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Cerebrovascular Autoregulation in Preoperative Neonates with Congenital Heart Disease

Compared to Healthy Controls

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy in Nursing

by

Nhu Nguyen Tran

2017

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ABSTRACT OF THE DISSERTATION

Cerebrovascular Autoregulation in Preoperative Neonates with Congenital Heart Disease Compared to Healthy Controls

by

Nhu Nguyen Tran

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2017

Professor Paul Michael Macey, Chair

Background: Congenital Heart Disease (CHD) is one of the leading birth defects in the United States, encompassing approximately 40,000 neonates (newborns) annually (American Heart Association, 2015; Reller, Strickland, Riehle-Colarusso, Mahle, & Correa, 2008). Advances in surgical technique and postoperative management result in approximately 1.3 million adults who are CHD survivors (American Heart Association, 2016). Despite efforts aimed at prevention and early detection of developmental delays in infants and children, many with CHD will have neurologic deficits lasting into adulthood, influencing employability, self-care, and quality of life (Pike et al., 2007; von Rhein et al., 2014). Large multicenter studies have ruled out surgical factors as independent predictors for these developmental delays leading to examination of factors more intrinsic to the neonate as the cause for poor outcomes (Gaynor et al., 2015; Newburger et al., 2012). A hypothesis not extensively examined is whether impaired

Cerebrovascular Autoregulation (CA), is responsible for poorer neurodevelopmental outcomes in preoperative neonates with CHD (Paulson, Strandgaard, & Edvinsson, 1990).

Purpose: The purpose of this study was to assess CA in neonates with and without CHD, and to evaluate the association of CA with neurodevelopmental outcomes. The specific aims of this study were to: 1) Compare CA between 28 preoperative neonates with CHD and 16 age- and gender-matched healthy neonates at less than 12 days of age; 2) Examine associations between impaired CA and abnormalities in motor, auditory, and visual functions when controlling for preoperative neonates with and without CHD; and 3) Exploratory Aim: Determine associations of clinical factors such as: a) 1 minute Apgar scores, b) cord pH, c) head circumference, and d) birth weight to impaired CA.

Methods: This study was a prospective, cross-sectional, 2-group case control design. We enrolled 44 neonates (28 with CHD and 16 healthy controls). Inclusion/exclusion criteria were chosen to decrease variability in CA. CA was determined using regional cerebral oxygenation (rSO₂) with the INVOS Somanetics Near Infrared Spectroscopy (NIRS) 5100C (Troy, MI) device and a postural change. The Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) measured neurodevelopmental outcomes.

Results: The X^2 test revealed no significant difference in impaired CA between CHD and control groups ($p = .38$). Multiple linear regressions showed CHD neonates significantly associated with poorer total neurodevelopmental scores ($\beta = 9.30, p = .02$) and motor scores ($\beta = 7.6, p = .04$) when controlling for CA status. Independent t-tests demonstrated baseline and sitting rSO₂ were significantly lower in the CHD neonates ($p < .00$).

Discussion: The results provide evidence of poorer developmental outcomes and hypoxemia in preoperative CHD neonates warranting further investigation of causes for delays.

For patients who might be at risk for impaired CA, some strategies to optimize cerebral blood flow are: 1) maintaining higher systolic blood pressures; 2) preventing episodes of hypoxemia and; 3) taking more time to change the patient's positions. Identifying the mechanism of injury and the neonates at higher risk of developing delays will assist healthcare providers in tailoring interventions to prevent neurodevelopmental delays in this vulnerable population.

The dissertation of Nhu Nguyen Tran is approved.

Ram Kumar Subramanyan

Felicia S. Hodge

Eufemia Jacob

Paul Michael Macey, Committee Chair

University of California, Los Angeles

2017

DEDICATION

To my family, friends, and coworkers for their love and support throughout this challenging and rewarding process.

To Buddha and Benny for always being excited to see me, even when I come home late at night.

To Barb Gross for your flexibility and support during my doctoral program.

To future doctoral students, know there is always light in the darkness although you may not see or feel it. Keep moving forward and you will reach your goal.

To all of the families who participated in and the people who helped with this study, this could not have been accomplished without your assistance.

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To all of the children and families affected by CHD, may this study and future studies help to improve the lives of survivors of CHD.

TABLE OF CONTENTS

ABSTRACT OF THE DISSERTATION	ii
DEDICATION.....	vi
TABLE OF CONTENTS	vii
LIST OF TABLES	xiii
LIST OF FIGURES	xiv
ACKNOWLEDGMENTS	xv
BIOGRAPHICAL SKETCH	xvii
CHAPTER ONE: INTRODUCTION.....	1
Congenital Heart Disease.....	1
Congenital Heart Disease & Neurologic Injury.....	2
Congenital Heart Disease & Cerebrovascular Autoregulation	3
Congenital Heart Disease & Neurodevelopmental Assessments in Neonates	5
Statement of the Study Purpose	6
Nursing Implications.....	7
Chapter Summary	7
CHAPTER TWO: REVIEW OF THE LITERATURE.....	9
Congenital Heart Disease.....	9
Congenital Heart Disease & Evidence of Neurologic Injury	10
Preoperative.....	11
Postoperative	12
Congenital Heart Disease & Symptoms of Neurologic Injury	13
Neonates	14
Infants & Children.....	15
Congenital Heart Disease & Potential Mechanisms of Neurologic Injury	16
Preoperative Risks.....	16

Definition of Cerebrovascular Autoregulation.....	19
Standard Measures of Cerebrovascular Autoregulation	20
Calculations for Cerebrovascular Autoregulation.....	21
Near Infrared Spectroscopy (NIRS)	22
Postural Changes to Induce Alterations in Blood Pressure.....	23
Cerebrovascular Autoregulation in Neonates & Pediatrics	24
Evaluation of Neurodevelopmental Status in Neonates	27
Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS).....	27
Chapter Summary	29
CHAPTER THREE: CONCEPTUAL FRAMEWORK.....	30
Interactions of System Concepts.....	35
Cardiovascular & Respiratory Systems	35
Cardiovascular & Nervous Systems.....	36
Nervous & Musculo-skeletal Systems	37
Constructs & Variables	38
Cardiovascular Status.....	38
Cerebral Status	41
Muscular Status.....	42
Empirical Indicators.....	42
Congenital Heart Disease	42
Cerebrovascular Autoregulation	43
Neurobehavioral Status	44
Assumptions.....	47
Chapter Summary	47
CHAPTER FOUR: METHODS.....	49
Design.....	49

Population & Setting.....	50
Sample Selection.....	50
Sample Size.....	51
Procedures.....	53
Information Session & Training of Research Team Members	53
Screening & Recruitment.....	53
Information & Consent	54
Enrollment Procedures	54
Data Collection Procedures.....	54
Instruments & Measures	56
Cerebrovascular Autoregulation (NIRS).....	56
Arterial Oxygenation (Pulse oximetry).....	60
Neurobehavioral Assessment (ENNAS).....	60
Procedure for Data Analyses	62
Specific Aim 1.....	62
Specific Aim 2.....	63
Exploratory Aim 3.....	63
Study Limitations.....	63
Threats to Internal Validity	63
Threats to External Validity	64
Protection of Human Subjects in Research.....	64
Privacy & Confidentiality	65
Potential Risks & Discomforts	66
Potential Benefits	66
Risk & Benefit Analysis	67
Payment to Participants	67
Costs of Participation.....	67

Treatment & Compensation for Injury	67
Chapter Summary	68
CHAPTER FIVE: RESULTS.....	69
Sample Characteristics.....	69
Chromosomal Anomalies.....	69
Birth Measures	69
Gender & Ethnicity	71
Congenital Heart Disease Neonates	71
Physiologic Measures & Regional Cerebral Oxygenation (rSO ₂).....	73
Physiologic Patterns of Participants.....	76
Neurodevelopmental Status	80
Research Aims	80
Specific Aim 1: Comparison of Proportion of Impaired Cerebrovascular Autoregulation between Groups.....	81
Specific Aim 2: Associations between Group, Cerebrovascular Autoregulation, & Neurodevelopment	82
Specific Aim 3: Association between Cerebrovascular Autoregulation & Clinical Factors ..	83
Secondary Analyses for Potential Confounds	83
Cerebrovascular Autoregulation Adjustment.....	83
Adjustments for Group, Cerebrovascular Autoregulation, & Neurodevelopmental Status....	84
CHAPTER SIX: DISCUSSION.....	86
Overview of Findings	86
Summary of Hypothesis Tests	87
Hypothesis 1: Cerebrovascular Autoregulation	87
Hypothesis 2: Cerebrovascular Autoregulation & Neurodevelopment.....	87
Hypothesis 3: Cerebrovascular Autoregulation & Clinical Factors.....	87

Cerebral Oxygenation	87
Cerebrovascular Autoregulation	89
Neurodevelopmental Status	91
Confounding Factors.....	92
Sample Characteristics	92
Chromosomal Anomalies.....	92
Severity or Type of Cardiac Diagnoses	93
Prostaglandin E1 (PGE 1).....	94
Age Effects.....	94
Gender Effects.....	95
Participant Variability	96
Neurobehavioral State.....	96
Cerebrovascular Autoregulation	97
NIRS Monitors	98
Limitations	99
Clinical Implications to Nursing & Healthcare Providers	100
Future Research	101
Conclusions.....	102
Appendices.....	103
Appendix 2-1. Congenital Heart Disease and Brain Injury	103
Appendix 2-2. Neurodevelopmental Outcomes in Congenital Heart Disease	111
Appendix 2-3. Cerebrovascular Autoregulation in Neonates	116
Appendix A. UCLA IRB Approval	120
Appendix B. CA One Pager	122
Appendix C. Recruitment Flyer: CHD.....	123

Appendix D. Recruitment Flyer: Healthy Controls	124
Appendix E. Screening Form	125
Appendix F. Telephone Script	126
Appendix G. Consent	129
Appendix H. Diagram of Devices	135
Appendix I. Image of NIRS Sensor & Monitor	136
Appendix J. Einstein Neonatal Neurobehavioral Assessment Scale	137
Appendix K. Procedure Form	147
Appendix L. Medical Abstraction Form	149
REFERENCES.....	154

LIST OF TABLES

Table 3-1. Body Systems Framework modified from Marieb and Hoehn (2007).....	33
Table 5-1. Participant characteristics by group.....	70
Table 5-2. Gender & ethnicity characteristics by group.....	71
Table 5-3. Cardiac Diagnosis for the Congenital Heart Disease Group.....	72
Table 5-4. Percentage of Cyanotic Heart Lesions	72
Table 5-5. rSO ₂ by group	73
Table 5-6. Percentage of Abnormal Neurodevelopmental (ND) Scores	80
Table 5-7. Statistical Tests for Each Specific Aim.....	80
Table 5-8. Cerebrovascular Autoregulation (CA) Status by Group	82
Table 5-9. Adjusted Cerebrovascular Autoregulation (CA) Status by Group	84
Table 5-10. Adjustment of Aim 2 with Confounding Factors	85

LIST OF FIGURES

Figure 3-1. Body Systems Framework from Marieb and Hoehn (2007).....	34
Figure 3-2. Concepts in Relation to the Body Systems Framework.....	38
Figure 3-3. Constructs in Relation to the Body Systems Framework.....	40
Figure 3-4. Empirical Model in Relation to the Body Systems Framework	46
Figure 5-1. Distribution of Age by Group	70
Figure 5-2. Distribution of rSO ₂ by Group	74
Figure 5-3. rSO ₂ Mean Values for Healthy Controls & Congenital Heart Disease.....	75
Figure 5-4. Typical Healthy Control (HC) Physiologic Measures	77
Figure 5-5. Typical Congenital Heart Disease (CHD: D-TGA) Physiologic Measures.....	78
Figure 5-6. Relative Change in rSO ₂ by Group	79

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PUBLICATIONS:

1. **Tran, N.**, Hackett, H., Cadaver, C., Fichera, S., and Azen, C. (2014) Comparison of calf and brachial blood pressures in infants: Is there a difference between calf and brachial blood pressures? Journal of Vascular Nursing, 32(4), 139-143. PMID: 25455319

SCHOLARLY PRESENTATIONS:

* **Tran, N.**, Hackett, H., Cadaver, C., Fichera, S., and Azen, C. 2013. Is There A Difference Between Calf and Brachial Blood Pressures? Podium presentation speaker, Sigma Theta Tau International Honor Society of Nursing 42nd Biennial Convention Conference, Indianapolis, IN.

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CHAPTER ONE: INTRODUCTION

Congenital heart disease (CHD) is the number one birth defect in the United States (March of Dimes, 2016), with an estimated 40,000 neonates born with CHD every year (American Heart Association, 2016). Approximately 25% of these neonates will require cardiac surgery within the first year of life (Oster et al., 2013), putting them at increased risk for developmental delays and neurologic deficits (Gaynor et al., 2015). These deficits can lead to rising healthcare costs related to utilization of services such as physical and speech therapies or increased length of stay, estimated at \$4,500 per inpatient hospital day (Pfundner, Wier, & Steiner, 2006). With advances in surgical technique and postoperative management, many neonates with complex cardiac defects are now surviving to adulthood (Marino et al., 2012), encompassing approximately 1.3 million adults with CHD (American Heart Association, 2016). Despite efforts aimed at prevention and early detection of developmental delays in infants and children, many with CHD will have neurologic deficits reaching into adulthood, potentially impacting employability, self-care, and/ or quality of life (Pike et al., 2007; von Rhein et al., 2014). Even with the mounting evidence of neurologic deficits associated with CHD, the exact etiology remains unclear (Gaynor et al., 2015; Newburger et al., 2012).

Congenital Heart Disease

Congenital heart disease is a structural problem with the heart or vessels near the heart that exist at birth (American Heart Association, 2015). There are wide spectrums of cardiac defects (over 35 types) with varying severities and prognoses. Defects are often classified according to disease severity (e.g. simple, moderate, or complex) or by the amount of pulmonary blood flow (e.g. increased, decreased, or normal). Some complex cardiac defects require surgical intervention shortly after birth due to severe hypoxemia resulting in cyanosis. Certain structural

defects can cause mixing of venous and arterial blood due to intra- or extra-cardiac shunts resulting in circulatory overload and/ or heart failure symptoms. Additionally, heart defects obstructing blood flow from the aorta can impair or reduce cerebral circulation. Neonates with CHD have altered blood flow related to the structural defect. However, it is unclear if abnormal cardiac physiology, surgical intervention, postoperative management, or combinations of these variables contribute to neurologic injury.

Congenital Heart Disease & Neurologic Injury

Neonates with CHD have neurologic injury identified in brain imaging studies before and after cardiac surgery (Goff et al., 2014; Licht et al., 2009; Miller et al., 2007). Results show gray and white matter injury with focal or diffuse damage in the frontal, parietal, occipital, hippocampal, and/ or middle cerebral territory (Galli et al., 2004; Hoffman, Brosig, Mussatto, Tweddell, & Ghanayem, 2013; Paquette et al., 2013). Many of these lesions are clinically silent in the neonatal period and not identified by routine cranial ultrasound (Block et al., 2010). Moreover, clinical manifestations of these deficits may not appear until later in development.

Numerous studies demonstrated neurologic injury in the CHD population (Goff et al., 2014; Licht et al., 2009; Miller et al., 2007). Multiple neurodevelopmental studies identified deficits in children with a variety of moderate to complex CHD (e.g. single ventricle physiology, transposition of the great arteries, and tetralogy of fallot) (Marino et al., 2012; Snookes et al., 2010; Tabbutt, Gaynor, & Newburger, 2012). Reports revealed mild to severe neurodevelopmental delays in up to 30% of children with CHD (Sananes et al., 2012). Early standardized neurodevelopmental assessments commonly identify gross and/ or fine motor deficits, and later evaluations uncover language and cognitive delay (Mussatto et al., 2014). Studies in older children and adolescents have identified difficulties in executive function,

memory, and self-care (Pike et al., 2007; von Rhein et al., 2014). Many studies report delays after cardiac surgery, but evidence of abnormalities exist even before this invasive procedure (Limperopoulos et al., 2000; Majnemer & Limperopoulos, 1999). Neonatal neurodevelopmental delays manifest differently from delays in children and adolescents with CHD. Common preoperative neonatal symptoms are motor abnormalities such as increased or decreased tone and reduced ability to suck and feed (Limperopoulos et al., 2000; Majnemer & Limperopoulos, 1999).

Although evidence of neurologic deficits exists, many studies have ruled out operative factors, leading to investigation of intrinsic factors as potential origins of delays and injuries. Intraoperative factors such as lowest temperature, blood gas management, duration of cooling, cardiopulmonary bypass, deep hypothermic circulatory arrest, regional cerebral perfusion, and length of anesthesia have not independently predicted worse neurologic outcomes (Gaynor et al., 2015; Newburger et al., 2012). Thus, research efforts have focused towards innate factors associated with CHD. One potential hypothesis is cerebrovascular autoregulation (CA), defined as the body's ability to maintain brain blood flow independently from hemodynamic changes (Caicedo et al., 2012; Paulson et al., 1990). Since the origin of neurologic deficits in children with CHD is unclear, understanding the mechanism of injury is needed in order to design future interventions to decrease developmental delays.

Congenital Heart Disease & Cerebrovascular Autoregulation

Under normal circumstances, intact CA is the body's homeostatic function maintaining constant brain blood flow independently from fluctuations in systemic blood pressure, such as during position changes or increased physical activity (Caicedo et al., 2012; Paulson et al., 1990). Baroreceptors and the autonomic nervous system assist in the regulation of cerebral blood

flow. However, the brain does not store large supplies of oxygen, so it depends on steady blood flow to replenish consumption. Irreversible damage will occur if hypoxia persists for more than five minutes (Purves, 2012). Since a child's brain consumes about 50% of the body's oxygen, it is essential to maintain CA.

Many disease processes can impair CA. In neonates, diseases causing hypoxemia such as asphyxia or respiratory distress syndrome can impair CA (Howlett et al., 2013; Paulson et al., 1990). Cerebrovascular autoregulation can also be impaired as a result of traumatic brain injury, stroke, and space occupying lesions such as tumors or hemorrhages (Czosnyka & Miller, 2014; Fontana et al., 2015; Paulson et al., 1990). Given the list of diseases impairing CA, it is likely neonates with CHD have some deficiency because of hypoxemia from altered cardiac physiology.

An indirect measure of CA uses regional cerebral oxygenation (rSO₂) measured by near infrared spectroscopy (NIRS). The CA is approximated with rSO₂ measured during a postural change (from supine to sitting), because blood pressure changes due to forces of gravity (Brady et al., 2010; Caicedo et al., 2012; Chock, Ramamoorthy, & Van Meurs, 2012). As cerebral blood flow increases or decreases, rSO₂ will fluctuate. When CA is intact (functioning normally), the continuous rSO₂ values are expected to remain relatively constant during position or blood pressure changes. The rSO₂ values measured by NIRS were correlated and validated with changes in cerebral blood flow with positron emitted tomography (PET), magnetic resonance imaging (MRI), and transcranial Doppler ultrasound in adult populations (Ito, Kanno, & Fukuda, 2005; Ohmae et al., 2006; Ono, Zheng, Joshi, Sigl, & Hogue, 2013). Monitoring rSO₂ measured by NIRS is part of standard care in managing critically ill preterm and term neonates, and during

and after cardiac surgery (Alderliesten et al., 2013; Ono et al., 2013; Papademetriou, Tachtsidis, Elliot, Hoskote, & Elwell, 2012).

Two studies examined impaired CA, intraoperatively and postoperatively, (using rSO₂ measured by NIRS) in term neonates with CHD (Brady et al., 2010; Buckley et al., 2010). However, CA measurements were calculated with correlations of rSO₂ and systemic blood pressure via an invasive arterial line. This type of intrusive blood pressure measurement is not appropriate for healthy neonates. Many studies also utilize rSO₂ measured by NIRS to measure CA in high risk preterm and term neonatal populations (Alderliesten et al., 2013; Chock et al., 2012; Howlett et al., 2013; Wagner, Ammann, Bachmann, Born, & Schibler, 2011). Despite the body of literature supporting the use of rSO₂ measured by NIRS in the neonatal population, studies have not examined the relationship between impaired CA and neurobehavioral status in neonates with CHD.

Congenital Heart Disease & Neurodevelopmental Assessments in Neonates

Although neonates with CHD are at higher risk for neurodevelopmental delay and neurologic injury, preoperative assessments of neurobehavioral status are not part of standard care. Therefore, it is unknown whether neurobehavioral status is associated with impaired CA. Cranial ultrasounds routinely replace neurobehavioral assessments. Many neonatal neurobehavioral assessment tools are available, such as the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS). These tools have many similarities, such as assessing the neonate's state, regulation, and auditory or visual responses. However, the ENNAS is the only validated tool in the healthy neonatal and CHD populations. Abnormalities found using the ENNAS highly correlated with a neurologic exam ($\kappa = 96.9\%$) in preoperative CHD neonates (Limperopoulos et al., 1997). Moreover, similar percentages of abnormalities were found using

the ENNAS (58%) and a neurologic exam (56%) in neonates with CHD before cardiac surgery (Majnemer et al., 2009). The high incidence of abnormal preoperative neurobehavioral status suggests the possibility of an intrinsic factor for these deficits. It is possible that impaired CA may explain abnormal neurobehavioral status. However, no studies examined associations between impaired CA and abnormal neurobehavioral status in preoperative neonates with CHD.

Statement of the Study Purpose

The purpose of this study is to evaluate whether preoperative neonates with CHD have impaired CA and if CA is associated with neurobehavioral function. The following specific aims, addressed in neonates less than or equal to 12 days of life, are to:

1. Compare CA status, using rSO₂ measured by NIRS (dependent variable [DV]) of preoperative neonates with CHD and healthy neonates (independent variable [IV]). CA will be defined as intact if the rSO₂ returns to the baseline (immediately before postural change) in less than or equal to 5 seconds after the postural change (supine to sitting). In contrast, if rSO₂ takes longer than 5 seconds to return to baseline, then CA is impaired.

Hypothesis 1: The proportion of preoperative neonates with CHD and impaired CA is significantly different than the proportion of healthy neonates with impaired CA.

2. Examine associations between impaired CA (IV) and abnormalities in motor, auditory, and visual functions (DVs) when controlling for preoperative neonates with and without CHD.

Hypothesis 2A: Preoperative neonates with CHD and impaired CA will have poorer total ENNAS scores.

Hypothesis 2B: Preoperative neonates with CHD and impaired CA will have poorer scores in motor, visual, or auditory functions.

3. Exploratory Aim: Determine whether impaired CA is associated with: 1) 1 minute Apgar scores; 2) cord pH acidosis; 3) head circumference; and 4) birth weight when accounting for age and gender.

**Hypothesis 3:* Preoperative neonates with impaired CA will be associated with one of the following: 1) low Apgar scores; 2) positive history of acidosis; 3) smaller birth head circumference; or 4) lower birth weight.

(*Although descriptive and statistical tests were performed, the study was not powered to fully test this hypothesis.)

Nursing Implications

Knowledge gained from the study will be applicable to nursing practice in the short term as a foundation for future research, into the long term with potential for improved treatments. If neonates with CHD have impaired CA, protocols can be written in order to implement strategies optimizing cerebral blood flow, such as maintaining higher mean blood pressures. Furthermore, nurses can refer neonates with impaired CA to care managers or coordinators for additional monitoring of neurologic status and developmental follow up. Future research may include investigation of interventions (such as statins, green tea extracts, or magnesium) to improve CA. Future studies may also evaluate whether changes in practice and/or interventions improve developmental outcomes.

Chapter Summary

In summary, neonates with CHD are at high risk for neurodevelopmental delay and the causes are unclear. A potential theory for developmental delay in this population relates to brain

injury which can occur in utero, intraoperatively, and postoperatively. Many of these neonates survive to adulthood with deficits that affect their abilities for employment, self-care, and quality of life. In order to prevent this injury from occurring, researchers must discover the culprit, which may be impaired CA. Unfortunately, many methods to measure CA are not appropriate for the neonatal population. Therefore, this study utilized postural changes and rSO₂ measured by NIRS as an indirect measure of CA in preoperative neonates with CHD compared to healthy controls and examined associations of impaired CA to neurobehavioral status. Uncovering the mechanism of damage in this high risk population may uncover new methods to prevent brain injury and neurodevelopmental delay.

CHAPTER TWO: REVIEW OF THE LITERATURE

Neonates with congenital heart disease (CHD) are prone to neurologic injury and developmental delays. The simultaneous embryologic development of the heart and brain; and compromised circulation from the heart defect may lead to altered cerebral blood flow and may contribute to neurologic damage (Klabunde, 2011). Certain structural defects cause mixing of venous and arterial blood because of intra- or extra- cardiac shunts leading to circulatory overload and/or heart failure symptoms (Klabunde, 2011). Additionally, heart defects producing obstruction of blood flow from the aorta can reduce cerebral circulation, which may also lead to future neurologic injury or delays.

Congenital Heart Disease

Many studies in children and adolescents with CHD have demonstrated problems with executive function, memory, and attention (Bellinger et al., 2011; Mussatto et al., 2014; Newburger et al., 2012; Sananes et al., 2012; Tabbutt et al., 2012; von Rhein et al., 2014). These problems lead to difficulties with self-care (e.g. remembering to take medications); quality of life (e.g. not feeling well enough to perform activities of daily living); and academic achievement (e.g. low grades because of the inability to recall homework assignments) (Bellinger et al., 2011; Mussatto et al., 2014; Newburger et al., 2012; Sananes et al., 2012; Tabbutt et al., 2012; von Rhein et al., 2014). Reports confirmed mild to severe neurodevelopmental delays in up to 30% of children with CHD (Sananes et al., 2012). Early standardized neurodevelopmental assessments commonly identify gross and/ or fine motor deficits, whereas later evaluations uncover language and cognitive delay (Mussatto et al., 2014). Cognitive deficits can negatively impact ability for future employment and increase morbidity and mortality in this population (Newburger et al., 2012; Pfuntner et al., 2006; Pike et al., 2007). A possible explanation for these deficits is

neurologic injury, which is present in about 20-40% of neonates with CHD before and after cardiac surgery (Galli et al., 2004; Hoffman et al., 2013; Paquette et al., 2013). However, causes of neurologic injury and developmental delay remain unclear. A potential cause of neurologic injury in neonates with CHD is impaired cerebral autoregulation (CA) (Caicedo et al., 2012; Paulson et al., 1990). The knowledge regarding CA at birth (before cardiac surgery) and the relationship with neurobehavioral status is limited in neonates with CHD. The review of the literature will focus on symptoms and outcomes associated with neurologic injury, potential mechanisms of injury, standard measures of CA, measurement of CA with near infrared spectroscopy (NIRS), and measurement of neurobehavioral status with the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS).

Congenital Heart Disease & Evidence of Neurologic Injury

Several neuroimaging reports have demonstrated neurologic injury in up to 40% of neonates with CHD before cardiac surgery (Andropoulos et al., 2010; Dimitropoulos et al., 2013; Drury et al., 2013; Mahle et al., 2002; Paquette et al., 2013). Many of these studies reported generalized white matter injury surrounding the periventricular area in approximately 20-30% of neonates with CHD (Andropoulos et al., 2010; Drury et al., 2013; Mahle et al., 2002; Paquette et al., 2013). Reports were general or vague descriptions of damage and many did not identify locations of injury. Studies specifying areas of neurologic injury in neonates with CHD indicated damage to parts playing integral roles in cognitive development and homeostatic functions. Damage to cerebral white matter is important because myelinated nerve fibers send communications to and from gray matter and facilitate homeostatic functions (Purves, 2012). Gray matter is equally significant because it contains synapses and cell bodies facilitating

neurologic functions such as speech, hearing, vision, and memory (Purves, 2012). Appendix 2-1 provides a list of articles on preoperative brain injury in neonates with CHD.

Preoperative

Preoperative neuroimaging such as magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) demonstrate brain injury in term and preterm neonates with CHD (Abdel Raheem & Mohamed, 2012; Andropoulos et al., 2010; Mahle et al., 2002; Paquette et al., 2013). This preoperative damage may support an intrinsic mechanism of injury and developmental delay. In term neonates with CHD, studies identified white matter injury, infarct, or hemorrhage in 13-43% of patients with single ventricle defects (Andropoulos et al., 2010; Block et al., 2010), and similar types of injuries in 19-30% with two ventricle defects (Andropoulos et al., 2010; Block et al., 2010; Drury et al., 2013). However, studies did not indicate whether evidence of brain injury is associated with impaired CA.

A study in preoperative preterm neonates found abnormal microvasculature and punctate white matter lesions in 42% of single and two ventricle physiology CHD, compared to a term control group (Paquette et al., 2013). After exclusion of preterm neonates with white matter lesions, neonates with CHD continued to show microstructural abnormalities in the splenium, potentially indicating another factor besides prematurity contributing to brain injury (Paquette et al., 2013). Furthermore, structural abnormalities were observed in thalamocortical regions, which have roles in homeostatic functions (Paquette et al., 2015). Therefore, it is possible that injury in the thalamocortical region may lead to impairment in homeostatic functions, perpetuating impaired CA in the preoperative CHD population.

Other studies provide evidence of brain injury in preoperative term neonates with CHD by evaluating cerebral lactate levels. Cerebral lactate is a marker for anaerobic metabolism,

which may occur after hypoxic ischemic insult. Elevated levels are often associated with inadequate oxygen delivery (Cetin et al., 2011). Mahle et al. (2002) found periventricular leukomalacia in 16%, infarct in 2%, and elevated brain lactate in 53% of 24 preoperative term neonates with CHD. Moreover, Abdel Raheem and Mohamed (2012) found a statistically significant higher ratio of lactate to choline in the gray matter of the thalamus in neonates with CHD compared to healthy controls ($p < 0.0001$), suggestive of neurologic injury.

The above studies provide evidence of brain injury in term and preterm neonates with single and two ventricle CHD before cardiac surgical repair. Some locations of injury are nonspecific; however, increased lactate levels and injury exist in regions controlling cognitive and homeostatic functions (i.e. frontal, parietal, temporal, and occipital regions).

Postoperative

Neurologic injury in neonates with CHD continues to occur in the postoperative period. Neonates without brain injury preoperatively demonstrate white matter injury postoperatively (Drury et al., 2013). Mild ischemic injury such as periventricular leukomalacia (PVL) is common after cardiac surgery and often related to hypoperfusion from cardiopulmonary bypass (CPB) (Galli et al., 2004; Mahle et al., 2002). Although lesions can resolve four to six months after open heart surgery, neurodevelopmental delays persist in this population (Andropoulos et al., 2010; Mahle et al., 2002; von Rhein et al., 2014). It is possible that PVL continues to be present, but the type of neuroimaging is not sensitive enough to detect it or an intrinsic factor contributes to delays.

Large multicenter trials have ruled out cardiac surgical factors as independent predictors for worse neurologic outcomes in children with CHD (Gaynor et al., 2015; Newburger et al., 2012). Some intraoperative factors believed to affect neurologic outcomes such as CPB, deep

hypothermic circulatory arrest (DHCA), regional cerebral perfusion, and length of anesthesia did not predict poorer neurologic outcomes. These factors have the potential to compromise cerebral circulation and were believed to increase risk for developmental delay and neurologic injury in children with CHD. However, Newburger et al. (2012) studied 321 neonates with hypoplastic left heart syndrome (HLHS) after undergoing the Norwood surgery and found other factors besides surgical factors associated with delays. Independent predictors of lower psychomotor scores for these complex single ventricle patients were clinical center, birth weight less than 2.5 kilograms, longer hospitalization, and increased complications between Norwood procedure discharge to 12 months of age. These factors in addition to lower maternal education were also significant predictors for mental development delays (Newburger et al., 2012).

Gaynor et al. (2015) also reported similar risk factors in children with single and two ventricle defects. Low birth weight predicted lower psychomotor scores, while decreased birth weight and lesser maternal education were associated with lower mental development. It is possible these factors may also predict impaired CA. However, the literature lacks studies determining if these factors are significant predictors of impaired CA in preoperative neonates with CHD.

Congenital Heart Disease & Symptoms of Neurologic Injury

Neurodevelopmental assessments typically occur postoperatively, at three to six months of age, into adolescence (Mussatto et al., 2014; Newburger et al., 2012; Sananes et al., 2012; von Rhein et al., 2014). Neonates with CHD exhibited neurologic injury on brain imaging before cardiac surgery (Andropoulos et al., 2010; Block et al., 2010; Drury et al., 2013; Goff et al., 2014; Mahle et al., 2002), but information on preoperative clinical findings or symptoms is lacking (Limperopoulos et al., 1997; Limperopoulos et al., 1999, 2000). Reports mentioned

changes in motor tone, sucking ability, and poor state regulation in neonates with CHD, but no studies made a direct association of these symptoms to brain injury or impaired CA (Limperopoulos et al., 1997; Limperopoulos et al., 1999, 2000). Appendix 2-2 lists articles related to symptoms of neurologic injury in neonates and children with CHD.

