Understanding the Neurological and Functional Development of Children with Critical Congenital Heart Disease

by

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Abstract

Critical congenital heart disease (cCHD) encompasses the most severe forms of congenital heart defects. To survive, infants with cCHD must undergo complex cardiac surgeries (CCS) in early life. Thanks to continuous improvements in the overall care of these children, survival rates have improved significantly, and now most children with cCHD can reach adulthood.

By the late twentieth century, as the percentage of children surviving CCS increased, researchers began to wonder about their neurodevelopment. Today, after more than three decades of further studies, it is clear that children with cCHD are at high risk for developmental delays. Developmental challenges commonly include deficits in cognitive, language, motor, behavior and social interaction abilities. These challenges arise from the cumulative effect of multiple recognized pre- and post-natal factors, and contrary to what was previously thought, these do not strictly relate to the presence of hypoxemia or the cardiac surgery itself.

By examining three issues not previously described in the literature, this thesis aims to improve the understanding of the neurological and functional developmental impact of CCS in children with cCHD. All three projects in this thesis include children with cCHD registered in the Western Canadian Complex Pediatric Therapies Follow-up Program (WCCPTFP). This inception cohort project identifies all infants born with cCHD who undergo early-life CCS at the Stollery Children's Hospital (Edmonton, Alberta), and follows them prospectively across western Canada. As part of this program, developmental outcomes are determined by multidisciplinary assessment at approximately 8 months, 21 months and 4.5 years of age.

The study presented in chapter 2 begins this work by assessing the frequency and presentation of chronic neuromotor disability (CND), including cerebral palsy and acute brain injury in

kindergarten-aged children who have survived CCS. Results indicated CND affects 6% of CCS survivors and almost 10% of those who have required more than one CCS. Most children with CND could ambulate without the need of a mobility device, and often had a high frequency of associated developmental impairments. Older age in days at first CCS, highest plasma lactate before first CCS, and undergoing more than one CCS were predictors of CND.

The thesis work continues in chapter 3, where a more specific group of kindergarten-aged children is examined: those who survive the Fontan operation. The aim of the study is to better understand the impact of this operation on the functional abilities of children, and its potential relation with stroke (an already recognized peri-operative complication). Overall, more than a quarter of children experienced deterioration of functional abilities following the Fontan operation. Both peri-operative stroke and older age at Fontan were predictors of decline of functional abilities.

Finally, in chapter 4, the relationship between the need for gastrostomy tube feeding (GTF) any time before the 21-month multidisciplinary assessment and the presence of developmental delays is assessed. Findings suggested GTF identifies CCS survivors at risk for developmental delay who would benefit from early developmental intervention. Presence of chromosomal anomaly, single ventricle anatomy, number of post-operative days with open sternum and total number of hospital days at CCS were predictors of GTF requirements before the 21-month assessment.

Together these three projects address key gaps in knowledge by describing outcomes not previously reported, all of which can have a significant impact on the participation of children in activities of everyday life. Efforts to prevent and to address these developmental difficulties should be undertaken.

Preface

The manuscript which comprises Chapter 2 of this thesis has been published as *Ricci MF, Andersen JC, Joffe AR, Watt MJ, Moez EK, Dinu IA, Garcia Guerra G, Ross DB, Rebeyka IM, Robertson CMT. Chronic Neuromotor Disability After Complex Cardiac Surgery in Early Life. Pediatrics. 2015;136(4):e922-933.* For this project, original data were collected by the WCCPTFP. I took part in all aspects of the study. I completed further data collection through chart review, undertook the data analysis, interpreted the results, and wrote the manuscript under the guidance of the co-authors. Dr. Robertson was the supervisory author and was involved with concept formation, data analysis and manuscript composition. Dr. Andersen and Dr. Watt gave specialty knowledge for the design as well as the interpretation of the data and review of the manuscript. Dr. Dinu and Ms. Khodayari Moez assisted with completion of the statistical analysis. Dr. Joffe, Dr. Ross, Dr. Rebeyka and Dr. Garcia Guerra participated in the design and management of the study and preparation and review of the manuscript.

The manuscript which comprises Chapter 3 of this thesis has been accepted for publication as *Ricci MF, Martin BJ, Joffe AR, Dinu IA, Alton GY, Garcia Guerra G, Robertson CMT. Deterioration of Functional Abilities in Children Surviving the Fontan Operation. Cardiology in the Young. 2018;Apr:1-8.* For this project, original data were collected by the WCCPTFP. I took part in all aspects of the study. I completed further data collection through chart review, undertook the data analysis, interpreted the results, and wrote the manuscript under the guidance of the co-authors. Drs. Robertson and Joffe were the supervisory authors and were involved with concept formation and manuscript composition. Dr. Dinu assisted with the completion of the statistical analysis. Drs. Martin and Garcia Guerra, as well as Ms. Alton gave specialty knowledge for the design as well as the interpretation of the data and review of the manuscript

The manuscript which comprises Chapter 3 of this thesis has been published as *Ricci MF, Alton GY, Ross DB, Dycken BJ, Moddeman DM, Robertson CMT. Gastrostomy Tube Feeding after Neonatal Complex Cardiac Surgery Identifies the Need for Early Developmental Intervention. The Journal of pediatrics. 2016;169:160-165.* For this project, original data were collected by the WCCPTFP. I took part in all aspects of the study. I undertook the data analysis, interpreted the results, and wrote the manuscript under the guidance of the co-authors. Dr. Robertson was

the supervisory author and was involved with concept formation, data analysis and manuscript composition. Drs. Dycken and Moddeman, as well as Ms. Alton gave specialty knowledge for the design as well as the interpretation of the data and review of the manuscript

The health research ethics boards at each of the WCCPTFP sites approved the three studies that comprise this thesis. All parents or legal guardians of the children included in the studies provided written consent for inclusion.

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List of Abbreviations

Abbreviations	Definition
ABAS-II	Adaptive Behavior Assessment System-II
ABI	Acquired Brain Injury
ASO	Arterial Switch Operation
Bayley-III	Bayley Scales of Infant and Toddler Development 3rd Edition
BSID-II	Bayley Scales of Infant Development, 2nd Edition
CCS	Complex Cardiac Surgery
CHD	Congenital Heart Disease
cCHD	Critical Congenital Heart Disease
CI	Confidence Interval
CND	Chronic Neuromotor Disability
CP	Cerebral Palsy
CPB	Cardiopulmonary Bypass
CPR	Cardiopulmonary Resuscitation
CT	Computed Tomography
DHCA	Deep Hypothermic Circulatory Arrest
ECMO	Extracorporeal Membrane Oxygenation
E-CPR	Extracorporeal Cardiopulmonary Resuscitation
EDI	Early Developmental Intervention
GMFCS	Gross Motor Function Classification System
GTF	Gastrostomy Tube Feeding
HLHS	Hypoplastic Left Heart Syndrome
ICU	Intensive Care Unit
IQ	Intellectual Quotient
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PaO2	Arterial Partial Pressure of Oxygen
PDA	Patent Ductus Arteriosus
PICU	Pediatric Intensive Care Unit
PGE-1	Prostaglandin E-1
SD	Standard Deviation
SES	Socioeconomic Status
TAPVC	Total Anomalous Pulmonary Venous Connection
TGA	Transposition of Great Arteries
TOF	Tetralogy of Fallot
VAD	Ventricular Assist Device
WCCPTFP	Western Canadian Complex Pediatric Therapies Follow-up Progra

Chapter 1: Introduction

1.1 STATEMENT OF PURPOSE

Congenital heart disease (CHD) is an anatomical heart defect present from birth. Every year, approximately 1.35 million children around the world are born with this condition.[1] It has been estimated that of all American children born with CHD, roughly a quarter have a critical form of congenital heart disease (cCHD)[2] ; this means survival for them is only possible when surgical procedures or catheter based interventions are completed during their first year of life. [3]

The way we look at children with cCHD has been changing significantly for the past seven decades, a response in part to advances in treatment and improvements in clinical outcomes. While in the past survival to adulthood was rare, currently more than 80% of children born in North America with cCHD survive past their first birthday.[2] Advances in the surgical and medical care of these children has led not only to increased survival rates, but also to recognition of a common "pattern of developmental sequelae",[4] that among other challenges includes deficits in cognitive, language, motor, behavior and social interaction abilities.[5] Research has demonstrated that among children with CHD, the prevalence of developmental impairments is directly proportional to the complexity of the heart defect;[6] and that the "neurodevelopmental challenges are more common in children and young adults with cCHD than all cardiovascular problems combined".[4]

In addition to identifying such challenges, outcomes research linking clinical care data to developmental outcomes, became a key element aiming to modify acute care practices and prevent potential detrimental effects on development. Examples of such modifications range from changes in the approach to organ support techniques during surgery,[7] to changes in the peri-

surgical use and administration of medication.[8,9] In so doing, outcomes research has highlighted the complexity of the subject, moving from a narrow focus that mainly looked at surgical factors as a primary explanation for developmental delays, to the wider understanding of multiple and additive factors playing a role in the developmental trajectory of these children. As survival rates continue to increase and surgical procedures and life-saving therapies continue to evolve, efforts to prevent and address disability must persist, especially as children that are more vulnerable are now surviving.[10,11]

This thesis project represents one such effort. This thesis addresses the importance of longitudinal follow-up of children with cCHD undergoing complex cardiac surgery (CCS), focusing on neurological, developmental and functional evaluation and outcomes. The project explores three main issues not previously reported in the literature:

- The presence of chronic neuromotor disability (CND), including cerebral palsy and acquired brain injury in kindergarten-aged children who have survived CCS.
- The deterioration of functional abilities in children surviving the Fontan operation, and its relation with peri-operative stroke.
- The presence of gastrostomy tube feeding (GTF) and its potential relation with developmental delays in children surviving CCS.

To provide context for this work, it will be useful first to briefly review the history of cCHD repair, the current knowledge on the neurodevelopmental profile of children with cCHD, and the possible pathogenesis behind the developmental disabilities that affect this population. Finally, I will provide the rationale behind my research.

1.2 HISTORY OF CRITICAL CONGENITAL HEART DISEASE REPAIR

Congenital cardiac surgery has rapidly evolved since Gross performed the first patent ductus arteriosus (PDA) ligation in 1938.[12] Progress in the 1940s was slow, as just a few operations could be done without cardiopulmonary bypass (CPB): PDA ligation, coarctation repair, and Blalock-Taussig Shunts. Hypothermia allowed for a handful of other relatively simple operations that could be done expeditiously. However, it was not until the 1950s, when John Gibbons had completed his pioneering work allowing for successful CPB, that significant progress was made allowing for what is now routine repair of CHD. Indeed, the first operation ever performed on CPB involved a congenital condition.[13]

Even for decades after the successful repair of initially simple lesions, development of procedures for complex biventricular lesions (such as transposition of the great arteries (TGA)), and palliative procedures for some single ventricle lesions (the Fontan operation for tricuspid atresia)[14], Hypoplastic Left Heart Syndrome (HLHS) remained uniformly fatal, with over 90% of afflicted children dying within 30 days of birth.[15] In the late 1970s, a number of authors, including Doty, Levitsky, and Behrendt described multiple possible surgical procedures for palliating HLHS.[16–18] However, no child survived all three stages of single ventricle palliation until 1983, when Norwood published his seminal paper describing a successful Fontan procedure in a child with HLHS.[19,20] Success remained rare in the following decade. Even in the early 1990s, survival in HLHS post-palliation was poor.[15]

Today, however, hospital survival post-Norwood, the first stage of palliation, is over 90% at centers of excellence.[21] While much credit is due to the pioneers of CPB and subsequent persistent surgeons, changes in the medical management of children with cCHD has also been

instrumental in improving survival. An important medical advancement was the discovery by Olley et al that Prostaglandin E-1 (PGE-1) could be used to maintain the patency of the ductus arteriosus, hence stabilizing children with a variety of obstructive lesions by maintaining blood flow to the lungs.[22] Though initially use of PGE-1 was described for maintaining ductal patency in children with obstructed pulmonary blood flow alone, it is now used in children with systemic blood flow obstruction such as those with HLHS. Prior to the routine use of PGE-1, surgical palliation was done on an emergent basis in children with tenuous physiology and critical metabolic derangement. This prevented proper operative work-up and likely contributed to brain injury prior to even starting the operation owing to hypoxemia, low blood flow, and other metabolic concerns. Owing to the relatively benign and manageable short-term side effects of PGE-1 usage, PGE-1 is started routinely in neonates with any sign of hypoxemia and malperfusion, even without a confirmed diagnosis of CHD. Thus, even while awaiting a diagnosis, children are hemodynamically stable and well oxygenated.

In summary, while the operations performed in early years were palliative and very high risk, fully corrective surgery or palliative procedures allowing for survival to adulthood are now being performed with low mortality at centers worldwide.

1.2.1 Current Survival Rates

Survival rates, as noted above, have increased significantly in the past decades. It is currently estimated that of all individuals born with all forms of CHD, 87% survive to age 1 year, while 81.4% survive to age 10 years.[23] Looking at children with cCHD, a study from the United States reported one-year survival has increased 15.1% from the period 1979-1993, to the period 1994-2005, (67.4 to 82.5% respectively).[2] Results from the Stollery Children's Hospital in Edmonton, showed two-year survival rates improved following the initiation of the Norwood

with right ventricle–to–pulmonary artery shunt instead of the previous modified Blalock-Taussig shunt.[24] And although long term mortality after the Fontan operation is still significant, 94% of children undergoing this operation are expected to survive after five years.[25]

1.3 NEURODEVELOPMENTAL OUTCOMES OF CHILDREN WITH CHD

1.3.1 Early Studies: Identifying Outcomes

Concurrently with the accomplishments made in the surgical and medical field, special attention was directed to the overall development of children with CHD. In 1949, Campbell and Reynolds looked at "walking" and "talking" as measures of general development.[26] Findings from their work demonstrated that half of the children with a cyanotic lesion were not walking by the age of 2 years, and only a small proportion were talking by 18 months of age. The authors emphasised the fact that "great delay" was uncommon, and that other added causes for delay should be investigated (including possible genetic causes) when a child presented with a cyanotic heart lesion and "great delay". Shortly afterward, Chazan et al published one of the first studies that formally assessed the intellectual and emotional development of children with CHD.[27] While their overall results showed normal cognitive abilities, a significant proportion of these children displayed "unusual slowness in reaction" and "speech defects".

While these studies were one of the first ones to look at the outcomes of children with CHD; in the 70s', 80s and 90's, as the surgical advances continued, increasing attention was given to the overall development of these children.

1.3.2 Understanding challenges: the role of The Western Canadian Complex Pediatric Therapies Follow-up Group

Numerous studies around the world were devoted to understand the long-term developmental outcomes of children with cCHD. In Canada, following the example of the neonatal follow-up clinics, The Western Canadian Complex Pediatric Therapies Follow-up Program (WCCPTFP) was stablished in 1996.[28] The program, constituted by members of different pediatric subspecialties (cardiology, intensive care, neonatology, developmental pediatrics, cardiovascular surgery), identifies all children with cCHD who undergo complex cardiac surgery at 6 weeks of age or less, and those having a palliative shunt at 6 months of age or less at the Stollery Children' Hospital. Those children whose parents agree to participate in the program are enrolled; their demographic, pre-, intra- and post-surgical information is prospectively collected. At pre-determined age levels, the cognitive, language, motor and social development, as well as the functional abilities, attention, behavior and overall health and well-being of the children who have survived is assessed using standardized developmental and neurocognitive measures. This is completed by a multidisciplinary team, which includes a nurse, physician, psychologist, occupational therapist, physiotherapist, dietician, audiologist, speech and language pathologist, and social worker. Although the cardiac surgery is conducted in Edmonton as the cardiac surgical hub for western Canada, the multidisciplinary follow-up is conducted in four provinces across western Canada. This follow-up does not only identify possible neurodevelopmental challenges, but also provides different services for the children including therapy support, prompt referrals to early developmental intervention (EDI), psychology counselling and parent education. Moreover, the WCCPTFP conducts outcomes research, "providing a basis for quality improvement".[28]

While the WCCPTFP is an excellent example of multidisciplinary care, it has not been the only program dedicated to the neurodevelopmental follow-up, service support, and quality

improvement in the care of children with cCHD. Different groups, particularly in the United States have dedicated many years of clinical and research work to improve the outcomes of these children. Their pioneer work has later expanded to multiple centers around the world. This world-wide research has led to the current understanding of the developmental challenges that may affect children with cCHD.

1.3.3 The Neurodevelopmental Profile of Children with cCHD

We now know that developmental disabilities are frequent, affecting almost 50% of children with cCHD. The most common developmental challenges in children with cCDH include low average cognitive abilities, fine and gross motor delays, attention difficulties, impulsive behavior, impaired language and visual-motor skills, deficits in social interaction and learning disabilities.[4–6,29–38] Permanent hearing loss and feeding difficulties are also frequently present.[9,39,40] As these children grow and reach adolescence, issues with executive function and health related quality of life are not uncommon.[5,6,41–43] What is important is that disabilities, although in general mild, tend to occur in combination,[6] having a significant impact on the participation of these children in different life settings, including the home, the school, and the community. Moreover, the mild nature of these disabilities make them somewhat harder to identify,[5,6] which might delay implementation of the much-needed supports.

1.3.4 The Pathogenesis Behind the Identified Developmental Disabilities

Thanks to the significant amount of research in the area, it is now understood that developmental challenges do not only arise from the lack of oxygen or from the surgical treatment itself; developmental challenges arise from the "cumulative effect" of multiple factors

that are uniquely related to each child.[5,6,10,29,44–46] Factors that have been researched and recognized as influencing the neurodevelopment of these children include:

1.3.4.1 Patient Specific Factors. Patient specific factors are characteristics that are inherent to the individual child and thus are not truly modifiable. One of the most consistently described patient specific factors is the presence of a genetic abnormality. Up to 30% of CHD is associated with a known genetic abnormality; most commonly these include Down Syndrome, trisomy 18, trisomy 13, chromosome 22q11.2 deletion syndrome and microdeletions.[47,48] In general, children with CHD and a known genetic abnormality have poorer developmental outcomes.[34,49] In addition, it has been well accepted that as the severity of the heart lesion increases, so do the associated developmental impairments.[6,41] In children with cCHD, birth at term (as compared with pre-term birth), and in particular birth at ≥39 weeks of gestation, is associated with higher cognitive, language, executive functioning, social, visual motor integration and fine motor skills at 4 years of age.[50]

1.3.4.2 Prenatal Factors. In recent years, more attention has been paid to the prenatal development of the brain in children with cCHD. Findings suggest that in fetuses with cCHD, the abnormal cardiac physiology and resulting hemodynamics lead to decreased oxygen delivery to the brain,[51–53] as well as to reduced oxygen consumption in the brain.[54] The described changes in brain circulation are associated with smaller, and less mature brains (as seen on neuroimaging) often resembling those of premature infants.[54–57] Recently, high pulsatility indexes at the umbilical artery level in fetuses with cCHD ("suggestive of placental insufficiency"), were found to be associated with worse developmental outcomes at 2 years of age.[58]

1.3.4.3 Post-natal, pre-surgical factors. The low oxygen delivery seen in fetuses continues through the first days of life; the so called "immature brains"[56] may be incapable of dealing with frequent postnatal fluctuations in cerebral perfusion and are at high risk of pre-surgical brain injury including periventricular leukomalacia and cerebral infarctions.[59,60] Other factors associated with pre-surgical injury include thromboembolism,[61] abnormal brain metabolism,[62] and abnormal "functional connectivity"[63] in critical areas of the brain. Younger age at first surgery has been associated with better developmental outcomes both in children with TGA,[64,65] and in children with HLHS.[66,67] Time of diagnosis of cCHD is considered crucial as children born without prenatal diagnosis have worse pre-surgical conditions.[68] In addition, prolonged pre-operative ventilation has been associated with worse neurodevelopmental outcomes in 18-month-old survivors.[46]

1.3.4.4 Surgical factors. Different surgical factors have been associated with adverse developmental outcomes. Results of the Boston Circulatory Arrest Trial, a randomized controlled study, showed children who received support consisting predominantly of cardiac arrest during open heart surgery, presented higher rates of post-operative neurological complications when compared to those who underwent organ support by predominantly CPB.[7] Despite still being considered a safer option when looking specifically at developmental outcomes, CPB has sometimes been found a risk factor for adverse outcomes, possibly due to brain injury resulting from micro emboli,[69] hemodilution,[70] and an increased inflammatory response.[71]

1.3.4.5 Post-surgical factors. Recognized post-surgical factors associated with worse developmental outcomes include high lactate values,[72] the presence of sepsis,[73] prolonged length of stay,[74] bolus administration of furosemide,[9] and the presence of seizures.[75] Likewise, the need

for cardiac extracorporeal membrane oxygenation (ECMO), considered standard of care for those children experiencing "cardiac failure refractory to medical care"[76] has been linked to acute neurologic insults, impaired cognitive and functional developmental outcomes, as well as low parent-reported quality of life at kindergarten age.[77–79]

Children with complex lesions may require a heart transplant. In a recent study, findings suggest children with cCHD who require a heart transplant have a significantly lower intellectual quotient (IQ) at 4.5 years of age when compared to those who also require heart transplantation but for a "failing anatomically" normal heart. [80] This may reinforce the difference between the brain of a child with cCHD that is exposed to multiple potential insults (from prenatal to post-surgical), and the normally developing brain of a child who suddenly requires a heart transplant following for example a diagnosis of a cardiomyopathy. In addition, requirement of a ventricular assist device (VAD), commonly used as a bridge for children waiting for heart transplantation, is associated with a high rate of neurologic insults, most commonly ischemic strokes.[81,82] The use of a VAD has not only been linked to high rates of brain injury, but also to low cognitive and functional abilities in kindergarten-age children.[83]

1.3.4.6 Environmental factors. The detrimental effect of socioeconomic disadvantage in the well-being and overall development of children has been known for many years.[84] Higher rates of CHD have been reported in low socio economic status (SES) areas,[85] and low SES has been associated with lower 1-year survival rates following the Norwood procedure.[86] Environmental factors play a significant role in the cumulative effect that was previously mentioned; as parents and their opportunity and ability to access care most likely play a role that is as important as the surgery itself. However, it is essential to understand we can modify the effect of environmental factors on the neurodevelopment of children, as for example early access

to developmental intervention and parental education have been shown to improve developmental outcomes.[87,88]

1.4 RATIONALE BEHIND MY THESIS PROJECT

There is no doubt that there has been a significant growth in the understanding of the developmental challenges that affect children with cCHD. In summary, we know children with cCHD are at high risk for developmental challenges, and that these challenges are secondary to the cumulative effect of multiple different factors that are related to each child, their medical condition(s), their treatment(s) and their own environmental factors. We also understand the essential role of longitudinal follow-up, recently highlighted in a scientific statement from the American Heart Association.[5]

However, through my clinical and research work done with the WCCPTFP, both as a fellow in developmental pediatrics and as a PhD student, I identified 3 specific gaps in knowledge in the neurodevelopmental trajectory of children with cCHD:

1. Although neuromotor delays have been described as possible long-term outcomes after cardiac surgery,[11,12] there has been a lack of clarity on the frequency, characteristics and risk factors for neuromotor disabilities, including cerebral palsy (CP) and acquired brain injury (ABI). Importantly, such conditions can have a strong impact on the health, participation and quality of life of children, especially if we consider that this is an already vulnerable population.
2. I developed a strong interest in the specific neurological and functional impact of the Fontan Procedure, the treatment of choice for palliative surgery for children with single ventricle and other complex heart conditions. During my time in clinics I realized many of the children

with cCHD that are followed in the WCCPTFP clinics suffered a deterioration of their functional abilities following the Fontan operation. When trying to understand prevalence and risk factors, I could not find a clear explanation for these outcomes without a large cohort with systematically recorded information.

3. Multidisciplinary follow-up of the children undergoing CCS can be challenging in many areas of the world, where human and economic resources might not be available. These children are often seen only by a cardiologist who might not recognize or be able to address the child's neurodevelopmental needs. Finding a simple way to enhance prompt identification of a high risk for developmental delay in children surviving early cardiac surgery became an interest of mine. Could the presence of a GTF in an infant after CCS identify those at risk for developmental delay in need for early developmental intervention?

By specifically researching these three questions I aim not only to better understand the impact of CCS on the health and development of these children, but also to obtain objective data that can help prevent disability. By identifying potentially modifiable variables associated with adverse outcomes, it becomes possible to change acute care practices, and iteratively, in the future, determine whether subsequent outcomes improve.

(It is useful to note, moreover, that while the following chapters do not reflect explicitly on participation, it is a further implication of their findings, as will be addressed briefly in the concluding chapter.)

Chapter 2: Chronic Neuromotor Disability after complex cardiac surgery in early life

2.1 ABSTRACT

Background/Objectives: Little is known about Chronic Neuromotor Disability (CND) including cerebral palsy and motor impairments after acquired brain injury in children surviving early complex cardiac surgery (CCS). We sought to determine the frequency and presentation of CND in this population while exploring potentially modifiable acute care predictors.

Methods: This prospective follow-up study included 549 children after CCS requiring cardio-pulmonary bypass at ≤6 weeks of age. Groups included those with only one CCS, mostly bi-ventricular CHD, and those with more than one CCS, predominantly single ventricle defects. At 4.5 years of age 420 (94.6%) children received multidisciplinary assessment. Frequency of CND is given as percentage of assessed survivors. Predictors of CND were analyzed using multiple logistic regression analysis.

Results: CND occurred in 6% (95% confidence interval (CI) 3.7%,8.2%) of 4.5-year survivors; for one CCS, 4.2%(CI 2.3%,6.1%) and more than one, 9.8% (CI 7%,12.6%). CND presentation showed: hemiparesis, 72%; spasticity, 80%; ambulation, 72%; intellectual disability, 44%; autism,16%; epilepsy,12%; permanent vision and hearing impairment, 12% and 8% respectively. Overall, 32% of presumed causative events happened prior to first CCS. Independent Odds Ratio (OR) for CND are: age (days) at first CCS, 1.08 (CI 1.04,1.12) (P<0.001); highest plasma lactate prior to first CCS (mmol/L), 1.13 (CI 1.03,1.23) (P=0.008); and more than one CCS, 3.57(CI 1.48,8.9) (P=0.005).

Conclusion: CND is not uncommon among CCS survivors. The frequency of associated disabilities characterized in this study informs pediatricians caring for this vulnerable population. Shortening the waiting period and reducing pre-operative plasma lactate levels at first CCS may assist in reducing the frequency of CND.

2.2 INTRODUCTION

Survival rates after complex cardiac surgery (CCS) in early infancy have increased.[89] Disabilities have become a concern as studies show children with congenital heart disease (CHD) often demonstrate deficits in cognitive abilities, social interaction,[5,38] language,[31] behaviour, [90] permanent hearing loss,[9] and health-related quality of life.[42] Neuromotor delays have also been described as possible long-term outcomes after cardiac surgery [30,91,92]; and acquired brain injury (ABI) has been recognized as a complication. Domi estimated that 1/185 children with CHD are at risk of stroke within the first 72 hours post-surgery, after which hemiparesis may occur.[93] Brain injury as detected by neuroimaging has been found in up to 30% of infants with CHD prior to surgery.[94] Generally motor impairments have been studied as part of a description of neurologic deficits, resulting in lack of clarity on the frequency and characteristics of neuromotor disabilities.

"Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain".[95] Twenty-four months is considered the maximum age that an acquired injury to the developing brain may be called CP,[96] thereafter the term ABI with motor impairment is used. CP is classified according anatomical distribution and typology of the motor disorder, functional motor abilities, accompanying impairments, neuroimaging findings, and the causation and timing whenever possible.[95] For this study, Chronic Neuromotor Disability (CND), a term modified from Golomb,[97] is used as an umbrella term to include CP and ABI (including stroke). The aims of this study are to determine the frequency of CND among 4.5-year-old survivors of early CCS requiring CPB; to describe CND

presentation according to the current CP classification; and to identify potentially modifiable acute care predictors that may lead to a reduction in the frequency of CND.

2.3 METHODS

This inception cohort outcomes study is part of a follow-up project conducted in six Developmental/Rehabilitation referral sites in western Canada: Vancouver, British Columbia; Edmonton and Calgary, Alberta; Regina and Saskatoon, Saskatchewan; Winnipeg, Manitoba.[28] Infants were identified at the time of first CCS and followed prospectively. At the time of CCS, predetermined demographic, pre-operative, intra-operative, and post-operative variables were collected. The study was approved by health research ethics boards at each site; parental or guardian consent was obtained.

2.3.1 Participants

All infants ≤6 weeks of age with CHD who were considered at greatest risk for adverse outcome because of the need for CCS requiring cardio-pulmonary bypass between September 1996 and December 2009 at the Stollery Children's Hospital, Edmonton, Canada were included. Children were divided into two groups, those with only one CCS, mostly bi-ventricular CHD, and those with more than one CCS, predominantly those with single ventricle defects. Children who died prior to the 4.5-year assessment and those lost to follow up were excluded.

2.3.2 Childhood clinical assessments

Multi-disciplinary assessments were performed at 4.5 years at the referral sites.[28] Each child was seen by a developmental pediatrician; if CND was suspected, a pediatric neurologist confirmed diagnoses. The CND nature, typology (spastic, dyskinetic, ataxic, hypotonic), anatomical distribution (unilateral-bilateral) of the motor disorder [98,99]; functional motor abilities,

(including oromotor involvement); accompanying impairments (intellectual disability; communication, vision, hearing impairments; epilepsy; autism spectrum disorder); and neuroimaging findings were recorded.[95] Medical records of children with confirmed CND diagnoses were independently reviewed by two investigators (MFR, CMTR). Chronological information within all clinical notes and neuroimaging reports was sought to identify presumed timing of likely causative events (including description of acute illness) that lead to the final diagnoses of CND. If the opinions of the two reviewers differed, then a third joint review was completed until consensus was reached. Accompanying impairments recorded prospectively in the database as previously described,[28] were confirmed. Visual impairment, corrected visual acuity in the better eye of < 20/60, was determined by ophthalmological reports. Hearing was evaluated by certified pediatric audiologists; sensorineural loss or auditory neuropathy bilateral loss at >25 dB HL from 500 to 4000 Hz was considered Permanent Hearing Impairment. Epilepsy was defined as the need for anti-epileptics at 4.5 years of age obtained by history and confirmed by medical reports. The diagnosis of Autism Spectrum Disorder was made by multidisciplinary teams following standardized testing.[28] Intellectual Disability was defined by the presence of both, 1) intellectual impairment (scores <70) as determined by formal psychological assessment by certified pediatric psychologists and 2) parent-completed questionnaire of adaptive functioning deficit (scores <70).

2.3.3 Measures

Standardized age-appropriate developmental measures and questionnaires used normative data from the United States. Each neurocognitive and functional measure has a mean score of 100, and Standard Deviation (SD) of 15; a score under 2 SD below mean (<70) is considered impairment. Wechsler Preschool and Primary Scales of Intelligence-Third Edition,[100] a gold

standard measure, provides individualized assessment for children 3 to 7.25 years of age giving performance, verbal and full-scale IQ. The Beery-Buktenica Developmental Test of Visual-Motor Integration, 5th Edition [101] measures the ability of children aged 2 to 18 years to copy geometric designs, an important preschool learning skill. The Adaptive Behavioral Assessment System-Second Edition (ABAS-II) [102] assesses independent and realistic-for-age behaviors using nine skill areas grouped into three composite domains: conceptual, practical and social. The motor skill is separate and included in the General Adaptive Composite score. Each age-based skill area scaled score has a mean of 10 and a SD of 3; scores <4 are 2 SD below mean and show impairment. The Gross Motor Function Classification System (GMFCS),[103,104] a five-level classification system based on the gross motor function of children with CP, with inter-rater reliability of 0.93,[105] was documented at age 4.5 years. The Blishen Index [106] is an indicator of socioeconomic status dependent on employment, education, and prestige value of an occupation, with a population mean of 43 and SD of 13.Maternal education was recorded in years of schooling at the time of the 4.5-year assessment.

2.3.4 Acute care variables

Acute care information in relation to CND (Table 2.1) includes surgical year, birth gestation (weeks) birth weight (grams), sex, multiple birth, chromosomal abnormality, antenatal diagnosis and pre-operative ventilation days; pre-operative and post-operative highest plasma lactate, inotrope score,[107] and lowest base deficit; age (days), weight (kg), cardio-pulmonary bypass time (min), X-clamp time (min), and use of deep hypothermic circulatory arrest (duration in min) at first CCS; single or bi-ventricular cardiac defect; the presence of pre- or post-operative sepsis, seizures, cardio-pulmonary resuscitation, dialysis; and the number of ventilated, intensive care unit and hospital days. Overall events recorded were: the number of CCSs with cardio-

pulmonary bypass for each child prior to the 4.5-year assessment, presence of sepsis, cardio-pulmonary resuscitation, dialysis, extracorporeal membrane oxygenation, heart transplant, ventricular assist device support, extracorporeal cardio-pulmonary resuscitation, and having more than one CCS.

2.3.5 Statistical analysis

Continuous variables are presented as means (SD) or medians (interquartile range), and categorical variables as counts and percentages. The frequency of CND is given as percentage of assessed survivors, using 95% confidence intervals (CI). Demographic, operative and peri-operative predictors of CND for all 25 children and, for a sub-set of those with unilateral CND, were analyzed using univariate and stepwise multiple logistic regression analysis. A total of 28 predictors were initially screened, complying with the regression model building rule of at least 10 patients for each predictor, given our sample size of 420 children. Multiple logistic regression analysis included variables significant at P value <0.10 and clinically relevant variables after screening for multicollinearity. Results are expressed as odds ratios (OR) with 95%CI; significance considered at <0.05. Data analyses were performed using Logistic procedure in SAS version 9.3.

