Fall 12-21-2011

Patterns of Weight Change in infants With Congenital Heart Disease Following Neonatal Surgery: Potential Predictors of Growth Failure

Sharon Y. Irving
University of Pennsylvania, ysha@nursing.upenn.edu

Patterns of Weight Change in infants With Congenital Heart Disease Following Neonatal Surgery: Potential Predictors of Growth Failure

Abstract
Abstract

Patterns of Weight Change in Infants with Congenital Heart Disease Following Neonatal Surgery: Potential predictors of growth failure

Sharon Y Irving

DISSERTATION SUPERVISOR: BARBARA MEDOFF-COOPER, RN, PhD

Congenital heart disease (CHD) is reported to have an incidence of 9 to 14 per 1000 live births with a prevalence estimated between 650,000 and 1.3 million persons in the United States (US). It is a structural malformation(s) of one or more heart chamber(s) and/or deformity of one or more of the major intrathoracic blood vessel(s) and the ensuing malady occurring during embryonic development. Up to one-third of infants with CHD, require surgical intervention. Improved surgical technique over the last several decades has seen an increased survival of neonates with CHD. Concomitantly there has been an emergence of co-morbidities. Growth failure is a common co-morbidity following neonatal surgery for CHD. More than 30% of these infants fall below the third percentile for weight early in their lives. Postsurgical physiology, disease severity, feeding dysfunction, and a hypermetabolic state may all contribute to growth failure, which has been associated with deficits in cognitive development, intellectual ability and neurodevelopment, effecting maturation and school performance. Early recognition and intervention of growth failure can improve health outcomes. The objective of this work is to identify patterns of growth and growth failure in infants with CHD and explore potential predictors that may be modifiable to mitigate growth failure and prevent the associated untoward consequences.

Degree Type
Dissertation

Degree Name
Doctor of Philosophy (PhD)

Graduate Group
Nursing

First Advisor
Barbara Medoff-Cooper, RN, PhD

Second Advisor
Martha A.Q. Curley, RN, PhD

Third Advisor
Virginia A. Stallings, MD

Keywords
growth failure, growth, energy expenditure, congenital heart disease, growth velocity

Subject Categories
Critical Care Nursing | Dietetics and Clinical Nutrition | Pediatric Nursing

PATTERNS OF WEIGHT CHANGE IN INFANTS WITH CONGENITAL HEART DISEASE FOLLOWING NEONATAL SURGERY: POTENTIAL PREDICTORS OF GROWTH FAILURE

SHARON Y IRVING, CRNP

A DISSERTATION

In

Nursing

Presented to the Faculties of the University of Pennsylvania

In

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2011

Dissertation Supervisor: _____

Barbara Medoff-Cooper, RN, PhD, FAAN
Ruth M. Colket Professor of Pediatric Nursing

Graduate Group Chairperson: _____

Marilyn S. Sommers, RN, PhD, FAAN
Lillian S. Brunner Professor of Medical-Surgical Nursing

Dissertation Committee:

Martha Curley, RN, PhD
Professor of Nursing

Charlene Compher, RD, PhD
Associate Professor of Nutrition Science

Virginia A Stallings, MD
Professor of Pediatrics

PATTERNS OF WEIGHT CHANGE IN INFANTS WITH CONGENITAL HEART DISEASE FOLLOWING NEONATAL SURGERY: POTENTIAL PREDICTORS OF GROWTH FAILURE

DEDICATION

To my parents:
You lived by the mantra “It takes a village”, and raised me in that way. *Thank you* for placing me in the “right village” and always believing and supporting even when you did not agree. I love you both. Mom, I wish you could see me now.

To my close and my extended family:
You believed when it was unbelievable. Thank You.

To my very first nursing preceptors: Brenda, Rose and Miss Mary and Mrs. J:
Thank you for the tireless hours of teaching, repeating, answering questions, and showing me how. You gave me the space to learn from you – look at what I have learned.

To my many mentors along the way:
Each of you has helped me walk this journey. Thank You.

“I would like to be a scholar in whatever I do, a scholar is never finished, he is always seeking and I am always seeking”.

Ahmad Jamal

ACKNOWLEDGEMENTS

First always in my life is God.

To my family:

There are no words that can ever thank you enough for all the love and the support and more love. Through the smiles and the tears, thank you, thank you, and thank you. I pray I make you proud.

To my “Cultural Heritage” sistahs:

Danica, Margo, Bridgette – thank you for ‘Paying it Forward’. I learned from your learning, your teaching and just by being in your presence. Thank you for welcoming me with open arms, big hearts and lots of love. Each of you are a part of the fabric that I am.

To my committee:

Thank you Barbara, Martha, Charlene and Ginanne. Each of you have inspired, you taught, you mentored, you pushed, you pulled and in the end – you nurtured.

ABSTRACT

PATTERNS OF WEIGHT CHANGE IN INFANTS WITH CONGENITAL HEART DISEASE FOLLOWING NEONATAL SURGERY: POTENTIAL PREDICTORS OF GROWTH FAILURE

SHARON Y IRVING

DISSERTATION SUPERVISOR: BARBARA MEDOFF-COOPER, RN, PhD

Congenital heart disease (CHD) is reported to have an incidence of 9 to 14 per 1000 live births with a prevalence estimated between 650,000 and 1.3 million persons in the United States (US). It is a structural malformation(s) of one or more heart chamber(s) and/or deformity of one or more of the major intrathoracic blood vessel(s) and the ensuing malady occurring during embryonic development. Up to one-third of infants with CHD, require surgical intervention. Improved surgical technique over the last several decades has seen an increased survival of neonates with CHD. Concomitantly there has been an emergence of co-morbidities. Growth failure is a common co-morbidity following neonatal surgery for CHD. More than 30% of these infants fall below the third percentile for weight early in their lives. Postsurgical physiology, disease severity, feeding dysfunction, and a hypermetabolic state may all contribute to growth failure, which has been associated with deficits in cognitive development, intellectual ability and neurodevelopment, effecting maturation and school performance. Early recognition and intervention of growth failure can improve health outcomes. The objective of this work is to identify patterns of growth and growth failure in infants with CHD and explore potential predictors that may be modifiable to mitigate growth failure and prevent the associated untoward consequences.

TABLE OF CONTENTS

INTRODUCTION……1

CHAPTER 1

The Problem: Growth Failure…….. 4

Methods…… 11

Purpose and Specific Aims ……13

Conclusion…….. 15

References……16

CHAPTER 2

Part 1: "*Growth Velocity over the First Year of Life Following Neonatal Surgery for Congenital Heart Disease"*

Abstract ……30

Definition of Terms …….. 31

References……44

Part 2: *"Resting Energy Expenditure at 3-Months of Age in Infants following Neonatal Surgery for Congenital Heart Disease"*

Abstract ……..59

Definition of Terms …….. 60

References……71

CHAPTER 3

National Institutes of Health Award Application…….... 83
"*The Use of Indirect Calorimetry (IC) to Measure Energy Needs in Mechanically Ventilated Children with Acute Lung Injury*"

References……119

CHAPTER 4

Summary and Conclusions…….…….. 127

Growth Monitoring ……...127

NIH Directors Early Independent Investigator Award Application ……133

References…….137

CLOSING…… 140

“LOOK AT US NOW”

LIST OF TABLES

CHAPTER 1

Table 1 Definition of Terms ……26

Table 2 *Comparison of infants with Congential Heart Disease enrolled versus not enrolled*……...27

Table 3 *Manuscripts and Specific Aims*…… 28

CHAPTER 2

Part 1

Table 2 *Primary diagnosis of infants with Congenital Heart Disease*... 50

Table 3 *Study sample demographics*…… 51

Table 4 *Mean (SD) growth parameters, healthy females and males*…… 52

Table 5 *Mean (SD) growth parameters, females and males with CHD*…….. 53

Table 6 *Mean (SD) growth parameters, healthy males and males with* CHD……..54

Table 7 *Mean (SD) growth parameters, healthy females and females with CHD*……..55

.

Part 2

Table 1 *Terms and Definitions*…….. 60

Table 2 *Congenital Heart Disease diagnoses of study sample*……..... 7

Table 3 *Growth, body composition and resting energy expenditure in all subjects at 3 months of age*……79

Table 4 *Regression model of covariates with strongest Contribution to REE kcal/day*……80

CHAPTER 3

Table 1 *Inclusion and exclusion criteria*……..... 99

Table 2 *Sample characteristics of healthy infants and infants with Congenital Heart Disease*……. 78

Table 3 *Growth, body composition and resting energy expenditure in all subjects at 3 months of age*……. 79

Table 4 *Regression model of covariates with strongest contribution to REE kcal/day*

CHAPTER 3

Table 1 *Inclusion and exclusion criteria*……..99

Table 2 *Study measurements*……...104

Table 3 *Estimated Timeline of study activity*……..113

LIST OF ILLUSTRATIONS

CHAPTER 1

Figure 1 *Conceptual Model of Potential Influences on Growth in CHD*…… 29

CHAPTER 2

Part 1

Figure 1 *Weight velocity z-score by gender*…….. 56

Figure 2 *Length velocity z-score by gender*……..57

Figure 3 *Head circumference velocity z-score by gender*……..58

Part 2

Figure 1 *Box plot graph of growth measures at 3 months of age*…….81

Figure 2 *Regression line of REE kcal/day for fat-free mass (FFM), kg from TOBEC*

CHAPTER 3

Figure 1 *Randomization schema*……..96

CHAPTER 4

Figure 1 *Modified conceptual model*……139

INTRODUCTION

Congenital heart disease (CHD) is defined as the structural malformation(s) of one or more heart chambers and/or deformities of the major intrathoracic blood vessels and the ensuing malady that occurs during embryonic development. The incidence of CHD reported to be 9 to 14 per 1,000 live births,[1-3] has a prevalence estimated between 650,000 and 1.3 million persons in the United States (US).[1,4,5] CHD accounts for as much as 50% of neonatal infant mortality and is considered to be the most common cause of infant death from a birth defect in the US.[6] Up to one third of infants born with CHD require surgical intervention early in their lives.[7] The Consortium of the Society of Thoracic Surgeons of Congenital Heart Surgery reported more than 60% of infants born between July 2004 and June 2008 presented for surgical intervention in the neonatal period (first 30 days of life).[8] As a disease entity, CHD contributes not only to the rate of infant mortality and to the prevalence of infant morbidity, but also to chronic childhood health conditions and the associated healthcare costs.

With improvement in surgical technique, medical treatment, and nursing care over the last few decades, there has been marked increase in the survival rate of neonates with CHD. Between 1979 and 1997, CHD-related mortality declined more than 39% in the US.[1] Along with improved survival of neonates and infants undergoing surgery for CHD, there has been a parallel emergence of co-morbidities in the survivors. Although non-cardiac concomitant conditions requiring services from pediatric subspecialists such as neurologists, pulmonologists, and orthopedics are frequently seen,[9] growth failure is one of the more common sequelae observed in infants with CHD.[10-12] More than 50% exhibit poor growth early in life and 30% fall below the third percentile for weight on standard growth charts for age and gender

during infancy.[13,14] The high prevalence of CHD, its contribution to infant morbidity and mortality and the association with poor growth in infancy are ongoing challenges in caring for these infants.

Growth is fundamental to pediatric care and often used as a gauge to measure the infant's health and well-being. For postsurgical infants with CHD, growth, particularly weight gain, may also be a measure of surgical success and disease management. Poor growth is common and well documented in infants with CHD both before and after surgical intervention.[10-12,14-18] Historically, poor growth also described as growth failure has been ascribed to the population sample studied, making it difficult to quantify and more difficult to generalize.[19,20] Recent data suggest suboptimal monitoring of growth measures, chronic medical problems that present with poor growth, and socioeconomic factors may all be associated with growth failure but are under-appreciated for their contribution to this condition.[21,22] This may in part be responsible for lack of an all-encompassing definition for growth failure adding to the difficultly of diagnosis and treatment. Growth failure in infants with CHD can be the result of feeding dysfunction resulting in inadequate nutrient intake, hemodynamic alterations related to the underlying cardiac physiology, alterations in body composition, neurologic immaturity, intercurrent illnesses, or disease severity.

There is no consensus on the definition of growth failure for infants and young children with CHD. The same primary cardiac diagnosis can present differently based on physiology and degree of hemodynamic impairment. This variability affects weight gain and adds to the complexity of defining and identifying growth failure in this population.

Regardless of the etiology, growth failure can have a long-lasting effect on overall health. Poor growth has also been associated with poor cognitive development and deficits in neurodevelopmental outcomes that extend well into childhood and adolescence.[23-27] Further investigation into potential contributing factors, physiologic associations, and possible modifiable elements that will lead to development of strategies and interventions to prevent and/or minimize growth failure in these infants will augment continued advances in surgical approach and improvements in care. A better understanding of growth failure and its contributing factors can lead to interventions to minimize or prevent its occurrence and improve health outcomes for these infants. An investigation into the pattern of growth in infants with CHD compared to healthy infants and exploring energy expenditure as a potential contributing factor to the poor growth often seen is the focus of this dissertation. For the purposes of this work, the terms ‘growth failure’ and ‘poor growth’ are synonymous and define the less than adequate growth described throughout. Table 1 is a definition of terms.