Neonates

The definition of a neonate is an infant less than 30 days of life (MedLine Plus, 2016a). Before cardiac surgery, up to 50% of the neonates with single and two ventricle CHD had neurodevelopmental abnormalities (Limperopoulos et al., 2000). Neurologic symptoms in neonates with CHD relate to motor function such as hyper/ hypotonia, lethargy, jitteriness, and asymmetric movements (Limperopoulos et al., 1999; Majnemer & Limperopoulos, 1999). These neonates also demonstrated poor behavior regulation, inefficient feeding, and lack of a suck reflex (Licht et al., 2009; Limperopoulos et al., 1999; Majnemer et al., 2009). A preoperative risk factor related to neurologic injury is low birth weight of less than 2.5 kilograms, potentially relating to altered blood flow from the heart defect (Mussatto et al., 2014; Tabbutt et al., 2012). In addition to lower birth weight, studies also reported microcephaly (head circumference less than 33 centimeters) in neonates with both single and two ventricle CHD (Majnemer et al., 2009; Newburger et al., 2012). Neonates with acyanotic heart defects tended to have more abnormal neurologic symptoms than those with cyanotic heart defects, but no explanation was given for this odd finding (Andropoulos et al., 2010; Block et al., 2010; Drury et al., 2013; Limperopoulos et al., 2000). However, these findings support neurodevelopmental abnormalities in neonates and children with CHD.

While previous studies provide evidence of neurobehavioral abnormalities and symptoms of brain injury in preoperative neonates with CHD, no studies evaluated impaired CA and the association with neurobehavioral status.

Infants & Children

From 6 months to 3 years of age, children with CHD show developmental delay in areas of cognition, motor skills, and language (Mussatto et al., 2014). A study on 4-5 year olds with CHD found lower scores on visual-motor integration compared to population norms (Hoffman et al., 2013). An example of problems with visual-motor integration is remembering shapes seen; then recalling and drawing the figures. Some visual-motor delays correlate with areas of injury seen in the neonatal period (Abdel Raheem & Mohamed, 2012; Paquette et al., 2013).

Neuroimaging in term neonates demonstrated injury in frontal, optic radiation, basal ganglia, and thalamic regions, which may contribute to motor, visual, and auto-regulatory delays (Abdel Raheem & Mohamed, 2012). Neuroimaging in preterm neonates with CHD displayed injury in the occipital lobes (Paquette et al., 2013). Neonatal symptoms of occipital injury may be a lack of visual tracking; this also has the potential to contribute to future visual problems. However, neonatal neuroimaging did not reveal all possible injuries, such as those related to language and executive function. The brain is complex and many of its functions and regions interconnect. Damage to one area of the brain may lead to problems or symptoms elsewhere; this may explain the lack of injury seen by neuroimaging.

A study on children with HLHS, after first stage surgical palliation at 14 months of age, showed lower psychomotor and mental scores on the Bayley Scales of Infant Development II, when compared to the normative population (Newburger et al., 2012). Interestingly, delays appear to be unrelated to procedures of open heart surgery, such as CPB and DHCA (Newburger

et al., 2012). Smaller head circumference and lower birth weight predicted lower developmental scores in these CHD children (Newburger et al., 2012).

Other studies reported nonspecific clinical and demographic findings associated with neurodevelopmental delays or symptoms such as low birth weight, length of hospital stay, and maternal sociodemographic factors (Newburger et al., 2012; Sananes et al., 2012; Tabbutt et al., 2012). Neurologic symptoms associated with injury in neonates with CHD may range from generic and subtle findings (e.g. low tone), to more specific deficits observed in formal neurodevelopmental testing with advanced age (e.g. deficits in motor coordination, visual-spatial, and executive function). However, there are no studies of neurobehavioral delays and associations to impaired CA.

Congenital Heart Disease & Potential Mechanisms of Neurologic Injury

Preoperative Risks

Clinical factors in neonates with CHD may contribute to neurologic injury. While in utero, an altered state of circulation from the cardiac defect may affect neurologic perfusion and growth (Marino et al., 2012). Increased fractional moving blood volume (in the third trimester) in normal fetuses was significantly associated with decreased neurobehavioral scores in motor, social, and attention measures (Mula et al., 2013). The exact cause of abnormal cerebral blood flow is unclear in the normal growing fetus, but evidence suggests alterations in cerebral circulation influences neurobehavioral performance. Studies also demonstrated neonates with CHD may have smaller head circumference, verified by lower cerebral to placental resistive indices when compared to healthy fetuses (Donofrio et al., 2003). This finding could be related to maternal conditions (e.g. advanced age) or altered in utero cerebral circulation due to the

anatomic obstruction of blood flow out of the aorta and transverse arch (Sommer, Hijazi, & Rhodes, 2008).

Another mechanism impacting brain tissue injury is arterial oxygen content in neonates with CHD. Depending on the cardiac defect, neonates may have lower arterial oxygenation contributing to neurologic injury (Block et al., 2010; Limperopoulos et al., 2000). A dual center study in 62 transposition of the greater arteries (TGA) and 30 single ventricle term neonates, examined the risk of brain injury before and after cardiac surgery (Block et al., 2010). Lowest arterial oxygenation content was associated with preoperative brain injury. These findings were similar to Limperopoulos et al. (2000), who observed a significant association between arterial oxygen (less than 85%) and abnormal neurobehavioral assessments in preoperative infants with CHD.

Studies also provided evidence of “neurologic immaturity” in term neonates with CHD, possibly contributing to the vulnerability of the brain (Abdel Raheem & Mohamed, 2012; Licht et al., 2009; Mahle et al., 2002). Abdel Raheem and Mohamed (2012) found term neonates with both acyanotic and cyanotic lesions manifest signs of neurologic immaturity, demonstrated by significantly lower levels of N-acetyl aspartate (NAA) to choline (Ch) ratio, increased diffusivity, and decreased white matter anisotropy (Abdel Raheem & Mohamed, 2012). Similarly, Licht et al. (2009) found brain immaturity (by approximately one month of age) in 42 neonates with HLHS and TGA.

Additionally, Miller et al. (2007) compared brain development and brain injury in 41 neonates with TGA and single ventricle CHD to healthy control term neonates and discovered brain immaturity in CHD similar to preterm neonates. The CHD neonates had significantly decreased NAA/ Ch ratio ($p = .003$), increased average diffusivity ($p < .0001$), decreased white

matter fractional anisotropy ($p < .001$), and increased in lactate/ Ch ratio ($p = .08$), all indicative of immaturity, which were similar to findings from Andropoulos et al. (2010). Although lactate was not used as evidence of injury, increased Score for Neonatal Acute Physiology–Perinatal Extension (SNAP–PE) rating was associated with higher ratios of lactate to choline ($p = 0.007$). These findings may partially explain how Apgar (**a**pppearance [skin color], **p**ulse [heart rate], **g**rimace [response to stimuli], **a**ctivity [tone], and **r**espiration) scores may be related to a brief period of altered oxygenation during transition from intra- to extra- uterine life. Preoperative injury was not significantly associated with brain immaturity, conflicting with previous reports of damage (Andropoulos et al., 2010; Goff et al., 2014).

Other studies correlated brain immaturity to injury. Goff et al. (2014) reported brain immaturity as a strong predictor for periventricular leukomalacia (PVL) ($p = 0.005$) in 57 neonates with HLHS type defects. Andropoulos et al. (2010) also associated low total maturity score with increased preoperative white matter injury ($p = .002$), late postoperative death ($p = .008$), and severity of postoperative brain injury ($p = .01$) in 67 neonates with both single and two ventricle CHD. Interestingly, the 3rd postoperative MRI showed a decreased percentage of abnormality, 29% compared to 56% preoperatively and 63% in the 2nd postoperative scans, consistent with findings by Mahle et al. (2002).

The above studies identified vulnerability of the brain due to altered cerebral blood flow related to CHD and overall findings of brain immaturity despite being at term gestational age. However, findings contradict associations of brain immaturity to injury. Lastly, the resolution of brain injury leads one to investigate intrinsic causal factors since delays persist into adolescence, even after repair of the cardiac defect. A plausible mechanism of injury may be associated with the heart condition, such as an intrinsic factor of impaired CA.

Definition of Cerebrovascular Autoregulation

Cerebrovascular autoregulation is the brain's homeostatic function in maintaining constant cerebral blood flow in the presence of fluctuations in systemic blood pressure, especially during activities such as positional changes or physical exercise (Caicedo et al., 2012; Kainerstorfer, Sassaroli, Tgavalekos, & Fantini, 2015; Paulson et al., 1990; Tiecks, Lam, Aaslid, & Newell, 1995). Homeostasis or the state of equilibrium describes the body's automatic response to restore balance across multiple systems, which includes CA for the brain. The homeostatic function of CA is important because the adult brain consumes approximately 20% of the body's oxygen content, which increases to 50% in children. Oxygen is consumed by aerobic metabolism and energy is utilized for active transport of ions to sustain and restore membrane potentials (Purves, 2012). Since the brain depends on aerobic metabolism, it requires continuous blood flow to replenish oxygen consumption. Deprivation of oxygen for more than 10 seconds leads to hypoxia and ensuing unconsciousness. If hypoxia persists for more than 5 minutes, irreversible brain damage occurs (Purves, 2012), thus maintaining CA is essential.

Impaired CA can be affected by internal and external factors such as traumatic brain injury, occlusive diseases of the arteries, prematurity, open heart surgery, body position, and interventions such as suctioning the endotracheal tube (Alderliesten et al., 2013; Brady et al., 2010; Czosnyka & Miller, 2014; Scheeren, Schober, & Schwarte, 2012). In neonates with hypoxemia, cerebral blood flow is dependent on systemic blood pressure because CA is impaired (Paulson et al., 1990). With this evidence, neonates with CHD may also have impaired CA. Despite factors influencing CA, when it is intact there is minimal disruption of blood circulating to the brain and cerebral blood flow is independent from systemic blood pressure changes. When CA is impaired, disruption of homeostasis occurs, and the brain does not receive adequate

circulation because cerebral blood flow is dependent on systemic blood pressure. Thus during periods of hypotension, the brain's circulation is compromised and cannot adjust to the needs of oxygen consumption. This leads to hypoxia, especially in vulnerable areas of the brain, resulting in cellular injury and/ or death, which may be visualized by neuroimaging. In turn, this brain injury may lead to developmental delay, thus maintaining CA may alleviate these deficits.

Standard Measures of Cerebrovascular Autoregulation

There are multiple “gold standard” measures of CA, but many are not appropriate or feasible for the neonatal population. Methods to measure cerebral blood flow velocity or cerebral pressure include positron emission tomography (PET) scan, MRI, transcranial Doppler ultrasound, intracranial pressure, and radionuclide or color labeled microsphere (Chock et al., 2012; Czosnyka & Miller, 2014; Liem & Greisen, 2010; Ono et al., 2013). Methods inducing blood pressure changes to measure CA are bilateral thigh cuffs, Valsalva maneuvers, vasopressor medications, and squat to stand (Fontana et al., 2015; Lucas et al., 2010; Meel-van den Abeelen, van Beek, Slump, Panerai, & Claassen, 2014; Rangel-Castilla et al., 2010). Comparisons of changes in blood pressure to cerebral blood flow (measured by ultrasound or neuroimaging) provides a measure of CA. Common features of these methods are the exact measure of cerebral blood flow velocity with correlations to mean arterial blood pressure. If cerebral blood flow does not correlate to blood pressure fluctuations, CA is intact. If cerebral blood flow changes with the blood pressure changes, then CA is impaired. However, in the context of neonatal care, these methods have some shortcomings.

These methodologies are cross-sectional in nature, only giving CA at one point in time, without a trending of measures. Patients do not routinely have invasive devices continuously measuring blood pressure or intracranial pressures (unless the patient is critically ill and it is

necessary) and constant noninvasive blood pressure monitoring can be extremely uncomfortable. The stimulation of blood pressure changes requires cooperation of the patient, such as modifications in breathing, which is challenging in neonates. Furthermore, transporting critically ill patients to imaging locations may be difficult, unsafe, and requires assistance of many trained personnel (Liem & Greisen, 2010). Thus, standard methods are not appropriate for the neonatal population.

Calculations for Cerebrovascular Autoregulation

Many formulas and methods to calculate CA are not practical for real time measures of CA. A common calculation to measure CA is the correlation coefficient, normally calculated by a moving correlation between cerebral blood flow velocity and cerebral perfusion pressure or arterial blood pressure (Lucas et al., 2010; Ono et al., 2013). Coefficients close to zero or negative values show no correlation in blood pressure and cerebral blood flow velocity, exhibiting intact CA. Coefficients close to one, show a positive correlation of blood pressure and cerebral blood flow velocity, demonstrating impaired CA.

Transfer function analysis measures spontaneous changes of blood pressure and cerebral blood flow velocity, then transforms arterial blood pressure and cerebral blood flow velocity with each beat, to a frequency (Hz) and amplitude (phase, gain, or coherence). These frequencies and amplitudes of arterial blood pressure and cerebral blood flow are then compared to each other (Katsogridakis et al., 2012; Meel-van den Abeelen et al., 2014).

$$TF_{xy}(f) = P_{xy}(f)/P_{xx}(f)$$

Where $P_{xy}(f)$ is the mean blood pressure and $P_{xx}(f)$ is the cerebral blood flow velocity. The oscillations of cerebral blood flow should not follow fluctuations of blood pressure, if it does, CA is impaired.

Another formula is the autoregulation index, a computer calculated hypothetical curve for cerebral blood flow velocity based on the subject's response to a steep blood pressure drop. The higher the autoregulation index the better the CA, numbers closer to zero, suggest impaired CA (Tiecks et al., 1995).

$$dP = (MABP - cABP) / (cABP - CCP)$$

$$x2 = x2 + (x1 - 2D \cdot x2) / (f \cdot T)$$

$$x1 = x1 + (dP - x2) / (f \cdot T)$$

$$mV = cVmca \cdot (1 + dP - K \cdot x2)$$

In this measure of dynamic CA, the person usually returns to baseline measures within 5 seconds (plus or minus 1 second). This return to baseline in 5 seconds demonstrates intact CA. Although these methods give a noninvasive measure of CA, the continuous monitoring of blood pressure is required. In the adult population, separate devices can noninvasively and continuously measure blood pressure (e.g. the Finapres) and the middle cerebral artery (e.g. transcranial Doppler ultrasound), but this type of technology is not available and may not be appropriate in the neonatal population. Furthermore, these methods require complex computerized calculations and are difficult to perform at the bedside.

Near Infrared Spectroscopy (NIRS)

Although multiple modalities can measure CA, a device indirectly measuring this response in the high risk neonatal population is near infrared spectroscopy (NIRS) (Goff, Buckley, Durduran, Wang, & Licht, 2010; Scheeren et al., 2012). The NIRS is a noninvasive, continuous device for measurement of regional cerebral oxygenation (rSO₂) (Alderliesten et al., 2013; Brady et al., 2010; Scheeren et al., 2012). The rSO₂ is an indirect measure of oxygenated and deoxyhemoglobin per a specific amount of blood (Scheeren et al., 2012). The NIRS is useful in neonates because their skulls are thin and photons are able to penetrate deeper into the

neonatal cortex (Goff et al., 2010). Advantages of using NIRS are: 1) the noninvasive nature of the device; 2) the continuous bedside measurement of rSO₂; and 3) the portability of the device (Goff et al., 2010; Scheeren et al., 2012). The disadvantages of NIRS are: 1) the cost of the device and sensors; 2) the sensitivity to movement, skin pigmentation with jaundice, and edema; and 3) the indirect measure of CA (Goff et al., 2010; Liem & Greisen, 2010; Scheeren et al., 2012). Despite the disadvantages, monitoring rSO₂ measured by NIRS is the standard of care in managing critically ill preterm and term neonates, during and after cardiac surgery, and for patients on extracorporeal membranous oxygenation in the United States and Europe (Alderliesten et al., 2013; Ono et al., 2013; Papademetriou et al., 2012). Therefore, NIRS is readily available and often already in use on neonates with CHD.

The NIRS has been reported as a valid and reliable indirect measure of CA in the preterm and term neonatal, and adult populations (Alderliesten et al., 2013; Bernal, Hoffman, Ghanayem, & Arca, 2010; Chock et al., 2012; Ono et al., 2013). Studies have described CA measured with NIRS in term neonates with CHD intraoperatively and postoperatively (Brady et al., 2010; Buckley et al., 2010). However, studies have not assessed preoperative CA in neonates with CHD.

Postural Changes to Induce Alterations in Blood Pressure

Postural changes are used to assess alterations in cerebral blood flow and/ or CA in adult and pediatric populations (Deegan et al., 2011; Endo et al., 2014; Kim et al., 2009). Deegan et al. (2011) assessed gender differences with CA utilizing the sit to stand technique in adults. Similarly, Kim et al. (2009) and Endo et al. (2014) examined changes in cerebral blood flow in the pediatric population with orthostatic changes employing the supine to standing technique. Although neonatal studies using postural changes were not found, evidence of cerebral

oxygenation changes measured by NIRS were reported during other clinical activities. Tax et al. (2011) demonstrated increases in mean cerebral oxygenation from 73.7 ± 6.9 to $75.1 \pm 6.9\%$ with NIRS when tilting the head of neonates. Karen et al. (2008) showed significant increases in oxygenated hemoglobin measured by NIRS in neonates responding to visual stimulation. Furthermore, Huning, Horsch, and Roll (2007) showed significant decreases in cerebral oxygenation (-2.135 ± 0.532 micromole/L) during umbilical line blood sampling in preterm neonates. Even though postural changes were not employed, these reports support changes in rSO₂ measured by NIRS during small movements or clinical care. Thus, it is assumed that postural changes will cause changes in cerebral perfusion due to forces of gravity (i.e. hydrostatic pressure) (Hinghofer-Szalkay, 2011). Therefore, postural changes and rSO₂ measured by NIRS was used in the study as an index for CA.

Cerebrovascular Autoregulation in Neonates & Pediatrics

Cerebral autoregulation is the body's homeostatic function maintaining constant brain blood flow independently from fluctuations in mean systemic blood pressure particularly during activities such as positional changes or physical exercise (Caicedo et al., 2012; Kainerstorfer et al., 2015; Paulson et al., 1990; Tiecks et al., 1995). In children, the brain consumes about 50% of the body's oxygen content. Hypoxia occurs if oxygen is deprived for greater than five seconds, and irreversible damage occurs if it persists for more than 5 minutes (Purves, 2012). Neonatal conditions causing hypoxemia, such asphyxia or respiratory distress syndrome, can impair CA (Alderliesten et al., 2013; Brady et al., 2010; Czosnyka & Miller, 2014; Paulson et al., 1990; Scheeren et al., 2012). Therefore, neonates with CHD are at risk for impaired CA related to hypoxemic states due to altered cardiac physiology. Appendix 2-3 lists reports of CA in neonates.

Chock et al. (2012) studied CA using NIRS in 28 very low birth weight (VLBW) preterm neonates treated for hemodynamically significant patent ductus arteriosus (PDA) compared to 12 control VLBW neonates. Impaired CA was measured with the pressure passivity index (PPI) using rSO₂ measured by NIRS and mean arterial blood pressures (MABP). Higher PPI was found after surgical ligation (indicating impaired CA) when compared to the control group ($p=0.04$) and group treated with Indocin ($p=0.0007$). Although not statistically significant, worsening neuroimaging abnormalities were identified in neonates undergoing surgical ligation. A larger sample size may have reached statistical significance. Strengths of this design were using a comparable control group and supporting NIRS assessment of CA. However, this study did not assess CA in preoperative CHD neonates and did not evaluate associations between impaired CA and neurobehavioral status. Therefore, the proposed study evaluated CA preoperatively in neonates with CHD and examined associations between CA and neurobehavioral outcomes.

Similarly, Alderliesten et al. (2013) explored CA in preterm neonates. The CA was compared in 30 preterm neonates who developed peri-intraventricular hemorrhage (PIVH) to 60 preterm neonates without PIVH. Correlations of MABP and rSO₂ measured by NIRS determined CA. Increased rSO₂ and decreased cerebral fractional tissue oxygenation extraction, suggested increased perfusion before severe PIVH. Correlations of MABP and rSO₂ were greater ($r > 0.5$) before developing PIVH, which indicated passivity and impaired CA, consistent with findings from Chock et al. (2012). Contrary to the assumption that decreased blood flow may relate to PIVH and brain injury, there was no association between hypoperfusion and PIVH. Strengths of this study are an adequate sample size and the use of a homogeneous control group. However, the study measured CA in a different high risk preterm neonatal population, used an off line/

computerized technique to measure CA, and did not assess correlations of impaired CA and neurobehavioral status.

In a slightly older high risk neonatal population, Howlett et al. (2013) investigated CA in term neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. The CA was measured with the hemoglobin volume index (HV_x), a correlation between rSO₂ measured by NIRS and MABP. Investigators found HV_x correlated with impaired CA during all three phases (i.e. hypothermia, rewarming, and normothermia) of therapeutic hypothermia. When MABP was <35 mm Hg, MABP and cerebral blood volume positively correlated, indicating pressure-passive vasoreactivity with impaired CA. Although no correlation value was provided, trending of rSO₂ followed blood pressure reactivity implying impaired CA. Similar to Alderliesten et al. (2013), neonates with more brain injury had higher rSO₂ values, possibly indicating decreased oxygen extraction from damaged brain tissue. These studies provide evidence of impaired CA in high risk term neonatal populations exposed to hypoxemia, and leads researchers to investigate this phenomenon in the CHD group.

Brady et al. (2010) conducted a pilot study in 54 term neonatal and pediatric patients undergoing cardiac surgery to determine the lower limits of pressure autoregulation. The CA was calculated with the cerebral oximetry index, a moving correlation of the patient's arterial blood pressure and rSO₂ measured by NIRS. The average cerebral oximetry index values were higher ($r > 0.4$) during and after cardiac surgery, suggestive of impaired CA. The study evaluated CA using rSO₂ measured by NIRS intraoperatively, not preoperatively, and did not determine associations of impaired CA with neurobehavioral status.

These studies provide evidence of impaired CA in high risk neonatal populations, such as neonates with CHD. However, these studies did not investigate neonates with CHD

preoperatively, did not use a bedside technique to measure CA, and did not examine associations between impaired CA and neurobehavioral status.

Evaluation of Neurodevelopmental Status in Neonates

Standardized neurobehavioral assessments for neonates with CHD are not performed routinely before cardiac surgery, unless it is clinically indicated. Reasons for the lack of neurobehavioral assessments are the acuity of patients before cardiac surgery and the use of a cranial ultrasound as a surrogate to detect neurologic abnormalities. However, brain injury and neurobehavioral abnormalities occur in approximately 20-50% of neonates with CHD before cardiac surgery (Andropoulos et al., 2010; Block et al., 2010; Galli et al., 2004; Limperopoulos et al., 1997; Limperopoulos et al., 1999; Paquette et al., 2013). Many neonatal neurobehavioral tools exist, with minimal clinical variations between instruments. Similarities of these assessments include testing neonatal state, regulation, response to stimuli, and neuromuscular and motor responses, which examine different areas of the brain (Noble & Boyd, 2012). Assessments have discriminative and predictive properties, evaluate normal from abnormal, and correlate with future deficits (Majnemer & Snider, 2005; Noble & Boyd, 2012). However, the ENNAS is the only tool validated in the healthy neonatal and CHD populations. Moreover, the literature lacks a “gold standard” for neurobehavioral assessments in neonates with CHD, especially preoperatively.

Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS)

The ENNAS has been used in the neonatal CHD population for more than 10 years, and is reported as a valid and reliable measure for neurobehavioral status (Limperopoulos et al., 1999). Limperopoulos et al. (1997) assessed 32 preoperative term neonates born with complex CHD and found neurobehavioral abnormalities in approximately 50%. Abnormalities found with

the ENNAS highly correlated to a neurologic exam by a pediatric neurologist (kappa = 96.9%) (Limperopoulos et al., 1997), which also provided validity of the ENNAS in CHD neonates.

In a later study, Limperopoulos et al. (1999) compared results of the ENNAS in preoperative CHD and healthy neonates. Of the 56 preoperative neonates with single and two ventricle defects, 20% had abnormal neurobehavioral assessments and 38% had borderline scores. Deviant scores were significantly different between neonates with CHD (mean, 3.86; standard deviation [SD], 2.4; median, 4.0) and healthy controls (mean, 0.5; SD, 0.7; median, 0). Neurologic symptoms in neonates with CHD were mostly related to motor function such as hyper/ hypotonia, lethargy, jitteriness, and asymmetric movements (Limperopoulos et al., 1999; Majnemer & Limperopoulos, 1999). These CHD neonates also demonstrated poor behavior regulation, inefficient feeding, and lack of a suck reflex (Licht et al., 2009; Limperopoulos et al., 1999; Majnemer et al., 2009). Furthermore, significant differences between control and CHD neonates were discovered in orienting responses (both visual and auditory subtests), and passive and active movements (i.e. head extension, head lag, muscle tone). The study had a strong design because of the control group, but it did not examine correlations to impaired CA.

Limperopoulos et al. (2000) further supported abnormalities by assessing neurobehavioral status in 56 neonates and 75 infants before and after cardiac surgery. Greater than 50% of neonates had neurobehavioral abnormalities before surgery, with irregularities persisting postoperatively. Additionally, 38% of infants with CHD had neurodevelopmental abnormalities before surgery. Arterial oxygen saturations < 85% were significantly associated with an abnormality in infants. Interestingly, neonates with acyanotic heart defects exhibited more abnormal neurologic symptoms than those with cyanotic heart defects; contrary to assumptions of worse findings in cyanotic disease (Limperopoulos et al., 2000). This study

supports the use of ENNAS, but did not assess the relationship between neurodevelopmental abnormalities and impaired CA.

More recently, Majnemer et al. (2009) assessed neurobehavioral status in 56 healthy neonates and 74 infants with CHD before cardiac surgery to explore predictors of neurodevelopmental delay. Similar to results of Limperopoulos et al. (1997), 58% of preoperative neonates exhibited abnormalities using the ENNAS. Some predictor variables at one and five years of age were microcephaly, arterial oxygen levels, acyanotic heart lesions, length of hospitalization, and maternal education. Although these studies suggest the presence of preoperative neurobehavioral abnormalities in neonates with CHD using the ENNAS, no studies examined associations between impaired CA and neurobehavioral abnormalities.

Chapter Summary

Neonates with CHD are at higher risk for neurologic injury and developmental delay. Neuroimaging demonstrated brain injury in neonates with CHD in utero, and before and after cardiac surgery. Common areas of injury existed in regions of the brain controlling cognitive and auto-regulatory functions. The periventricular area was the most identified region of neurologic injury. A possible mechanism of injury is impaired CA, which will be indirectly measured with rSO₂ measured by NIRS during postural changes. Even with the mounting evidence of brain injury preoperatively, neonates rarely have formal neurobehavioral assessments before cardiac surgery. It is unknown whether abnormal neurobehavioral status relates to impaired CA. It is also unclear if preoperative neonates with CHD have impaired CA. Therefore, the study investigated whether preoperative neonates with CHD have impaired CA and whether impaired CA is associated to neurobehavioral status.

CHAPTER THREE: CONCEPTUAL FRAMEWORK

Congenital heart disease (CHD) is one of the leading birth defects in the United States, affecting approximately 40,000 neonates each year (American Heart Association, 2015). Neonates with CHD are at risk for developmental delay and brain injury (Gaynor et al., 2015), but the cause is unclear (Gaynor et al., 2015; Hoffman et al., 2013; Mussatto et al., 2014; Newburger et al., 2012). Recently, large multicenter studies have ruled out operative factors as independent predictors of delays and injuries, leading investigation towards intrinsic factors (Gaynor et al., 2015; Newburger et al., 2012). One possible source of neurologic delay and injury is impaired cerebrovascular autoregulation (CA) leading to inadequate blood flow to the brain, especially during fluctuations in systemic blood pressure (Caicedo et al., 2012; Paulson et al., 1990).

In order to test the hypothesis that brain injury and neurologic delay may be explained by impaired CA, the study examined the relationship between impaired CA, neurobehavioral status, and clinical factors in preoperative neonates with CHD. The theoretical framework used to guide the study was the general system theory (Von Bertalanffy, 1950), which describes complex entities (in this study, systems of the human body) and interactions between those systems (Marieb & Hoehn, 2007). The body systems encompass the nervous, endocrine, lymphatic, respiratory, cardiovascular, digestive, urinary, reproductive, integumentary, skeletal, and muscular systems (Marieb & Hoehn, 2007). Table 3-1 describes the ten subsystems of the body systems framework (Marieb & Hoehn, 2007). Systems most relevant to the study were the cardiovascular, nervous, and muscular systems (Figure 3-1). The constructs of these systems are cardiac, cerebral, and muscular status. Specifically, a description will be given of the cardiac defects, cerebrovascular autoregulation, and neurobehavioral status (motor, auditory, and visual

functions). These constructs are part of the cardiac, nervous, and muscular systems (respectively) and their interactions will be described. Components from the respiratory system are included because blood is circulated to the lungs for oxygenation, but it was not the focus of the study. An example of interactions between the body systems is CHD affecting blood circulation and oxygen delivery to vital organs of the body, such as the lungs and brain; potentially leading to decreased tissue perfusion in those areas, resulting in decreased systemic oxygenation and brain injury (Marieb & Hoehn, 2007).

Body systems do not function independently, but work together to maintain homeostasis; which is the underlying concept for this framework (Marieb & Hoehn, 2007). Homeostasis or the state of equilibrium, is the body's automatic response to maintain stability in the functions required to sustain a normal, operating human being (Meleis, 2012). Neonates with CHD have a disruption of homeostasis. The CHD leads to hypoxemia and impairs the brain's ability to maintain circulation. Hypoxemia leads to hypoxia, particularly during fluctuations in blood pressure (e.g. hypotension), and possibly tissue death if hypoxia persists for greater than 5 minutes. Cerebral tissue death may result in or perpetuate impaired CA and abnormalities in neurobehavioral status.