2.4 RESULTS

From September 1996 to December 2009, 549 infants of ≤6 weeks of age had their first CCS requiring cardio-pulmonary bypass; 105 (19.1%) children died and 24 were lost to follow-up by assessment age, leaving 420 (94.6 % of survivors) to receive multidisciplinary assessment at a mean age of 55.2 months (6.6) (Figure 2.1). At first CCS, 117 (27.9%) had single ventricle anatomy (74 had Norwood surgery for classical HLHS), 157 (37.4%) had Transposition of Great

Arteries (TGA) (99 with intact ventricular septum), 54 (12.9%) had Total Anomalous Pulmonary Venous Connection repair and 135 (32.1%) had other cardiac abnormalities. The age at first CCS for all 420 children was 12 (8.6) days; for those with single ventricle, 11.3 (6.9), and with biventricular defects, 12.3 (9.5) days. Of the 420 children, 288 had only one CCS, and 132 had two or more CCSs.

2.4.1 Frequency of CND

CND occurred in 25 (6%) (CI 3.7%, 8.2%) of assessed children; 4.2% (CI 2.3%, 6.1%) of those who had one CCS, and 9.8% (CI 7%, 12.6%) of those with more than one CCS. CND occurred in 10.3% (CI 7.4%, 13.2%) of those with single ventricle defect. Five children with CCS at ≤6 weeks had late death after 2 years of age and before the 4.5-year assessment; none of these had suspect motor impairment.

2.4.2 Characteristics of children with CND

Table 2.2 shows the description of the 25 children with CND at 4.5 years; 18/25 (72%) had unilateral motor impairment, half with right hemiparesis; 20/25 (80%) had spasticity; 18/25 (72%) had GMFCS I or II; and 4/25 (16%) had bulbar and oromotor involvement requiring gastrostomy. The presumed timing of the events leading to CND occurred within the first 5 days post-operatively for only two children and none occurred on the operative day. Those 25 with CND had their first CCS on day 17.9 (12.1), on average 6.3 days after those without CND. For the eight children with the presumed timing happening prior to first CCS, half of which had TGA, the age at surgery was 24.6 (13.1) days, on average 13 days after those without CND, only two of these eight children had antenatal CHD diagnoses. For those seven with presumed timing of causative event happening after the first CCS but before any further CCS, the age at first

surgery was 14.8 (10.7) days, on average 3.2 days later than those without CND. In addition, 10 children had the presumed causative event at a subsequent surgery (Figure 2.2).

Thirty-six (8.6%) of 420 children were born prematurely; 5 had CND. Presumed causative events for three of these were not directly related to gestation. Neuroimaging of two of these children suggests the causative insult may have been antenatal. Both were born at 36 weeks, Cases 1 and 4 (Table 2.2).

2.4.3 Childhood growth, health and accompanying impairments

Accompanying impairments for the 25 children with CND are found on Table 2.3. Intellectual disability occurred 20 times more commonly than the expected 2.23% determined from population normative values.

2.4.4 Prediction of CND

Univariate and stepwise multiple logistic regression analyses are shown in Table 2.4. According to the multiple regression model, OR for CND is 1.08 for each day the first CCS is delayed beyond the date of birth, and 1.13 for each mmol/L of plasma lactate elevation in the pre-operative period at first CCS. Adjusting for the presence of these predictors, OR for CND is 3.57 (CI 1.48,8.9) (P=0.005) if more than one CCS is needed.

Focusing only on the 18 children with unilateral CND and omitting from analysis those with bilateral CND, the multiple regression model showed the OR is 1.03 (CI 1.004,1.05) (P=0.019) for each unit of pre-operative inotrope used, 1.29 (CI 1.07,1.33) (P=0.001) for each mmol/L of plasma lactate elevation in the pre-operative period, and 1.07(1.005, 1.13) (P=0.032) for each day the first CCS is delayed. Every one kilogram increase of weight at the time of

surgery reduces unilateral CND (OR, 0.42) (CI 0.18,0.97) (P<0.001). Adjusting for the presence of these predictors, OR for unilateral CND is 12.23(CI 3.38, 44.23) (P<0.001) if more than one CCS is needed.

2.5 DISCUSSION

This study presents information relevant to practitioners caring for newborns with CHD, those assessing and assisting young survivors with CCS and those meeting their rehabilitative needs. Frequency information on CND following CCS is not readily available, a classification including accompanying impairments of these specific children has not been reported, and little is known about the causation and potentially modifiable predictors that may assist prevention.

We have shown CND is not uncommon among preschool survivors of CCS, especially for those needing more than one CCS. This supports the role of re-operation in stroke as reported by Domi.[93] After early CCS, motor disability is more common than that in the general population, where the prevalence of CP remains about 2-3 per 1000 live births [108–113] and similar to CP among premature infants.[109,112,113] Our results support others, "among children who acquire cerebral palsy postnatally, there is an excess of non-cerebral birth defects, particularly cardiac defects". [109] Overall post-natal acquired CP is about 5.5% of all CP: for 1998 it was reported as 0.41 (CI 0.14,0.67) per 10,000 live births.[114]

The majority of our patients presented with spasticity, the most common motor disorder type of CP.[115] Unilateral distribution was the most common presentation, contrasting with the literature where bilateral spastic CP is most prevalent.[109,112] Our findings align with results from a study by Golomb showing 87% of children with CP after perinatal arterial ischemic stroke present with hemiplegia.[97] We have found 72% of the children with CND have GMFCS levels of I or II with

somewhat more ability to ambulate than previous findings in children with CP in the general population both in Europe and North America.[110,111]

In our study, children after CCS with CND presented with a higher rate of accompanying impairments including intellectual disability, autism, epilepsy and vision impairment than those without CND. This supports other studies showing children with CP have a higher frequency of associated impairments than in the general population.[110,111] We found CCS survivors with CND, have a greater percentage of intellectual disability and autism, but a lower rate of epilepsy compared with children with CP in the literature,[112,113] including less epilepsy and visual impairment than children described in the European Registry with postnatally acquired CP.[114] The frequency of permanent hearing impairment among those with CND and those without was similar in our study; this may have been associated to ototoxicity as previously reported.[9]

Of particular importance is our described association between the presumed timing of events leading to CND and timing of the CCS. We found that the presumed causative event for CND rarely occurred in the 0- to 5-day postoperative window, which has been considered a vulnerable period.[93] Overall, 32% of presumed causative events took place prior to first CCS, TGA being the most common diagnosis among these children. This might be related to already described abnormalities of brain microstructure and metabolism. [62,116,117] However, 40% of presumed causative events took place beyond first CCS, and in this group, single ventricle defects were overrepresented.

Our study shows an older age at first CCS, high pre-operative lactate levels and more than one CCS are predictors of CND. The analysis of the children with unilateral CND confirms the importance of similar predictors and adds high pre-operative inotrope score and lower weight

at first CCS as predictors. We found the OR for CND is 1.08 for each day added to the pre-operative period of first CCS. These findings underlie the importance of further investigation of earlier CCS[65–67,117,118] and lead to the question; are waiting times for surgery longer in infants with CND secondary to illness and therefore the child is not stable for surgery, or are other medical and social situations affecting the time of surgery? Special attention needs to be paid to this concept of 'readiness to treat'. Mahle reported that antenatal diagnosis leads to a reduction of early peri-operative neurological insults in neonates with HLHS.[119] The lack of antenatal diagnosis in 6 of 8 children with presumed causative events before first CCS in this study supports this finding. Recent studies show antenatal diagnostic rates for CHD are increasing [120]; this may result in fewer adverse pre-operative events. Finally, the OR for CND is 1.13 for each mmol/L of pre-operative plasma lactate elevation at first CCS. Increased pre-operative lactate levels have been found to be associated with lower functional abilities after CCS,[121] with mental and/or motor delay in children undergoing arterial switch operations,[122] and as indicator of post-operative mortality and morbidity.[46,72,123] Preoperative plasma lactate levels and age at surgery are modifiable variables that could potentially lead to a reduction in CND the same way other advances have affected specific prevalence rates of CP.[110,114] Specific in-utero and peri-operative neuroprotective strategies to achieve these goals should be further investigated.[124,125]

The strengths of this study include the high proportion of children assessed at 4.5 years of age with detailed classification of each child with CND and evaluation of the presumed timing of likely causative events. The main limitations are the small number of children with CND, the single center performing CCS, neuroimaging dictated by clinical need without uniform testing, and difficulty determining the timing of an earlier insult with manifestation as a sudden neurological symptom. Other variables that may predict CND may not have been recorded; these

potential confounders can limit the certainty about the potentially modifiable predictors found. Potential bias might have been introduced by excluding children who died, especially those who died prior to the 2-year-old assessment, as we do not know if these children had pre- or post-operative neurologic insults which may have manifested as CND had the child survived.

2.6 CONCLUSION

Our findings provide evidence that CND is not uncommon among CCS survivors. Health professionals need to be aware of this and complete careful neurological examinations to allow for early, specific rehabilitative therapies. Ongoing surveillance with multidisciplinary assessments are paramount because these children may present not only with motor impairments, but with high rates of additional associated impairments requiring intervention. Findings also suggest that presumed causative events infrequently happen in the early postoperative period, and often occur while awaiting surgery. Strategies to shorten the waiting time for, and to prevent high plasma lactate levels prior to first CCS, may assist in reducing the presence of motor impairments in this population. These study results can assist both general pediatricians and pediatric subspecialists in providing more informed antenatal and postnatal counseling, as well as anticipatory guidance for families. Larger studies to further explore the mechanisms and risk factors of CND in CCS survivors are needed.

Table 2.1: Description of 4.5-year old children with and without chronic neuromotor disability after early complex cardiac surgery, n=420: mean (SD), median (interquartile range), n (%).

	TOTAL n=420	Chronic Neuromotor Disability	
		No n=395	Yes n=25
A. Pre-operative first CCS			
Family socioeconomic status*	43.6 (13.6) 42 (18)	43.6 (13.6)	43 (13.2)
Mother total schooling: years	13.4 (2.8) 13 (3)	13.5 (2.8)	13.9 (2.7)
Birth region within Northern Alberta	167 (39.8%)	160 (40.5%)	7 (28.0%)
Birth gestation: weeks	38.9 (1.7) 39 (2)	39 (1.7)	38.4 (2)
Birth weight: grams	3326.8 (577.2) 3310.5 (738)	3340.1 (571.2)	3117 (641.9)
Sex: male	265 (63.1%)	252 (63.8%)	13 (52%)
Multiple birth	14 (3.3%)	12 (3%)	2 (8%)
Chromosomal abnormality	32 (7.6%)	29 (7.3%)	3 (12%)

	TOTAL n=420	Chronic Neuromotor Disability	
		No n=395	Yes n=25
Antenatal diagnosis	123 (29.3%)	112 (28.4%)	11 (44%)
Ventilation days	5.7 (5.8) 5 (7)	5.38 (5.4)	10.2 (9)
Inotrope score**	7 (14.1) 0 (0, 10)	6.6 (12.6)	14.6 (28.2)
Highest plasma lactate level: mmol/L	3.5 (3.4) 2.5 (2)	3.3 (3.2)	5.7 (4.8)
Lowest Base-deficit	-4.5 (4.5) -4 (6)	-4.4(4.3)	-7.0 (7.0)
B. Intra-operative first CCS			
Year of surgery	2003.9 (3.6) 2004 (6)	2003.8 (3.6)	2004.8 (3.7)
Age at surgery: days	12 (8.6) 10 (8)	11.6 (8.2)	17.9 (12.2)
Single Ventricle	117 (27.9%)	105 (26.6%)	12 (48%)
Weight: Kg	3.39 (.59)	3.4 (.59)	3.23 (.67)

	TOTAL n=420	Chronic Neuromotor Disability	
		No n=395	Yes n=25
	3.4 (.8)		
CPB: min	112.3 (48.5) 101 (59)	111.5 (47.6)	125.7 (60.8)
X-clamp time: min	53.8 (24.7) 52 (29)	54.0 (24.5)	50.4 (28.6)
DHCA: yes	298 (71%)	280 (70.9%)	18 (72%)
DHCA time only for the that who have it: min (n=298)	24.5 (17.4) 22 (26)	24.4 (17.5) (n=280)	26.2 (16.8) (n=18)
C. Post-operative: first CCS			
Day 1-5 highest plasma lactate: mmol/L	5.8 (3) 5 (3.3)	5.8(2.9)	6.5(4.0)
Day 1-5 highest inotrope score	14.9 (13.4) 11 (13)	14.8 (13.1)	17.1 (18.2)
Day 1-5 lowest Base-deficit	-2.5 (3.4) -2 (3)	-2.5 (3.4)	-3.4 (3.7)
D. Overall first CCS			
Sepsis	75 (17.9%)	70 (17.7%)	5 (20%)

	TOTAL n=420	Chronic Neuromotor Disability	
		No n=395	Yes n=25
Seizures	41 (9.8%)	39 (9.9%)	2 (8%)
CPR	15 (3.6%)	13 (3.3%)	2 (8%)
ECMO	20 (4.8%)	18 (4.6%)	2 (8%)
Dialysis	42 (10%)	41 (10.4%)	1 (4%)
All ventilated days	17 (15.7) 13 (12)	16.6 (15.5)	24 (18.3)
All ICU days	19.5 (17.7) 14 (11)	19.4 (17.9)	20.9 (12.2)
All hospital days	31.4 (29.4) 23 (19)	31 (29.5)	37.1(27.7)
E. Overall prior to 4.5-year assessment			
Sepsis	80 (19%)	72 (18.2%)	8 (32%)
CPR	20 (4.8%)	14 (3.5%)	6 (24%)
Dialysis	45 (10.7%)	43 (10.9%)	2(8%)
ECMO	24 (5.7%)	20 (5.4%)	4 (16%)
Heart Transplant	10 (2.4%)	8 (2%)	2 (8%)
VAD	2 (.5%)	1 (.3%)	1 (4%)
E-CPR	5 (1.2%)	3 (.8%)	2 (8%)

	TOTAL n=420	Chronic Neuromotor Disability	
		No n=395	Yes n=25
Number of interventions with CPB before 4.5 years	1.6 (1.0) 1 (2)	1.6 (.95)	2.0 (1.0)
More than one intervention with CPB	132 (31.4%)	119 (30.1%)	13 (52%)

* Blishen Index[106]
** Inotrope score[107]
IS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min)

Abbreviations: CCS: Complex Cardiac Surgery-CPB: Cardio-pulmonary Bypass-CPR: Cardio-pulmonary Resuscitation-DHCA: Deep hypothermic circulatory arrest-ECMO: Extracorporeal Membrane Oxygenation-E-CPR: Extracorporeal Cardio Pulmonary Resuscitation-ICU: Intensive Care Unit-CND: Chronic Neuromotor Disability-VAD: Ventricular Assist Device

Table 2.2: Description of chronic neuromotor disability at 4.5years of age in children surviving complex cardiac surgery in early life

Cases	Dominant type of tone or movement abnormality	Anatomic Distribution	GMFCS	Presumed timing of causative event in relation to Complex Cardiac Surgery	Chronological age at time of attributed event	Acute illness at presumed timing of causative event	Investigative neuroimaging at acute illness
A. Uni-lateral							
1	Spasticity	Right hemiparesis	II	Likely antenatal. Pulmonary atresia-Tricuspid regurgitation reconstruction	Uncertain	Uncertain	MRI: Periventricular leukomalacia
2	Spasticity	Left hemiparesis	II	9 days before Norwood stage 1 for classical HLHS	2 days	Cardiac arrest requiring resuscitation	CT:Right middle cerebral artery distribution infarct

3	Spasticity	Left hemiparesis	I	2 days before ASO with no ventricular septal defect	10 days	Cardiogenic shock	CT: Right middle cerebral artery distribution infarct
4	Spasticity	Right hemiparesis	II	4 days before ASO with no ventricular septal defect	1 day	Cardiogenic Shock	MRI: Periventricular venous infarct
5	Spasticity	Left hemiparesis	I	1 day before ASO	1 month	Seizures	CT: Hemorrhagic transformation of infarcts in the right hemisphere MRI:Acute watershed infarcts in both cerebral hemispheres, most severe in the right frontal and parietal lobes.