CHAPTER 1

The Problem: Growth Failure

Understanding Growth and Growth Failure

Whereas growth is fundamental to pediatric health and is often a measure of overall well-being, poor growth, evidenced by a decrease in previously attained weight and/or a negatively altered pattern of weight gain, is often associated with poor health, chronic illness, and acute or chronic malnutrition. The first year of life is the time of the most rapid ex utero growth. In infancy, lack of adequate energy, protein, and other nutrient intake will likely result in adverse effects on growth and has potential to affect neurodevelopmental maturation and behavior.[24,28,29] Numerous studies have linked poor growth in infancy with diminished intellectual ability, lower than average Intelligence Quotient (IQ) and negative cognitive and behavioral outcomes in childhood and adolescence.[29-32]

The typically developing infant gains between 20 to 30 grams per day in the first 6 months of life following an expected physiologic weight loss that may reach and can exceed 10% of birth weight; in months 6 thru 12, weight gain slows to between 10 to 20 grams per day.[13,33,34] Adequate nutrient intake in infancy is crucial to promote a positive energy balance to support best potential for brain growth, neurologic development, and physical maturation. In the second year of life, physical development changes and weight gain further slows down to approximately 8 grams per day, while brain growth, estimated by head circumference measurement is expected to increase an average of 0.33 centimeters (cm) per week and continue development late into childhood.[24,35] Incremental gains in crown-to-heel length average 0.66 cm per week in the first 6 months of life, slowing to approximately 1.2 cm per month between 6 and 12 months of age.[13,24] Many neonates with CHD do not meet these parameters despite being born

full term and within the normal weight range for age and gender at birth.[36,37] The inability to attain and maintain growth parameters within an acceptable range for age and gender, and/or a significant decrease from an established pattern of growth are indicators of growth failure and if not corrected can lead to associated physical and neurodevelopmental consequences.[23,28-32,38]

The definition of growth failure in the pediatric medical and/or nursing literature is ambiguous and lacks a uniformly accepted approach to identify those infants at risk for and who exhibit poor growth. In general, growth failure, most often called failure to thrive (FTT), is defined as a disruption of the expected rate of growth, and can be the prelude to significant morbidity and mortality.[39] The most common description of FTT is weight-for-age at or below the third to fifth percentile on more than one consecutive weight-for-age assessment, or weight-for-age measurements that descend two or more percentiles on a standard growth chart for age and gender.[39-41] The definition of FTT can also be specific to the infant, by describing weight gain that negatively deviates from an established pattern of growth.[41] Terms such as FTT, growth deficiency, growth failure, growth faltering, poor growth, protein energy malnutrition, and under-nutrition, are used interchangeably to describe less-than-adequate weight gain and poor physical development seen in infancy and early childhood.[13,41-44]

Consequences of Growth Failure

Researchers have investigated prolonged, inadequate growth in early infancy and its effect on cognitive and neurodevelopmental maturation. Bhoomika and colleagues[30] found growth failure, the result of poor nutrition, to be associated with cognitive impairments, decreased acquisition of intellectual processes and poor development of executive functions, including visual-spatial skills, working memory and

attention span. Dykman et al[31] related deficits in growth measurements to deficiencies in cognitive development, poor school achievement and adverse behavior in school-aged children. In a population study of over 1,800 infants, McDougall and colleagues[29] found growth failure in the first two months of life to be a risk factor for decreased intellectual ability, lower IQ and developmental delay. Black et al[45] reported cognitive deficiencies inclusive of poor work habits, deficient math skills and behavioral problems in 130 children with a known diagnosis of growth failure. These researchers also describe attenuation of the cognitive and neurobehavioral impairments they observed with early sustained intervention for both the child with growth failure and the primary parental caregiver.[45] Collectively these studies provide evidence of a strong association between inadequate nutrient intake in early infancy and growth failure that have implications for negative cognitive, neurodevelopmental and behavioral outcomes in childhood.

Growth Failure in CHD

For the infant with CHD who has undergone neonatal surgery, poor growth is a common co-morbidity that may have multiple factors contributing to its etiology. Factors presumed to affect weight change and contribute to poor growth in these infants can singularly or in combination include hemodynamic abnormalities related to cardiac physiology and disease severity,[13,32,46] inadequate nutrient intake,[1,5,45] gastrointestinal malabsorption,[12,47-50] neurologic insults,[12,36,47,51] and presumed increase in energy expenditure.[11,33,52-55] Additionally, these infants may have fluid losses as high as 10% to 15% compared to healthy infants, losses that can be attributed to tachypnea, poor fluid intake, and the necessary use of diuretics for fluid regulation related to the underlying cardiac disease.[13,14,36,56] The dynamics of these factors and the impact they can have

pre- and/or postsurgical intervention may contribute to the growth failure often exhibited by these infants. Figure 1 conceptualizes potential influencing factors on growth for infants with CHD who have undergone neonatal surgery.

The relationship between growth failure and cardiac physiology has long been a topic of discussion and investigation. The literature is robust with studies demonstrating that infants with cyanotic lesions and postoperative single-ventricle (SV) physiology exhibit more significant growth failure than infants with acyanotic disease or those with two normally functioning ventricles.[14,15,17,48,57-60] The degree of growth failure has been associated with severity of hemodynamic impairment and/or the presence of heart failure.[13,60] A right-to-left or left-to-right shunt between either the atria or the ventricles affects the infant's hemodynamics and presumably has a negative effect on weight gain contributing to growth failure in this population. Cyanotic defects, such as Tetralogy of Fallot, Tricuspid Atresia and Hypoplastic Left Heart Syndrome are associated with right-to-left shunting of blood flow at the ventricular level, resulting in hypoxemia, often causing disturbances in both weight gain and attainment of stature.[13,60,61] Alternatively, acyanotic lesions, Aortic Stenosis, Coarctation of the Aorta and Ventricular Septal Defect that manifest left-to-right shunting of blood at the atrial or ventricular level affects weight rather than stature in the pre-operative stage of disease.[14,62] Regardless of the cardiac anatomy, growth failure for neonates and infants with CHD is a significant challenge and warrants further investigation to identify causal factors that if corrected may decrease morbidity and improve health outcomes.

In addition to growth measures of weight, length and head circumference, there is high interest among healthcare providers and families in the behavioral, neurodevelopmental and cognitive outcomes following surgical intervention for CHD.

An association has been established between growth failure and increased infant irritability.[63] Previous work from the parent study of this dissertation, reported infants with CHD, particularly those with postoperative SV physiology were more likely to exhibit growth failure, and have an increased level of irritability and negative behaviors.[64] Limperopoulos et al[27] reported a combination of preoperative, perioperative and postoperative factors influenced neurodevelopmental outcomes they observed in infants 12 to 18 months after neonatal surgery for CHD. These researchers found infant weight to be a significant predictor of motor and cognitive deficits at 2 years of age.[27] The Boston Circulatory Arrest Trial, a large longitudinal study evaluated the neurodevelopmental status of participants at one, four and eight years of age following infant surgery for CHD in which the participants were randomized to either cardiac arrest or low-flow cardiopulmonary bypass for intraoperative organ support.[37,65-67] Study findings demonstrated moderate neurologic deficits in motor coordination, and visual-motor integration, with mild deficits in speech and language, thought to be associated with the use of cardiac arrest versus the low flow cardiopulmonary bypass option during infant surgery.[35,64-66] In a review of eight studies, Snookes and colleagues[68] reported consistent delay in cognitive and motor development following surgery for CHD in early infancy. In an extensive review of the literature reflecting progressive changes in cardiac surgery conducted by Shillingford and Wernovsky[23] a number of consistent themes regarding neurologic outcomes for children with CHD who had undergone surgery in infancy were discovered. The authors cite common themes of: 1) prevalence of attention deficits and behavior problems; 2) deficits in visual-motor integration, visual-spatial challenges, and abnormalities in speech and language development; 3) impaired development of

executive functioning; and 4) an association between intraoperative use of hypothermic cardiac arrest and/or cardiopulmonary bypass with neurodevelopmental abnormalities as sequela of surgery during infancy for cardiac disease.[23] Predictors of these post surgical deficits may or may not include the primary underlying cardiac defect, the surgical approach, the decision for repair versus palliation, use of, type and duration of intraoperative organ support, and/or the existence of an unknown pre-surgical neurologic or genetic abnormality.[25,38,68-71] Collectively, the evidence points to the need for close, repeated assessment of growth measures and incremental neurodevelopmental testing in infants and young children following surgical intervention for CHD to promote early identification of neurodevelopmental problems that may be minimized with prompt intervention(s).

Other factors that potentially influence weight gain and growth in infants with CHD following neonatal surgery include metabolic rate and energy balance. A positive energy balance, the direct result of energy intake that exceeds energy utilization, is necessary to support somatic growth, neurobehavioral development, and long-term health.[72-74] The utilization of energy is divided between that required for basal metabolic functions, thermal effects of digestion, requirements for tissue accretion, weight gain, and the cost of physical activity.[73] In general, neonates have a higher metabolic rate compared to older children and adults, they require more kcal/kg of body weight.[24,75] It is postulated that infants with CHD, particularly those with heart failure, require an increased energy intake to attain and maintain growth measurements within an

acceptable range for age and gender. This increased requirement is thought to be from an increased oxygen consumption and inadequate caloric intake related to poor feeding ability, gut dysmotility, and/or gastrointestinal malabsorption.[14,76] Infants with

heart failure may be in a fixed hypermetabolic state prior to and/or immediately following surgery, secondary to an increase in cardiopulmonary work and postoperative stress.[52,60] This hypermetabolic state, whether or not it is fixed, may affect the infants' energy intake and energy utilization. Growth failure often seen in infants with CHD following surgery may be the result of an imbalance between energy intake and energy utilization, however, available data do not consistently support this hypothesis.[10,14,17,48,55,60] To date, studies suggesting an association between increased energy expenditure and poor growth in infants and children with complex CHD have yielded mixed results and are inconclusive due to study design, sample size, and a heterogeneous participant group.[52,61,73,77,78]

Research endeavors specifically directed at examining energy intake and utilization by neonates and infants with CHD prior to, immediately following, and at an extended postsurgical time may elucidate the role energy balance and alterations in have on weight gain and the subsequent growth of infants with CHD. With the known association between growth failure and poor neurodevelopmental and cognitive outcomes, it is essential to improve knowledge and understanding of factors contributing to poor growth in this population. This will better prepare healthcare providers to identify signs of growth failure, develop strategies toward decreasing the incidence of poor growth in infants with CHD, and increase their ability to achieve maximal growth, neurodevelopmental and intellectual potential.

Methods

Parent Study: "Feeding Behaviors and Energy Balance in Infants with Congenital Heart Disease"

The current body of work stems from a large, prospective study entitled: "Feeding Behaviors and Energy Balance in Infants with Congenital Heart Disease" (NIH/NINR R01 NR002093; MO1-RR00240; UL1-RR-024134), Principal Investigator: Barbara Medoff-Cooper, PhD, RN, FAAN, heretofore known as the "parent study." Study approval was obtained from both Institutional Review Boards of The Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania, Philadelphia.

Study Design

The parent study design was a prospective, longitudinal design, from a single center convenience sample.

Study Setting

The parent study is a single-institution investigation conducted at CHOP, a 430-bed tertiary care facility serving the metropolitan Philadelphia area. During the study period, March 2003 through May 2007, more than 1,100 neonates were admitted to the Cardiac Intensive Care Unit (CICU) for evaluation of cardiac disease. The CICU staff consists of surgeons, physicians, nurses, respiratory therapists and ancillary staff specially trained in the intervention and therapeutic care of infants and children with congenital and acquired cardiac disease.

Sample Population

Infants were screened following surgery and if eligible parents/guardians were approached for enrollment. During the study period, 667 neonates in the CICU met criteria; of these, 502 families were approached with 164 enrolled, a 33% consent rate.

The low rate of consent is multi-factorial and reflects challenges faced in this research effort. These included absence of parent or guardian for consent, parental refusal to participate, parental perceived study burden and inability or unwillingness to return to CHOP for study visits. Additionally there were simultaneous ongoing studies in the CICU competing for enrollment of the same group of infants. Many infants who met criteria were from referral institutions where they would return for continued care and thus be unavailable for study visits. Demographic characteristics of infants with CHD who were not enrolled were similar to the enrolled group for gender, age, race, ethnicity and post-operative physiology (Table 2). Healthy infants that served as the control group were recruited from primary care practices affiliated with CHOP and self-referral from surrounding communities. Demographic information on healthy infants not enrolled was not available. Total enrollment in the parent study was 242 combined cardiac and healthy infants. Race and ethnicity of the infants was assigned by parental self-identification. Families unwilling or unable to return to CHOP for study visits were not enrolled.

Eligibility criteria for all infants included $\geq$36 weeks post-menstrual age and birth weight $\geq$2,500 grams. Infants with CHD who underwent surgical intervention during the first 6 weeks of life, and did not have known multiple congenital, facial, chromosomal and/or complex gastrointestinal anomalies or congenital and/or acquired neurologic diagnoses were eligible for enrollment. Postoperative classification as SV or BV physiology was completed in keeping with established standards.[79]

Data Acquisition

The study protocol commenced following hospital discharge when the infant was 3-months of age. All data was obtained during study visits in the outpatient Clinical

and Translational Research Center and the Nutrition and Growth Lab at CHOP, by trained research staff. The study protocol did not include assessment of type, amount, or caloric density of daily nutrient intake or the rate of feeding advancement, the only distinction referred to oral and device or device-assisted feedings. Dietary recall diaries were provided to families as part of the study protocol, with instruction to record nutrient intake for 3-days prior to or immediately following each study visit. The research staff phoned families bi-monthly to inquire on the infant's status and to maintain interest in study participation.

Purpose and Specific Aims

The aim of the parent study was to develop a model to predict poor growth in postsurgical infants with CHD through a over the first year of life. Sub-analyses of data from the parent investigation has culminated in two studies that focus on examination of factors related to growth and growth failure in infants with CHD who underwent surgery in the first six weeks of life. These studies are presented in chapter two. The first is a descriptive examination of the pattern of growth velocity over the first year of life. This is a novel approach to describing growth as the study uses the new World Health Organization (WHO) child growth velocity standards.[80] The aim of this study was to examine the pattern of growth velocity, inclusive of weight, length, and head circumference for infants with CHD physiology compared to healthy controls. Growth velocity, defined as the change in measure over time, is considered a superior assessment of growth and more accurate than attained measures.[80] Assessment of growth velocity allows early detection of poor growth which can indicate alterations in health and well-being or inadequate nutrient intake thereby facilitating early identification of infants at risk for growth failure.[80,81]

The second study in chapter two examines resting energy expenditure (REE) in infants with CHD compared to healthy infants at 3-months of age. There were two aims to this study, 1) to examine differences in REE between infants with CHD compared to healthy infants at 3 months of age and 2) to investigate if differences exist among infants with CHD having SV versus BV physiology. This study uses WHO[82] child growth standards for weight, length and head circumference for children from birth to 5 years of age. These standards represent the best physiologic description of growth for infants and children living in ideal environments.[73,80,82]

In chapter three, a grant application was developed and submitted for consideration of an Early Independent Investigator award in response to a call from the National Institutes of Health for educational-institution sponsored candidates. This proposal embraces a modified approach to the principle of translational research. Applying knowledge and skills gained through the course of this dissertation work in the measurement and analysis of energy expenditure the goal of this proposal was to identify differences between measured energy expenditure and the use of prediction equations to prescribe caloric intake for children with acute lung injury requiring mechanical ventilation. Using indirect calorimetry to measure energy expenditure will allow tailored prescriptions for energy intake for critically ill children, in whom good nutrition has a vital role in the process of recovery. Outcome measures for this proposal include: 1) increased number of ventilator-free days, 2) decreased weight loss, 3) decreased loss of lean body mass and 4) decreased length of stay. Table 2 describes the subject for each manuscript, and the grant proposal with the related specific aim.

Conclusion

Multiple factors have an influence on growth in infants with CHD following neonatal surgery. Postsurgical physiology, severity of illness, feeding ability, neurologic status, and energy expenditure may all contribute to growth failure that many of these infants exhibit. The overall aim of this body of work is to explore the pattern of weight change and investigate factors that contribute to or influence growth or growth failure in the postsurgical infant with CHD. Monitoring growth velocity and understanding energy needs and the relationship they share with adequate growth will enable first-line care providers to better assess and intervene if growth failure is evident. Early recognition and intervention of growth failure can potentially improve patient outcomes and overall health. This work aims to initiate thoughtful collaboration among healthcare providers to address the challenge(s) of growth failure in neonates and infants with CHD who have undergone surgical intervention early in infancy.

References

1. Rosamond W, Flegal K, Furie K, et al. Heart Disease and Stroke Statistics 2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2008;117:e25 - e146.

2. Winlaw D. Congenital heart disease in the 21st century. *Crit Care Resusc.* 2007;9(3):270 - 274.

3. Hoffman JI, Kaplan S. The Incidence of Congenital Heart Disease. *J Am Coll Cardiol.* 2002;39(12):1890-1900.

4. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J.* 2004;147(3):425-439.

5. American Heart Association. Congenital Cardiovascular Defects - Statistics 2008 Update. 2008; http://www.americanheart.org/downloadable/heart/1236975010111CONG.pdf. Accessed October 2, 2009.

6. Schultz AH, Localio AR, Clark BJ, Ravishankar C, Videon N, Kimmel SE. Epidemiologic Features of the Presentation of Critical Congenital Heart Disease: Implications for Screening. *Pediatr.* 2008;121(4):751 - 757.

7. Dorfman AT, Marino BS, Wernovsky G, et al. Critical heart disease in the neonate: Presentation and outcome at a tertiary care center. *Pediatr Crit Care Med.* 2008;9(2):193-202 110.1097/PCC.1090b1013e318166eda318165.

8. Jacobs JP, Jacobs ML, Mavroudis C, Lacour-Gayet F, Tchervenkov C. *Data Analyses of The Society of Thoracic Surgeons Congenital Heart Surgery Database*: Duke University Medical Center;2009.

9. Massin MM, Astadicko I, Dessy H. Noncardiac comorbidities of congenital heart disease in children. *Acta Paediatr.* 2007;96:753-755.

10. Eskedal LT, Hagemo P S, Seem E, et al. Impaired weight gain predicts risk of late death after surgery for congenital heart defects. *Arch Dis Child.* Jun 2008;93(6):495-501.

11. Davis D, Davis S, Cotman K, et al. Feeding difficulties and growth delay in children with hypoplastic left heart syndrome versus d-transposition of the great arteries. *Pediatr Cardiol.* Mar 2008;29(2):328-333.

12. Jadcherla SR, Vijayapal AS, Leuthner S. Feeding abilities in neonates with congenital heart disease: a retrospective study. *J Perinatol.* 2009;29:112 - 118.

13. Steltzer M, Rudd N, Pick B. Nutrition Care for Newborns with Congenital Heart Disease. *Clin Perinatol.* 2005;32:1017 - 1030.

14. Forchielli ML, McColl R, Walker WA, Lo C. Children with congenital heart disease: a nutrition challenge. *Nutrition Review.* 1994;52(10):348-353.

15. Peterson RE, Wetzel GT. Growth failure in congenital heart disease: where are we now? *Current Opinion in Cardiology.* 2004;19(2):81-83.

16. Sholler GF, Celermajer JM. Cardiac surgery in the first year of life: The effect on weight gains of infants with congenital heart disease. *Aust Paediatr J.* 1986;22:305 - 308.

17. Menon G, Poskitt EM. Why does congenital heart disease cause failure to thrive? *Arch Dis Child.* 1985;60(12):1134-1139.

18. Jackson M, Poskitt EM. The effects of high-energy feeding on energy balance and growth in infants with congenital heart disease and failure to thrive. *Br J Nutr.* 1991;65(131 - 143).

19. Rabinowitz S, Katturupalli M, Rogers G. Failure to Thrive. *Pediatrics: General Medicine*. 2010; http://emedicine.medscape.com/article/985007-overview. Accessed October 20, 2010.

20. Bauchner H. Failure to Thrive. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia: WB Saunders; 2007:184 - 187.

21. Grimberg A, Kutikov JK, Cucchiara AJ. Sex Differences in Patients Referred For Evaluation of Poor Growth. *J Pediatr.* 2005;146:212 - 216.

22. Grimberg A, Ramos M, Grundmeier R, et al. Sex-Based Prevalence of Growth Faltering in an Urban Pediatric Population. *J Pediatr.* 2009;154:567 - 572.

23. Shillingford AJ, Wernovsky G. Academic performance and behavioral difficulties after neonatal and infant heart surgery. *Pediatr Clin N Am.* 2004;51:1625 - 1639.

24. Heird WC. Nutritional Requirements. In: Behrman Richard E, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: W.B. Saunders; 2004:153-190.

25. Dittrich H, Buhrer C, Grimmer I, Dittrich S, Abdul-Khaliq H, Lange PE. Neurodevelopment at 1 year of age in infants with congenital heart disease. *Heart.* 2003;89:436 - 441.

26. Hirose Y, Ichida F, Oshima Y. Developmental status of young infants with congenital heart disease. *Pediatr Int.* 2007;49:468 - 471.

27. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr.* 2002;141:51 - 58.

28. Locklin M. The Redefinition of Failure To Thrive From a Case Study Perspective. *Pediatr Nurs.* 2005;31(6):474-479.

29. McDougall P, Drewett RF, Hungin APS, Wright CM. The detection of early weight faltering at the 6-8-week check and its association with family factors, feeding and behavioural development. *Arch Dis Child.* 2009;94(7):549-552.

30. Bhoomika KR, Shobini RL, Chandramouli BA. Cognitive development in children with chronic protein energy malnutrition. *Behav Brain Funct.* 2008;4(31):1-12. http://www.behavioralandbrainfunctions.com/content/4/1/31.

31. Dykman RA, Casey PH, Ackerman PT, McPherson WB. Behavioral and Cognitive Status in School-Aged Children With a History of Failure to Thrive During Early Childhood. *Clin Pediatr.* 2001;40:63 - 70.

32. Drewett R, Emond A, Blair P, Emmett P. The importance of slow weight gain in the first 2 months in identifying children who fail to thrive. *J Reprod Infant Psychol.* 2005;23(4):309-317.

33. Schwalbe-Terilli C, Hartman DH, Nagel ML, et al. Enteral Feeding and Caloric Intake in Neonates After Cardiac Surgery. *Am J Crit Care.* 2009;18(1):52 - 57.

34. Nommsen-Rivers LA, Dewey KG. Growth of Breastfed Infants. *Breastfeed Med.* 2009;4(Supplment 1):S45 - S-49.

35. Gale CR, O'Callaghan FJ, Godfrey KM, Law CM, Martyn CN. Critical periods of brain growth and cognitive function in children. *Brain.* 2004;127(2):321 - 329.

36. Owens JL, Musa N. Nutrition Support After Neonatal Cardiac Surgery. *Nutr Clin Pract.* Apr-May 2009;24(2):242-249.

37. Bellinger DC, Wypij D, Kuban KCK, et al. Developmental and Neurological Status of Children at 4 Years of Age After Heart Surgery With Hypothermic

Circulatory Arrest or Low-Flow Cardiopulmonay Bypass. *Circulation.* 1999;100:526-532.

38. Bjarnason-Wehrens B, Dordel S, Schickendantz S, et al. Motor development in children with congenital cardiac diseases compared to their healthy peers. *Cardiol Young.* 2007;17:487 - 498.

39. Needlman RD. Growth and Development. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: Saunders; 2004:23 - 40.

40. Stewart CL, Goody CM, Branson R. Comparison of Two Systems of Measuring Energy Expenditure. *JPEN J Parenter Enteral Nutr.* May 1, 2005 2005;29(3):212-217.

41. Steward DK, Ryan-Wenger NA, Boyne L. Selection of growth parameters to define failure to thrive. *Journal of Pediatric Nursing.* 2003;18(1):52-59.

42. Failure to Thrive. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village: American Academy of Pediatrics; 2009.

43. Kessler DB. Failure to Thrive and Pediatric Undernutrition, Historical and Theoretical Context. In: Kessler DB, Dawson P, eds. *Failure to Thrive and Pediatric Undernutrition, A Transdisciplinary Approach*. Baltimore: Paul H. Brookes Publishing Co; 1999:3 - 17.

44. Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. *Arch Dis Child.* February 1, 2007 2007;92(2):109-114.

45. Black MM, Dubowitz H, Krishnakumar A, Starr RH. Early Intervention and Recovery Among Children With Failure to Thrive: Follow-Up at Age 8. *Pediatr* 2007;120(1):59 - 69.

46. Nicolson SC, Steven JM, Jobes DR. Hypoplastic Left Heart Syndrome. In: Nichols DG, Cameron DE, Greeley WJ, Lappe DG, Ungerleider RM, Wetzel RC, eds. *Critical Heart Disease in Infants and Children*. St. Louis: Mosby; 1995:863 - 884.

47. Medoff-Cooper B, Irving SY, Marino BS, et al. Weight change in infants with a functionally univentricular heart: from surgical intervention to hospital discharge. *Cardiol Young.* 2011;21(2):136 - 144.

48. Kelleher DK, Laussen P, Teixeira-Pinto A, Duggan C. Growth and correlates of nutritional status among infants with hypoplastic left heart syndrome (HLHS) after stage 1 Norwood procedure. *Nutrition.* 2006;22:237 - 244.

49. Unger R, DeKleermaeker M, Gidding SS, Christoffel K. Improved Weight Gain With Dietary Intervention in Congenital Heart Disease. *Am J Dis Child.* 1992;146:1078-1084.

50. Malagon I, Onkenhout W, Klok M, van der Poel P, Bovill J, Hazekamp M. Gut permeability in neonates after a stage 1 Norwood procedure. *Pediatr Crit Care Med.* 2005;6(5):547 - 549.

51. Dooley KJ, Bishop L. Medical management of the cardiac infant and child after surgical discharge. *Crit Care Nurs Q.* 2002;25(3):98 - 104.

52. Avitzur Y, Singer P, Dagan O, et al. Resting energy expenditure in children with cyanotic and noncyanotic congenital heart disease before and after open heart surgery. *JPEN J Parenter Enteral Nutr.* January 1, 2003 2003;27(1):47-51.

53. Mitchell IM, Davies PS, Day JM, Pollock JC, Jamison PG. Energy expenditure in children with congenital heart disease, before and after cardiac surgery. *J Thorac Cardiovasc Surg.* 1994;107:374 - 380.

54. Puhakka K, Rasanen J, Leijala M, Peltola K. Metabolic Effects of Corrective Surgery in Infants and Children with Congenital Heart Defects. *Br J Anaesth.* 1993;70:149 - 153.

55. Nydegger A, Bines JE. Energy metabolism in infants with congenital heart disease. *Nutrition.* 2006;22:697 - 704.

56. Sadowski SL. Congenital Cardiac Disease in the Newborn Infant: Past, Present, and Future. *Crit Care Nurs Clin North Am.* 2009;21(1):37-48.

57. Mehrizi A, Drash A. Growth disturbance in congenital heart disease. *J Pediatr.* 1962;61(3):418-429.

58. Linde LM, Dunn OJ, Schireson R, Rasof F. Growth in children with congenital heart disease. *The Journal of Pediatrics.* 1967;70(3):413 - 419.

59. Vogt KN, Manlhiot C, van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic Growth in Children With Single Ventricle Physiology: Impact of Physiologic State. *J Am Coll Cardiol.* 2007;50(19):1876-1883.

60. Varan B, Tokel K, Yilmaz G. Malnutrition and growth failure in cyanotic and acyanotic congenital heart disease with and without pulmonary hypertension. *Arch Dis Child.* 1999;81:49 - 52.

61. Boctor DL, Pillo-Blocka F, McCrindle BW. Nutrition After Cardiac Surgery for Infants With Congenital Heart Disease. *Nutr Clin Pract.* 1999;14:111-115.

62. Ackerman IL, Karn CA, Denne SC, Ensing GJ, Leitch CA. Total But Not Resting Energy Expenditure is Increased in Infants with Ventricular Septal Defects. *Pediatr.* 1998;102(5):1172 - 1177.

63. Steward DK, Moser DK, Ryan-Wenger NA. Biobehavioral characteristics of infants with failure to thrive. *J Pediatr Nurs.* 2001;16(3):162-171.

64. Torowicz D, Irving SY, Hanlon AL, Sumpter DF, Medoff-Cooper B. Infant Temperament and Parental Stress in 3-Month Old Infants After Surgery for Complex Congenital Heart Disease. *J Dev Behav Pediatr.* 2010;31:in press.

65. Bellinger DC, Jonas RA, Rapport LA, et al. Developmental and Neurologic Status of Children After Heart Surgery with Hypothermic Circulatory Arrest or Low-Flow Cardiopulmonary Bypass. *N Engl J Med.* 1995;332(9):549 - 555.

66. Bellinger DC, Wypij D, duPlessis AJ, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. *J Thorac Cardiocasc Surg.* 2003;126(5):1385 - 1395.

67. Bellinger DC, Bernstein JH, Kirkwood MW, Rapport LA, Newerger JW. Visual-Spatial Skills in Children After Open-Heart Surgery. *J Dev Behav Pediatr.* 2003;24(3):169-179.

68. Snookes SH, Gunn JK, Eldridge BJ, et al. A Systematic Review of Motor and Cognitive Outcomes After Early Surgery for Congenital Heart Disease. *Pediatr.* 2010;125(4):e818 - e827.

69. Massaro AN, El-dib M, Glass P, Aly H. Factors associated with adverse neurodevelopmental outcomes in infants with congenital heart disease. *Brain and Development.* 2008;30:437 - 446.

70. Hovels-Gurich HH, Bauer SB, Schnitker R, et al. Long-term outcome of speech and language in children after corrective surgery for cyanotic or acyanotic cardiac defects in infancy. *Eur J Paediatr Neurol.* 2008;12:378-386.

71. Majnemer A, Limperopoulos C, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C. A New Look at Outcomes of Infants with Congenital Heart Disease. *Pediatr Neurol.* 2009;40(3):197 - 204.

72. Kurpad AV, Muthayya D, Vaz M. Consequences of inadequate food energy and negative energy balance in humans. *Public Health Nutr.* 2005;8(7A):1053 - 1076.

73. Butte NF. Energy Requirements of Infants and Children. Paper presented at: Nestlé Nutrition Workshop Series. Paediatric Programme, 2006.

74. Pierro A, Eaton S. Metabolism and nutrition in the surgical neonate. *Seminars in Pediatric Surgery.* 2008;17:276 - 284.

75. Leitch CA. Growth, nutrition and energy expenditure in pediatric heart failure. *Prog Pediatr Cardiol.* 2000;11(3):195-202.

76. Kogon BE, Ramaswamy V, Todd K, et al. Feeding Difficulty in Newborns Following Congenital Heart Surgery. *Congenit Heart Dis.* 2007;2:332 - 337.

77. Bines JE, Truby HD. Measurement of resting energy expenditure in infants. *J Paediatr Child Health.* 2004;40:380-383.

78. Li J, Zhang G, Herridge J, et al. Energy expenditure and caloric and protein intake in infants following the Norwood procedure. *Pediatr Crit Care Med.* 2008;9(1):55 - 61.

79. Rhodes LA, Colan SD, Perry SB, Jonas RA, Sanders SP. Predictors of survival in neonates with critical aortic stenosis. *Circulation.* 1991;84:2325 - 2335.

80. World Health Organization. *WHO Child Growth Standards. Growth Velocity based on weight, length and head circumference: Methods and development*. Geneva, Switzerland: World Health Organization; 2009.

81. Zemel BS. A Commentary on the Construction of Weight Velocity Charts. *Nutrition in Clinical Practice.* 2009;24(5):651 - 653.

82. World Health Organization. *WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index for age: Methods and development*. Geneva, Switzerland: World Health Organization; 2006.

Table 1 Definition of Terms

Term	Definition
Acyanotic	Absence of cyanosis; oxygenated blood in systemic circulations
Bi-ventricle (BV)	Normal two ventricle cardiac physiology; right ventricle receives blood from the systemic circulation pumps to the pulmonary circulation; left ventricle receives blood from the pulmonary circulation pumps to the systemic circulation
Congenital Heart Disease (CHD)	Anatomic or physiologic abnormality of the heart occurring in utero
Congestive Heart Failure (CHF)	The heart cannot deliver adequate cardiac output to meet the metabolic demands of the body
Cyanotic	Deoxygenated blood in the systemic circulation; pale or blue discoloration to skin, face, hands, mucous membranes; related to type of cardiac defect and resulting physiology
Growth Failure	Weight attainment or weight change velocity is significantly below that of other infants of same sex and age, based on a prescribed reference standard
Infant	Child from 1 month to 12 months of age
Neonate	Newborn infant from birth to 30 days of life
Postsurgical physiology	Functional and anatomic physiology of blood flow following surgical intervention for congenital heart disease
Single Ventricle (SV)	Cardiac defect with one functioning ventricle for pulmonary and systemic blood flow
Weight Attainment	Weight measured at a point in time; may be assessed as kilogram or z-score
Weight Change Velocity	Weight measured over specified time increments; may be assessed as kilograms, z-score, or percentiles over time

Table 1 Comparison of infants with Congenital Heart Disease enrolled versus not enrolled.*

Characteristics	Total Enrolled *% of n* = 242	Not Enrolled % of *n* = 338
Gender		
Male	61	76
Female	39	57
Post Operative Physiology[a]		
SV	33	22
BV	33	18
Healthy Controls[b]	33	-
Race[c]		
African-American	18	9
Asian	1	<1
Caucasian	69	54
More than 1 Race	6	-
Unknown/No Response	6	8
Ethnicity[c]		
Non-Hispanic	64	40
Hispanic	7	5
Unknown/No Response	29	4

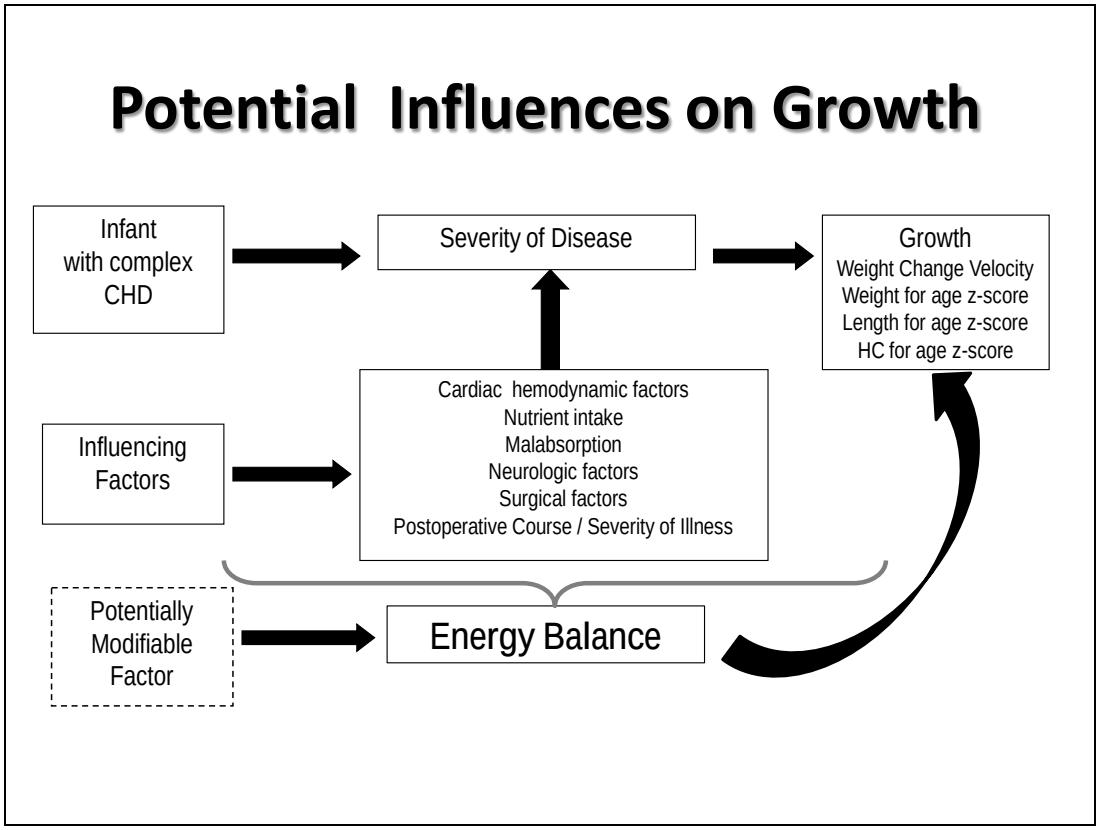
*Rounded % of total for each characteristic;
[a]Physiology data for not enrolled subjects not confirmed
[b]Comparable information on the unrecruited healthy infants was not available
[c]Data for race and ethnicity in the not enrolled participants is incomplete; race and ethnicity is assigned based on parent self-identification after enrollment

Table 2 Manuscripts and Specific Aims

Chapter	Specific Aim
Chapter 2	
Section 1 Growth Velocity over the First Year of Life Following Neonatal Surgery for Complex Congenital Heart Disease	To examine the pattern of growth velocity of weight, length, and head circumference for infants with postsurgical classification as SV physiology compared to healthy age-matched controls over the first year of life.
Section 2 Resting Energy Expenditure at 3 Months of Age in Infants with Complex Congenital Heart Disease Following Neonatal Surgery	To investigate differences in energy expenditure between infants with CHD who have a postoperative classification as single-ventricle or two-ventricle physiology as compared to healthy age-matched controls at 3 months of age.
Chapter 3	
The Use of Indirect Calorimetry (IC) to Measure Energy Needs in Mechanically Ventilated Children with Acute Lung Injury	Use of IC derived measurements of - energy expenditure to prescribe nutrient intake specific to energy needs in critically ill, mechanically ventilated pediatric patients to increase ventilation-free days, decrease hospital stay, and improve overall outcome following critical illness in a specific patient population.

Description of manuscripts of the dissertation

Figure 1 Conceptual Model of Potential Influences on Growth in CHD



Conceptualization of the potential components and processes having an effect on growth in infants following neonatal surgical intervention for CHD

CHAPTER 2

Part 1

Growth Velocity over the First Year of Life Following Neonatal Surgery for Congenital Heart Disease

Abstract

Background: Growth failure is well documented in infants with CHD. Poor growth in infancy has an effect on cognitive and neurobehavioral development. Assessment of growth velocity will identify infants at risk for growth failure.

Objective: To assess growth using World Health Organization (WHO) growth velocity standards.

Study Design: A descriptive, a sub-analysis from a prospective, longitudinal study in a large, metropolitan, cardiac center.

Methods: Infants with CHD were recruited following surgery. Healthy infants were from primary practices and surrounding community. Growth measures were every 3 months. WHO velocity z-scores were calculated. Student's *t*-test was used to assess differences between the groups.

Results: A total of 120 infants were included, 69 with CHD, 45% had SV physiology and 55% with BV. There were 65% males, and 80% were Caucasian. Males and females had statistically significant lower weight velocity z-score (males and females $p<0.001$) for the birth to 3-month interval. In subsequent intervals there was no difference in weight. Head circumference were different in velocity z-score only at the birth to 3-month interval for males (males $p<0.001$; females ($p<0.05$). Other velocity z-scores were not different.

Conclusion: Infants with CHD demonstrate poor growth velocity early in infancy. There was no difference in growth velocity after the birth to 3-month interval. WHO growth velocity standards are useful and may be more appropriate to assess growth patterns for infants with CHD.

Definition of Terms

Term	Definition
Bi-Ventricle (BV)	Normal two-ventricle cardiac physiology
Congenital Heart Disease (CHD)	Anatomic and/or physiologic abnormality of the heart occurring in utero, present at birth
Growth Failure	Weight attainment or weight change velocity that is significantly below reference standards for age and gender
Growth Velocity	Weight, length, head circumference measured over time; assessed as centimeters, grams, kilograms, or z-score
Infant	Child from 30 days to end of 12 month
Neonate	Newborn child from birth to 30 days of life
Postsurgical physiology	Functional and anatomical physiology of blood flow following surgical intervention for congenital heart disease
Single Ventricle (SV)	Cardiac defect with one functioning ventricle for pulmonary and systemic blood flow
Weight Attainment	Weight measured at a point in time; assessed as centimeters, grams, kilograms

Growth Velocity over the First Year of Life Following Neonatal Surgery for Congenital Heart Disease

Introduction

Growth is often a gauge of an infant's health, well-being and ability to thrive; it is fundamental to pediatric healthcare. In the US, current American Academy of Pediatrics guidelines recommend growth measurements at specified intervals to monitor an infant's growth progress.[1,2] The first year of life is a period of rapid growth, adequate nutrient intake is necessary to ensure acceptable weight gain, appropriate increase in stature and support best potential for brain development. Alterations in growth that occur during the first year and cause the infant to fall below reference standards, may indicate growth failure and can have long-reaching consequences for neurobehavioral development, cognitive function and school performance.[3-6] Infants with congenital heart disease (CHD), who have undergone surgery in the neonatal period, often fall short of growth measurements that meet gender- and age-specific reference standards, putting them at risk for consequences of the poor neurodevelopment that can result from growth failure in early infancy.[7-10]

In 2006, the World Health Organization (WHO) introduced international child growth standards consisting of z-scores and percentile curves for male and female children aged 0 to 5 years.[11] These standards describe how children should grow versus a depiction of attained growth at a point in time. Experts agree that the WHO standards represent the best physiologic growth for children under optimal environmental conditions, with adequate nutrition, free of psychological, socio-economic and ethnicity biases.[11] As an adjunct to the growth standards, WHO researchers developed growth velocity standards, introduced in 2009.[12] Growth velocity

defined as the change in measure over time, accounts for the normal individual pattern of variability characteristic of saltatory, catch-up or slow-down growth.[12] Growth velocity can be highly variable, despite this it is considered a superior assessment and may prove to be more appropriate than attained growth values. It allows for early detection of infants and children at risk of falling below reference growth trajectories.

To better understand growth and growth patterns of infants with CHD following surgery in the neonatal period, we examined growth velocity using the WHO standards.[12] The aim of this study is to describe the velocity of growth for weight, length, and head circumference over the first year of life in 3-month intervals for infants with CHD following neonatal surgery as compared to healthy infants of similar age and gender. Table 1 is a definition of terms and abbreviations.

Study Design and Setting

This is a descriptive sub-analysis from a convenience sample of a prospective, longitudinal study conducted at The Children's Hospital of Philadelphia (CHOP), between March 2003 and May 2007. Study approval was obtained from the CHOP Institutional Review Board, and informed consent was obtained prior to commencement of study procedures.

Study Sample

Neonates were recruited from the Cardiac Intensive Care Unit at CHOP. Healthy infants from primary care practices affiliated with CHOP and the community at large served as the control group. Eligible participants were 36 weeks post-menstrual age with birth weight of $\geq$ 2,500 grams. Birth data were extracted from records that accompanied the infant to CHOP or by parental report for healthy infants. Infants with known or overt chromosomal abnormalities, multiple congenital and/or facial

anomalies, or complex gastrointestinal or congenital and/or acquired neurologic insults were not eligible as these factors are associated with poor growth. Infants with CHD were classified as single ventricle (SV) or biventricular (BV) physiology in the usual manner.[13] Race and ethnicity were assigned based on parent self-identification.

Study Methods

All study visits were conducted at CHOP in the Clinical and Translational Research Center and the Nutrition and Growth Lab. Study measurements were obtained by research personnel using standard protocol.[14] Design of the larger study included study visits in 3-month intervals beginning at 3-months of age through 12 months. Goal timing of study visits was set within 2 weeks before or after the infant's birth date. Infants who attended a minimum of two of five study visits, one being the 3-month visit and had birth weight data were included in this analysis.

Weight was measured in kilograms (kg) using a Scale-Tronix (Scale-Tronix, White Plains, NY, USA) infant pan scale, accurate to 5 gm. Recumbent length measured in centimeters (cm) was obtained using an infant length board (Holtain Limited, Crymuch, UK) accurate to 0.1 cm. Head circumference was measured using a non-stretchable tape and measured to 0.1 cm (McCOY Health Science Supply, Maryland Heights, MO, USA). Measurements were obtained in triplicate, and the calculated mean used for analysis. Using WHO standards,[11,15] measures of weight, length, and head circumference were converted to z scores. Calculations for weight growth velocity were calculated in four, 3-month intervals. Velocities for length and head circumference were calculated for three intervals owing to incomplete birth data for these measures.

Statistical Analysis

All analyses were completed using the SAS V9.2 (SAS Institute, Cary, NC) statistical analysis program. Statistical significance was determined at the $p<0.05$ level. Descriptive statistics of the means, standard deviations, medians, and minimum and maximum values for each measure were calculated. Distribution plots were used to assess normality of the data.

Velocity for each growth parameter for each infant for each time interval was calculated using the equation:

unit of measure/day = Δ in growth parameter ÷ length of interval in days,

where the change (Δ) in growth parameter is the difference between the measured weight, length or head circumference obtained at two contiguous study visits. That change was then divided by the time interval in days between study visits. The result is the unit of measure/day. An example of calculation for weight velocity is:

20.8 gm/day = 5800 gm – 3550 gm ÷ 108 days,

where 5800 gm is the 3-month visit weight, 3550 gm is the birth weight, 108 days is the number of days between birth and the 3-month study visit, resulting in 20.8 gm/day weight change over 108 days.

The next step was to correct the velocity to the specified 3-month interval of the study protocol. This was done by multiplying the derived unit of measure by 91.2 to account for months with 30 and 31 days. The result is a value representing the change specific to a 3-month interval. Using the example above:

1897 gm over 3 months (total weight change) = 20.8 gm/day x 91.2 days.

The same procedures were repeated to calculate the velocity of length and head circumference for each infant for each time interval.

Velocity z-score for each growth parameter was then calculated using the WHO equations[12] based on 3-month intervals, 0 – 3, 3 – 6, 6 – 9, and 9 – 12, as specified in the larger study protocol. To enable comparison of the groups, z-scores were calculated using the lambda (L), mean (M), standard deviation (S), and delta values specified in the WHO procedure for the 3-month intervals indicated.[12] The WHO velocity z-score was calculated using the equation:

[12],

where represents the growth parameter increment (weight, length or head circumference) for *t*, the visit age interval; LMS values are from the WHO tables for 3-month intervals by gender. Once velocity z-scores were calculated for all parameters, two-sided Student's *t*-test was used to compare differences at each interval between healthy infants to infants with CHD by gender.

Results

There were 130 infants who met inclusion criteria. Three infants with CHD died prior to study completion due to complications of their cardiac disease. Five healthy infants did not have birth weight data and two families withdrew from study participation. There were 120 infants included at the initiation of this analysis. Of these, 69 were infants with CHD, 31 (45%) with SV physiology, 38 (55%) with BV physiology; 51 were healthy infants. The distribution of diagnoses for infants with CHD is presented in Table 2. Data are presented by gender with healthy infants compared to infants with CHD, as small sample size did not permit examination of the data in infants with CHD by physiology. The number of participants at each visit, for each measure and each interval was determined. Study sample demographics are presented in Table 3. The data are grouped and presented by growth parameter, illustrating the group mean,

WHO z-score, parameter measurement change over time and WHO velocity z-score (Tables 4, 5, 6, and 7).

Birth weight in grams and z-score were not different among the groups. The mean attained weight was significantly less for males with CHD compared to healthy males (5517 gm, z-score -1.4, $p<0.001$) at 3-months, with a statistically significant decreased weight change in the birth to 3 month interval (2015 gm, $p<0.001$*).* The weight velocity z-score further demonstrated this decreased weight change, z-score -1.82, $p<0.001$ compared to healthy males. This trend of decreased mean attained weight continued and remained negative and statistically significant in males for each time point (Table 6). There was a 20% drop in attendance from the 3-month to 6-month visit and a 22% drop from the 6-month to 9-month visit. At 12 months, males with CHD had 89% attendance, a 40% increase from the 9- month visit. The attained weight at 12 months although still significantly less than healthy in males (9398 gm, $p=0.04$) showed improvement. There was no difference in weight change or weight velocity z-score after the birth to 3-month interval.

Females with CHD demonstrated a statistically significant decrease in attained weight (5422 gm, $p=0.02$) at the 3-month visit compared to healthy females. The birth to 3-month interval weight change (1764 gm) and weight z-score velocity (-1.8) were also significantly lower ($p<0.001$) than for healthy females. Attained weight, weight z-score, weight change, and weight velocity z-score were not different between females with CHD and healthy females at any other time point or interval. Females with CHD represented the smallest number of participants at each study visit. Table 7 compares healthy females to females with CHD for each growth parameter.

Males with CHD demonstrated significantly lower attained length at each study visit compared to healthy males; the length z-score, length change and length velocity z-score were not different (Table 6). Head circumference showed a similar pattern to weight in males with CHD compared to healthy males, with the exception of the 12-month visit where attained head circumference was not different between the groups. The head circumference velocity z-score for males (0.1) was negatively significant at the birth to 3-month interval, $p<0.01$. No other intervals were different from those in healthy males.

Length for females with CHD was not different from healthy females at any visit or any time interval. The attained measure for head circumference in females with CHD was significantly lower (39 cm, $p<0.05$) than in healthy females at the 3-month visit, no difference was demonstrated in attained measurement, head circumference z-score, head circumference change or head circumference velocity z-score for any other time point or time interval. Females with CHD demonstrated a drop in attendance of 26% from the 3 to 6-month visit, 29% from the 6 to 9-month visit and an increase of 43% from the 9 to 12-month visit, which has a critical impact on the findings. In addition, there was more than 20% missing data for each measurement across the study critically affecting the findings and limiting the conclusions that can be derived.

Discussion

In this study, using the new WHO growth and growth velocity standards to evaluate infants with CHD compared to healthy infants of similar age and gender, we demonstrate decreased attained weight, decreased interval weight change and negative weight velocity z-scores in both males and females with CHD at 3-months of age. The small sample size and missing data necessitate cautious interpretation of

these findings. Despite this, these data give promise for better understanding of the pattern of growth in infants with CHD who have undergone neonatal surgery.

Infants are expected to gain between 20 and 30 grams/day in the first 6 months of life following a physiologic weight loss in the first days of life up to and exceeding 10%.[16-18] This rate of growth is different in exclusively breastfed infants.[17] From these data, it appears that on average infants with CHD are at the lower end of this expected range for weight gain or do not meet it, particularly in the first 3-months of life. In our study, males with CHD showed a mean weight change in the birth to 3- month interval of 2015 gm, approximately 22gm/day; the mean weight change in healthy males was approximately 29 gm/day. Using the WHO growth velocity standards, this change is equal to a weight velocity z-score of -1.82 and corresponds to the 3rd to 5th percentile of weight velocity for age and gender. In the same birth to 3-month period, females with CHD demonstrated a weight change of 19 gm/day compared to 27 gm/day in healthy females; they too are in the 3rd to 5th percentile with a corresponding weight velocity z-score of -1.8. For the birth to 3-month interval, both females and males with CHD demonstrated growth velocity below the 5th percentile by WHO standards. Although these are the mean values of the respective groups, it is the low weight velocity z-scores in conjunction with low attained weight that are of concern. These values represent significant growth failure at this time interval, supporting the existing evidence that describes poor weight gain in infants with CHD in early infancy. The attained weight in males with CHD remained statistically significant and below that of healthy males throughout the study period. Following the birth to 3-month interval weight change and weight velocity z-scores were not different for males or females

with CHD compared to healthy infants of the same gender, suggesting catch-up growth occurs subsequent to 3-months of age.

Attained length for males with CHD was significantly below that of healthy males at each study visit (Table 6) however, the change in length and length velocity z-score were not different, suggesting that although length at 3-months of age is lower than that in healthy infants, the rate of increase is the same. Length for female infants with CHD was not different from healthy females in our study sample. Several studies of infants with CHD report linear growth delay in early infancy, with catch up growth for length commencing later in infancy and progressing at a slower rate than weight catch up growth.[10,19,20] These studies suggest that delayed attainment of length in infants with CHD following neonatal surgery is reversible.

Head circumference is the best determinant of brain growth.[21,22] In males with CHD in our study sample, attained head circumference was decreased from that of healthy males with no difference by 12 months of age. Females with CHD demonstrated a negative statistically significant difference only at 3-months and only for the attained head circumference measurement (39 cm, p=0.01); this finding is likely skewed due to small sample size. Research suggests that prenatally, infants with CHD have smaller brain volume and decreased brain growth; this low volume presents at birth as small head circumference and may indicate global neurologic immaturity.[21-23] This decreased brain volume and the potential for slow brain growth can have a direct effect on neurodevelopment, cognition, and behavior in childhood.[22,24]

Monitoring growth parameters is an important component of care for infants and young children, particularly infants with CHD who have undergone neonatal surgery. Although limited, the data presented show significantly decreased growth in males and

females at 3-months of age with promise for catch up in late infancy. We used WHO standards for growth[11] and growth velocity[12] to evaluate these data as it is believed these standards provide a more precise assessment of how growth is occurring over time compared to how it has occurred at a point in time. Ross and colleagues[25] demonstrated a downshift or poor weight attainment in early infancy, at 2 to 4 months of age, and found to be predictive of later poor growth despite an interval period of growth recovery. These researchers suggest that healthcare providers use acceleration and deceleration standards to identify patterns of growth in infants at risk, initiate stringent monitoring procedures and provide early interventions for those infants whose pattern of growth in early infancy suggests growth failure.[25]

Poor growth in early infancy has been associated with infant irritability, cognitive impairments, delayed development of executive functions, developmental delay, poor school achievement, and deficits in motor, speech and language skills.[4,5,26,27] In a population based study, Gale et al[28] reported prenatal head growth and head growth during infancy to be particularly important determinants for subsequent intelligence, further, they found head growth after infancy did not appear to compensate for decreased growth during infancy. McDougall et al[4] studied over 1800 infants with documented poor growth in the first months of life and found an association to decreased intellectual ability and lower IQ at school age. These studies present evidence of an association between poor growth in infancy and negative impact on neurodevelopment and intelligence in childhood.

The data presented here, demonstrate growth failure in the infants with CHD. Contributing factors that may have a role in poor growth evidenced in infants with CHD include inadequate energy intake to promote a positive energy balance,[29-32]

gastrointestinal tract abnormalities,[33,34] neurologic immaturity,[21,23,35] and feeding dysfunction.[36-38] Regardless of the etiology, the potential short and long-term consequences of poor growth can be detrimental to the infant and are a focus of interest. Reviews of studies investigating neurobehavioral and neurodevelopmental outcomes following surgery for CHD have consistently found reports of delay in cognitive and motor development, attention deficits and altered development of speech and language skills.[6,39-41] These documented consequences of growth failure and the impact they can exert on growth and long-term intellectual development are ample cause to further investigate contributors to poor growth in this population and seek viable interventions to minimize its occurrence.

Study Limitations

Limitations include this being a convenience sample from a single center with high illness acuity of cardiac disease. There was a large amount of missing data resulting in small sample size. Dietary intake records were not available to assess energy intake simultaneously with growth in these infants. All birth data were parent report or extracted from the transfer record that accompanied the infants with CHD. Some bias may exist in that families who enrolled were motivated to participate in a complex study protocol.

Conclusion

Poor growth is a common morbidity in infants with CHD who have undergone neonatal surgery. In this study, the use of the WHO growth and growth velocity standards presents a novel approach to examine growth in our cohort of infants with CHD. We found a pattern of poor growth in the birth to 3-month interval across gender, a time usually associated with rapid growth and development. From these limited data,

growth in all measures appears to begin catch-up following the initial interval of poor growth. Further study with a larger sample is and fewer missing data points is necessary for a better evaluation of these findings. However, these data are important and may be the first to use the WHO growth velocity standards to evaluate growth in a cohort of chronically ill infants. Use of this methodology may assist providers in early identification of poor growth in infants with CHD following surgery in the neonatal period and facilitate timely interventions to prevent or minimize growth failure, decreasing the risk for and potential of negative cognitive and neurodevelopmental sequelae associated with poor growth in early infancy, particularly in infants with CHD.

References

1. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Bright Futures Steering Committee. Recommendations for Preventive Pediatric Health Care. *Pediatr.* 2007;120(6):1376.

2. Lampl M, Thompson AL. Growth Chart Curves Do Not Describe Individual Growth. *Am J Hum Biol.* 2007;19:643 - 653.

3. Drewett R, Emond A, Blair P, Emmett P. The importance of slow weight gain in the first 2 months in identifying children who fail to thrive. *J Reprod Infant Psychol.* 2005;23(4):309-317.

4. McDougall P, Drewett RF, Hungin APS, Wright CM. The detection of early weight faltering at the 6-8-week check and its association with family factors, feeding and behavioural development. *Arch Dis Child.* 2009;94(7):549-552.

5. Dykman RA, Casey PH, Ackerman PT, McPherson WB. Behavioral and Cognitive Status in School-Aged Children With a History of Failure to Thrive During Early Childhood. *Clin Pediatr.* 2001;40:63 - 70.

6. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, Hyperactivity, and School Performance in a Population of School-Age Children With Complex Congenital Heart Disease. *Pediatr.* 2008;121(4):e759 - e767.

7. Thommessen M, Heiberg A, Kase BF. Feeding problems in children with congenital heart disease: the impact on energy intake and growth outcome. *Eur J Clin Nutr.* 1992;46:457 - 464.

8. Cohen MI, Bush DM, Ferry Jr RJ, et al. Somatic growth failure after the Fontan operation. *Cardiol Young.* 2000;10:447 - 457.

9. Vaidyanathan B, Radhakrishnan R, Sarala DA, Sundaram KR, Kumar RK. What Determines Nutritional Recovery in Malnourished Children After Correction of Congenital Heart Defects. *Pediatr.* 2009;124:e294 - e299.

10. Schuurmans FM, Pulles-Heintzberger CFM, Gerver WJM, Kester ADM, Forget P-PH. Long-term growth of children with congenital heart disease: a retrospective study. *Acta Paediatr.* 1998;87:1250 - 1255.

11. World Health Organization. *WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index for age: Methods and development*. Geneva, Switzerland: World Health Organization; 2006.

12. World Health Organization. *WHO Child Growth Standards. Growth Velocity based on weight, length and head circumference: Methods and development*. Geneva, Switzerland: World Health Organization; 2009.

13. Rhodes LA, Colan SD, Perry SB, Jonas RA, Sanders SP. Predictors of survival in neonates with critical aortic stenosis. *Circulation.* 1991;84:2325 - 2335.

14. Lohman TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Books; 1988.

15. World Health Organization. *WHO Child Growth Standards. Head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age*. Geneva, Switzerland: World Health Organization; 2007.

16. Heird WC. Nutritional Requirements. In: Behrman Richard E, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: W.B. Saunders; 2004:153-190.

17. Nommsen-Rivers LA, Dewey KG. Growth of Breastfed Infants. *Breastfeed Med.* 2009;4(Supplment 1):S45 - S-49.

18. Needlman RD. Growth and Development. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: Saunders; 2004:23 - 40.

19. Vogt KN, Manlhiot C, van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic Growth in Children With Single Ventricle Physiology: Impact of Physiologic State. *J Am Coll Cardiol.* 2007;50(19):1876-1883.

20. Hasan BS, Bendaly EA, Alexy RD, Ebenroth ES, Hurwitz RA, Batra AS. Somatic growth after fontan and mustard palliation. *Congenit Heart Dis.* Sep 2008;3(5):330-335.

21. Licht DJ, Shera DM, Clancy RR, et al. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiocasc Surg.* 2009;137(3):529 - 537.

22. Gale CR, O'Callaghan FJ, Godfrey KM, Law CM, Martyn CN. Critical periods of brain growth and cognitive function in children. *Brain.* 2004;127(2):321 - 329.

23. Majnemer A, Limperopoulos C, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C. A New Look at Outcomes of Infants with Congenital Heart Disease. *Pediatr Neurol.* 2009;40(3):197 - 204.

24. Limperopoulos C, Tworetzky W, Doff B, et al. Brain Volume and Metabolism in Fetuses With Congenital Heart Disease: Evaluation With Quantitative Magnetic Resonance Imaging and Spectroscopy. *Circulation.* 2009;121:26 - 33.

25. Ross ES, Krebs NF, Shroyer ALW, Dickinson LM, Barrett PH, Johnson SL. Early growth faltering in healthy term infants predicts longitudinal growth. *Early Hum Dev.* 2009;85 583 - 588.

26. Steward DK, Moser DK, Ryan-Wenger NA. Biobehavioral characteristics of infants with failure to thrive. *J Pediatr Nurs.* 2001;16(3):162-171.

27. Bhoomika KR, Shobini RL, Chandramouli BA. Cognitive development in children with chronic protein energy malnutrition. *Behav Brain Funct.* 2008;4(31):1-12. http://www.behavioralandbrainfunctions.com/content/4/1/31.

28. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN, Team TALSoPaCS. The influence of head growth in fetal life, infancy and childhood on intelligence at the ages of 4 and 8 years. *Pediatr.* 2006;118:1486 - 1492.

29. Schwalbe-Terilli C, Hartman DH, Nagel ML, et al. Enteral Feeding and Caloric Intake in Neonates After Cardiac Surgery. *Am J Crit Care.* 2009;18(1):52 - 57.

30. Unger R, DeKleermaeker M, Gidding SS, Christoffel K. Improved Weight Gain With Dietary Intervention in Congenital Heart Disease. *Am J Dis Child.* 1992;146:1078-1084.

31. Pillo-Blocka F, Adatia I, Sharieff W, McCrindle BW, Zlotkin S. Rapid advancement to more concentrated formula in infants after surgery for congenital heart disease reduces duration of hospital stay: A randomized clinical trial. *J Pediatr.* 2004;145(6):761-766.

32. Forchielli ML, McColl R, Walker WA, Lo C. Children with congenital heart disease: a nutrition challenge. *Nutrition Review.* 1994;52(10):348-353.

33. Malagon I, Onkenhout W, Klok M, van der Poel P, Bovill J, Hazekamp M. Gut permeability in neonates after a stage 1 Norwood procedure. *Pediatr Crit Care Med.* 2005;6(5):547 - 549.

34. Harrison AM, Davis S, Reid JR, et al. Neonates with hypoplastic left heart syndrome have ultrasound evidence of abnormal superior mesenteric artery perfusion before and after modified Norwood procedure. *Pediatr Crit Care Med.* 2005;6(4):445 - 447.

35. Dooley KJ, Bishop L. Medical management of the cardiac infant and child after surgical discharge. *Crit Care Nurs Q.* 2002;25(3):98 - 104.

36. Einarson KD, Arthur HM. Predictors of oral feeding difficulty in cardiac surgical infants. *Pediatr Nurs.* Jul-Aug 2003;29(4):315-319.

37. Kogon BE, Ramaswamy V, Todd K, et al. Feeding Difficulty in Newborns Following Congenital Heart Surgery. *Congenit Heart Dis.* 2007;2:332 - 337.

38. Medoff-Cooper B, Irving SY. Innovative Strategies for Feeding and Nutrition in Infants with Congenitally Malformed Hearts. *Cardiol Young.* 2009;19(Suppl. 2):90 - 95.

39. Snookes SH, Gunn JK, Eldridge BJ, et al. A Systematic Review of Motor and Cognitive Outcomes After Early Surgery for Congenital Heart Disease. *Pediatr.* 2010;125(4):e818 - e827.

40. Bjarnason-Wehrens B, Dordel S, Schickendantz S, et al. Motor development in children with congenital cardiac diseases compared to their healthy peers. *Cardiol Young.* 2007;17:487 - 498.

41. Hovels-Gurich HH, Bauer SB, Schnitker R, et al. Long-term outcome of speech and language in children after corrective surgery for cyanotic or acyanotic cardiac defects in infancy. *Eur J Paediatr Neurol.* 2008;12:378-386.

Table 2 CHD Primary diagnosis of infants with Congenital Heart Disease

Primary Diagnosis	Postsurgical Physiology	
	Single Ventricle *% of N* = 31	Bi-Ventricle *% of N* = 38
Hypoplastic Left Heart Syndrome	59	
Tricuspid Atrestia	16	
Double Inlet Left Ventricle	6	
L-Transposition of Great Arteries	3	
D-Transposition of Great Arteries	6	47
Double Outlet Right Ventricle	3	3
Valvular Pulmonary Atresia	6	3
Coarctation of the Aorta		21
Tetrology of Fallot		11
Interrupted Aortic Arch		5
Truncus Arteriosus		2
Aortopulmonary Window		2
Valvular Aortic Stenosis		2
Total Anomalous Pulmonary Venous Return		3

Distribution of diagnoses across sample of infants with CHD, with postsurgical cardiac classification

Table 3 Study sample demographics

	Healthy Infants	Infants with Congenital Heart Disease	
		Single Ventricle	Bi-Ventricle
N	51	31	38
Gender			
Female	19	8	15
Male	32	23	23
Race			
AA	13	4	-
Asian	1	-	-
Caucasian	33	26	37
>1	2	-	1
Not Reported	2	1	-
Ethnicity			
Hispanic	2	2	3
Non-Hispanic	42	21	25
Not Reported	6	8	9

Gender, race, and ethnicity distribution of study sample.

Table 4 Mean (SD) growth parameters, healthy females and males

	Healthy Females					Healthy Males				
Time	Birth	3	6	9	12	Birth	3	6	9	12
n	19	19	19	17	19	32	32	32	24	27
Age (d)	0	98 (15)	194 (18)	270 (11)	374 (17)	0	93 (9)	191 (15)	276 (14)	370 (17)
Wt[a] gm	3304 (0.5)	5984 (0.8)	7379 (0.8)	8376 (1.0)	9195 (1.1)	3576 (0.6)	6272 (0.6)	7969 (1.0)	9213 (0.7)	9952 (1.0)
z-score	0.1 (1.1)	-0.1 (1.0)	-0.1 (0.9)	0.1 (1.0)	0.1 (0.9)	0.4 (1.1)	-0.2 (0.8)	-0.1 (1.0)	0.3 (0.6)	0.2 (1.0)
Wt Δ, gm[b]		2461 (562)	1419 (393)	903 (460)	918 (303)		2653 (601)	1570 (404)	1194 (546)	875 (377)
Wt z-vel[c]		-0.3 (1.1)	-0.2 (1.0)	-0.2 (1.3)	0.6 (0.9)		-0.6 (1.1)	-0.1 (1.0)	0.5 (1.7)	0.3 (1.1)
Lt[a] cm		61 (2.8)	66 (2.1)	70 (2.3)	73 (1.2)		62 (2.4)	69 (2.8)	73 (3.0)	77 (3.0)
z-score		-0.31 (1.3)	-0.0 (0.9)	0.3 (1.3)	-0.3 (0.8)		0.3 (1.1)	-0.0 (1.0)	0.6 (1.3)	0.3 (1.2)
Lt Δ, Gm[b]			5.5 (2.1)	-0.1 (1.0)	3.7 (1.4)			5.5 (2.1)	4.6 (1.5)	3.4 (1.3)
Lt z-vel[c]			-0.5 (2.0)	-0.3 (1.6)	-0.2 (1.5)			-0.2 (1.1)	0.3 (1.5)	-0.5 (1.5)
HC[a] cm		40 (1.4)	43 (1.1)	45 (1.3)	45 (1.0)		41 (1.3)	44 (1.2)	46 (1.1)	47 (1.3)
z-score		0.5 (1.0)	0.5 (0.8)	0.8 (1.0)	0.4 (0.7)		0.4 (1.1)	0.3 (0.8)	0.5 (1.0)	0.5 (1.0)
HC Δ, Gm[b]			2.7 (0.5)	1.8 (0.7)	0.7 (1.3)			2.7 (0.6)	1.7 (0.6)	1.2 (0.5)
HC z-vel[c]			-0.5 (2.0)	-0.3 (1.6)	-0.2 (1.5)			-0.2 (1.1)	0.3 (1.5)	-0.5 (1.5)

*Weight for birth data only; [a]Parameter means (SD), [b]Parameter interval Δ (SD), [c]Parameter interval velocity z-score

Table 5 Mean (SD) growth parameters, females and males with CHD

	Females with CHD					Males with CHD				
Time	Birth	3	6	9	12	Birth	3	6	9	12
n	23	23	17	12	21	46	46	37	29	41
Age (d)	0	99 (16)	192 (17)	272 (12)	375 (17)	0	96 (13)	189 (15)	277 (16)	380 (19)
Wt[a] gm	3491 (0.5)	5422[§] (0.7)	6982 (0.9)	8217 (1.0)	9119 (1.1)	3396 (0.5)	5517[‡] (0.9)	7257[¥] (1.0)	8303[‡] (1.1)	9398[§] (1.1)
z-score	0.0 (1.0)	-0.9 (1.0)	-0.6 (1.1)	-0.1 (1.0)	0.0 (1.0)	0.1 (1.0)	-1.4 (1.2)	-1.0 (1.1)	-0.7 (1.2)	-0.4 (1.1)
Wt Δ, gm[b]		1764[‡] (545)	1524 (246)	1056 (296)	901 (424)		2015[‡] (606)	1607 (347)	1080 (493)	833 (506)
Wt z-vel[c]		-1.8[‡] (1.3)	0.1 (0.7)	0.3 (0.8)	0.5 (1.2)		-1.82[‡] (1.2)	0.0 (1.0)	0.2 (1.4)	0.2 (1.5)
Lt[a] cm		60 (2.5)	66 (3.4)	71 (2.8)	74 (3.0)		60[‡] (2.8)	66[¥] (2.5)	70[‡] (2.9)	75[§] (2.8)
z-score		-0.4 (1.2)	-0.6 (1.4)	0.3 (1.2)	0.0 (1.1)		-0.4 (1.2)	-0.7 (1.1)	-0.8 (1.2)	-0.6 (1.2)
Lt Δ, gm[b]			6.5 (1.3)	4.8 (1.5)	3.8 (1.2)			6.4 (1.5)	4.7 (1.0)	3.3 (2.0)
Lt z-vel[c]			0.5 (1.2)	0.4 (1.5)	-0.1 (1.3)			0.1 (1.3)	0.4 (1.0)	-0.2 (1.4)
HC[a] cm		39[§] (1.1)	43 (1.0)	45 (1.6)	46 (1.6)		40[‡] (1.7)	43[§] (1.4)	45[§] (1.7)	46 (1.6)
z-score		-0.34 (1.1)	-0.2 (0.9)	-0.4 (1.3)	0.0 (1.2)		-0.9 (1.4)	-0.3 (1.1)	-0.3 (1.4)	-0.0 (1.3)
HC Δ, gm[b]			3.0 (0.4)	1.6 (1.0)	1.3 (0.7)			3.3[§] (0.7)	1.7 (1.0)	1.4 (0.8)
HC z-vel[c]			0.5 (1.2)	0.4 (1.5)	-0.1 (1.3)			0.1[¥] (1.3)	0.4 (1.0)	-0.2 (1.4)

*Weight for birth data only; [a]Parameter means (SD), [b]Parameter interval Δ (SD), [c]Parameter interval velocity z-score; Student's t-test significance levels [§]$p<0.05$, [¥]$p<0.01$ [‡]$p<0.001$

Table 6 Mean (SD) growth parameters, healthy males and males with CHD

	Healthy Males					Males with CHD				
Time	Birth	3	6	9	12	Birth	3	6	9	12
n	32	32	32	24	27	46	46	37	29	41
Age (d)	0	93 (9)	191 (15)	276 (14)	370 (17)	0	96 (13)	189 (15)	277 (16)	380 (19)
Wt[a] gm	3576 (0.6)	6272 (0.6)	7969 (1.0)	9213 (0.7)	9952 (1.0)	3396 (0.5)	5517[‡] (0.9)	7257[¥] (1.0)	8303[‡] (1.1)	9398[§] (1.1)
z-score	0.4 (1.1)	-0.2 (0.8)	-0.1 (1.0)	0.3 (0.6)	0.2 (1.0)	0.1 (1.0)	-1.4 (1.2)	-1.0 (1.1)	-0.7 (1.2)	-0.4 (1.1)
Wt Δ, gm[b]		2653 (601)	1570 (404)	1194 (546)	875 (377)		2015[‡] (606)	1607 (347)	1080 (493)	833 (506)
Wt z-vel[c]		-0.6 (1.1)	-0.1 (1.0)	0.5 (1.7)	0.3 (1.1)		-1.82[‡] (1.2)	0.0 (1.0)	0.2 (1.4)	0.2 (1.5)
Lt[a] cm		62 (2.4)	69 (2.8)	73 (3.0)	77 (3.0)		60[‡] (2.8)	66[¥] (2.5)	70[‡] (2.9)	75[§] (2.8)
z-score		0.3 (1.1)	-0.0 (1.0)	0.6 (1.3)	0.3 (1.2)		-0.4 (1.2)	-0.7 (1.1)	-0.8 (1.2)	-0.6 (1.2)
Lt Δ, gm[b]			5.5 (2.1)	4.6 (1.5)	3.4 (1.3)			6.4 (1.5)	4.7 (1.0)	3.3 (2.0)
Lt z-vel[c]			-0.2 (1.1)	0.3 (1.5)	-0.5 (1.5)			0.1 (1.3)	0.4 (1.0)	-0.2 (1.4)
HC[a] cm		41 (1.3)	44 (1.2)	46 (1.1)	47 (1.3)		40[‡] (1.7)	43[§] (1.4)	45[§] (1.7)	46 (1.6)
z-score		0.4 (1.1)	0.3 (0.8)	0.5 (1.0)	0.5 (1.0)		-0.9 (1.4)	-0.3 (1.1)	-0.3 (1.4)	-0.0 (1.3)
HC Δ, gm[b]			2.7 (0.6)	1.7 (0.6)	1.2 (0.5)			3.3[§] (0.7)	1.7 (1.0)	1.4 (0.8)
HC z-vel[c]			-0.2 (1.1)	0.3 (1.5)	-0.5 (1.5)			0.1[¥] (1.3)	0.4 (1.0)	-0.2 (1.4)

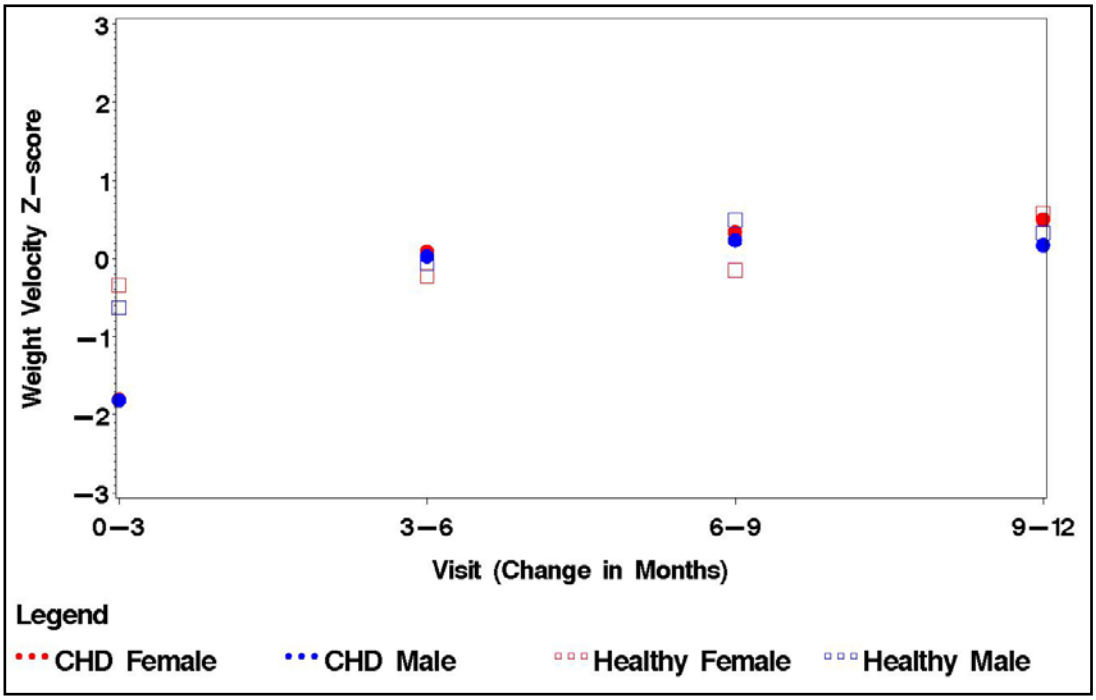
*Weight for birth data only; [a]Parameter means (SD), [b]Parameter interval Δ (SD), [c]Parameter interval velocity z-score; Student's t-test significance levels [§]$p<0.05$, [¥]$p<0.01$ [‡]$p<0.001$

Table 7 Mean (SD) growth parameters, healthy females and females with CHD

	Healthy Females					Females with CHD				
Time	Birth	3	6	9	12	Birth	3	6	9	12
n	19	19	19	17	19	23	23	17	12	21
Age (d)	0	98 (15)	194 (18)	270 (11)	374 (17)	0	99 (16)	192 (17)	272 (12)	375 (17)
Wt[a] gm	3304 (0.5)	5984 (0.8)	7379 (0.8)	8376 (1.0)	9195 (1.1)	3491 (0.5)	5422[§] (0.7)	6982 (0.9)	8217 (1.0)	9119 (1.1)
z-score	0.1 (1.1)	-0.1 (1.0)	-0.1 (0.9)	0.1 (1.0)	0.1 (0.9)	0.0 (1.0)	-0.9 (1.0)	-0.6 (1.1)	-0.1 (1.0)	0.0 (1.0)
Wt Δ, gm[b]		2461 (562)	1419 (393)	903 (460)	918 (303)		1764[‡] (545)	1524 (246)	1056 (296)	901 (424)
Wt z-vel[c]		-0.3 (1.1)	-0.2 (1.0)	-0.2 (1.3)	0.6 (0.9)		-1.8[‡] (1.3)	0.1 (0.7)	0.3 (0.8)	0.5 (1.2)
Lt[a] cm		61 (2.8)	66 (2.1)	70 (2.3)	73 (1.2)		60 (2.5)	66 (3.4)	71 (2.8)	74 (3.0)
z-score		-0.31 (1.3)	-0.0 (0.9)	0.3 (1.3)	-0.3 (0.8)		-0.4 (1.2)	-0.6 (1.4)	0.3 (1.2)	0.0 (1.1)
Lt Δ, Gm[b]			5.5 (2.1)	-0.1 (1.0)	3.7 (1.4)			6.5 (1.3)	4.8 (1.5)	3.8 (1.2)
Lt z-vel[c]			-0.5 (2.0)	-0.3 (1.6)	-0.2 (1.5)			0.5 (1.2)	0.4 (1.5)	-0.1 (1.3)
HC[a] cm		40 (1.4)	43 (1.1)	45 (1.3)	45 (1.0)		39[§] (1.1)	43 (1.0)	45 (1.6)	46 (1.6)
z-score		0.5 (1.0)	0.5 (0.8)	0.8 (1.0)	0.4 (0.7)		-0.34 (1.1)	-0.2 (0.9)	-0.4 (1.3)	0.0 (1.2)
HC Δ, Gm[b]			2.7 (0.5)	1.8 (0.7)	0.7 (1.3)			3.0 (0.4)	1.6 (1.0)	1.3 (0.7)
HC z-vel[c]			-0.5 (2.0)	-0.3 (1.6)	-0.2 (1.5)			0.5 (1.2)	0.4 (1.5)	-0.1 (1.3)

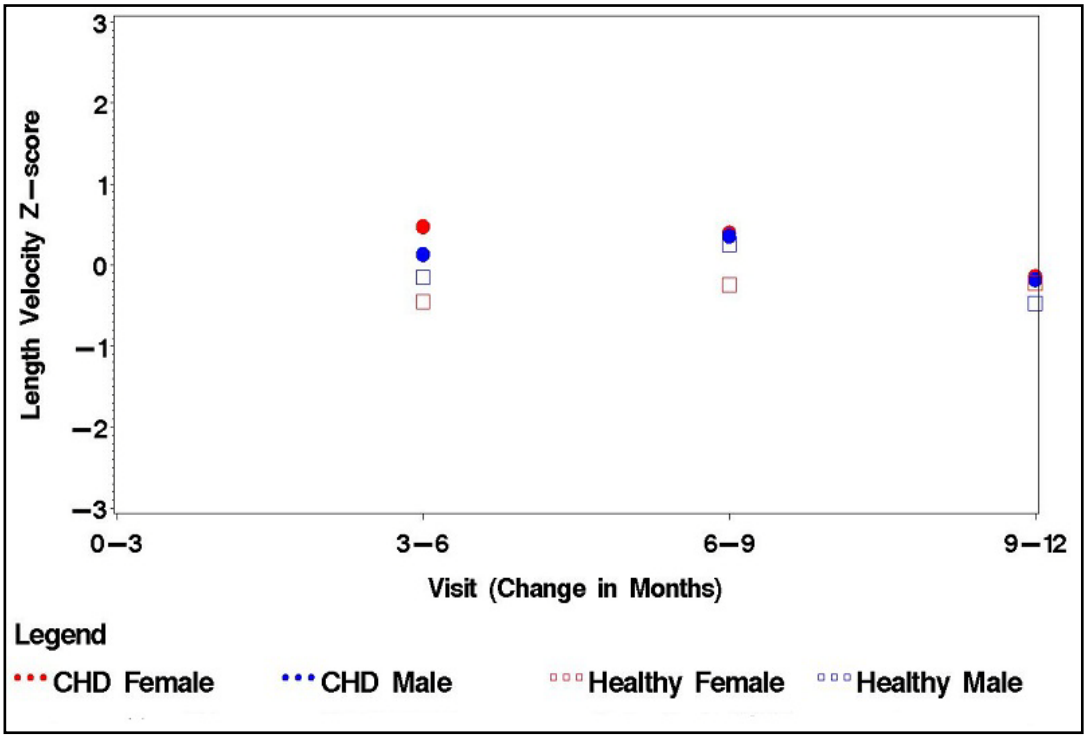
*Weight for birth data only; [a]Parameter means (SD), [b]Parameter interval Δ (SD), [c]Parameter interval velocity z-score; Student's t-test significance levels [§]$p<0.05$, [‡]$p<0.001$

Figure 1 Weight velocity z-score by gender



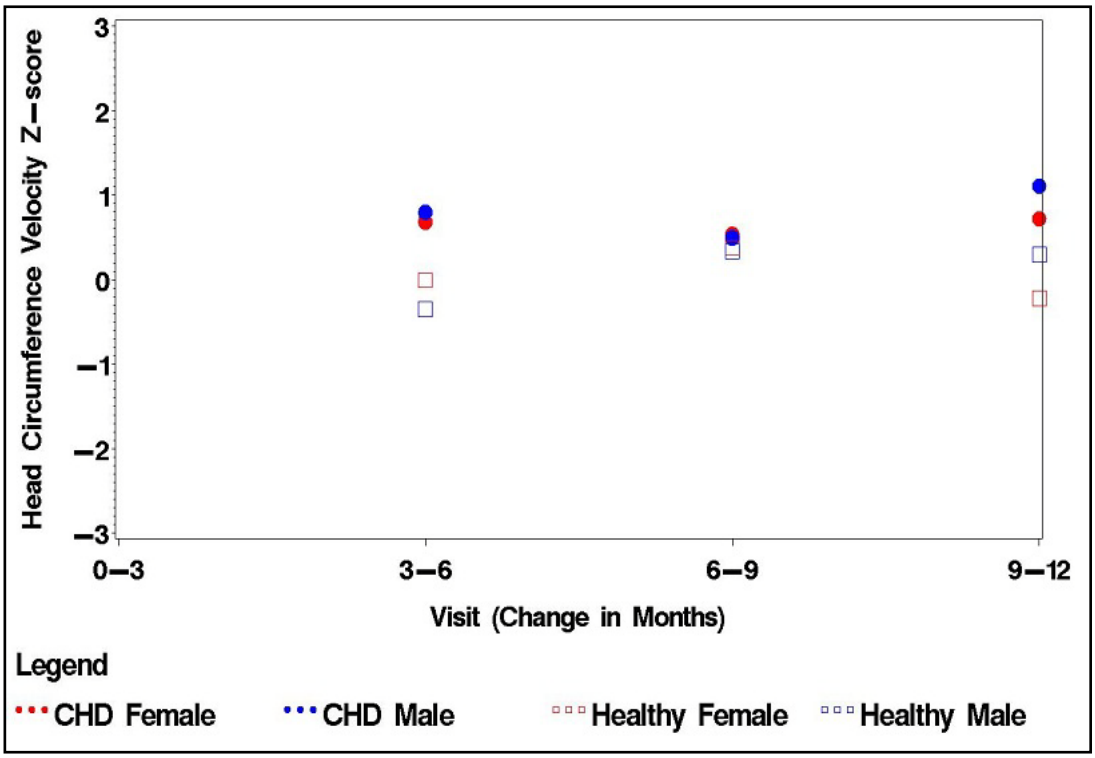
Graph illustrating weight velocity z-score by gender in 3-month intervals.
Student's *t*-test to compare healthy to infants with CHD of same gender: males -1.82, $p<0.001$; females -1.80, $p<0.001$

Figure 2 Length velocity z-score by gender



Graph illustrating illustrating length velocity z-score by gender in 3-month intervals. Birth length data not available. No difference between the groups. Student's *t*-test to compare healthy to infants with CHD of same gender.

Figure 3 Head circumference velocity z-score by gender



Graph illustrating head circumference velocity z-score by gender in 3-month intervals. Birth length data not available. No difference between the groups. Student's *t*-test to compare healthy to infants with CHD of same gender.

CHAPTER 2

Part 2

Resting Energy Expenditure at 3-Months of Age in Infants Following Neonatal Surgery for Congenital Heart Disease

Abstract

Background: Growth failure is well recognized in infants with Congenital Heart Disease (CHD). Poor growth can impact physiologic and neurodevelopmental outcomes.

Study Aim: To determine resting energy expenditure (REE), body composition and weight at 3-months of age in infants with CHD. A secondary aim was to identify predictors of REE.

Design and Methods: Sub-analysis of a prospective, single center cohort with single ventricle (SV) and bi-ventricle (BV) physiology. Anthropometric measurements, REE, and body composition were obtained at 3-months. Analysis included chi-square for association between categorical variables, *t*-tests, ANOVA and ANCOVA to compare differences. Pearson's correlation was used to examine linear relationships.

Results: Of the 44 infants with CHD, 18% had SV physiology. Infants with SV and BV physiology had lower weight for age z scores compared to healthy infants -1.1 for SV (p=0.001) and -1.0 for BV (p<0.005). Infants with SV and BV physiology had lower % body fat compared to healthy controls (SV 23.7%; BV 22.7%) but had similar REE as the control group. Fat free mass and infant age were positively correlated with REE.

Conclusion: Cardiac physiology was not a predictor of REE kcal in this study sample. Infants with CHD had lower weight for age z score and decreased % body fat at 3 months of age. These data suggest that inadequate caloric intake contributes to growth failure in infants with CHD.

Table 1 Definition of Terms

Abbreviation	Term
BV	Biventricular Physiology
CHD	Congenital Heart Disease
FM	Fat Mass, kg
FFM	Fat Free Mass, kg
REE	Resting Energy Expenditure, Kcal/day
%Sch	Schofield equation percent predicted
SV	Single Ventricle Physiology
%WHO	WHO equation percent predicted

Introduction

Growth failure is well recognized in infants with Congenital Heart Disease (CHD). Despite surgical intervention in the neonatal period, more than 50% of these infants exhibit inadequate growth,[1,2] with greater than 30% falling below the third percentile for weight early in life.[3] Poor somatic growth in infancy has the potential to impact physiologic and neurodevelopmental outcomes well into childhood and adolescence.[4,5] The etiology of poor growth in infants following neonatal surgery for CHD is likely multi-factorial and may in part result from inadequate energy intake or an increase in energy expenditure, resulting in an energy imbalance. Strong correlations have been demonstrated between growth failure early in life and long term cognitive deficiencies, including poor arithmetic performance, attention deficit, aggressive behavior and poor social and emotional development.[4,5] We reported a high rate of growth failure at hospital discharge in infants with both single ventricle (SV) physiology and biventricular (BV) circulation following neonatal surgery.[6,7] Poor weight gain in the post-operative period prior to hospital discharge was associated with post-operative complications, and timing of initiation of nutrient intake. These findings are similar to other reports that suggest infants with CHD receive less than adequate caloric intake to support normal weight gain and growth.[8-14]

There have been multiple investigations into the energy needs of infants with CHD in the pre-operative and post-operative period. The results are mixed and may be due to study design, small sample size, or a diverse sample of infants with cardiac disease.[15-23] The primary aim of this study was to determine whether there are differences in resting energy expenditure (REE), body composition, and somatic growth at 3-months of age in infants who have undergone neonatal surgery for CHD compared to healthy infants, and whether differences are present among infants with

CHD classified postoperatively as SV versus BV physiology. A secondary aim was to identify predictors of REE in infants with CHD compared to healthy infants.

Study Design and Setting

This is a sub-analysis from a prospective, cohort study investigating predictors of growth in postoperative infants with CHD conducted at The Children's Hospital of Philadelphia (CHOP) from March 2003 through May 2007. Study approval was obtained from the CHOP Institutional Review Board. Informed consent was obtained from a parent or guardian of each participant prior to initiation of study protocol.

Sample Population

Study participants were recruited from the Cardiac Intensive Care Unit at CHOP. Healthy infants served as the control group and were recruited from primary care practices, and the community at large. Eligibility for all infants included post-menstrual age $\geq$ 36 weeks and birth weight $\geq$ 2500 grams. Infants with CHD who underwent cardiac surgical intervention during the neonatal period (first 30 days of life) and did not have known multiple congenital, facial, chromosomal or complex gastrointestinal anomalies or congenital and/or acquired neurological insults were eligible. Infants were classified postoperatively as SV or BV physiology in accordance with established standards.[24] Race and ethnicity of the infants were assigned by the parent's self-identification. Families unable or unwilling to return to CHOP for study visits were not enrolled.

Study Measurements

Measurements were obtained during the 3-month outpatient visit to the Clinical and Translational Research Center (CTRC). The measurements were obtained by research personnel according to standard protocol.[25]

Anthropometric Measurements

Weight, length and head circumference measurements were obtained prior to measurement of REE and body composition on all participants. Weight was measured in kilograms (kg) using a scale accurate to 5 grams (Scaletronix, White Plains, NY, USA). Infant recumbent length, was assessed using an infant length board (Holtain Limited, Crymuch, UK) accurate to 0.1 cm and head circumference was measured using a non-stretchable measuring tape accurate to 0.1 cm (McCOY Health Science Supply, Maryland Heights, MO, USA). Measurements were obtained in triplicate, the calculated mean was used in analysis. Birth weight was extracted from the transfer records accompanying the infant to CHOP and by parental report for the control group. All measurements were converted to z-scores using World Health Organization (WHO) standards.[26]

Resting Energy Expenditure

REE was measured in the CTRC by open-circuit indirect calorimetry using a canopy based computerized metabolic cart (Sensor Medic 2900 Z; Sensor Medics, Yorba Linda, CA, USA) in a thermal-neutral, noise-restricted environment. Measurements were performed during a minimum 30 minute period of infant sleep following an ad libitum feeding of breast milk or the infant's usual formula given within one hour of the start of REE measurement. Infants who were device fed did not have feeds infusing during REE measurement. In infants, sleeping energy expenditure is used as a proxy for REE due to the practical considerations of measuring energy expenditure.[27-29] The metabolic cart measures infant respiratory gas exchange of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) in 1-minute intervals. The initial period of infant adjustment and any period of significant movement that altered REE were excluded from analysis. Studies with less than 15 minutes of usable data were eliminated from analysis. The remaining data points were averaged and the

modified Weir equation[30] was used to calculate the REE. The results of the measured REE are expressed as kcal/day, and as a percent of the predicted values using Schofield (%Sch)[31] and WHO (%WHO)[32] equations. The Schofield equation adjusts for age, gender, weight and length, while the WHO equation adjusts for age, gender and weight.

Body composition

Body composition was measured using the Total Body Electrical Conductivity (TOBEC) instrument (TOBEC; model HP- Pediatric, 2 EM-SCAN, Springfield, IL), [33,34] TOBEC is based on a two-compartment model consisting of fat mass (FM) and fat free mass (FFM). Infants were swaddled in a blanket to restrict movement with extremities extended and held parallel to the trunk of the body. The swaddled infant was then placed supine on the TOBEC sled. A minimum of five measurements were performed, the mean FFM and FM in kg and % body fat are reported.

Statistical Analysis

Statistical analysis was performed using SAS V9.2 (SAS Institute, Cary, NC). Infants with CHD were analyzed by SV and BV physiology classification to identify differences between the groups. In addition, the SV and BV physiology groups were compared separately to the healthy infants. Distribution plots were used to assess normality of all variables. Chi-square was used to test the association between the categorical variables. Descriptive statistics of the means, standard deviations, and minimum and maximum values for the continuous variables and computation of frequencies and percentages for categorical variables were calculated. