Neurodevelopmental Outcomes in Infants with Hypoplastic Left Heart Syndrome after Hybrid Stage I Palliation

Dissertation

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By
Sharon Laneau Hill Cheatham, MSN, ACNP-BC
Graduate Program in Nursing
The Ohio State University
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Dissertation Committee:
Deborah Steward, RN, PhD, Advisor
Keith Yeates, PhD
Jill Heathcock, PhD
Abstract

Background: Congenital heart disease (CHD) is the most common of all birth defects and is the leading cause of infant morbidity and mortality (American Heart Association, 2010). Hypoplastic left heart syndrome (HLHS) is 100% fatal without palliation. Despite increased survival, since a surgical strategy was developed nearly 30 years ago, neurodevelopmental outcomes and quality of life are poor. The purpose of this study is to examine cerebral blood flow and neurodevelopment of infants born with HLHS after Hybrid Stage I palliation.

Methods: HLHS infants who underwent Hybrid Stage I palliation and healthy age-matched control subjects underwent transcranial Doppler at baseline, 2, 4, and 6 months of age. Systolic, diastolic, and mean velocities, as well as pulsatility index in the middle cerebral artery was recorded. Developmental assessment was performed at 2 and 4 months, using the Test of Infant Motor Performance (TIMP), and at 6 months of age, or prior to undergoing the second staged surgical repair, using the Bayley Scales of Infant and Toddler Development, 3rd edition and results were compared.

Results: The HLHS group scored lower compared to controls on the TIMP at 2 months of age (p=0.002), -1 to -2 standard deviation (SD) below the norm, and 4 months of age (p=0.0019), within -1 SD of the norm. Motor skills were significantly lower in the HLHS group compared with controls (p=0.049), however not significant for cognitive (p=0.29).
or language ($p=0.68$) at 6 months. There was no significant correlation between transcranial Doppler velocities and cognitive, language, or motor skills at 6 months of age.

**Conclusions:** Infants with HLHS who undergo Hybrid Stage I palliation score lower on standardized testing when compared to normal controls and the norm-referenced population. Cerebral blood flow velocity did not predict neurodevelopmental outcomes.
Dedication

This is dedicated to my children, Suzanne and Garrett, for their unconditional love and support throughout my professional career. I am grateful for being blessed with such wonderful children. For my parents, when I count my blessings, I always count them twice. And to John, who is my rock. You inspired me to take that leap of faith, striving for perfection, and always thinking outside the box...anything is possible. You have left footprints on my heart forever.
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Vita

Education

June 1979………………………………A.S. Nursing, Massasoit Community College

June 1989………………………………B.S. Nursing, Stonehill College

June 1998………………………………M.S. Nursing, Northeastern University

2008 to present…………………………PhD program, College of Nursing, The Ohio State University

Professional Experience

August 2002 – present The Heart Center at Nationwide Children’s Hospital, Columbus, OH
Interventional Cardiology Nurse Practitioner
Acute Care Nurse Practitioner in Cardiac Catheterization & Interventions

May, 2001 – June 2002 The Nemours Cardiac Center, Orlando, FL
Advanced Registered Nurse Practitioner in Cardiac Catheterization and Interventions, Electrophysiology and Pacing.

October, 1998 – May, 2001 The Floating Hospital for Children at New England Medical Center, Boston, MA
Nurse Practitioner Pediatric Cardiology / Electrophysiology.

July 1993 - Sept 1998 The Floating Hospital for Children at New England Medical Center, Boston, MA
Staff Nurse Pediatric Cardiology / Electrophysiology

June 1992 - Nov. 1992
The Floating Hospital for Children at New England Medical Center, Boston, MA
Neonatal Intensive Care Unit Acting Nurse Manager

May 1986 - July 1993
The Floating Hospital for Children at New England Medical Center, Boston, MA
Neonatal Intensive Care Unit - Assistant Nurse Manager

Sept. 1983 - May 1986
The Floating Hospital for Children at New England Medical Center, Boston, MA
Neonatal Intensive Care Unit
Neonatal Staff Nurse, Neonatal Transport Nurse

June 1979 - Sept. 1983
Carney Hospital, Dorchester, MA
Staff nurse and charge nurse

Awards

National Institute of Health, National Institute of Nursing Research
Ruth L. Kirschstein National Research Service Award Individual Fellowship (NRSA)
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Chapter 1

Introduction and Overview

Congenital heart disease (CHD) is the most common of all major birth defects. The estimated incidence for babies born with CHD is 8-9 out of 1,000 live births annually (Centers for Disease Control and Prevention, 2010; Hoffman & Kaplan, 2002; National Institute of Health, 2012). This translates into approximately 35,000 babies each year in the United States alone (National Institute of Health, 2012) and 1.35 million newborns annually worldwide (van de Linde, et al., 2011). Moderate to severe forms of CHD have been reported from 6/1000 to as high as 19/1000 live births (Lloyd-Jones, et al., 2009). With advanced imaging and technology, and more referrals to pediatric cardiologists, more and more minor CHD lesions are being diagnosed. Notably, at least 3 out of 1,000 babies born with CHD require either transcatheter intervention or cardiac surgery early in life (Hoffman & Kaplan, 2002).

Compared to normal cardiac anatomy (Figure 1), hypoplastic left heart syndrome is a severe form of CHD characterized by underdevelopment of the left ventricle and ascending aorta, with critical stenosis or atresia of the mitral and aortic valves, a small, undersized left ventricle, and diminutive ascending aorta (Figure 2). Up until 1980, hypoplastic left heart syndrome was considered inoperable and a fatal diagnosis as the patent ductus arteriosus (PDA), which provides systemic cardiac output and coronary
artery perfusion by backward or retrograde aortic blood flow, normally constricts and closes within several days of birth. Traditional palliative options include three open heart staged surgical procedures over the first few years of life. More recently a combined surgical and transcatheter approach conducted on the beating heart, off cardiopulmonary bypass, has become a viable option for stage I palliation, so called Hybrid Stage I palliation (Figure 3). Over the last three decades, as staged surgical procedures, technology, perfusion, and intensive care management has improved, the mortality rate associated with hypoplastic left heart syndrome has decreased at many centers.

The Center for Disease Control and Prevention (CDC) reports congenital heart defects as the main cause of death for 27,960 individuals in the United States from 1999 through 2006 with approximately half occurring during the first year of life (Centers for Disease Control and Prevention, 2012). Additionally, the CDC and the report on neonatal deaths attributed to CHD, hypoplastic left heart syndrome was the most common congenital heart defect which was noted as the underlying cause of neonatal death for white infants (480 [27%]) and black infants (126 [26%]); 38% of the neonatal deaths were listed as "congenital malformation of heart, unspecified." From 2004 to 2006, the adjusted national prevalence estimated hypoplastic left heart syndrome at 1 in 4,344 births with an estimated 960 annual cases and 2.3 per 10,000 live births (Centers for Disease Control and Prevention, 2012).

As survival rates have increased with hypoplastic left heart syndrome, much of the focus has been on outcomes, one of which being neurologic outcomes. It is well
documented in the literature that long-term neurodevelopmental outcomes in children with hypoplastic left heart syndrome is less than ideal, and virtually not reported in the literature for the hypoplastic left heart cohort who has undergone an alternative approach to the traditional staged palliation, referred to as the Hybrid Stage I palliation, which is hereby the foundation of this research.

The following presents the state of the science to date in treatment of hypoplastic left heart syndrome, including review of anatomy and physiology, palliative surgical options, outcomes, and what is known in terms of neurodevelopment. A prospective, longitudinal, non-randomized research study is presented on a sample of hypoplastic left heart syndrome babies who have undergone the Hybrid Stage I procedure, an alternative strategy to the traditional first staged surgical palliation. This study is designed to examine neurodevelopment and test the overall working hypothesis that there is a correlation between cerebral blood flow and neurodevelopmental outcome in infants after Hybrid Stage 1 palliation for HLHS. The following presents the aims of the study:

Aim 1: Evaluate cerebral blood flow after Hybrid Stage I palliation for HLHS using transcranial Doppler

Hypothesis: Infants with HLHS will have decreased cerebral blood flow when compared to healthy controls.

Aim 2: Compare neurodevelopmental outcomes between infants with HLHS and healthy controls.
Hypothesis: Infants with HLHS will have lower scores on the Test of Infant Motor Performance and Bayley Scales of Infant and Toddler Development, 3rd edition across time when compared to healthy controls.

Aim 3: Within each group, determine whether cerebral blood flow is a predictor of neurodevelopmental status.

Hypothesis: Within each group, cerebral blood flow will be predictive of neurodevelopment.

Multiple measurements of variables were obtained over time, during the first six months of life. This included transcranial Doppler ultrasound of blood flow in the middle cerebral artery, developmental assessment, height, weight, and head circumference. Variables were compared to normal healthy control subjects and published or norm referenced data. Study findings were analyzed and the results are summarized in the ensuing chapters.
Chapter 2

Hypoplastic left heart syndrome: Update 2012

Hypoplastic left heart syndrome (HLHS) accounts for 4-8% of all congenital heart disease (CHD) and is one of the most severe and complex forms of CHD (American Heart Association, 2010; Morris et al., 1990; Pigula et al., 2007). This complex lesion is 100% fatal without palliation.

Cardiac anatomy

The diagnosis of HLHS consists of a complexity of left sided heart lesions: a small and underdeveloped left ventricle, a diminutive ascending aorta, with critical mitral and aortic valve stenosis or atresia (Figure 2). An opening between the upper chambers of the heart, atrial septal defect, is usually present. If an atrial septal defect is not present and the atrial septum is intact, these babies are born critically ill, quickly become extremely acidotic, and will succumb to death almost immediately unless an opening in the atrial septum is created immediately after birth. Otherwise, HLHS physiology is actually very well tolerated in utero, fetuses are usually carried to full term gestation, tolerating the stressors of birth, and are born with Apgar scores comparable to the normal newborn. However, it is unknown whether alteration in physiology and cerebral blood flow to the fetal brain is adequate during gestation.
HLHS anatomy and physiology can result in alteration in cerebral blood flow and ultimately inadequate oxygenation to the brain. Fetal brain growth and development is dependent upon an adequate supply of necessary nutrients and oxygenated blood flow. In the developing embryo, intracranial circulation is visible as early as 8 weeks gestation. Normal fetal circulation with preferential cerebral blood flow results from streaming of highly oxygenated blood from the mother to the fetus via the ductus venosus, to the inferior vena cava, across the foramen ovale to the left atrium, left ventricle, ascending aorta, and delivers oxygenated blood to the brain and body. Blood flow velocity waveforms in the middle cerebral artery in the fetus are normally highly pulsatile and end-diastolic measurement become more prominent in gestation with 75% end-diastolic frequencies noted in fetuses between 18-25 weeks gestation and noted in all fetuses after 34 weeks gestation (Vyas et al, 1990).

The fetus with HLHS does not have this preferential oxygenated blood flow delivery to the brain. The majority of blood flow is via the ductus venosus to the inferior vena cava and does not cross the foramen ovale to the left sided heart chambers. The blood is directed from the right atrium to the right ventricle where it is ejected across the pulmonary valve to the pulmonary artery. A very small amount of blood flow goes out to the right and left lung for growth and development. However, with the majority of blood flows across the patent ductus arteriosus (PDA) to the descending aorta to perfuse the body. Antegrade blood flow from the left ventricle to the ascending aorta and head and neck vessels may be either absent or severely diminished in fetuses and neonates with HLHS. They are dependent upon retrograde or backward blood flow, from the PDA, to
the aortic arch to supply the brain, as well as backward flow to the ascending aorta to supply the coronary arteries.

The normal fetal brain has a mechanism which autoregulates cerebral blood flow, altering cerebral vascular resistance in accordance with changes in oxygen delivery. The fetus with HLHS has low cerebral vascular resistance, compared to normal fetuses (Donofrio et al., 2003; McElhinney et al., 2009). This helps to enable retrograde aortic blood flow to the brain as previously described.

**Cerebral anatomy: the operculum**

The cerebral operculum refers to the area of the frontal, parietal, and temporal lobes which overlies the insula, and with apposition of these lobes, the sylvian fissure is formed. In the developing embryo, the operculum starts to form around 20 weeks gestation when the cortical plate thickens and indents at the insular. The temporal and parietal regions develop faster than the anterior region of the frontal lobe. The area folds over covering the insula area, forming the horizontal sylvian fissure. The anterior portion of the insula remains open until the frontal lobe covers the insula when the fetus reaches term gestation. Opercularization has been described as the expression of functional maturity of the brain (Chen et al., 1995; Larroche, 1977; Larroche, 1967; Guibaud et al., 2008). The operculum covers areas of the brain involved with speech and language, as well as the motor aspects of speech. This is Brodmann’s areas 44, referred to as Broca’s area, and area 45 anteriorly, as well as area 22 and 39 posteriorly. Landmarks and measurement of the separation of the operculum by magnetic resonance imaging (MRI) have been reported by Tatum and colleagues (1989) as well as by Chen and colleagues
Tatum et al (1989) found that normal separation of the sylvian fissure should not exceed 3mm and that an open operculum may indicate developmental arrest. Similarly, Chen et al (1995) found the inter-opercular distance in the sylvian fissure in normal healthy infants should not be greater than 4.5mm anteriorly and 0.5mm distance posteriorly. The open operculum has been described in newborns with HLHS. It is an interesting question if there is an association between the HLHS fetus with an open operculum and cognitive outcome. This has not been studied.

**Genetic and Prenatal Factors**

Although recurrent congenital cardiovascular malformations in families have been reported, the malformations are not always the same. The etiology of left ventricular outflow tract malformations, which includes HLHS, remains unknown. A strong genetic component for left ventricular outflow tract malformations have been reported (McBride, et al., 2005), however gene discovery or common pathway specifically for HLHS has yet to be determined. Connexin43 channels are intricately gated by phosphorylation. Connexin subunits form a hydrophilic pore which allow cell to cell exchange of ions, metabolites, and molecules which facilitate signaling pathways for normal heart development (Britz-Cunningham, et al., 1995).

Mutations and polymorphisms in the connexin43 gap junction gene have been identified as a possible factor in the development of HLHS (Dasgupta et al., 2001). Denaturing gradient gel electrophoresis was used to separate normal and variant bands of DNA from the connexin43 gene, coding critical sites for phosphorylation gating of connexin43 channels. After separation, DNA underwent cycle sequencing. Results
demonstrated connexin43 mutations in 8 out of 14 children with HLHS and 1 with atrio-ventricular canal defect. However, 6 children with HLHS lacked mutations. No mutations were found in 46 normal controls or in other forms of congenital heart defects (Dasgupta et al., 2001).

McBride, et al, (2009) first reported on linkage analysis on families with multiple LVOT malformations. McBride, et al. (2009) hypothesized that left ventricular outflow tract malformation susceptibility loci, including HLHS, may be identified using a linkage approach with multiplex families. The results of linkage analysis found evidence suggesting linkage on chromosome 2p23.2, chromosome 12p21.2, and chromosome 16p12.2. Significant non-parametric linkage score (NPLS) in HLHS families were noted for chromosome 2p15 (NPLS = 3.17) with additional suggestive peaks on chromosome 19q13 (NPLS=2.16) and 10q21 (NPLS=1.94) (McBride, et al, 2009). These results showed a significant linkage signal for HLHS on 2p23.

In another study, a cohort of 91 unrelated subjects with left ventricular outflow tract malformations, including HLHS, were analyzed and genomic DNA was screened for mutations in NOTCH1. The mutations in NOTCH1 that alter function of the signaling pathway were found in subjects with aortic valve stenosis, coarctation of the aorta, and HLHS (McBride, et al., 2008). Their findings support the notion that left ventricular outflow tract defects may have a complex genetic inheritance.

Reamon-Buettner et al. (2008) showed that transcription factor heart and neural crest derivatives expressed 1 (Hand1) function is impaired in HLHS. Hand1 is part of
tissue-specific basic helix-loop-helix (bHLH) transcription factors. It is expressed in specific regions of the pre-developed linear heart tube and becomes localized in the outer curvature of the left ventricle and developing outflow tract as well as in the outer curvature of the right ventricle at post-looping of the linear heart tube. Reamon-Buettner (2008) studied hypoplastic hearts and identified a frame shift mutation in 24 out of 31 hypoplastic left or right ventricles consisting of a deletion of a G nucleotide at position 376, affecting the amino acid sequence from Alanine 126 in the bHLH domain.

In 2008, Gambetta, et al., performed gene-expression analysis and profile of the atrial septum of children born with HLHS and compared it to age-matched controls of children born with other congenital heart disease lesions. They identified components of the biological pathways affected in HLHS, suggesting defects in chromatin remodeling, cell cycle regulation, and transcriptional regulation in HLHS. Their findings help support the concept that decreased atrial filling during fetal cardiac development may inhibit the progression of left heart growth during fetal life (Gambetta, et al., 2008).

All of these findings are suggestive that there is a complex, sub-cellular or molecular, genetic component to HLHS. However the etiology of HLHS is most likely multi-faceted and remains unknown. Neural tube formation for the central nervous system is also occurring simultaneously during cardiac development. Brain maturation and structure has also been characterized in newborns with congenital heart disease.

High levels of prenatal stress between 16-20 weeks of gestation have been reported to positively correlate with difficult temperament at 6 months of age in the
infant, but negatively correlate to scholastic achievement and behavior at 7 years of age (Niederhofer, et al., 2000). Typically, fetal cardiac echocardiography is performed between 18-22 weeks gestation and the fetal diagnosis of HLHS may be determined. This may result in tremendous prenatal maternal stress which ultimately may have an adverse effect short term on the fetus, as well as long term for the infant and child. Maternal trait anxiety has been associated with altered distribution of fetal blood flow, lower pulsatility index in the fetal middle cerebral artery, and small for gestational age fetuses (Sjostrom, et al., 1997). The maternal stress effect is a complex entity for the developing fetus, effects of which are not completely understood.

Clearly, there is a growing body of evidence suggestive that prenatal factors and cerebral development in HLHS is abnormal in the fetus (Goldberg et al, 2000; Limperopoulos et al, 1999; Mahle et al, 2002; Miller et al, 2007; Hinton et al, 2008). Several studies have reported white matter injury, periventricular leukomalacia and microcephaly in fetuses and neonates (Shillingford et al, 2007; Hinton et al, 2008; Mahle et al, 2002; Licht et al, 2004; Glauser et al, 1990). Periventricular leukomalacia is the result of injury to the white matter, with suspected etiology from several contributing factors particularly hypoxic ischemic injury of immature oligodendrocytes and the watershed area surrounding the small arteries which penetrate from the cortex. The watershed area is highly sensitive to changes in perfusion pressure and is supplied by the middle cerebral artery. This leads us to the focused interest in evaluating cerebral blood flow in the middle cerebral artery, particularly in the area of the pars opercularis.
In searching the literature, a study by Mahle et al (2001) of 216 infants diagnosed prenatally with HLHS was noted to have fewer intraoperative neurologic events, such as seizures, than those diagnosed postnatally. Additionally, postnatal diagnosis of HLHS was associated with an increased risk and severity of metabolic acidosis preoperatively. Kern and colleagues (1998) reported that a prenatal diagnosis of HLHS in fetuses were more stable neurologically preoperatively than those diagnosed postnatally. However, Mahle et al, (2000) reported that there was no significant improvement in neurodevelopmental outcome in HLHS infants who were diagnosed in utero. It seems the results of such a study would be dependent upon individual birth centers. A prenatal diagnosis allows for family education and careful planning for a controlled delivery in a tertiary center with appropriate personnel to manage the neonate immediately after birth. Although it has been suggested that post-operative lactate levels may impact outcome, pre-operative acidosis may be just as important in terms of morbidity and outcome.

Miller et al., (2007) studied 41 term newborns with congenital heart disease, 12 of who had single ventricle physiology, and performed MRI, magnetic resonance spectroscopy, and diffusion tensor imaging studies preoperatively and compared to normal term neonates. Acquired brain injury was noted in the congenital heart disease group; preoperative stroke and white matter injury were focal in nature. All control newborns had normal MRI scans. Impaired brain metabolism and microstructure were identified in the congenital heart disease group, despite visible injury on MRI. These results help support the growing evidence that brain development is impaired while in utero. This may be due to altered cerebral perfusion and oxygenation.
This in turn leads us back to the question of whether there is adequate cerebral perfusion for brain growth and development given the physiology associated with HLHS. A correlation may exist, which may even begin in utero, between cerebral blood flow and neurodevelopmental outcome in infants with HLHS.

**Options for Surgical Stage I Palliation**

**Norwood Procedure**

The traditional staged Norwood procedure consisted of three staged palliative open heart surgeries during the first few years of life. This was first performed in 1980 and the first staged surgical palliation to the Fontan completion was performed by Norwood and his colleagues and reported in 1983 (Norwood et al, 1980; Norwood et al, 1983). The stage I Norwood procedure (Figure 3) is typically performed within the first few days of life and carries the highest mortality. This first staged procedure involves excision of the atrial septum (atrial septectomy), ligation and division of the PDA, division and over sewing of the main pulmonary artery trunk proximal to the bifurcation of the left and right pulmonary arteries, reconstruction of the ascending aorta by anastomosis of the diminutive ascending aorta to the pulmonary artery, patch augmentation of the aortic arch, and anastomosis of a 3.5 – 4.0 mm shunt graft from the systemic artery to pulmonary artery. Currently, the systemic to pulmonary shunt is a referred to as a modified Blalock-Taussig shunt (mBTS), which is a Gore-Tex tube placed between the right innominate artery and the right pulmonary artery, to augment pulmonary blood flow. The Norwood procedure is performed utilizing deep hypothermic
circulatory arrest and cardiopulmonary bypass (CPB). Staged surgical palliation has remained the gold standard for palliation of HLHS. Despite improvements in surgical technique over the past three decades, the mortality rate associated with HLHS remains highest of all congenital heart disease within the first year of life (Boneva et al, 2001; Ohye et al., 2010).

Although the mortality rate for the Norwood operative procedure itself has decreased in experienced centers, the morbidity has not. The Norwood procedure has been associated with long-term deficits in neurodevelopment including lower full-scale intelligence quotient (FSIQ), delayed motor development and neurologic injury (Kern et al,1998; Mahle & Wernovsky, 2004; Mahle et al, 2004; Mahle et al, 2006; Tabbutt et al, 2008; Rogers et al, 1995; Visconti et al, 2006; Bellinger et al, 1995; Bellinger et al,1999). The mechanisms that account for these deficits are not fully elucidated, however the profound effect of hypothermic circulatory arrest and prolonged CPB were thought to play important causative roles, most likely due to the residual effects of their influence on cerebral blood flow and perfusion (Bellinger et al, 1995; Bellinger et al, 1999; Ferry et al, 1990; Newburger et al, 1993).

Hypoxemia and reperfusion injury from prolonged CPB and deep hypothermic circulatory arrest during the traditional Norwood procedure has been associated with increased risk of poor neurologic outcomes (Wypij et al, 2003). Bellinger and colleagues have reported children who undergo deep hypothermic circulatory arrest are at a greater risk for delayed motor development and neurologic injury (Bellinger et al, 1995; Bellinger et al, 1999). Long-term neurologic sequelae have also been well documented
(Ferry et al, 1990; Newburger et al, 1993). CPB time, degree of hypothermia, selective antegrade or retrograde cerebral perfusion, as well as time periods of circulatory arrest vary amongst centers and individual operative procedures. Alterations in cerebral blood flow, microembolization, and the significant inflammatory response from cardiopulmonary bypass have also been suggested as possible etiologies for neurologic injury (Glauser et al, 1990, Shillingford et al., 2007; Newburger et al., 1993; Dent et al., 2006; Mahle et al., 2002). Additionally, birth weight, prematurity, and anatomical complexity add to the risk and are significant factors in managing neonates with HLHS. Although overall surgical survival rate after Norwood Stage I has improved, with experienced centers reporting 70–90% survival, the reported 5 year survival remains suboptimal with ranges between 40-61% (Tweddell et al, 2002; Stasik et al, 2006; Bove, 1998, 1999, 2004; Bove et al., 2004; Mahle et al, 2000; Alsoufi et al, 2007).

**Norwood-Sano procedure**

The Norwood-Sano procedure is a variation of the Norwood procedure. A right ventricle to pulmonary artery (RV-PA) shunt to augment pulmonary blood flow during the first stage palliation for HLHS was actually first performed in 1981 by Norwood (Norwood et al, 1981). However, this was too large of a shunt, resulting in pulmonary over circulation and failure of the right ventricle, and was abandoned for the aorto-pulmonary shunt or BT shunt. Modification to the RV-PA shunt using a smaller graft, termed the Norwood-Sano or “Sano” procedure (Figure 4), named after Sunji Sano, MD, a cardiothoracic surgeon in Okayam, Japan, was first performed in 1998 and has become popular in many centers as an alternative to the modified BT shunt. The purpose is also to
provide a more reliable and pulsatile blood flow to the pulmonary arteries and lungs. The Sano modification (Figure 4) utilizes a smaller, 4-5mm RV-PA non-valved, polytetrafluoroethylene shunt to augment pulmonary artery blood flow (Sano et al., 2003). The Norwood-Sano operation is currently being performed in many institutions in addition to the traditional Norwood Stage I procedure for HLHS. The Sano operation eliminates the diastolic run-off into the pulmonary bed which is seen in with the modified BT shunt, and decreases the ventricular volume overload (Ohye, et al., 2004). It may also reduce complications associated with low, diastolic systemic pressure such as necrotizing enterocolitis. However this is not proven.

The Sano operation has some reported disadvantages of right ventricle dilation from free pulmonary shunt regurgitation, shunt obstruction, occlusion, and development of false right ventricular aneurysm (Sano et al, 2003). Like the traditional Stage I Norwood, the Sano operation still requires the use of CPB and circulatory arrest in the neonatal period which again adds to the risk of developing cerebral neuronal injury from ischemia, cerebral hemorrhage, embolization, and the neurologic effects of the systemic inflammatory response from CPB. There is also the unknown effect of a right ventriculotomy incision on the systemic right ventricle.

In a multi-center (15 centers) randomized clinical trial, supported by the National Heart, Lung, and Blood Institute, comparing two different shunt types for infants undergoing the Norwood procedure, 275 infants had a modified BT shunt, and 274 infants had a RV-PA shunt, (Ohye et al., 2010; Ohye, et al., 2008). Transplantation-free survival at 12 months was higher for the RV-PA shunt compared to the modified BT
shunt (74% vs. 64%, P=0.01). However, more transcatheter interventions and complications occurred in the RV-PA shunt group. Follow up at 32 ± 11 months revealed no significant difference between the two groups (Ohye et al, 2010). Although valuable information was learned from this study in terms of the primary outcome of death or cardiac transplantation at 12 months, no developmental testing was performed during this study for comparison of two surgical strategies and developmental outcomes.

**Hybrid Stage I procedure**

The Hybrid Stage I palliation (Figure 5) offers an alternative management strategy for newborns with HLHS (Galantowicz & Cheatham, 2005; Galantowicz et al, 2008; Akintuerk et al, 2002; 2007; Pill, et al., 2008; Bacha, et al., 2006; Bacha, 2008; Chen & Parry, 2009). The rationale for performing the Hybrid procedure versus the Norwood procedure is to completely avoid cardiopulmonary bypass, circulatory arrest, and the associated surgical risks early in the neonatal period, and to ultimately improve long term outcomes. The Hybrid Stage I procedure shifts the major open heart surgery, including the risks associated with cardiopulmonary bypass, to approximately 6 months of age and 6 kg with the idea that with maturity, cardiopulmonary bypass will be better tolerated at a later age well beyond the neonatal period and after transitioning to extra-uterine life. Prior to the Hybrid Stage I procedure, the ductus arteriosus is kept patent by prostaglandin E1 intravenous infusion. The entire cardiac output is maintained and dependent upon the patent ductus arteriosus (PDA).

The Hybrid Stage I palliation involves a combination of cardiothoracic surgical and interventional techniques performed in the same setting. Hybrid Stage I palliation is
performed without stopping the heart and does not require cardiopulmonary bypass. This is a great advantage for initial palliation as it helps to avoid or lessen the inflammatory response associated with cardiopulmonary bypass. This treatment strategy involves placing bilateral branch pulmonary artery bands and a PDA stent, through a small median sternotomy on the beating heart, usually during the first week of life. Additionally, at a later date, a balloon atrial septostomy is performed to create an adequate sized atrial septal defect or opening between the left and right atrium. During the initial Hybrid Stage I palliation, the surgeon places a 1-2mm wide Gore-Tex band around the left and right pulmonary arteries. This is followed by placement of either a self-expandable or balloon-expandable stent in the ductus arteriosus by the interventional cardiology team through a small sheath placed in the main pulmonary artery. The pulmonary artery bands control blood flow to the lungs and protect the pulmonary bed from high pressure, while the PDA stent provides a reliable means of maintaining cardiac output and retrograde aortic perfusion to the brain and coronary arteries. Once the PDA stent is in place, prostaglandin E1 infusion is discontinued immediately. Cardiac catheterization is performed at a separate setting prior to discharge or when the atrial septal defect becomes restrictive of blood flow from the left atrium. At that time a balloon atrial septostomy is performed in order to allow unobstructed blood flow from the left atrium to the right atrium, thus completing Stage I palliation.
Operative, post-operative, and interstage factors

The human body normally has a protective mechanism to initiate an inflammatory response to destroy what it recognizes as foreign and “not self.” A systemic inflammatory response syndrome can occur from cardiopulmonary bypass as a result of surgical trauma itself, blood coming in contact with non-physiological surfaces such as the bypass circuit, or ischemia and endotoxins (Kats et al, 2010). Multiple factors contribute to the systemic inflammatory response as a result of cardiopulmonary bypass including activation of the coagulation cascade, both intrinsic and extrinsic pathways, along with increased fibrinolytic activity, activation of the complement system, leukocyte activation including pro-inflammatory cytokines, endothelial cell activation, and platelet activation. The end products of the complement system activation may contribute to tissue injury due to pro-inflammatory effects. Studies have shown administering glucocorticoid can help decrease pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) interleukin (IL) -6, and IL-8, as well as increase IL-10, an anti-inflammatory cytokine (Kats et al., 2010). Endotoxin come from gram negative bacteria cell walls and is produced by intestinal flora. However, when endotoxin is in the circulation it binds to various receptor sites and leads to cytokine production and an inflammatory response (Kats et al, 2010). Studies have found endotoxins to be present in the cardioplegia solution, priming fluid for the cardiopulmonary bypass circuit, contaminated extracorporeal circuits, pulmonary artery catheters, intravenous fluids and banked blood product used for transfusion, drugs, and surgical instruments (Andersen et al, 1987; Nilsson et al, 1990; Miller & Levy, 1997; Kats et al, 2010). The overall systemic
inflammatory response following cardiopulmonary bypass contributes to post-operative management of patients with HLHS who have undergone the Norwood procedure. Complications from the systemic inflammatory response may ultimately affect major organ systems, such as cardiac, respiratory, renal, and in particular the brain and neurologic function (Paparella et al, 2002; Kats et al, 2010).

A variety of management strategies have been investigated to eliminate the inflammatory response from cardiopulmonary bypass. From a pharmacologic approach, corticosteroids have been used prophylactically before and during cardiopulmonary bypass, however routine use is controversial. Selective digestive decontamination by pharyngeal and gastric application of non-absorbable antibiotics has been reported in adult coronary artery bypass graft and valvular surgery patients (Martinez-Pellus et al, 1993). Results showed lower endotoxin levels in the treated group compared to the control group, however there was no difference in clinical outcomes. Other strategies that have been employed include off-pump versus on-pump technique, pulsatile versus nonpulsatile flow, and normothermia versus hypothermia, as well as pharmacologic therapies to reduce the inflammatory response (Day & Taylor, 2005; Hill et al., 1995; Mongero et al., 2001; Engelman et al., 1995). The fact remains that despite decreased endotoxin and lactate levels, the body still elicits an inflammatory response to the surgical trauma itself and manipulation of the heart.

In the immediate post-operative period following the Norwood or Norwood Sano procedure, the cardiothoracic intensive care management team needs to be adept at closely monitoring and treating lactate levels. The effects of cardiopulmonary bypass and
the systemic inflammatory response can alter multiple organ systems, resulting in post-operative complications. At times, the neonate will have difficulty being separated from cardiopulmonary bypass and will require extracorporeal membrane oxygenation (ECMO). Frequently, before transfer to the cardiothoracic intensive care unit, it is not possible to close the chest in the immediate postoperative period for the Norwood or Norwood-Sano patient, which adds another source of morbidity and surgical procedure. Inotropic support in these patients is common.

Unlike the immediate post-operative outcomes in the Norwood or Norwood-Sano patient, the post-operative care after Hybrid Stage I is remarkably different. In 40 HLHS patients, after Hybrid Stage I palliation, with a median weight of 3.2kg, Galantowicz et al (2008) reported 52% of Hybrid patients are extubated in the operating room, while 85% are extubated within 24 hours. Inotropic support was not required in any patient and 79% of patients were feeding within 24 hours. No patient required ECMO support or delayed sternal closure. There was a reported 97.5% hospital survival to discharge with the average length of stay 4.5 days in the cardiothoracic intensive care unit (CTICU) and the average postoperative length of stay in the hospital was 13 days (Galantowicz et al, 2008). Although the Hybrid patients appear to do better post-operatively compared to the Norwood patients with shorter time to extubation, initiation of enteral feeds, shorter CTICU and hospital length of stay, there is uncertainty regarding oxygenation and perfusion to the brain due to the anatomy of the persistent retrograde aortic blood flow. More importantly, neurocognitive development and deficits are unknown at this time and to date there is only one study reported in the literature (Knirsch, et al., 2012).
The interstage period between Stage I and Comprehensive Stage II surgical palliation for HLHS is a vulnerable period in terms of infants reaching their nadir with hematocrit and hemoglobin levels, as well as their immune system and protection from maternal antibodies. The Hybrid patients are at some degree of risk for developing intimal proliferation within the stented ductus as the nature of the ductal tissue wants to close, with the risk of creating retrograde arch obstruction, recoarctation at the distal PDA stent, decreased RV function. Hybrid Stage I palliation is independent of patient size unlike the Norwood or Norwood-Sano palliation; babies as small as 1 kg have been successfully palliated (Galantowicz et al., 2008; Cua et al., 2004). These extreme preterm babies are at risk for other comorbidities such as interventricular hemorrhage and necrotizing enterocolitis. Any of these events can lead to hospitalization, cardio-respiratory support, and cardiac catheterization with interventional therapy. These infants need to be closely monitored with echocardiograms and electrocardiograms as outpatients. Many centers have incorporated a home monitoring program for recording daily intake for caloric monitoring, daily weight, and oxygen saturation monitoring.

**Stage II palliation**

The second staged reconstruction for HLHS after the Norwood procedure is performed at approximately 6 months of age and consists of a cavopulmonary anastomosis of the superior vena cava to the right pulmonary artery and takedown of the Blalock-Taussig shunt by ligation and division. This second surgery is a bidirectional Glenn shunt or hemi-Fontan (Figure 6). Both will have the same physiology. The difference between the bidirectional Glenn and the hemi-Fontan is the transected cardiac
side of the superior vena cava from the right atrium is anastomosed to the undersurface of the right pulmonary artery and a patch applied. This will decrease the amount of cardiopulmonary bypass time at the final Fontan completion.

The second staged reconstruction after Hybrid Stage I palliation is termed the Comprehensive Stage II procedure (Figure 7). This is considered the big open heart surgery for staged palliation for HLHS. This incorporates removal of the PDA stent and pulmonary artery bands, removal of the atrial septum, anastomosis of the diminutive ascending aorta to the main pulmonary artery, and anastomosis of the diminutive ascending aorta to the pulmonary artery and augmentation of the transverse aortic arch.

**Stage III – Fontan completion**

The third and final stage of reconstruction, the Fontan, is normally completed around 18-24 months of age. This is the total cavopulmonary connection where the inferior vena cava is now anastomosed to the pulmonary artery via an extra cardiac pericardial baffle, completing the circuit (Figure 8). A small 4-5mm fenestration may be performed to act as a pressure “pop-off” allowing a small amount of “blue” blood to shunt across to the “red” blood side. This may increase the risk of an embolic event, therefore anticoagulation therapy is usually recommended. Fenestrations may be closed non-surgically using a device in the cardiac catheterization suite at a later age.

**Outcomes and neurodevelopment**

When comparing cohorts of HLHS patients between surgical eras, different surgical palliation strategies, and neurodevelopmental outcomes, it will be important to
compare a cohort of patients with uniform risk. This will require excluding babies who have HLHS with intact atrial septum, who present with cyanosis and acidosis, and require emergent creation of an atrial septal defect at birth. These patients are known to be at higher risk for mortality and morbidity. Additionally, babies with severe prematurity and HLHS are also identified as a higher risk group, as are those with genetic syndromes, right ventricle dysfunction with significant tricuspid regurgitation due to perinatal asphyxia, and those babies born with HLHS who were not identified prenatally, were discharged home and the PDA closes resulting in cardiovascular collapse.

Mahle and colleagues (2002) compared serial brain MRI studies in 24 neonates with complex CHD who underwent open heart surgery. Studies were performed preoperatively, early post-operatively (between 5-12 days) and late post-operatively between 3-6 months. Diagnoses included 13 neonates with single ventricle physiology; 8 of which had HLHS. From a structural standpoint, 4 subjects were noted to have an open operculum. Pre-operatively, 6 out of 24 (25%) were found to have ischemic lesions; 4 with periventricular leukomalacia (PVL) and 2 with small infarcts. In the early postoperative scan, (n=21) new or worsened lesions were noted in 14 subjects (67%); this included 9 subjects with new PVL, 4 subjects with significant infarcts. New or worsened lesions were noted in 7 of 12 (58%) patients who underwent the Norwood procedure (figure 2). In the late post-operative scan, only 1 subject developed a new infarct. PVL from early scans resolved in all subjects. Preoperatively 53% of subjects had increased white matter lactate levels consistent with ischemia.
In another study by Dent and colleagues (2006) pre- and post-surgical brain MRI studies were performed after the Norwood procedure using regional cerebral perfusion. Ischemic lesions were noted in 5 out of 22 patients (23%) compared to new or worsened lesions in 11 out of 15 (73%) patients. Neonates with HLHS undergoing a Norwood procedure who had prolonged (>180 minutes) postoperative regional cerebral oxygen saturation of 45% or lower, had new or worsened ischemia on early postoperative MRI (Dent et al, 2006). What is considered a “safe” threshold for hypoxia and cerebral ischemia is yet to be determined for neonates undergoing open heart surgery. Multiple variables can influence this threshold including shorter deep hypothermic cardiac arrest and cross clamp time (Goldberg et al, 2007; Hanley, 2005), utilization of regional low flow perfusion, as well as perfusion flow rate (Ohye et al, 2009; Goldberg et al 2007), and oxygen saturation variability (Fenton et al, 2005; Kurth et al, 2001).

In a five year study by Glauser and colleagues (1990), findings at neonatal autopsy reported one-third of HLHS infants had central nervous system anomalies and/or were microcephalic. In another study, aortic morphometry and microcephaly was evaluated in 129 term neonates with HLHS with a median head circumference at the 18th percentile at birth (Shillingford et al, 2007). The mean birth weight was 3.2 ± 0.5 kg. The average head circumference ± standard deviation (SD) was 33.9 cm ± 1.6 cm, with average percentile 26.5 ± 20 percent. Mean and SD of the ascending aortic diameter was 3.2 ± 1.5mm. Head circumferences were found to be disproportionately smaller than birth weight and length, with 12% microcephaly noted. They noted a significant correlation between those with microcephaly and a smaller ascending aortic diameter.
All of these studies suggest that having a diminutive ascending aorta with an atretic or severely stenotic aortic valve, may result in abnormal cerebral development in the HLHS fetus.

Not all children with HLHS have neurocognitive deficits and in fact, most have a normal IQ and fall within the normal range for standardized testing. Goldberg and colleagues (2007) showed that the average FSIQ score for 19 subjects with HLHS was 97.9 after the third and final stage with Fontan palliation. Wernovsky et al, (2000) reported on a large series of HLHS patients after completing the third staged palliation, the Fontan procedure. After undergoing a battery of developmental testing and adjusting for socioeconomic status, statistically significant lower IQ was associated with deep hypothermic circulatory arrest in HLHS patients. Mean FSIQ was 95.7 + 17.4 (p<0.006 compared to normal) and 10 patients had FSIQ scores <70 (p=0.001). Wernovsky (2000) concluded that Fontan patients who received palliation in the 1980’s have cognitive and academic function within normal range; however, overall lower than the general population. However, other studies reported major developmental disabilities during the same era (Rogers, et al 1995).

A later study by Mahle et al., (2000) reported neurocognitive outcomes on 28 HLHS patients who had undergone the Norwood procedure. The findings showed a median FSIQ of 86, 18% of these patients had significant mental retardation (FSIQ < 70). This study demonstrated that only preoperative seizures significantly correlated with lower FSIQ. Kern, et.al. (1998) reported moderate neurocognitive impairment, with
medians scores for FSIQ, verbal IQ, and performance IQ of 88, 91 and 83, respectively, in HLHS patients after the Norwood procedure in 14 preschool subjects ages 3-6 years and compared to family controls. In a study by Tabbutt, et al. (2008) 88 children with HLHS were tested at 1 year of age, using the Bayley Scales of Infant Development, second edition (BSD II) (Bayley, 1993) for Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI). Although the median MDI was 90, 11% of children had scores <70, 2 standard deviations (SD) below the normative population. Interestingly, PDI scores were more adversely affected with a median score of 73, and 48% of children scoring <70, again 2 SD below the norm. These results are similar to findings by Goldberg et al, (2007) with PDI scores lower than MDI scores, both before second staged surgery (P < .0001) and at 1 year (P < .0001). Similarly, in a study by Visconti et al (2006), 29 infants with HLHS did not perform well on the BSD II at one year of age. Results showed median MDI and PDI scores of 87.7 and 75.2, demonstrating a low average and mild delay respectively. Mental development and motor development are both impacted, with motor development being more affected. Deficits in neurodevelopment continue to be prevalent well into school-age. Neuropsychological testing demonstrates that school-age children were well below normative values (Mahle et al, 2006).

Wernovsky et al., (2000) found mean FSIQ was significantly lower compared with the normal population and 7.8% of test subjects had FSIQ scores <70. After controlling for socioeconomic status, lower IQ and independent risk factors for low achievement scores was associated with HLHS and deep hypothermic circulatory arrest.
Previous studies examined children with single ventricle physiology who underwent the Fontan operation (third and final staged palliation) and found IQ scores were lower compared to the normal population, however intelligence scores were within 1 SD of the norm (Uzark et al., 1998; Goldberg et al., 2000). Goldberg et al. (2000) compared HLHS and non-HLHS patients who under Fontan completion between 1989 and 1994. The overall mean scores were within normal range however the HLHS group scored lower than the non-HLHS group. Socioeconomic status, cardiac arrest and perioperative seizures were associated with lower neurodevelopmental outcome. Visuomotor and visuospatial skills, as well as language proficiency have also been reported below expected norms (Mahle et al., 2006). Based upon neurologic examination, Mahle et al. (2000) reported 67% of HLHS patients met screening criteria for attention deficit hyperactivity disorder, 18% had attention problems, 18% had behavior problems, and 20% of scores were identified for concerns of anxiety and depression. Shillingford et al. (2008) also reported clinically significant scores for inattention and hyperactivity in school aged children with complex CHD, almost half of which had staged reconstruction for HLHS and single ventricle.

In a more recent prospective study, a Finland group evaluated 22 patients with HLHS and 14 with univentricular heart (single ventricle physiology) and compared them with 42 healthy control children at a median age of 30.2 months (Sarajuuri et al., 2010). The children were evaluated using the BSD II. The results showed a mean MDI score was significantly lower (89.9) in patients with HLHS compared to control subjects (105.5, P < .001), whereas there was no difference between patients with other single
ventricle lesions (98.5) and control subjects. The mean PDI score in the HLHS group (80.7, P < .001), as well as in the univentricular heart group (94.5, P = .016), demonstrated a statistically significant lower score compared with control subjects (105.3) (Sarajuuri et al., 2010).

In a similar study, Atallah et al (2008) performed standardized developmental testing using the BSD II on 94 children with HLHS comparing different surgical strategies in different eras. The Norwood modified Blalock Taussig Shunt (Norwood-mBTS) era was from 1996-2002 (n=62) and the Norwood Right Ventricle to Pulmonary Artery (Norwood-RVPA) (Figure 4) era was from 2002-2005 (n=32). Early and 2-year mortality rates were 23% and 52% respectively in the mBTS era, and 6% and 19% in the RVPA era. The mean MDI scores were not significantly different between groups. The mean PDI scores were significantly higher and the incidence of psychomotor delay <70 was significantly lower for the RVPA group. High serum lactate levels were identified as an independent predictor of 2-year mortality for both groups. As with many of these studies, this study did not reach statistical power to show a statistical difference in the 2 groups for early mortality.

In a more recent study, Mahle, et al. (2012) studied the subjects from the Single Ventricle Reconstruction Trial (Ohye, et al., 2010) and used a classification and regression tree analysis model to predict severe neurodevelopment impairment, defined as the PDI score of less than 70. Using the BSD II, 138 out of 313 (44%) scored less than 70. Predictors identified included intensive care unit length of stay greater than 46 days,
birth weight less than 2.7 kilograms, genetic syndromes and other anomalies, additional cardiac procedures, and the use of at least 5 medications at hospital discharge. The model correctly identified 75% of infants with a PDI score less than 70 (Mahle, et al., 2012).

HLHS from the Single Ventricle Reconstruction Trial were also assessed at 14.3 ± 1.1 months of age for psychomotor and mental development using the BSD II. Scores were compared to norm referenced data. PDI and MDI scores were significantly decreased compared to age matched controls. Independent predictors for low scores included the institution, birth weight less than 2.5 kilograms, length of hospital stay, complications, genetic syndrome, and lower maternal education for MDI (Newburger, et al., 2012). Furthermore, the study concluded that “impaired neurodevelopment” was related to “innate factors” and overall morbidity during infancy, versus intra-operative management (Newburger, et al., 2012). This suggests that in order to improve neurodevelopmental outcomes, the focus should not be related to surgical management in the operating room, but perhaps in early interventions in neurodevelopment.

The first report comparing outcomes between the Norwood procedure and the Hybrid procedure in 31 HLHS and other univentricular hearts showed no difference in mortality at 1 year of age (31% in the Hybrid group versus 39% in the Norwood group, p= .71) (Knirsch, et al., 2012). Surgical treatment strategy had no effect on outcomes. Mortality was associated with low birth weight, older age at initial surgical palliation, and a smaller diameter of the ascending aorta. Median PDI scores were significantly lower than the norm (PDI 57, range 49–99, P < 0.001). Predictors of lower motor scores
included hospital length of stay and lower weight at the second staged surgery. Median MDI scores were also lower than the norm-referenced data. The MDI scores were associated with longer mechanical ventilation, longer intensive care and overall hospital length of stay. This raises the question whether supplementary developmental interventions can be performed while hospitalized.

**Conclusions**

The Hybrid Stage I procedure offers advantages over the Norwood and Norwood-Sano procedures as the Hybrid does not require deep hypothermic circulatory arrest or cardiopulmonary bypass (Galantowicz & Cheatham, 2005; Galantowicz et al., 2008). The physiology however, remains the same, or similar to fetal physiology for retrograde aortic arch blood flow to the brain and perfusion of the coronary arteries. After the Hybrid procedure and up until the second staged surgical palliation, the Comprehensive Stage II procedure performed at approximately 6 months of age, blood flow to the brain is maintained through the PDA and is dependent upon retrograde flow of blood to the aortic arch vessels and ultimately the vessels that perfuse the brain. It is presumed that there is an adequate supply of oxygenated blood to the brain to prevent neurologic injury and promote growth and development of the central nervous system. What is unknown is the impact of the Hybrid procedure on short and long term neurodevelopmental outcomes, although the first study to report developmental outcomes comparing the Norwood to the Hybrid shows no difference. The Comprehensive Stage II procedure is considered the big open heart surgical repair for those who underwent Hybrid Stage I. This is a long
complicated surgery, essentially incorporating part of the traditional Stage I palliation, as well as the second stage of palliation, with the philosophy that the 5-6 month old infant is more mature to tolerate cardiopulmonary bypass and circulatory arrest.

Now that the Hybrid Stage I is an accepted and practiced management strategy, there is an ethical obligation to investigate in a scientific and systematic way, the neurodevelopmental outcomes in HLHS infants who undergo Hybrid Stage I palliation and ultimately compare them with infants who have had Norwood Stage I, as well as the Norwood-Sano procedure. However, it will be difficult to perform a multi-center, randomized clinical trial, with all three surgical strategies given the difference in surgical technique, experience, or preference by cardiothoracic surgeons. Decisions are often collaborative between the surgeon, cardiologist, and family on which strategy would provide the best outcome. However, institution to institution neurodevelopmental outcomes can be studied and compared using standardized testing methods, regardless of the initial choice of Stage I palliation. The following chapter presents an initial investigation into the development of infants born with HLHS, who undergo the Hybrid Stage I palliation.
Chapter 3

Neurodevelopment following Hybrid Stage I for HLHS

Introduction

Hypoplastic left heart syndrome (HLHS) is a complex form of congenital heart disease which requires three open heart surgeries during the first few years of life. HLHS was a fatal diagnosis, the only option being comfort care, up until 1980. The first staged open heart surgical procedure was first reported in the early 1980s (Norwood, et al., 1981; Norwood, et al., 1983). During the ensuing years morbidity and mortality were high and neurodevelopmental outcomes were not favorable. A variety of factors may collectively contribute to the neurodevelopmental outcome in neonates who are born with HLHS including genetic and epigenetic factors, prenatal cerebral blood flow effecting brain growth and development, and open heart surgery in the newborn period. Over the recent decades morbidity and mortality have improved. Advances in surgical technique, pre- and post-operative management, cerebral oxygen monitoring particularly during surgery, as well as advancement in bypass circuits and perfusion technique may all have contributed to increased survival. However, despite these improvements and increased survival, HLHS continues to have the worst neurodevelopmental outcomes compared to other forms of congenital heart disease. To date, very little is known on
neurodevelopmental outcomes in children with HLHS who have undergone Hybrid Stage I, Comprehensive Stage II, and Fontan completion. The following report describes neurodevelopmental outcomes in infants with HLHS after Hybrid Stage I palliation.

**Background**

Neurodevelopmental outcome studies have been reported in children with HLHS who have undergone the traditional staged Norwood palliation showing a lower level of mental and psychomotor deficits compared to other forms of congenital heart disease, as well as normal controls (Sarajuuri et al., 2010; Sarajuuri et al., 2009; Atallah et al., 2008; Tabbutt et al., 2008; Visconti et al., 2006; Goldberg et al., 2007; Goldberg et al., 2000).

Rogers, et al (1995) examined neurodevelopment after palliative surgery for HLHS, in a small cohort of 11 patients and reported 7 of these children (64%) had major developmental disabilities. Kern, et al. (1998) reported moderate neurocognitive impairment, with medians scores for full scale intelligence quotient (FSIQ), verbal intelligence quotient (IQ), and performance IQ of 88, 91 and 83, respectively, in HLHS patients after the Norwood procedure in 14 preschool subjects ages 3-6 years and compared to family controls. A study of 88 children with HLHS, who underwent staged reconstruction, were tested at 1 year of age, using the Bayley Scales of Infant Development, second edition (BSD II) (Bayley, 1993) for Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI). The median MDI was 90, however 11% of children had scores <70, 2 standard deviations (SD) below the normative population. Interestingly, PDI scores were more adversely affected with a median PDI score of 73, with 48% of children scoring <70, again 2 SD below the norm. Years later,
these results are similar to findings by Goldberg et al, (2007) with PDI scores lower than MDI scores both before second staged surgery (P < .0001) and at 1 year (P < .0001).

Similarly, in a study by Visconti et al (2006), 29 infants with HLHS did not perform well on the BSD II at one year of age. Results showed median MDI and PDI scores of 87.7 and 75.2, demonstrating a low average and mild delay respectively.

Not all children born with HLHS have neurocognitive deficits. In fact, HLHS is a heterogeneous group and most have a normal IQ and fall within the normal range for standardized testing. Goldberg and colleagues (2007) showed that the average FSIQ score for 19 subjects with HLHS was 97.9 after the third and final stage with Fontan palliation. Wernovsky et al, (2000) reported on a large series of HLHS patients after Fontan completion. After undergoing a battery of developmental testing for overall pre-academic and academic function, and adjusting for socioeconomic status, statistically significant lower IQ was associated with deep hypothermic cardiac arrest in HLHS patients. Mean FSIQ was 95.7 + 17.4 (p<0.006 compared to normal) and 10 patients had FSIQ scores <70 (p=0.001). Wernovsky (2000) concluded that Fontan patients who received palliation in the 1970’s-1980’s have cognitive and academic function within normal range, however overall lower than the general population.

Contrary to this study, Mahle et al., (2000) reported neurocognitive outcomes on 28 HLHS patients who had undergone the Norwood procedure. The findings showed a median FSIQ of 86, 18% of these patients had significant mental retardation (FSIQ < 70). This study revealed that only preoperative seizures significantly correlated with lower
FSIQ. Deficits in neurodevelopment continue to be prevalent well into school-age. Neuropsychologic testing demonstrated that school-age children were well below normative values (Mahle et al, 2006).

In a select cohort of children with single ventricle who underwent the Fontan operation, standardized testing for FSIQ and achievement testing was performed at a median age of 11.1 years (Wernovsky et al., 2000). Mean FSIQ was significantly lower compared with the normal population and 7.8% of test subjects had FSIQ scores <70. After controlling for socioeconomic status, lower IQ and independent risk factors for low achievement scores was associated with HLHS and deep hypothermic circulatory arrest. Previous studies examined children with single ventricle physiology who underwent the Fontan operation (third and final staged palliation) and found IQ scores were lower compared to the normal population. However, intelligence scores were within 1 SD of the norm (Uzark et al., 1998; Goldberg et al., 2000; Forbess et al., 2001). Goldberg et al. (2000) compared HLHS and non-HLHS patients who under Fontan completion between 1989 and 1994. The overall mean scores were within normal range, however the HLHS group scored lower than the non-HLHS group. Socioeconomic status, cardiac arrest and perioperative seizures were associated with lower neurodevelopmental outcome.

Visuomotor and visuospatial skills, as well as language proficiency have also been reported below expected norms (Mahle et al., 2006). Based upon neurologic examination, Mahle et al (2000) reported 67% of HLHS patients met screening criteria for attention deficit hyperactivity disorder. The investigators found 18% of children had
attention problems, 18% had behavior problems, and 20% of scores were identified for concerns of anxiety and depression. Shillingford et al. (2008) also reported clinically significant scores for inattention and hyperactivity in school aged children with complex congenital heart disease, almost half of which had staged reconstruction for HLHS and single ventricle physiology.

A Canadian group studied early childhood neurodevelopment and compared the results to preschool neurocognitive results in children with complex congenital heart disease who initially underwent cardiac surgery under 6 weeks of age (Creighton et al., 2007). Developmental assessments were performed at a mean age of 22 months using the BSD II, and compared with the 5 year assessment. The subscales included the MDI and the PDI. Out of the 85 children studied, 14 had HLHS and underwent the Norwood procedure. For this subset of patients with HLHS, 5 year survival was only 54%. The study reported a correlation between the MDI at 2 years and the FSIQ at 5 years ($r=0.9197; p< .001$). Additionally, non-HLHS complex forms of congenital heart disease scored higher than the Norwood HLHS group on PDI, performance IQ, and visual motor integration. This showed a high correlation between the two time intervals of testing, early childhood development to preschool, and a high negative predictive value was reported within categories of intelligence.

In a similar study, Atallah et al (2008) performed standardized developmental testing using the BSD II on 94 children with HLHS comparing different surgical strategies in different eras. The Norwood modified Blalock Taussig Shunt (Norwood-
mBTS, figure 3) era was from 1996-2002 (n=62) and the Norwood Right Ventricle to Pulmonary Artery (Norwood-RVPA), described in previous chapters (figure 4), era was from 2002-2005 (n=32). Early and 2-year mortality rates were 23% and 52% respectively in the mBTS era, and 6% and 19% in the RVPA era. The mean MDI scores were not significantly different between groups. The mean PDI scores were significantly higher and the incidence of psychomotor delay <70 was significantly lower for the RVPA group. High serum lactate levels were identified as an independent predictor of 2-year mortality for both groups. As with many of these studies, this study did not reach statistical power to show a statistical difference in the 2 groups for early mortality.

In 2008, Tabbutt et al. reported on 83 children who underwent staged reconstruction for HLHS and variants of single ventricle physiology who were tested at one year of age using the BSD II. The median birth weight was 3.3 kg (range 2.1-4.5 kg). Twenty-five patients (28%) had a confirmed or suspected genetic syndrome. Results for the neuromuscular assessment were abnormal in 57 patients (65%). A median MDI score was 90. Ten patients (11%) scored <70 which represents 2 standard deviations below the mean for the general population. The median PDI score was 73. A total of 42 patients (48%) scored <70. Contrary to other studies, there was no association between deep hypothermic circulatory arrest and neurodevelopmental outcomes. Gestational ages varied from 32 – 40 weeks. However, younger gestational age, the presence of a genetic syndrome, and the need for preoperative intubation were identified as significant risk factors associated with negative neurodevelopmental outcomes.
In a more recent prospective study, a Finland group evaluated 22 patients with HLHS and 14 with univentricular heart (single ventricle physiology) and compared them with 42 healthy control children at a median age of 30.2 months (Sarajuuri et al., 2010). The children were evaluated using the BSD II. The results showed the mean MDI was significantly lower (89.9) in patients with HLHS than in control subjects (105.5, P < .001), whereas there was no difference between patients with non-HLHS single ventricle (98.5) and control subjects. The mean PDI in the HLHS group (80.7, P < .001) as well as in the single ventricle group (94.5, P = .016) demonstrated a statistically significant lower score compared with control subjects (105.3) (Sarajuuri et al., 2010).

In a more contemporary study, Mahle, et al. (2012) studied the subjects from the Single Ventricle Reconstruction Trial and used a classification and regression tree analysis model to predict severe neurodevelopment impairment as defined as the psychomotor development index score of less than 70. Using the BSD II, 138 out of 313 (44%) scored less than 70. Predictors identified included intensive care unit length of stay greater than 46 days, birth weight less than 2.7 kilograms, genetic syndromes and other anomalies, additional cardiac procedures, and the use of at least 5 medications at hospital discharge. The model correctly identified 75% of infants with a PDI score less than 70 (Mahle, et al., 2012).

HLHS subjects from the Single Ventricle Reconstruction trial were also assessed at 14.3 ± 1.1 months of age for psychomotor and mental development, also using the BSD II. Scores were compared to norm referenced data. PDI and MDI scores were
significantly decreased compared to age matched controls. Independent predictors for low scores included the institution, birth weight less than 2.5 kilograms, length of hospital stay, complications, genetic syndrome, and lower maternal education for MDI (Newburger, et al., 2012). Furthermore, the study concluded that “impaired neurodevelopment” was related to “innate factors” and overall morbidity during infancy, versus intra-operative management (Newburger, et al., 2012). This suggests that in order to improve neurodevelopmental outcomes, the focus should not be related to surgical management in the operating room. Early interventions are needed in these infants. It is important to note, all of these studies were performed on children with HLHS who have undergone the traditional Norwood staged palliation.

The first published study on neurodevelopmental outcomes in infants with HLHS and other univentricular hearts who underwent Hybrid Stage I palliation versus the Norwood procedure was reported recently (Knirsch, et al., 2012). Results showed no significant difference in 1 year mortality. Additionally, the PDI and MDI scores were comparable in both groups (Hybrid n=9 and Norwood n=11), although significantly lower than the norm at 1 year of age. Similar to previous development studies on Norwood subjects, motor impairment was high. This study, like others, is limited to the small sample size in a single institution without randomization.

The purpose of this research study is to compare neurodevelopmental outcomes in HLHS infants after Hybrid Stage I palliation, with age-matched, normal healthy infants. Specifically, the investigators seek to understand how the early motor, language, and
intellectual development of infants with HLHS who have undergone the Hybrid Stage I procedure compares to that of healthy babies. The working hypothesis is infants with HLHS will have lower developmental scores across time when compared to healthy controls.

Methods

Study Design

The study is a longitudinal, repeated measures design, descriptive and prospective in nature. Institutional Review Board approval was obtained prior to initiation of the study. Between 2010 and 2012, all neonates admitted to Nationwide Children's Hospital with a diagnosis of HLHS were screened for meeting inclusion/exclusion criteria recruitment (Table 1). Those families who chose to have Hybrid Stage I palliation and met the criteria for this procedure, were approached for study recruitment and potential enrollment.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥36 weeks gestation</td>
<td>Healthy newborns</td>
</tr>
<tr>
<td>Planned Hybrid Stage I</td>
<td>≥36 weeks gestation</td>
</tr>
<tr>
<td>Willing to follow up</td>
<td>Willing to follow up</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>&lt;36 weeks gestation</td>
<td>&lt; 36 weeks gestation</td>
</tr>
<tr>
<td>Chromosomal abnormality</td>
<td>Birth asphyxia</td>
</tr>
<tr>
<td>Known central nervous system injury, or paralysis</td>
<td>Apgar score &lt;5 @ 5 minutes</td>
</tr>
<tr>
<td>Maternal history of drug or alcohol abuse during pregnancy</td>
<td>Resuscitation at birth</td>
</tr>
<tr>
<td>Congenital heart disease, medical diagnosis, central nervous system injury, paralysis, seizures, active infection</td>
<td>Chromosome abnormality</td>
</tr>
<tr>
<td></td>
<td>Maternal history of drug or alcohol abuse during pregnancy</td>
</tr>
</tbody>
</table>

Table 1. Inclusion and exclusion criteria of HLHS and control groups

Attempts to recruit normal healthy control subjects were performed through hand delivery of letters to post-partum mothers of normal full term newborns at The Ohio State
University, Columbus, Ohio and advertising emails to employees at Nationwide Children’s Hospital, Columbus, Ohio, as well as screening the appointment roster for newborn visits in the out-patient ambulatory clinic at Nationwide Children’s Hospital, and word of mouth. Subjects were screened to meet the inclusion/exclusion criteria.

Informed consent was obtained on all subjects prior to enrollment in the study. Incentives were used to help retain enrolled study participants included paid parking, as well as gift cards to a local department store, $20 at the 2 month visit, $25 at the 4 month visit, and $30 at the 6 month visit.

The standardized tools used for measures of developmental assessment were the Test of Infant Motor Performance (TIMP) (Campbell, 2007) and the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley, 2006). Three domains within the Bayley Scales were utilized for assessment: cognitive, language, and motor, with subscales of receptive and expressive language, and gross and fine motor scales. Composite scores in the HLHS group will be compared with corresponding scores in the control group as well as norm-referenced data. A score of 100 ± 15 defines the mean ± SD of the normative sampled population.

Test of Infant Motor Performance

The TIMP has been normed on a United States national sample of 990 infants selected to reflect the racial/ethnic distribution of low birth weight infants (Campbell, 2005). It is used to diagnosis developmental delay in gross motor skills. The TIMP tests the observed and elicited motor behavior in infants between the ages of 34 weeks post-conceptional age and 4 months post-term to predict motor performance at 12 months.
The tool is a 42-item assessment of observed items of postural control and active movement, and from elicited items tested by positioning in space and with visual and auditory stimuli. The testing takes approximately 30 - 45 minutes. Test-retest reliability has been performed and shows that infant scores are stable across a 3 day period (Campbell et al., 2005). Therefore, a single test can be used for clinical decisions if the infant’s status allowed for optimal performance.

Construct validity testing of the TIMP has been performed and the 3 month sensitivity and specificity of the TIMP exceeds many other developmental tests at a similar age (Campbell et al., 2002). At 3 months of age the percent of accurately predicting the outcome of an infant's motor performance using the TIMP is 87% (Kolobe et al., 2004). This indicates that those infants who performed poorly at 3 months will continue to do so at preschool age and those infants who performed well at 3 months can be expected (91% probability) to continue to perform well at preschool age.

Age standards and scores for performance on the TIMP are reported starting at 34 weeks post conceptual age through 17 weeks post term (Campbell, 2002). The TIMP is reliable and valid only up until 4 months of age, thereafter a change in the assessment tool is required.

Bayley Scales of Infant and Toddler Development, Third Edition

The Bayley Scales of Infant and Toddler Development, Third Edition (BSD III) (Bayley, 2006), is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 and 42 months of age. This assessment tool is norm-referenced and covers all core developmental
domains. The purpose of this tool is to diagnose developmental delays within the three administered domains: cognitive, language, and motor. The last two domains, social-emotional and adaptive behavior are questionnaires. For the trained healthcare professional or therapist administering the tool, the average assessment takes approximately 45 minutes for infants under 12 months of age. Scoring begins at the letter that corresponds to the correct age and items are scored 0 or 1, based on whether the skill was achieved. The basal is established with three passes in a row and scoring is performed until a ceiling is reached which are five failures in a row. The raw scores are added and converted to scaled scores (1-19; mean=10, SD=3) using a conversion table. Scaled scores can be converted to composite scores and percentile ranks can be determined.

Validity

Confirmatory Factor Analysis was performed for Cognitive, Language, and Motor Scales. There is a relatively high correlation between BSID III Cognitive and Language composites and the Wechsler Preschool and Primary Scale of Intelligence-Third Ed. \((r=.71-.83)\). Moderate correlations were demonstrated between BSID III Language composite and Preschool Language Scale 4th ed. Auditory comprehension and expressive communication was moderate \((r = .51-.71)\). Moderate correlations between BSID III Motor composite and Peabody Developmental Motor Skills 2nd edition \((r = .49-.70)\). No long-term predictive validity is available.

While the Bayley Scales covers all core developmental domains and is norm-referenced for ages 1-42 months, the reliability was lowest \((r = .71)\) for the 1-5 month age
group. Additionally, the test-retest reliability was as low as $r = .67$ in the 2-4 month range. In order to assess motor, cognitive, and language domains using a reliable measure, the BSID-III was chosen, starting at 6 months of age.

**Reliability**

Reliability of the BSID-III is high, particularly in children over 6 months of age, demonstrated by internal consistency reliability with correlation for cognitive $r = .91$, language $r = .93$, fine motor $r = .86$, expressive communication and gross motor $r = 0.91$. The lowest reliability reported is $r = .71$ in receptive and expressive communication subtests for infants in the age group of 1-5 months.

The BSID-III has good test-retest reliability. The average test-retest reliability correlation is $r = .80$ or higher across all ages, however ranging as low as $r = .67 - .80$ for 2-4 months and higher, $r = .83 - .94$, for ages 33-42 months.

Developmental assessment was performed on all subjects using standardized developmental assessment tools. Infant motor skills were assessed using the TIMP at two and four months of age. Subscales of the BSD III were used for assessing gross and fine motor skills, expressive and receptive language, and cognitive skills at six months of age. Although these assessment tools are standardized and norm-referenced for the general population, a normal healthy control group was used for comparison to infants born with HLHS. Including a normal healthy control group for comparison may be important to distinguish mild behavior or developmental differences that otherwise may not be identified using only the published norm-referenced data.
In order to control for experimenter bias, all study subject evaluations for developmental testing were performed by an experienced therapist, adept at using both tools. Attempts were made to keep testing conditions the same including the examination room, lighting, noise level, free from distractions, and for the baby to be in a calm, awake state. Evaluations were performed within a 2 week window at the designated time intervals at 2, 4, and 6 months of age. All testing was performed prior to HLHS infants undergoing the second staged open heart surgery and if clinical status allowed during the testing period.

Scoring

Raw scores were obtained using both assessment tools. The TIMP included 13 observed items while the infant was laying supine, starting with the head in the midline position. Midline is defined to include 15 degrees to either side of the midline. The baby was observed; the infant was credited with 1 point for yes, and 0 points for no, or not being observed. Items 18 through 42 are elicited items. Verbal and visual prompts may be used, however no more than three trials are allowed for each elicited test item. Items which test right and left are scored individually. Depending on the elicited item, scoring is from 1-6. Observed and elicited items are totaled and compared to age standards and scores for performance on the TIMP. Mean ± SD and range of raw scores are reported and are categorized as average (+ 1SD), low average (+ -.5 and -1SD), below average (+ -1 and -2SD), and far below average (-2SD below the mean).

For the BSD III, the starting point was determined by chronological age. Scoring was performed according to the administration manual. A score of 1 is awarded if the
item is performed, and 0 if the item is not accomplished by the infant. Once the ceiling is reached, the raw scores are totaled, and converted to scaled scores according to the tables presented in the administration manual. Scaled scores range from 1-19, mean of 10 and a SD of 3. Based on the scaled scores, composite scores and percentile ranks with confidence intervals at the 95% level were determined for cognitive, language, and motor skills. Composite scores are based on the sums of the subtest scaled scores, ranging from 40-160, mean of 100, and a SD of 15. A total of 68% of the population falls between 85 and 115 (± 1 SD). The 95% confidence interval more accurately represents a range where the true score for the child may fall. A score <70, >2 SD below the expected mean, will be considered severely delayed.

Other variables collected included anthropometric measures for growth parameters. Head circumference and weight gain will serve as a marker for brain growth and development.

Statistical Analysis

Descriptive statistics were provided for all variables. Mean and standard deviation were calculated for continuous variables. For continuous variables, two samples t-test or Mann-Whitney U-test where appropriate for point group comparisons, while using paired-t test or Wilcoxon signed-rank test for matched pairs was used. For repeated measurement, a mixed model analysis of variance was used, which reduces the error term, increases the power of analysis, and is powerful to deal with missing data. A power analysis was performed a-priori. Using an alpha of .05, at 80% power, with a moderate
effect size, for a single group with 3 repeated measures, 14 subjects are needed in each group. P<0.05 will be considered as statistically significant. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

A total of 22 newborns with HLHS were screened and 18 subjects were enrolled. A total of 110 normal newborns were screened, however recruitment yielded only 6 enrollments as control subjects. Demographic variables are presented in Table 2. Weight, height, and head circumference were lower in the HLHS group. The median head circumference at birth in the control group was 36.1 centimeters (cm) (range 34.3 - 39cm) compared to 33.5cm (range 30.5 - 36.5cm) in the HLHS group (p=0.0036). This places the HLHS group in the 15% versus the control group in the 97% for head circumference based on the World Health Organization standards.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLHS n=18</th>
<th>Controls n=6</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation in weeks</td>
<td>39</td>
<td>40</td>
<td>0.0277*</td>
</tr>
<tr>
<td>Apgar score (1, 5 min)</td>
<td>8, 9</td>
<td>8, 9</td>
<td>0.1506/0.5801</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.16</td>
<td>3.99</td>
<td>0.2712</td>
</tr>
<tr>
<td>Birth height (cm)</td>
<td>50</td>
<td>53</td>
<td>0.7381</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>33.5</td>
<td>36.2</td>
<td>0.0036*</td>
</tr>
<tr>
<td>Male / female</td>
<td>11 / 7</td>
<td>2 / 4</td>
<td>0.3572</td>
</tr>
</tbody>
</table>

Table 2. Demographic variables of subjects in HLHS group vs. control group displayed as median. Significant at p<.05*
During the study period there were 9 infants who had a cardiac arrest requiring resuscitative measures. There were 4 deaths in the HLHS group. Two patients’ clinical status was critical and assessment was not performed at 4 months. One patient went on to orthotopic heart transplant, 1 patient was clinically unstable for testing, and 1 patient went to an early stage II surgical repair, therefore these patients did not undergo 6 month assessment.

The median age for 2 month testing (n=14) was 62 days, 4 month testing (n=12) was 117 days, and 6 month testing (n=11) was 170 days of age in the HLHS group. The median age at testing in the control group (n=6) was 62, 120, and 181 days respectively. Overall TIMP scores (HLHS and controls) were higher at 4 months than 2 months ($p<0.0001$). The HLHS group scored significantly lower compared to controls on the TIMP at 2 months of age ($p=0.002$), and at 4 months of age ($p=0.0019$). The mean TIMP score at 2 months was 63.9 ± 18.1, median score 61.5 (range 30 - 98), in the HLHS group, placing them -1 to -2 SD below the norm. Control subjects scored a mean of 94.5 ± 10, median 91 (range 85 - 112), which places them just above the mean for norm referenced data. At 4 months of age, the mean TIMP score was 108.3 ± 14.9, median score 111 (range 83-127) in the HLHS group, and mean of 133 ± 4, median 133 (range 128-138) in the control group. This placed the HLHS group -.5 to -1 SD below the norm referenced mean, and the control group within 1 SD above the norm referenced mean.

At 6 months of age, a mean composite score in the HLHS group of 78.9 ± 16.4 was obtained on the standardized measure of motor development, the mean composite score of 88.5 ± 12.4 on the standardized measure of language development, and the mean
score of 90.5 ± 16 on the standardized measure of cognitive assessment, all relative to infants of comparable age. Individual scores for the HLHS group are presented in Figure 9. There was a statistically significant difference between the HLHS group and the control group in motor (fine and gross) skills ($p=0.049$). However, there was no significant difference for cognitive ($p=0.29$) and language (receptive and expressive) skills ($p=0.68$) at 6 months. All scores are displayed in Table 3 and results are displayed in Table 4. Motor skills were significantly lower in the HLHS group at 6 months of age compared to control subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>N Obs</th>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLHS</td>
<td>18</td>
<td>Cognitive</td>
<td>11</td>
<td>90.4</td>
<td>95.0</td>
<td>55.0</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Language</td>
<td>11</td>
<td>88.5</td>
<td>89.0</td>
<td>62.0</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motor</td>
<td>11</td>
<td>78.9</td>
<td>74.0</td>
<td>46.0</td>
<td>103</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>Cognitive</td>
<td>6</td>
<td>99.7</td>
<td>102.5</td>
<td>84</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Language</td>
<td>6</td>
<td>88.8</td>
<td>94</td>
<td>58</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motor</td>
<td>6</td>
<td>97.8</td>
<td>107</td>
<td>68</td>
<td>110</td>
</tr>
</tbody>
</table>

Table 3. Descriptive statistics composite scores at 6 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 month Bayley Cognitive</th>
<th>6 month Bayley Language</th>
<th>6 month Bayley Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.2883</td>
<td>0.6849</td>
<td>0.0489*</td>
</tr>
</tbody>
</table>

Table 4. Comparison between HLHS and Control Subjects at 6 months, significant at .05*

Descriptive classifications by level of performance for composite language scores are presented in Table 5 for the HLHS group and normative population (Bayley, 2006). Descriptive classifications by motor skill level of performance are presented in Table 6.
for the HLHS group compared to the normative population (Bayley, 2006). Although the majority of HLHS subjects fall within the average to borderline classification, a small group of HLHS scores are classified as extremely low.

<table>
<thead>
<tr>
<th>*Composite Language Score</th>
<th>*Classification</th>
<th>*Sample% (N=1700)</th>
<th>HLHS % (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥130</td>
<td>Very Superior</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>Superior</td>
<td>7.9</td>
<td>0</td>
</tr>
<tr>
<td>110-119</td>
<td>High Average</td>
<td>14.2</td>
<td>0</td>
</tr>
<tr>
<td>90-109</td>
<td>Average</td>
<td>51.4</td>
<td>45.4</td>
</tr>
<tr>
<td>80-89</td>
<td>Low Average</td>
<td>14.4</td>
<td>36.4</td>
</tr>
<tr>
<td>70-79</td>
<td>Borderline</td>
<td>7.6</td>
<td>9.1</td>
</tr>
<tr>
<td>≤ 69</td>
<td>Extremely Low</td>
<td>2.4</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Table 5. Percent Classification of Language Composite Scores vs. Normative Data *(Bayley Scales of Infant and Toddler Development, third ed, Bayley, 2006)*

<table>
<thead>
<tr>
<th>*Composite Motor Score</th>
<th>*Classification</th>
<th>*Sample % (N=1700)</th>
<th>HLHS % (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥130</td>
<td>Very Superior</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>Superior</td>
<td>7.9</td>
<td>0</td>
</tr>
<tr>
<td>110-119</td>
<td>High Average</td>
<td>14.2</td>
<td>0</td>
</tr>
<tr>
<td>90-109</td>
<td>Average</td>
<td>51.4</td>
<td>36.4</td>
</tr>
<tr>
<td>80-89</td>
<td>Low Average</td>
<td>14.4</td>
<td>9.1</td>
</tr>
<tr>
<td>70-79</td>
<td>Borderline</td>
<td>7.6</td>
<td>36.4</td>
</tr>
<tr>
<td>≤ 69</td>
<td>Extremely Low</td>
<td>2.4</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Table 6. Percent Classification of Motor Composite Scores vs. Normative Data *(Bayley Scales of Infant and Toddler Development, third ed, Bayley, 2006)*
Discussion

The Hybrid approach to HLHS is a viable option in the initial palliation of babies with this disease. Studies assessing neurodevelopment in HLHS demonstrate significantly lower development scores or intelligence scores compared to the normal age-matched population (Mahle, et al., 2002; Wernovsky, et al., 2000; Goldberg, et al., 2007; Tabbutt, et al., 2008; Newburger, et al., 2012; Knirsch, et al, 2012). Cognitive development in HLHS is also impaired compared with controls, however, does not appear to be as effected.

The landmark multicenter study by Ohye and colleagues (2010) is the first surgical study randomizing patients to Norwood versus Norwood-Sano palliation for staged surgical repair for HLHS. Newburger (2012) found no difference in developmental outcomes based on either of these surgical techniques in this same cohort of HLHS children at approximately 14 months of age. PDI and MDI scores were both well below the norm with PDI <70 in 44% and MDI <70 in 16%. The question remains if the Hybrid technique will yield similar results. Only one study to date has been presented in the literature focusing on neurodevelopmental outcomes in this cohort of HLHS patients following Hybrid Stage I palliation. Although this adds to the literature, it is difficult to generalize results to all HLHS undergoing Hybrid Stage I palliation based on a Hybrid sample of 9 subjects. Therefore, short and long term neurodevelopmental outcomes still remain unknown.

Based on the results of this study, neurodevelopment appears to lag behind normal controls from the time of initial assessment at 2 months of age and continues
through 5-6 months of age, at the second staged surgical procedure. The median composite motor score of 74 (range 46 – 103) was approaching the level of being considered severely delayed and warrants referral for intervention. This places this specific study cohort in the median 4\textsuperscript{th} percentile rank, and mean 17\textsuperscript{th} percentile, for motor development. However, these are basically theoretical values based on the normal distribution. The findings in this study, along with previously reported more recent studies, supports the growing evidence that neurodevelopment is impaired during fetal life. Demographic results in the current study are consistent with other studies. Smaller head circumference and weight in the HLHS group possibly suggests stunted brain growth and development.

Most other neurodevelopment studies have used an earlier (2\textsuperscript{nd}) edition of the Bayley Scales. The third edition, used in the current study, is a revision of the Bayley Scales of Infant Development, 2\textsuperscript{nd} edition. The third edition was designed with five domains to meet the federal and state guidelines for assessing development in infants and children. Normative data was updated using a sample representing the United States census from 2004. Psychometric properties were strengthened. New items were added to encompass a greater floor and ceiling within each scale, while other items which were difficult to administer or score were removed. Despite there being no universal definition of developmental delay, the Bayley Scales of Infant and Toddler Development, third edition can aid in diagnosing developmental delay comparing scores to the normative population.
Up until recently no good practice guidelines were in place for evaluating patients with CHD for developmental delay or identifying patients at risk for neurocognitive impairment. Recently, the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council published a scientific statement on neurodevelopmental outcomes in children with CHD (Marino, et al., 2012). Infants with HLHS are considered high risk for developmental delay and the committee recommends frequent and routine assessment in the medical home (Marino, et al., 2012).

Limitations

The major limitation of the study is the biased, small sample size, particularly not having an equal number of subjects in each group, and not reaching statistical power for testing despite the total number of subjects enrolled in the HLHS group. Attrition through death, readmissions for hemodynamic instability requiring resuscitation efforts and prolonged mechanical ventilation, as well as early Comprehensive Stage II open heart surgery, contributed to missing data points and not reaching power. Fifty percent of HLHS subjects suffered a cardiac arrest which required intubation and resuscitation during the study period. A total of 78% underwent an additional unplanned cardiac catheterization, 50% of whom required some form of interventional procedure during the catheterization, i.e. placing a stent in the retrograde aortic arch, or creating a larger atrial septal defect. Some infants’ clinical status was too critical to undergo developmental testing. This is a vulnerable period, between Hybrid Stage I palliation and Comprehensive Stage II, for this at-risk group. Multiple uncontrolled variables most
likely contributed to the motor function delays, including mechanical ventilation, prolonged intensive care and hospital length of stay, cardiac output and oxygen saturation, hemoglobin levels for oxygen carrying capacity, level of maternal education, and even socio-economic status. The convenience sample adds bias to the sample population and due to the study design, randomization was not possible.

**Conclusions**

A multi-center randomized clinical study evaluating HLHS patients who undergo all three surgical strategies, Norwood, Norwood-Sano, and Hybrid, is necessary to compare long terms outcomes in the current era. Ideally, the study protocol needs to standardize post-operative care management and perform pre- and post-operative brain imaging studies, such as MRI, as well as use standardized norm-referenced developmental assessment tools, and compare the results to normal healthy controls. In the interim, short term, interstage assessment using standardized assessment evaluation tools, as well as careful monitoring for adequate cerebral blood flow for growth and development, are crucial prior to undergoing the second and final staged open heart surgical repair.

Early developmental screening utilizing norm-referenced assessment tools such as the Bayley Scales of Infant and Toddler Development, Third Edition, should be recommended as a standard of care in children with HLHS. Providing developmental screening can help identify children at risk and provide developmental support for gross and fine motor skills, as well as receptive and expressive language development.
Developmental assessment, support and intervention needs to begin in the newborn period and continue throughout childhood.
Chapter 4

Assessment of Cerebral Blood Flow in HLHS after Hybrid Stage I Palliation

Background

Measurement of cerebral blood flow by Doppler ultrasound is gaining interest for several reasons, including potential alterations in cerebral blood flow during fetal development, evidence of brain tissue changes at birth, and smaller head circumference prior to any intervention. In addition, there is beginning evidence of alterations in cerebral blood flow after birth. Because of the concern over neurodevelopmental outcomes for infants with hypoplastic left heart syndrome (HLHS), researchers have begun to examine brain development during fetal life.

Fetal brain development depends upon oxygenated blood distribution and obstruction. Alteration in cerebral blood flow patterns may affect normal brain development and studies have shown that fetuses with HLHS have white matter injury on neuropathology examination (Glauser, et al., 1990; Hinton, et al., 2008; Mahle, et al., 2002).

Cerebral blood flow velocity in the circle of Willis, first measured in 1982 (Aaslid, et al.1982), remains fairly constant by autoregulation. Cerebral blood flow is defined as cerebral perfusion pressure divided by cerebral vascular resistance of the arterioles. When cerebral perfusion pressure drops, the resistance vessels dilate to
decrease the resistance, versus when cerebral perfusion pressure increases, the vessels constrict to increase vascular resistance, keeping the cerebral blood flow constant.

Doppler ultrasound has been performed in normal fetuses as well as fetuses with intrauterine growth retardation. A finding of increased cerebral diastolic blood flow in the latter group has been suggestive of a compensatory autoregulation mechanism for increased flow to the brain (Arbeille et al., 1997; Mari & Deter, 1992; Donofrio et al., 2003). Fetuses with HLHS have been noted to have the lowest cerebral-placental resistance ratio by Doppler, decreased weight, and smaller head circumference (Donofrio et al., 2003; Kaltman et al., 2005). Abnormal cerebral blood flow in neonates with congenital heart disease have been reported (Limperopoulos, et al., 2000; Te Pas, et al., 2005). Normally, cerebral blood flow velocity increases throughout infancy and can be measured in the middle and anterior cerebral artery non-invasively using transcranial Doppler sonography (Ilves et al., 2008).

In the only study in which cerebral blood flow was examined prior to the first surgical repair, newborn infants with HLHS had decreased cerebral blood flow (Licht et al., 2004). In addition, there was a significant correlation between cerebral blood flow and white matter injury. At present, there have been no reported evaluations of cerebral blood flow in HLHS patients who have undergone Hybrid Stage 1 palliation. It is only presumed that these infants have adequate cerebral blood flow and are developing normally during the interstage period between Hybrid Stage I and the Comprehensive Stage II. This is a vulnerable and critical time for this high risk group.
Magnetic resonance imaging (MRI) studies have shown white matter injury preoperatively, as well as an increased number of new lesions postoperatively in HLHS (Hinton, et al., 2007). Earlier studies indicate deep hypothermic circulatory arrest and cardiopulmonary bypass required with the Norwood and Norwood-Sano Stage I procedures have a negative correlation on neurodevelopmental outcomes (Wypij, et al., 2003; Limperopoulos, et al., 2001; Andropoulis, et al., 2012; Bellinger, et al., 2003; 1999). This suggests that a relationship exists between deep hypothermic circulatory arrest and neurologic injury. Contrary to this and despite these findings in these earlier studies, a recent report by Newburger, et al. (2012) found no significant correlation between operative factors such as cardiopulmonary bypass, deep hypothermic cardiac arrest, and regional cerebral perfusion.

MRI has been the gold standard for brain imaging, however is not always possible to obtain in HLHS patients. Transcranial Doppler (TCD) technology is an alternative imaging modality, which can assist in evaluating cerebral hemodynamics. Using the temporal bony window, TCD offers non-invasive, excellent resolution and is robust for measuring peak systolic, diastolic, and mean pressures, pulsatility index, and calculating cerebral resistance, particularly in the middle cerebral artery (Bode and Wais, 1988; Polito, et al., 2006). TCD has been performed in normal, small for gestational age, and intrauterine growth retarded fetuses (Arduini & Rizzo, 1990; Kaltman, et al., 2004; Mari, et al., 1989; Mari & Deter, 1992; Mari, et al., 1994; Mari, et al, 2005; Mari, et al., 2007), preterm (van Bel, et al., 1989) and term infants (Ilves, et al., 2008), as well as HLHS (Donofrio, et al., 2003; 2011) and fetuses with right and left sided heart obstructive
lesions including 14 fetuses with HLHS (Kaltman, et al., 2005). Arduini and Rizzo (1990) studied 1556 normal fetuses using transcranial Doppler to provide pulsatility index values as reference limits. The findings of this large population study have been used for normative data in healthy fetuses and compared to pulsatility index measurements converted into Z-scores in other studies (Kaltman, et al., 2005).

Transcranial Doppler is able to detect cerebral blood flow during open heart surgery with deep hypothermic circulatory arrest and cardiopulmonary bypass in neonates with flow rates as low as 10 ml/kg per minute (Zimmerman, et al., 1997). Normative values and what is considered adequate cerebral blood flow for growth and development without risk of neural injury in patients with HLHS who undergo Hybrid Stage I palliation is yet to be determined. Performing TCD measurements in HLHS patients and comparing them to a normal healthy control group and associated neurodevelopment, may help answer this question.

Bode (1988) studied cerebral blood flow velocity changes in response to hypocapnia and hypercapnia in premature infants. The reported correlation between mean velocity and transcutaneous carbon dioxide was poor ($r = 0.42$). Carbon dioxide reactivity was absent in patients with interventricular hemorrhage and a patent ductus arteriosus. The age and arousal state of the infant can have an effect on the velocity. Blood flow velocity can change in response to vessel diameter change even though blood flow is constant. It is unclear what velocity is needed for adequate cerebral blood flow in HLHS babies after Hybrid Stage I palliation and during the interstage period.
The purpose of this study is to assess cerebral blood flow velocity in the middle cerebral artery over time in babies with HLHS who undergo Hybrid Stage I palliation, and compare findings with normal healthy age-matched controls. In addition, the study seeks to evaluate whether there is a relationship between cerebral blood flow velocity and neurodevelopmental outcomes in HLHS infants who undergo Hybrid Stage I palliation.

**Methods**

**Study Design**

The study is a prospective, case comparison, mixed model design with repeated measures which will allow the subjects to be their own controls in this biased convenience sample. A repeated measures design is the examination of data longitudinally and assessment of change over time. The time interval for collecting data points is the same for all subjects. Data points will be collected at baseline, 2, 4, and 6 months.

Institutional Review Board approval was obtained prior to initiation of the study. Between April 2010 and November 2012, all neonates admitted to Nationwide Children’s Hospital with a diagnosis of HLHS were screened for recruitment. Parents of newborns with HLHS undergoing Hybrid Stage I palliation were approached for recruitment and potential enrollment.

Normal healthy newborns were recruited as control subjects. Recruitment was through hand delivery of letters to post-partum mothers of normal full term newborns at The Ohio State University, Columbus, Ohio and advertising emails to employees at
Nationwide Children’s Hospital, Columbus, Ohio, as well as screening the appointment roster for newborn visits in the out-patient ambulatory clinic at Nationwide Children’s Hospital, and word of mouth. Subjects were screened to meet the inclusion and exclusion criteria.

**Inclusion Criteria**

The inclusion criteria for control subjects included age matched healthy newborns, gestational age greater than or equal to 36 weeks, no known medical diagnosis, illness or disease, no genetic or chromosomal abnormality, and willingness to participate in follow up assessment. Inclusion criteria in the HLHS group included neonates born greater than or equal to 36 weeks gestation with a diagnosis of HLHS or a variant of HLHS, admitted to Nationwide Children’s Hospital, and planned Hybrid Stage I procedure, and willingness to participate in follow up.

**Exclusion Criteria**

The purpose of the exclusion criteria in the control group is to specifically exclude any variable which may have impacted fetal brain growth and development, or variables which may be the result of injury to the brain, such as hypoxic-ischemic insult resulting in a low Apgar score, seizure activity or hydrocephalus. Any central nervous system injury involving the spinal cord or paralysis will be excluded. Fevers in neonates under 1 month of age are often treated with intravenous antibiotics to cover sepsis. Systemic infection can affect any organ system, including the brain, and could potentially be life threatening if not treated accordingly. Finally, any maternal history of drug or alcohol abuse during the pregnancy could have impacted normal embryologic
development, or caused fetal brain injury which may result in abnormal
eurodevelopment or long term neurologic sequelae. Therefore, exclusions in the control
group will include gestational age < 36 weeks, history of birth asphyxia, Apgar scores
less than 5 at 5 minutes or requiring resuscitation after birth, congenital heart disease,
history of seizures, hydrocephalus, any genetic syndrome or chromosomal abnormality,
spinal cord injury, paralysis or partial paralysis including brachial plexus injury, febrile
illness or active infection, and maternal history of drug or alcohol abuse during
pregnancy. Exclusion criteria in the HLHS group includes prematurity less than 36 weeks
gestation, known genetic or chromosomal abnormality, central nervous system injury,
spinal cord paralysis, and maternal history for drug or alcohol abuse.

Informed consent was obtained on all subjects prior to enrollment in the study. To
maintain anonymity and protect health information, patient identifiers were removed and
all study information was stored in a password protected computer, and/or in a locked
cabinet in a locked office within the institution. Being a longitudinal study, incentives
were used to help retain enrolled study participants. A parking voucher was provided at
each visit, as well as a gift card to a local department store, $20 gift card at the 2 month
visit, $25 at the 4 month visit, and $30 at the 6 month visit.

**Technical imaging**

A Pediatric Neurologist, trained in TCD and brain imaging studies, provided
training for a standard protocol for imaging cerebral blood flow using the TCD machine.
Inter-rater reliability was demonstrated through a training protocol of the investigator
with repeat simulation. All TCD measures were obtained by either the Pediatric Neurologist or the principal investigator.

Transcranial Doppler (TCD) sonography and a 2 megahertz (MHz) Doppler probe was used to assess the middle cerebral artery in all study subjects in the HLHS group, as well as the control group. The anatomical bifurcation of the middle cerebral artery served as the reference point for within-subjects, thereby minimizing measurement error. Cerebral blood flow velocity is the rate of blood flow over time through cerebral vessels. The highest (peak), lowest (end-diastolic), and average (mean) blood flow velocities are based on the systolic and diastolic phases of the cardiac cycle. These values are used to calculate an index for variability of the pulsatile flow.

Insonation is performed through the bilateral bony temporal window in each subject using a conventional transcranial Doppler machine with 2-MHz transducer (Viasys, Companion III, Madison, WI). The Doppler probe is placed approximately 1 centimeter in front of the external auditory meatus and 1-2 cm above the zygomatic arch to direct the ultrasound beam. Gate depths are adjusted until the bifurcation of the middle cerebral artery and anterior cerebral artery is identified. While maintaining transducer position and angulation, blood-flow parameters were recorded including maximum mean blood flow velocity (MV), peak systolic velocity (PV), end-diastolic velocity (EDV), and pulsatility index (PI). Gosling’s formula (Gosling & King, 1975) was used to calculate the pulsatility index (PV−EDV/MV). The blood flow direction and waveform shape recorded is an electronic spectral image of cerebral blood flow. The relative depths from the reference bifurcation depth will remain consistent between study subjects and
between exams in the same subjects. All examinations are performed while the subject is in a stable or quiet state. Variables recorded included peak systolic velocity, end-diastolic velocity, mean velocity, and pulsatility index measured in cm/second. In order to improve reliability measures for TCD and help reduce the standard error of measurement, 3 measurements were recorded and averaged. Variables were measured at baseline, and at 2, 4, and 6 months of age and results were compared between groups.

Cognitive, language, and motor skill domains were also tested at 6 months of age using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley, 2006). The overall findings of the TCD variables over time were then compared to the scores of developmental testing for cognitive, language, and motor skills.

**Statistical analysis**

Descriptive statistics were provided for all variables. Mean and standard deviation were calculated for continuous variables. Two samples t-test or Mann-Whitney U-test, where appropriate, for point group comparisons, while paired-t test or Wilcoxon signed-rank test for matched pairs were used for continuous variables. Pearson product-moment correlation coefficient and Spearman rho rank order correlation coefficient were used to examine the extent to which TCD scores were associated with neurodevelopment scores. For repeated measurement, a mixed model analysis was used, which reduces the error term, increases the power of analysis, and is powerful to deal with missing data. A power analysis was performed a-priori. Using an alpha of .05, at 80% power, with a moderate effect size, for a single group with 4 repeated measures, 13 subjects will be needed in
each group. P<0.05 will be considered as statistically significant. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

**Results**

A total of 22 newborns with HLHS were screened and 18 HLHS who met criteria were enrolled. A total of 110 normal newborns were screened and recruited for enrollment, however only 6 normal newborn control subjects were enrolled.

Demographic variables are reported in Table 6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HLHS n=18</th>
<th>Control n=6</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation in weeks</td>
<td>39</td>
<td>40</td>
<td>0.0277*</td>
</tr>
<tr>
<td>Apgar score (1, 5 min)</td>
<td>8, 9</td>
<td>8, 9</td>
<td>0.1506/0.5801</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.16</td>
<td>3.99</td>
<td>0.2712</td>
</tr>
<tr>
<td>Birth height (cm)</td>
<td>50</td>
<td>53</td>
<td>0.7381</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>33.5</td>
<td>36.2</td>
<td>0.0036*</td>
</tr>
<tr>
<td>Male / female</td>
<td>11 / 7</td>
<td>2 / 4</td>
<td>0.3572</td>
</tr>
</tbody>
</table>

Table 7. Demographic variables displayed as median. Statistically significant at p<0.05*
TCD measures were performed at 4 points in time, at a median age of 5 days, 62 days, 117 days, and 170 days in the HLHS group and 11 days, 62 days, 120 days, and 181 days in the control group. Overall, there was a significant difference in peak systolic velocity ($p=0.0031$), end-diastolic velocity ($p<0.0001$), mean velocity ($p<0.0001$) (Table 8) and pulsatility index ($p=0.0011$) (Table 9) between the HLHS group and the control group. A significant trend in change over time increase was noted for peak systolic velocity ($p<0.0016$) and mean velocity ($p<0.0046$).

The HLHS group scored lower than controls in all three domains of development, however only motor skills were significantly different ($p=0.0489$) (Table 7). There was no significant correlation between TCD variables and cognitive, language, and motor skills, as performed using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley, 2006), at 6 months of age (Table 8).

### Table 8. Neurodevelopment comparison between HLHS and Control Subjects at 6 months, significant at .05*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bayley Cognitive</th>
<th>Bayley Language</th>
<th>Bayley Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.2883</td>
<td>0.6849</td>
<td>0.0489*</td>
</tr>
</tbody>
</table>

### Table 9. Transcranial Doppler and neurodevelopment scores compared at 6 months of age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cognitive correlation p value</th>
<th>Language correlation p value</th>
<th>Motor correlation p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>$r= -0.128$ $p=0.6237$</td>
<td>$r= 0.114$ $p=0.6621$</td>
<td>$r= -0.124$ $p=0.6360$</td>
</tr>
<tr>
<td>mean</td>
<td>$r= 0.286$ $p=0.2658$</td>
<td>$r= 0.226$ $p=0.3841$</td>
<td>$r= 0.356$ $p=0.1616$</td>
</tr>
<tr>
<td>EDV</td>
<td>$r= 0.114$ $p=0.6627$</td>
<td>$r= 0.013$ $p=0.9586$</td>
<td>$r= 0.07$ $p=0.7852$</td>
</tr>
<tr>
<td>PSV</td>
<td>$r= 0.087$ $p=0.7383$</td>
<td>$r= 0.068$ $p=0.7953$</td>
<td>$r= 0.296$ $p=0.2494$</td>
</tr>
</tbody>
</table>
Discussion

Single ventricle anatomy may be comprised of a variety of anatomical diagnoses in congenital heart disease (CHD) abnormalities including hypoplastic right ventricle, unbalanced atroventricular canal with either a dominant right or left ventricle, or hypoplastic left heart syndrome (HLHS) which involves a constellation of left sided abnormalities. HLHS and HLHS variants involve hypoplasia and underdevelopment of the left ventricle, aortic valve atresia or stenosis, mitral valve atresia or stenosis, and a diminutive ascending aorta. The surgical management strategies with three staged surgical palliative surgeries are Norwood, Norwood-Sano or Hybrid Stage I, Stage II (Bidirectional Glenn cavopulmonary anastomosis) or Comprehensive Stage II, and the final stage III completion, the Fontan operation. Although all single ventricle physiology infants undergo staged palliation, not all have the same risk of morbidity and mortality, especially when it comes to neurodevelopmental outcomes. Single ventricle physiology of a hypoplastic right ventricle has fetal cerebral blood flow similar to normal newborns but quite unlike those with HLHS where cerebral blood flow is dependent upon retrograde or backward flow across the ductus arteriosus to the aortic arch to perfuse the brain and the coronary arteries.

Head circumference serves as an indirect measure of adequate brain growth. For infants born with HLHS, head circumference measurements at birth that are below average suggest inadequate brain development (Shillingford, et al., 2007). Newborn infants with HLHS have been found to have smaller head circumferences when compared to healthy controls (Hinton, et al., 2008; Manzar, et al., 2005; Shillingford, et al., 2007),
which was also present in this study cohort of HLHS subjects. It is worrisome that the smaller head circumferences were not proportionate to measures of weight and length, and that a smaller head circumference at birth is most likely reflective of alterations in cerebral blood flow (Hinton, et al., 2008; Shillingford, et al., 2007).

The method used for obtaining TCD measures is operator dependent. The imaging requires a high level of skill to acquire quality images of cerebral blood flow in the cerebral arteries, in particular if an infant is not being cooperative. Transcranial Doppler has been used as a screening tool in infants undergoing cardiac surgery to evaluate cerebral blood flow and as an alternative to non-invasive infrared spectroscopy, which measures regional cerebral oxygenation (Fraser & Andropoulos, 2008). Transcranial Doppler may detect alterations in cerebral perfusion which may lead to cerebral tissue ischemia and ultimately neurologic injury. Early detection and prevention of cerebral ischemia and hypoxemia is crucial for prevention of long term neurologic sequelae. Doppler mean pressures may not be capable of detecting small changes in pressure. Taking multiple measures in a single subject may provide a value which is closer to the true measure. TCD has been used to measure the pulsatility index serially as a noninvasive measure associated with cerebral perfusion pressure and intracranial pressure (Bellner, et al., 2004). Although a correlation between these variables was reported, this is not a true measure.

This is the first study to evaluate cerebral blood flow velocities in HLHS infants who undergo Hybrid Stage I palliation. Based on the findings in the current study, overall TCD measures are lower compared to normal age-matched controls. This may be due to
variables such as mechanical ventilation, medication, hemoglobin and hematocrit, or intensive care and hospital length of stay, which were not controlled for. However, in comparing baseline TCD results in the current study to published reference values of flow velocities in the middle cerebral artery at 0-1 month of age (Bode, 1988), results are very similar. Comparing TCD results in the current study, at a median age of 170 days or 5.6 months, to published reference values for 5-6 month old normal infants (Bode, 1988) all measures are lower in the HLHS group. For example, reference values of the flow velocity in the middle cerebral artery for a 5-6 month old: peak systolic velocity 109, end-diastolic velocity 45, mean velocity 71, with a calculated pulsatility index of 0.9; compared with corresponding median measures in the HLHS group of: 86, 17, 49, and 1.5 respectively. When comparing overall group difference of change with time, there is a significant trend noted in the peak systolic and mean velocity. However, this is expected as normally blood pressure parameters increase from the neonatal period.

Limitations

The greatest weakness of this study, being non-experimental in nature, is the lack of control over the independent variable of cerebral blood flow, as it is inherently not manipulable. The independent variable cannot be manipulated and although the sample selection is a biased convenience sample, the researcher has no control over the cerebral blood flow, even if an interaction exists. Technology dependent devices are subject to calibration and error in measurement which can be a limitation for interpreting study results. The limitations of this measurement include lack of machine calibration for TCD
which can alter output data and the use of two different TCD machines due to machine failure, although they were from the same company.

**Threats to internal and external validity**

Significant events that may impact the testing of variables and results for HLHS babies included additional hospital admissions, prolonged intensive care and hospital length of stay, additional interventional or surgical procedures, particularly those performed under anesthesia, and cardiac arrest requiring resuscitation. Age-matched controls helped eliminate the maturation threat in this longitudinal study.

Attrition, particularly related to mortality, was expected during the course of the study in the HLHS group. Additionally, although control subjects did not drop out, missing data points resulted from study appointment cancelations. Selection bias is a noted threat to the internal validity. Given the nature of the disease with HLHS, randomization was not an option. Matching with control subjects, in addition to having an adequate sample size helped control for this.

The sampling of the HLHS population is limited based on the incidence of the disease. Although a small sample size is a threat to external validity and generalizing to the overall population, reaching statistical power would strengthen the results of the study. Another possible threat to external validity is the sampling of infants from the same geographic location. Although this is true in the control group, the HLHS infants came from a variety of geographic locations outside the Columbus area, as well as outside the state of Ohio.
Sources of measurement error in relation to the accuracy and precision of TCD for systematic error may be from the portable TCD system, including the Doppler display, measures of depth range, measures of standard test parameters, color resolution display, or the 2 MHz Doppler probe.

**Conclusions**

Transcranial Doppler is a safe, non-invasive method for monitoring cerebral blood flow velocity using serial measurements. Although no significant correlation between TCD and neurodevelopmental outcome measures of cognitive, language, and motor skills were noted in this study, this is still an important finding. Transcranial Doppler values, in 5-6 month old infants with HLHS who undergo Hybrid Stage I palliation, are lower than the values in normal age-matched infants. Unfortunately, the inability to control variables effecting these values does not allow satisfactory comparison, but may show a trend. The alternative management strategy for HLHS using Hybrid Stage I palliation, which relies on retrograde cerebral perfusion, does not appear to have any worse adverse effects on neurodevelopmental outcomes scores when compared to the traditional Norwood Stage I as reported in previous chapters. A larger sample size may allow for statistically significant TCD findings to be more predictive of neurodevelopmental outcomes in this high risk patient population.
References


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analysis of left ventricular outflow tract malformations (aortic valve stenosis, coarctation of the aorta, and hypoplastic left heart syndrome). *European Journal of Human Genetics : EJHG*, DOI: 10.1038/ejhg.2008.255


Appendix A: List of Abbreviations

Ao  aorta
bHLH  basic helix loop helix
BSD II  Bayley Scales of Infant Development, 2nd edition
BSD III  Bayley Scales of Infant and Toddler Development, 3rd edition
CHD  congenital heart disease
cm  centimeter
cm/sec  centimeter per second
CPB  cardiopulmonary bypass
CTICU  cardiothoracic intensive care unit
EDV  end-diastolic velocity
FSIQ  full scale intelligence quotient
HLHS  hypoplastic left heart syndrome
IVC  inferior vena cava
kg  kilogram
LA  left atrium
LPA  left pulmonary artery
LV  left ventricle
mBTS  modified Blalock-Taussig
MDI  mental development index
MPA  main pulmonary artery
MRI  magnetic resonance imaging
MV  mean velocity
NPLS  non-parametric linkage score
PDA  patent ductus arteriosus
PDI  psychomotor development index
PI  pulsatility index
PSV  peak systolic velocity
PVL  periventricular leukomalacia
RA  right atrium
RPA  right pulmonary artery
RV  right ventricle
RV-PA  right ventricle to pulmonary artery
SD  standard deviation
SVC  superior vena cava
TIMP  Test of Infant Motor Performance
**Figure 1** Normal heart anatomy with patent ductus arteriosus (A&B) Arrows depict direction of normal blood flow (B) (Sisk, M., 2012, reprinted with permission)

SVC superior vena cava

IVC inferior vena cava

RA right atrium

RV right ventricle

MPA main pulmonary artery

PDA patent ductus arteriosus

RPA right pulmonary artery

LPA left pulmonary artery

PV pulmonary veins

LA left atrium

LV left ventricle

Ao aorta

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Figure 2  Hypoplastic left heart syndrome (HLHS) with arrows showing direction of blood flow. (Sisk, M., 2012, reprinted with permission)

SVC superior vena cava
IVC inferior vena cava
RA right atrium
RV right ventricle
MPA main pulmonary artery
PDA patent ductus arteriosus
Ao aorta
RPA right pulmonary artery
LPA left pulmonary artery
PV pulmonary veins
LA left atrium
LV left ventricle
**Figure 3** Norwood stage I palliation for HLHS (close up and unroofed view)

The pulmonary artery has been transected at its bifurcation and the distal end over sewn. Pulmonary blood flow is provided through a modified Blalock-Taussig shunt. The aortic arch is augmented with a patch and connected to the proximal main pulmonary artery. The atrial septum is also removed for unrestricted blood flow from the left atrium to the right atrium (not shown). (Sisk, M., 2012, reprinted with permission)
Figure 4  Norwood –Sano Stage I for HLHS

The pulmonary artery has been transected at its bifurcation and the distal end over sewn. Pulmonary blood flow is provided through a right ventricle to pulmonary artery (RV-PA) shunt. The aortic arch is augmented with a patch and connected to the proximal main pulmonary artery. The atrial septum is also removed for unrestricted blood flow from the left atrium to the right atrium (not shown). (Sisk, M., 2012, reprinted with permission)
Figure 5  Hybrid Stage I palliation for HLHS

Pulmonary artery bands are placed around the left and right pulmonary arteries (LPA, RPA), a bare metal stent is placed in the patent ductus arteriosus (PDA), and balloon atrial septostomy is performed to create an opening between the upper heart chambers to allow unobstructed blood flow returning from the left atrium to the right atrium. (copyright Nationwide Children’s Hospital, reprinted with permission)
Figure 6  Comprehensive Stage II palliation

The patent ductus arteriosus (PDA) stent and the right and left pulmonary artery bands are removed, the main pulmonary artery is divided and over sewn, and the small ascending aorta is anastomosed to the pulmonary artery with patch augmentation of the transverse aortic arch. The superior vena cava (SVC) is divided and over sewn on the cardiac side, and anastomosed to the right pulmonary artery for venous return from the SVC out to both lungs. (copyright Nationwide Children’s Hospital, reprinted with permission)
**Figure 7** Bidirectional Glenn – Stage II repair for HLHS

Cavopulmonary anastomosis of superior vena cava to the right pulmonary artery and takedown of the Blalock-Taussig shunt. “Blue” blood from upper body returns to lungs through the superior vena cava anastomosis. “Blue” blood from lower body returns to heart from the inferior vena cava and is pumped out the “neoaorta” across augmented aortic arch, mixing unoxygenated blood with oxygenated blood results in lower oxygen saturations. (Sisk, M., 2012, reprinted with permission)
**Figure 8** Extra cardiac Fontan – 3rd and final stage for HLHS palliation

Total cavo-pulmonary connection – the inferior vena cava and superior vena cava connect to the pulmonary artery allowing all venous blood to flow to the lungs. (Sisk, M., 2012, reprinted with permission)
Figure 9  Development Scores in HLHS group
Scatter plot demonstrating composite scores for developmental testing at 6 months
Figure 10  Median transcranial Doppler cerebral velocities
Figure 11  Median transcranial Doppler pulsatility index of HLHS and control groups

Overall group difference $P=0.0011$