6	Spasticity	Left hemiparesis	II	11 days after ASO with no ventricular septal defect	16 days	Septic shock	MRI: Acute venous thrombosis with multiple white matter infarcts in right frontal, parietal and occipital areas
7	Spasticity	Right hemiparesis	II	2.5 months after pulmonary arterioplasty	3 months	Cardiac arrest requiring resuscitation	MRI: Left parietal infarct
8	Spasticity	Left hemiparesis	I	4 months after ASO with ventricular septal defect	5 months	Pneumococcal meningitis	CT: Hypodensity in right parietal area MRI: Right parafalcine infarct in the occipital region

9	Spasticity	Right hemiparesis	II	30 days before Glenn for classical HLHS	5 months	Cardiac arrest requiring resuscitation	CT: Infarcts in right and left frontal lobe
10	Spasticity	Right hemiparesis	II	7 days after Glenn for classical HLHS	8 months	E. coli sepsis - Disseminated coagulopathy	MRI: Watershed lesions and acute areas of infarction bilaterally
11	Spasticity	Right hemiparesis	II	7 days after Glenn for classical HLHS	6 months	Acute right sided weakness	MRI: Watershed lesions and acute areas of infarction bilaterally
12	Spasticity	Left hemiparesis	II	17 days after Glenn, post critical aortic stenosis repair	4 months	Left focal seizure	MRI: No significant intracranial abnormality

13	Spasticity	Right hemiparesis	I	4 months after Glenn for classical HLHS	10 months	Acute right sided weakness	MRI: Left middle cerebral artery distribution infarct
14	Spasticity	Left hemiparesis	I	3 days after Fenestrated Fontan, for classical HLHS	3 years 11 months	Acute left sided weakness	MRI: Large right middle cerebral artery distribution infarction and left watershed infarcts
				Previous: 2.5 months after Norwood	3 months	Cardiac arrest requiring resuscitation	MRI: Left frontal subcortical infarct

15	Spasticity	Left hemiparesis	I	5 days after Fenestrated Fontan for classical HLHS	3 years	Acute left sided weakness and hemianopsia	MRI: Right anterior cerebral artery and middle cerebral artery distribution stroke with multifocal infarcts on both hemispheres
16	Spasticity	Right hemiparesis	III	8 days after Fenestrated Fontan for classical HLHS	3 years 11 months	Pneumonitis and desaturation	CT: Acute ischemic injury in left hemisphere
				Previous: 7 days after Tricuspid valve reconstruction	1 month	Right subdural hematoma	MRI: Right subdural hematoma

17	Spasticity	Left hemiparesis	II	9 days after Fenestrated Fontan, for classical HLHS	4 years 6 months	Acute Left side weakness	CT: Right frontal lobe hemorrhagic infarct
18	Spasticity	Right hemiparesis	II	27 days after failed Fenestrated Fontan for classical HLHS, and on day 15th of Ventricular assistive device	3 years 3 months	Acute right sided weakness	CT:Left subdural hematoma
B. Bi-lateral							
1	Hypotonia with increased DTR's	Quadri-paresis	IV	16 days before surgery for Interrupted aortic arch repair-type B	2 days	Pre-transfer cardiogenic shock	MRI: Enlargement of ventricles and extra axial cerebrospinal fluid spaces

2	Hypotonia with increased DTR's	Quadri-paresis	IV	12 days before Pulmonary artery reconstruction associated with AV canal	1 month	Gram negative sepsis	MRI: Intracranial hemorrhage
3	Spasticity	Left triparesis	II	9 days before ASO	14 days	Focal seizures	MRI: Small frontal infarct and dural sinus thrombosis
4	Mild Hypotonia with increased Deep Tendon Reflexes	Quadri-paresis	III	21 days after TOF repair	23 days	Cardiac arrest requiring resuscitation	MRI: Atrophy of the white matter
5	Dyskinesia	Quadri-paresis	V	2 months Post TOF arterioplasty	1 ½ months	CA requiring resuscitation	MRI: Diffuse cerebral ischemia

6	Dyskinesia	Quadri-paresis	V	3 months after simple TAPVC	3 months	E. coli sepsis - Disseminated coagulopathy	MRI: Global ischemia
7	Spasticity	Diparesis	II	2 years post complex TAPVC	2 years	Endocarditis and Subclavian thrombosis	MRI: Increased signal in peritrigonal regions

Abbreviations: ASO: Arterial Switch Operation-CT: Computed Tomography-HLHS: Hypoplastic Left Heart Syndrome-MRI: Magnetic Resonance Imaging-TAPVC: Total Anomalous Pulmonary Venous Connection-TGA: Transposition of Great Arteries-TOF: Tetralogy of Fallot

Table 2.3: Growth, health and accompanying impairments after early complex cardiac surgery in relation to chronic neuromotor disability, n=420: mean (SD), median (interquartile range), n (%)

	TOTAL n=420	Chronic Neuromotor Disability		*t*-test *	*P*-value, Fisher's Exact sig**
		No n=395	Yes n=25		
Outcome Variables					
Height: Z-score	-0.34 (1.45) -0.15 (-1.2, .2)	-0.31 (1.5)	-0.8 (1.3)	1.642	0.11
Weight: Z-score	-0.19 (1.08) 0.0 (-.8, .6)	-0.18 (1.8)	-0.44 (1.0)	1.169	0.24
Microcephaly	31 (7.4%)	24 (6.1%)	7 (28%)		0.001
Gastrostomy at any time after first surgery	67 (16%)	57 (14.4%)	10 (40%)		0.002
Number of hospitalizations not related to cardiac treatment	1.6 (2.5) 1 (0,2)	1.8 (2.4)	2.4 (1.9)	-1.553	0.12

	TOTAL n=420	Chronic Neuromotor Disability		*t*-test *	*P*-value, Fisher's Exact sig**
		No n=395	Yes n=25		
Number of hospitalizations related to cardiac treatment	1.4 (2.1) 0 (0, 2)	1.3 (2)	2.6 (2.9)	-2.229	0.04
Number of medical specialist in addition to pediatrician	2.2 (1.6) 2 (1, 3)	0.3 (.7)	0.7 (.5)	-2.705	0.007
Medication for chronic pulmonary disease	58 (13.8%)	52 (13.2%)	6 (24%)		0.14
Medication for chronic cardiac disease	140 (33.3%)	126 (31.9%)	14 (56%)		0.02
Vision impairment	8 (1.9%)	5 (1.3%)	3 (12%)		0.009
Permanent hearing impairment	24 (5.7%)	22 (5.6%)	2 (8%)		0.65
Epilepsy	8 (1.9%)	5 (1.3%)	3 (12%)		0.009
Autism Spectrum Disorder	15 (3.6%)	11 (2.8%)	4 (16%)		0.009
Full-scale IQ: <70[100]	61 (14.1%)	50 (12.7%)	11 (44%)		<0.001

	TOTAL n=420	Chronic Neuromotor Disability		*t*-test *	*P*-value, Fisher's Exact sig**
		No n=395	Yes n=25		
Performance IQ: <70[100]	49 (11.7%)	38(9.6%)	11 (44%)		<0.001
Verbal IQ: <70[100]	56 (13.3%)	45 (11.4%)	11 (44%)		<0.001
Visual-motor Integration: <70[101]	46 (11%)	37(9.4%)	9 (36%)		0.001
ABAS communication: <4[102]	44 (10.5%)	37 (9.4%)	7 (28%)		0.01
ABAS motor: <4[102]	37 (8.8%)	29 (7.35%)	8 (32%)		0.001
ABAS GAC: <70[102]	74 (17.6%)	59 (14.9%)	15 (60%)		<0.001
Intellectual Disability	51 (12.1%)	40 (10.1%)	11 (44%)		<0.001

* Student's *t*-test, two-sided
**Fisher's two-sided test

Abbreviations: ABAS: Adaptive Behavioral Assessment System-GAC: General Adaptive Composite- IQ: Intelligence Quotient

Table 2.4: Predictors of chronic neuromotor disability after early complex cardiac surgery (n=420). Logistic Regression – Odds Ratio and 95% Confidence Intervals

	Prediction of Chronic Neuromotor Disability, n=25			
	Univariate Logistic Regression		Multiple Logistic Regression	
	Odds Ratio	*P*-value	Odds Ratio	^{P}-value
A. Pre-operative first CCS				
Family Socioeconomic status	1 (0.97,1.3)	0.82		
Mother total schooling: years	1.07 (0.93, 1.23)	0.32		
Birth region within Northern Alberta	0.57 (0.23, 1.4)	0.22		
Birth gestation: weeks	0.83 (0.68,1.01)	0.07		
Sex: male	1.63 (0.72,3.66)	0.24		
Chromosomal Abnormality	1.72 (0.49, 6.09)	0.4		
Antenatal diagnosis	1.99 (0.87, 4.51)	0.10		
Ventilation days	1.1 (1.04,1.15)	<0.001		

	Prediction of Chronic Neuromotor Disability, n=25			
	Univariate Logistic Regression		Multiple Logistic Regression	
	Odds Ratio	*P*-value	Odds Ratio	[P]-value
Inotrope score	1.02 (1,1.04)	0.015	1.02 (1.00, 1.04)	0.052
Highest plasma lactate level: mmol/L	1.13(1.05, 1.23)	0.002	1.13 (1.03, 1.23)	0.008
Lowest Base-deficit	0.9 (0.84,0.97)	0.005		
B. Intra-operative first CCS				
Year of surgery	1.08 (0.96, 1.26)	0.199		
Age at surgery: days	1.06 (1.03, 1.1)	0.001	1.08 (1.04, 1.12)	<0.001
Weight: Kg	0.6 (0.31,1.19)	0.15		
CPB: min	1.01 (1,1.01)	0.16		
X-clamp time: min	0.99 (0.98, 1.01)	0.48		
C. Post-operative first CCS				
Day 1-5 Highest plasma lactate: mmol/L	1.07 (0.95, 1.21)	0.24		

	Prediction of Chronic Neuromotor Disability, n=25			
	Univariate Logistic Regression		Multiple Logistic Regression	
	Odds Ratio	*P*-value	Odds Ratio	P-value
Day 1-5 Highest inotropes score	1.01 (0.99,1.04)	0.42		
Day 1-5 Lowest Base-deficit	0.93 (0.83, 1.03)	0.18		
D. Overall first CCS				
Sepsis	1.16 (0.42, 3.20)	0.773		
Seizures	0.79(0.18, 3.49)	0.76		
Dialysis	0.36 (0.05,2.73)	0.32		
All Ventilated days	1.02 (1, 1.04)	0.03		
All ICU days	1.004(0.984, 1.025)	0.676		
All hospital days	1.005 (0.995-1.016)	0.324		
E. Overall prior to 4.5-year assessment				

	Prediction of Chronic Neuromotor Disability, n=25			
	Univariate Logistic Regression		Multiple Logistic Regression	
	Odds Ratio	*P*-value	Odds Ratio	[P]-value
Sepsis	2.11 (0.88,5.08)	0.095		
Dialysis	0.71 (0.16,3.13)	0.653		
More than one CCS	2.51 (1.11,5.67)	0.026	3.57 (1.48, 8.93)	0.005

Abbreviations: CCS: Complex Cardiac Surgery-CPB: Cardiopulmonary Bypass-ICU: Intensive Care Unit

Figure 2.1: Flowchart of death, lost, and assessed children after complex cardiac surgery at ≤6 weeks of age from the years 1996 to 2009.

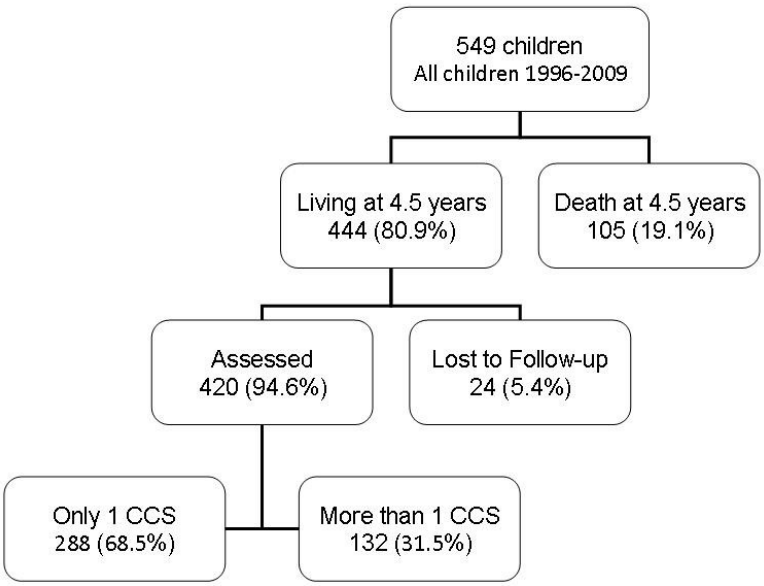
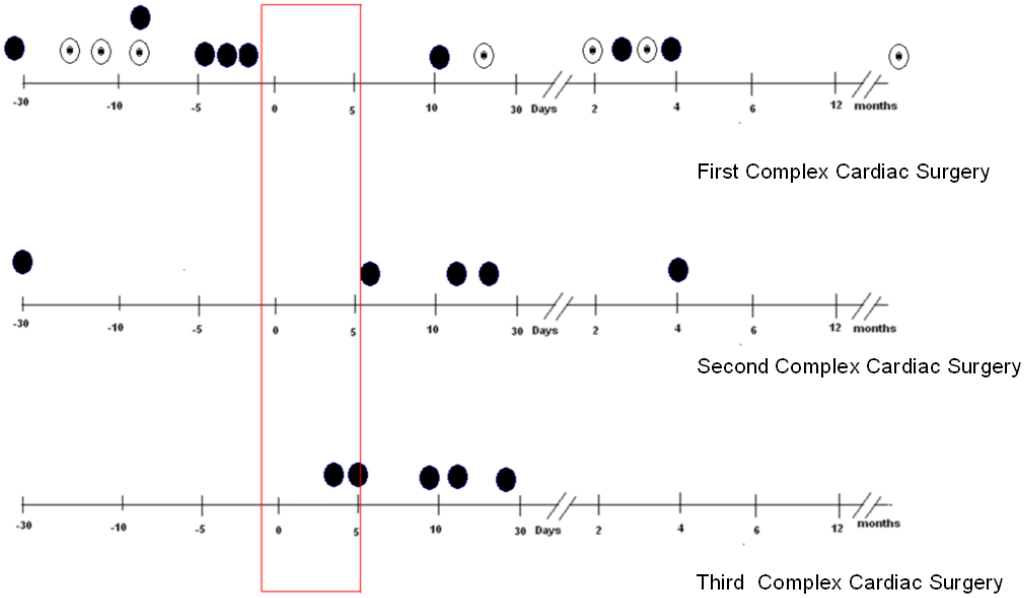


Figure 2.2: Timing of the presumed causative event that lead to chronic neuromotor disability in relation to complex cardiac surgery. n=25

•unilateral, ⊙bilateral



Chapter 3: Deterioration of Functional Abilities in Children Surviving the Fontan Operation

3.1 ABSTRACT

Background/Objectives: Functional abilities are needed for activities of daily living. In general, these skills expand with age. We hypothesized that, contrary to what is normally expected, children surviving the Fontan may have deterioration of functional abilities, and that peri-Fontan stroke is associated with this deterioration.

Methods: All children registered in the Western Canadian Complex Pediatric Therapies Follow-up Program who survived a Fontan operation (1999-2016) were eligible for inclusion. At age 2 (pre-Fontan) and 4.5 years (post-Fontan), the Adaptive Behavior Assessment System-II general adaptive composite score was determined (population mean: 100, standard deviation: 15). Deterioration of functional abilities was defined as ≥1standard deviation decrease in pre- to post-Fontan scores. Peri-operative strokes were identified through chart review. Multivariable logistic regression analysis determined predictors of deterioration of functional abilities.

Results: Of 133 children (mean age at Fontan 3.3 years (standard deviation 0.8), 65% male), mean (standard deviation) general adaptive composite score was 90.6 (17.5) at 2 years and 88.3 (19.1) at 4.5 years. Post-Fontan, deterioration of functional abilities occurred in 34 (26%) children, mean decline: 21.8 (7.1) points. Evidence of peri-Fontan stroke was found in 10 (29%) of the children that had deterioration of functional abilities. Peri-Fontan stroke, (Odds Ratio 5.00 (95%CI 1.74,14.36)), and older age at Fontan, (Odds Ratio 1.67 (95%CI 1.02, 2.73) predicted functional deterioration.

Conclusion: The trajectory of functional abilities should be assessed in this population, as more than 25% experience deterioration. Efforts to prevent peri-Fontan stroke, and to complete the Fontan operation at an earlier age, may lead to reduction of this deterioration.

3.2 INTRODUCTION

Children with cCHD are at high risk for developmental delay. [29] Among the developmental challenges they may experience, limitations in functional abilities have been reported in up to 40%.[126] Functional abilities represent the set of skills that allow a person to perform activities of daily life.[102] Attainment of these abilities is one of the cornerstones of childhood, [127] as they are essential to taking part in different life situations, including taking care of one's self and building relationships with others. Functional abilities develop throughout a child's life; they evolve and expand with age.[102,127] As a result, repeated evaluation of functional abilities is a key component of the assessment of children at risk for developmental delays.[102]

Such evaluation may be particularly important following the Fontan operation. Generally, two open-heart surgeries, numerous lifesaving therapies and repeated hospital stays precede this final step in single ventricle palliation. The added effects of these events place children undergoing the Fontan at high risk for developmental delay.[128] Moreover, although post-Fontan survival rates are high, [25]surviving children often face medical[129] and emotional[130] challenges. In particular, children undergoing the Fontan are at high risk for stroke, [131–134] which on its own can affect functional abilities.[135] However, to date, little is known about the possible impact of the Fontan operation on functional abilities.

We hypothesized that deterioration of functional abilities is not uncommon after the Fontan operation, and that peri-Fontan stroke is often the event leading to this decline. The objectives of this study were i) to determine the frequency of a pre- to post-Fontan deterioration of functional abilities, ii) to ascertain the frequency of peri-Fontan stroke among those with and

without a deterioration of functional abilities, and iii) to identify potentially modifiable variables that may predict this deterioration.

3.3 METHODS

This study was conducted with children registered in the WCCPTFP. This inception cohort project prospectively identifies and follows all infants born with congenital heart disease who undergo complex cardiac surgery at ≤6 weeks of age at the Stollery Children's Hospital (Edmonton, Canada). Even though the pediatric cardiac surgical care for western Canada is regionalized, the neurodevelopmental follow-up of the registered children is conducted in six sites across four provinces. Specific details of this program have been previously reported.[28] This study has approval from the health research ethics boards at each site. Children's parents or legal guardians signed informed
consent.

3.3.1 Participants

All children registered with the WCCPTFP who underwent a Fontan operation from 1999 to 2016 were eligible for inclusion. To reflect current practices at our institution, children who underwent a Norwood with a modified Blalock-Taussig shunt operation as their first stage palliation were excluded; those who died were also excluded. Finally, children lost to follow-up or who refused or had incomplete Adaptive Behavior Assessment System-II [102] questionnaires were excluded from the final analysis.

3.3.2 Childhood Clinical Assessments

All children registered with this follow-up program undergo multidisciplinary assessment at approximately 21 months (pre-Fontan) and 4.5 years of age (post-Fontan).[28] At each of these visits, the Adaptive Behavior Assessment System-II is completed to measure functional abilities. This tool specifically measures what an individual can do "without the assistance of others."[127] In the case of children, the child's primary caregiver completes the Adaptive Behavior Assessment System-II. For the specific age group of 1 to 5 years, the Adaptive Behavior Assessment System-II evaluates functional abilities using 10 skill areas. Each skill area has a mean score of 10 and a standard deviation of 3. The skill areas of communication, functional pre-academics, and self-direction construct the Conceptual Adaptive Domain; the leisure and social skill areas construct the Social Adaptive Domain; while the self-care, home living, community use, and health and safety skill areas form the Practical Adaptive Domain. These three adaptive domains, combined with the motor skill area, provide a general adaptive composite score (normative population mean of 100 and a standard deviation of 15).

3.3.3 Definitions

The presence of deterioration of functional abilities was defined as ≥ 1 standard deviation decrease in the post-Fontan general adaptive score in comparison to the pre-Fontan score. Peri-operative stroke was defined as clinical evidence of a brain insult[131] happening anytime between the time of Fontan operation and the first 30 days post-operatively. To avoid missing the diagnosis, stroke was identified in several ways. All children's acute medical records during the Fontan hospitalization were retrospectively reviewed for any evidence of acute stroke. The identified strokes were cross-checked with the follow-up program database (prospectively records "abnormal neuroimaging"), and with a review of all neuroimaging done during the

Fontan hospitalization. A major post-operative complication was defined as any of: convulsions, cardiopulmonary resuscitation, sepsis, dialysis, need for urgent cardiac catheterization, need for extracorporeal membrane oxygenation, or need for ventricular assist device. Accompanying neurologic impairments are recorded prospectively in the Follow-up Program database. Chronic neuromotor disability[136] was defined as the presence of permanent motor difficulties secondary to a diagnosis of cerebral palsy or acquired brain injury. Permanent sensory hearing impairment was defined as a sensorineural loss or auditory neuropathy bilateral loss of > 25 dB HL from 500 to 4000 Hz. Seizure disorder was defined by the use of antiepileptic medication at the time of the multidisciplinary assessment.

3.3.4 Data Collection

Demographic data collected prospectively for each child included gestational age, sex, chromosomal abnormality, antenatal diagnosis, main cardiac diagnosis of hypoplastic left heart syndrome and family socioeconomic status (as determined by the Blishen Index).[106] Pre-Fontan data recorded prospectively included presence of recognized disability and number of surgeries with cardiopulmonary by-pass, stage one and stage two surgery type, and age at stage two surgery. Prospectively obtained acute care information in relation to the Fontan included: age and weight, type of Fontan, use of fenestration, use of aortic cross-clamp, use of deep hypothermic circulatory arrest and/or fibrillatory arrest; minutes of cardiopulmonary by-pass; arrival in intensive care intubated; and post-operative day 1 and day 2-5 inotrope score[107], highest lactate, and red blood cells transfusion requirements; delayed sternal closure, presence of major complication, days in intensive care unit, days of ventilation, and total length of hospital stay including intensive care unit and non-intensive care unit days (Table 1).

3.3.5 Statistical analysis

Continuous variables are presented as means (standard deviation) or medians (interquartile range) and categorical variables as counts and percentages. Frequency of deterioration of functional abilities and peri-Fontan stroke are given as percentage of the assessed survivors with 95% confidence interval. Comparisons between those with and without deterioration of functional abilities were completed using Student t-test for continuous variables and Fisher's exact/chi-square test for categorical variables. Potential predictors of deterioration of functional abilities were analyzed using multivariable logistic regression analysis. Variables with univariate $P< 0.10$ were presented to the model. Using a likelihood ratio test we examined the combination of covariates to find the best fit for our model. A conditional stepwise forward selection method was used to confirm the final model. Two-sided P values <0.05 were considered statistically significant.

3.4 RESULTS

3.4.1 Description of the Cohort

During the study period, 192 children registered with the WCCPTFP underwent a Fontan operation at the Stollery Children's Hospital. Of these, 145 were eligible for study inclusion; children were excluded because of having a Norwood with a modified Blalock-Taussig shunt operation (n=29), being too young for 4.5-year-old multidisciplinary assessment (n=11), or dying before 4.5 years (n=7). In addition, 3 children were lost to follow-up, the parents of 4 children refused to participate, and 5 children had incomplete data at the 21-month-assessment. The final study cohort was comprised of 133 children (92% of eligible children) (Figure 3.1).

For the 133 children, mean age at the time of the Fontan operation was 3.3 (0.8) years (median, 3.2) and mean weight was 14 (1.8) kilograms. Sixty-seven (50%) children had HLHS, 61 (46%) had an extra-cardiac Fontan, while 100 (75%) had a fenestrated Fontan. Mean ages at pre- and post-Fontan multidisciplinary assessment were 22 (6) months and 4.6 (0.5) years, respectively. Mean pre- and post-Fontan general adaptive composite scores were 90.6 (17.5) and 88.3 (19.1) (Table 3.1).

A total of 18 (13.5%) children had clinical evidence of peri-Fontan stroke. Mean post-Fontan general adaptive composite score for all 18 children with stroke was 76.9 (21) versus 90.1 (18.3) among children without stroke (p=0.01) (Figure 3.2).

3.4.2 Deterioration of Functional Abilities

Pre- to post-Fontan deterioration of functional abilities occurred in 34/133 (26%) children. Of those with deterioration, 19 (56%) had HLHS, 20 (59%) were male, 17 (50%) underwent an extra-cardiac Fontan, and 27 (79%) children had a fenestrated Fontan. Mean pre- to post- Fontan decline was 21.8 points (7.1), 96.3 (17.5) to 74.5 (16.6). Figure 3.3 shows the trajectory of each of the three adaptive domains among those with a deterioration of functional abilities; the practical domain showed the largest decline. Mean age at pre- and post-Fontan multidisciplinary assessment was not statistically different among children with and without deterioration. At the time of their 4.5-year multidisciplinary assessment, children with deterioration of functional abilities were more likely to have a chronic neuromotor disability (p=0.02); otherwise the groups were similar (Table 3.2).

3.4.3 Deterioration of Functional Abilities and Stroke

Evidence of peri-Fontan stroke was found in 10/34 (29%) of children with deterioration of functional abilities, and in 8/99 (8%) of children without this deterioration (p=0.002). The most common clinical presentations of stroke were hemiparesis, which occurred in 12/18 (67%) children, 2 of whom also had associated aphasia, and seizures which occurred in 5/18 (28%) children. One child presented with isolated decreased level of consciousness. Fifteen (83%) children had neuroimaging confirming the presence of stroke; the parents of 3 children refused to complete in-hospital neuroimaging, but pediatric neurologists interpreted the child's clinical findings as stroke in the acute period. Most children, 16/18 (89%) were recognized to have had a stroke during the first 10 post-operative days, at a median 6.5 days post-operatively. Two of the 24 children who had deterioration of functional abilities but no recognized peri-operative stroke had surveillance neuroimaging later in life showing evidence of stroke; as timing was unknown, they were not considered as peri-operative stroke in our study.

In those with deterioration of functional abilities, children with stroke had a mean decline in general adaptive composite score of 26.1 (9.6) points, compared to a mean decline of 20 (5.3) points among those without stroke (p=0.08). In addition, children with deterioration of functional abilities and stroke had a statistically significant larger decline in the social domain when compared to those with deterioration of functional abilities but without stroke (25.6 (12) versus 16.9 (8.4); p=0.04). The differences in decline in the other two domains were not statistically significant. Finally, among those with deterioration of functional abilities, both children with and without stroke had their lowest mean composite scores in the practical domain.

3.4.4 Prediction of Deterioration of Functional Abilities

In the univariable analysis, presence of clinical stroke, arrival in intensive care intubated, and age at Fontan were associated with deterioration of functional abilities with a p value <0.1 (*P*= 0.003, *P*=0.07 and *P*=0.05 respectively). However, in the multivariable logistic regression, only clinical stroke (multivariable OR 5.00, 95% CI 1.74, 14.36; *P*=0.003), and older age at Fontan (per year of age, multivariable OR 1.67, 95% CI 1.02, 2.73; *P*=0.04) were significant predictors of deterioration of functional abilities. No other demographic, patient or operative characteristics were significantly associated with deterioration of functional abilities.

3.5 DISCUSSION

By assessing the trajectory of functional abilities in a large cohort of children undergoing the Fontan operation, we have found that more than one quarter have a pre- to post-Fontan deterioration of functional abilities. In addition, we found this deterioration is frequently associated with peri-Fontan stroke. Overall our cohort of children display pre- and post-Fontan general adaptive composite scores that are lower than the population mean, but still within one standard deviation from population normative values. Of concern, in those recognized as having a deterioration of functional abilities, the mean post-Fontan general adaptive composite score was almost 2 standard deviations below the normative mean.

Different authors have previously identified delays in functional abilities in children surviving open-heart cardiac surgery; Limperopoulos found limitations in functional abilities in up to 40%,[126] Alton et al reported delays in functional abilities both at 21 months and 4.5 years of age,[121,137] and more recently Brosig et al showed functional abilities are a specific area of concern in these children. [34] While longitudinal changes in adaptive behavior have been

investigated in certain populations,[138–140] no authors have previously considered the trajectory of functional abilities in relation to the Fontan operation.

Much as cognitive development, functional abilities "are relative to one's age".[141] Acquisition of skills for daily living should develop steadily throughout the childhood years. As children grow and the demands of everyday life increase, functional abilities must expand rather than decline, as we found in 26% of our children. [141] Of the three domains that comprise the general adaptive composite score, we found the practical domain had the greatest decline. This finding is consistent with Laraja et al; they studied 52 children who underwent fetal aortic valvuloplasty finding delays in functional abilities, with practical skills significantly lower than normative population values.[142] Alton et al have reported low self-care skills (part of the practical domain) in children surviving the Norwood operation.[137] It has been proposed that while the learning process is represented in the conceptual domain, and the socialization process in the social domain, the practical domain represents maturation.[143] This impact on maturation might partly explain why more than 50% of adult Fontan survivors are still living at home with their parents, and continue to have specific worries about their health, their abilities to work and to live independently. [43]

Overall, 13.5% of children in our study showed clinical evidence of peri-operative stroke. This is similar to findings from Bellinger et al,[132] but higher than what has been reported by other authors.[131,133,134] While these studies[131,133,134] include all children that underwent a Fontan, our study only included children who underwent the Fontan but who also had their first complex cardiac surgery at ≤ 6 weeks (registration criteria). Thus, it is possible that our study may have selected children with a more complex cardiac lesion, which may explain the difference in our findings.

In addition, we found stroke occurred in 29% of the children with deterioration of functional abilities. It is not surprising that stroke can affect functional abilities, as impairments in different functional skills have been described in children with stroke[135] and other types of brain injury.[144,145] Although we initially hypothesized the majority of deterioration of functional abilities would be secondary to stroke, we were unable to find a clear cause for the deterioration of functional abilities in more than half of the children. One explanation for this could be that stroke can explain more of the deterioration of functional abilities cases but is often under-recognized. A recent study from Cheng showed 41% of stroke diagnosis in children with heart disease was found only on surveillance imaging studies.[146] Similar findings were reported by Bellinger et al;[132] they found 40% of strokes in adolescents surviving the Fontan were initially missed by clinical assessment alone. In children, initial symptoms of stroke are often not clear,[147,148] and children with stroke often "grow into their deficits".[149] The fact that among those with deterioration of functional abilities we identified two children with missed strokes of uncertain timing also reflects clinical under-recognition. There are other potential explanations for deterioration of functional abilities. Rempel describes that parents of children with HLHS tend to normalize their children's development as a response to the uncertainty about their children's future.[150] Generally speaking, at 21 months, children do not spend much time with peers. Parents may therefore be more prone to normalize development at that age, giving their children higher scores on the Adaptive Behavior Assessment System-II than they deserve. After the Fontan, children are older and gradually spend more time with peers, which might lead to less normalization as parents are faced with the reality of what other children the same age are capable of doing.

Importantly, we found that older age at Fontan predicts deterioration of functional abilities. This is not the first study to show that older age at Fontan may be associated with worse post-operative outcomes. Worse post-operative exercise capacity[151] and lower cognitive abilities[152] have been associated with older age at Fontan. Achieving the Fontan circulation later in life means the developing brain continues to be exposed to hypoxia for a longer period. The continuous effect of chronic hypoxia at a time characterized by rapidly increasing cognitive functions and emerging imagination[153] might be particularly deleterious.[154]

We endeavored to construct a clinically relevant definition of deterioration of functional abilities. This would not only allow us to identify children within our own cohort who have experienced a substantive deterioration, but also allow for further research in this area. While half a standard deviation difference has been described to recognize clinically significant changes in adult self-completed questionnaires,[155] in our study we considered a full standard deviation decline would provide more interpretable results; in particular, considering the Adaptive Behavior Assessment System-II used in this age group is not a self-completed but a parent-completed questionnaire. Moreover, a drop of 1 standard deviation places patients in a different descriptive classification (e.g. from average to below average). Further work correlating deterioration of functional abilities with future skills and educational and career achievements will be important to lend credence to our definition.

Our study has several limitations. On average, the program follow-up assessment took place 12.9 months after the Fontan operation. We would expect that most acute events and interventions that explain deterioration occur at the time of surgery; children are more likely to be in steady state in the year post Fontan. However, it is possible that deterioration of functional abilities occurred due to events we could not identify occurring well before or after the time of the Fontan

operation. In addition, neuroimaging could not be obtained for all children with clinical evidence of stroke, and thus we could not confirm the diagnosis in three children. The data on stroke and its timing were confirmed retrospectively, and thus subject to ascertainment bias. As in any observational study, our results cannot prove cause and effect relationships. A number of children suffered a stroke but did not experience deterioration of functional abilities; the reasons why in certain cases stroke leads to deterioration of functional abilities, and not in others needs to be further investigated. Our study also has several strengths. This is a large cohort of children having the Fontan operation, and long-term follow-up was obtained in 133/145 (92%) of survivors. In addition, other than the diagnosis of stroke, all data on potential predictors of deterioration of functional abilities were obtained prospectively.

3.6 CONCLUSION

Our work shows more than one quarter of children have deterioration of functional abilities following the Fontan operation. At this early stage in development, recognition of a deterioration of functional abilities can help understand future potential life challenges. More importantly, it can guide the use of interventions, proven to improve the functioning of the child.[141,156] We identified two potentially modifiable independent predictors of deterioration of functional abilities after the Fontan operation: peri-operative stroke and older age at Fontan. In addition to prevention of peri-operative stroke, efforts should be made to recognize strokes when they occur to allow for earlier intervention. Finally, completion of the Fontan operation at a younger age may help reduce deterioration of functional abilities, and warrants further study.

Table 3.1: Description of 133 children undergoing the Fontan operation in relation to deterioration of functional abilities: mean (SD), median (interquartile range), n (%)

	Total n:133	Deterioration of Functional Abilities		*P*-value
		NO n:99	YES n:34	
A. Demographic				
Family SES	44.2 (13.5) 42 (34, 54.5)	45.3 (13.1)	41 (14.5)	0.11
Gestational age: weeks	38.8 (1.8) 39 (38, 40)	38.8 (1.8)	38.9 (1.8)	0.90
Sex: male	86 (65%)	66 (67%)	20 (59%)	0.41
Chromosomal abnormality: yes	3 (2%)	2 (2%)	1(3%)	0.99
Antenatal Diagnosis: yes	100 (75%)	77 (79%)	23 (68%)	0.20
Main cardiac diagnosis: HLHS	67 (50%)	48 (49%)	19 (56%)	0.46
B. Pre-Operative Fontan				
Pre-Fontan diagnosed motor or sensory disability	18 (14%)	13 (13%)	5 (15%)	0.78

Number of surgeries with CBP prior to Fontan				
1	40 (30%)	31 (31%)	9 (26%)	0.59
2	90 (68%)	65 (66%)	25 (74%)	
3	3 (2%)	3 (3%)	0	
Stage 1 surgery:				
Non-Norwood	48 (36%)	38 (38%)	10 (29%)	0.35
Norwood Sano	85 (64%)	61 (62%)	24 (71%)	
Stage 2 surgery:				
Glenn				
Type of Glenn				
Bidirectional Right	114 (86%)	83 (85%)	31 (91%)	0.69
Bidirectional Left	4 (3%)	4 (4%)	0	
Bilateral	13 (10%)	10 (10%)	3 (9%)	
Kawashima	1 (1%)	1 (1%)	0	

Age at Glenn (months) 	5.8 (1.7) 5.5 (4.5, 6.5)	5.7 (1.5)	5.9 (2.1)	0.58
C. **Intra-operative Fontan**				
Fontan Year	2010 (2.7) 2011 (2009, 2013)	2010 (2.6)	2010 (2.9)	0.69
Age at Fontan (years)	3.3 (.8) 3.2 (2.78, 3.6)	3.2 (.8)	3.5 (.9)	0.05
Weight at Fontan (Kg)	14 (1.8) 13.9 (12.9, 15)	14 (1.8)	14 (1.8)	0.74
Type of Fontan -Intra-extracardiac -Extracardiac -Lateral Tunnel -Other	 43 (32%) 61 (46%) 26 (20%) 3 (2%)	 33 (33%) 44 (44%) 20 (20%) 2 (2%)	 10 (29%) 17 (50%) 6 (18%) 1 (3%)	0.93
Fenestrated	100 (75%)	73 (74%)	27 (79%)	0.51
CPB minutes	89.9 (35.6)	90.5 (36.8)	88.5 (32.1)	0.78

	86 (67, 104)			
X-clamp used	78 (59%)	59 (60%)	19 (60%)	0.70
DHCA used	9 (7%)	7 (7%)	2 (6%)	0.85
Fibrillation used	27 (20%)	19 (19%)	8 (24%)	0.59
Arrival in PICU intubated	35 (26%)	22 (22%)	13 (38%)	0.07
C. Post-Operative Fontan				
Day 1 inotrope score* 	7.4 (8.2) 5 (2, 10)	7.4 (8.3)	7.6 (8.1)	0.90
Day1 Lactate highest mmol/L	4.4 (2.1) 3.9 (3, 5.3)	4.4 (2.3)	4.4 (1.7)	0.97
Day1 Lowest Arterial pH	7.3 (0.05) 7.28 (7.3, 7.3)	7.3 (0.05)	7.3 (0.05)	0.88
Day1 red blood cells transfusion required	20 (15%)	14 (14%)	6 (18%)	0.62
Day 2-5 inotrope score*	3.9 (8.5) 0 (0,4)	3.6 (8.1)	5.2 (9.6)	0.34
Day 2-5 highest lactate	2.4 (1.8)	2.3 (1.8)	2.7 (1.4)	0.15

	1.9 (1.4, 2.9)			
Day 2-5 Lowest Arterial pH	7.3 (0.1) 7.3 (7.2, 7.4)	7.3 (0.1)	7.3 (0.1)	0.80
Day 2-5 red blood cells transfusion required	19 (14%)	14 (14%)	5 (15%)	0.88
Delayed sternal closure	7 (5%)	5 (5%)	2 (6%)	0.99
Clinical Stroke**	18 (14%)	8 (8%)	10 (29%)	0.002
Days in ICU	5.7 (14.3) 3 (2, 4)	5.18 (13.1)	7.21 (17.6)	0.48
Days of ventilation	1.28 (2.80 0 (0,1)	1.18 (2.85)	1.56 (2.7)	0.50
Length of stay (days)	16.9 (24.5) 10 (8, 16)	16.74 (25.1)	17.41 (23.2)	0.89
Major complication post Fontan***	19 (12%)	14 (11%)	5 (13%)	0.78

*Calculated as per Wernovsky and colleagues.[107]
IS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min)

**History of peri-Fontan stroke was present in 1/47 (2%) excluded children (1/7 died, 0/11 too young for assessment, 0/29 Norwood BT); and in 1/12 (8%) of the children with incomplete Follow-up (1/5 incomplete 21-months ABAS-II, 0/4 parents refused, 0/3 lost to follow-up).

***Major post-operative complication was defined as any of: convulsions, cardiopulmonary resuscitation, sepsis, dialysis, need for urgent cardiac catheterization, need for extracorporeal membrane oxygenation, or need for ventricular assist device.

Abbreviations: CPB: cardiopulmonary bypass –DFA: deterioration of functional abilities- DHCA: deep hypothermic circulatory arrest- HLHS: Hypoplastic left heart syndrome - ICU: intensive care unit- PaO2: arterial partial pressure of oxygen- PICU: pediatric intensive care unit-SES: socioeconomic status.

Table 3.2: Childhood profile in relation to Deterioration of Functional Abilities following the Fontan operation: n = 133, mean (SD), median (interquartile range), n (%).

Outcome Variables	Total n=133	Deterioration of Functional Abilities		p-value
		No n=99	Yes n=34	
Height Z-score	-0.73 (1.1) -0.6 (-1.5, 0)	-0.67 (1.1)	-0.92 (1.2)	0.25
Weight Z-score	-0.37 (1.1) -0.2 (-1, 0.5)	-0.27 (1.03)	-0.66 (1.17)	0.07
Cardiac meds required yes	126 (95%)	93 (94%)	33 (97%)	0.68
Number of hospitalizations not related to cardiac treatment	0.67 (1.5) 0 (0, 1)	0.56 (1.3)	1 (2.2)	0.46
Number of hospitalizations related to cardiac treatment	1.89 (1.5) 2 (1,2)	1.95 (1.5)	1.74 (1.4)	0.16
Seizure disorder	4 (3%)	3 (3%)	1 (3%)	0.99
Sensorineural hearing loss, bilateral	12 (9%)	8 (8%)	4 (12%)	0.50
Chronic Neuromotor Disability	16 (12%)	8 (8%)	8 (24%)	0.02

Figure 3.1 Flowchart of death, lost, excluded and assessed children undergoing the Fontan operation from 1999 to 2016. (WCCPTFP: Western Canadian Complex Pediatric Therapies Follow-up Program. Norwood BT: Norwood with a modified Blalock-Taussing shunt. ABAS-II: Adaptive Behavior Assessment System-II).

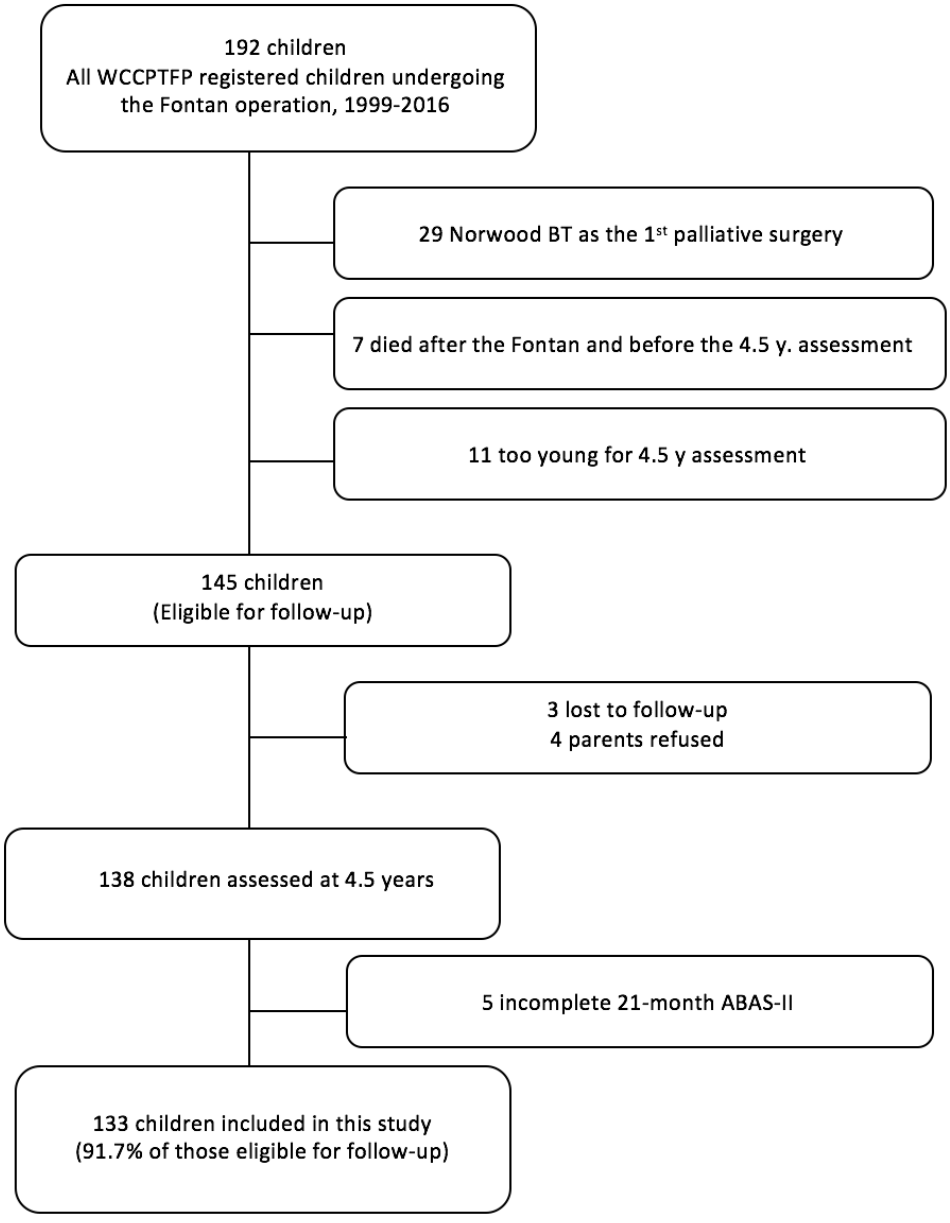


Figure 3.2 Stroke leads to deterioration of functional abilities (n=133). Pre- and Post-Fontan General Adaptive Composite scores (mean and standard deviation): for those without clinical peri-operative stroke 90.2 (17) to 90.1 (18.3); for those with clinical peri-operative stroke 92.9 (20.7) to 76.9 (21).

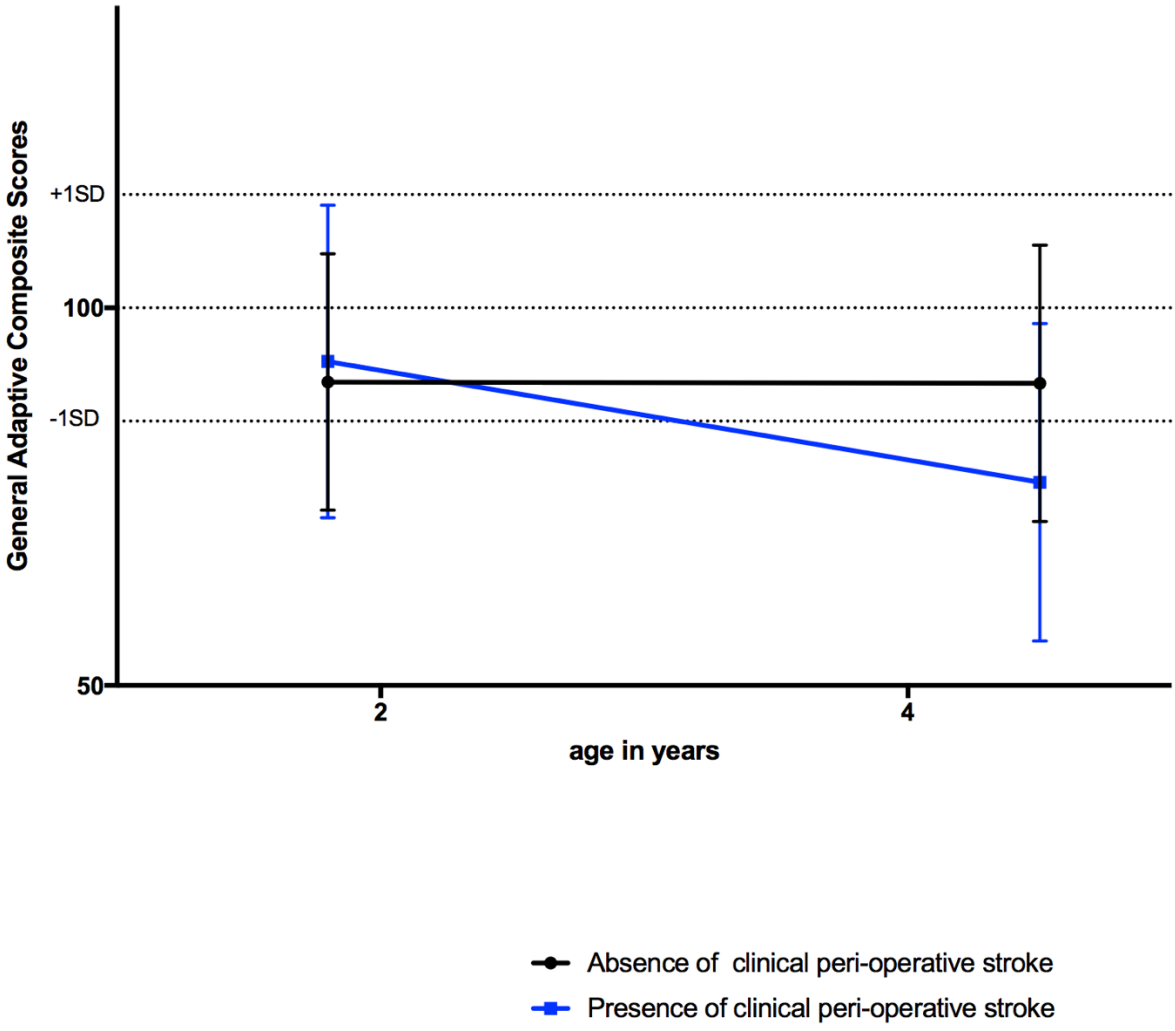
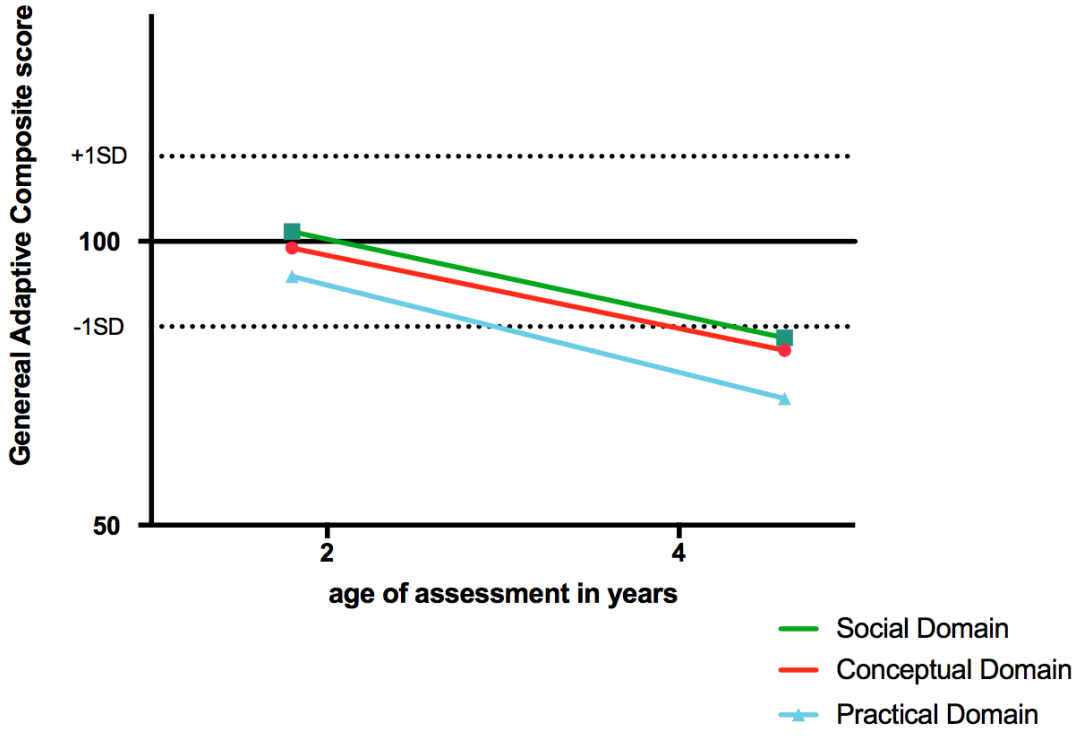


Figure 3.3 The trajectory of the three adaptive domain's scores for children with Deterioration of functional abilities (n=34). Pre- and Post-Fontan scores (mean and standard deviation) for each domain were as follow: Social Domain 101.7 (18.3) to 83 (15.5), Conceptual Domain 98.8 (17.8) to 80.8 (17.4), Practical Domain 93.8 (17.2) to 72.3 (15.5).



Chapter 4: Gastrostomy Tube Feeding after Neonatal Complex Cardiac Surgery Identifies the Need for Early Developmental Intervention

4.1 ABSTRACT

Objectives: To compare the proportion of developmental delay in early complex cardiac surgery (CCS) survivors with and without gastrostomy tube feeding (GTF). To explore acute care predictors of GTF that might help improve care in CCS survivors.

Study Design: This comparison study of two groups within an inception cohort included 334 CCS survivors after cardio-pulmonary bypass at ≤6 weeks of age (2005-2012) who did not require extracorporeal membrane oxygenation or heart transplantation. Children were assessed at 21±3 months with the Bayley Scales of Infant and Toddler Development, 3rd edition and the Adaptive Behavior Assessment System, 2nd edition: General Adaptive Composite score. Delay was determined by scores >2 SD below mean. Chi-square test compared groups. Predictors of GTF were analyzed using Multiple Logistic Regression analysis, results expressed as Odds Ratio (OR) with 95% Confidence Interval (CI).

