as behavioral deviations including short attention spans and hyperactivity (Kramer 1989, Bass 2006).

In studies assessing multiple congenital heart diseases in children, HLHS subgroups notoriously scored worse on tests of neurological and psychological development. In a ten-year retrospective review, Wernovsky et al. (2003) stated that the cognitive outcome in children with simple cardiac lesions such as an atrial septum defect (ASD) is generally comparable to the normal population, whereas children with repaired, complex, cyanotic heart lesions exhibit cognitive deficiencies. Neurodevelopmental morbidity is common in children with functional single ventricles (FSV) and even more frequent in children with HLHS. As the surgical treatment of FSV bears similarity to that of HLHS (Fontan operation), patients with FSV constitute an important comparative population when examining neurodevelopment in HLHS patients.

Standard tests of cognitive and visual-motor abilities, neurodevelopment and behavior have been used in studies of infants and school-aged children with HLHS since 1995 (Rogers). Rogers et al. administered the first neurological assessment of 11 HLHS patients, born between September 1986 to August 1991, aged 38 ± 20 months, at different stages of palliative treatment. He found that 64% exhibited signs of major developmental disabilities and that mental retardation was more prevalent in children who had survived the Fontan operation. Furthermore, neurodevelopmental delays were associated with acquired microcephaly (89%), and 73% of all test subjects demonstrated this abnormality.

Kern et al. later assessed the IQ (Wechsler Test), visual-motor integration (Beery Test) and adaptive behavior (Vineland Adaptive Behavior Scale or VABS) of 14 HLHS patients (average age 4.4 years, born between 1990 and 1996) who had undergone the Hemi-Fontan operation. The median full scale IQ was 88 (normal = 100 ± 15) and 50% of children received scores over 85. Three of the four worst scoring patients demonstrated cerebral abnormalities such as ischemic injury and atrophy on cerebral imaging or EEG. Scores on the Beery test were below average (82 ± 12 , normal = 100 ± 15), and the children performed worst on the motor skills subset of the VABS. In this study, a negative correlation was found between circulatory arrest time during the Norwood operation (mean 56 minutes) and IQ score (Kern 1998).

In a study by Mahle et al. in 2000, parents of 115 school-aged children with HLHS described their children as being in good (34%) or excellent (45%) health and demonstrating average (42%) or above average (42%) academic performance. These children were born before 1992 and underwent, on average, 57.3 minutes of DHCA exposure during the Norwood operation and a total average of 134.3 minutes during all three operations. According to a standardized IQ test (WISC-III) given to 28 of these patients, the median full-scale IQ score was 86, and mental retardation (IQ < 70) was seen in 18% of patients. Language skills were significantly lower than in the reported normal population, 69.5% of the study group displayed symptoms of Attention Deficit and Hyperactive Disorder (ADHD), and gross motor abnormalities were found in 49.8% upon clinical examination by a pediatric neurologist. In this study, the occurrence of preoperative seizures predicted a lower IQ score.

Goldberg et al. (2000) published encouraging results showing an average Full Scale IQ Score (Wechsler) of 93.8 ± 7.3 in HLHS children operated between 1989-1996. A control group comprised of patients with a non-HLHS functional single ventricle lesion scored an average of 107.0 ± 7.0 . In the HLHS group, verbal scores were normal and only motor skills measured below average on the VABS. A behavioral questionnaire completed by the parents (CBCL) revealed no abnormalities. In this subgroup, low socioeconomic status, intraoperative seizures and the presence of circulatory arrest were significant risk factors for a lower IQ score.

Williams et al. (2000) examined the survival (Kaplan-Meier), developmental status (Ages and Stages Questionnaire) and quality of life (Infant/Toddler Child Health Questionnaire or Child Health Questionnaire Parent Format-28) of 106 children who were undergoing surgical repair of HLHS between 1990-1999. The one and five-year survival rate was 58% and 54%, respectively. Developmental delays were more notable in children after the first stage of surgical repair than after the second and third steps. At the time of evaluation, children had not yet reached any of the developmental milestones characteristic of that age group. The quality of life testing after second stage repair, however, revealed that children had greater physical capabilities compared to post-Norwood results although they still experienced discomfort, pain and poor general health. After stage three, children demonstrated significant behavioral problems and social limitations. They had lower self-esteem and global health. In this study, DHCA time (mean 51 minutes during Norwood procedure) significantly correlated with developmental delay,

quality of life and physical health problems. Developmental skills, communication and gross motor skills were inadequate in this cohort.

Twenty-six children treated for HLHS with heart transplantation listed between 1993 and 1998 showed results similar to children who received staged surgical repair (Ilke 2003). Median full scale IQ and psychomotor developmental index scores were 88 and 86.5, respectively, which is significantly lower than the population norm. DHCA duration during heart transplantation did not correlate with neurodevelopmental status. The DHCA time averaged 64.7 minutes and was not significantly different from DHCA exposure used for staged palliation during this operative era. The authors argue that non-operative parameters, such as genetic disposition, affect the neurodevelopmental outcome of this population more than surgical approach. However, this study found a significant negative correlation between neurodevelopmental outcome and the time spent on the transplant waiting list. Fatality rates of children on the waiting list approached 30% at some institutes.

Preoperative Variables and Cerebral Abnormalities

Whether treated with orthotopic cardiac transplantation or staged reconstructive surgery, HLHS patients were found to perform poorly on tests of neurodevelopment. Several studies have raised the suspicion of underlying genetic abnormalities or prenatal circulatory conditions, which may be partially responsible for these developmental delays. The following contains a description of congenital and acquired cerebral abnormalities diagnosed through autopsy or brain imaging in subjects with HLHS.

Genetic Abnormalities

In 1988, 83 autopsies on HLHS cadavers from spontaneous/induced abortions and early death were performed. The cadavers were examined for major genetic disorders and extracardiac conditions (Natowicz 1988). In 11% of cases, a cytogenetically-confirmed chromosomal abnormality such as Turner syndrome or Trisomy 18 was found. Five percent displayed Mendelian disorders (such as Apert or Holt-Oram syndrome) and 12% showed at least one major extracardiac anomaly. Overall, an underlying genetic disorder or major extracardiac abnormality

was detected in 28% of the cases. Some CNS and craniofacial abnormalities such as microcephaly (small brain size), micrencephaly (low brain weight), agenesis of the corpus callosum, cerebellar dysplasia or partial fusion of the cerebral hemispheres were observed. This study suggests that subtler genetic variations in HLHS subjects are likely to be found and emphasizes the need for further testing of survivors.

Cerebral Abnormalities

In 1990, Glauser et al. published 2 pathologic anatomical studies: the first dealt with congenital abnormalities, while the second described acquired brain lesions in newborns with HLHS. The same study cohort was examined in both studies. A postmortum, pathological diagnosis of HLHS was the only inclusion criteria for the study cohort. 28/41 infants in these studies were correctly diagnosed with HLHS in the premortum period and the average age of death was 31 days. The first study found that 29% of the examined patients had a major or minor congenital CNS anomaly, among these were microcephaly (36%), micrencephaly (27%) and an immature cortical mantle (21%). Genetic abnormalities were found in 17% of patients (Holt-Oram, Smith-Lemli-Optiz, VATER association, Trisomy 18 and Monosomy X) and extracardiac anomalies affected the lungs, kidneys and intestines. The second study found that 45% of the 41 examined cadavers demonstrated acquired neuropathologic brain lesions including combinations of intracranial hemorrhaging and hypoxic-ischemic lesions. Approximately half of the examined population underwent at least one palliative surgical procedure and a correlation existed between DHCA times exceeding 40 minutes and the presence of acquired neuropathology. Among the hypoxic-ischemic lesions, periventricular leukomalacia (PVL) was most common (55%). Significant correlations were found between the presence of hypoxic-ischemic cerebral damage/intracranial hemorrhage and decreased brain perfusion (defined as low diastolic blood pressure) and glucose-oxygen delivery (measured in the premortum period).

Brain imaging studies support some of the abovementioned findings in the HLHS survivor population. In Goldberg's (2000) neurodevelopmental report on 26 HLHS Fontan survivors, 52% of the participants were found to have a cerebral abnormality, 45% of which

were ischemic or infarct-related and 10% of which were congenital abnormalities (two subjects with an Arnold Chiari malformation and one child with a brainstem syrinx). In a study from 2006 with 22 test subjects, no congenital structural abnormalities appeared on preoperative MRIs although 23% of pre-Norwood MRIs demonstrated evidence of ischemic lesions (Dent 2006). Twenty percent of the patients had mild diffuse slowing on preoperative EEGs, and 2/22 patients showed regional cerebral oxygen saturation (rSo₂) below 45% for more than 60 minutes in the preoperative period. After the Norwood procedure, primarily using regional cerebral perfusion, 24% of the patients died and 73% of all surviving patients showed either new or aggravated lesions. Forty-seven percent of these included periventricular leukomalacia (PVL) and 53% were ischemic or hemorrhagic-ischemic lesions. Eighty-eight percent had normal postoperative EEGs whereas 68% withstood rSo₂ less than 45% for over 180 minutes. The results presented in this study provide strong evidence for the development of cerebral ischemic damage in neonates with HLHS, worsening after the Norwood operation.

Preoperative neuropathology is prevalent in patients with other types of cyanotic CHDs. In a study of infants with single and double-ventricle CHDs in which the use of CPB was employed for operative correction, structural cerebral abnormalities (open operculum) and ischemic lesions were identified using MRI in 17% and 25% of 21 subjects, respectively. In 67% of the subjects, new or aggravated lesions were detected postoperatively. Forty-two percent of these were periventricular leukomalacia. There was no correlation between the type of operation and the occurrence of neuropathology, however, 58% of 19 patients in the HLHS subpopulation had new or aggravated lesions after the Norwood procedure (Mahle 2002). In this study, over 50% term infants exhibited elevated brain lactate, which strongly correlated with the number of preoperative lesions (Mahle 2002). In a study by Hanrahan et al. (1999), high levels of brain lactate detected using proton spectroscopy correlated with lesions in the basal ganglia, which were representative of hypoxic-ischemic cerebral damage.

Periventricular Leukomalacia (PVL)

PVL describes the damage or apoptosis of white-matter in brain tissue along the ventricles. The infant brain is particularly susceptible to white-matter injury, and PVL is

commonly seen in premature babies. Cerebral hypoperfusion, hypoxia and intraventricular hemorrhage additionally increase the incidence of PVL. In 82 patients undergoing CPB for surgical repair of a CHD (40% of cases HLHS), postoperative PVL was identified using MRI in over 50% of patients, and it significantly correlated with diastolic hypotension and hypoxemia in the early postoperative period (Galli 2004). The majority of postoperative lesions resolved within six months following the operation, however, patients with periventricular white-matter injury appearing in MRI after neonatal surgery were more likely to develop subsequent ADHD, and they demonstrated developmental delay, perceptual impairments, mental retardation, visual-motor and visual-spatial deficits (Mahle 2002, Dent 2006, Galli 2004). Spontaneous recovery of PVL in the late postoperative period has been observed (Mahle 2002) and may reflect postoperative inflammation of the low, white-matter content of a neonatal brain.

A study of preoperative cerebral blood flow (CBF) using pulsed arterial spin-label perfusion MRI demonstrated low, and in some cases, drastically reduced CBF in neonates with complex congenital heart defects (Licht 2004). Preoperative cerebral hypoperfusion was associated with PVL in this study. The authors discussed that PVL and other preoperative features including microcephaly, increased white matter lactate and the persistence of an open opercula may be suggestive of chronic cerebral hypoperfusion, thus negatively affecting the brain before surgical intervention.

The Brain Sparing Phenomenon

Fetal echocardiography and pulsed Doppler has allowed for more accurate examination of *in utero* cardiac conditions. The brain sparing phenomenon, described as the compensatory redistribution of blood flow to enhance fetal cerebral perfusion, was originally found in cases of placental insufficiency (Woo 1987). This autoregulatory mechanism, which is measured by detecting a decreased cerebral vascular resistance index (RI) and cerebral-to-placental resistance ratio (CPR), has been demonstrated in children with some types of CHD (Donofrio 2003, Kaltman 2005). This was interpreted as an indicator of cerebral hypoxemia and/or nutrient deficiency that resulted from abnormal cardiac pump quality or substrate redistribution in the ventricle(s). In one study, the extent of brain sparing corresponded to head circumference;

fetuses weighing more than two kilograms and demonstrating a low CPR had smaller head circumferences compared to controls (Donofrio 2003). Brain sparing was most apparent in fetuses with hypoplastic left and right heart syndrome. On their date of birth (corrected for gestational age), newborns with HLHS had a smaller average head circumference ($33.27 \pm 1.88\text{cm}$) compared to the other study subpopulations and a disproportionately smaller average head circumference relative to birth weight (Rosenthal 1996). These results were interpreted as potential inadequacy of this compensatory cerebral blood flow in affected infants. Stunted intrauterine cerebral growth in these cases suggests that a single ventricle cannot effectively counteract cerebral substrate shortages.