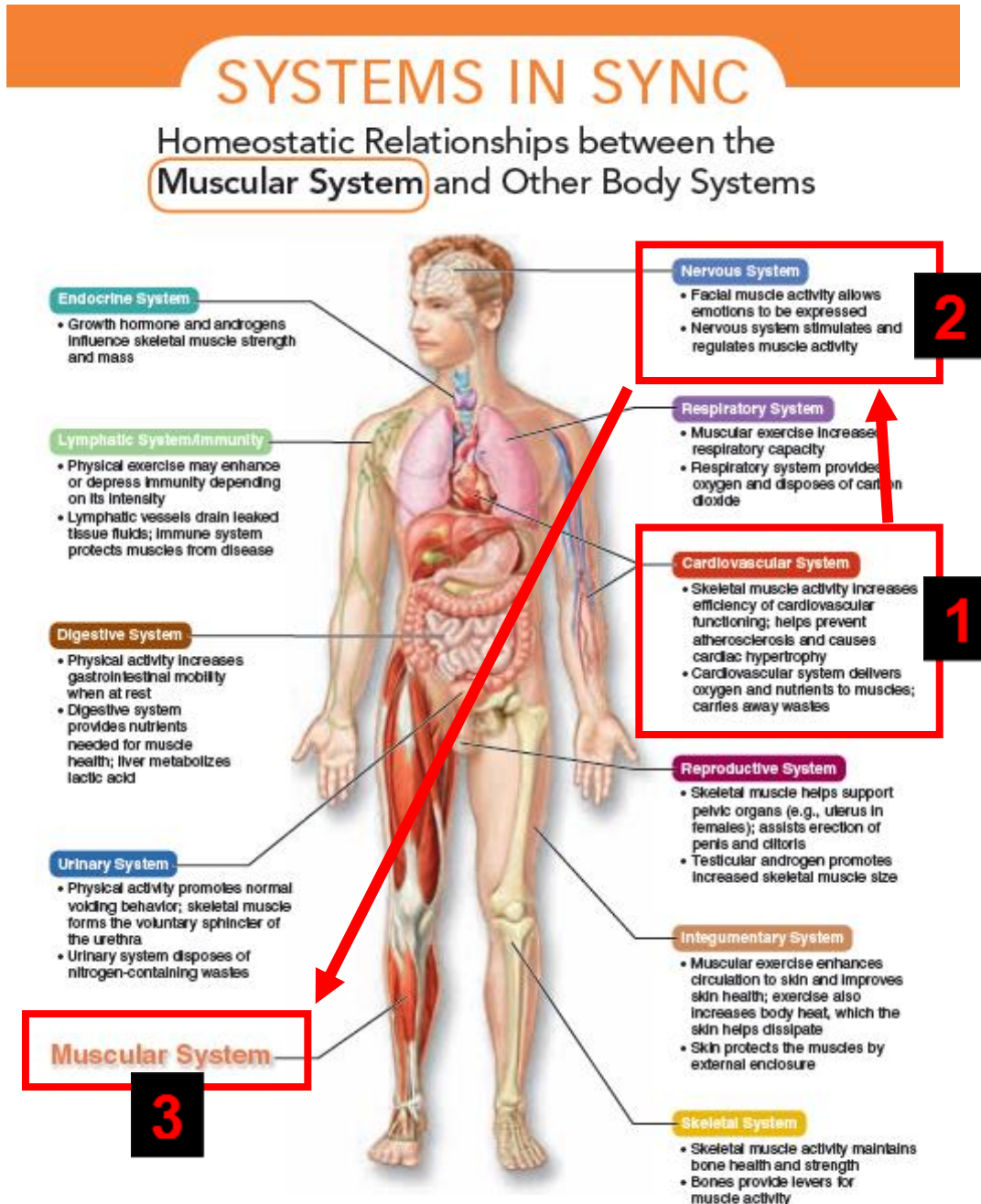
Interactions specific to the study were between: 1) **cardiovascular** and respiratory systems, because the cardiac defects affect oxygenation in the blood; 2) **cardiovascular** and **nervous** systems, since cardiac defects influence delivery of oxygenated blood to the brain (from hypoxemia or altered cerebral blood flow); and 3) **nervous** system and **musculo-skeletal** systems, due to decreased oxygen levels in the brain damaging cerebral tissue, leading to changes in sensory (auditory, visual) and motor functions. Specifically, the heart pumps blood into the systemic and pulmonary circulation. Cardiac defects can cause mixing of deoxygenated

and oxygenated blood, obstructions of blood flow to the lungs (for oxygenation), and/ or from obstruction of blood flow to the body (Sommer et al., 2008). This can lead to inadequate circulation and/ or oxygenation due to decreased arterial content of the circulating blood (Sommer et al., 2008). Hypoxemic blood is then circulated to the brain, a highly vascular organ consuming approximately 50% of the body's oxygen content in children (Purves, 2012). Hypoxemia may lead to brain tissue hypoxia, and eventually brain tissue death during prolonged exposure. Brain tissue death or injury can manifest with changes in neurobehavioral status. The body's neurobehavioral status involves the brain's processing of sensory input, analyzing information into a motor command, and then converting that information into motor responses (Purves, 2012). Thus, damage to cerebral tissue may lead to changes in movement or reactions. However, injury may also occur at the muscular and/ or skeletal system level, which can also affect neurobehavioral status.

Table 3-1. Body Systems Framework modified from Marieb and Hoehn (2007)

Body system	Function	Variables
Cardiovascular	Provides circulation to the body and lungs Works in conjunction with the respiratory system by sending deoxygenated blood to the lungs for oxygenation	Congenital heart disease (CHD) - may alter perfusion to the brain or may cause hypoxemia
Nervous	Facilitates homeostatic functions Thalamus- responsible for relaying sensory information to specific regions of the brain for processing Hypothalamus- regulation of homeostasis Hippocampus- facilitates memory	Hypoxemia or altered perfusion from CHD may lead to impaired Cerebral (brain) autoregulation . When impaired, cerebral blood flow is not maintained resulting in tissue <i>hypoxia/ischemia</i> , prolonged hypoxia leads to brain tissue injury and/or death, especially to the vulnerable areas e.g. thalamus and hippocampal regions; potentiating/continuing the brain cell <i>injury/death</i> . Cellular brain tissue injury/death can lead to problems <i>processing</i> and <i>relaying sensory</i> information.
Endocrine	Growth hormone and androgen production	
Respiratory	Provides oxygen and carbon dioxide exchange	oxygenation
Muscular/Skeletal	Facilitates movement and protection of vital organs	Problems processing and relaying sensory information will be demonstrated by changes in motor, auditory, and visual functions (i.e. Neurobehavioral status)
Lymphatic	Facilitates immunity- drains leaked tissue fluids	
Digestive	Provides nutrients and facilitates waste excretion	
Urinary	Facilitates nitrogen based waste excretion	
Reproductive	Facilitates hormone production and sexual propagation	
Integumentary	Facilitates temperature regulation and acts as the first line of defense	

Figure 3-1. Body Systems Framework from Marieb and Hoehn (2007) with permission from Pearson Education. This study focuses on the: 1) Cardiovascular, 2) Nervous, & 3) Muscular systems. The framework conveys the relationships between these systems, as well as other body systems.



Interactions of System Concepts

Cardiovascular & Respiratory Systems

The heart and blood vessels encompass the cardiovascular system (National Institutes of Health, 2016a). The normal heart has four chambers, with septums separating the top atria and bottom ventricles (Hill & Iaizzo, 2015). Veins bring blood to the heart and arteries carry blood away from the heart (National Institutes of Health, 2016a). Pulmonary arteries deliver deoxygenated blood to the right side of the heart, which then sends blood to the lungs for oxygenation. Oxygenated blood is returned to the left side of the heart, via the pulmonary veins, and circulated to the body through the aorta (National Institutes of Health, 2016a). Blood must travel through many vessels and chambers; therefore, CHD is likely to affect blood flow and oxygenation.

Cardiac status is directly linked to respiratory status because blood is sent to the lungs for oxygenation and gas exchange (Kattwinkel et al., 2010). Neonates without CHD manifest a healthy cardiovascular system with audible heart tones without a murmur, oxygen saturations greater than 95%, and no evidence of peripheral or central cyanosis. Neonates with CHD are born with a structural defect in the chambers or vessels of the heart. Defects can cause mixing of arterial (oxygenated) and venous (deoxygenated) blood, which may affect cerebral circulation and oxygenation. Blood flow from the heart to the brain begins at the brachiocephalic trunk and common carotid artery; feeding the right and left cerebral arteries (Purves, 2012). Because of the close connection of the heart and brain, there is a high likelihood that a structural defect of the heart would influence circulation of the brain.

Cardiovascular & Nervous Systems

The nervous system consists of the central (CNS) and peripheral (PNS) nervous systems (National Institutes of Health, 2016b). The CNS includes the brain and spinal cord; the PNS includes nerves branching from the spinal cord to the rest of the body. The brain sends information through the spinal cord and nerves of the PNS to control movement of muscles and function of organs (National Institutes of Health, 2016b). Damage to the PNS or CNS can result in changes in movement or function. The PNS and CNS can be further divided into the autonomic and somatic nervous system. The autonomic nervous system regulates involuntary processes such as heart rate and respirations (National Institutes of Health, 2016b). The somatic nervous system controls voluntary processes and purposeful motor movements, such as walking or eating. Because parts of the nervous system (such as the brain) are highly vascular; steady blood flow to replenish oxygen consumption is required (Purves, 2012). Any alteration of blood flow or oxygenation (such as hypoxemia from CHD) may lead to tissue hypoxia; prolonged hypoxia will lead to cellular necrosis. Neural tissue damage or death may be reflected in changes in movement or neurobehavioral status. Neonates with CHD are at risk for decreased cerebral blood flow due to the cardiac defect.

Baroreflex

Under normal circumstances, systemic blood pressure changes are sensed by arterial baroreceptors in the carotid sinuses and aortic arch (Purves, 2012). The sinus nerve of Hering innervates the carotid sinus baroreceptors, which branch from the glossopharyngeal nerve (IX cranial nerve). Aortic arch baroreceptors are innervated by the aortic nerve, which then combine with the vagus nerve (X cranial nerve) (Klabunde, 2011). Baroreceptors are stretch receptors responding to fluctuations in blood pressure, either with rate of change or steady state. The most

important role of the baroreceptor is responding to rapid decreases in blood pressure (because of reduced firing from the baroreceptors), which increases sympathetic nervous system activity and decreases the vagal response. This response occurs quickly in less than two to three seconds, leads to improved heart rate and systemic vascular resistance (thus cardiac output), and restores blood pressure (Klabunde, 2011).

Nucleus Tractus Solitarius, Hypothalamus, & Medulla

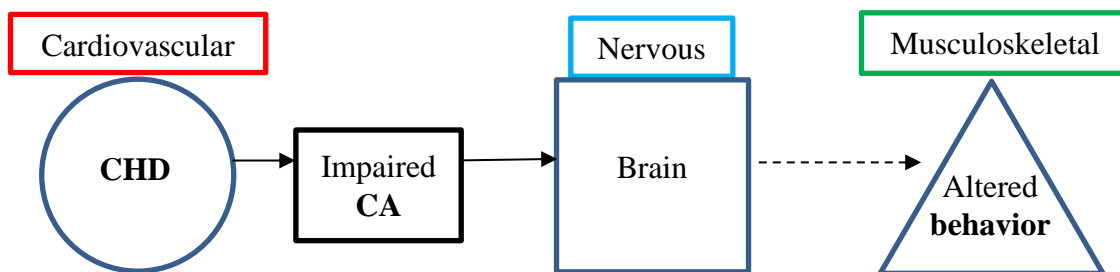
The glossopharyngeal nerve (IX cranial nerve) and vagus nerve (X cranial nerve) both travel to the nucleus tractus solitarius (NTS) located in the medulla of the brainstem (Klabunde, 2011). The NTS modulates the activity of sympathetic and parasympathetic (vagal) neurons in the medulla, which then regulate the autonomic control of the heart and blood vessels by sending information to the hypothalamus (Klabunde, 2011). The hypothalamus sends information to the autonomic neurons within the medulla, which responds by increasing sympathetic outflow and decreasing parasympathetic (vagal) outflow. In the brain, this causes a change in the diameter of cerebral blood vessels, which regulates blood flow. These parts work in coordination; maintaining homeostasis and cerebral blood flow. Furthermore, the thalamus facilitates relaying sensory information to specific regions of the brain for processing, such as auditory or visual stimuli. Thus, damage to these cerebral regions can further perpetuate impaired CA and possible changes in neurobehavioral status.

Nervous & Musculo-skeletal Systems

The muscular system consists of the muscles, tendons, ligaments, connecting tissue, and organs (PubMed Health, 2016). In addition to assisting with movement, the muscular system provides support and stability to the skeletal system. Coordination of the muscular and skeletal systems facilitates movement. Specifically, an interaction between the nervous system (brain)

and musculo-skeletal system leads to purposeful movements. The brain has major influence over movement of muscles in the musculo-skeletal system (Purves, 2012). Therefore, damage to cerebral tissue may result in changes in movement and musculo-skeletal function. The “healthy” neonate is expected to have normal neurobehavioral status because the normal heart and blood vessels maintain adequate cerebral oxygenation, blood flow, and autoregulation. Normal neonates manifest a healthy muscular system with adequate tone, appropriate responses to auditory and visual stimuli, strong oral suck, and no tremors. If abnormalities in movement have been ruled out at the muscular system level, then further investigation points to causes from the nervous system. Refer to figure 3-2 for concepts in relation to the body systems framework.

Figure 3-2. Concepts in Relation to the Body Systems Framework



Constructs & Variables

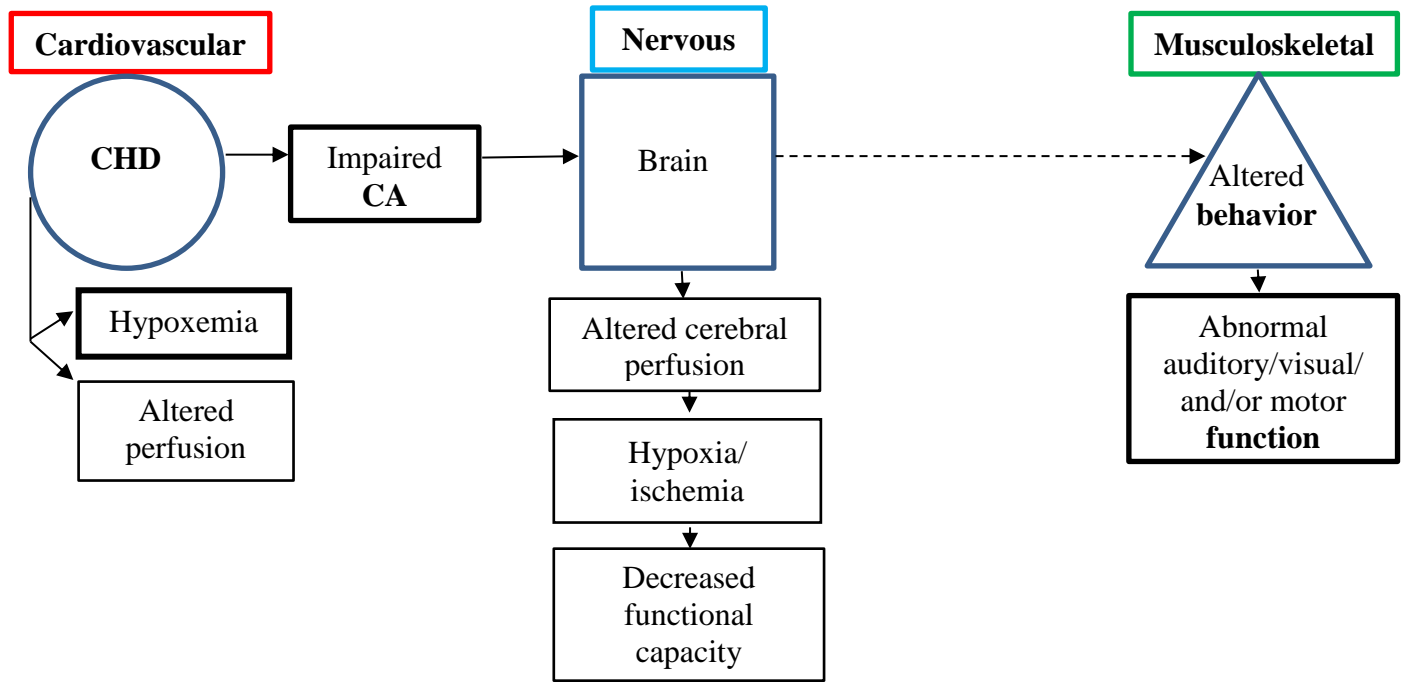
Cardiovascular Status

Neonatal cardiovascular status may be assessed with the neonate’s skin color. Normal skin color is pink with mild acrocyanosis (bluish hue) to the hands and feet because of circulatory transition from intra- to extra-uterine life (Steinhorn, 2008). Acrocyanosis usually resolves within approximately 10 minutes. Neonatal cardiovascular status can also be assessed by heart rate, which can be palpated via the umbilical cord (after birth) or auscultated with a stethoscope on the left upper chest. A heart rate greater than 80 beats per minute (BPM) is acceptable, but the ideal heart rate is greater than 100 BPM (Medline Plus, 2016b). Another assessment of cardiovascular status

is palpating the neonate's central or peripheral pulses or measuring blood pressure. Strong pulses on all four extremities can indicate a healthy cardiovascular status or normal blood pressure with weeks in gestational age used as a quick measure for the minimum value of mean blood pressure.

When CHD is suspected in neonates, a noninvasive echocardiogram is performed to evaluate structures of the heart (e.g. chambers, valves, and vessels) and to confirm the diagnosis. Neonates with mild or simple heart defects, such as an atrial septal defect, can be treated with medications and close monitoring of cardiovascular status. Cardiac surgery would not be necessary unless the lesion caused severe hypoxemia, pulmonary edema, or heart failure symptoms. Neonates with more complex or severe defects, such as hypoplastic left heart syndrome (HLHS), require surgical intervention usually within the first week of life. Heart defects are classified as cyanotic (blue), causing hypoxemia because of mixing of venous and arterial blood, or acyanotic (pink) which has more normalized oxygenation (Sommer et al., 2008). The assessments listed above evaluate cardiac status and severity of CHD. Refer to figure 3-3 for the constructs in relation to the body systems framework.

Figure 3-3. Constructs in Relation to the Body Systems Framework



Cerebral Status

Cerebral circulatory anatomy is the same for neonates with and without CHD. However, cardiac defects may lead to decreased blood flow and oxygenation to different areas of the brain, such as the basal ganglia and thalamic regions, which are linked to motor and homeostatic mechanisms. Another vulnerable area is the hypothalamus, also linked to the body's auto-regulatory responses (Purves, 2012). The body's mechanism to regulate cerebral blood flow is intact CA. Cerebral blood flow is maintained when auto-regulatory mechanisms respond to changes in blood pressure by increasing blood flow to areas requiring more oxygenation (under normal conditions, independently from systemic blood pressure) (Caicedo et al., 2012; Paulson et al., 1990). When CA is intact, changes in blood pressure should not affect blood flow to susceptible regions of the brain.

When CA is impaired, cerebral blood flow is compromised. Neonates having prematurity, respiratory distress syndrome, and open heart surgery are at risk for impaired CA (Alderliesten et al., 2013; Brady et al., 2010; Czosnyka & Miller, 2014; Paulson et al., 1990; Scheeren et al., 2012). When CA is impaired, cerebral blood flow is dependent on systemic blood pressure, resulting in decreased perfusion of the brain, especially during hypotension. The decreased blood flow leads to cerebral hypoxia and may result in tissue injury or death. Cerebral neuroimaging studies have demonstrated brain injury in about 20-40% of neonates even before cardiac surgery (Goff et al., 2014; Licht et al., 2009; Miller et al., 2007; Paquette et al., 2015). The evidence suggests that inadequate cerebral tissue perfusion leads to hypoxia, resulting in tissue injury and/ or death.

Cerebral blood flow can be evaluated using magnetic resonance imaging (MRI) or positron emitted tomography (PET); however, these procedures are not performed routinely before neonatal cardiac surgery. Cranial ultrasound may be used to determine intraventricular hemorrhage (IVH);

however, it is not normally used to measure CA in the preoperative CHD neonate. Regional cerebral oxygenation (rSO₂) measured by near infrared spectroscopy (NIRS) has been used as an indirect measure of cerebral blood flow and CA. Decreased cerebral blood flow affects cerebral tissue oxygenation, and may lead to brain tissue damage. Brain tissue damage affects the musculo-skeletal system function, which can be indirectly assessed by changes in motor behavior (neurobehavioral status).

Muscular Status

Neonates with CHD have a higher risk for abnormal neurobehavioral status because of hypoxemia and altered cerebral blood flow. Studies demonstrate abnormal neurobehavioral status affecting motor, visual, and auditory functions (Limperopoulos et al., 1997; Limperopoulos et al., 1999, 2000; Majnemer et al., 2009). Some neonates with CHD also have small head circumference, low birth weight, and neurodevelopmental delays (Hoffman et al., 2013; Mussatto et al., 2014; Newburger et al., 2012). These clinical factors may be related to decreased cerebral blood flow resulting from the structural defect of the heart. Neonatal neurobehavioral status can also be evaluated with reflexes, ability to independently consume oral feedings, consolability, and cry.

Empirical Indicators

Congenital Heart Disease

Neonates with prenatal diagnosis of CHD will have a postnatal echocardiogram confirming the heart lesion with documentation in the medical record. In addition, portions of neonatal cardiovascular, respiratory, and neurobehavioral status are evaluated using an Apgar score, which is evaluated at 1 and 5 minutes after birth. The Apgar score represents appearance (skin color), pulse (heart rate), grimace (response to painful stimuli), activity (muscle tone), and respiration. A

total Apgar score greater than 8 at 1 and 5 minutes after birth demonstrates a healthy transition from intra- to extra-uterine life. Scores less than 7, may indicate poor cardiovascular status and the need for medical intervention (Dalili et al., 2016). Cardiovascular status is also evaluated using the critical CHD (CCHD) screening; required by the state of California, before the neonate is discharged home (Jones, Howarth, Nicholl, Mat-Ali, & Knowles, 2016). The screen measures oxygen saturation using pulse oximetry applied simultaneously to the right hand and a lower extremity for 5 minutes. Oxygen saturations (spO_2) greater than 95%, with less than or equal to 3% difference between the hand and foot are indicative of adequate cardiovascular status. Neonates with oxygen saturations lower than 95% or greater than 3% difference between the hand and foot, are evaluated two more times (with 1 hour between each screening). Neonates who do not pass the CCHD screen (three times) are referred for further evaluation of CHD.

Cerebrovascular Autoregulation

The rSO_2 measured by NIRS is an indirect measure of CA when placed on the forehead. Intact CA was defined as rSO_2 values returning to baseline in less than or equal to 5 seconds after the position change from supine to sitting. Impaired CA was defined as rSO_2 values taking greater than 5 seconds to return to baseline after the postural change (Aaslid, Lindegaard, Sorteberg, & Nornes, 1989; Tiecks et al., 1995). Reference ranges for baseline rSO_2 in preterm and term neonates varies. Neonates may have low rSO_2 (45-65), medium (65-85), or high (85-95) (Alderliesten et al., 2013; Hoffman et al., 2013; Howlett et al., 2013; Pichler et al., 2013). Additionally, an increased lactate level (supporting acidosis) can be an indirect measure of cerebral tissue injury and decreased oxygenation in neonates with CHD (Abdel Raheem & Mohamed, 2012; Miller et al., 2007; Shedeed & Elfaytouri, 2011). Therefore, lactate levels were obtained from medical records.

Neurobehavioral Status

Neurobehavioral status was evaluated using the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS). The ENNAS has 20 items and 4 summary items, which assessed the interaction of the brain (auditory and visual responses) and musculo-skeletal system (motor response). Items are scored independently using a 3 or 18 point ordinal scale. Total scores with greater than or equal to 7 items scored outside the normal reference range were considered abnormal (Kurtzberg et al., 1979). Abnormal neurobehavioral status suggests possible brain injury or an alteration in nervous system function and may require further evaluation and follow up. A total score with 3 to 6 items outside the normal reference range, suggested borderline neurobehavioral status. Total scores with less than or equal to 2 items outside the normal reference range, suggested adequate neurobehavioral status (Majnemer & Snider, 2005).

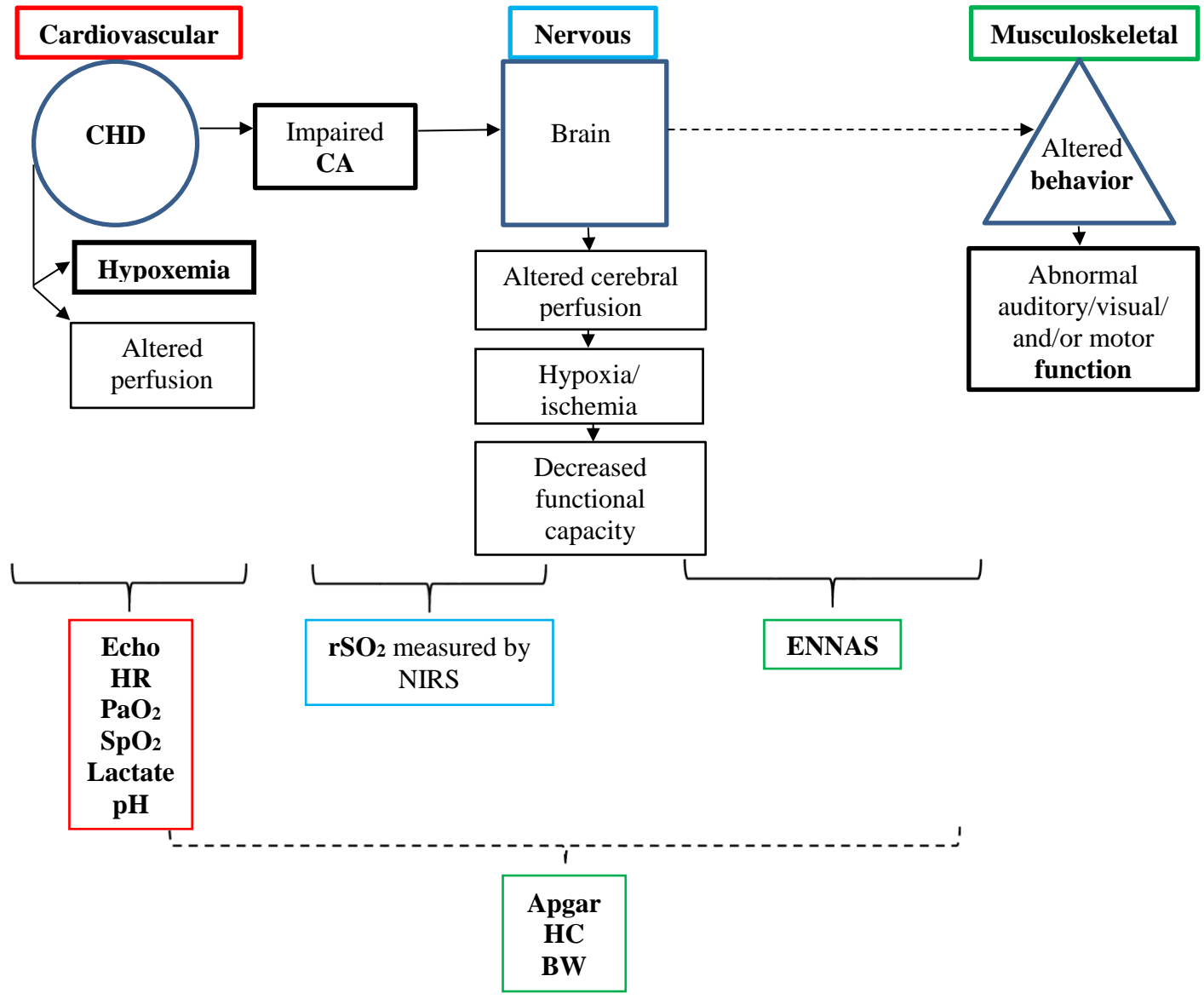
The ENNAS will evaluate 3 areas - motor, auditory, and visual functions. The motor assessments of the ENNAS evaluate: 1) spontaneous movements, 2) tone, 3) rooting, 4) sucking, 5) arm recoil, 6) grasp, 7) head extension, 8) traction, 9) head lag, 10) popliteal angle, 11) Moro reflex, 12) tonic neck reflex (TNR), 13) extremity movement, 14) ventral suspension, and 15) cuddliness. The motor functions items (head extension, extremity movement, ventral suspension, rooting, sucking, Moro, TNR, grasp, and popliteal) scoring greater than 1 are within norms (scores range from 0 to 2 or 3). The motor function items for traction, head lag, and arm recoil are within norms if scores are greater than 2 (scores range from 0 to 3). Spontaneous movement (range 0 to 4), tone (range 0 to 6), and cuddliness (range 1 to 4) are within norms if scores are greater than 3.

Auditory functions were evaluated with responses using: 1) a bell, 2) rattle, and 3) voice. The individual bell and voice scores greater than 10 are within norms (score range from 0 to 18). The rattle score greater than 13 is considered within the norm (score range 0 to 18). A combined

score of all three auditory tests greater than 40 are within norms (score range 0 to 54) (Kurtzberg et al., 1979).

Visual assessments include: 1) following the bull's eye, 2) following the face-voice, 3) optic blink, and 4) rotation. Individual bull's eye and face-voice scores greater than 13 are within norms (score range 0 to 24). A combined score for the bull's eye and face-voice of greater than 29 is within the norm (score range 0 to 48). The optic blink score greater than 1 is within norms (score range 0 to 2). Similarly, the score for rotation greater than 1 is within norms (range 0 to 3). All scoring of the items followed recommendations by the ENNAS developers (Kurtzberg et al., 1979). Refer to figure 3-4 for constructs and empirical indicators.

Figure 3-4. Empirical Model in Relation to the Body Systems Framework



Assumptions

A general assumption of the study was that hypoxemia resulting from CHD (cardiac system), leads to impaired CA, affecting cerebral circulation and oxygenation (nervous system), which was demonstrated by abnormal neurobehavioral status (muscular). Another study assumption was that blood pressure momentarily decreases (due to forces of gravity) during the postural change (from supine to sitting) because of hydrostatic pressure. Lastly, it was assumed that inadequate cerebral tissue perfusion leads to hypoxia, resulting in tissue injury and/ or death, and changes in neurobehavioral status.

Chapter Summary

Neonates with CHD are at risk for altered cerebral blood flow and oxygenation; which may lead to impaired CA and poor brain tissue perfusion. Decreased blood flow and oxygenation may occur in different areas of the brain, such as the basal ganglia and thalamic regions, which control motor and homeostatic mechanisms. The damage potentiates cerebral tissue injury and may lead to alterations in neurobehavioral status. The body systems framework guides this study, and explains interactions between the cardiac and respiratory; cardiac and nervous; and nervous and musculo-skeletal systems. Interactions between the systems reflect changes in CA and neurobehavioral status. An echocardiogram confirmed CHD (cardiovascular status). The rSO₂ measured by NIRS indicated whether CA is intact or impaired (cerebral status). The ENNAS measured neurobehavioral status (motor, auditory, visual responses). If preoperative neonates with CHD have impaired CA, findings from the study may be used to change practice, such as maintaining higher mean blood pressures or routinely performing preoperative neurobehavioral assessments. The study on CA may lead to future research identifying whether improving autoregulation (with

interventions such as magnesium, statins, or green tea extracts) is an approach that may increase outcomes in the CHD population.

CHAPTER FOUR: METHODS

The purpose of this study was to evaluate whether preoperative neonates with congenital heart disease (CHD) have impaired cerebrovascular autoregulation (CA) and to examine if CA was associated with neurobehavioral status. First, the study compared preoperative neonates with CHD and healthy neonates (independent variable [IV]), who were less than or equal to 12 days of life, and the status of CA (dependent variable [DV]), using regional cerebral oxygenation (rSO₂) measured by near infrared spectroscopy (NIRS). The study tested the hypothesis that the proportion of preoperative neonates with CHD and impaired CA was greater than the proportion of healthy neonates with impaired CA. Second, the study examined associations between impaired CA (IV) and abnormalities in motor, auditory, and visual function (DVs) when controlling for preoperative neonates with and without CHD. The study tested the hypothesis that preoperative neonates with CHD and impaired CA had poorer total Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) scores and had poorer scores in motor, visual, and auditory functions than healthy neonates. Third (exploratory aim), the study assessed whether impaired CA was associated to clinical factors such as: 1) Apgar scores, 2) acidosis, 3) head circumference, and 4) birth weight when controlling for age and gender in neonates with and without CHD. The study tested the hypothesis that neonates with impaired CA had associations with one of the following: 1) low Apgar scores, 2) positive history of acidosis, 3) small head circumference, or 4) low birth weight.

Design

The proposed study used a comparative, observational design, using two groups of neonates; one group was neonates with CHD and the second group was healthy neonates without CHD. Observations and measurements were taken at two time periods, first at baseline or supine

position, and second after a change from supine to the sitting position. The duration of observation will be five minutes for each time period.

Population & Setting

The CHD sample was recruited prenatally from the Heart Institute at Children's Hospital Los Angeles (CHLA) at the following sites: 1) Institute for Maternal Fetal Health (IMFH) for neonates with prenatal diagnosis of CHD; 2) Cardiothoracic Intensive Care Unit (CTICU) for neonates with CHD requiring intensive care; and 3) Cardiovascular Acute (CVA) for neonates with CHD needing acute care. The Heart Institute of CHLA has the largest volume of CHD patients in Southern California and performs approximately 250 to 275 neonatal cardiac surgeries per year. The diagnoses ranged from simple CHD, such as atrial septal defects (ASD), ventricular septal defects (VSD), and coarctations of the aorta; to complex CHD, such as hypoplastic left heart syndrome (HLHS), truncus arteriosus, and transposition of the greater arteries (TGA).

Neonates without CHD or "healthy neonates" were recruited from the Alta Med well baby clinics and from employees at CHLA. The recruitment sites provided an adequate number and ethnically diverse sample. The principal investigator (PI) sought approval for recruitment from respective units at each institution prior to data collection. The PI holds an appointment at CHLA.

Sample Selection

The inclusion criteria for neonates with CHD diagnosis were: 1) less than or equal to 12 days of age before cardiac surgery; 2) gestation greater than or equal to 37 weeks; 3) with heart defects (structural problems that are present at birth, which can involve: interior walls of the heart, valves inside the heart, and/ or arteries and veins that carry blood to the heart or the body);

and 4) hemodynamic stability. All neonates regardless of type of CHD (acyanotic vs. cyanotic; simple vs. complex) will be included. The exclusion criteria were: 1) any documented genetic syndromes (e.g. Down's, Trisomy 18, Trisomy 13, CHARGE, Cri du Chat, Turner, Fragile X, Trisomy X, and Prader Willi); 2) vasopressor support (e.g. dopamine); 3) intubated on mechanical ventilation; 4) on antibiotics for a documented infection, 5) documented intraventricular hemorrhage (IVH); 6) documentation of infant of substance abusing mother (ISAM); 7) documentation of maternal chorioamnionitis; 8) documentation of steroids (maternal use in the last trimester or neonatal use); and 9) documented intrauterine growth restriction (IUGR) or small for gestational age (SGA). The exclusion criteria were chosen to minimize the variability in CA. Given these criteria, and based on previous experience with recruitment using similar standards, approximately 2-3 neonates per month were eligible for this study.