Results: 67/334 (20%) of survivors had GTF any time before the 21-month assessment. Developmental delays in children with GTF were: cognitive 16(24%), motor 18(27%), language 24(36%) vs. without GTF 7(3%), 8(3%) and 32(12%) respectively (P<0.001). Gastrostomy group had almost eight times the number of children delayed on the General Adaptive Composite score. Independent OR for GTF are: presence of a chromosomal abnormality, OR:4.6(95%CI:1.8,12.0) (P=0.002), single ventricle anatomy, OR:3.4(95%CI:1.7, 6.8) (P<0.001), total postoperative days of open sternum, OR:1.15(95%CI: 1.1,1.3)(P=0.031) and total number of hospital days at CCS, OR:1.03(95%CI:1.1, 1.04)(P=0.002).

Conclusion: GTF identifies CCS survivors at risk for delay, who would benefit from Early Developmental Intervention. The described mostly non-modifiable predictors may guide counselling of these children's families.

4.2 INTRODUCTION

Recent improvements in diagnosis, surgical techniques and overall care of children with congenital heart disease (CHD) have resulted in increased survival rates.[157] More recently, the focus of attention has been shifting to improving developmental outcomes as it is well recognized that children with CHD surviving complex cardiac surgeries (CCS) are at risk for neurodevelopmental disabilities.[5]

In the last decades, early developmental intervention (EDI) programs have become a key element in the assistance of children who have, or are at risk of having, developmental delays. EDI provides multidisciplinary services to children from birth to school entry to "promote children's health and well-being, enhance emerging competencies, minimize developmental delays, remediate existing or merging disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning".[158] EDI is known to positively impact outcomes across developmental domains, including motor, language, cognitive and social/emotional development, overall health, as well as family empowerment.[87,159,160] Prompt recognition of the need for referral is essential to provide support as early as possible.

The primary goal of gastrostomy tube feeding (GTF) is to enhance growth and nutrition. Indications for GTF usually include children with swallowing difficulties, poor oral intake, feeding disorders and/or congenital anomalies.[161,162]Although initiation of GTF might at times represent a challenging decision for parents and caregivers, studies have shown the positive impact GTF has on the overall health and outcomes of children requiring non-oral feedings.[163–165] A recent study showed benefits included reduced vomiting, increased oral intake, improved parent and child relation and satisfaction during meals.[166]

Feeding difficulties are a common obstacle in the postoperative period after CCS for CHD.[39] Nutritional challenges present in children with CHD are generally the result of reduced caloric intake, reduced intestinal absorption associated with increased energy loss. [163] It has been estimated that approximately 10-18% of children require GTF after their initial CCS. [39,167] Feeding difficulties in this population might have different origins including laryngopharyngeal dysfunction, present in approximately 48% of patients after the Norwood procedure, underlying neurological conditions and vocal cord paralysis.[40]

It is also known that in general, children with developmental or acquired disabilities are at greater risk for requirement of GTF.[165] We hypothesized the presence of GTF in an infant at any time after the first CCS could potentially be used as a simple identifier for an increased risk of the presence of developmental delay and need for EDI. The main objective of this study is to compare the proportion of different types of developmental delay in CCS survivors with and without GTF. A secondary objective of the present study is to explore and better understand pre- and post-CCS predictors of GTF that might help improve care and counseling of these children's families.

4.3 METHODS

4.3.1 Design

This study is part of an inception cohort follow-up project conducted in six Developmental/Rehabilitation referral sites in western Canada: Vancouver, British Columbia; Edmonton and Calgary, Alberta; Regina and Saskatoon, Saskatchewan; and Winnipeg, Manitoba.[28] Infants were identified at the time of first CCS and followed prospectively. At the time of the first CCS, predetermined demographic, pre-operative, intra-operative, and post-

operative variables were collected. The need for GTF at any time is recorded. At the study center GTF is indicated when tube feeding extends beyond 30 days; delay in the initiation may be secondary to parental refusal or delayed referral to a surgeon. The health research ethics boards at each site approved the study, and all parents or legal guardians provided written consent.

4.3.2 Subjects

Participants included infants who had CCS at ≤6 weeks requiring cardio-pulmonary bypass between 2005 and 2012 at the Stollery Children's Hospital, Edmonton, Canada; and who did not require extracorporeal membrane oxygenation or heart transplantation at any time prior to the 21-month assessment. Children who died prior to the 21-month assessment and those lost to follow-up were excluded. We also excluded children assessed with the Bayley Scales of Infant Development, 2nd Edition (BSID-II)[168] rather than the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley-III)[169] and those children for whom assessment results were yet not available.

4.3.3 Early Childhood Clinical Assessments

Multi-disciplinary assessments were performed at 21 months of age at each of the referral sites. Certified pediatric psychologists and psychometrists administered the Bayley-III[169] (cognitive, language, motor) and the Adaptive Behavior Assessment System-II (ABAS-II):[102] General Adaptive Composite. Delay in both measures was determined by scores >2 SD below mean, i.e. scores in the lowest 2.27% of normative population. The Bayley-III[169] is an individually administered test that assesses the cognitive, language (receptive and expressive communication) and motor (fine and gross motor skills) functioning of infants between 1 month and 42 months of age. The child's chronological age is calculated at the time of the testing,

adjusting for prematurity until 24 months of age. This widely used tool identifies risk for developmental delay giving useful information to assist clinicians in determining the need for EDI. Each of the five subtest results are derived as scaled scores that range from 1–19, with a mean of 10 and a standard deviation (SD) of 3. These are then converted into composite scores with a mean of 100 and a SD of 15. The ABAS-II,[102] a caregiver completed questionnaire, measures the functional and realistic-for-age skills necessary for independent daily living using nine skill areas grouped into three composite domains: conceptual, social, and practical which combined with the motor skill area give the General Adaptive Composite score, reflective of functional abilities (mean of 100 and a SD of 15). Family socioeconomic status was determined by the Blishen Index,[106] an indicator dependent on employment, education, and prestige value of an occupation, based on the main family wage earner with a population mean of 43 and SD of 13. Maternal education was recorded in years of schooling at the time of the 21-month assessment.

4.3.4 Acute care variables

Acute care information (Table 4.1) included birth gestation (37 completed weeks considered term), sex, chromosomal abnormality, antenatal diagnosis; pre-operative and post-operative (day 1-5 and day 6-10) highest plasma lactate, inotrope score;[107] total postoperative days with an open sternum; age, weight, single ventricle cardiac defect, cardio-pulmonary bypass time, X-clamp time, and use of deep hypothermic circulatory arrest at first CCS; the overall at first CCS presence of pre- or post-operative sepsis, cardio-pulmonary resuscitation, vocal cord paralysis, dialysis; and the number of ventilated days and hospital days.

4.3.5 Statistical Analysis

Categorical variables are presented as proportions and continuous variables are presented as means (SD) or medians (IQR). Frequency of gastrostomy tube requirement is given as percentage of assessed survivors, using 95% confidence intervals (CI). Descriptive variables for outcomes were analyzed with Student *t* test and chi-square test. Multiple logistic regression analysis included demographic, operative and peri-operative predictors of GTF having *P* value <0.10 after screening for multicollinearity. Results are expressed as odds ratios (OR) with 95% CI; significance considered at <0.05. Data analyses were performed using IBM SPSS Statistic Data Editor Version 22. Results were confirmed with the Akaike model selection using R software version 3.2.1.

4.4 RESULTS

Four hundred and seven children had neonatal CCS requiring cardio-pulmonary bypass; none had extracorporeal membrane oxygenation or heart transplantation prior to the 21-month assessment. Of these 407, 35 (8.6%) died. From the 372 survivors, 18 (5%) were lost to follow-up, eight (2%) were assessed using the BSID-II[168] rather than the Bayley-III[169] and for 12 (3%) their assessment results were not yet available. The remaining 334 (90%) received multidisciplinary assessment at a mean age of 21$\pm$ 3 months and were included in this study. (Figure 4.1) A total of 111(33%) children had single ventricle anatomy, 123 (37%) had Transposition of Great Arteries, 34 (10%) had Total Anomalous Pulmonary Venous Connection repair and 66 (20%) had other cardiac abnormalities.

GTF was required in 67 (20%) survivors at any time before the 21-month assessment. Of these, 35 (52%) had single ventricle anatomy, 48 (72%) were males, 10 (15%) had a chromosomal abnormality and 44 (65.7%) had antenatal diagnosis. (Table 4.1) Two (4.5%) had

intestinal malrotation requiring the Ladd procedure.

At the 21-month assessment 12 (18%) still required GTF. Overall 47 (70%) continue to require GTF after the age of 6 months.

4.4.1 Childhood profile in relation to requirement of Gastrostomy tube feeding

The comparison of the different types of developmental delay between children with and without GTF are found in Table 4.2. Comparing the Bayley-III language and motor subtests, 24% of children with GTF presented receptive language delay, 25.4% expressive language delay, 15% fine motor delay and 31.3% gross motor delay versus 5.6%, 6%, 0.7% and 4.1% present respectively in children without GTF (P<0.001). Calculating the developmental age equivalent scores of these children, "average age in months at which a given raw score is typical,"[169] the level of receptive and expressive communication skills in the GTF group is equivalent to those skills normally present in a 10-month-old, while the fine and gross motor function is equivalent to those of an 11-month-old.

Overall in the GTF group cognitive delay was eight times more common, language delay was three times more common and motor delay was nine times more common than among CCS survivors without GTF requirement. The GTF group had almost 8 times more the number of children delayed on functional abilities as shown by the General Adaptive Composite than the non-GTF group. Higher rates of associated health problems, including poor growth, number of hospitalizations, need for specialist involvement and need for chronic medication, were also evident in the GTF group.

Among children requiring GTF, 94% of the children with cognitive delays, 79% of the children with language delays and 94% of the children with motor delays, required GTF to

continue after the age of 6 months. Analysis according to time to GTF placement showed no significant difference in delay.

Omitting those children with single ventricle anatomy from the analysis, results showed the following delays in those with GTF: cognitive 41%, language 47%, motor 38%, functional abilities 50% versus no GTF 2%, 11%, 2.3%, and 5% respectively (P<0.001). The frequency of chromosomal abnormalities in this subgroup of children with biventricular defects and GTF was 31.3%.

Finally, omitting 25 children with chromosomal abnormalities from the analysis, and comparing the remaining children with and without GTF, statistically significant differences were still found in cognitive (18% vs. 2%), language (33% vs. 10%), motor (20% vs. 2%) and functional abilities (35% vs. 4%) (P<0.001).

4.4.2 Predictors of Gastrostomy tube feeding requirement

Univariate and multiple logistic regression analysis found independent statistically significant OR for requirement of GTF any time after first CCS were: presence of a chromosomal abnormality, OR: 4.6 (95%CI:1.8,12.0) (P=0.002), single ventricle anatomy, OR:3.4 (95%CI:1.7, 6.8) (P<0.001), total postoperative days of open sternum, OR:1.15 (95%CI: 1.1,1.3)(P=0.031) and total number of hospital days at first CCS, OR:1.03 (95%CI:1.1, 1.04)(P=0.002)

4.5 DISCUSSION

This study shows that among children with CHD surviving early CCS, the presence of GTF, a useful and much utilized way of enhancing nutrition, can be used as a simple identifier

for increased developmental delay and the need for EDI. Overall 20% of survivors required GTF any time prior to their 21-month assessment. This is somewhat higher than what has been described by Kogon and his group who reported an overall 10% of gastrostomy in newborns following CHD surgery.[39] In their study, 30% of children did not require cardio-pulmonary bypass, and only children who had cardiac surgery within the first 15 days of life were included. These differences from our cohort might explain their lower frequency of GTF. Our described frequency is closer to the 18% reported in children after the Norwood procedure for HLHS.[167]

We found the Bayley-III and ABAS-II scores obtained at the 21-month multidisciplinary assessment showed that children with GTF present with higher rates of developmental delay including cognitive, language and motor delay, together with functional abilities delay as identified by caregivers when compared with children without GTF. The delay might have been greater if the BSID-II would have been used, as studies suggest results of the latest version of this tool, the Bayley-III are usually higher and might overestimate children's abilities.[170,171] Recent research proposes usage of cut-off score <85 rather than <70 in the cognitive and language subtests of the Bayley-III to better define moderate and severe developmental delay. [172]

More than half of the children with GTF and delays still required the GTF after the age of 6 months. This high proportion might indicate that continued need for GTF after 6 months of life might be a stronger indicator of developmental delay and need for EDI. Results also showed the level of development of children with GTF and delays >2 SD is 9 to 10 months behind expected for age. Therefore, EDI strategies starting at the developmental level of the child would be essential to provide appropriate activities and support the optimal development of the child, i.e. strengthening parent-child interactions, encouraging parents to introduce simple and new words while listening and responding to early vocalizations.

Half of the children with GTF had single ventricle defects, this is in keeping what has been shown in previous studies describing more difficulty with feeding and weight gain in the post-operative period comparing patients with HLHS and less complex cardiac defects.[173] Nonetheless, after excluding all the children with single ventricle defects from the analysis, delays were still more prominent among children with biventricular cardiac defects and GTF. Similar results were found when excluding children with chromosomal abnormalities; children with GTF requirements continued to present with higher rates of delays in all areas of development. This supports the idea that not only patients with single ventricle defects or chromosomal abnormalities should be seen as developmentally vulnerable, but that special attention needs to be paid to all children requiring GTF.

The reasons for a higher frequency of delay in children requiring GTF may be the result of a combination of factors, including some of these children being sicker, longer periods of hospitalization, and associated underlying neurological conditions. The presence of the gastrostomy tube in the abdomen might also lead to avoidance of "tummy time", a well-known position that contributes to motor skills development allowing strengthening of the shoulder muscles, full rotation of the neck and development of antigravity extensor control.[174] Decreased time in prone position has been found to be associated with delayed achievement of gross motor milestones.[175] EDI would provide the families of these children with useful resources to promote motor development, as well as it would provide support to prevent the already described oral aversion and the long-term complications with eating and drinking skills.[176]

It is important to recognize that among children without GTF, the frequency of cognitive and motor delay is similar to what is seen in the general population, compared with normative data. The number of children needing GTF any time before the age of 21 months could then be used as

an outcome measure of acute care. Increasing the number of CCS survivors that feed well and do not require GTF could reflect healthier children and improved acute care.

Finally, our analysis showed GTF requirement is 4.6 times more common in children with chromosomal abnormalities, and 3.4 times more frequent in children with single ventricle defects, both possibly described as "patient-specific factors".[177] Children with single ventricle defects and children with chromosomal abnormalities have already been recognized to be at greater risk for feeding difficulties and slow weight gain. [173,178] In addition to this, the odds of requiring GTF increases by 1.15 for each day the sternum remains open in the postoperative period. Delayed sternal closure is commonly used in children with or at risk of hemodynamic instability after CCS.[179] This supports the findings by Kogon and colleagues,[39] who found arriving to intensive care unit with an open sternum was a risk factor for the development of feeding difficulties including GTF. Finally, the OR for GTF is 1.03 for each day added to the hospitalization period at CCS. Prolonged hospital stay has already been associated with poor outcomes in this population, including late neurological morbidity.[74] All of the described predictors are not likely to be modifiable conditions that could lead to a decrease in the requirement of GTF. However, these predictors might be useful in guiding the counseling of these children's families.

The high proportion of children assessed at 21 months of age is a strength of this study. The main limitation is the lack of uniform criteria for the indication of GTF, which is dependent upon referral practices and medical team preferences. In addition, this study did not determine underlying conditions, such as oral feeding dysfunction or muscle weakness. The aim was to determine whether the simple and obvious visible finding of having GTF may allow prompt identification of high risk children for referral to early developmental intervention. Finally,

delays in functional abilities might have been overestimated as feeding skills, already known to be impacted in these children, are part of the practical domain represented in the overall General Adaptive Composite score.

4.6 CONCLUSION

Developmental delays are more common among CCS survivors presenting with need for GTF; almost 8 times more frequent in some areas of development. The major contribution of this study is a simple way to enhance prompt identification of at risk survivors after CCS to maximize the benefits of EDI. With the already recognized advantages that GTF brings to survivors requiring nutritional support, early recognition of possible delays and prompt referral to EDI may lead to enhancement of their overall development. General pediatricians, cardiologists, surgeons and acute care staff working without multidisciplinary teams or where psychological assessments are not available might find this information useful. Referral to EDI should not be delayed. Community EDI programs will also benefit from these results that provide a clear picture of the different types of delay in this particular population.

Table 4.1: Description of 2-year-old children in relation to gastrostomy tube feeding after early complex cardiac surgery, n=334: mean (SD), median (interquartile range), n (%)

	Total n=334	Gastrostomy Tube Feeding		X^2 t-test	P-value
		No n=267	Yes n=67		
A. Pre-operative first CCS					
Family socioeconomic status*	44.1 (14.7) 42 (34, 54)	44.2 (14.72)	43.5 (14.72)	0.332	0.74
Mother total schooling: years	13.8 (2.9) 13.5 (12, 16)	13.9 (2.9)	13.6 (2.7)	0.585	0.559
Birth gestation: weeks	38.7 (1.9) 39 (38, 40)	38.7(1.9)	38.7(1.9)	0.08	0.936
Sex: male	220 (65.9%)	172 (64.4%)	48 (71.6%)	1.24	0.265
Chromosomal abnormality	25 (7.5%)	15 (5.6%)	10 (14.9%)	6.7	0.01

	Total n=334	Gastrostomy Tube Feeding		X^2 t-test	P-value
		No n=267	Yes n=67		
Antenatal diagnosis	162 (48.5%)	118 (44.2%)	44 (65.7%)	9.89	0.002
Inotrope score**	5.6 (8.65) 0 (0, 10)	5.6 (8.3)	5.6 (10)	-0.004	0.996
Highest plasma lactate level: mmol/L	3 (2.5) 2.3 (1.8, 3.4)	3.1 (2.7)	2.8 (1.5)	0.616	0.54
B. Intra-operative first CCS					
Age at surgery: days	13.9 (10.2) 10 (7, 16)	13.7 (10.2)	14.4 (10.4)	-0.486	0.627
Single Ventricle	83 (24.9%)	48 (18%)	35 (52.2%)	33.67	<0.001
Weight: Kg	3.4(0.6) 3390 (3, 3.8)	3.4 (0.6)	3.4 (0.602)	-0.177	0.86

	Total n=334	Gastrostomy Tube Feeding		X^2 t-test	P-value
		No n=267	Yes n=67		
CPB: min	110.2 (41.8) 102 (80, 138.3)	110.1 (41.7)	110.8 (42.6)	-0.117	0.9
X-clamp time: min	56.2 (23.8) 55 (37, 70)	56.8 (24.3)	53.7 (21.7)	0.969	0.33
DHCA: yes	240 (71.9%)	184 (68.9%)	56 (83.6%)	5.7	0.017
C. Post-operative: first CCS					
Day 1-5 highest plasma lactate: mmol/L	4.9 (2.2) 4.55 (3.3, 6.2)	4.8 (2.2)	5.3 (2.2)	-1.64	0.1
Day 1-5 highest inotrope score	10.7 (7.8) 10 (5, 15)	10 (7.6)	13.6 (8.2)	-3.45	0.001

	Total n=334	Gastrostomy Tube Feeding		X^2 t-test	P-value
		No n=267	Yes n=67		
Day 6-10 highest plasma lactate mmol/L	1.4 (0.9) 1.2 (1, 1.5)	1.37 (0.9)	1.5 (1.2)	-1.04	0.3
Day 6-10 highest inotrope score	1.8 (3.5) 0 (0, 2)	1.6 (3.5)	2.5 (3.3)	-1.96	0.005
Postoperative open sternum (days)	2.3 (2.7) 3 (0, 4)	2.1 (2.5)	4.1(2.8)	-5.84	<0.001
D. Overall 1st operation					
Sepsis	28 (8.4%)	19 (7.1%)	9 (13.4%)	2.783	0.095
CPR	9 (2.7%)	3 (1.1%)	6 (9%)	12.53	<0.001
Vocal Cord Paralysis	26 (7.8%)	13 (4.9%)	13 (19.4%)	18.5	<0.001
Dialysis	42 (12.6%)	26 (9.7%)	16 (23.9%)	9.75	0.002

	Total n=334	Gastrostomy Tube Feeding		X^2 t-test	P-value
		No n=267	Yes n=67		
All ventilated days	12.81 (9.5) 10 (6, 16)	11.6 (8.1)	17.63 (12.6)	-3.72	<0.001
All hospital days	26 (17.6) 21 (14, 31)	23.2 (14.6)	37.3 (23.44)	-4.7	<0.001

Variables with a *P*-value <0.1 were entered into the Multiple Logistic Regression analysis

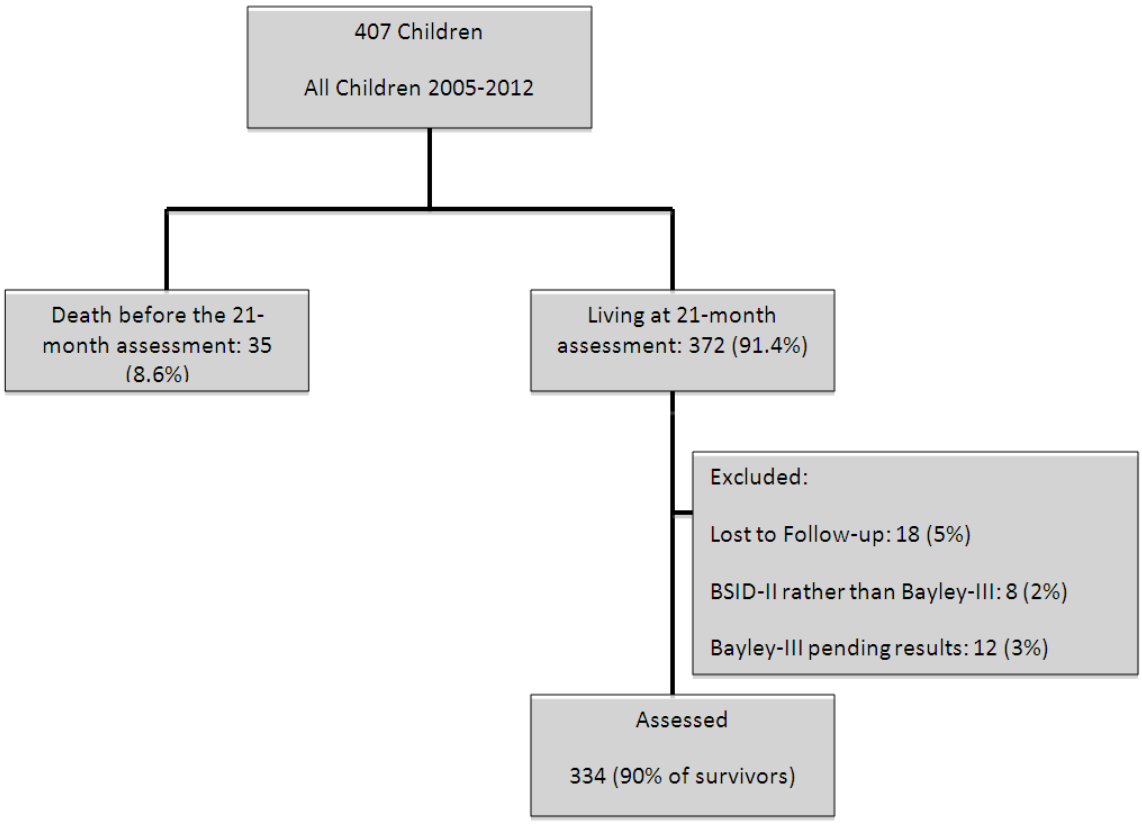
*Blishen Index [106]
** Inotrope Score [107]

Table 4.2: Childhood profile in relation to gastrostomy tube feeding after early complex cardiac surgery, n=334: mean (SD), median (interquartile range), n (%)

	Total n=334	Gastrostomy Tube Feeding		χ^2 t-test	ρ-value
		No n=267	Yes n=67		
Outcome Variables					
Height Z-score	-0.39 (1.31) -0.2 (-1.1, 0.32)	-0.17 (1.22)	-1.26 (1.34)	5.6	<0.001
Weight Z-score	-0.28 (1.25) -0.11 (-1.1, 0.5)	-0.15 (1.26)	-0.81 (1.06)	4.35	<0.001
Head Circumference Z-score	-0.32 (1.23) 0 (-0.6, 0.63)	0.05 (1.15)	-0.38 (1.47)	2.21	0.03
Number of hospitalizations not related to cardiac treatment	0.7 (1.4) 0 (0,1)	0.5 (1)	1.6 (2.2)	-6.01	<0.001
Number of hospitalizations related to cardiac treatment	0.6 (1.1) 0 (0,1)	0.5 (0.9)	1.2 (1.4)	-5.26	<0.001

Number of specialist seen excluding attending doctor	2.3 (1.9) 2 (1,3)	2 (1.5)	3.3 (2.5)	-5.39	<0.001
Medication for Chronic cardiac disease: yes	117 (35%)	69 (25.8%)	48 (71.6%)	49.36	<0.001
Medication for Chronic Pulmonary disease: yes	30 (9%)	15 (5.6%)	15 (22.4%)	18.43	<0.001
Bayley-III cognitive <70	23 (6.9%)	7 (2.6%)	16 (23.9%)	37.75	<0.001
Bayley-III cognitive Composite Score	92.4 (14.3) 95 (85, 100)	94.7 (12.2)	82.9 (17.7)	5.17	<0.001
Bayley-III language <70	56 (16.8%)	32 (12%)	24 (35.8%)	21.8	<0.001
Bayley-III language Composite Score	88 (17.8) 89 (77, 100)	90.7 (16.2)	77.3 (19.5)	5.2	<0.001
Bayley-III motor <70	26 (7.8%)	8 (3%)	18 (26.9%)	42.51	<0.001
Bayley-III motor Composite Score	90.9 (15.6) 94 (82, 100)	94.2 (13.4)	77.7 (16.9)	7.4	<0.001
ABAS General Adaptive Composite <70	39 (11.7%)	13 (4.9%)	26 (38.8%)	59.81	<0.001
ABAS General Adaptive Composite Score	91.3 (17.7) 92 (80.7, 102.3)	94.6 (14.8)	78.16 (21.9)	5.8	<0.001

Figure 4.1: Flowchart of death, lost, and assessed children after complex cardiac surgery at ≤6 weeks of age from the years 2005-2012.



Chapter 5: Conclusion

This PhD thesis explores three topics that have not been described previously in the literature. In so doing, it adds valuable information to the current understanding of the neurodevelopmental challenges that may affect children with cCHD, as well as to the potential variables that could be modified to prevent disability.

5.1 SUMMARY OF FINDINGS

The three projects focus on children followed longitudinally by the WCCPTFP, an inception cohort follow up program that identifies children undergoing CCS in early life at the Stollery Children's Hospital, and follows them prospectively across western Canada. The program is intended to provide services for the children and their families while looking to improve the quality of their care through the study of outcomes research.

The first project looked specifically at the presence of CND in kindergarten-aged children with cCHD. We found CND is not uncommon, affecting 6% of all CCS survivors and almost 10% of those requiring more than one CCS. Most children with CND present with spasticity and unilateral distribution, and can ambulate without the need of a mobility device. Contrary to what would be generally expected, the presumed events leading to a diagnosis of CND rarely happened in the early postoperative period, and over a quarter of all events happened while the child was waiting for the first CCS. Finally, older age at first CCS, high pre-operative lactate levels at the first CCS, and having had more than one CCS were found to be statistically significant predictors of CND.

In the second project, the focus was narrowed to those children undergoing the Fontan operation. We aimed to better understand the impact of this operation on the functional abilities

of children, and its potential relation with stroke (an already recognized peri-operative complication). Overall, more than a quarter of children experienced deterioration of functional abilities following the Fontan operation. Importantly, the greatest decline was seen in the practical domain of functional abilities, which may explain the challenges currently seen in the young-adult population of Fontan survivors.[43] Both peri-operative stroke and older age at Fontan were statistically significant predictors of the decline of functional abilities.

The third and final project aimed to investigate the possible relationship between the use of a GTF any time before the 21-month assessment and developmental delays. Findings suggest GTF identifies CCS survivors at risk for developmental delay who would benefit from developmental intervention. Although mostly not modifiable conditions, the presence of chromosomal anomaly, single ventricle anatomy, the number of post-operative days with open sternum and the total number of hospital days at CCS were predictors of GTF requirements before 21-month assessment. Although GTF is not thought to be causally related to developmental delays, the presence of GTF did permit identification of those at high risk of delay who would benefit from intervention.

5.2 IMPROVING "PARTICIPATION"

These three projects relate to each other on multiple levels: a) they review young children experiencing cardiac surgery early in life, b) they all examine developmental outcomes, and c) they determine potentially modifiable predictors of the studied patient-relevant outcomes. As a developmental pediatrician, it is essential for me to recognize these three projects all relate to the concept of *participation*, defined as the "ability of the child to be involved in meaningful and age appropriate life situations".[180] In recent years, and thanks to a paradigm shift initiated by the

World Health Organization and its International Classification of Functioning, Disability and Health for children and Youth (ICF-CY) framework,[180] disability is no longer interpreted based on the medical condition, but more importantly is based on the actual functional consequences of the condition and the limits that these functional consequences impose for the participation of children in daily life.[181]

As a consequence, as stated by Imms and colleagues, "participation in meaningful life activities should be an essential intervention goal."[182] Children's participation can be enhanced when health professionals anticipate and recognize developmental challenges early, permitting directed interventions and directed family and community counseling. The end goal is to impact the child's environmental/personal factors so that the recognized "activity limitations"[180] that result from their developmental challenges, do not translate to a "participation restriction."[180]

In the context of cCHD, and specifically in the context of this PhD work, the following are implications:

a) Given that 6% of kindergarten children who have undergone CCS present CND, special attention should be paid to their physical examination. Clinical signs of CND should be specifically ruled out. This is especially important if we think that most children present as GMFCS level I and II, which means that their clinical signs may be particularly subtle. An earlier CND diagnosis can lead to earlier intervention (for example: constraint induced movement therapy), as well as to modifications to their environments in order to facilitate the child reaching their full potential for participation.

b) As another example, even if it takes years of work and collaboration to lower the rate of peri Fontan stroke, even now we can actively look for and recognize those with a post-Fontan decline in functional abilities. Once deterioration is recognized, then interventions should be directed to address the child's difficulties and improve daily-life participation (for example: adaptive skills training).

c) Finally, recognition of developmental challenges in pre-school children who have or have required GTF can lead to prompt referral to early intervention, especially since current data show that despite the high frequency of developmental delays in children of cCHD, use of EDI remains low. [183]

5.3 IMPLICATIONS FOR RESEARCH AND PRACTICE

These three projects have not only led to a better understanding of the neurodevelopmental profile of children with CHD; they have provided me with a significant learning experience. This has both changed the way I consider future research and impacted my clinical work as a developmental pediatrician. It will be useful to recapitulate, in this conclusion, some of the most important insights I have gained in these last four years of PhD work.

- **The complex association between organic disease and the developing brain**. The link between the developing brain and the organic disease is an endless process affected by multiple different factors. Focusing exclusively on the surgical procedure or the disease itself as potential explanations for the developmental challenges limits the understanding of these children's clinical picture. My research findings implicate many factors to be considered when reviewing the health and development of children who have had CCS.

In addition, the crucial importance of "the early years" on the structural and functional development of the child's brain cannot be overemphasized.[184]

- **The role of outcomes research**. Outcomes research is an essential tool which can determine what is currently happening within any patient population, including what therapies are being used, and what outcomes are achieved. But more importantly, it can provide us with an opportunity to make changes in current treatment modalities and therapies to improve future outcomes. Since findings of potentially modifiable variables associated with outcomes are not proven to be cause-effect relationships, as advances in the medical field continue to develop (some guided by findings such as in this PhD), outcomes research must be used to iteratively evaluate the results.
- **The importance of knowledge translation**. Research projects are only the first step in a long journey to improve outcomes for these children. New knowledge should be shared in as many different formats as possible, such as publications, rounds, presentation, at every available opportunity, with the health care team, hospital administration and potential future researchers. It is imperative to include the children, their families, teachers, and other members of their community in the sharing of new knowledge, to maximize the daily life participation of these children. Every member of a child's family and surrounding community can help a child participate more fully.
- **The value of multidisciplinary work**. My research has allowed me to see the value of multidisciplinary work. This work would not have been possible without my collaboration with PICU intensivists, Cardiovascular surgeons, Cardiologists, nurses, therapists, Psychologists, pediatric rehabilitation specialists, general surgeons and other developmental pediatricians. We cannot elicit change or make improvements to care

provided without the valuable input of the many members of the team caring for these children.

- **The role of medical databases**. The only way to effectively conduct meaningful outcomes research is through the use of medical databases. These databases require meticulous data collection and maintenance which can only be achieved through the collaborative work of data extractors, data managers, researchers, and biostatisticians. Clinical researchers, while not necessarily experts, should have a working knowledge of biostatistics.
- **The role of ongoing research**. Each research project, while answering some questions, raises further questions that warrant more research. Some of these new questions are discussed in the next section.

5.4 AVENUES OF FUTURE RESEARCH

New research ideas have already arisen from the results of my completed projects. One such idea is to further review data to determine factors associated with delays in the timing of the first CCS. By identifying and changing potentially modifiable variables associated with the timing of this surgery, we may be able to reduce the frequency of delay and potential CND. Additionally, although potentially challenging and prohibitively expensive, pre- and post-Fontan neuroimaging could allow for a better understanding of the incidence of, and causes of post-Fontan deterioration of functional abilities. Finally, I would like to examine the knowledge level of key community resources, such as teachers, regarding the outcomes of children who have had CCS. Here, the ultimate aim would be to provide outreach education to key stakeholders in the community who will be involved with these children, and who are poised to improve access and

delivery of interventions that facilitate the child reaching their full potential and participation in everyday life.

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