Intraoperative Variables

Because CNS abnormalities and neurodevelopmental deficits in the postoperative period are evident in children with HLHS, intraoperative neuroprotection has become a crucial area of research. Cardiac support methods such as CPB and DHCA have been a primary focus of investigation and have been associated with many adverse effects. Causal factors may include the prolonged alteration of blood quality and nutrient value that occurs when blood is filtered through the circuits or the mechanical redistribution of cerebral blood flow. Similarly, pH, hematocrit and temperature management have been analyzed for their effects on neurological morbidity.

The numerous benefits and disadvantages of these supportive techniques have sparked much debate among scientists. While the treatment and survival of children with severe CHDs would certainly not have been possible without the implementation of CPB and DHCA, these cardiac supportive methods have primarily been held responsible for neurological deficits in the last 30 years of pediatric heart surgery. This debate has fueled research leading to a better understanding of the fundamental cellular mechanisms involved in cerebral injury and has aided in the attenuation and prevention of these conditions.

Deep Hypothermic Circulatory Arrest (DHCA)

Hypoxic-ischemic and hypoperfusion-induced brain injuries are common problems associated with prolonged intraoperative DHCA use in infants. Advances in this field have

focused on minimizing cerebral oxygen requirements and maximizing oxygen availability (Du Plessis 1999). Several studies have suggested “safe” duration periods, ranging from 39-65 minutes (Greeley 1991, Scallan 2004), in which the brain can compensate for nutrient and blood flow disruption. Other studies have proposed an even shorter DHCA exposure of 20 minutes, corresponding to the time in which the brain maintains aerobic activity. During anaerobic metabolism, the amount of cerebral lactate increased (Kimura 1994) and drastic depletion of ATP levels occurred (Kawata 1993). This was shown to cause ionic pump failure and intracellular calcium-induced neuronal injury (Siesjo 1989). These data support other studies demonstrating that the degree of brain injury and vascular resistance increased with the total time of DHCA exposure (Wells 1983, Rossi 1989). Although most of these studies were not performed in human subjects, they have provided abundant evidence for shorter “safe” DHCA duration times of 20-30 minutes. Implementing short periods of brain reperfusion after 20 minutes of DHCA was proposed in the early 70s and has since been supported by several authors (Barratt-Boyes 1971, Kimura 1998). These studies concluded that the brain can recover after exposure to short periods of DHCA but suffers considerable injury after a prolonged duration of DHCA-induced anaerobic metabolism.

Low-flow cardiopulmonary bypass (CPB)

At flow levels 35-50 mL/kg/min, cerebral perfusion is not compromised during CPB utilization (Newberger 1993, Mezrow 1994). After CPB, markers of hypoxic-ischemic and hypoperfusion-induced brain injury such as increased brain lactate and decreased ATP levels were not identified to the same degree as seen after DHCA (van der Linden 1999, Swain 1991). Low-flow support for 120 minutes in dogs (25mL/kg/min) caused as much neurological injury as 60 minutes of DHCA (Watanabe 1989). Although CPB has repeatedly been shown to result in fewer neurological complications than DHCA, significant sequelae such as microembolism, macroembolism, insufficient perfusion and inflammatory phenomena cannot be completely eliminated. Due to the greater size of the bypass circuit, a higher systemic inflammatory response is seen after CPB. The activation of coagulation and complement systems causes increased cytokine production, which leads to increased vascular resistance, capillary permeability and interstitial edema (McBride 1996).

DHCA versus CPB

Several of the aforementioned studies described negative correlations between DHCA/CPB support time and hospital mortality (Kern 1998) and between DHCA/CPB time and neurodevelopmental outcome in the HLHS population (Kern 1998, Goldberg 2000, Williams 2000). In a large neurological outcome study after complex CHD surgery, the **Boston Circulation Arrest Studies**, 171 patients with D-transposition of the great arteries were randomly assigned to a surgical treatment with primarily DHCA or CPB support (Newberger 1993, Bellinger 1995, Bellinger 1999, Wypig 2003). These children were followed up at one, four, eight and 12 years of age. Neonates in the DHCA group had a higher risk of clinical seizures, required longer for recovery of normal EEG brain activity and exhibited a greater release of cerebral creatine kinase in the first six hours after surgery (Newberger 1993). At one year of age, a longer DHCA time and intraoperative EEG seizures were associated with abnormalities seen on MRI brain scans, and were inversely related to psychomotor development index scores. Thirty-four percent of these 171 children had abnormal neurologic examinations compared to 0% of abnormalities as neonates. Clinical seizures and ictal EEG activity detected in the first 48 hours after surgery on infants were associated with an increased risk of neurological abnormalities at one year of age (Bellinger 1995). At four years of age, perioperative seizures were associated with a lower IQ score, and the DHCA group demonstrated worse outcomes on tests of motor and speech skills. At eight years, a DHCA threshold of 41 minutes was established, below which no general adverse effect on neurodevelopmental outcome was detected. Intellectual abilities, fine motor function and speech production scores were lower in children who received DHCA for longer than 41 minutes (Bellinger 1999). There was an association between DHCA duration exceeding 40 minutes and the incidence of EEG seizures in the postoperative period. The occurrence of postoperative EEG seizures was not predictive of a poor intellectual outcome in tests performed at one year of age in this study (Gaynor 2006).

CPB and DHCA both demonstrate inherent risks and side effects, yet the literature shows more consistent, adverse associations between DHCA duration and severe neurologic sequelae.

In recent years, however, it has been hypothesized that a substantial amount of cerebral injury occurs in the postoperative period and not during CPB/DHCA support. Toxic mediators, such as free radicals released during hypoxic or reperfusion injury, can damage neurons or cause apoptosis when the brain's postoperative energy requirements are highest (Ditsworth 2003). Postoperative conditions such as low cardiac output and increased cerebrovascular resistance amplified and/or caused cerebral hypoperfusion (Scallan 2004). This resulted in compromised neuronal protection and oxygen delivery to the brain (Oku 1994). After CPB management during the Norwood procedure, cerebral oxygen saturation decreased rapidly and remained at a notably lower level than somatic oxygen saturation levels, which suggests a localized increase in cerebral vascular resistance. These changes remained apparent throughout the early postoperative period and were associated with new or worsened ischemic injuries on brain MRI scans (Dent 2006). In another related study, patients with significantly lower systemic venous oxygen saturation levels in the period following the Norwood operation had abnormal cognitive and visual-motor test scores at four years of age (Hoffman 2005).

Synopsis of Previous Studies

Postoperative follow-up studies of cognitive function reveal that children with HLHS generally scored in the low-normal range and that approximately one in six children was mentally disabled (IQ score < 70) (Kern 1998). In one study, children scored a full-scale IQ average of 93.8, whereas visual-motor skills were below average and motor skills were generally weak (Goldberg 2000). Behavioral problems and evidence of hyperactivity were common test findings, and the children reached developmental milestones later than the normal population. The most significant factors correlating to IQ score were DHCA duration, seizures and low socioeconomic status (Rogers 1995, Kern 1998, Goldberg 2000, Williams 2000). In all studies, parents unanimously reported that their children exhibited normal behavior and academic performance.

Studies on **preoperative variables and cerebral abnormalities** showed that approximately 17% of HLHS children exhibited a genetic aberration and 12% had extracardiac anomalies. Microcephaly was seen in 73% of cases and ischemic cerebral lesions in 23% (Natowicz 1988). In general, preoperative CNS anomalies were found in 29% of children (Glauser 1990). Anywhere from 45% to 73% of patients were found to have new cerebral

lesions after the Norwood procedure. These lesions were primarily hemorrhagic or hypoxic-ischemic and correlated significantly to prolonged DHCA exposure. PVL was seen in approximately 51% of postoperative cases and was related to ADHD, developmental delays, mental retardation and visual-motor deficits later in life. Normal postoperative EEGs were seen in 88% of patients, although 68% demonstrated reduced regional cerebral O₂ perfusion (Natowicz 1988, Dent 2006). Brain sparing was found most commonly in fetuses with HLHS when compared to other CHDs (Donofrio 2003).

Prolonged use of DHCA and CPB during staged surgical repair in the **intraoperative period** was shown to negatively affect neurodevelopmental well-being, mortality and lead to abnormal cognitive and visual-motor scores in the HLHS population (Kern 1998, Goldberg 2000, Williams 2000). In a large study of children who underwent D-transposition of the great arteries, DHCA was associated with an increased risk of intraoperative seizures, a delayed return to normal EEG brain activity, MRI changes, abnormalities on neurological examination, lower IQ scores and worse motor and speech function. “Safe” DHCA durations ranged from 20 – 65 minutes, yet some authors suggested allowing periods of cerebral reperfusion every 20 minutes to maintain aerobic activity. CPB is not as commonly associated with hypoxic-ischemic brain injury as DHCA, but it is related to micro- and macroembolic complications (Boston Circulatory Arrest Studies).

The Study at Hand - Hypotheses

The numerous cognitive and psychological evaluations of children with CHDs, in particular HLHS, raised our interest in the outcome of the HLHS population after surgical treatment at our Institute: the Pediatric Heart Center at the University Hospital of Schleswig-Holstein in Kiel, Germany (UKSH). In accordance with previous studies, we hypothesized that these children would score lower than the normal population on tests of cognition and of psychological and developmental functioning (1). We expected intraoperative factors such as DHCA, especially during the Norwood operation, to have a considerable effect on tested outcomes compared to other pre- or postoperative variables (2). Finally, we predicted that surgical variables alone could not explain the neurodevelopmental deficits we expected to find in our study population (3). Because this study assessed the first cohort of infants with HLHS operated at our clinic (January 1996 - December 2000), we expected their outcomes to be worse

than infants operated during later operative eras because of subsequent progress of operative techniques and technology, including the introduction of ASCP. Colleagues are currently analyzing this hypothesis.

The Pediatric Heart Center in Kiel is one of the largest HLHS operative centers in Germany and is, to our knowledge, the first center in Europe to report on the neurodevelopmental outcome of HLHS patients. This is also the first study to consider the effects of a surgical era on cognitive test results. The data presented here provide the groundwork for upcoming neurodevelopmental studies at our Institute.

Equally important in modern cardiologic and operative management is the integration of special education and psychological care for our patients and their families. Comprehensive consideration of the effects of HLHS corrective staged surgery on a child's development will allow us to provide a more supportive environment for current and future patients and their families.

III. METHODS

All testing for this clinical trial was conducted from April 2005 – June 2006. Operation data and subsequent patient information of the study population were collected retrospectively. Correlations between these factors and cognitive results were analyzed in the fashion of an explorative study.

Study Group

All children operated at our Institute presenting with classic HLHS born between January 1996 and December 1999 were asked to participate in this study by mail. Cardiac anatomy consisting of mitral or aortic valve stenosis or atresia was classified as classic HLHS and any patients with HLHS-variation or other single functional ventricles were excluded from psychological testing as were patients with diagnosed genetic abnormalities. All patients underwent the Norwood Operation without antegrade selective cerebral perfusion (ASCP) during DHCA. The degree of neuroprotection and the psychomotor development of patients who received ASCP (introduced to our clinic in 2000) is currently being evaluated by colleagues. Cerebral diagnostic procedures such as CCT, cerebral MRI or ultrasound were performed at the discretion of the caring physician if clinically indicated.

Patient Records

Perinatal information and procedural details from each operation (Norwood, Hemi-Fontan and Fontan Operations) as well as from additional hospital stays were collected from our institute-specific HLHS Data Bank at our clinic and from the patients' archived health records. Height, weight and peripheral oxygen saturation values were collected on the day of testing from colleagues conducting research on the same study group (Möller 2009). These data were, in part, separately analyzed for correlation to the tested neurodevelopmental skills.

Correlations to Neurodevelopmental Outcome

Selected variables pertaining to the pre-, post- or intraoperative period of all three operative steps were statistically evaluated for their effect on neurodevelopmental outcome. The following variables were tested for each operative step: date of operation, peripheral oxygen

saturation, DHCA time, CPB time, and complications. The cumulative value of each of the latter three categories was also tested separately for statistical significance. From the pre-Norwood period, additional data were included such as the diameter of the ascending aorta, the anatomy of the aortic and mitral valves (stenotic or atretic), as well as the presence of a prenatal diagnosis. The effect of tunnel fenestration closure on test results was not analyzed in this study.