Inclusion criteria for neonates without CHD were: 1) neonates less than or equal to 10 days old and 2) no documented pre- or postnatal medical conditions. Exclusion criteria were: 1) identified genetic syndromes; 2) on antibiotics for a documented infection; 3) documented IVH; 4) documentation of ISAM; 5) documentation of maternal chorioamnionitis; 6) documentation of maternal use of steroids in the last trimester; and 7) documented IUGR or SGA.

Sample Size

Power analyses were run from G*Power (version 3.1) for the three aims and were calculated using an alpha of 0.05 and power of 0.80 (Faul, Erdfelder, Buchner, & Lang, 2009). For specific aim #1: to compare CA (using rSO₂ measured by NIRS) between groups, a χ^2 with 1 degree of freedom was used to determine total sample size of 32 subjects to detect a large (0.5) effect size. A large effect size is reasonable based on previous studies in patients with CHD, demonstrating significant differences compared to controls (Al Nafisi et al., 2013; Arduini et al.,

2011; Paquette et al., 2013). Arduini et al. (2011) found large effects when comparing cerebral placental ratios (Cohen's d 0.9), ratios of head to abdominal circumference (0.9), and mean umbilical artery velocity (0.8) in CHD and control fetuses. Similarly, Al Nafisi et al. (2013) found significant differences ($p < .01$) in ventricular outflow of 22 fetuses with left sided CHD compared to 12 healthy fetuses. Paquette et al. (2015) also found large effects (0.75) when comparing fractional anisotropy with cerebral MRI's in 21 preterm neonates with CHD and 27 controls. In the adult population, Salinet, Robinson, and Panerai (2015) found a large effect (0.79) in patients with stroke compared to controls. No studies compared CA in CHD and healthy neonates, thus effect sizes were based on studies with similar populations or topic.

For specific aim #2: to examine associations between impaired CA and abnormalities in motor, auditory, and visual function (using scores on the ENNAS), multiple linear regression was used to determine a total sample size of 25 subjects to detect a large (0.35) effect size. For the neurobehavioral assessment, a large effect size is reasonable because previous studies in CHD neonates compared to healthy controls demonstrated (Cohen's d 1.9) significant differences in total abnormal scores with the ENNAS (Limperopoulos et al., 1999; Majnemer & Limperopoulos, 1999). Additionally, Majnemer, Rosenblatt, and Riley (1993) showed significant differences in abnormal scores, behavior, and tone ($p < .001$) between 74 high risk and 37 healthy neonates using the ENNAS. Effect size could not be calculated; however, the low p value gives a high level of confidence for large effects.

For exploratory aim #3: to identify clinical factors associated with impaired CA, logistic regression was used to determine a total sample size of 67 subjects to detect a large (0.5) effect. However, the study was not based on this power analysis.

Overall, for a large effect size, a minimum of 32 subjects is required. Previous research, in CA with preoperative CHD neonates from Dr. Jodie Votava-Smith at CHLA, demonstrated recruitment rate of 24 neonates in two years, an average of two neonates with CHD per month. Due to time constraints (limited time of only 8 months for recruitment) and lack of resources, a pilot sample may need to be decreased to a total sample size of 24 subjects (12 CHD and 12 healthy controls). However, all attempts were made to recruit as many subjects as possible during the time period.

Procedures

After receiving approvals from CHLA and the University of California, Los Angeles (UCLA) institutional review boards (IRBs), the procedures detailed below were implemented. The PI performed all of the data collection and study procedures. Refer to appendix A for UCLA IRB approval.

Information Session & Training of Research Team Members

The PI met with physicians, nurse practitioners, and nurses at CHLA to provide study information, recruitment, enrollment, and data collection procedures. The information sessions took place before or after change of shift; and took approximately 5 to 10 minutes. A one page study summary (Appendix B) and copies of study flyers (Appendix C for CHD and D for healthy neonates) were circulated and distributed.

Screening & Recruitment

The PI accessed electronic medical records to identify neonates meeting age and diagnosis criteria. A waiver of consent was obtained to assess study eligibility (see Appendix E for the screening form). The appropriate primary health care provider was notified of eligible patients in order to request permission to approach parent(s)/legal guardian. Study recruitment

flyers (Appendix C and D) were distributed to parents. Parents of potentially eligible neonates were approached during prenatal visits in coordination with a nurse care manager at the IMFH, Heart Institute, or with the cardiologist. A copy of the telephone screening script is located in Appendix F.

Information & Consent

At a mutually agreed upon time (in a private and quiet location), the PI explained detailed study information and allowed parents to ask questions and express concerns. Time was given for parents to discuss with family members and the health care team as needed. Parent(s)/ legal guardian were allowed to make a decision to participate between the time study information was provided up until the neonate was 12 days old. If the parent(s)/ legal guardian agreed to participate, all study procedures were explained as outlined in the consent form. When parents agreed, consents were signed (see Appendix G for the consent).

Enrollment Procedures

Enrollment occurred after signing of consents. The PI informed the health care provider of the neonate's participation. Study participation was one time (cross sectional), indirectly measuring CA, performing the neurobehavioral assessment, and obtaining clinical and demographic information from medical records.

Data Collection Procedures

After enrollment, the PI notified the bedside RN of patient enrollment in the study. The PI coordinated an optimal time for performing study procedures (e.g. not within 1 hour of an invasive procedure, such as line placement or transportation off of the floor). The procedures occurred in three phases: 1) preparation of the neonate; 2) collection of clinical variables and data from observations of the neonate in supine and sitting position; and 3) collection of

demographics and clinical information from medical records. The procedures are described below.

Preparation (25 minutes)

1. Placed rSO₂/ NIRS sensor on the center of the neonate's forehead.
2. Placed pulse oximetry sensor on the neonate's right hand. The right hand was used due to its close proximity to cerebral arterial oxygen saturation (see Appendix H for a diagram with sensor placements on the neonate).
3. Connected pulse oximeter and NIRS sensors to respective monitors (see Appendix I for an image of the NIRS sensor and monitor).
4. Connected monitor cables to the Cardiopulmonary Corporation (Bernoulli) data acquisition system, and ensured the recording system was functioning properly.
5. Assessed for tension on any tubing (if applicable) or monitor cables.
6. Assessed neurobehavioral status using the ENNAS (see Appendix J for the ENNAS).

Collection of Clinical Variables (15 minutes)

1. Monitored and recorded rSO₂, oxygen saturation, heart rate, respirations, blood pressure (if applicable), neonate's state/ behavior, and room conditions (see Appendix K for the procedure form) while patient is in supine position (5 minutes).
2. After 5 minutes, placed the neonate in a sitting (90°) position, supporting the back, shoulders, posterior aspect of the neck, and occipital area of the head in alignment with left hand; the chest with right hand; and the chin and frontal portion neck, with the thumb and middle finger. Position changes from supine to sitting are part of routine care, such as diaper changes, bathing, holding, or burping, and should not lead to unnecessary stress to the neonate.

3. Monitored and recorded rSO₂, oxygen saturation, heart rate, respirations, blood pressure (for the inpatient participant's), neonate's state/ behavior, and room condition (e.g. single or double room and noise level) while patient is in sitting position (5 minutes).
4. After 5 minutes, removed sensors, and repositioned neonate for comfort. Notified the bedside RN of completion of data collection for the study.

Collection of Demographics & Medical Information (30 minutes)

Electronic medical records were reviewed to collect neonatal and maternal demographic and clinical information. Systematic collection of neonatal and maternal information was performed using the Medical Abstraction Form (Appendix L). Maternal information included pregnancy and birth history, maternal complications, pregnancy exposures, maternal medications, and comorbidities from the medical record and from the mother (for information not available in the medical record). Neonatal information included birth and medical history, ethnicity, gender, and age. For neonates with CHD, clinical information included cardiac anatomy, birth history, comorbidities, current medications, lab values (hematocrit, lactate, blood gas values, and total bilirubin), oxygen saturation, and medical interventions from date of admission to enrollment date.

Instruments & Measures

Cerebrovascular Autoregulation (NIRS)

The Covidien INVOS Somanetics NIRS 5100C (Minneapolis, MN) is a noninvasive device used to measure rSO₂ (Alderliesten et al., 2013; Brady et al., 2010; Scheeren et al., 2012). Comparison rSO₂ values, from supine to sitting, were used as an indirect measurement of CA. The rSO₂ reflects tissue oxygenation in the capillary, venous, and arterial vasculature (Ito et al.,

2005). The NIRS proprietary algorithm uses the Beer-Lambert law stating light absorption is proportional to the concentration of a light absorbing substance (i.e. oxygenated and deoxyhemoglobin) and the length the light has to travel (i.e. cerebral blood flow/volume). Thus, changes in oxygenated and deoxyhemoglobin in the cerebral microvasculature and cerebral blood volume are reflected in the rSO₂ value (Kainerstorfer et al., 2015; Ohmae et al., 2006). The rSO₂ will decrease with lower hemoglobin concentrations and vasodilation. Similarly, an increase in rSO₂ will reflect increased hemoglobin and vasoconstriction. The rSO₂ value remaining relatively constant despite changes in systemic blood pressure reflects an intact CA. On the other hand, rSO₂ values fluctuating with changes in systemic blood pressure reflects impaired CA. Studies support using INVOS NIRS to measure CA in neonates and it is the most widely used device in published studies (Alderliesten et al., 2013; Brady et al., 2010; Buckley et al., 2010; Ono et al., 2013).

The biomedical engineering department at CHLA performs annual maintenance and quality controls for the NIRS device. The PI ensured the NIRS devices used in the study have annual maintenance completed before study procedures begin. The manufacturer calibrates the device and sensor, and an identifying number in the sensor allows a second calibration when connected to the NIRS monitor. The INVOS NIRS internally performs quality controls when the device powers on. The NIRS is the standard device for measurement of rSO₂ during cardiac surgery and in intensive care units for neonates at CHLA. Manufacturer target and threshold levels are numeric values and percentage change, with typical values ranging from 60-80. Levels less than 50 or greater than 20% change are triggers for intervention. Images of the sensor and monitor are located in Appendix I.

NIRS Measure of CA

The study tested for impaired CA in neonates by changing position, from supine to sitting, to induce a blood pressure change. It was assumed that blood pressure changed due to forces of gravity during the postural change (Czosnyka & Miller, 2014). In order to measure dynamic CA, rSO₂ baseline values must be recorded and measurements need to be taken within 15 seconds after a steep blood pressure change (Kainerstorfer et al., 2015). Baseline rSO₂ values in preterm and term neonatal populations were low when values are 45 to 65, medium when values were 65 to 85, and high when values were 85 to 95. However, evaluation of CA was not determined by low, medium, or high values, but how values return to baseline after the postural change (Alderliesten et al., 2013; Hoffman et al., 2013; Howlett et al., 2013; Pichler et al., 2013). CA was defined as intact if the rSO₂ returns to the baseline in less than or equal to 5 seconds after the postural change (sitting). CA was defined as impaired in neonates if rSO₂ values take greater than 5 seconds to return to baseline.

NIRS Validity

Previous studies demonstrated validity of INVOS NIRS in neonates and pediatrics. A study in 31 children with CHD, undergoing cardiac catheterization, showed rSO₂ significantly correlated ($r = 0.83, p < 0.0001$) to venous bulb saturation and central venous oxygen saturation ($r = 0.93, p < 0.0001$) (Nagdyman et al., 2008). Additionally, Wagner et al. (2011) examined CA by inducing blood pressure changes with intravenous phenylephrine in 24 neonatal and pediatric patients in the intensive care unit using a correlation of rSO₂ to cerebral blood flow. Cerebral deoxygenated hemoglobin signal and direct cerebral blood flow had significant correlations. Spearman's rank correlation coefficient between the change in the hemoglobin difference and

total, to the blood flow index was 0.78 and 0.73. Findings from these studies support validity of rSO₂ measured by NIRS as an indirect measure of CA.

NIRS Reliability

Previous studies demonstrated reliability of NIRS in preterm neonates, term neonates, and pediatrics. Pellicer et al. (2005) studied CA in 59 preterm neonates on vasopressor support using rSO₂ measured by NIRS. Changes in mean arterial blood pressure (MABP) with epinephrine and dopamine were significantly correlated with changes in rSO₂ in preterm neonates during different time intervals ($r = 0.28$; $p = .03$) and ($r = 0.32$; $p = .013$) (Pellicer et al., 2005). Another study in 142 preterm neonates requiring intervention for low blood pressure compared with preterm controls without anti-hypotensive medications demonstrated similar results. No significant change occurred in rSO₂ with a mean of 68% (range 48%–90%) before treatment versus mean of 69% (range 50%–89%) after treatment (Bonestroo, Lemmers, Baerts, & van Bel, 2011). In the pediatric CHD population, Abdul-Khaliq, Troitzsch, Berger, and Lange (2000) found correlations between rSO₂ and jugular bulb oximetry ($r = 0.93$, $p < 0.001$) in 30 infants and children (mean age 4.5 years) undergoing cardiac catheterization. Findings from these studies support reliability of NIRS.

NIRS Sensitivity & Specificity

The INVOS NIRS manufacturer's manual provided sensitivity and specificity information. In 50 adult patients undergoing carotid endarterectomy (CEA), sensitivity and specificity of rSO₂ were evaluated for detecting post-CEA hyperperfusion (100% and 86.4%, respectively), with a cutoff point of 5% (Ogasawara et al., 2003). The 5% cutoff point was also used in the study because the literature and manufacturer support this level. However, information regarding cerebral rSO₂ accuracy is challenging because there is no true reference

value (per INVOS NIRS manufacturer pocket guide). The United States Food and Drug Administration uses a proxy called fSO₂, which is an estimate of arterial and venous blood. The manufacturer uses fSO₂ in the proprietary algorithm to calculate rSO₂. The manufacturer does not provide information on neonatal sensitivity and specificity levels.

Arterial Oxygenation (Pulse oximetry)

The Masimo Radical 7 pulse oximeter (Irvine, CA) is the standard device used for measurement of arterial oxygen saturation (SpO₂) at CHLA. Oxygen saturation was expected to be greater than 95% for healthy controls. In neonates with cyanotic CHD, oxygen saturations of 75% to 85% were not unusual because of mixture of venous and arterial blood. Reliability and validity of the Masimo pulse oximeter for measurement of arterial oxygenation were demonstrated in 225 mechanically ventilated neonates and pediatrics with arterial lines (Ross, Newth, & Khemani, 2014). The SpO₂ measurements from the pulse oximeter highly correlated with oxygenation from arterial lines with the SpO₂ range from 91% to 97%.

Neurobehavioral Assessment (ENNAS)

The ENNAS is a series of standard measurements originally developed by neurologists (Kurtzberg et al., 1979) at the Albert Einstein College of Medicine in New York to evaluate motor, auditory, and visual function in infants less than 30 days old (see ENNAS in Appendix J). The ENNAS also includes four summary items representing cuddliness, spontaneous movements, tremor, and tone. Scoring individual items range from 0 (absent) to 18 (increasing responses). However, not all items were used for the total composite score, only 22 items were scored per the tool developer's scoring. Total scores with greater than or equal to 7 items outside the norm (or $\geq 32\%$) signify abnormal neurobehavioral status. Total scores with three to six items outside the norm (or 14% to 27%) indicate borderline abnormal neurobehavioral status.

Total scores with less than or equal to two items outside the norm (or 9 %) are indicative of normal neurobehavioral status (Majnemer & Snider, 2005). Administration of the ENNAS does not require certification and completion takes approximately 15-30 minutes.

Motor Function

Motor functions consisted of 19 items, with only 15 items scored. The motor functions included: 1) head control (head extension, head lag, active head extension (prone [not scored]), and ventral suspension); 2) reflexes (rooting, sucking, arm recoil, grasp, Moro reflex, and tonic neck reflex); and 3) muscle strength and movement (lateral position preference [not scored], traction, withdrawal [not scored], popliteal angle, extremity movement [prone], tone, spontaneous movement, tremor [not scored], and cuddliness). Scores range from 0 (absent) to 3 (increasing responses). Items were then evaluated as scores within normal or outside the normal range based on previously published norms (Kurtzberg et al., 1979).

Auditory Function

Auditory functions represented responses to three auditory stimuli (rattle, bell, and voice). Items representing auditory functions were scored as 0 (no response) to 18 (increasing responses), for a possible total score of 54. A total score less than 40 is outside the range of normal. Individual items for the bell and voice stimuli have a minimum score of 10, and the rattle has a minimum of 13 to be within norms (Kurtzberg et al., 1979).

Visual Function

Visual functions represented responses to four visual stimuli (bull's eye, face-voice, optic blink, and rotation). Items representing visual function were scored as 0 (no response) to 24 (increasing responses). A total score of less than 29 for the bull's eye, and face – voice stimuli were outside the range of normal. Individual scores for bull's eye and face-voice stimuli with a

minimum score of 13 were within norms. Similarly, for optic blink and rotation stimuli, the individual scores with a minimum of 1 were within norms. Scoring of the items was based on recommendations by the original authors of the ENNAS (Kurtzberg et al., 1979).

Validity

Validity of the ENNAS was tested in term neonates with CHD, using a neurologic exam (Limperopoulos et al., 1997; Limperopoulos et al., 2000; Majnemer et al., 2009). Abnormal results using the ENNAS highly correlated with abnormal neurologic exams, showing agreement at 96.9% and kappa = 0.94 (Limperopoulos et al., 1997; Limperopoulos et al., 2000). Majnemer et al. (1993) reported evidence of discriminative validity of the ENNAS indicating abnormalities in 74 high risk neonates, while also showing normal findings in healthy neonates ($p < 0.05$). Wallace, Rose, McCarton, Kurtzberg, and Vaughan (1995) reported predictive validity with the ENNAS. Visual and auditory abnormalities in 144 very low birth weight preterm neonates significantly correlated with lower cognitive scores during reassessments at 1 and 6 years of life ($p < 0.05$). Inter-rater reliability ($r = 0.97$) has been demonstrated in 118 low birth weight neonates at 40 weeks corrected gestational age, and 76 full term neonates (Kurtzberg et al., 1979).

Procedure for Data Analyses

All data was entered and analyzed using Statistical Software for Social Sciences (SPSS v.22, Chicago, IL). Descriptive statistics (frequencies, percentages, means, and standard deviations) were used for demographic variables.

Specific Aim 1

To compare preoperative neonates with CHD and healthy neonates less than or equal to 12 days of life (independent variable [IV]) and CA status using rSO₂ measured by NIRS

(dependent variable [DV]). CA will be defined as intact if rSO₂ returns to the baseline in less than or equal to 5 seconds following the postural change (sitting). The χ^2 or Fisher's exact tested the hypothesis that the proportion of preoperative neonates with CHD who show evidence of impaired CA is significantly greater than the proportion of neonates without CHD.

Specific Aim 2

To examine associations between impaired CA (IV) and abnormalities in DVs motor, auditory, and visual function when controlling for neonates with and without CHD. Multiple linear regression models tested the hypothesis that preoperative CHD neonates with impaired CA will have associations with poorer ENNAS total scores (a higher % of abnormal ENNAS scores) and poorer scores of the either the motor, visual, and auditory stimuli.

Exploratory Aim 3

To identify clinical factors such as: 1) Apgar scores, 2) acidosis, 3) head circumference, and 4) birth weight, associated with impaired CA when controlling for age and gender in neonates. Normal logistic regression tested the hypothesis that preoperative neonates with impaired CA were associated with any of the following: 1) Apgar scores, 2) cord blood pH, 3) birth head circumference, or 4) birth weight.

Study Limitations

Threats to Internal Validity

One potential threat to internal validity is instrumentation. Only one method of measuring CA was implemented and was not compared to another standard measure. However, some CHD neonates with arterial lines will have CA measured with a second method. Thus, comparisons can be made between the two methods of measuring CA in those particular neonates. A second threat to internal validity is selection bias. All CHD neonates will be included regardless of the

type of CHD (acyanotic vs. cyanotic; simple vs. complex). For example, neonates with left ventricular outflow tract obstruction, such as coarctation of the aorta and hypoplastic left heart are included; these types of defects may have increased disposition for impaired CA due to physiology of the heart defect. However, it is unclear whether neurobehavioral abnormalities are associated with these types of heart defect (Limperopoulos et al., 2000). Since neurobehavioral abnormalities were present in both cyanotic and acyanotic CHD, all neonates with CHD, regardless of type of defect were included.

Threats to External Validity

Since CHLA is not a birthing center, healthy controls were recruited from Alta Med and from employees. Attempts were made to maintain a constant environment at the differing locations. For example, study procedures were performed in a calm environment (e.g. dimming lights and waiting at least 1 hour after an invasive procedure). A threat to external validity was that CHD and healthy samples may not be representative of different ethnicities because of the limited sample size. Attempts were made to recruit an ethnically diverse sample of neonates with and without CHD in order to increase generalizability of results. Another threat was the small sample size due to restricted recruitment time and limited resources. Attempts were made to recruit the minimum of 32 subjects. The last threat to external validity was the possibility of age- and gender- controls not matching due to difficulties in recruiting neonates less than 12 days old. Attempts were made for age- and gender- matching; however, subjects were not excluded if these criteria were not met.

Protection of Human Subjects in Research

Human subject protection approval was obtained from UCLA and CHLA IRBs. The PI complied with the Collaborative Institutional Training Initiative (CITI) Human Subjects

Research course and the Health Insurance Portability and Accountability Act (HIPAA) certification at all institutions.

Parents of neonates were informed that: 1) study participation was voluntary; 2) the care of the neonate was not be compromised if the parent refused to participate; and 3) the parent had the right to decline to answer any questions or withdraw from the study at any time. A written explanation of study objectives, protocol, and researcher affiliation was provided during the informed consent process.

Privacy & Confidentiality

The PI requested a waiver of HIPAA authorization for eligibility screening, but obtained HIPAA permission for study participation. The private health information (PHI) collected for this study was not to be reused or disclosed, except as indicated in the IRB application. The PI followed the data security plan outlined in the IRB application to protect identifiers from improper use or disclosure.

The study recruited neonates, who are considered a vulnerable population. Information obtained during the study procedures were kept confidential. All personal information was coded to protect the participant's anonymity. Electronic data was stored in an encrypted storage device and a computer with password protected software. A hard copy of data including personal or private identifiable data was stored in a locked file cabinet in a locked office with limited access to the PI or study members. After study completion, all data files were stripped of personal identifiers per institutional protocols. Precautions were taken to minimize the risk of breach in confidentiality by following good clinical practices, hospital policies, and safety precautions in data storage.

Potential Risks & Discomforts

Though risks were minimal, potential risks associated with study participation were: 1) breach in confidentiality; 2) erythema or rash related to rSO₂/ NIRS sensor placement on the skin; 3) discomfort during movement or neurobehavioral assessment; 4) oxygen desaturation during agitation or movement; and 5) the rare chance of line dislodgement. Precautions were taken to minimize these risks. To minimize risk of erythema or rash, sensor application followed manufacturer and institutional guidelines. If rash or erythema occurred, the attending physician was notified for further evaluation and treatment, if necessary. Comfort measures were provided to neonates such as gentle talking, rocking, patting, giving the pacifier, or gloved finger in order to minimize discomfort or oxygen desaturation during agitation or movement. Parents were also able to console neonates during the neurobehavioral assessment. In the intensive care units, the neonate's bedside nurse was present during all study procedures to administer or titrate oxygen as needed. The PI withdrew neonates unable to be consoled or calmed within 10 minutes during study procedures. If the neonate had intravenous or umbilical lines, the PI ensured an adequate amount of tubing length to minimize dislodgement with position change. Line dislodgement is a normal risk associated with routine care during hospitalization, such as during position changes, diaper changes, bathing, holding, or burping the neonate.

Potential Benefits

There was no direct benefit to the parent or neonate in participating in the research study. However, the potential benefit to society was increased knowledge related to CA and associations of CA to neurobehavioral status in the neonatal population.

Risk & Benefit Analysis

The benefits outweighed the risks in the proposed study. The potential benefit to society was increased knowledge possibly leading to the development of a new treatment or therapy to improve CA or minimize risk for impaired CA. In addition, although individual neonates may not have benefited from participation, results of this study made important contributions to understanding potential causes of neurologic deficits in children with CHD. The risk/benefit ratio was favorable for this study and adverse events are not anticipated. Postural changes are routine in caring and handling of neonates.

Payment to Participants

Parents of neonates received a \$50 Target gift card upon completion of all study measures. Participants with partial completion of study measures received a \$25 Target gift card. The amount was minimal, reducing the possibility of monetary coercion related to recruitment, and was a small token of appreciation for participation in the study.

Costs of Participation

All procedures and uses of equipment were performed at no financial cost to the family. There were no other costs associated with participation in the study.

Treatment & Compensation for Injury

If neonates were injured as a result of being in this study, the attending physician would prescribe treatment. Parents were informed that financial compensation was not available in the event of injury during participation in the research. Parents were instructed to call and notify the attending physician immediately if parents believe the neonate was injured during study participation.

Chapter Summary

The methods chapter presented the design, sample, settings, data collection procedures, and planned data analyses. Reliability and validity of NIRS to measure CA and the ENNAS to measure neurobehavioral status were presented. The data analyses plan described the proposed statistical tests to achieve study aims. Lastly, limitations of the study were included, addressing the internal and external validity of the study. Findings from the study increased knowledge about CA in neonates with CHD and may lead to the development of a new treatment or therapy to improve CA or minimize risk for impaired CA, and thereby improving neurobehavioral outcomes in neonates with CHD.

CHAPTER FIVE: RESULTS

This chapter presents the findings of the study. Section one describes the study participants and physiologic measures, and section two describes participant's neurodevelopmental (ND) status. Section three addresses the research aims: 1) comparing cerebrovascular autoregulation (CA) status between congenital heart disease (CHD) and healthy neonates; 2) CA and the association to ND status; 3) CA impairment and associations to clinical factors. Section four covers the secondary analyses including assessments of potential confounding factors.

Sample Characteristics

The total sample size was 44 neonates, 28 had CHD and 16 were healthy.

Chromosomal Anomalies

Five neonates had chromosomal anomalies including chromosomal duplications and deletions that were discovered after enrollment. Two neonates had deletions (q 24.3 on Chromosome 2; 22q Di George) and three had duplications (867 Kb - 4q34.3 and 68Kb - X p11.22); 16p13.11 and 47 XYY; 6q24-q26).

Birth Measures

The sample's birth weight (2.2 to 4.4 kilograms), length (44 to 58 centimeters), and head circumference (29 to 38 centimeters) were within normal ranges in both groups. Table 5-1 illustrates the sample's characteristics separated by healthy and CHD groups. There was a significant difference in mean ages between the healthy (6.9 ± 2.6 days) and CHD (2.9 ± 2.8 days) groups. The CHD group was significantly younger, about 3 days old, compared to the controls that averaged 7 days of age ($p < .000$). Figure 5-1 demonstrates the distribution of ages

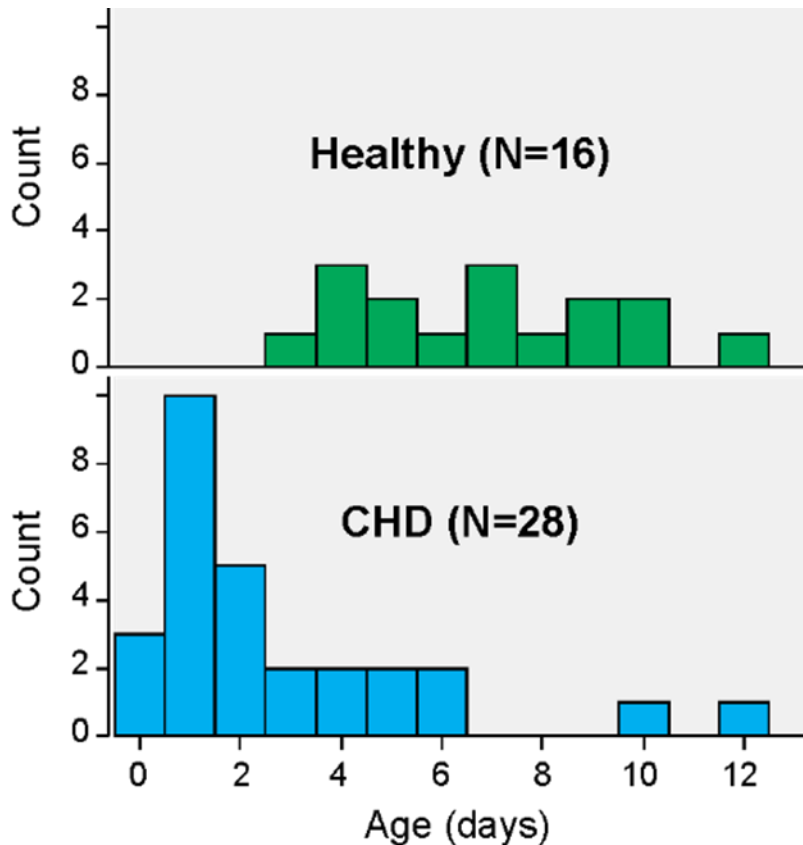
between the two groups. However, there were no significant differences in weight, length, head circumference, gestational age at birth and at time of exam, and in the one minute Apgar scores.

Table 5-1. Participant characteristics by group. Difference p values were based on independent samples t-test comparison of means.

Variable	Healthy			CHD			p value
	Mean	± SD [Range]	N	Mean	± SD [Range]	N	
Age (days)	6.9	± 2.6 [3-12]	16	2.9	± 2.8 [0-12]	28	.00*
Weight (kg)	3.29	± .39 [2.7-4.0]	15	3.36	± .61 [2.2-4.3]	28	.70
Birth Length (cm)	50	± 2.7 [44.5-55.3]	15	50	± .13 [45-58.4]	28	.70
Birth Head Circ. (cm)	34.5	± 1.36 [32-36.5]	10	34.4	± .09 [29.5-38]	28	.92
Birth Gest. Age (weeks)	39	± 1.16 [36.2-40.5]	15	39	± .94 [37-41]	28	.87
Exam Gest. Age (weeks)	40	± 1.21 [37.5-41.4]	15	39.4	± .08 [37-42.1]	28	.18
Apgar (1 min)	8.2	± .63 [7-9]	10	7.7	± .73 [1-9]	27	.39

* = $p < 0.05$

Figure 5-1. Distribution of Age by Group



Gender & Ethnicity

There were significantly more females (75%) in the healthy group. The CHD group had significantly more males (67.9%, $p = .01$). There were significantly more Caucasian's (46.7%) in the healthy group and more Latino's (68%, $p = 0.03$) in the CHD group. Table 5-2 demonstrates the sample's ethnicity and gender.

Table 5-2. Gender & ethnicity characteristics by group. p-values for group differences in distributions assessed with Chi-square test.

Variable	Healthy N (%)	CHD N (%)	Total	p value
	16 (36.4%)	28 (63.6%)	44	
Gender				.01*
Male	4 (25%)	19 (67.9%)	23 (52.3%)	
Female	12 (75%)	9 (32.1%)	21 (47.7%)	
Race				.03*
Caucasian	7 (46.7%)	6 (21.4%)	13	
Latino	3 (20%)	19 (67.9%)	22	
Asian	2 (13.3%)	1 (3.6%)	3	
Other	4 (25%)	2 (7.1%)	6	

* = $p < 0.05$

Congenital Heart Disease Neonates

There were wide variations in the type and severity of cardiac defects. Many had either D- transposition of the greater arteries (D-TGA) ($n = 5$; 17.9%) or hypoplastic left heart syndrome (HLHS) ($n = 5$; 17.9%). Some of the other defects were double outlet right ventricle ($n = 2$; 7.1%), double inlet left ventricle ($n = 2$; 7.1%), tetralogy of fallot ($n = 2$; 7.1%), tricuspid atresia ($n = 2$; 7.1%), coarctation of aorta ($n = 2$; 7.1%), or ventricular septal defect and interrupted aortic arch ($n = 2$; 7.1%). Table 5-3 displays the variety of cardiac defects. The majority of the CHD neonates (78.6%) had cyanotic heart lesions. Table 5-4 shows the percentages of cyanotic heart disease participants.

Some neonates with CHD ($n = 11$; 39%) were on noninvasive supplemental oxygen, ranging from minimal support such as nasal cannula (NC) ($n = 3$) to higher support such as nasal

cannula intermittent mechanical ventilation (NCIMV) (n = 4; 14%). Three CHD neonates were on high flow nasal cannula. One CHD neonate was on nasal continuous positive airway pressure.

Table 5-3. Cardiac Diagnosis for the Congenital Heart Disease Group

Cardiac Defect	CHD N (%)
Tricuspid Atresia	2 (7.1%)
Double Inlet Left Ventricle (DILV)	2 (7.1%)
Double Outlet Right Ventricle (DORV)	2 (7.1%)
D- Transposition of Greater Arteries (TGA)	5 (17.9%)
Truncus Arteriosus	1 (3.6%)
Tetralogy of Fallot (TOF)	2 (7.1%)
Hypoplastic Left Heart Syndrome (HLHS)	5 (17.9%)
Tricuspid Atresia/ Hypoplastic Right Ventricle (HRV)	1 (3.6%)
Aortic Stenosis (AS)	1 (3.6%)
Coarctation of the Aorta (COA)	2 (7.1%)
Heterotaxy	1 (3.6%)
Shone's Complex	1 (3.6%)
Ventricular Septal Defect (VSD)/ Interrupted Aortic Arch (IAA)	2 (7.1%)
Cor Triatriatum	1 (3.6%)

Table 5-4. Percentage of Cyanotic Heart Lesions

Group	Healthy	N	birth cyanosis		Total
			No	Yes	
			16	0	16
		% within Group	100.0%	0.0%	100.0%
		% within birth cyanosis	72.7%	0.0%	36.4%
	CHD	N	6	22	28
		% within Group	21.4%	78.6%	100.0%
		% within birth cyanosis	27.3%	100.0%	63.6%
Total		N	22	22	44
		% within Group	50.0%	50.0%	100.0%
		% within birth cyanosis	100.0%	100.0%	100.0%

Physiologic Measures & Regional Cerebral Oxygenation (rSO₂)

There were significant differences in the regional cerebral oxygenation (rSO₂) in the supine position between the healthy (80.6 ± 7.9) and CHD groups (68.0 ± 9.7). The rSO₂ values were also significantly lower in the CHD group in the sitting position. The average 1 minute supine (80.3 ± 7.75 vs 68.9 ± 9.8) and 30 second sitting rSO₂ (80.4 ± 8.1 vs 67.3 ± 10.3, *p* < .000) also indicated significant group differences. Table 5-5 shows the rSO₂ of the two groups in the different positions. Figure 5-2 shows the distribution of supine rSO₂ by group. The healthy neonates (individually) had a higher supine rSO₂ compared to the CHD. Additionally, Figure 5-3 gives a visual depiction of the actual values of lower mean rSO₂ for CHD participants compared to healthy controls.

Table 5-5. rSO₂ by group. Difference *p* values were based on independent samples t-test comparison of means.

Variable	Healthy			CHD			<i>p</i> value
	Mean	± SD	<i>N</i>	Mean	± SD	<i>N</i>	
Supine rSO ₂	80.62	7.88	16	68.04	9.74	28	.00*
Sitting rSO ₂	81.58	7.35	16	67.25	10.23	28	.00*
rSO ₂ Supine and Sitting Diff.	0.94	1.01	15	1.43	1.35	28	.23
1 min. Avg. Supine rSO ₂	80.35	7.45	16	68.88	9.81	28	.00*
30 sec. Avg. Sitting rSO ₂	80.47	8.12	16	67.30	10.34	28	.00*
Avg. rSO ₂ Diff.	.12	.67	16	2.03	1.68	28	.34

* = *p* < 0.05

Figure 5-2. Distribution of rSO₂ by Group

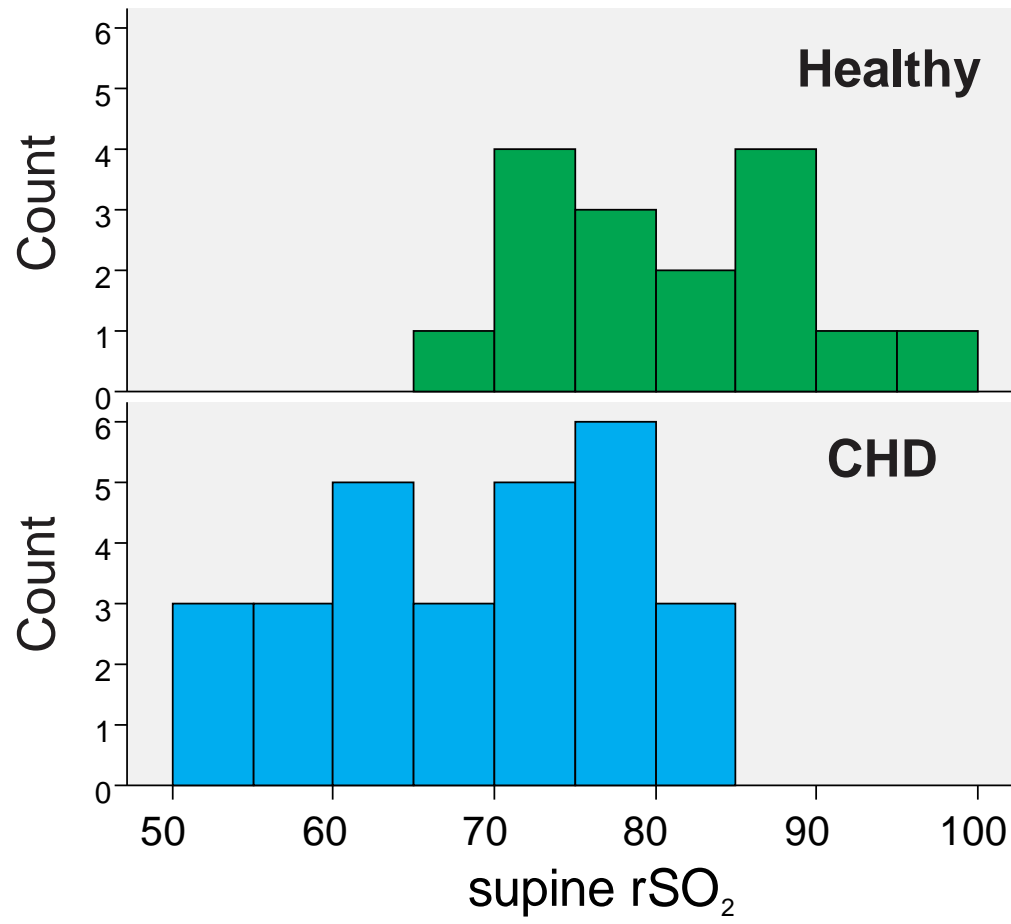
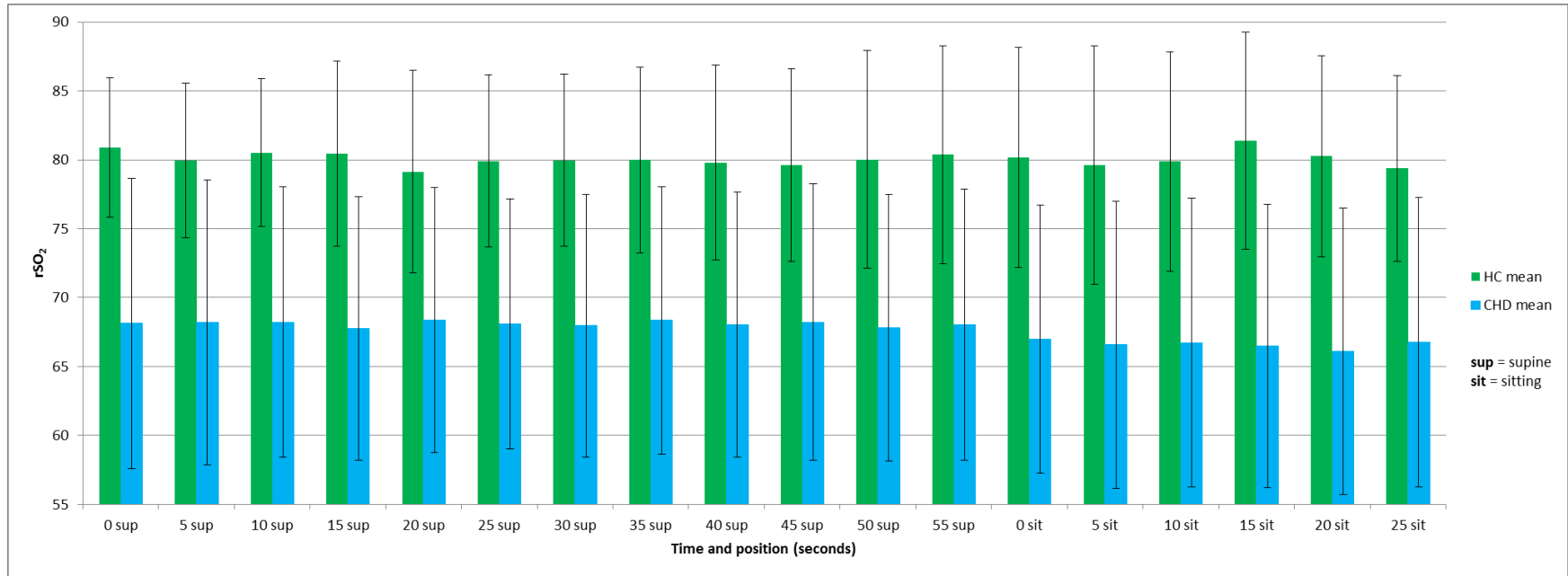


Figure 5-3. rSO₂ Mean Values for Healthy Controls (HC) & Congenital Heart Disease (CHD)



Physiologic Patterns of Participants

The physiologic trends for a typical healthy neonate indicated little fluctuations in the cerebral (rSO₂) and arterial oxygen (SpO₂) saturations before and after the 0 time point (the time of the postural change). Figure 5-4 depicts the physiologic trends of a typical healthy neonate including the rSO₂, SpO₂, heart rate, and respiratory rate for the 5 minutes supine and 5 minutes sitting positions.

In contrast, the physiologic trends of a typical neonate with CHD indicated more fluctuations and variability, with extreme peaks and drops in rSO₂, compared to the healthy neonate's trends. Figure 5-5 shows the physiologic trends of a typical CHD neonate including the rSO₂, SpO₂, heart rate, respiratory rate, and mean arterial blood pressure for the 10 minute timeframe. The mean arterial blood pressure in the neonates with CHD was not appropriate in the healthy neonate.

Figure 5-6 shows the relative change in rSO₂ response between the CHD and healthy groups. The healthy controls had minimal fluctuations (less than 2% drop) in rSO₂ response before and after the postural change (0 time point). Conversely, the CHD group had a decrease in rSO₂ of 2% to 10% at 10 seconds and a 5% to 10% drop at 20 seconds from 0 time point. At the 60 second supine position, both groups returned to baseline with little variation. However, after the postural change, the CHD group was much lower the rSO₂ values compared to the healthy group.

Figure 5-4. Typical Healthy Control (HC) Physiologic Measures

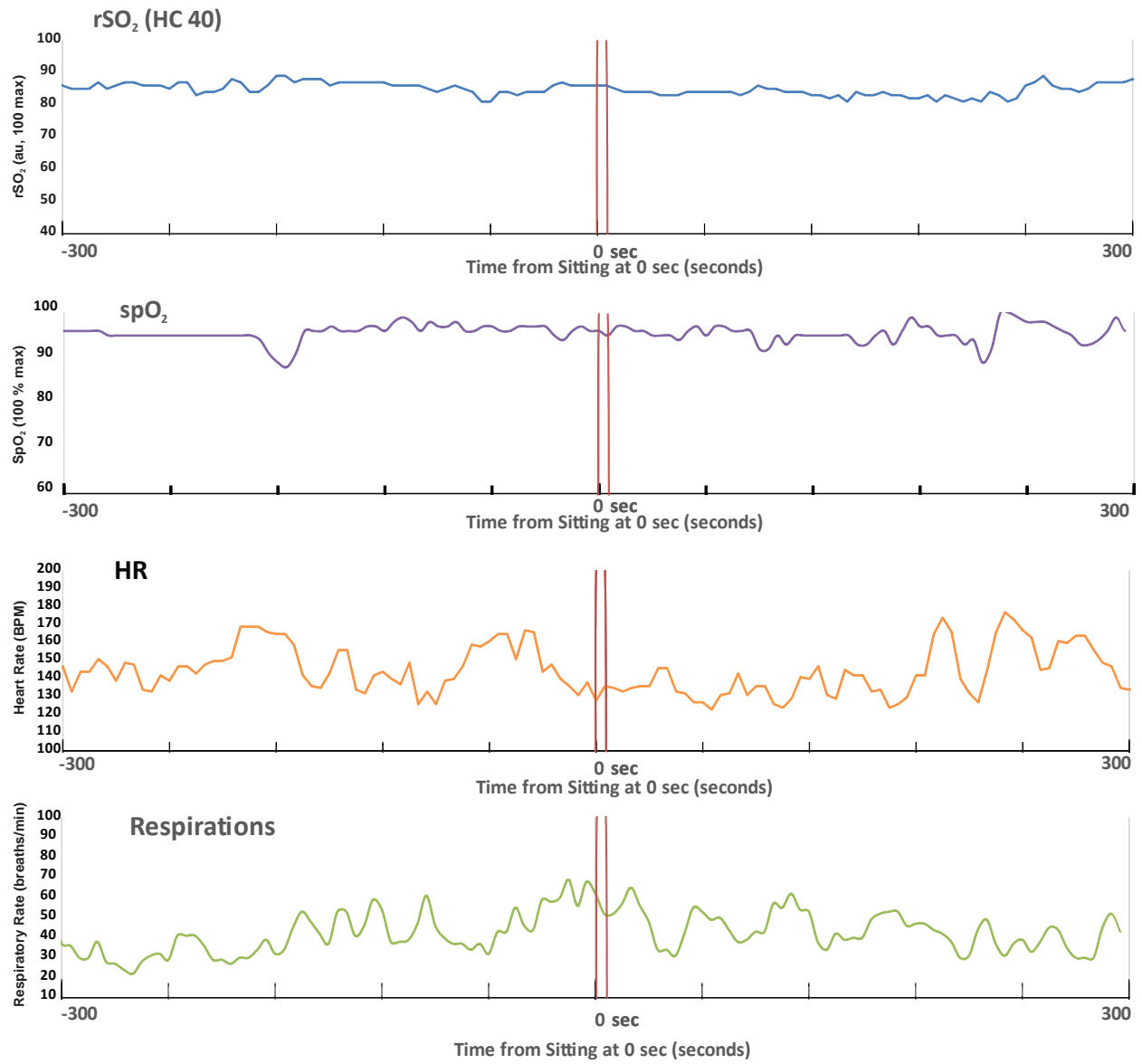


Figure 5-5. Typical Congenital Heart Disease (CHD: D-TGA) Physiologic Measures

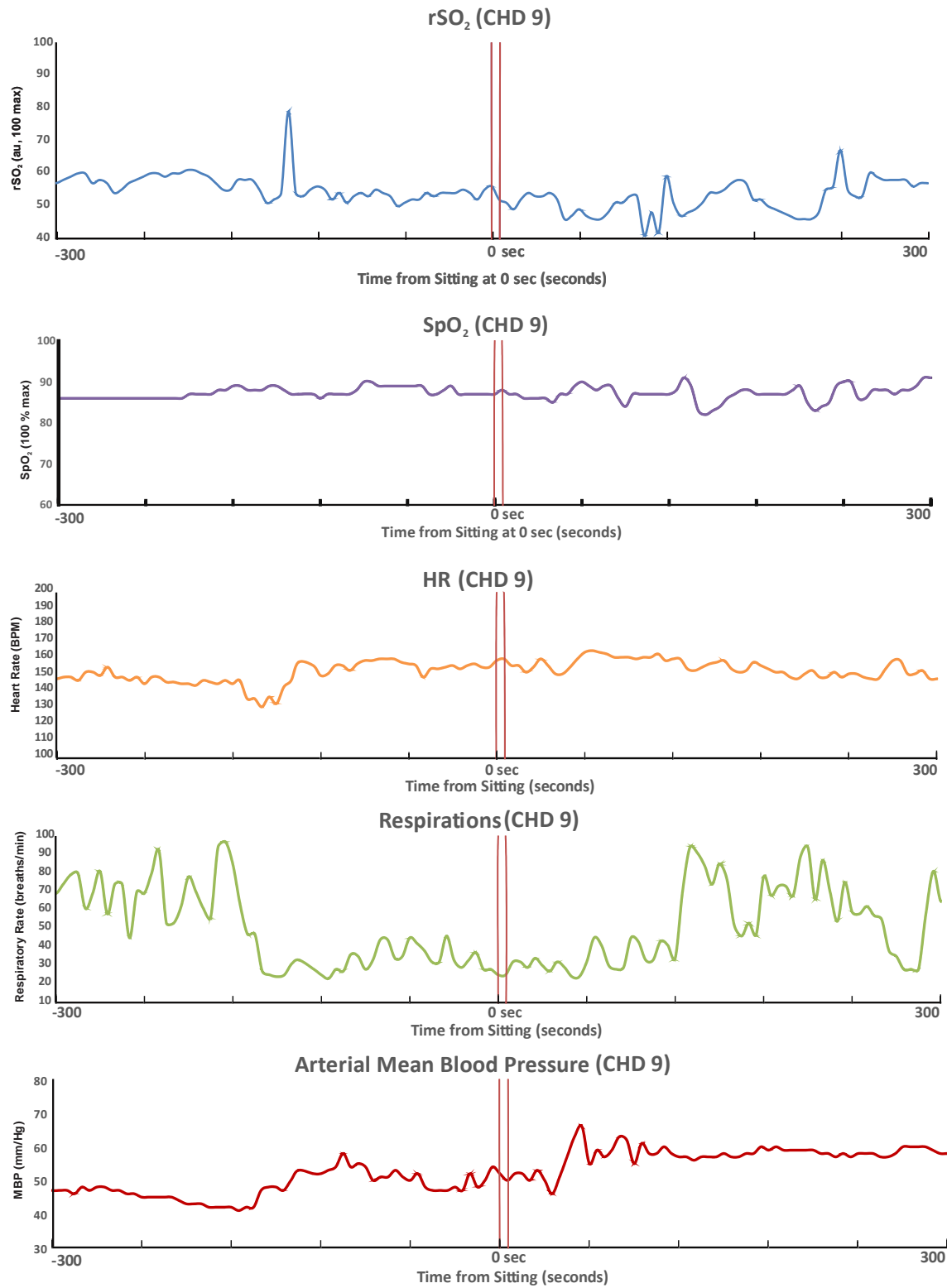
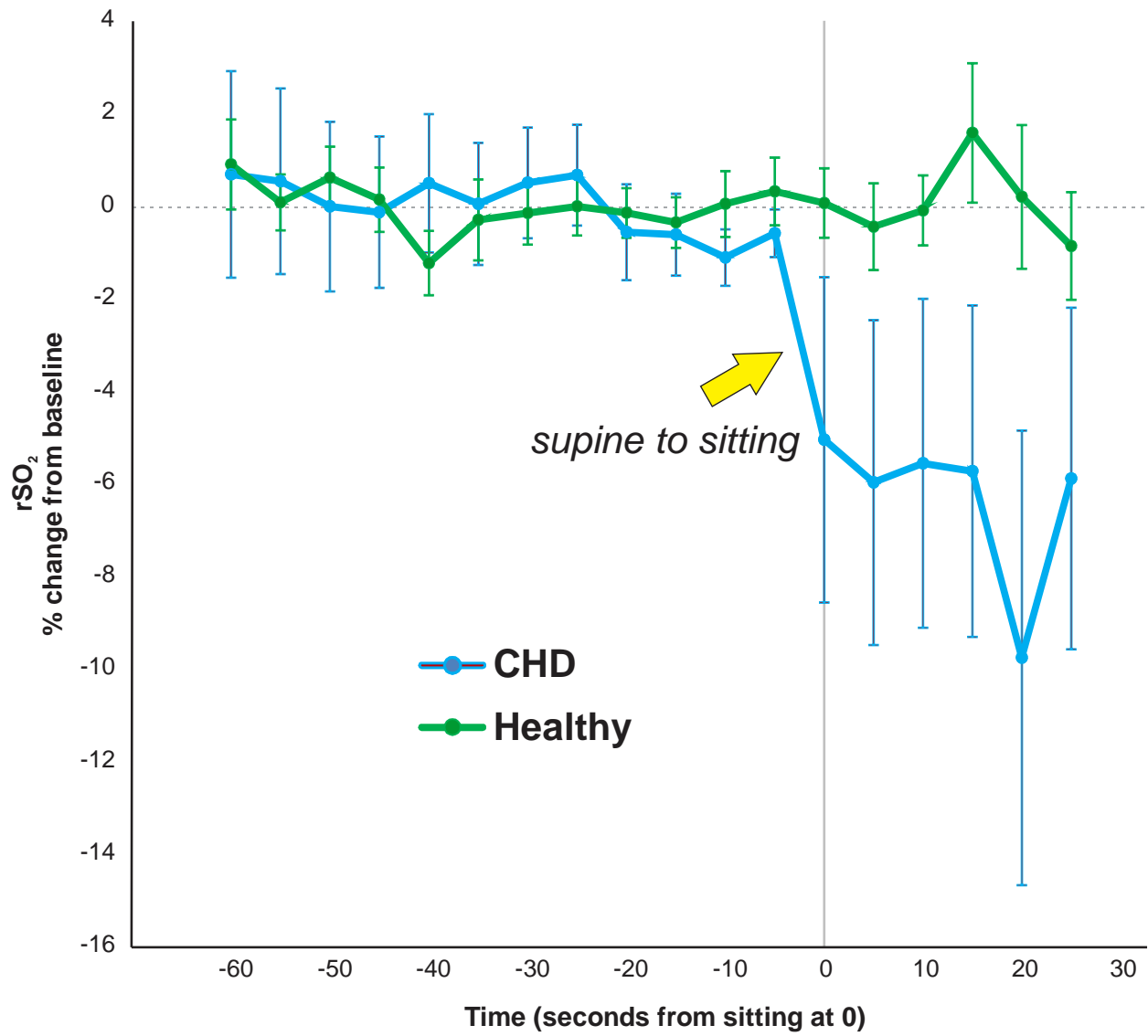


Figure 5-6. Relative Change in rSO₂ by Group

Change in rSO₂ from supine to sitting



Neurodevelopmental Status

Significant differences were found in the percentage of abnormal scores in the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) between the CHD (21.0% ± 10.9%) and healthy (30.9 ± 11.9%, $p = .01$) neonates. Table 5-6 displays the average percentage of abnormal neurodevelopmental scores per group. When examining the total abnormal ENNAS scores for categorically (normal versus abnormal), 39% of the CHD neonates had abnormal scores.

Table 5-6. Percentage of Abnormal Neurodevelopmental (ND) Scores

	Group	N	Mean	Std. Dev.	Std. Error of Mean
% Abnormal ND Score	Control	16	21.0632	10.93458	2.73364
	CHD	28	30.8813	11.93673	2.25583

Research Aims

Table 5-3 presents the variables, summary of findings, and the statistical tests that were used to tests hypotheses for Specific Aims 1, 2, 3.

Table 5-7. Statistical Tests for Each Specific Aim

Aim	Independent variables	Dependent variable	Hypothesized outcomes	Statistical Test	p value	R^2
1	Group (CHD/HC)	↓CA	CHD-↓CA > HC-↓CA	χ^2	.38	N/A
2	Group Covariate (CA)	% Abnormal ENNAS	CHD-↓CA-% Abnormal ENNAS > HC-↓CA-% Abnormal ENNAS	Multiple linear regressions	.02* .28	.17
2A	Group Covariate (CA)	% Abnormal Auditory	CHD-↓CA-% Abnormal Auditory > HC-↓CA-% Abnormal Auditory	Multiple linear regressions	.10 .12	.13

Aim	Independent variables	Dependent variable	Hypothesized outcomes	Statistical Test	<i>p</i> value	R ²
2B	Group Covariate (CA)	% Abnormal Visual	CHD-↓CA-% Abnormal Visual > HC-↓CA-% Abnormal Visual	Multiple linear regressions	.91 .06	.09
2C	Group Covariate (CA)	% Abnormal Motor	CHD-↓CA-% Abnormal Motor > HC-↓CA-% Abnormal Motor	Multiple linear regressions	.04* .36	.13
3	1 minute Apgar Cord pH Birth Head Circ. Birth Weight	↓CA	↓1 minute Apgar ~↓CA ↓pH ~↓CA ↓Birth Head Circ. ~↓CA ↓Birth Weight ~↓CA	Logistic Regressions	.57 .72 .52 .45	.12

CHD = CHD, HC = healthy control, CA = cerebrovascular autoregulation, ENNAS = Einstein Neonatal Neurobehavioral Assessment Scale, * = $p < 0.05$

Specific Aim 1: Comparison of Proportion of Impaired Cerebrovascular Autoregulation between Groups

The *a priori* operational definition for intact CA was rSO₂ returning to baseline within five seconds after the postural change. Conversely, impaired CA was defined as rSO₂ not returning to baseline within five seconds. There were 21/28 (75%) neonates with CHD who had impaired CA compared to 10/16 (62.5%) healthy neonates. The chi square test, however, indicated no significant difference in proportion of impaired CA between CHD and control groups, ($p = .38$). Table 5-8 shows the detailed values of CA status by group.

Table 5-8. Cerebrovascular Autoregulation (CA) Status by Group. Each group's % is circled. Group differences in distributions assessed with Chi-square test.

		CA Status			
		Intact	Impaired	Total	
Group	Healthy	N	6	10	16
		% within Group	37.5%	62.5%	100.0%
		% within Impaired CA	46.2%	32.3%	36.4%
	CHD	N	7	21	28
		% within Group	25.0%	75.0%	100.0%
		% within Impaired CA	53.8%	67.7%	63.6%
Total		N	13	31	44
		% within Group	29.5%	70.5%	100.0%
		% within Impaired CA	100.0%	100.0%	100.0%

Specific Aim 2: Associations between Group, Cerebrovascular Autoregulation, & Neurodevelopment

Multiple linear regression analyses tested hypothesis 2. The CHD group had significantly poorer total neurodevelopmental scores when controlling for CA status ($\beta = 9.3, p = .02$). Although the level of significance was not reached, neonates with CHD and impaired CA had higher abnormal neurodevelopmental scores ($\beta = 4.2, p = .28$). When testing hypothesis 2A, multiple linear regression revealed no significant associations of group with increased auditory abnormalities while controlling for CA ($\beta = 18.8, p = .12$). Interestingly, though not significant, impaired CA was associated to higher percentages of auditory abnormalities while controlling for group ($\beta = 21.3, p = .10$). Testing of hypothesis 2B resulted in similar outcomes. Multiple linear regression showed no significant differences between the CHD and healthy groups for visual abnormalities while controlling for CA ($\beta = 1.0, p = .91$). Opposite to expectations, but not achieving significance, impaired CA was associated to lower percentages of visual

abnormalities while controlling for group ($\beta = -17.8, p = .06$). When testing hypothesis 2C, CHD was significantly associated to higher percentages of motor abnormalities while controlling for impaired CA ($\beta = 7.6, p = .04$). There was no significant association with poorer motor scores and impaired CA when controlling for group ($\beta = 3.5, p = .36$). Table 5-7 shows the aims, independent variables, dependent variables, hypotheses, p values and R square (if applicable).

Specific Aim 3: Association between Cerebrovascular Autoregulation & Clinical Factors

Logistic regression assessed clinical factors associated with impaired CA. Impaired CA was not significantly associated with clinical factors such as: one minute Apgar scores ($p = .57$), cord pH levels ($p = .72$), birth head circumference ($p=.52$), and birth weight ($p=.45$). Table 5-7 summarizes the aims, independent variables, dependent variables, hypotheses, p values and R square (if applicable).

Secondary Analyses for Potential Confounds

Cerebrovascular Autoregulation Adjustment

The *a priori* definition of impaired CA was defined as rSO₂ taking greater than 5 seconds to return to baseline after the postural change. However, this definition may have been too liberal because 63% of the healthy controls and 75% of the CHD were categorized as impaired CA. In order to adjust for this, the definition for impaired CA was adjusted to greater than 3 point difference in supine (baseline) and sitting rSO₂. This new definition made all of the healthy controls have intact CA. After this adjustment, none of the healthy controls and 11% of the CHD had impaired CA. Similarly, using the Fisher's Exact test, the difference was not significant ($p = .29$). Table 5-9 demonstrates the adjusted CA values, with all healthy controls having intact CA.

Table 5-9. Adjusted Cerebrovascular Autoregulation (CA) Status by Group. Each group's % is circled.

Group	Healthy	N	CA Status		Total
			Intact	Impaired	
			16	0	16
		% within Group	100.0%	0.0%	100.0%
		% within Impaired	39.0%	0.0%	36.4%
	CHD	N	25	3	28
		% within Group	89.3%	10.7%	100.0%
		% within Impaired	61.0%	100.0%	63.6%
Total		N	41	3	44
		% within Group	93.2%	6.8%	100.0%
		% within Impaired	100.0%	100.0%	100.0%

Adjustments for Group, Cerebrovascular Autoregulation, & Neurodevelopmental Status

To control for significant group differences in age, gender, and ethnicity, these variables were added to the multiple linear regression models. No significant differences were found between group and abnormal ENNAS scores when accounting for covariates such as CA status, gender, age, and ethnicity ($\beta = 6.3, p = .24$). However, the R square = .24 for the model is strong. No significant differences were found among different ethnic groups (Caucasians, Latinos, Asians, and other) and poorer developmental scores when controlling for group (CHD vs. healthy), CA status, gender, and age ($\beta = 2.2, p = .65$; $\beta = 6.9, p = .19$). Similarly, no significant differences were found between group and poorer auditory scores when controlling for CA status, gender, age, and ethnicity ($\beta = 3.9, p = .82$). Oddly, impaired CA neonates had *almost* significantly better visual scores than the intact CA neonates when controlling for group (CHD vs. healthy), gender, age, and ethnicity ($\beta = -18.4, p = .05$). However, *nearly* significant associations were found between age and poorer visual scores when controlling for group (CHD vs. healthy), CA status, gender, and ethnicity ($\beta = 3.0, p = .05$). Lastly, no significant differences

were found between group and abnormal motor scores when accounting for covariates such as CA status, gender, age, and ethnicity, ($\beta = 3.7, p = .47$). Table 5-10 shows adjustments for the aims, independent variables, dependent variables, hypotheses, p values, and R square.

Table 5-10. Adjustment of Aim 2 with Confounding Factors

Aim	Independent variables	Dependent variable	Hypothesized outcomes	Statistical Test	p value	R²
2	Group				.24	.24
	Covariates: CA	%	CHD-↓CA-% Abnormal	Multiple	.41	
	Gender	Abnormal	ENNAS > HC-↓CA-%	linear	.83	
	Age	ENNAS	Abnormal ENNAS	regressions	.22	
	Ethnicity				.65	
2A	Group				.82	.18
	Covariates: CA	%	CHD-↓CA-% Abnormal	Multiple	.12	
	Gender	Abnormal	Auditory > HC-↓CA-%	linear	.99	
	Age	Auditory	Abnormal Auditory	regressions	.31	
	Ethnicity				.43	
2B	Group				.17	.23
	Covariates: CA	%	CHD-↓CA-% Abnormal	Multiple	.05	
	Gender	Abnormal	Visual > HC-↓CA-%	linear	.98	
	Age	Visual	Abnormal Visual	regressions	.05	
	Ethnicity				.99	
2C	Group				.47	.26
	Covariates: CA	%	CHD-↓CA-% Abnormal	Multiple	.52	
	Gender	Abnormal	Motor > HC-↓CA-%	linear	.53	
	Age	Motor	Abnormal Motor	regressions	.08	
	Ethnicity				.88	

CHD = CHD, HC = healthy control, CA = cerebrovascular autoregulation, ENNAS = Einstein Neonatal Neurobehavioral Assessment Scale

CHAPTER SIX: DISCUSSION

This chapter provides a discussion of the main findings. The first section addresses an overview of the findings and hypotheses testing. The second portion covers potential confounding factors. The third section discusses the limitations. The fourth section involves the implications to nursing practice and health care practitioners. The fifth section includes future research.

Overview of Findings

The main findings of the study support hypoxemia and neurodevelopmental delay in CHD. The study did not detect higher levels of impaired CA in CHD compared to healthy neonates. Although a significant difference was not identified, the study validated hypoxemia and variability in the CHD neonates. The study also found significantly poorer neurodevelopmental scores in CHD neonates when controlling for impaired CA. Furthermore, when examining neurodevelopmental outcomes solely, the CHD group continued to have higher percentages of abnormal scores. These results support the current body of neurodevelopmental literature in CHD children (Limperopoulos et al., 1997; Limperopoulos et al., 2000; Marino et al., 2012; Mussatto et al., 2014). However, when examining the neurodevelopmental assessment by function, i.e. auditory, visual, and motor, the CHD group had significantly poorer motor scores when controlling for impaired CA. Lastly, there was no association of clinical factors such as birth weight, birth acidosis, 1 minute Apgar scores, and birth head circumference with impaired CA. However, the study uncovered other potential confounding factors and participant variability.

Summary of Hypothesis Tests

Hypothesis 1: Cerebrovascular Autoregulation

The study tested the hypothesis that preoperative CHD neonates would have a significantly different quantity of impaired CA to that of healthy neonates. However, this hypothesis was unsupported because no significant difference was detected.

Hypothesis 2: Cerebrovascular Autoregulation & Neurodevelopment

The study tested the hypothesis whether preoperative neonates with CHD and impaired CA would have associations with poorer neurodevelopmental scores. This hypothesis was unsupported. There was no significant association with CA status when controlling for the influence of group, CHD versus healthy. However, there were significant associations between poorer developmental scores and group (CHD and healthy) when controlling for CA status.

Hypothesis 3: Cerebrovascular Autoregulation & Clinical Factors

Although the study was not powered to test this exploratory aim (based on anticipated effect size), this hypothesis tested whether clinical factors such as one minute Apgar scores, birth acidosis, birth head circumference, and birth weight would be associated to impaired CA. This exploratory aim was unsupported. The literature supports associations of decreased birth weight (less than 2.5 kilograms) and lower head circumference (less than 33.5 centimeters) to poorer developmental scores. The study sought to understand if those factors also associated with CA.

Cerebral Oxygenation

Cerebral oxygenation was substantially lower for the CHD neonates compared to the healthy controls, in both supine and sitting positions. The difference may be attributed to the cyanotic heart defects of the CHD group. This finding of lower cerebral oxygenation is consistent with the literature in the CHD and high risk neonatal groups (Alderliesten et al., 2013;

Brady et al., 2010; Chock et al., 2012). This dissertation study's cerebral oxygenation range in the CHD neonates was 50 – 80s. Brady et al. (2010) examined CA in neonates and infants with CHD and found similar cerebral oxygenation ranges from 50 – 95. However, this study included both CHD and healthy neonates and included cyanotic heart lesions. Brady et al. (2010) assessed cerebral oxygenation only in CHD infants and excluded cyanotic CHD children, which may explain the higher oxygenation levels of that study. Alderliesten et al. (2013) studied preterm neonates born at less than 32 weeks gestational age who developed periventricular hemorrhage. The preterm neonatal cerebral oxygenation ranged from 40 – 90. The lower cerebral oxygenation may be due to the prematurity of this particular study population. Chock et al. (2012) also assessed CA in very low birth weight preterm neonates with and without patent ductus arteriosus (PDA). Similar to this study's findings, neonates with PDA had lower cerebral oxygenation ranging from 64 – 72 compared to the control neonates with ranges from 71 – 77.

This dissertation study's healthy control cerebral oxygenation ranged from the high 60 – 90s. Pichler et al. (2013) examined cerebral oxygenation in term neonates immediately after delivery and found ranges of 59 – 88. Pichler et al. (2013) cerebral oxygenation findings in the healthy neonate are slightly lower than this study's results. Their difference in findings may be due to the neonate's physiologically transitioning from intrauterine to extrauterine life, with partial patency of the ductus, resulting in lower cerebral oxygenation (Pichler et al., 2013). The healthy neonates in this study were approximately 7 days old and had completed the transition from intrauterine to extrauterine life, with a closed PDA and thus a higher cerebral oxygenation.

With the knowledge that the brain needs a constant flow of oxygen rich blood and has a high metabolic rate (consumes oxygen at a high pace) (Purves, 2012), it is likely the physiologically lower oxygen (hypoxemic) levels in CHD may contribute to neurodevelopmental

delay. Hoffman et al. (2013) found significant associations of lower intraoperative cerebral oxygenation and poorer visual-motor assessments in children with CHD. In other neonatal conditions that cause hypoxemia, such as respiratory distress syndrome or asphyxia, impaired CA is present (Howlett et al., 2013; Paulson et al., 1990). Thus, it is surprising that a significant amount of impaired CA was not discovered in our CHD sample.

Cerebrovascular Autoregulation

No significant difference was discovered in CA between CHD and healthy groups. However, the direction of the moderate effect was towards impaired CA ($d = .4$, $r = .2$). We based the power calculations and analyses on large effect sizes on studies demonstrating significant differences in cerebral blood flow or cerebral injury in neonates with CHD compared to controls (Al Nafisi et al., 2013; Arduini et al., 2011; Paquette et al., 2013). No study specifically examined impaired CA in CHD and control neonates. Others have studied impaired CA comparing high risk neonates with and without patent ductus arteriosus (PDA) or intraventricular hemorrhage (IVH) (Alderliesten et al., 2013; Chock et al., 2012). Those researchers used the pressure passivity index to measure CA, which is the correlation of brain oxygenation to the arterial blood pressure. Therefore, the postural change technique may not have been sensitive enough to capture impaired CA.

The nonsignificant finding differs than the literature in CA and CHD (Brady et al., 2010; Buckley et al., 2010). However, those studies lacked of a comparative control group and examined CA during open heart surgery in infants with CHD. The nonsignificant results could have also been attributed to the technique used to assess CA which utilized the postural change. Previous literature in neonates demonstrated significant changes in cerebral blood flow with minimal changes in head movement, clinical care, or visual stimulation (Huning et al., 2007;

Karen et al., 2008; Tax et al., 2011). Thus, we presumed we would find significant changes utilizing the postural change technique, since this was a more drastic autonomic challenge. Since no study previously employed this autonomic challenge in the neonatal population, this was a pioneering protocol.

Furthermore, the NIRS monitor and Bernoulli data acquisition sampled the data at a mildly delayed rate, thus information may not be captured in real time. The NIRS has an approximately 0.5 to 1 second delay and the Bernoulli only samples data every 5 seconds. This rate of sampling coupled with the NIRS monitor delay potentially influenced the findings. Although this negative influence is unlikely since most of the research on CA utilized the INVOS NIRS device and discovered impaired CA (Alderliesten et al., 2013; Chock et al., 2012).

The *a priori* operational definition for impaired CA may have been inaccurate since it was based on adult and pediatric data (Deegan et al., 2011; Endo et al., 2014; Kim et al., 2009) and captured CA at one point in time. The operational definition of CA may have needed to be examined at a more distant time point to capture the change, for instance at the 30 second or 1 minute post postural change time. The initial examination at 5 seconds after sitting may have contributed to the lack of difference seen between groups. A reexamination at the 30 second and 1 minute time interval after the postural change can be assessed in the future and may potentially lead to differing results. There may also be a range of impairment in CA from mild to more severe because the CHD neonates tended to have greater differences in the supine and sitting cerebral oxygenation compared to the controls. Additionally, the trending of the cerebral oxygenation in the CHD neonate's demonstrated greater variability, with more peaks and drops compared to the controls.

The neonate's behavioral states could have also affected the findings (Kurtzberg et al., 1979; Noble & Boyd, 2012). A majority of the healthy neonates were comfortably sleeping during the supine and sitting positions. However, some (approximately 4) of the CHD neonates were mildly distressed during the protocol. For example, a few neonates were easily agitated would cry intermittently during the study procedures. The neonates were soothed with a pacifier, gentle talking, or patting, but this intervention could have also affected the CA response.

Neurodevelopmental Status

CHD neonates had higher significantly poorer neurodevelopmental scores compared to the controls. This result supports the current body of literature demonstrating significant differences in developmental assessments between healthy and CHD participants (Limperopoulos et al., 1997; Limperopoulos et al., 1999, 2000). The significant group difference may also have been due to the age difference of the CHD and healthy neonates. However, when we controlled for gestational age at the time of the assessment, significant differences were still found ($p = .02$). Thus, it appears that the neurodevelopmental results were valid.

The neonate's state could have influenced the neurodevelopmental findings. All efforts were made to console the neonate and maintain the neonate's comfort. Despite these efforts, a few neonates became upset during the developmental assessment. The crying state may have influenced the neonate's response, for instance after the neonate is calmed, he/ she may be too tired to turn his/ her head towards the direction of the sound of the bell. Thus, in this case the neonate would have an abnormal score.

When examining the total abnormal developmental scores categorically, 39% of the CHD neonates had total abnormal scores. This result is slightly lower than previous neurodevelopmental studies in children with CHD, which found up to 50 – 75% abnormalities

(Limperopoulos et al., 2000; Mussatto et al., 2014). The difference in abnormal scores may have been due to a slightly older population, Limperopoulos et al. (2000) assessed neonates from 9 – 16 days of life, and Mussatto et al. (2014) assessed infants at 6 – 37 months of life.

Confounding Factors

Sample Characteristics

Although we attempted to recruit a homogenous sample, there were some areas of heterogeneity that had the potential to affect the findings. There were significant differences in age, gender, and ethnicity between groups. When all three covariates were added to the multiple linear regression models, the only significant association was with poorer visual scores and age. Thus, it seems that these covariates did not bias the findings.

The CHD neonates had differing clinical status. For instance, some CHD neonates were on room air while others were on noninvasive ventilator support. This may have also influenced the results. At a later time, data can be extracted and further analyses can be run to account for varying clinical factors.

In addition to Children’s Hospital Los Angeles’s (CHLA) tertiary status, it is also located in the center of a large Southern California metropolitan city with a majority Latino population. This resulted in a 68% Latino CHD group. However, after rerunning the multiple linear regression models to control for age, gender, and ethnicity, no significant differences were found in poorer developmental scores. Thus, it appears that these confounding factors may not have affected the findings.

Chromosomal Anomalies

A few of the CHD participants had chromosomal anomalies discovered after enrollment. These genetic anomalies ranged from Di George syndrome to chromosomal translocations or

duplications, such as XYY. Although five of the CHD participants had chromosomal abnormalities, these anomalies can result in no cognitive effects to very mild to severe effects, and may not manifest until school age. Thus, the extent of the neurodevelopmental delay is unknown. Since the neurodevelopmental effects are unknown, data from these participants was utilized. These chromosomal anomalies have the potential to affect the neurobehavioral assessment. However, the findings of higher abnormal neurobehavioral assessments in most of the CHD participants (even the participants without chromosomal anomalies), leads one to believe that the participants with the chromosomal anomalies did not bias the neurobehavioral assessment results.

Severity or Type of Cardiac Diagnoses

We enrolled and recruited participants with any type of CHD. This had the potential to affect the results of impaired CA because it is known that participants with left ventricular outflow tract obstructions (LVOTO) have altered cerebral blood flow (Klabunde, 2011). Because there was no significant difference between CA in CHD and healthy neonates, we believe the results were unbiased. Additionally, 28.6% of the CHD participants had LVOTO, compared to 75% of CHD neonates with impaired CA. Since the proportion of CHD neonates with impaired CA was much greater than the amount of participants with LVOTO, it appears the study captured CA status for all of the CHD neonates.

CHLA performs the largest amounts of pediatric cardiac surgery in the western U.S. and cares for neonates with the most severe heart defects because it is a tertiary center. This may have influenced the differences seen in cerebral oxygenation and type of CHD enrolled. However, the study was limited to the fetal CHD seen at the Institute for Maternal and Fetal Health (IMFH) and the CHD neonates admitted to the Cardiothoracic Intensive Care Unit

(CTICU). This study was powered for all CHD and not for specific subgroups, such as single ventricle or cyanotic defects. The physiology of single ventricles and cyanotic defects cause the neonates to have a preexisting lower baseline arterial oxygenation (Klabunde, 2011).

Approximately, 78% of the CHD neonates had cyanotic defects. This may explain significant difference in baseline and sitting rSO₂.

Prostaglandin E1 (PGE 1)

Many of the CHD neonates were on intravenous prostaglandin E1 (PGE 1) drips. PGE 1 maintains the patency of the ductus arteriosus in order to facilitate systemic circulation in neonates with CHD (Huang et al., 2013). Thus, this medication has strong vasodilatory effects. Although PGE 1 relaxes the smooth muscle of the ductus arteriosus, those effects can also influence the other vessels of the body. This vasodilatory effect could have influenced the CA findings because the body's normal vasoconstriction response would be inhibited. Thus, these neonates would have increased vasodilation and decreased vasoconstriction because of the PGE 1 resulting in a minimal change in cerebral oxygenation. Alternatively, if the CHD neonate's on PGE 1 had systemic vasodilation, one would theorize a larger decrease in cerebral oxygenation because of the dramatic drop in cerebral blood flow from the postural change. This would result in a larger difference in supine and sitting cerebral oxygenation. Therefore, the influence appears to favor impaired CA since the study found 75% of the CHD neonates fell into that category. However, this level of impaired CA is much greater than the number of on PGE 1.

Age Effects

The ages of the participants ranged from 0-12 days of life. Although we attempted to recruit age and gender matched healthy neonates with CHD participants, the healthy recruitment was difficult. The plan to recruit healthy participants from Hollywood Presbyterian Medical

Center (HPMC) was deferred because the hospital was transitioning institutional review boards (IRB) and was not reviewing or approving new studies. Thus, healthy neonatal recruitment occurred mostly from the employees at CHLA. Furthermore, healthy control attrition occurred when mother's had cesarean sections or realized they were too overwhelmed to return to CHLA to perform study measures within 12 days of delivery.

Additionally, most of the healthy neonate's mothers were not discharged from the birthing hospital until 1 to 3 days after vaginal delivery and about 4 days after caesarean sections, barring complications. After these mothers settled home, they wanted several days to acclimate to the new baby before returning to the hospital. This resulted in much older healthy controls. Measures in the CHD neonate needed to be performed before cardiac surgery, as well as before any other invasive procedure occurred. This resulted in younger CHD participants.

Most of the CHD neonates were less than 3 days old and the healthy controls were about 7 days old. This was a significant difference between age and group ($p < .000$). The difference could have affected the CA and neurobehavioral assessment findings because the healthy neonates were slightly older and more mature. However, when performing statistical analyses on age effects on impaired CA, there were no statistical differences ($p = .89$). This leads one to believe age may have affected results. Moreover, there was no significant association to abnormal neurodevelopmental scores with age in days when controlling for group and gestational age at the time of exam ($p = .23$).

Gender Effects

The healthy participants had significantly more female and the CHD group had more male participants ($p = .01$). This gender difference may have influenced the results. However, no

significant difference was discovered when examining gender effects on impaired CA ($p = .60$) and neurobehavioral results ($p = .25$). Thus, we do not believe gender biased the findings.

Participant Variability

When examining the rSO₂ graphs plotted over the 10 minute period while supine and sitting, it appears that the healthy neonates had less variability compared to the CHD neonates. The variability suggests a potential mechanism of injury and supports further examination. Moreover, the rSO₂ variability in the CHD neonates corroborates our theory of impaired CA or altered cerebral blood flow. Because the healthy neonates appeared to have more stable rSO₂, it suggests consistent cerebral blood flow. Future analyses can examine whether group variability was statistically significant.

Neurobehavioral State

Reports have supported significant differences in healthy and CHD neonates using the ENNAS and other neurodevelopmental tools (Limperopoulos et al., 1997; Limperopoulos et al., 2000; Marino et al., 2012; Mussatto et al., 2014). The results of this study add to this current body of knowledge. Although the ENNAS is slightly antiquated and not utilized commonly, it was a reliable and accurate tool. The significant difference in abnormal developmental scores validates the assessments and the scorer. The principal investigator (PI) had neurodevelopmental training, and assessed and scored all of the study participants. The PI knew the participants group status, which could have biased the results of the neurodevelopmental assessments. However, the PI scored and examined each participant using standard methods and protocol. Thus, it is unlikely participant's group influenced the PI.

Not all portions of the neurobehavioral assessment were performed on all of the participants. The reasons for incomplete assessments were because neonates would not open

their eyes for the visual portions, because of a change in the clinical status, or due to invasive lines. Specifically, participant number 4 was on high flow nasal cannula on the day of the initial assessment, but parents requested the completion of the exam the following day because of the many procedures performed previously that day. Upon return the next morning, the baby had an endotracheal tube in place because of overnight respiratory decompensation. Therefore, only some parts of the exam were completed.

The neurobehavioral items that were assessed in all 44 participants were: 1) bell, 2) rattle, 3) voice, 4) rooting, 5) sucking, 6) popliteal angle, 7) spontaneous movement, 8) tone, and 9) cuddliness. Although all items of the neurobehavioral assessment were not performed on all of the participants, when analyzing the 9 items assessed in all 44 participants, there continued to be a significant difference between CHD and healthy groups ($p = .01$). There were similar results when comparing the neurobehavioral assessment in totality as well as partially with the 9 items completed by all participants. It does not appear that incomplete neurobehavioral assessments influenced the findings.

Cerebrovascular Autoregulation

Because no other studies utilized the postural change in the neonatal population, the *a priori* definition was based on previous literature on adults and older infants. The *a priori* definition of impaired CA was defined as rSO_2 not returning to baseline within 5 seconds after the postural change. This definition may have been too liberal because 63% of the healthy controls and 75% of the CHD fell into the impaired CA category. After we adjusted the operational definition for impaired CA to eliminate the healthy controls, 11% of the CHD had impaired CA. The adjusted CA definitions results were similar to the *a priori* results showing no significant difference ($p = .18$).

The adjusted CA with neurodevelopmental and clinical factor results were similar to the original findings. Using independent t-tests, there was no significant association of impaired CA to abnormal neurodevelopmental scores ($p = .74$). Using multiple linear regressions, the CHD group was significantly associated to poorer neurodevelopmental scores while controlling for impaired CA ($\beta = 9.96, p = .01$). When examining the functions separately, there were no significant findings for auditory and visual functions. However, the CHD group was significantly associated to poorer motor scores while controlling for impaired CA ($\beta = 8.39, p = .03$). Additionally, no clinical factors (e.g. birth weight, 1 minute Apgar scores, birth head circumference, cord pH levels) were associated with impaired CA. Although the original *a priori* definition for impaired CA may have been too liberal, adjustments to exclude healthy neonates resulted in similar findings. Thus, it appears there was no influence of the *a priori* definition of impaired CA definition.

NIRS Monitors

Two different INVOS NIRS monitors measured rSO₂ in the healthy and CHD participants. Most of the healthy participants were measured on a different INVOS NIRS monitor than the monitor used for the CHD participants. This occurred because a stand-alone research tower with its own INVOS NIRS, pulse oximeter monitor, and data acquisition system was utilized on the healthy neonates. The rationale for using this research tower was because of its' portability for the potential recruitment of the HPMC and Alta Med clinic neonates. The use of different INVOS NIRS monitors may have theoretically affected the rSO₂ findings. However, a systematic difference in readings of rSO₂ is unlikely due to the manufacturer's controls and CHLA's biomedical engineering maintenance and oversight of the monitors. Additionally, the last few healthy neonates were measured with the same INVOS NIRS monitors used for the

CHD neonates. Those rSO₂ readings were in the high 80's similar to the readings of the research tower INVOS NIRS.

Limitations

This study only had a sample of 44 participants, which may explain the non-significance between groups and CA. A larger sample may have shown significant differences in rSO₂ results. However, the sample and effect size were based on large effects of previous studies on comparing cerebral blood flow in CHD versus healthy neonates (Arduini et al., 2011; Chock et al., 2012; Paquette et al., 2013) or CA in adults with stroke versus healthy with similar sample sizes (Salinet et al., 2015). No studies compared CA in CHD versus healthy neonates. Despite the limited sample size, a majority of articles on CA in CHD children had comparable sample sizes (Brady et al., 2010; Howlett et al., 2013; Huning et al., 2007; Tax et al., 2011). Participant variability may have also affected the CA measures. We expected the neonates to physiologically respond in a particular fashion, however, the expected autonomic response may not have occurred or been captured in the analyzed timeframe. Recruitment was difficult because of the highly stressful time for parents and the vulnerable population of neonates with CHD. Furthermore, parents of healthy controls had difficulties returning to the hospital for the neonatal measures because of the stressors of a new baby.

Other potential confounding factors such as sample, chromosomal anomalies, varying types of cardiac lesions, and demographic disparities were addressed above in the confounding factors section. These study limitations had the potential to effect the study results and findings. Although we attempted to account for confounding factors, we could not address all influences.

Clinical Implications to Nursing & Healthcare Providers

There are several strategies for optimizing cerebral blood flow. Healthcare practitioners could optimize cerebral blood flow by: 1) maintaining higher systolic blood pressures; 2) avoiding and preventing episodes of hypoxemia and; 3) taking more time to change the patient's positions. Higher blood pressures can be maintained with intravenous inotropes such as dopamine or vasopressors such as epinephrine, if appropriate. In order to prevent hypoxemic events, healthcare providers can preserve the neonate's comfort with noninvasive approaches such as swaddling or utilizing a pacifier, to more invasive techniques such as intravenous pain medications (e.g. fentanyl) or sedatives (e.g. versed), if needed. Lastly, clinicians can be more mindful and careful during position changes by avoiding quick or abrupt movements and slowly and gently moving the neonate. While these strategies are commonly implemented, nurses and other health care providers may not have paid attention to the potential effects of changing neonatal positions such as from supine to sitting that may have physiological effects on cerebral oxygenation and CA. These practical changes in care will maximize cerebral blood flow in patients at risk for impaired CA.

Additionally, because of the high percentage of developmental delay in preoperative CHD neonates, nurses and other health care providers need to instruct and make appropriate referrals for developmental assessments and follow-up, both before and after open heart surgery. Preoperative developmental assessments have the potential to identify at risk neonates much earlier in their healthcare time course. Earlier identification of delays may help to improve the child's quality of life with earlier interventions. Furthermore, close developmental screening and follow-up will ensure that these children will receive the appropriate developmental services and

interventions, if necessary. These changes in screening practices have the potential to identify CHD neonates who may be at higher risk for developmental delays.

Future Research

Future studies with larger sample sizes are needed to determine whether CHD and impaired CA are associated with poorer neurodevelopmental scores. In the future, it is also possible to explore other confounding factors which may have biased the results. For example, analyses on whether the clinical conditions, such as supplemental oxygen, influenced CA. It may be that CA is multifactorial and affected by many other conditions that were not examined in this study. Strategies for risk assessment, early recognition, and referral to appropriate developmental specialists are needed to be developed and tested to determine whether these strategies may improve neurodevelopmental outcomes in neonates with CHD.

The results of this study suggest the presence of greater variability in cerebral oxygenation in CHD neonates, this variability could also be examined in conjunction with impaired CA. The significantly lower supine and sitting rSO₂ supports hypoxemia in CHD and the directions of the poorer neurodevelopmental outcomes were towards CHD and impaired CA. These preliminary results warrant further examination of hypoxemia and CA as a cause of developmental delays in children with CHD. The infants included in this dissertation study were assessed cross-sectionally and across a wide range of ages. A prospective, longitudinal study (at much more specific ages that are identical across groups) is needed to identify differences in the developmental trajectories of CA across groups and to associate abnormalities in those trajectories in the CHD group with more rigorous and detailed methods for assessing neurodevelopmental outcomes.

Conclusions

Although this study was not able to determine the association between impaired CA and neurodevelopmental outcomes, it supports the need for more mindful position changes to minimize the potentially harmful physiological effects of hypoxemia and possibly impaired CA. The poorer neurodevelopmental scores in neonates with CHD also reinforce the need for risk assessments and early recognition and intervention of neurodevelopmental delays. Because not all neonates with CHD have developmental delay, identifying those at higher risk for delay, such as those with impaired CA, may help to decrease the incidence of delays in this vulnerable population. This knowledge of risk for developmental delay will help the healthcare provider tailor care with interventions to improve cerebral blood flow, as well as to provide closer neurodevelopmental monitoring and follow up. Discharge instructions may also inform parents about the potential risk of delay and may provide referrals to neurodevelopmental specialists.

The hope is to decrease or prevent developmental delay in this vulnerable population through the identification of a mechanism of brain injury. This study is a preliminary step in identifying the potential mechanism of injury. Future studies are necessary to clearly identify the associations of impaired CA to developmental abnormalities. If a strong association is uncovered, future research can focus on interventions such as statins or green tea extracts to help improve impaired CA, potentially decreasing brain injury and developmental delays.

APPENDICES

Appendix 2-1. Congenital Heart Disease and Brain Injury

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
Abdel Raheem, M. M., & Mohamed, W. A. (2012). Impact of congenital heart disease on brain development in newborn infants. <i>Annals of Pediatric Cardiology</i> , 5(1), 21-26. doi:10.4103/0974-2069.93705	52 term neonates with CHD [cyanotic (n=21) and acyanotic (n=31)] compared to healthy term controls (n=15)	Intrinsic factors associated with brain development and brain injury in neonates with CHD compared to healthy controls.	Prospective, comparative study in Saudi Arabia	Brain MRI and MRS images Mean diffusivity values were calculated via diffusion tensor imaging Mean N-acetyl aspartate (NAA)/ choline (Ch) and lactate/Ch metabolite ratios were calculated from 3 dimensional MRS Severity of illness in neonatal CHD assessed with Score for Neonatal Acute Physiology–Perinatal Extension (SNAP–PE)	CHD had significant decrease in NAA/Ch ratio ($p < .001$), increase in average diffusivity ($p < .0001$), decrease white matter fractional anisotropy ($p < .001$) showing immaturity and increase in lactate/Ch ratio which is indicative of brain injury ($p < .0001$) compared to controls. Cyanotic CHD had more brain immaturity and signs of brain injury (frontal, posterior, periorlandic, optic radiation, thalamus, basal ganglia, calcarine) than acyanotic CHD ($p < .05$). Brain immaturity was associated with a higher risk for brain injury in both cyanotic and acyanotic CHD.
Andropoulos, D. B., Hunter, J. V., Nelson, D. P., Stayer, S. A., Stark, A. R., McKenzie, E. D., . . . Fraser, C. D.,	67 Neonates (<30 days of age) with CHD [two groups; SV (n=35) and 2V (n=21)]	Intrinsic and procedural factors associated with brain injury and brain immaturity assessed by MRI	Prospective, observational study	Brain MRI obtained before and 7 days after surgery with a 3 rd MRI done at 3-6 months	Preoperative WMI, infarction, or hemorrhage, seen in 28% of both groups.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
Jr. (2010). Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. <i>J Thorac Cardiovasc Surg</i> , 139(3), 543-556. doi:10.1016/j.jtcvs.2009.08.022	undergoing cardiac surgery having cardiac surgery with hypothermic (<30°C) CPB for ≥ 60 minutes	before and after heart surgery using a high flow CPB protocol.		Brain maturity was assessed from T1 and T2 weighted images and scored based on the TMS Measured rSO2/NIRS (INVOS) and followed treatment protocol if reading <50% preoperatively, intraoperatively, and 72 hours postoperatively	No association of prolonged low rSO2 <45% with postoperative brain injury. Abnormality on MRI scans (56% preoperative, 63% postop, 75% overall). 36% incidence of new WMI, infarction or hemorrhage, with 45% of the SV group having new findings versus 25% of 2V group ($p = .13$). Brain immaturity associated with a higher risk for brain injury in both SV and 2V CHD.
Block, A. J., McQuillen, P. S., Chau, V., Glass, H., Poskitt, K. J., Barkovich, A. J., . . . Miller, S. P. (2010). Clinically silent preoperative brain injuries do not worsen with surgery in neonates with congenital heart disease. <i>Journal of Thoracic & Cardiovascular Surgery</i> , 140(3),	92 term neonates (67% d-TGA and 33% SV)	Determine risk of preoperative brain injury with cardiac surgery.	Multi-center, prospective study	Brain MRI scans [1.5 Tesla Signa Echo-Speed system for UCSF; Seimens 1.5 Tesla Avanto for UBC subjects] obtained before and after cardiac surgery Brain injury was assessed using T1 and T2 images and mean diffusivity maps from diffusion tensor imaging	43% of neonates had brain injury on preoperative MRI, stroke 23, WMI 21, and IVH 7. Preoperative brain injury was associated with balloon atrial septostomy ($p = .003$) and lowest arterial oxygen saturation ($p = .007$). Preoperative brain injury [stroke, WMI or IVH] was not a risk factor for extending or acquiring a new postoperative injury.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
550-557. doi:10.1016/j.jtcvs. 2010.03.035					
Drury, P. P., Gunn, A. J., Bennet, L., Ganeshalingham, A., Finucane, K., Buckley, D., & Beca, J. (2013). Deep hypothermic circulatory arrest during the arterial switch operation is associated with reduction in cerebral oxygen extraction but no increase in white matter injury. <i>Journal of Thoracic & Cardiovascular Surgery</i> , 146(6), 1327-1333. doi:10.1016/j.jtcvs.2013.02.011	18 term neonates with TGA undergoing the arterial switch operation [11 used DHCA and 7 with CPB only].	Identify an association with neurophysiologic recovery or > risk for brain injury and short periods of DHCA.	Prospective, observational study	Neurophysiologic recovery was measured using continuous rSO ₂ /NIRS (INVOS) and EEG monitoring during and after surgery Brain MRI [1.5 Tesla Magnetom Avanto] was obtained preoperatively and 5-7 days postoperatively. Brain injury assessed via T1 and T2 weighted images and axial diffusion –weighted images	Preoperative WMI present in 27.3% of neonates in DHCA group and 28.6% in non-DHCA group. New postoperative WMI present in 18.2% DHCA and 42.9% non-DHCA. EEG amplitude significantly lower in DHCA ($p < .05$) and lower cerebral oxygen extraction ($p = .07$). DHCA during arterial switch was associated with reduced rSO ₂ extraction during recovery, but no increased risk of WMI.
Goff, D. A., Shera, D. M., Tang, S., Lavin, N. A., Durning, S. M., Nicolson, S. C., . . . Licht, D. J. (2014). Risk factors for preoperative	57 neonates with HLHS or variant [HLHS (n=55), DORV with mitral atresia (n=2)] 38.7 ± 2.3 weeks	Risk factors associated with brain development and brain injury in neonates with CHD	Prospective, observational study	Preoperative brain MRI [Siemens scanners before 2005 1.5T Sonata, '05-08 3T Trio, after 1.5T Avanto] PVL assessed by T1 hyperintensity with or	Preoperative PVL was identified in 19% TMS score of 9.69 ± 0.95 Brain immaturity was a strong predictor for PVL ($p = .005$)

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
periventricular leukomalacia in term neonates with hypoplastic left heart syndrome are patient related. <i>Journal of Thoracic & Cardiovascular Surgery</i> , 147(4), 1312-1318. doi:10.1016/j.jtcvs.2013.06.021				without restriction of water diffusion on diffusion-weighted imaging Brain maturity was assessed from T1 and T2 weighted images and scored based on the TMS	Non-modifiable patient related factors such as brain immaturity put neonates at risk for brain injury.
Licht, D. J., Shera, D. M., Clancy, R. R., Wernovsky, G., Montenegro, L. M., Nicolson, S. C., . . . Vossough, A. (2009). Brain maturation is delayed in infants with complex congenital heart defects. <i>Journal of Thoracic & Cardiovascular Surgery</i> , 137(3), 529-536; discussion 536-527. doi:10.1016/j.jtcvs.2008.10.025	42 term neonates with CHD [HLHS (n=29), TGA (n=13)] Mean gestational age 38.9 ±1.1 weeks	Brain development in neonates with CHD	Prospective, observational study	Preoperative brain MRI Images [Siemens 3.0T Trio (New York, NY)] PVL was assessed as T1 hyperintensity and corresponding T2 signal loss in the periventricular white matter Brain maturity was assessed from T1 and T2 weighted images and scored based on the TMS	Significantly lower TMS in CHD compared to non-CHD with similar gestational age 36-37 weeks ($p < .0045$), 38-43 weeks ($p < .0001$) Mean head circumference (34.6 ± 1.1 cm) 1 standard deviation below normative range for age. Brain immaturity (approximately 1 month premature) in HLHS and TGA neonates which may increase risk for brain injury.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
<p>Mahle, W. T., Tavani, F., Zimmerman, R. A., Nicolson, S. C., Galli, K. K., Gaynor, J. W., . . . Kurth, C. D. (2002). An MRI study of neurological injury before and after congenital heart surgery. <i>Circulation</i>, 106(12 Suppl 1), 1109-1114. Retrieved from http://circ.ahajournals.org/content/106/12_suppl_1/1109.full.pdf</p>	<p>24 term neonates [SV (n=13) and 2V (n=11)]</p> <p>Median age 39.4 weeks (range 36-41.1)</p>	<p>To determine the pattern and time course of neurologic injury after surgery with CPB.</p>	<p>Prospective, observational study</p>	<p>Serial brain MRIs [1.5 Tesla Seimens Magnetom] were performed at the following time periods: 1) OR day; 2) 5-7 days postoperative; and 3) 3-6 months postoperative</p> <p>Brain injury was assessed via T1 and T2 weighted images and axial diffusion – weighted images</p> <p>Pre- intra- and postoperative clinical data collected</p>	<p>Preoperative MRI showed PVL in 4 patients (16%) and infarct in 2 subjects (8%). Preoperative MRS revealed elevated brain lactate in 19 subjects (53%).</p> <p>Early postoperative lesions [PVL identified in 48%, new infarct (19%), and hemorrhage (33%)] and new or worsening lesions in 67% of subjects.</p> <p>No patient or procedure related factors identified to contribute to early postoperative lesions.</p> <p>Resolution of lesions occurred 4-6 months after surgery. However, long-term functional outcomes are unclear.</p>
<p>Miller, S. P., McQuillen, P. S., Hamrick, S., Xu, D., Glidden, D. V., Charlton, N., . . . Vigneron, D. B. (2007). Abnormal brain development in newborns with</p>	<p>41 term neonates with CHD [TGA (n=29),SV(n=12)] compared to healthy term controls (n=16)</p>	<p>Brain development and brain injury in neonates with CHD compared to healthy controls.</p>	<p>Prospective, comparative study</p>	<p>Brain MRI and MRS images</p> <p>Mean diffusivity values were calculated via diffusion tensor imaging</p> <p>Mean NAA/Ch and lactate/Ch metabolite</p>	<p>Preoperative MRI showed brain injury (WMI, stroke, IVH) in 41% of TGA and brain injury (WMI, stroke) in 17% SV; new postop MRI showed WMI in 25 % TGA and WMI and stroke in 50% SV.</p>

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
congenital heart disease. <i>New England Journal of Medicine</i> , 357(19), 1928-1938. doi:10.1056/NEJMo a067393				ratios were calculated from 3 dimensional MRS Severity of illness in neonatal CHD assessed with Score for Neonatal Acute Physiology–Perinatal Extension (SNAP–PE)	CHD had significant decrease in NAA/Ch ratio ($p = .003$), increase in average diffusivity ($p < .0001$), decrease white matter fractional anisotropy ($p < .001$) and increase in lactate/Ch ratio ($p = .08$) which is indicative of immaturity. CHD have brain immaturity similar to preterm neonates increasing risk of brain injury. Evidence of brain injury preoperatively and postoperatively. SV have higher incidence of injury postoperatively.
Paquette, L. B., Wisnowski, J. L., Ceschin, R., Pruetz, J. D., Detterich, J. A., Del Castillo, S., . . . Panigrahy, A. (2013). Abnormal cerebral microstructure in premature neonates with congenital heart disease. <i>American Journal of Neuroradiology</i> ,	21 preterm neonates with CHD compared to 27 preterm and 28 term neonates without CHD. CHD subjects (5 HLHS, 2 Ebstein Anomaly, 3 COA, 2 TGA, 1 DORV, 8 ASD/VSD/PD)	To evaluate cerebral microstructural abnormalities (WMI) in preterm CHD neonates compared to control groups. To assess an association between WMI and other clinical variables.	Comparative study	Retrospective brain MRI images [MRI 1.5 Tesla GE Healthcare Medical Systems] evaluated both before and after surgery as part of longitudinal follow-up Clinical and demographic information collected Cerebral microvascular abnormalities were assessed via T1 and T2	42% of the preterm neonates with CHD had punctate white matter lesions. Vulnerability of the splenium (related to visual/spatial function) in all CHD neonates. Diffuse microstructural abnormalities observed in preterm neonates with CHD, strongly associated with punctate white matter lesions.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
34(10), 2026-2033. doi:10.3174/ajnr.A 3528				weighted images and voxelwise method for analyzing diffusion tensor imaging	
Paquette, L. B., Votava-Smith, J. K., Ceschin, R., Nagasunder, A. C., Jackson, H. A., Bluml, S., . . . Panigrahy, A. (2015). Abnormal development of thalamic microstructure in premature neonates with congenital heart disease. <i>Pediatr Cardiol</i> , 36(5), 960-969. doi:10.1007/s00246-015-1106-8	21 preterm neonates with CHD compared to 27 preterm and 28 term neonates without CHD. CHD subjects (5 HLHS, 2 Ebstein Anomaly, 3 COA, 2 TGA, 1 DORV, 8 ASD/VSD/PD)	To evaluate cerebral thalamic microstructural abnormalities (WMI) in preterm CHD neonates compared to control groups. To assess an association between WMI and other perioperative variables.	Comparative study	Retrospective brain MRI images [MRI 1.5 Tesla GE Healthcare Medical Systems] evaluated both before and after surgery as part of longitudinal follow-up Clinical and demographic information collected Cerebral microvascular abnormalities were assessed via T1 and T2 weighted images and voxelwise method for analyzing diffusion tensor imaging	Abnormal thalamic and optic radiation microstructure was most strongly associated with elevated first arterial blood gas pO ₂ and elevated preoperative arterial blood gas pH ($p < 0.05$). The preterm neonates with CHD vulnerability of the brain, specifically the thalamocortical region.
Shedeed, S. A., & Elfaytouri, E. (2011). Brain maturity and brain injury in newborns with cyanotic congenital heart disease. <i>Pediatric Cardiology</i> , 32(1), 47-	38 term neonates with cyanotic CHD compared to healthy term controls (n=20).	Brain development and brain injury in neonates with CHD compared to healthy controls.	Prospective, comparative study in Egypt	Brain MRI and MRS images [MRI 1.5 Tesla Philips ACS-NT] Mean diffusivity and fractional anisotropy values were calculated via MRS	NAA/Ch significantly lower in cyanotic CHD (0.55 ± 0.08) compared to controls (0.67 ± 0.11) ($p < 0.001$). Mean ratio of lactate to Ch higher in CHD (0.14 ± 0.04) compared with controls (0.09 ± 0.04) ($p < 0.001$). Mean diffusivity higher 1.41 ± 0.06 in CHD compared to 1.27 ± 0.07 in

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
54.doi:10.1007/s00246-010-9813-7				Mean NAA/Ch and lactate/Ch metabolite ratios were calculated from 3 dimensional MRS	control ($p < 0.001$), and mean value for white-matter fractional anisotropy lower 0.19 ± 0.03 in CHD and 0.25 ± 0.08 in controls ($p < 0.001$). Increased risk for brain injury due to brain immaturity in neonates with cyanotic CHD.

ASD=atrial septal defect; CHD=congenital heart disease; COA=coarctation of the aorta; CPB=cardiopulmonary bypass; DHCA= deep hypothermic circulatory arrest; DORV=double outlet right ventricle; EEG=electroencephalogram; HLHS=hypoplastic left heart syndrome; IVH=intraventricular hemorrhage; MRI=magnetic resonance image; MRS=magnetic resonance spectroscopy; NIRS=near infrared spectroscopy; PDA=patent ductus arteriosus; PVL=periventricular hemorrhage; rSO2= regional cerebral oxygenation; SV=single ventricle; TGA=transposition of the great arteries; TMS=total maturation score; VSD=ventricular septal defect; WMI=white matter injury; 2V=two ventricle

Appendix 2-2. Neurodevelopmental Outcomes in Congenital Heart Disease

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
Hoffman, G. M., Brosig, C. L., Mussatto, K. A., Tweddell, J. S., & Ghanayem, N. S. (2013). Perioperative cerebral oxygen saturation in neonates with hypoplastic left heart syndrome and childhood neurodevelopmental outcome. <i>The Journal of Thoracic Cardiovascular Surgery</i> , 146(5), 1153-1164. doi:10.1016/j.jtcvs.2012.12.060	21 HLHS neonates after stage 1 palliation Median age at testing (56.3 ± 5.5 months)	Assess correlation of cerebral hypoxia during neonatal cardiac surgery and later ND delays.	Longitudinal study	ND outcomes were measured with Beery-Buktenica Developmental Test of Visual Motor Integration (VMI); Wechsler Preschool and Primary Scale of Intelligence III Matrix Reasoning Score; Developmental Neuropsychological Assessment Visual Attention Scale; Differential Ability Scales II Naming Vocabulary Test and INVOS NIRS, clinical, demographic, and surgical information were collected	Mean visual-motor integration was 93.4±14, slightly less than the population norm ($p < .05$). Perioperative stage 1 palliation rSO ₂ was significantly lower in low to abnormal visual-motor integration (63.6 ±8.1 vs 67.8 ±8.1, $p < .05$). Age, weight, rSO ₂ , arterial oxygen saturation, CPB and DHCA times, and later stroke predicted visual-motor integration ($R^2 = 0.53$, $p < .001$). Avoiding cerebral hypoxia may improve the outcomes in CHD.
Limperopoulos, C., Majnemer, A., Rosenblatt, B., Shevell, M. I., Rohlicek, C., & Tchervenkov, C. (1997). Agreement between the neonatal	32 term neonates with complex CHD, before cardiac surgery Mean age at time of	Degree of agreement between a neurologic exam and standardized neurobehavioral assessment.	Prospective, observational study	A pediatric neurologist performed a standard neurological exam which was compared to the scores obtained with the ENNAS, which assessed neurobehavioral status [greater than 3 is	Significant association between both examiners ($p < .0001$), with a crude agreement of 96.9%. Complete agreement in the documentation of any asymmetry and absent suck.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
neurological examination and a standardized assessment of neurobehavioural performance in a group of high-risk newborns. <i>Pediatric Rehabilitation</i> , 1(1), 9-14.	evaluation (14 ± 11.6 days)			considered abnormal]	ENNAS is consistent and valid, can detect abnormal neuro exam in CHD neonates.
Limperopoulos, C., Majnemer, A., Shevell, M. I., Rosenblatt, B., Rohlicek, C., & Tchervenkov, C. (2000). Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. <i>Journal of Pediatrics</i> , 137(5), 638-645. doi:10.1067/mpd.2000.109152	131 children with CHD (56 term neonates [cyanotic 75% and acyanotic 25%] and 75 infants [cyanotic 58% and acyanotic 42%]) were evaluated before and after surgery Neonatal: preop mean age at evaluation 8.8 ± 8.2 days (median, 6.0 days), postop mean of 22.8 ± 17.3 days (median, 18	Describe the preoperative and postoperative ND status of neonates and infants with CHD.	Prospective, observational study	A pediatric neurologist examination and ENNAS scores were obtained before and after surgery and compared for consistency in findings (normal versus abnormal).	Neurobehavioral abnormalities in >50% of neonates before surgery. Acyanotic CHD more likely to have abnormalities than those with cyanotic defects ($p < .05$). For infants, arterial oxygen saturations <85% were significantly associated with an abnormality ($p = .03$). Neonatal preoperative abnormalities included poor behavioral state observed in 62%, feeding difficulties in 34%, seizures in 7%, and microcephaly in 36%. Neurodevelopmental abnormalities are common in young infants with CHDs.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
	<p>days) after surgery</p> <p>Infant mean age of 7.1 ± 5.5 months (median, 5.7 months), postop mean of 19.1 ± 5.5 days (median, 12 days) after surgery</p>				
<p>Mussatto, K. A., Hoffmann, R. G., Hoffman, G. M., Tweddell, J. S., Bear, L., Cao, Y., & Brosig, C. (2014). Risk and prevalence of developmental delay in young children with congenital heart disease. <i>Pediatrics</i>, 133(3), e570-577. doi:10.1542/peds.2013-2309</p>	<p>99 infants with CHD [SV (n=34) and 2V (n=65)]</p> <p>Age at time of evaluation ranged from 5.5 to 37.3 months.</p> <p>3 categories: SV anatomy without genetic syndrome, 2V anatomy without genetic syndrome, and clinical diagnosis of genetic syndrome</p>	<p>ND skills and predictors of DD in children with CHD in early childhood after cardiac surgery.</p>	<p>Longitudinal, repeated measures study.</p>	<p>Median time interval between visits was 6.0 months (inter-quartile range 5.9–6.4) with 3-6 evaluations.</p> <p>ND outcomes measured with Bayley Scales of Infant Development, Third edition (BSID-III). Developmental delay defined as > 1 SD below normal.</p> <p>SES measured with the Hollingshead 4 Factor Index.</p>	<p>75% had DD in ≥ 1 area at ≥ 1 assessments.</p> <p>SV and 2V, without genetic syndrome had normalizing motor scores improving significantly over time ($p < .01$).</p> <p>Age, need for tube feeding, longer CPB time, and shorter time since last hospitalization were significant predictors of developmental outcomes.</p> <p>Longitudinal surveillance needed for children with CHD because exposure to risk and prevalence of DD changes over time.</p>

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
<p>Newburger, J. W., Sleeper, L. A., Bellinger, D. C., Goldberg, C. S., Tabbutt, S., Lu, M., . . . Gaynor, J. W. (2012). Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the single ventricle reconstruction trial. <i>Circulation</i>, 125(17), 2081-2091. doi:10.1161/circulationaha.111.064113`</p>	<p>314 infants with HLHS or other type of SV who underwent the Norwood procedure.</p> <p>Mean age at time of evaluation 14.3±1.1 month (range, 12.2–19.5 months)</p>	<p>ND outcomes at 14 months of age after the Norwood procedure</p>	<p>Multi-center, prospective study</p>	<p>ND outcomes measured with Bayley Scales of Infant Development, -Second Edition (BSID-II), which gives Psychomotor Development Index (PDI) and the Mental Development Index (MDI). Mean normative scores for PDI and MDI is 100±15</p> <p>Demographic and clinical variables collected.</p> <p>ND evaluators blinded to shunt type</p>	<p>Mean PDI 74±19 and MDI 89±18 scores lower than normative means (each $p < .001$).</p> <p>Independent predictors of lower PDI score ($R^2=26\%$) were clinical center ($p = .003$), birth weight <2.5 kg ($p = .023$), longer Norwood hospitalization ($p < .001$), and complications between Norwood discharge and age 12 months ($p < .001$).</p> <p>Independent risk factors for lower MDI score ($R^2=34\%$) were center ($p < .001$), birth weight <2.5 kg ($P=.04$), genetic syndrome/anomalies ($p = .04$), lower maternal education ($p = .04$), longer ventilation after Norwood ($p < .001$), and complications after Norwood discharge to age 12 months ($p < .001$).</p> <p>ND delays in Norwood survivors are highly associated with innate factors</p>

CHD=congenital heart disease; CPB= cardiopulmonary bypass; DD=developmental delay; DHCA=deep hypothermic circulatory arrest; ENNAS=Einstein Neonatal Neurobehavioral Assessment Scale; HLHS=hypoplastic left heart syndrome; ND=neurodevelopmental; NIRS=near infrared spectroscopy; rSO2= regional cerebral oxygenation; SES=socioeconomic status; SV=single ventricle; 2V=two ventricle

Appendix 2-3. Cerebrovascular Autoregulation in Neonates

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
Alderliesten, T., Lemmers, P. M., Smarius, J. J., van de Vosse, R. E., Baerts, W., & van Bel, F. (2013). Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. <i>J Pediatr</i> , 162(4), 698-704.e692. doi:10.1016/j.jpeds .2012.09.038	30 preterm neonates (≤ 32 weeks) with postnatal periventricular hemorrhage (PIVH) compared to 60 matched controls	The ability of rSO ₂ , cerebral fractional tissue oxygen extraction (cFTOE), and autoregulation in identifying neonates at risk for developing PIVH.	Prospective, comparative study in the Netherlands Sub-analysis of a prospective observational cohort of 650 preterm neonates	CA estimated by a correlation of MABP and rSO ₂ /NIRS (INVOS) cFTOE calculated as (SaO ₂ -rSO ₂)/SaO ₂ PIVH diagnosed by cranial ultrasound, grade I-II considered mild-moderate and grade III-IV severe PDA confirmed by echocardiogram Demographic and clinical variables collected.	MABP-rSO ₂ correlation was >0.5 significantly more often before mild/moderate PIVH and after severe PIVH compared with controls. rSO ₂ was higher and cFTOE lower in infants before severe PIVH MABP-rSO ₂ correlation indicates more blood pressure-passive brain perfusion in infants with PIVH ~ impaired CA Continuous assessment of patterns of rSO ₂ and arterial blood pressure may identify those at risk for severe PIVH
Brady, K. M., Mytar, J. O., Lee, J. K., Cameron, D. E., Vricella, L. A., Thompson, W. R., . . . Easley, R. B. (2010). Monitoring cerebral blood flow pressure autoregulation in	54 neonates and infants with CHD [septal defect=20, shunt defects=6, obstructive = 10, valvar=11, transplant=5, and other=2]	To determine the lower limits of pressure autoregulation in pediatric patients undergoing cardiac surgery with CPB.	Prospective, observational study	CA measured with cerebral oximetry index (COx), a moving correlation between MABP and rSO ₂ /NIRS (INVOS) to detect the lower limit of pressure autoregulation (LLA).	Hypotension was associated with increased values of COx ($p < .0001$). LLA could be determined using a threshold COx value of 0.4.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
pediatric patients during cardiac surgery. <i>Stroke</i> , 41(9), 1957-1962. doi:10.1161/stroke.aha.109.575167	Mean age 56 ± 65 months			Demographic and clinical variables collected.	Mean LLA for the cohort using this method was 42±7 mm Hg COx may be useful to identify arterial blood pressure-dependent limits of CA during CPB.
Chock, V. Y., Ramamoorthy, C., & Van Meurs, K. P. (2012). Cerebral autoregulation in neonates with a hemodynamically significant patent ductus arteriosus. <i>J Pediatr</i> , 160(6), 936-942. doi:10.1016/j.jpeds.2011.11.054	28 very low birth weight (VLBW) neonates (401-1500 grams) compared to 12 control VLBW infants	Compare CA in VLBW neonates treated medically or surgically for PDA.	Prospective, comparative study	CA measured with pressure passivity index (PPI), a correlation between MABP and rSO2/ NIRS (INVOS) to determine and loss of autoregulation. Baseline cranial ultrasound before treatment PDA confirmed by echocardiogram Demographic and clinical variables collected.	Neonates more likely to have greater PPI within 2 hours after surgical ligation compared with those treated with conservative management ($p = .04$) or indomethacin ($p = .0007$). Greater baseline PPI was correlated with hydrocortisone use ($p = .003$). Dopamine use ($p = 0.05$) and lower 5 minute Apgar score ($p = 0.02$) associated with PPI. CA more intact after medical treatment of a PDA compared with surgical ligation. Neonates may be at increased risk for cerebral

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
					pressure passivity six hours after surgical ligation of PDA.
Howlett, J. A., Northington, F. J., Gilmore, M. M., Tekes, A., Huisman, T. A., Parkinson, C., . . . Lee, J. K. (2013). Cerebrovascular autoregulation and neurologic injury in neonatal hypoxic-ischemic encephalopathy. <i>Pediatr Res</i> , 74(5), 525-535. doi:10.1038/pr.2013.132	24 neonates being treated with therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE) Mean gestational age was 39.2 ± 1.5 weeks	Describe the relationship between CA and neurologic injury in HIE	Prospective observational study	CA measured with hemoglobin volume index (HVx), which is the relationship between rSO2/NIRS (INVOS) and MABP. Optimal BP is the blood pressure range in which the cerebral vasculature has maximal pressure reactivity. Brain MRIs (1.5-Tesla Magnetom Avanto) obtained 3–7 d after treatment on 9 ± 3 days of life (range: 4–14 d). Injury graded as none, mild, moderate, or severe.	HVx successfully identified optimal BP during therapeutic hypothermia, 77% rewarming, and 86% normothermia MABP and CBV positively correlated, when MABP was <35 mm Hg, indicating pressure-passive vasoreactivity with impaired autoregulation. The linear regression line is illustrated ($E(Y) = 56.3 + 0.06X$; 95% confidence interval for slope: 0.04, 0.08; $p < 0.0001$). Neonates with moderate/severe injury in paracentral gyri, white matter, basal ganglia, and thalamus spent a greater proportion of time with MABP below optimal BP. Maintaining MABP within or above optimal BP reduces risk of neurologic injury.

ARTICLE	SUBJECTS/ AGE	OBJECTIVE	STUDY DESIGN	METHODS/ MEASURES	RESULTS/ CONCLUSIONS
Wagner, B. P., Ammann, R. A., Bachmann, D. C., Born, S., & Schibler, A. (2011). Rapid assessment of cerebral autoregulation by near-infrared spectroscopy and a single dose of phenylephrine. <i>Pediatr Res</i> , 69(5 Pt 1), 436-441. doi:10.1203/PDR.0b013e3182110177	24 term and/or preterm neonates and infants with differing medical conditions [asphyxia, head trauma, stroke, sepsis, CHD, etc.]	Correlation of rSO ₂ /NIRS with cerebral blood flow (CBF) after single dose phenylephrine (PE).	Prospective study in Queensland, AU.	CA measured with autoregulation index (ARI) calculated by dividing the difference between rSO ₂ /NIRS (NIRO 500) and MABP at baseline measure and post PE. + ARI is an increase in CBF when the MABP increased shows impaired CA.	Hemoglobin-based ARI and Blood Flow Index-based ARI were significant with correlation coefficients of 0.78. Validates dynamic autoregulation based on cerebral deoxyhemoglobin signals.

CA=cerebral autoregulation; CBV=cerebral blood volume; CPB=cardiopulmonary bypass; MABP=mean arterial blood pressure; MRI=magnetic resonance image; NIRS=near infrared spectroscopy; PDA=patent ductus arteriosus; rSO₂=regional cerebral oxygenation

Appendix A. UCLA IRB Approval

5/11/2016

<https://webirb.research.ucla.edu/WEBIRB/Doc/0/1JISASM6SBN4H2OCVKMEIL222B/fromString.html>



University of California Los Angeles
11000 Kinross Avenue, Suite 211
Los Angeles, CA 90095-1694

<http://ohrpp.research.ucla.edu>
GC-IRB: (310) 825-7122
M-IRB: (310) 825-5344

APPROVAL NOTICE

DATE:	5/10/2016
TO:	NHU TRAN SCHOOL OF NURSING
FROM:	JAMES MC GOUGH, MD Chair, MIRB3
RE:	IRB#15-001575-AM-00002 Change of study location Cerebral Autoregulation in Neonates with Congenital Heart Disease compared to Healthy Neonates Version: 1

The UCLA Institutional Review Board (UCLA IRB) has approved the above-referenced study. UCLA's Federalwide Assurance (FWA) with Department of Health and Human Services is FWA00004642.

Submission and Review Information

Type of Submission	Amendment
Type of Review	Expedited
Approval Date	5/9/2016
Expiration Date of the Study	10/28/2018
Funding Source(s)	N/A

Specific Conditions for Approval

<p>– Research Participants Bill of Rights - By California law, a copy of the Research Participants Bill of Rights in a language in which the participant is fluent must be given to all research participants in this study as there is a real or foreseeable risk of biomedical harm.</p> <p>– Translations Needed - Please submit translated copies of your [contact information, ad and notices, recruitment, screening, consent documents] as an amendment(s) before recruiting or consenting any subjects for whom these translations are required. [If medical study being conducted in CA—Be sure and provide subjects with the appropriately translated Research Participant's Bill of Rights. Numerous translations are available for download on the HRPP website at http://www.ohrpp.research.ucla.edu/pages/bill-of-rights.</p>

<https://webirb.research.ucla.edu/WEBIRB/Doc/0/1JISASM6SBN4H2OCVKMEIL222B/fromString.html>

1/2

Regulatory Determinations

-- **Children as Subjects** - The UCLA IRB determined that the research meets the requirements of 45 CFR 46.404 for research involving children as subjects.

-- **Expedited Review Category(ies)** - The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110 categories 4 and 5.

-- **Three Year Extended Approval** - The UCLA IRB has determined that this study meets the criteria for a 3 year extended approval. (For reference, please see the OHRPP guidance document "Extended Approval for Minimal Risk Research Not Subject to Federal Oversight" at http://ora.research.ucla.edu/OHRPP/Documents/Policy/4/Extended_Approval.pdf)

Currently approved recruitment and/or consent documents:

N/A

Important Note: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other UCLA clearances and approvals or other external agency or collaborating institutional approvals may be required before study activities are initiated. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity.

General Conditions of Approval

As indicated in the PI Assurances as part of the IRB requirements for approval, the PI has ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The PI and study team will comply with all UCLA policies and procedures, as well as with all applicable Federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- Ensuring that the personnel performing the project are qualified, appropriately trained, and will adhere to the provisions of the approved protocol,
- Implementing no changes in the approved protocol or consent process or documents without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notifying the IRB as soon as possible afterwards),
- Obtaining the legally effective informed consent from human subjects of their legally responsible representative, and using only the currently approved consent process and stamped consent documents, as appropriate, with human subjects,
- Reporting serious or unexpected adverse events as well as protocol violations or other incidents related to the protocol to the IRB according to the OHRPP reporting requirements.
- Assuring that adequate resources to protect research participants (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if adequate resources become unavailable.
- Arranging for a co-investigator to assume direct responsibility of the study if the PI will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as co-investigator in this application, or advising IRB via webIRB in advance of such arrangements.

Appendix B. CA One Pager

MR Imaging of Perinatal Brain Injury (parent study) **Autoregulation of Cerebral Blood Flow in Neonates with Congenital Heart Disease Compared to Healthy Controls (sub-study)**

Project Summary:

The overall goal is to determine whether cerebral autoregulation (CA) is impaired in neonates with congenital heart disease (CHD), and whether impaired CA is associated with abnormal neurobehavioral status.

Specific Aims:

1. Compare cerebral oxygenation (an index of CA) between neonates with CHD and age and gender matched healthy neonates less than or equal to 10 days of life.
2. Examine associations between neurobehavioral symptoms and impaired CA.
3. Identify the clinical and demographic factors associated with abnormal CA in neonates who are less than or equal to 10 days of life with and without CHD.

Study Design:

2 Group Comparative (CHD vs. age- and gender matched healthy neonates)

Pre-Cardiac Surgery measurements:

1. Cerebral oxygenation using NIRS measured in supine and sitting positions.
 - a. Noninvasive measure of frontal lobe oxygenation levels
 - b. Validated indirect measure of CA in newborns- abnormal CA demonstrated by a longer time (> 5 seconds or > 10%) to return to baseline rSO₂/NIRS
2. Noninvasive oxygen saturation via the pulse oximeter measured in supine and sitting positions.
3. Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS)

Subjects:

16 CHD - neonates (\leq 10 days of age) admitted to CHLA

16 full term neonates – HPMC or Alta Med

Inclusion/Exclusion Criteria:

1. Neonates (\leq 10 days of age) with any CHD before cardiac surgery
2. Healthy Neonates (\leq 10 days of age) without congenital heart defects
3. \geq 37 weeks gestation
4. No documented genetic syndromes or multiple congenital anomaly
5. No documented infections
6. No documented intraventricular hemorrhage (IVH)
7. No documented infant of substance abusing mother (ISAM) or prenatal illicit drug use
8. No documented history of maternal chorioamnionitis or steroids in the last trimester
9. No documented small for gestational age (SGA) or intrauterine growth restriction (IUGR)

Subject Payment: \$50 dollar Target gift card upon completion of all study measures

If you have questions or potential subjects to refer, please contact:

Nhu Tran, MSN, RN

Doctoral Student, UCLA, and Clinical Research RN, CHLA

Phone: 562-397-2262 Email: ntran@chla.usc.edu

Appendix C. Recruitment Flyer: CHD

RESEARCH STUDY IN NEWBORNS WITH CONGENITAL HEART DISEASE (CHD)



**Do you have or anticipate the birth of a newborn
with CHD?**

Is your newborn less than 3 days old?

Did you have an uncomplicated pregnancy?

- We are conducting a research study to learn how the body regulates blood flow to the brain during a position change in newborns both with and without CHD.
- Study participation requires a neurologic assessment, brain oxygenation measures with a noninvasive sensor placed on the forehead while the newborn is changed from a lying to sitting position. Total newborn participation time is 38 minutes.
- Volunteers will receive a \$50 gift card as compensation for participation.
- If you answered **“yes”** to any of the above questions, please contact Nhu Tran RN, MSN (Principle Investigator) **323-361-6355** or email at ntran@chla.usc.edu for more information.

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Appendix D. Recruitment Flyer: Healthy Controls

RESEARCH STUDY IN HEALTHY NEWBORNS



Do you have or anticipate the birth of a healthy newborn?

Is your newborn less than 3 days old?

Did you have an uncomplicated pregnancy?

- We are conducting a research study to learn how the body regulates blood flow to the brain during a position change in newborns both with and without congenital heart disease.
- Study participation requires a neurologic assessment, brain oxygenation measures with a noninvasive sensor placed on the forehead while the newborn is changed from a lying to sitting position. Total newborn participation time is 38 minutes.
- Volunteers will receive a \$50 gift card as compensation for participation.
- If you answered “**yes**” to any of the above questions, please contact Nhu Tran RN, MSN (Principle Investigator) **323-361-6355** or email at ntran@chla.usc.edu for more information.

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Appendix E. Screening Form

Date Screening Started _____

Date Screening Completed _____

Inclusion / Exclusion	Inclusion Criteria Met (Yes or No)	Exclusion Criteria Met (Yes or No)	Information obtain from Parent / Chart / Physician	Initials of Screener
Congenital Heart Disease or Control				
Neonate ≤ 10 days old				
≥ 37 weeks gestation				
Hemodynamically stable				
Documented pre or post-natal medical conditions (healthy only)				
Documented Genetic syndrome				
Intubated				
Inotropic support				
Documented infection				
Documented Intraventricular hemorrhage				
Documented infants of substance abusing mother (ISAM)				
Documented maternal chorioamnionitis				
Documented steroid use (maternal in the last trimester or neonatal)				
Documented SGA/IUGR				

IRB Approved Screener (print name)

IRB Approved Screener (signature)

Appendix F. Telephone Script

Cerebral Autoregulation in Neonates with Congenital Heart Disease compared to Healthy Neonates

SCRIPT FOR INTRODUCING STUDY TO POTENTIAL PARTICIPANTS OR PARENTS OF POTENTIAL PARTICIPANTS AND INITIAL SCREENING THROUGH THE TELEPHONE

The following script would be in response to the participant expressing an interest to participate in the study through the telephone. They will be speaking with the Principal Investigator from the school of nursing.

Thank you for calling about the study on Control of Blood Flow in Newborns with Congenital Heart Disease compared to Healthy Newborns” My name is Nhu Tran and I am the Principal Investigator. I need to ask you a few questions in order to determine whether your baby is eligible to be part of the research. Before I begin, let me tell you about the research.

The purpose of the study is to learn about the control of blood flow in the brain when the baby’s position is changed from lying down to sitting up. If you or your baby is eligible, the baby will be tested for muscle function, hearing, and visual function. A sensor will be applied to the forehead to measure the amount of oxygen. The baby will be observed for five minutes. The baby’s position will then be changed from lying down to sitting. The baby will be observed for another five minutes.

Would you like to continue with the screening to determine if you and your baby are eligible? The screening will take about 5 minutes or less. You may feel uncomfortable answering questions about your medical history. You do not have to answer any questions you do not wish to answer and you may stop at any time. Your participation in the screening is voluntary. A decision whether or not to participate in the screening will not affect your relationship with UCLA or CHLA. You will not benefit from the screening.

Your answers will be confidential. No one will know the answers except for the research team.

If you and your baby are eligible and would like to be part of the study, your answers will be kept with the research records. If you or your child does not qualify for the study, your answers will be destroyed.

Would you like to continue with the screening?

[If no, thank the person and hang-up].

[If yes, continue with the screening].

For Neonates with Heart Disease:

Does your baby have a congenital heart defect? (Yes / NO)

Is your baby, less than or equal to 3 days old? (Yes / NO)

Did you experience any complications during pregnancy or during delivery? (Yes / NO)

For Healthy Control Group:

Is your baby, less than or equal to 3 days old? (Yes / NO)

Did you experience any complications during pregnancy or during delivery? (Yes / NO)

[If yes, include the following at the end of the screening]:

Thank you for answering the screening questions.

[Indicate whether the person is eligible, requires additional screening at the clinic, or is not eligible and explain why.]

If the potential subject requires additional screening for eligibility

Because you responded “yes” to having a child with congenital heart defect and did not experience complications during pregnancy or during delivery, we will need to further screen your medical records for eligibility. Do you allow us to further investigate details of your baby’s heart defect and your pregnancy and delivery by obtaining information from your doctor and / or medical records? (Yes / NO)

[If no, thank the person and hang-up].

[If yes, include the following at the end of the screening]:

This information will be kept confidential and will be destroyed if you are not eligible to participate upon review of your records or verification from your physician. I will call you back to notify you of eligibility for study participation. *[Obtain phone number and hang-up]*

If the potential subject does not meet the study criteria

Because your baby has had heart surgery, had an infection and is on antibiotics, or because you used steroids in the last three months of your pregnancy, you are NOT eligible for the study. *[Thank the person and hang-up]*

If the potential subject meets the study criteria

I have a copy of the consent that I can mail / email to you or give you in person at your next clinic appointment. I can also read the consent to you now over the telephone. Please feel free to let us know if you have any questions that we can answer for you.

If you agree to participate, please mail back the signed consent form in the pre-stamped envelope. You can also give us the consent if you agree to participate in the study today (day of clinic visit). You will also be asked to sign a general medical release form that will allow us to obtain information about your health and the baby’s heart disease from your doctor and medical records.

After we have received your signed informed consent and general medical release form, we will contact you to set up an appointment to complete the study. The study will take approximately

45 minutes of your time. In appreciation for your time and willingness, you will be given a \$50.00 Target gift card at the end of the study.

The study is not being done to improve your baby's condition or health. There is a risk that the skin may have irritation from the sensor for measuring oxygen, or the oxygen levels may decrease with agitation or movement during the procedure. Comfort measures will be provided to the baby such as the pacifier, swaddling, or gentle rocking so that the oxygen levels are maintained with agitation or movement. To minimize the risk of irritation in the skin, we will follow manufacturer and CHLA's guidelines when placing the sensor on the forehead. If a rash occurs, the baby's physician will provide treatment. Your participation is voluntary. If you chose not to participate, that will not affect your right to health care or other services to which you are otherwise entitled. All information you provide will be kept confidential.

Do you have any questions about the screening or the research? I am going to give you - telephone numbers to call if you have any questions later. Do you have a pen? If you have questions about the research screening, you may call Nhu Tran at 323-361-6355 (work) and she will answer your questions.

If you have questions regarding the rights of research subjects or if you have complaints or concerns about the research and cannot reach the Principal Investigator; or just want to talk to someone other than the Investigator, you may call the UCLA Office of the Human Research Protection Program at (310) 825-7122 or Children's Hospital Los Angeles, Human Subjects Protection Program office at (323) 361-2265.

Appendix G. Consent

University of California, Los Angeles

CONSENT/PERMISSION/ASSENT¹ TO PARTICIPATE IN A RESEARCH STUDY

Cerebral Autoregulation in Neonates with and without Congenital Heart Disease

Blood Flow to the Brain of Newborns Born with Congenital Heart Disease and Healthy Newborns

• **INTRODUCTION**

You are invited to be part of a research study conducted by Nhu Tran, RN, BSN, MSN, and Paul Macey, PhD, from the School of Nursing at the University of California, Los Angeles (UCLA) and the Heart Institute at Children’s Hospital Los Angeles (CHLA). You are invited to be part of the study because your child is a newborn that is less than or equal to 3 days old, is healthy, or has a congenital heart defects (CHD). About 45 newborns with CHD and 45 healthy newborns will be enrolled at CHLA. Being part of the study is completely voluntary. Please read the information below and ask questions about anything you do not understand before deciding whether or not to be part of the study.

• **PURPOSE OF THE STUDY**

The purpose of the study is to compare healthy newborns and newborns with CHD on blood flow to the brain during position change, and whether blood flow to the brain is associated with movement, hearing, and vision.

• **PROCEDURES**

The time to participate will be about 45 minutes and all observations and measurements will be done in the baby’s room. If you agree to be part of the study, the following will happen:

- Information will be collected from your medical record about your pregnancy and your baby’s birth, complications during pregnancy and during delivery, exposures to harmful substances, medications, and illnesses. Information will also be collected about the baby’s heart defects, birth history, other conditions, current medications, lab results, oxygen levels, and medical treatments.
- A sensor will be attached to the baby’s forehead, which will be connected to a device called near infrared spectroscopy (NIRS). The NIRS will record blood flow to the brain. Another sensor will be placed on the right hand, which will be attached to a device called pulse oximetry. The pulse oximetry will record oxygen level in the blood. The procedure will take approximately 10 minutes.
- The baby will then be observed for five minutes while lying flat. After five minutes, the baby will held in a sitting position and will be observed for another 5 minutes. The procedure will take approximately 10 minutes.
- The monitoring equipment will be removed, which will take approximately 3 minutes.

¹ This form also serves as the permission form for the parent(s) to read and sign. In this case, “You” refers to your child.

- The baby's movement, hearing, and vision will then be tested. The procedure will take approximately 15 minutes.

- **POTENTIAL RISKS AND DISCOMFORTS**

The following will describe potential risks and discomforts during the study. While we have listed the most common risks and discomforts, please be aware that the research study may involve risks that are currently unforeseeable and therefore cannot be described.

Risk of breach in confidentiality. The baby's and your information will be protected. Electronic data will be stored in an encrypted storage device and a computer with password protected software. A hard copy of data including personal or private identifiable data will be stored in a locked file cabinet in a locked office with limited access to the PI. After study completion, all data files will be stripped of personal information.

- Skin irritation or rash related to the near infrared spectroscopy (NIRS) probe. To minimize the risk of redness, irritation, or rash, we will follow the guidelines outlined by the manufacturer and CHLA. If a rash occurs, the baby's physician will provide treatment.
- Discomfort from movement during muscle, hearing, and visual testing procedures. To minimize risk of discomfort, measures will be provided to the baby such as gentle talking, rocking, patting, or giving the pacifier or gloved finger. Parents will also be able to console the newborn during the testing.
- Decreased oxygen levels during agitation or movement. Comfort measures will be provided to the baby such as gentle talking, rocking, patting, or giving the pacifier or gloved finger to maintain oxygen levels during agitation or movement.
- Rare chance of line dislodgement. If the baby has intravenous or umbilical lines, the PI will make sure there is enough tubing length to decrease the chance that the lines may be dislodged during position change. However, lines being dislodged are a normal risk associated with routine care during hospitalization.

- **ANTICIPATED BENEFITS TO SUBJECTS**

There is no direct benefit as a result of being part of the research.

- **ANTICIPATED BENEFITS TO SOCIETY**

The potential benefit to society is that we will gain information about the blood flow to the brain and about the relationship between blood flow to the brain and movement, hearing, and vision in newborns with and without congenital heart disease. The risk/benefit ratio is favorable for this study and adverse events are not anticipated.

- **ALTERNATIVES TO PARTICIPATION**

This is not a treatment study. You may choose not to be part of the study. Being part of the study will not affect the care and/or treatment of your baby.

- **PAYMENT FOR PARTICIPATION**

- In appreciation for your time, and willingness to allow your child to be part of the study, you will receive a \$50 Target gift card at the end of the study.
- If your child is unable to complete the study due to agitation or instability, you will receive a \$25 Target gift card if half of the study is completed.
- You will be asked to sign a receipt of payment form. If you choose to withdraw from the study, and not complete all required observations, you will be paid for the extent that your baby was able to be part of the study.

- **FINANCIAL OBLIGATION**

You are not responsible for any of the costs involved in the study. Neither you nor your insurance company will be billed for being part of the research.

- **PRIVACY AND CONFIDENTIALITY**

Members of the research team and, if appropriate, your physicians and nurses will know that you are being part of the research study. All results will be kept confidential but may be made available to you and/or your physician, if you wish. No information about you or provided by you during the research will be disclosed to others without your written permission, except:

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- if required by law (i.e., child or elder abuse, harm to self or others, reports of certain infectious diseases).

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

Authorized representatives of the UCLA and CHLA Institutional Review Board (IRB) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

- **PARTICIPATION AND WITHDRAWAL**

Being part of the research is **VOLUNTARY**. Your choice about whether or not to be part of the study will have no effect on your care, services, or benefits at UCLA or Children's Hospital Los Angeles. If you agree to be part of the study, but later decide to withdraw from the study, you may do so without affecting your rights to health care, services, or other benefits at UCLA or Children's Hospital Los Angeles. Please contact the Principal Investigator if you wish to withdraw from the study.

- **WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR**

The investigator may withdraw you from being part of the research if necessary to protect your baby's or your health or if other situations arise that make it necessary to do so. If your baby experience side effects or becomes ill during the research or cannot be calmed after 10 minutes of comfort measures, you may have to drop out even if you would like to continue. The investigator, Nhu Tran, RN, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is

part of the research plan that people who develop certain conditions may not continue to participate.

- **NEW INFORMATION**

If there is significant new information found during the course of the study or the research plan is changed in a way that might affect your decision to continue to be part of the study, you will be informed, and your consent to continue in the study may be requested.

- **HOW TO OBTAIN INFORMATION**

If you have any questions or concerns about the research, please feel free to contact anytime:

Principal Investigator: Nhu Tran, RN, MSN

Phone: 323-361-6355

Email: ntran@chla.usc.edu

Faculty Sponsor: Paul Macey, PhD

Phone: 424-234-3244

Email: pmacey@ucla.edu

- **FINANCIAL INTEREST OF THE INVESTIGATOR**

This study is not funded. If your physician is an investigator for this study, he/she is interested in both your healthcare and the conduct of this research. You are not under any obligation to participate in a research study conducted by your physician.

- **RIGHTS OF RESEARCH SUBJECTS**

You may withdraw from this study at any time and discontinue participation without penalty. You are not waiving any legal claims, rights, or remedies because of your participation in this research study. If you have questions regarding the rights of research subjects or if you have complaints or concerns about the research and cannot reach the Principal Investigator; or just want to talk to someone other than the Investigator, you may call Children’s Hospital Los Angeles, Human Subjects Protection Program office at (323) 361-2265 or UCLA Office of the Human Research Protection Program (OHRPP) at (310) 825-7122.

Contact for future research

May someone from CHLA contact you to invite you to participate in future research? Please provide your initials beside your decision.

_____ Yes _____ No [for subject to complete, if the subject is 14 years or older]

_____ Yes _____ No [for parent to complete, if subject is a minor]

SIGNATURE OF RESEARCH SUBJECT (If the subject is 14 years or older)

Your signature below indicates

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;

- You consent/assent to your participation in this research study; and
- You will be given a copy of the Experimental Subject’s Bill of Rights, a signed copy of this form, and a signed copy of the HIPAA authorization form.

 Print Name of Subject

 Signature of Subject

 Date

SIGNATURE OF PARENT(S)/LEGAL GUARDIAN(S) (If the subject is a minor)

Your signature(s) below indicates

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to your child’s participation in this research study;
- You agree to your own participation in this research study; and
- You will be given a copy of the Experimental Subject’s Bill of Rights, a signed copy of this form, and a signed copy of the HIPAA authorization form.

 Print Name(s) of Parent(s)/Legal Guardian(s)

 Signature of Parent/Legal Guardian

 Date

 Signature of Parent/Legal Guardian

 Date

SIGNATURE OF INDIVIDUAL OBTAINING CONSENT

I have explained the research to the subject and/or the subject’s parent(s)/legal guardian(s) and have answered all of their questions. I believe that they understand all of the information described in this document and freely give consent/permission/assent to participate.

 Print Name of Individual Obtaining Consent

Signature of Individual Obtaining Consent Date

SIGNATURE OF WITNESS (if applicable)

My signature as Witness indicates that the subject and/or the subject's parent(s)/legal guardian(s) voluntarily signed this consent/permission/assent form in my presence.

Print Name of Witness

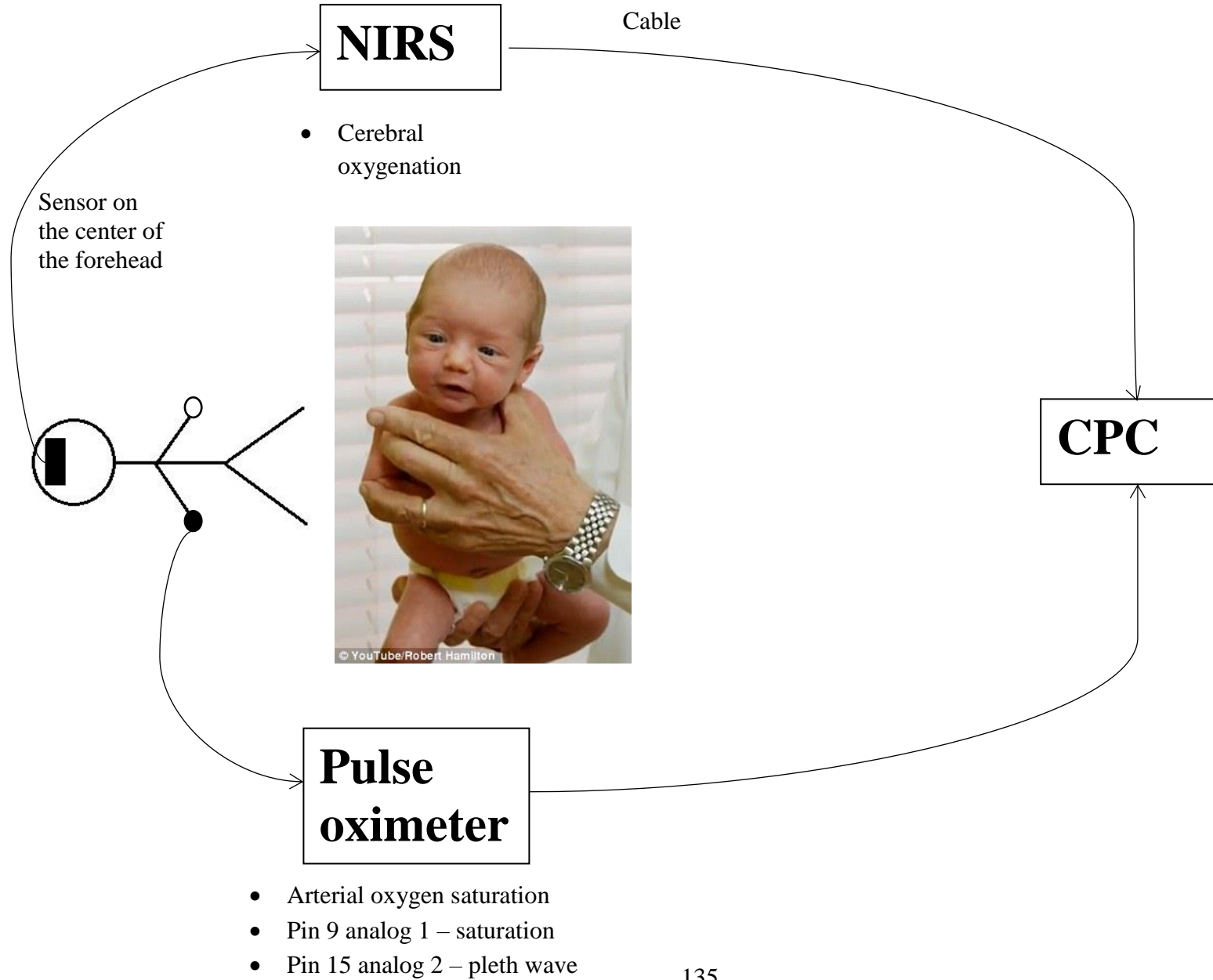
Signature of Witness Date

SIGNATURE OF INTERPRETER (if applicable)

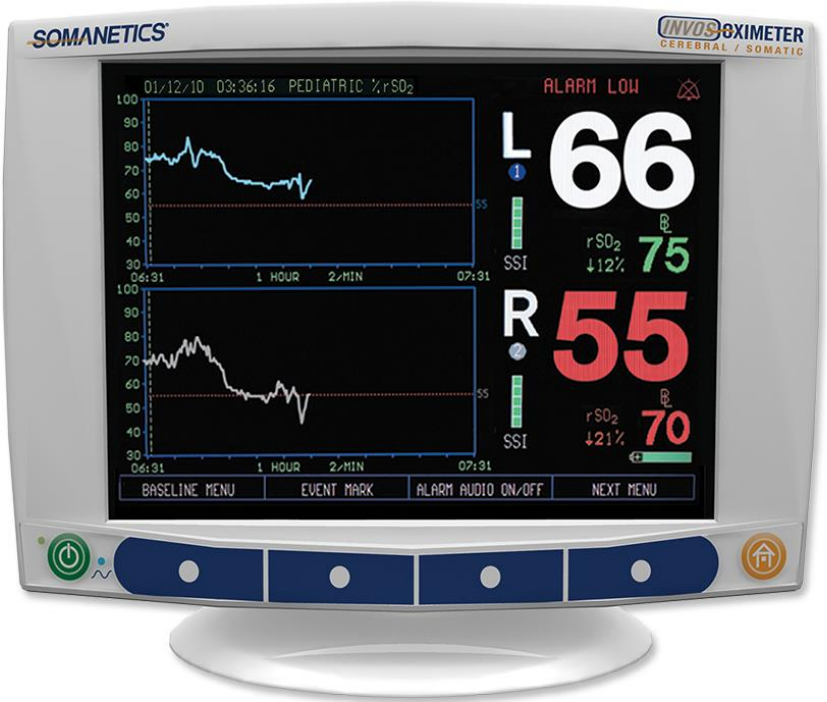
Print Name of Interpreter

Signature of Interpreter Date

Appendix H. Diagram of Devices



Appendix I. Image of NIRS Sensor & Monitor



2-Channel Monitor

Appendix J. Einstein Neonatal Neurobehavioral Assessment Scale

BELL		10	18
RATTLE	○	13	18
VOICE	○	10	18
BULLS - EYE	○	13	24
FACE - VOICE	○	13	24
HEAD EXTENSION	○	1	3
TRACTION	○	2	3
HEAD LAG	○	2	3
EXTREMITY MOVEMENT	○	1	3
VENTRAL SUSPENSION	○	1	3
OPTIC BLINK	○	1	2
ROOTING	○	1	3
SUCKING	○	1	3
ROTATION	○	1	3
MORO	○	1	3
TNR	○	1	2
GRASP	○	1	3
POPLITEAL ANGLE	○	1	3
ARM RECOIL	○	3	4
SPONTANEOUS MOVEMENT	○	6	4
TONE	○	3	4
CUDDLINESS	○		

EINSTEIN EVALUATION RECORD

Baby's Name _____ Date: _____

Examiner: _____ Scorer: _____

Study Number

MCH Chart Number

Sex (1=Male; 2=Female)

Chronological Age in Days

Gestational Age at Birth

Gestational Age at Time of Exam

0=AGA; 1=SGA; 2=LGA

Birthweight (grams)

Present Weight (grams)

Number of Minutes Since Last Feed

Was Baby Fed During Exam? (1=Yes; 2=No)

1=In-Hospital; 2=Outpatient

Number of Days Since Discharge

Head Circumference (centimeters)

SCORE SHEET

	<u>STATE</u>	<u>SCORE</u>
1. <u>LATERAL POSITION PREFERENCE</u> (3,4) (3 trials)		
1 = right	□□□	□
2 = left	□□□	□
3 = midline	□□□	□
2. <u>POPLITEAL ANGLE</u> (3,4)		
0 = 150 - 180°	R □□□	□
1 = 120 - 150°	L □□□	□
2 = 90 - 120°		
3 = < 90°		
3. <u>ROOTING</u> (3, 4, 5)		
0 = absent		
1 = slight twitch or movement of mouth toward stimulated side	R □□□	□
2 = head movement and mouth movement to stimulated side	L □□□	□
3 = full head turn toward stimulated side with grasping motion of lips		
4. <u>SUCKING</u> (3,4)		
0 = absent	□□□	□
1 = weak and intermittent with little pressure		
2 = intermittent with strong pressure		
3 = continuous vigorous with strong, constant pressure		

5. VISUAL FOLLOWING - BULLSEYE (3,4) (4 trials)

- 0 = no following response
- 1 = fixates, brief transient following
- 2 = fixates, intermittent good following
- 3 = sustained fixation, following with eyes or with head and eyes

STATE SCORE

R L

R->L

L->R

R->L

L->R

6. AUDITORY ORIENTING (3,4) (3 trials)

- 0 = no orienting response
- 1 = quieting, eyes brightening
and widening, blink, no eye movement
- 2 = quieting, eyes brightening
and widening, some searching movements with eyes only
- 3 = eyes brightening and searching
with head turning to side of sound

RATTLE

STATE SCORE

R

L

R

L

R

L

BELL

STATE SCORE

R

L

R

L

R

L

VOICE

STATE SCORE

R

L

R

L

R

L

7. VISUAL FOLLOWING - FACE AND VOICE (3,4) (4 trials)

0 = no fixation on face

1 = fixation, brief transient following

2 = fixation intermittent good following

3 = sustained fixation, steady following
with eyes or head and eyesSTATE SCORE

R L

□□□ R->L □□

□□□ R->L □□

□□□ R->L □□

□□□ R->L □□

8. OPTIC BLINK (3,4) (2 trials, right and left)

0 = absent

1 = weak or intermittent

2 = consistent response

R □□□ □

L □□□ □

R □□□ □

L □□□ □

9. ARM RECOIL (3,4)

0 = absent

1 = slow, weak flexion

2 = moderate flexion

3 = brisk flexion

R □□□ □

L □□□ □

10. HEAD EXTENSION (3,4)

0 = no extension

1 = attempts extension with difficulty; rolling

2 = good righting; falls back when sitting upright

3 = complete and sustained righting

□□□ □

11. GRASP (3,4)

- 0 = absent
- 1 = short, weak grasp
- 2 = moderate grasp
- 3 = supports weight, sustained grasp

STATE SCORE

<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	R <input type="checkbox"/>
	L <input type="checkbox"/>

12. TRACTION (3,4)

- 0 = no flexion, no resistance to extension of arms
- 1 = slight flexion, then extension
- 2 = moderate flexion
- 3 = resistance to extension; semi-flexion maintained

<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/>
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13. HEAD LAG (3,4)

- 0 = no flexion; head hangs passively down
- 1 = slight intermittent flexion, rolling
- 2 = moderate flexion; head remains in upright position for at least 3 seconds
- 3 = head remains in line with body

<input type="checkbox"/>

14. MORO (3,4) (5 trials)

- 0 = absent
- 1 = extension of forearms at elbow
and extension of fingers
- 2 = 1 plus abduction of arms at shoulder
- 3 = 2 plus adduction of arms

<u>STATE</u>	<u>Score</u>	<u>Consol Latency</u>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

15. WITHDRAWAL (3)

- 0 = absent
 1 = weak flexion
 2 = strong flexion
 3 = vigorous flexion with alternating extension

<u>STATE</u>	<u>Score</u>	<u>Consol Latency</u>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

16. TONIC NECK REFLEX (3,4)

- 0 = absent
 1 = transient
 2 = sustained

<u>STATE</u>	<u>Score</u>	<u>Consol Latency</u>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

17. ACTIVE HEAD EXTENSION (PRONE) (4)

- 0 = no head extension
 1 = weak and transient extension
 2 = extension for < 10 seconds
 3 = extension for at least 10 seconds duration

<u>STATE</u>	<u>SCORE</u>
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/>

18. EXTREMITY MOVEMENT (PRONE) (4)

- 0 = absent
 1 = weak and uncoordinated movements
 2 = coordinated crawl with stimulation
 3 = coordinated crawl without stimulation

19. VENTRAL SUSPENSION (4,5)

- 0 = flaccid; head and extremities hanging down
 1 = head hanging; some flexion of extremities
 2 = transient lifting of head; semi-flexion of extremities
 3 = sustained lifting of head in line with trunk
 and extension of lower extremities (occasional
 flexion of lower extremities is seen, but head
 and back are in line)

<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/>
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20. ROTATION (3,4)

0 = no ocular response

1 = lateral deviation

2 = lateral deviation toward side of stimulation

and post-rotational deviation to opposite side

3 = lateral deviation and post-rotational nystagmus

4 = nystagmus during rotation

STATESCORE

SUMMARY ITEMS**SCORE**21. CUDDLINESS (3,4,5)

- 1 = resists and/or thrashes and/or stiffens
- 2 = lies passively
- 3 = molds and relaxes only with patting,
rocking and talking
- 4 = always molds, relaxes and clings

22. SPONTANEOUS MOVEMENTS

- 0 = none
- 1 = few movements
- 2 = moderate number of movements
- 3 = high moderate
- 4 = marked frequency, consistent movement

23. TREMOR: A) INCIDENCE (1,2,3,4)

- 0 = absent
- 1 = rare
- 2 = marked (frequent)

TREMOR: B) QUALITY (1,2,3,4)

- 1 = coarse (low frequency, high amplitude >3 cm)
- 2 = fine (high frequency, low amplitude < 3cm)
- 3 = both coarse and fine

TONUS (3,4,5)

- 0 = hypotonic (little or no resistance to manipulation)
- 1 = slightly floppy
- 2 = normal
- 3 = slightly hypertonic
- 4 = moderately hypertonic (exaggerated resistance
to extension of extremities, tendency for head
extension to predominate)
- 5 = opisthotonic (sustained extensor posture of head
and trunk)
- 6 = mixed tonicity across head, trunk, upper
and lower extremities

SUMMARY

1. GENERAL APPEARANCE:
2. HEAD PREFERENCE: a) spontaneous:
 b) test item:
3. RESPONSE TO SENSORY STIMULI: a) visual - bullseye:
 b) auditory - rattle:
 bell:
 voice:
 c) combined - face and voice:
 d) dominant modality:
4. MOTOR: a) head control - flexion:
 extension:
 prone:
 ventral suspension:
 b) amount of spontaneous movements:
 c) tremors:
 d) asymmetry:
5. TONE:
6. TEMPERMENT: a) response to visual stimuli:
 b) response to auditory stimuli:
 c) response to manipulation:
 d) overall temperament:
 e) predominant state:
7. REACTION TO ADVERSIVE STIMULI: a) irritability:
 b) consolability:
 c) cuddliness:
8. ANY UNUSUAL SITUATIONS:

Appendix K. Procedure Form

	Preparation	Minute 0-5	Min. 6-10	Min. 11-26	Min. 27-32	Min. 32.10 sec Immediate	Min. 32.11-37	Min. 37-38
Procedure: Document actual time for each step	Speak with bedside RN	Attach NIRS to forehead and pulse ox to R hand	Connect probes to monitor and ensure neonate's comfort	Complete ENNAS	Monitor readings in supine position	Place neonate in sitting (90°) position	Monitor readings in sitting position	Remove equipment
Intervention:								
Pacifier								
Rocking								
Patting								
Diaper Δ								
Fed								
Color:								
Pink								
Pale								
Jaundice								
Red								
Dusky**								
Resp. (RPM)								
Regular								
Irregular								
Slow								
Fast								
HR (BPM)								
HR Range								
O2 Sat %								
O2 Sat Range								
NIRS Value								
NIRS Range								
Supplemental O2 and type*								
A-Line Value and type*								
A-Line Range (S/D/M)								
State:								
Deep sleep								
Light sleep								
Drowsy								

	Preparation	Minute 0-5	Min. 6-10	Min. 11-26	Min. 27-32	Min. 32.10 sec Immediate	Min. 32.11-37	Min. 37-38
Procedure: Document actual time for each step	Speak with bedside RN	Attach NIRS to forehead and pulse ox to R hand	Connect probes to monitor and ensure neonate's comfort	Complete ENNAS	Monitor readings in supine position	Place neonate in sitting (90°) position	Monitor readings in sitting position	Remove equipment
Awake								
Fussy Awake								
Crying								
Room:								
Quiet								
Noisy								
Single								
Double								
Notes:								

*= only if applicable, **=notify health care provider

Appendix L. Medical Abstraction Form

1. Subject ID:
2. Date: MM/DD/YY _____
3. Site:
 - a. CHLA = 0
 - b. HPMC = 1
 - c. UCLA = 2
4. Group:
 - a. Control = 0
 - b. CHD = 1
5. Demographic Information
 - a. DOB: MM/DD/YY _____
 - b. Age (days):
 - c. Gender:
 - i. Male = 0
 - ii. F = 1
 - d. Ethnicity:
 - i. Caucasian (nonhispanic) = 0
 - ii. Hispanic/Latino = 1
 - iii. Asian/Pacific Island = 2
 - iv. African American = 3
 - v. Middle Eastern = 4
 - vi. Other = 5 _____
6. Maternal Factors
 - a. Maternal Age (years): _____
 - b. IDM or GDM:
 - i. No = 0
 - ii. Yes = 1
 - c. Maternal hemorrhage:
 - i. No = 0
 - ii. Yes = 1
 - d. Magnesium Sulfate:
 - i. No = 0
 - ii. Yes = 1
 - e. Placenta Previa/Abruption:
 - i. No = 0
 - ii. Yes = 1
 - f. Other Complications:
 - i. No = 0
 - ii. Yes = 1 _____

7. Birth History

- a. Birth Weight (kg): _____
- b. Current Weight (kg): _____
- c. Birth Length (cm): _____
- d. Head Circumference (cm): _____
 - i. Not recorded
- e. Gestational Age (if records indicate full term document 40 weeks): _____
- f. Ballard Exam: _____
 - i. Not recorded
- g. APGARS:
 - i. 1min _____
 - ii. 5min _____
- h. Cyanosis at Birth:
 - i. No = 0
 - ii. Yes = 1
- i. Cord gases:
 - i. ph: _____
 - ii. pCO₂: _____
 - iii. pO₂: _____
 - iv. Bicarb: _____
 - v. BE: _____
 - vi. Not recorded
- j. NSVD or C/S
 - i. NSVD = 0
 - ii. C/S = 1
- k. Reason for C/S
 - i. Repeat C/S = 0
 - ii. Fetal distress = 1
 - iii. Breach = 2
 - iv. Other = 3 _____
- l. Birth Complications:
 - i. None = 0
 - ii. Nuchal chord = 1
 - iii. Chorioamnionitis = 2
 - iv. Meconium aspiration = 3
 - v. Other = 4 _____
- m. Resuscitated after birth?
 - i. None = 0
 - ii. Blow by = 1

- iii. Positive pressure ventilation (PPV) = 2
 - iv. Chest compressions = 3
 - v. Narcan/naloxone = 4
 - vi. Other = 5 _____
 - n. Cardiac Arrest:
 - i. No = 0
 - ii. Yes = 1
 - o. Cardiac Arrest Information:
 - i. Length: _____
 - ii. Times: _____
- 8. PDA
 - a. Not evaluated = 0
 - b. Yes = 1
- 9. PFO
 - a. Not evaluated = 0
 - b. Yes = 1
- 10. Feeding:
 - a. No = 0 _____
 - b. Yes = 1
- 11. Tube Feeding:
 - a. No = 0
 - b. Yes = 1
- 12. Current Medications (mg/kg) at the time of measurement?
 - a. None = 0
 - b. Yes = 1 _____
- 13. Cardiac Diagnosis:
 - a. Not applicable = 0
 - b. Tricuspid Atresia = 1
 - c. DILV = 2
 - d. DORV = 3
 - e. Unbalanced AVC = 4
 - f. Pulmonary Atresia/IVS = 5
 - g. TAPVR = 6
 - h. D-TGA = 7
 - i. Truncus Arteriosus = 8
 - j. Tetralogy of Fallot = 9
 - k. HLHS = 10
 - l. HRHS = 11

- m. Ebstein's Anomaly =12
 - n. Aortic Stenosis = 13
 - o. Pulmonary Stenosis = 14
 - p. Other = 15 _____
14. Single Ventricle Type
- a. Not applicable = 0
 - b. Left = 1
 - c. Right = 2
 - d. Indeterminate = 3
15. Arterial Line:
- a. No = 0
 - b. Yes = 1
16. A line location:
- a. Not applicable = 0
 - b. Umbilical = 1
 - c. Peripheral = 2
 - d. Left or Right Radial = 3
 - e. Left or Right Femoral = 4
 - f. Left or Right Posterior Tibial = 5
17. PreOp cranial U/S:
- a. No = 0
 - b. Yes = 1 _____
18. Lab data
- a. Date MM/DD/YY _____
 - b. Hgb: _____
 - c. Hct: _____
 - d. Lactate: _____
 - e. Total Bilirubin: _____
19. Arterial Blood Gas (ABG)
- a. Not recorded
 - b. pH: _____
 - c. pCO2: _____
 - d. paO2: _____
 - e. Base: _____
20. FiO2%
- a. Room air (21%) = 0
 - b. Other = 2 _____

SNAPPE-II™ Score

Parameter Points	No Points	Moderate	Severe
Birth Weight (gm)	≥1000gm 0	750-999 10	<750 17
Small for Gestational Age	≥3 rd 0	< 3 rd 12	
Apgar at 5 minutes	7-10 0		< 7 18

SNAP-II™ Score

Parameter Points	No Points	Moderate	Severe	Extreme
Lowest Mean Blood Pressure	≥ 30 0	20 - 29 9	< 20 19	
Lowest Temperature (°F)	> 96 0	95 - 96 8	<95 15	
PaO ₂ /FiO ₂ Ratio	≥ 2.5 0	1.0- 2.49 5	0.3 - .99 16	< 0.3 28
Lowest Serum pH	≥ 7.20 0	7.10 -7.19 7	< 7.10 16	
Seizures	None/single 0		Multiple 19	
Urine Output (cc/kg/hr)	> 0.9 0	0.1 - 0.9 5	< 0.1 18	

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