All adverse neurological events and non-neurological pre- and postoperative complications considered “severe” were included in the statistical analyses. These included shock and required use of inotropic medication, respiratory insufficiency and intubation, cardiopulmonary resuscitation, life-threatening arrhythmias (such as a third degree atrioventricular block), severe pericardial tamponade, necrotizing enterocolitis, closure of the Blalock-Taussig shunt and acute renal or liver failure (Table 1).

Operative and Clinical Methods

In the first days of life patients were administered prostaglandins to maintain patency of the ductus arteriosus as well as sodium nitroprusside for afterload reduction. A dose of methylprednisolone and antithrombin III was given four and two hours prior to surgery. Preoperative inotropic support was administered only to infants presenting in shock. During the postoperative period, sodium nitroprusside, enoximone and adrenaline were given for inotropic support.

The pH-stat method was used during cooling and bypass, and the alpha-stat method was used during rewarming. A low-flow strategy with 30 – 50% of cardiac output was employed while on bypass.

Intraoperatively, all patients received a modified BT-Shunt using DHCA. In this cohort, antegrade selective cerebral perfusion was not used during any operative step.

Control Group

A healthy child was matched to each member of our study group based on age (± 3 months) and sex. All children in the control group had been treated for a banal illness in the past at the Department of Pediatrics, UKSH in Kiel, Germany and were contacted by mail. A child was determined “healthy” if they did not suffer from a chronic or debilitating genetic, psychiatric

or physical illness. Their archived health records were reviewed and the parents were questioned by phone regarding their child's current health status. Any children with known cardiac or neurological illnesses or diagnosed learning difficulties were excluded from the control group.

A doctoral candidate (A.D.) and a UKSH pediatrician (A.K.F.) tested children in the study and control groups. For the patient cohort, all testing was performed in the morning at UKSH in a quiet, bright room. All testing for the control children was performed in the afternoon at the child's homes in quiet rooms. During this time, parents completed questionnaires regarding their child's behavior and quality of life. All completed test results were reviewed and evaluated by a child psychologist (C.O.M.) at the clinic and the parents were later informed of their child's performance.

Two project members were selected to conduct the psychological testing due to the large number of children initially evaluated. Both testers abided by the same standardized testing methods to uphold their reliability. The University Ethics Committee approved all methods of testing, questioning and study/control group selection before the commencement of this project and informed consent was obtained from all participating families.

Testing Materials

The Kaufman Assessment Battery for Children (K-ABC) and the Developmental Test of Visual-Motor Integration (VMI) were the standardized tests selected to most accurately evaluate the cognitive and psychomotor capabilities of the study and control groups. In addition, three standardized questionnaires: Child Behavior Checklist (CBCL), Children Quality of Life (KINDL), Socioeconomic Status (SES) and one non-standardized Daily Life Inquiry (DLI) were completed by the parents to evaluate their child's quality of life, behavioral development and to estimate the family's socioeconomic status.

The Kaufman Assessment Battery for Children (K-ABC)

Kaufman and Kaufman, 1983; Spreen and Strauss 1991

The K-ABC is divided into 15 subtests that evaluate intellectual functioning (or IQ) based on the *mental processing* (MP) and *achievement* (AS, achievement score) abilities of the test subject. This test is designed for children aged 2:6-12:6, and is especially useful for

examining younger children and children with suspected learning disabilities. Fifteen game-oriented tasks such as memorizing, math games, puzzles and riddles assess the subject's intellect over a period of 30-90 minutes. Due to its extensive assessment of nonverbal ability, the K-ABC is also helpful for subjects with communication handicaps. Five of the subtests assess the *achievement* or the subject's learned, factual knowledge and skills, such as reading or identifying famous people. The remaining 10 subtests determine the *mental processing* or problem-solving abilities in new situations by ordering, organizing and analyzing information. Based on the neuropsychological theory of bi-hemispheric brain function, the mental processing subtests are dichotomized into sequential (three subtests) and simultaneous (seven subtests) processing (Kandel 2000). This enables one to more specifically categorize intellect in test subjects and may help isolate the anatomical localization responsible for certain abilities or deficits. The K-ABC, in addition to the Wechsler Scale, is the most frequently used test of intellectual development for children and is shown to be representative of school performance. Listed below are the 15 subtests as well as the intellectual scale and age range for which they are used:

- 1) Magic Window (Mental Processing-Simultaneous; Age range: 2:6-4:11)
- 2) Face Recognition (Mental Processing-Simultaneous; Age range: 2:6-4:11)
- 3) Hand Movements (Mental Processing-Sequential; Age range: all)
- 4) Gestalt Closure (Mental Processing-Simultaneous; Age range: all)
- 5) Number Recall (Mental Processing-Sequential; Age range: all)
- 6) Triangles (Mental Processing-Simultaneous; Age range: 4:0-12:6)
- 7) Word Order (Mental Processing-Sequential; Age range: 4:0-12:6)
- 8) Matrix Analogies (Mental Processing-Simultaneous; Age range: 5:0-12:6)
- 9) Spatial Memory (Mental Processing-Simultaneous; Age range: 5:0-12:6)
- 10) Photo Series (Mental Processing-Simultaneous; Age range: 6:0-12:6)
- 11) Expressive Vocabulary (Achievement; Age range: 2:6-4:11)
- 12) Faces and Places (Achievement; Age range: all)
- 13) Arithmetic (Achievement; Age range: 3:0-12:6)
- 14) Riddles (Achievement; Age range: 3:0-12:6)
- 15) Reading/Understanding (Achievement; Age range: 7:0-12:6)

The standard score on the achievement and mental processing sections of the test is 100 ± 15 . The combined AS and MP scores are referred to as "IQ". An IQ score under 70 points is classified as mentally disabled and a score between 70 – 85 is labeled as a learning disability.

Developmental Test of Visual-Motor Integration, Beery Test (VMI)

Beery 1967

The Beery Test is an assessment of visual-motor integration skills, in which test subjects copy 24 geometrical drawings as accurately as possible. The shapes increase in difficulty (from lines and circles to 3-dimensional boxes and rings) and the test subjects are awarded points depending on the precision of their drawings. The lengthy form of the VMI (used in this study) is devised for children aged 3-18 and is best suited for preschool and elementary-aged children (ages 4-9). Depending on the child's age, skills and concentration abilities, the test lasts approximately 15 to 30 minutes.

The VMI was originally designed to detect visual-motor problems in younger children but is currently used as a predictor of school performance, arithmetic and reasoning skills, and identifies some types of cognitive disabilities (Colarusso 1980). Due to the universality of the geometric forms, gender, culture, socioeconomic status and race do not significantly influence test results. The standard test score is 100 ± 15 .

Child Behavior Checklist (CBCL/4-18)

Achenbach, T.M. 1991

The Child Behavior Checklist is designed for children between 4-18 years of age and is a questionnaire which provides a standardized description of a child's behavior. The parent or guardian completes this two-part checklist regarding the subject's activities, school performance and social relations (Part 1) as well as 120 items concerning their behavioral/emotional patterns and physical well-being (Part 2).

Only Part 2 was statistically analyzed in this study. This questionnaire has been used internationally since the 1980s for purposes of analyzing child and adolescent mental health. Behavioral abnormalities are grouped into 8 different cross-informant syndromes or subgroups, which fall into two major categories: introversion and extroversion (or Internalizing and Externalizing Problems, Table 2). The total score (CBCLt) is an overall assessment of the child's behavior. All scores depend on the child's age, sex and results of the general population. Results are expressed in T-values or percentiles. The population T-value mean is 50 ± 10 and behavioral/emotional problems are scored as existent (>70) or borderline existent (65-70).

Children Quality of Life - Questionnaire (KINDL, Proxy-version)

Ravens-Sieberer & Bullinger, 1998

Health-related quality of life was assessed using a questionnaire completed by the parents or guardians of our test subjects. The Kiddy-KINDL is used for healthy or ill children between the ages of 4-7 and the Kid-KINDL for ages 8-16. By determining how often a child exhibited certain emotions or behavior, such as crying or laughing, a general life quality score and six subscores were obtained. This questionnaire has an additional “illness” module for specific life-quality changes surrounding an acute or chronic ailment. The KINDL elements of life quality are: somatic and psychological well-being, self-worth, family, friends, school and an overall score. This questionnaire enables clinicians to identify children or adolescents with potential mental health problems or to quantify the effects of a rehabilitative therapy.

Socioeconomic Status (SES)

Winkler, J. 1998

The Scientific Institute of German Doctors (Das Wissenschaftliche Institut der Ärzte Deutschlands, WIAD) established a questionnaire to determine the socioeconomic status of German residents. The SES score is determined based on the level of completed education, professional occupation and salary of the parents or guardians of our test subjects. Each level or category is awarded points and the higher amount of total points represents a higher socioeconomic class (lower class: score 3-8; middle class: 9-14; upper class: 15-21). Statistical analyses were performed using social class.

Daily Life Inquiry (DLI)

Parents or guardians answered several questions regarding their child’s schooling, eating habits, medications and time spent watching television or playing video games. The parents of the children in the study group answered additional questions concerning the time/place of the HLHS diagnosis and the professional advice received at the time. These data were not included in the statistical analysis of this study.

Statistical Analysis

All collected data were processed with SPSS Version 13.0 (SPSS, Inc, Chicago, Illinois, USA). Continuous nonparametric data were evaluated for correlation significance using Spearman's correlation coefficient. Categorical data were analyzed using the Kruskal-Wallis test. Test results from the patient and study cohort were compared using the Mann-Whitney U-Test. All correlations with a p-value ≤ 0.05 were considered significant. Multiple variable comparisons (alpha adjustments) were not performed in this study.

IV. RESULTS

Study Group Composition:

81 children with HLHS who were born between 1996-2001 and had undergone cardiac reconstruction were followed up at UKSH. From this cohort, 28 patients died, four had HLHS-variant anatomy and the remaining children were invited for testing at our clinic. 45 of the possible 49 families responded to our invitation; two patients chose not to participate in our study and two were lost to follow-up. Nineteen of these children received ASCP and 26 did not. The 26 non-ASCP patients are reviewed in this study and all were born between January 1996 and December 1999. All but two of these children underwent all three palliative operations at UKSH. One child received the final two palliative steps at UKSH. Another child received only the Fontan operation at UKSH. Due to recurrent pleural effusions, one child received a Take-Down Operation 2.5 years after the Fontan Operation. Four patients were unable to be tested due to advanced stages of mental disability (three males, one female).

Demographics:

At the time of testing, the HLHS patients and control children averaged 6.9 ± 1.4 years and 6.9 ± 1.5 years of age, respectively. A total of 22 study patients (14 males, 8 females) and 21 control children (13 males, 8 females) were tested in intellectual functioning. The families in the HLHS and control groups scored an average of 13.52 and 16.50 points, respectively, on the socioeconomic status (SES) questionnaire placing the HLHS group in the upper middle class and the control group in the lower upper class. This socioeconomic index demonstrated statistical significance ($p = 0.027$), whereas the social class (lower, middle and upper class) did not differ among the study and control group (Chi-square test significance 0.249).

Postoperative Results, Test Battery

Tests of Intellectual Function

The doctoral candidate administered 70% of the intellectual functioning tests and the UKSH pediatrician completed the remaining 30%. There was no statistical difference among their results ($p > 0.388$).

K-ABC

The HLHS patients who completed the IQ test battery scored, on average, 74.4 ± 17.0 IQ on the mental processing scale (MP), which was 32.1 points less than the control group. Similarly, the score for the HLHS patients on the achievement scale (AS) was 70.7 ± 17.8 IQ or 35.2 points less than the control group (Table 3). Fifty-nine percent of the HLHS patients scored less than 70 IQ points on the achievement scale, 18% between both 70-85 and 85-100 points and only one child (4%) scored over 100 points. Forty-five percent of the study group scored less than 70 IQ points on the mental processing scale, 32% between 70-85, 9% between 85-100 and three children (13%) scored over 100 points. In the control group, 29% scored between 85-100 and 71% over 100. All K-ABC scales including sequential and simultaneous mental processing as well as the nonverbal subgroups showed significantly lower scores ($p < 0.001$) for the HLHS patients (standard score: 100 ± 15 ; Table 3, 4; Figure 5,6).

VMI

Similar to the IQ test battery, the Visual-Motor Integration scores from the HLHS group were lower than the control group ($p < 0.001$; Table 3, 4). The HLHS group scored on average 73.5 ± 13.7 and the control group 105.7 ± 9.1 (standard score: 100 ± 15 ; Figure 7).

Parental Questionnaires

CBCL

In contrast to the intellectual functioning tests, the behavioral questionnaire scores completed by the parents were not statistically different between the HLHS and control group. The total (CBCLt) and externalizing score (CBCLext) for the control group was 56.0 ± 8.1 and 54.7 ± 8.5 , respectively and 61.6 ± 10.0 and 58.4 ± 9.5 , respectively for the HLHS group (Population average T-score: 50 ± 10 , clinical behavior problems > 65). The internalizing score (CBCLint) for the control group was 55.1 ± 7.1 and 56.7 ± 8.7 for the HLHS group. The behavioral scores show that both cohorts did not exhibit behavioral abnormalities. There was no statistically significant difference among them, although the HLHS group scored slightly higher than the controls ($p = 0.054$, Table 3, 4; Figure 8).

Quality of Life (KINDL)

No statistical difference was seen between the HLHS and control group on the overall Quality of Life questionnaire (KINDL). The HLHS group scored, on average, 78.0 ± 10.1 and the study group 80.3 ± 5.2 (standard score 100 ± 15 ; $p = 0.619$, Table 3,4; Figure 9).

Preoperative Results

A consistent negative correlation was seen between the **diameter of the ascending aorta**, measured using two-dimensional echocardiography, and the intellectual, and visual-motor outcome (MP: $p = 0.013$; AS: $p = 0.016$; VMI: $p = 0.017$, Table 6a and b, Figure 10). A strong negative trend was seen between this variable and behavioral outcome (CBCLt: $p = 0.054$). On average, the ascending aorta at birth was 3.82 mm wide. The status of the **mitral and aortic valves** at birth (i.e. atretic, stenotic) did not affect neurodevelopment. The number of **total complications** per subject occurring before the Norwood Operation, such as multiorgan failure, cardiogenic shock or neurological problems also demonstrated a significant negative effect on the intelligence quotient (MP: $p = 0.047$ and AS: $p = 0.014$). A total of 8/22 patients (36%) had severe preoperative complications (Figure 14) including various forms of shock (13%), necrotizing enterocolitis (4.5%), liver (23%) and renal failure (27%). There were no neurological complications, such as seizures, recorded in the preoperative period. The **peripheral O₂ saturation** or a **prenatal diagnosis** of the child's heart condition had no effect on the intellectual or behavioral test outcome.

In the study group, the mean head circumference, body weight and height (34.7 ± 1.6 cm; 3276 ± 654 g; 51.5 ± 3.0 cm, respectively) as well as the 1,5 and 10 minute APGAR scores were all within the normal range. Two mothers (9%) had abnormal pregnancies; none of which belonged to the group of four mothers that were alerted to their child's syndrome in the prenatal period (ultrasound diagnosis).

Operative Results

Norwood Operation

Strong negative correlations were found between the **DHCA** duration during the Norwood operation and the mental processing (MP: $p \leq 0.005$, $r = -0.620$) and achievement (AS: $p = 0.025$, $r = -0.432$, Table 6a and b, Figure 11) IQ scores. A positive correlation was noted between DHCA time and CBCLt ($p = 0.001$, $r = 0.628$). There was a strong negative trend between DHCA time and the Visual-Motor Integration (VMI: $p = 0.052$, $r = -0.365$). DHCA duration averaged 63.6 ± 15.4 minutes and ranged from 38-102 minutes (Table 5). Children exposed to more than 56 minutes of DHCA scored significantly worse on the MP scale than those who underwent 56 minutes or less ($p = 0.025$). Average MP scores were 86.7 when exposed to 56 minutes or less of DHCA and 68.7 after a longer exposure (Table 7, Figure 13). Prolonged **CPB** exposure correlated positively with mental processing and visual-motor skills (average duration 82 ± 55.5 min; MP: $p = 0.036$, $r = 0.412$; VMI: $p = 0.039$, $r = 0.403$) and negatively with behavior problems (Table 5, 6a and b, $p = 0.030$, $r = -0.428$).

A later **operation date** (ranging from January 1996 to January 2000) correlated positively with higher MP and AS scores ($p = 0.005$ and $p = 0.024$, respectively, Table 6a and b, Figure 12).

The number of **complications** per subject after the Norwood operation negatively correlated with MP and VMI outcome (Table 6a and b, $p = 0.029$ and $p = 0.040$, respectively, Figure 15) but not with AS ($p = 0.157$). After the Norwood operation, 15/19 (79%) patients suffered severe complications. These included severe cardiac arrhythmias 9/19 (47%), renal failure 3/19 (16%), BT shunt problems 5/19 (26%), seizures 6/19 (31%) and cardiopulmonary resuscitation (2/19 or 10%). Seven children suffered only one of these complications and eight suffered two or more complications. Postoperative data were missing from three children.

Preoperative peripheral oxygen saturation averaged $86.6 \pm 7.4\%$ and was not found to significantly correlate with test results (Table 5, 6a and b).

Hemi-Fontan Operation

Similar to the Norwood procedure, DHCA time and the date of operation correlated with neurodevelopmental outcome. **DHCA** duration was significantly associated with MP and Quality

of Life (Table 5, 6, $p = 0.028$, $r = -0.432$ and $p = 0.012$, $r = 0.544$, respectively) but not AS or VMI scores. All but one child operated at UKSH between July 1996 and July 2000 underwent DHCA during the Hemi-Fontan operation. DHCA lasted, on average, 32.0 ± 20.8 minutes and ranged from 5-73 minutes. CPB time averaged 112.6 ± 31.7 minutes, ranged from 53-152 minutes and was positively, significantly associated with MP, AS and tended towards significance in Quality of Life scores ($p = 0.006$, $p = 0.021$ and $p = 0.058$, respectively). There was a positive correlation between the **date of operation** and MP ($p = 0.009$) and Quality of Life ($p = 0.006$). There was a strong positive trend between the date of operation and VMI score ($p = 0.051$). The **total number of complications** per subject did not significantly correlate to test results. Fewer complications were recorded after the Hemi-Fontan operation compared to the Norwood postoperative period: 10/22 (45%) children suffered one severe complication and only one child suffered two complications. Complications included severe cardiac arrhythmias (9/22 children or 41%), neurological complications (2/22 or 9%) and one child underwent cardiopulmonary resuscitation. No clinical seizures were noted after the Hemi-Fontan operation. **Preoperative peripheral oxygen saturation** averaged $75.5 \pm 1.9\%$ and was not found to significantly correlate with test results.

Although not statistically analyzed, the average weight of the study group was lower at the Hemi-Fontan operation than at any other time. 13/22 (60%) patients fell below the 5th percentile on the weight-for-age percentile curve. In fact, only one child's body weight was above the 50th percentile. Similarly, the head circumference of 7/22 (32%) patients fell below the 5th percentile. Height was widely distributed from below the 5th to 90th percentile and was, on average, between the 25th and 50th percentile.

Fontan Operation

In the final operative step, **DHCA** presence (MP: $p = 0.014$, AS: $p = 0.044$) and duration (Table 5, 6, MS: $p = 0.009$, AS: $p = 0.036$) was significantly associated with the intelligence quotient. In this step, DHCA was used on only 5/22 (22%) patients. These five patients underwent, on average, 44 minutes of DHCA exposure ranging from 35 to 60 minutes. The DHCA duration of these 5 patients alone did not significantly correlate with neurodevelopment ($p = 0.411$).

During the Fontan operation, there was no effect of **CPB** time on neurodevelopmental outcome, and CPB support averaged 95.6 ± 37.3 minutes and ranged from 50 – 232 minutes. The **date** on which the operation was performed (March 1997 – June 2003) had a highly significant effect on neurodevelopmental outcome (MP: $p = 0.000$, AS: $p = 0.004$, VMI: $p = 0.005$). There was no significant correlation between the total number of **adverse events** per subject and intellectual or behavioral outcome for the Fontan operation. Severe arrhythmias were the only recorded adverse event after the final operative step and affected 9/22 (41%) children. **Preoperative peripheral oxygen saturation** averaged $81.3 \pm 3.6\%$ and was not found to significantly correlate with any test results.

At the time of the third operation, the majority of children fell into average height and weight percentile groups. Only 3/22 (13%) and 5/22 (23%) of the patients' height and weight, respectively, was below the 5th percentile.

Cumulative Results

The total **DHCA** exposure from all three operative steps significantly correlated with test results on intellectual and visual-motor abilities (Table 6a and b, MP: $p = 0.000$, AS: $p = 0.012$, VMI: $p = 0.022$). On average, these children underwent a total of 101.5 ± 44.7 minutes of deep hypothermic circulatory arrest time ranging between 64 – 188 minutes. The total **CPB** time did not significantly correlate with our test results but totaled, on average, 277.7 ± 87.1 minutes (range: 164 – 466 minutes). Total DHCA and CPB time included exposure during the palliative steps and/or any necessary operative corrections. The total number of **adverse events** per subject strongly correlated with intellectual outcome (MP: $p = 0.001$, AS: $p = 0.005$, VMI: $p = 0.020$) but was not associated with behavioral or Quality of Life (KINDL) test results. The **preoperative peripheral oxygen saturation** levels from all three operative procedures averaged $82.5 \pm 3.2\%$ did not correlate with cognitive outcome.

The total operation time did not correlate with study outcome. A statistical difference among surgeons was not analyzed.

Untested Children

The four children from our Institute who were unable to participate in the study due to advanced stages of mental disability underwent, on average, longer periods of DHCA exposure during the Norwood operation than the tested children (untested children: 81.0 ± 30.7 minutes, tested children: 63.6 ± 15.4 minutes) and all four suffered severe postoperative complications. Three out of four children suffered prolonged, repetitive clinical seizures in the immediate postoperative period and one child was suspected to have plexus hemorrhage in cerebral ultrasound. Another child was resuscitated twice and two of the four children were reoperated due to postoperative complications. The DHCA duration of these four children did not differ from the tested children during the Hemi-Fontan and Fontan operation.

Day of Testing

Peripheral oxygen saturation on the day of testing averaged $91.9 \pm 5.3\%$ and ranged from 79 – 98%. 54% of the patients had oxygen saturation levels equal to or lower than 95%. These values correlated significantly with neurodevelopmental test scores including behavior, intelligence and Quality of Life scores (Table 5, 6a and b MP: $p = 0.009$; AS: $p = 0.032$, VMI: $p = 0.003$, CBCT: $p = 0.003$, QL: $p = 0.020$). On the day of testing, the **height and weight** of the study group was average (51st and 54th percentile, respectively).

V. DISCUSSION

Intellectual Function

Our data demonstrate that children with HLHS perform worse on tests of **intellectual function** than healthy control children. Specifically, objective assessments of their visual-motor skills, mental processing and their learned, academic knowledge indicates that their performance is inferior compared to children without this condition.

Poor results on tests of intellectual function may be indicative of difficulties in the child's current or future school performance, in their logistical reasoning or problem solving skills, or in their ability to absorb new information. A child who scores between 70 and 85 points is defined as having a learning disability, whereas a score under 70 points is classified as a mental disability. In this study, 45% of HLHS children were diagnosed with a mental disability, 32% with a learning disability and 21% fell into the normal IQ range (based on MP score).

In most cases, children diagnosed with a learning disability are able to attend normal schools, however, integrative help in form of a counselor or personal tutor is often required to assist with the child's individual scholastic needs. Most children in this category will learn to read and write with the aid of individualized training. As young adults, professional training is generally obtained through vocational schools (warehouse worker, kitchen assistant, construction worker, etc).

Children diagnosed with a mental disability are, in most cases, unable to learn to read and write. They require special schooling and can later obtain jobs through centers for individuals with special needs. Parents and teachers should be aware of these specific limitations and encourage additional academic, psychological and familial support when needed.

As mentioned above, the average IQ range in a normal population is 85-115 points. However, a subtle increase in test scores of intellectual quotient (approximately 10 points) is observed when tests have been in use for over 10 years (Flynn 1984). The K-ABC version used in this study was released in 1992, therefore indicating an overestimation of IQ scores by ca. 10-15 points. An overestimation of the K-ABC by approximately 3-5 IQ points compared to the WISC-R (Naglieri 1984) used in other studies (ex: Mahle 2000) has also been noted. The Kaufman-ABC is nonetheless a reliable tool frequently used to diagnose learning disabilities, assess reading and writing skills and to predict a child's scholastic success. The Beery Test

(VMI) is a reliable indicator of some cognitive disabilities and is a predictor of school performance, arithmetic and reasoning skills.

Intraoperative Period

The most consistent significant operative variable affecting neurodevelopmental outcome was the duration of **deep hypothermic circulatory arrest**. Particularly infants receiving 57 minutes or more of DHCA during the Norwood operation performed worse on tests of intellect (MP, $p = 0.025$) and visual-motor skills. The DHCA duration during the Hemi-Fontan and Fontan operation also significantly correlated with mental processing scores. The presence of DHCA at the Fontan operation, regardless of duration, strongly affected MP. Cumulative DHCA times from all three palliative steps, including the use of DHCA for necessary operative revisions, negatively correlated with tests of intelligence and visual-motor skills.

Neurological complications and long-term neurodevelopmental abnormalities after prolonged DHCA exposure in children with CHDs have been repeatedly documented in the literature (Haka-Ikse 1978, Dickinson 1979, Wells 1983, Bellinger 1991, Kern 1998, Limperopoulos 2002). Similarly, in cohorts of children with HLHS, lower cognition scores significantly correlated with longer DHCA exposure times (Wernovsky 2003). DHCA has been shown to cause direct hypoxic-ischemic cerebral injury and to increase the risk of cerebral complications in the postoperative period. As a result of altered cerebral perfusion in the prenatal period, or due to congenital brain anomalies or genetic polymorphisms found in some subjects (Natowicz 1988, Wernovsky 2003), children with HLHS may be more susceptible to DHCA and CPB-induced hypoxic-ischemic injury than children with other CHDs undergoing similar operations (Glaser 1990, Wernovsky 2003). This, however, is rather speculative and has not been proven. In a study of infants with D-transposition of the great arteries, Wypig et al. described a DHCA safe period of less than 41 minutes (2003). This duration exceeds the time in which the brain maintains aerobic activity (approximately 20 minutes) but may correlate to a time-related increase in vascular resistance or other ischemic reactions. Infants exposed to DHCA exceeding this threshold demonstrated more neurodevelopmental abnormalities compared to those who were exposed for less than 41 minutes. In this study, we observed a negative correlation between DHCA duration and neurodevelopmental outcome, and a

significant decline in test results after 57 minutes of DHCA (see Figure 11, 13). Only two infants in our study cohort underwent less than 41 minutes of DHCA and their average MP IQ score was 88.5.

Four children could not be tested due to advanced stages of mental disability. These children were exposed to longer periods of DHCA during the Norwood operation and similar lengths during the Hemi-Fontan and Fontan procedure compared to the study group (Norwood DHCA for untested children: 81.0 ± 30.7 minutes, tested children: 63.6 ± 15.4 minutes). All four children suffered severe postoperative neurological complications after the Norwood operation. These results, although not quantifiable in this subpopulation, support the hypothesis that a prolonged DHCA exposure, in particular during the first operative step, leads to a worse cognitive outcome. These cases also suggest that prolonged DHCA time may result in a higher susceptibility to postoperative complications, which may be an independent predictor of cognitive outcome.

The DHCA duration for HLHS palliative correction was extensive during the first few years of operative experience at our Institute. This was due, in part, to the lack of data regarding the severe neurological sequelae of DHCA during this operative era. With increasing proficiency and the advance of operative techniques, such as antegrade selective cerebral perfusion (ASCP), DHCA duration has decreased and neurodevelopmental outcome has improved substantially over time at this Institute (Furck 2010). In fact, the study at hand demonstrates a consistent, significant correlation between improved IQ and VMI scores and a **later operation date**. This trend was observed during all three palliative steps and implies that improved surgical techniques and skills gained during the first era of HLHS operative experience at this Institute led to better outcomes. On the MP scale, no child undergoing the Norwood or Hemi-Fontan procedure between 1996 and 1998 scored over 77 IQ points and only children operated in 1999 or January 2000 received over 85 IQ points. Similarly, nearly all subjects who underwent the Fontan operation in 2002 received MP scores over 85 IQ and the one child operated in June, 2003 received an MP score of 104 IQ, the highest score in the study group.

The neurological sequelae from **CPB**, such as microembolism and inflammatory phenomena, have been well documented in the literature (McBride 1996) and negatively

correlated with neurodevelopmental outcome in study groups (Scallan 2004, Oku 1994). Cumulative CPB exposure and CPB duration during the palliative steps did not negatively correlate with intelligence quotient scores in this study. Due to the high significance of DHCA exposure on the cognitive outcome, an accurate assessment of CPB length and exposure is difficult to obtain in this study population. Comparative studies of the effect of CPB and DHCA alone was well demonstrated by the Boston Circulatory Arrest Studies (Bellinger 1995) in subjects with D-Transposition of the great arteries but cannot be replicated in the HLHS population.

Postoperative Complications

In our study, children that suffered severe postoperative complications after the Norwood operation displayed more neurodevelopmental deficits at school age. The cumulative presence of complications significantly affected outcome, whereas individual, organ-specific problems (including cardiac arrhythmias, clinical seizures, multiorgan failure and other neurological complications) in the postoperative periods did not affect outcome.

After the Norwood operation, 27% of study children suffered postoperative clinical **seizures**. There was no record of other severe neurological complications seen in the group. Among the four untested children in the group, three experienced clinical seizures and the fourth child suffered another severe neurological complication in the postoperative period.

Other studies (Goldberg 2000, Mahle 2000, Bellinger 1995 and Bellinger 1999) found that the presence of clinical seizures was a risk factor for later developmental problems. In an analysis by Goldberg et al. (2000), intraoperative seizures correlated with lower neurodevelopmental outcomes in HLHS and non-HLHS single ventricle subgroups. In the Boston Circulatory Arrest Studies of the D-transposition of the great arteries, EEG seizures were associated with cerebral MRI abnormalities and lower scores on the Psychomotor Development Index at age one (Bellinger 1995). In the same cohort at age 2.5, early postoperative seizures (both clinical and EEG) were associated with lower motor function and abnormal neurological examination and MRI brain scans (Rappaport 1998). At age four, both clinical and EEG-detected seizures correlated with lower average IQ scores and an increased risk of neurological abnormalities (Bellinger 1999). Gaynor et al. (2005) found that DHCA duration exceeding 40 minutes was associated with increased EEG seizure incidence in the postoperative period. EEG

seizures in this study were "...defined by the appearance of a sudden, repetitive, evolving, stereotyped, ictal pattern with a definite beginning, middle, and end; a minimum duration of 10 seconds; and a minimum amplitude of 2 μ V" (1279). In the Gaynor study, the median number of seizures recorded in a 48-hour period was 36. None of these episodes were recorded clinically. In this study, the HLHS population demonstrated the highest incidence of seizures compared to other study subpopulations, which may have resulted from the increased incidence of acquired ischemic brain injury from prolonged DHCA exposure. This study also emphasizes the gross underestimation of true seizure activity by solely recording its clinical presence. Clinical seizures may be suppressed due to the high amount of sedative agents administered in the postoperative period or may be missed without continual video observation. The 27% of clinically diagnosed, post-Norwood seizures in the study population at hand (35% when including the four untested children) is most certainly an underestimation of the EEG seizure activity.

The total number of adverse events per subject after all operative procedures significantly affected neurodevelopmental outcome, whereas the occurrence of complications after the Hemi-Fontan and Fontan operations did not. This is indirectly indicative of the decreased complexity and lower operative risk associated with the final two procedures compared to the Norwood operation. Some inherent risks of the Hemi-Fontan and Fontan operations were also likely decreased due to shorter operation duration and DHCA exposure compared to the Norwood operation. Hospital stays were also reportedly shorter after these procedures. The most frequent type of complication after the second and third operative step was hemodynamically significant cardiac arrhythmias followed by neurological complications (not including seizures).

Some studies (Newburger 2003, Limperopulus 2002) illustrated an association between the length of hospital stay and cognition. Longer ICU and hospital stays correlated with lower IQ scores and poor math achievement. Factors affecting a prolonged hospital stay were multifactorial, such as extensive use of inotropic medication and variables affecting cerebral perfusion (CPB and DHCA). The length of hospital stay was not statistically analyzed in the study at hand but is a direct reflection of the severity of the child's condition/complications and may be a predictor of neurodevelopmental outcome.

Due to the retrospective nature of this study, pre-, intra- or postoperative complications were recorded and analyzed based on hospital records collected from the study group. The assessment of their severity and immediate consequences were determined through our interpretation of the physician's notes and examination records. These factors limited the objective evaluation of the complications recorded.

Preoperative Period

The total number of **complications** in the preoperative period in the study at hand negatively influenced MP and AS scores. The most common adverse event was renal failure, followed by liver failure, presumably due to early cardiogenic shock. None of the infants experienced preoperative seizures, although in a multivariate analysis by Mahle et al., the occurrence of preoperative seizures alone predicted a lower full-scale IQ score in an HLHS cohort (2000).

In this study, a prenatal diagnosis of hypoplastic left heart syndrome did not affect the long-term intellectual abilities in the study group. A prenatal diagnosis of this condition, however, provides obvious advantages regarding appropriate preparation of postnatal care and surgical intervention, which may reduce the occurrence of severe, preoperative complications. In a study by Sivaragan et al. (2009), a prenatal HLHS diagnosis significantly improved the clinical course in the pediatric intensive care unit. Infants received prostaglandin treatment earlier than in cases without a prenatal HLHS diagnosis and were less likely to be ventilated. They had lower serum lactate levels, a lower peak creatinine and alanine aminotransferase levels. The presence of a prenatal diagnosis in this study, however, did not correlate with an increased survival rate after the first and second stages of surgical palliation. In study at hand, infants with a prenatal HLHS diagnosis experienced 0.25 complications per individual, whereas infants without a prenatal diagnosis experienced 0.82 complications per individual. These differences were not statistically significant but demonstrate an advantage for the prenatal diagnosis group. In a study from this Institute by Stieh et al., the absence of a prenatal diagnosis was a central risk factor leading to an adverse outcome when preoperative strategies were retrospectively compared in 72 children with HLHS (2006).

HLHS, in comparison to other CHDs such as anomalous pulmonary venous return and transposition of the great arteries, is among the most frequently detected congenital heart defects encountered in prenatal echocardiographic diagnoses (Friedberg 2009). A prenatal diagnosis can allow parents of affected fetuses to make thoughtful decisions regarding the continuation/termination of pregnancy or postnatal compassionate care/operative treatment options. Appropriate parental counseling should include current data regarding the survival rates and outcomes of children with HLHS.

Peripheral Oxygen Saturation

Due to the partially saturated blood supply pumped into both the systemic and pulmonary circulation systems after the Norwood operation, the lowest average peripheral oxygen saturation was observed before the Hemi-Fontan operation (75.5%). The final two operative steps, which separate arterial from venous blood circulation in the body, slowly improved the peripheral oxygen saturation seen in our results. The post-Fontan saturation values (measured on the day of testing) were higher than at any other time ($91.9 \pm 5.3\%$). Peripheral oxygen saturation before and after fenestration closure was not analyzed in this study.

The peripheral oxygen saturation on the day of testing correlated negatively with cognitive outcome, whereas peripheral oxygen saturation at the time of the three operative steps did not. This unexpected correlation in our data likely has only limited scientific significance as the peripheral capillary saturation is not directly representative of cerebral oxygen supply and therefore cannot adequately explain a variation in cognitive outcome.

In a study by Hoffman (2005), however, delayed neurodevelopmental outcome and ischemic brain injury in four year-old children with HLHS correlated with post-Norwood systemic venous oxygen saturation (S_{vo_2}). Systemic venous oxygen saturation (measured in the superior vena cava) is primarily supplied by cerebral blood flow and may therefore be used as an indirect indicator of cerebral oxygen supply. Infants with low S_{vo_2} after the Norwood operation demonstrated neurodevelopmental abnormalities (and abnormal VMI and CBCL scores) compared to children with higher S_{vo_2} saturation. Future research groups at this Institute will measure cerebral oxygen supply using a near infrared technique throughout palliative treatment to more accurately evaluate its effect on neurodevelopmental outcome.

Other Influential Factors on IQ

The poor IQ test results presented in this study could be attributed to difficulties in test taking abilities. Although not objectively quantified in this study, some members of the group experienced problems concentrating on test material and were highly irritable and hyperactive. Colleagues currently conducting behavioral testing of this cohort may reveal new insights into these observations and their influence on IQ outcome.

Several differences in testing conditions of the study and control groups must be considered as possible intervening variables in the presented results. The children with HLHS were tested in an office at the University Hospital in the same building where they underwent their operative steps and numerous follow-up examinations. The building and surrounding hospital personnel could have evoked feelings of angst or unease in the individuals, thus affecting their ability to concentrate on the task at hand. Children in the study group were tested in the morning, in many cases after a follow-up physical exam. Children in the control group were tested in the familiar, trusted environment of their own homes during the early afternoon. Much research has been performed in the past years regarding optimal test-taking hours for children, particularly with respect to their age or type (synchrony: individual's preference to time of day, for example, morning or evening type). Most studies agree that younger children perform better in the morning, whereas older children (age 8+) tend to perform better in the afternoon (Goldstein 2007). Due to scheduling conflicts, an internal control to eliminate the effects of synchrony and chronotype (time at which cognitive operations are performed) in this study is not available.

Moderate physical activity has been associated with better school performance and cognition in elementary school children (Hillman 2009, Evenland-Sayers 2009). Children with severe CHDs often lead more inactive lifestyles due to physical limitations and/or parental uncertainty (Longmuir 2009). Decreased physical exertion capacity in children with CHDs correlated with poor results on tests of motor skills, visual-motor skills and school performance. A lack of physical exertion capability also correlated with behavioral problems (Delamater 2003). This variable could have affected our test results. Möller et al. (2009) analyzed the physical abilities of 46 children with HLHS in a cohort from our Institute including some children from this study. A marked reduction of physical exertion capacity was noted due to an inadequate heart rate increase and abnormal ventilatory response. This study concluded that the

physical limitations seen in children with HLHS should not discourage them from participating in leisure sports.

Behavior and Quality of Life

Despite poor test scores, parents did not describe any irregularities in their children's **quality of life, behavior** or emotions. In general, parents described their children as being happy and playful regardless of their repetitive and lengthy hospital visits. Although gratifying, some results of parental questionnaires differed staunchly from cognitive test results and the proctors' subjective assessments of these children, specifically regarding behavior. Many children in the HLHS test group had difficulties concentrating during the exam and were irritable and aggressive. A thorough psychological examination of these behavioral traits, as well as possible causal associations, was not examined in this study.

Mahle et al. found similar results in his study of 115 school-aged children with HLHS. Here, parents described their children as being in good (34%) or excellent (45%) health and having an average (42%) or above average (42%) academic performance when, in fact, one-third of the children were receiving special education and 18% were mentally disabled (2000). In literature by Reynolds et al. (1992) and DuPaul et al. (1999), 45% of children with HLHS had abnormal attention scores and 39% had abnormal hyperactivity scores on a Rating Scale for ADHD.

Observational studies of parents of chronically ill children demonstrated differences in the assessment of their children's conditions and abilities compared to parents of healthy children (Sarimski 2001). The authors suggested that an underlying fear of the parent's children becoming critically ill or dying caused them to be generally overly-protective and wish to maintain constant supervision of their children. Parents tended to be less critical when evaluating their child's physical or intellectual abilities and were simply be happy that their child was alive. Alternatively, parents overestimated their child's abilities compared to healthy children, perhaps as an expression of denial of their illness. In our experience, parents who are able to realistically judge their child's strengths and weaknesses aid substantially in the therapeutic process. A more objective analysis of these criteria should be repeated over time as children grow and are challenged by new social and academic environments.

Congenital Abnormalities

Several studies (Wernovsky 2003, Ilke 2003) argue that extracardiac congenital abnormalities or genetic differences in children with HLHS are more influential on intellectual outcome than postpartum operations or complications. Wernovsky et al. (2003) identified genetic polymorphisms in children with CHDs, which increase inflammatory responses to cerebral ischemia or CPB. Ilke et al. found that infants with HLHS treated with heart transplantation scored significantly lower on tests of intelligence and demonstrated abnormal behavior compared to the general population regardless of the duration of the DHCA exposure (2003).

One study found that 36% of 295 infants with HLHS have CNS abnormalities such as congenital microcephaly (Glaser 1990). Wernovsky et al. (2003) described additional congenital brain abnormalities seen in children with CHDs, such as an absent corpus callosum and incomplete operculization, which he argued could lead to further CNS injury regardless of management philosophy. It should be noted that autopsy results used in some of these studies are useful for their fundamental information on extracardiac HLHS anatomy, yet it is unclear whether these phenomena or genetic abnormalities in particular, could affect neurodevelopmental outcome and be expected in the survivor population today. Some of the cadavers analyzed (Natowicz 1988, Glaser 1990) were from spontaneous/induced abortions or early infant deaths and, therefore, are unlikely representatives of the children tested in our study. At birth, the study infants tested here demonstrated no evidence of congenital microcephaly and had a head circumference in the normal range (mean 34.7 ± 1.6 cm). Cerebral magnetic resonance imaging is currently being performed on children with HLHS after the Fontan operation at this Institute. In the cohort examined thus far, congenital cerebral abnormalities have not been identified.

In the study at hand, a smaller aortic diameter correlated significantly with an improved neurodevelopmental outcome. Although echocardiographic measurements of the ascending aorta in this study are subjective to the individual examiner, this finding suggests a paradoxical improvement in cerebral perfusion induced from a more restrictive ascending aorta. In fetal development, oxygenated blood supplies the common carotid arteries in an anterograde fashion via the ascending aorta. In children with HLHS, the cerebral vessels are partially perfused in a

retrograde fashion via the ductus arteriosus and descending aorta (Figure 1). It is possible that higher grades of ascending aortic constriction induce increased retrograde perfusion to the carotid and cerebral arteries. Studies have demonstrated complex and abnormal aortic arch flow patterns in fetal hypoplastic left heart syndrome and a decrease in cerebrovascular resistance (the brain sparing phenomenon) indicating abnormal cerebral perfusion (Kaltman 2005, Pekkan 1994). Specific measurements of cerebral blood flow dependent on aortic diameter in fetuses with hypoplastic left heart syndrome have not, to our knowledge, been reported and represent an important area of research in children with this condition.

Summary

The purpose of this study was to assess the intellectual and behavioral outcome of children operated during the first era of HLHS surgical repair at our Institute. To our knowledge, this is the first evaluation of its kind among European institutions.

Compared to a healthy control group and the general population, children in our study group demonstrated significantly reduced intellectual and visual-motor test scores. Forty-five percent of study group participants were found to be mentally disabled thus requiring special-needs schooling. Thirty-two percent were diagnosed a learning disability and 21% fell into the normal IQ range (based on MP score).

Low intelligence scores in this study resulted, at least in part, from prolonged DHCA exposure during palliative operative treatment. Exposure exceeding 56 minutes resulted in significantly lower MP scores. The number of cumulative complications also affected intellectual outcome. CPB time did not correlate negatively with neurodevelopmental scores and preoperative peripheral oxygen saturation was not found to be a reliable parameter of cerebral oxygen supply.

In contrast to the stark difference in IQ results between the HLHS and normal population, were similar behavior and quality of life (KINDL) scores. According to parents of affected children, significant behavioral abnormalities or a decreased quality of life were not apparent. Objective testing of these parameters at later developmental stages is essential and will reflect new variables of long-term operative success in this cohort.

Following studies for later operative eras using newer operative techniques, such as antegrade selective cerebral perfusion, are currently in progress. Through our research we hope to better understand the long-term consequences of operative palliation, the neurodevelopmental sequelae of standard and advanced surgical methods and, in turn, better counsel expecting parents in the decision-making process. The children evaluated in this study and their caretakers should be followed/counseled closely especially in regard to school performance. It is essential that psychological support and special education needs be addressed in children with poor test results, in addition to extensive counseling for affected parents.

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VII. FIGURES

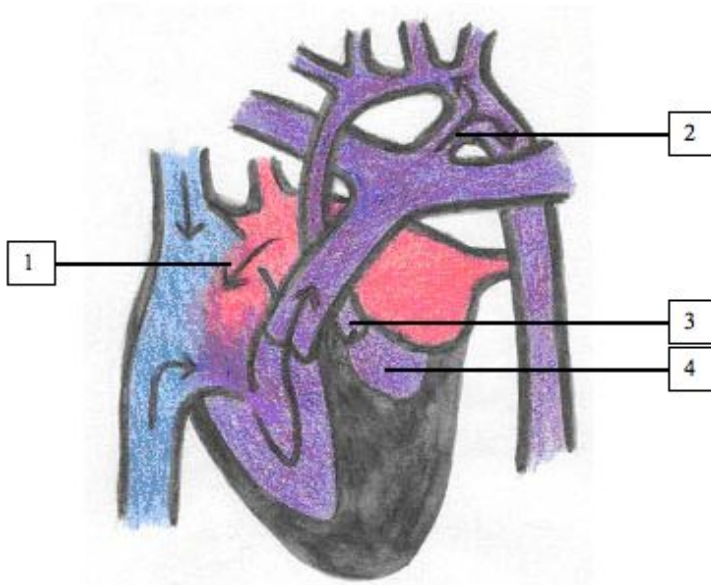
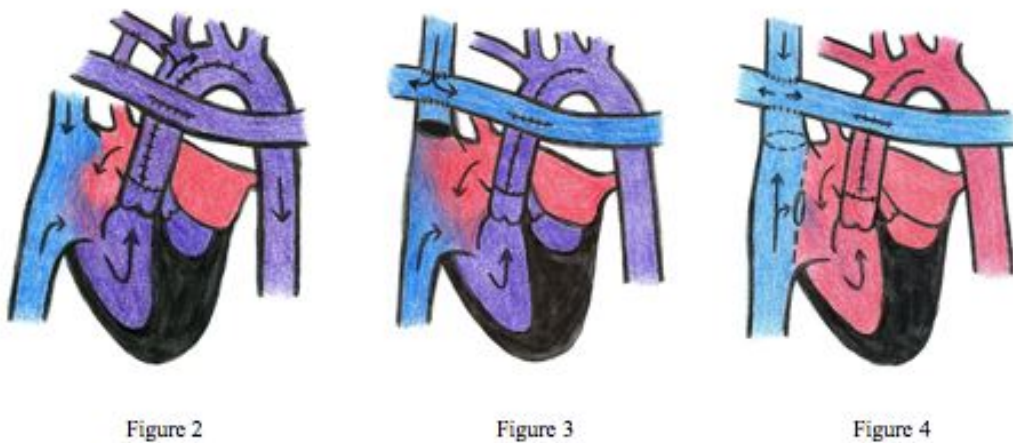


Figure 1: Hypoplastic left heart syndrome, preoperative anatomy. 1- patent foramen ovale, 2-patent ductus arteriosus, 3-narrowed aorta, 4- hypoplastic left ventricle (courtesy of Dr. A. Pollmeier).



Figures 2-4: Stages of operative correction of hypoplastic left heart syndrome. From left to right: Norwood procedure, Hemifontan operation and Total Cavopulmonary Connection (TCPC or Fontan operation, courtesy of Dr. A. Pollmeier).

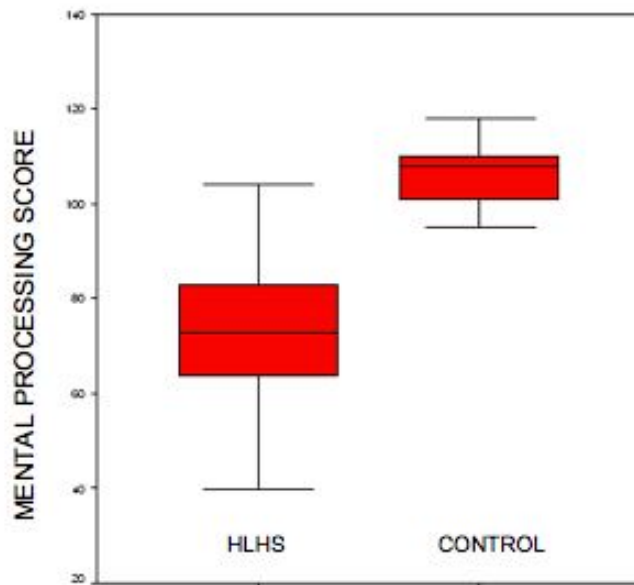


Figure 5: Mental Processing (MP) test results of study group (left) and control group (right). Groups are significantly different ($p = 0.000$).

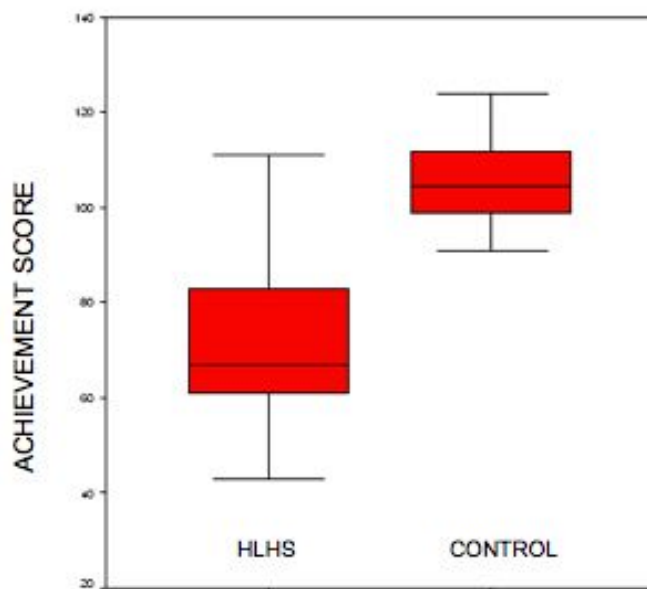


Figure 6: Achievement Score (AS) of study group (left) and control group (right). Groups are significantly different ($p = 0.000$).

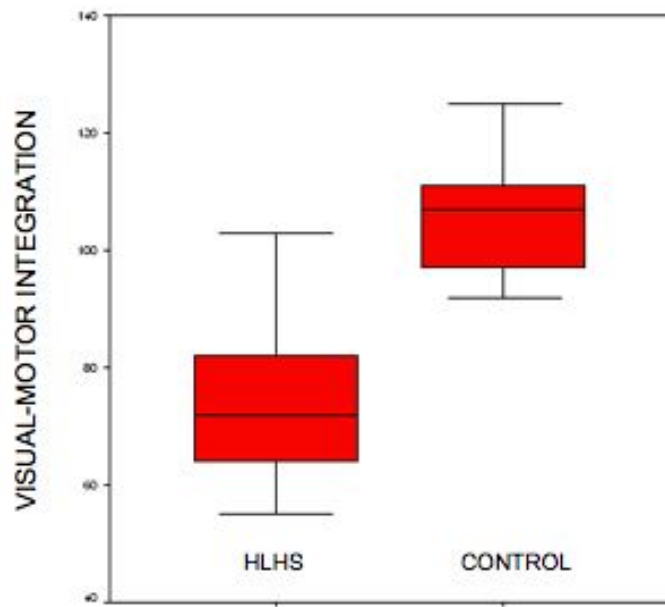


Figure 7: Visual Motor Index (VMI) of study group (left) and control group (right). Groups are significantly different ($p = 0.000$).

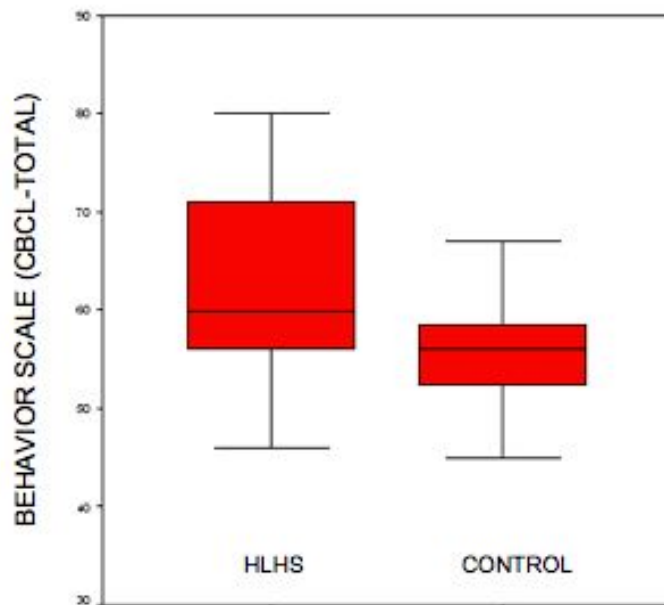


Figure 8: Child Behavior Checklist (CBCL) results of study group (left) and control group (right). There was no significant difference between groups ($p = 0.054$).

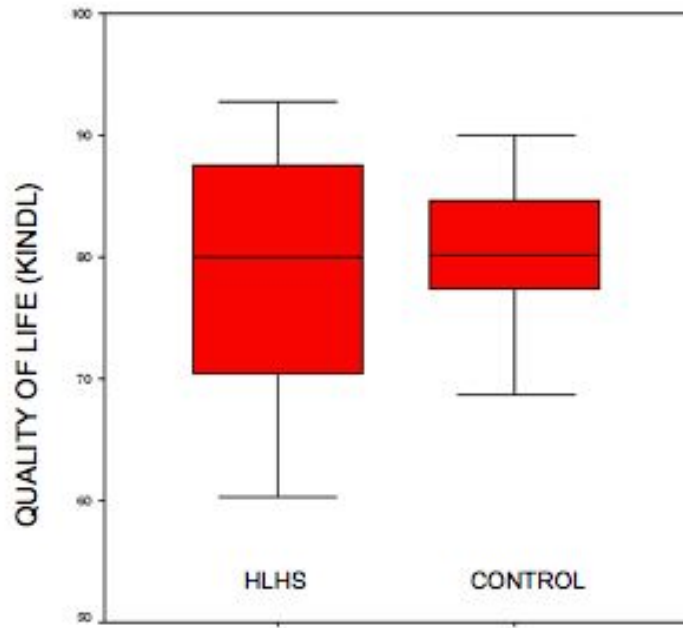


Figure 9: Quality of life (KINDL) scores of study group (left) and control group (right). There was no significant difference between groups ($p = 0.619$).

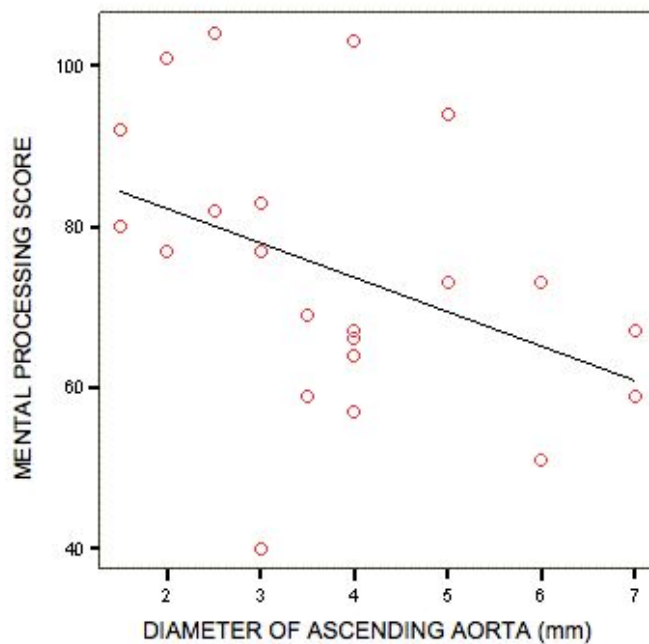


Figure 10: Mental Processing (MP) score and its correlation to the diameter of the ascending aorta. Correlation significant $p = 0.013$

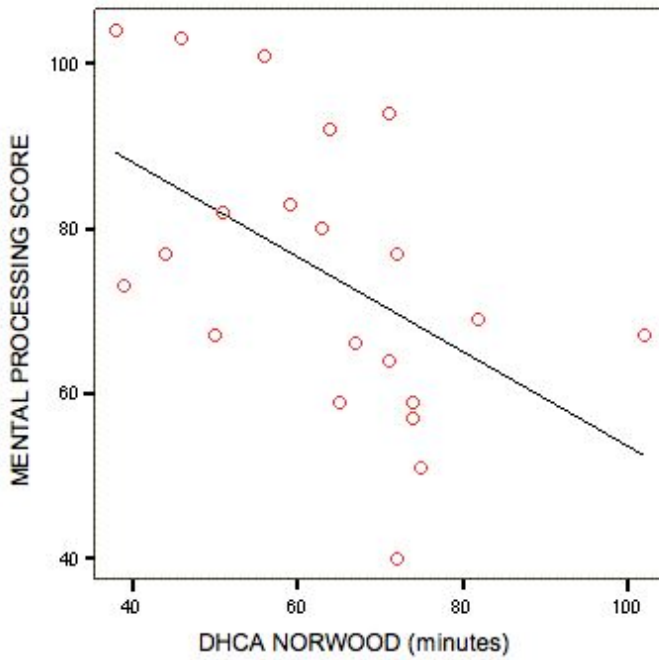


Figure 11: Mental Processing (MP) score and its negative correlation to DHCA duration (minutes) during the Norwood procedure. Correlation significant $p = 0.001$

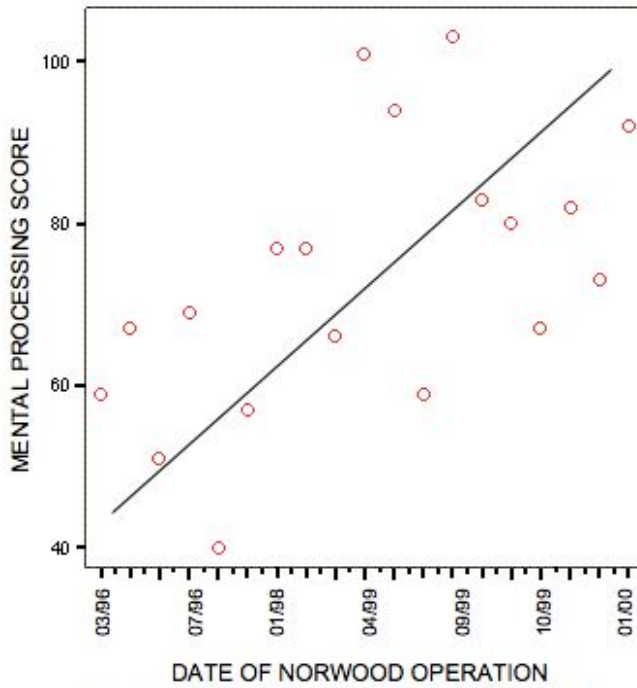


Figure 12: Mental Processing (MP) score relative to the date of the first operative procedure. Correlation significant $p = 0.005$

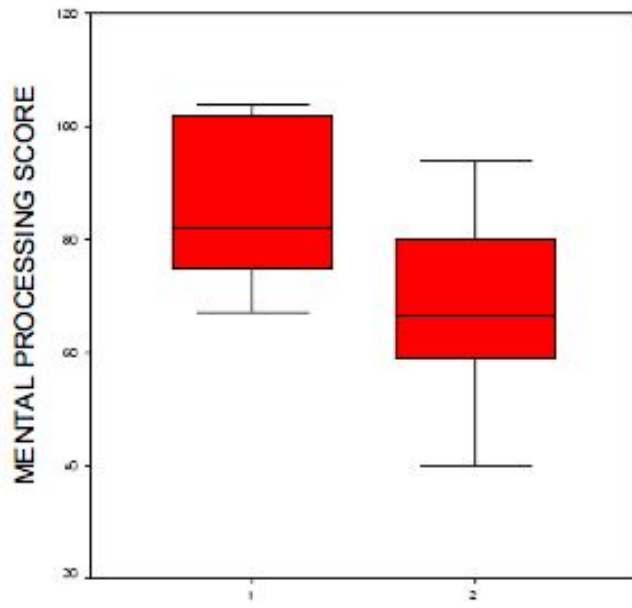


Figure 13: Mental Processing scores \leq 56 minutes (1) and $>$ 56 minutes (2) of DHCA exposure during Norwood operation, $p = 0.025$

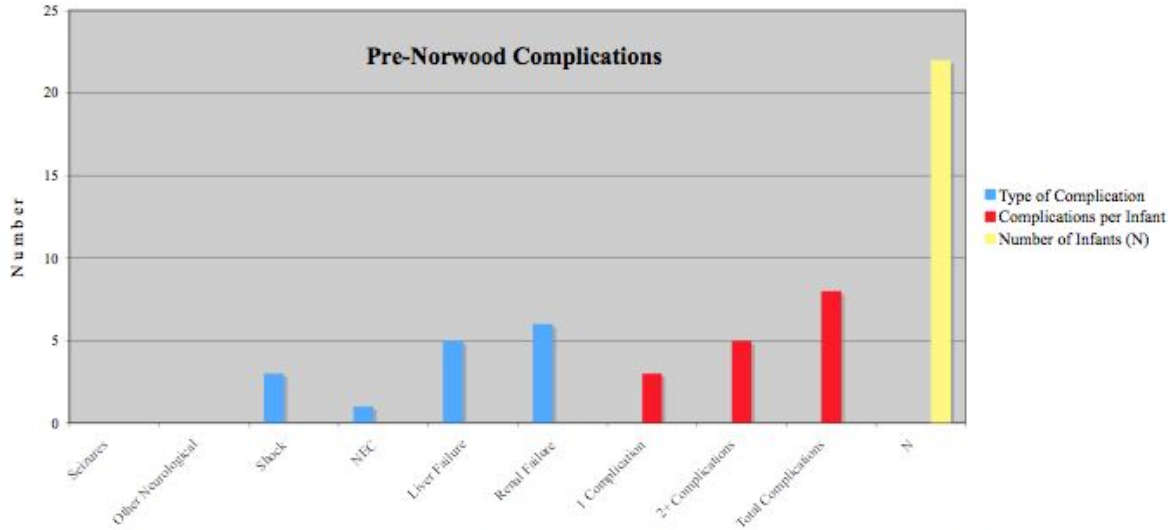


Figure 14: Pre-Norwood complications presented by type of complication (blue). The most common complication was renal failure and no neurological complications were observed. A total of 8 infants suffered pre-Norwood complications (one severe complication was seen in 3 subjects and multiple, severe complications were seen in 5 subjects, red). The number of complications per subject correlated significantly to IQ parameters. Pre-Norwood complication data were available for 22/22 subjects (yellow). NEC = necrotizing enterocolitis

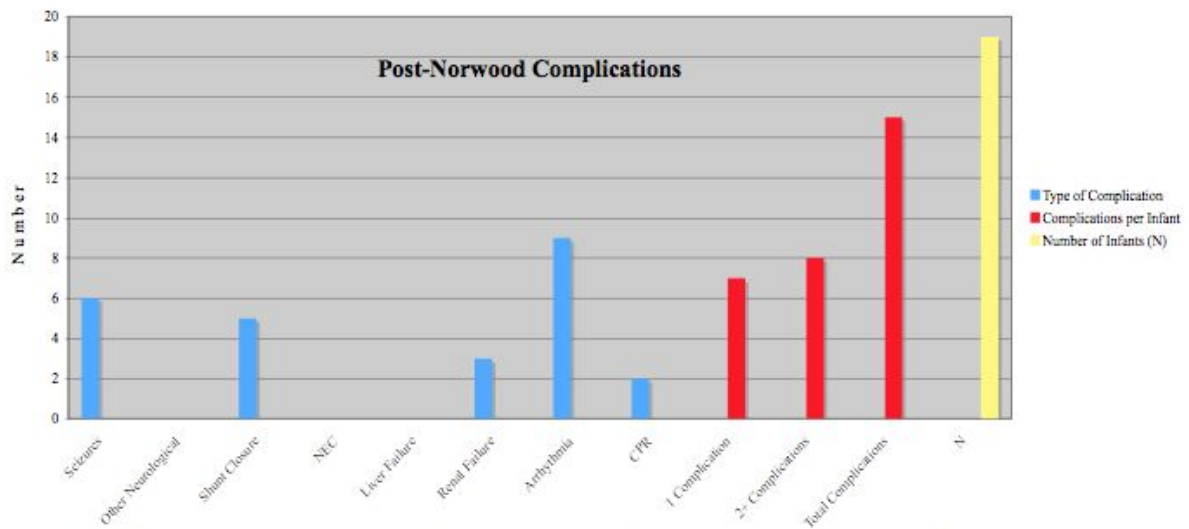


Figure 15: Post-Norwood complications presented by type of complication (blue). The most common complication was cardiac arrhythmia (9/19) and seizures (6/19) were second in frequency. A total of 15 infants suffered post-Norwood complications (one severe complication was seen in 7 subjects and multiple, severe complications were seen in 8 subjects, red). The number of complications per subject correlated significantly to mental processing and visual-motor integration scores. Post-Norwood complication data were available for 19/22 subjects (yellow). NEC = necrotizing enterocolitis, CPR = cardiopulmonary resuscitation

VIII. TABLES

Table 1: Variables included in statistical analyses

Pre-Norwood	Norwood, Hemi-Fontan and Fontan Operation	Cumulative Analysis
<ul style="list-style-type: none"> • Anatomic Subtype • Diameter asc. aorta (mm) • Cumulative complications (NEC, seizures, other neurological, hepatic, renal, shock) • Prenatal Diagnosis • Peripheral O₂ Saturation 	<ul style="list-style-type: none"> • Cardiopulmonary Bypass Time • Circulatory Arrest Time • Cumulative complications of operation (seizures, other neurological, hepatic, renal, shock, CPR, arrhythmia, shunt closure) • Date of Operation • Peripheral O₂ Saturation 	<ul style="list-style-type: none"> • Cardiopulmonary Bypass Time • Circulatory Arrest Time • Cumulative complications of all operations (seizures, other neurological, hepatic, renal, shock, CPR, arrhythmia, shunt closure) Test Day: • Peripheral O₂ Saturation

Table 2: CBCL/4-18
Classification of behavioral problems

Problems and Cross-Informant Syndromes	
Internalizing	Externalizing
Withdrawn/Depressed	Thought Problems
Somatic Problems	Attention Problems
Anxious/Depressed	Aggressive Behavior
Social Problems	Rule-Breaking Behavior

Table 3: Average \pm standard deviation and median/range scores of HLHS and control groups

Test Battery	HLHS Mean \pm SD	HLHS Median (Range)	Controls Mean \pm SD	Controls Median (Range)
MP	74.4 \pm 17.0	73.0 (40-104)	106.5 \pm 7.0	108 (95-118)
AS	70.7 \pm 17.8	67.0 (43-111)	105.9 \pm 9.7	104.5 (91-124)
VMI	73.5 \pm 13.7	72.0 (55-103)	105.7 \pm 9.1	107.0 (92-125)
CBCLt	61.6 \pm 10.0	60.0 (46-80)	56.0 \pm 8.1	56.0 (41-79)
QL	78.0 \pm 10.1	79.9 (60.3-92.7)	80.3 \pm 5.2	80.1 (68.7-90.0)
SES	13.5 \pm 4.1	14.5 (3-21)	16.5 \pm 4.2	18.0 (3-21)

MP-Mental Processing (intellectual score); AS-Achievement Scale (intellectual score); VMI-Visual-Motor Integration; CBCLt-Child Behavior Checklist-total score; QL-Quality of Life Score; SES-Socioeconomic Status; CBCL standard score is 50 ± 10 , SES: lower (3-8); middle (9-14) and upper class (15-21); standard scores of all others are 100 ± 15 .

Table 4: Test Performance, HLHS versus Control Children

Test Battery	p-value
MP	0.000**
AS	0.000**
VMI	0.000**
CBCLt	0.054
QL	0.619
SES	0.109

Mann-Whitney analysis of neurodevelopmental test results for HLHS patients versus control children; all tests of intellectual functioning (MP, AS, VMI) are significantly different. MP-Mental Processing; AS-Achievement Score; VMI-Visual Motor Index; CBCLt-Child Behavior Checklist – total score; QL-Quality of Life; SES-Socioeconomic Status (social class)

**Highly significant p-value

Table 5: Perioperative and Operative Patient Data

Variable	Norwood	Hemi-Fontan	Fontan	Test day
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age at Operation	7.9 ± 4.6 days	6.0 ± 1.8 mo	2.2 ± .9 yr	6.9 ± 1.4 yr
Weight(kg)/Height(cm) at Admission	3.2 ± 0.6/ 51.5 ± 3.0	6.0 ± 1.0/ 64.8 ± 4.2	11.6 ± 2.7/ 86.7 ± 9.3	23.5 ± 3.5/ 120.5 ± 8.6
BSA (m ²)	0.2 ± 0.0	0.3 ± 0.0	0.5 ± 0.9	0.89 ± 0.11
Head Circumference (cm)	34.7 ± 1.6	40.0 ± 1.9	49.0 ± 2.4	NA
DHCA Time (min)	63.6 ± 15.4**	32.0 ± 20.8*	10.2 ± 19.2*	NA
CPB Time (min)	82 ± 55.5*	112.6 ± 31.7*	95.6 ± 37.3	NA
Operation Time (min)	316.0 ± 129.2	315.3 ± 113.2	230.8 ± 51.6	NA
O ₂ Saturation (%)	86.6 ± 7.4	75.5 ± 1.9	81.3 ± 3.6	91.9 ± 5.3*
pH	7.38 ± 0.6	NA	NA	NA

*Factors with a significant correlation to cognitive function $p \leq 0.05$

**Factors with a highly significant correlation to cognitive function $p \leq 0.005$

DHCA-deep hypothermic circulatory arrest; CPB-cardiopulmonary bypass

pH-values from Norwood operation only, O₂ Saturation values measured peripherally and at hospital admittance (preoperative). NA-not applicable

Table 6a: Significance of Preoperative/Perioperative/Postoperative Variables and Correlation to Cognitive Function

Period	Variable	MP	AS	VMI	CBCt	QL
Pre-op	Anatomic Subtype	0.416	0.239	0.180	0.666	0.818
	Diameter Asc. Aorta	0.013*	0.016*	0.017*	0.054	0.146
	Complications	0.047*	0.014*	0.320	0.187	0.038
	Prenatal Diagnosis	0.551	0.267	0.392	0.097	0.314
	Oxygen Saturation	0.498	0.489	0.475	0.286	0.070
Norwood	CPB Duration	0.036*	0.196	0.039*	0.030*	0.354
	DHCA Duration	0.001**	0.025*	0.052	0.001**	0.362
	Complications	0.029*	0.157	0.040*	0.310	0.466
	Date of Operation	0.005**	0.083	0.024*	0.160	0.058*
	Oxygen Saturation	0.145	0.278	0.272	0.436	0.102
Hemi-Fontan	CPB Duration	0.006*	0.021*	0.130	0.149	0.058
	DHCA Duration	0.028*	0.069	0.097	0.496	0.012*
	Complications	0.470	0.368	0.489	0.212	0.431
	Date of Operation	0.009*	0.060	0.051	0.260	0.006*
	Oxygen Saturation	0.218	0.482	0.275	0.389	0.385
Fontan	CPB Duration	0.305	0.241	0.205	0.243	0.178
	DHCA Duration	0.009*	0.036*	0.092	0.203	0.048*
	Complications	0.238	0.258	0.125	0.208	0.348
	Date of Operation	0.000**	0.004**	0.005**	0.085	0.089
	Oxygen Saturation	0.354	0.252	0.459	0.237	0.310
Cumulative Data	CPB Duration	0.399	0.284	0.372	0.397	0.219
	DHCA Duration	0.000**	0.012*	0.022*	0.071	0.156
	Complications	0.001**	0.005**	0.020*	0.069	0.168
Test Day	Oxygen Saturation	0.009*	0.032*	0.003**	0.003**	0.020*

Pre-, peri- and postoperative variables and effect on intellectual functioning/ behavior.

MP-Mental Processing Score, AS-Achievement Score, VMI-Visual-Motor Integration, CBCLt-Child Behavior Checklist, total score, QL-Quality of Life (KINDL), CPB-Cardiopulmonary Bypass, DHCA-Deep Hypothermic Circulatory Arrest

*p ≤ 0.05, **p ≤ 0.005

Table 6b: Correlation Coefficients (r) of Preoperative/Operative/ Postoperative Variables and Correlation to Cognitive Function

Period	Variable	MP	AS	VMI	CBCt	QL
Pre-op	Diameter Asc. Aorta	-0.474*	-0.460*	-0.452*	0.353	-0.263
	Complications	-0.367*	-0.468*	-0.106	0.199	0.430
	Oxygen Saturation	0.002	-0.007	-0.016	0.142	-0.415
Norwood	CPB Duration	0.412*	0.203	0.403*	-0.428*	0.102
	DHCA Duration	-0.620**	-0.432*	-0.365	0.628**	0.092
	Complications	-0.443*	-0.244	-0.410*	0.122	0.023
	Date of Operation	0.573**	0.331	0.459*	-0.241	-0.424
	Oxygen Saturation	0.242	0.136	0.140	-0.037	-0.324
Hemi-Fontan	CPB Duration	0.543*	0.446*	0.258	-0.238	-0.396
	DHCA Duration	-0.423*	-0.334	-0.296	0.003	0.544*
	Complications	-0.017	-0.076	0.006	0.179	0.044
	Date of Operation	0.520*	0.360	0.376*	-0.153	-0.611*
	Oxygen Saturation	-0.185	-0.011	-0.142	0.067	0.076
Fontan	CPB Duration	-0.115	-0.158	-0.185	-0.157	-0.231
	DHCA Duration	-0.496*	-0.390*	-0.294	0.187	0.403*
	Complications	-0.160	-0.146	-0.257	-0.182	0.099
	Date of Operation	0.676**	0.562**	0.545**	-0.311	-0.343
	Oxygen Saturation	0.085	0.150	0.024	-0.161	-0.125
Cumulative Data	CPB Duration	-0.058	-0.129	-0.074	-0.059	-0.195
	DHCA Duration	-0.660**	-0.479*	-0.432*	0.324	0.252
	Complications	-0.604**	-0.535**	-0.441*	0.149	0.241
Test Day	Oxygen Saturation	0.524*	0.420*	0.598**	-0.596**	0.501*

Pre-, peri- and postoperative variables and effect on intellectual functioning/ behavior. MP-Mental Processing Score, AS-Achievement Score, VMI-Visual-Motor Integration, CBCLt-Child Behavior Checklist, total score, QL-Quality of Life (KINDL), CPB-Cardiopulmonary Bypass, DHCA-Deep Hypothermic Circulatory Arrest
*r value of $p \leq 0.05$, **r value of $p \leq 0.005$

Table 7: Norwood DHCA Time and Outcome

GROUP	DHCA(min)	MP*	AS	VMI
Group 1 (37%)	≤56	86.7±15.6	80.8±18.6	78.5±15.0
Group 2 (63%)	>56	68.7±14.8	66.0±15.9	71.1±12.9

DHCA times are divided into two groups and the mean ± standard deviation of intellectual functioning and visual-motor integration are given. Percentage of study population in parentheses. * $p \leq 0.05$ significant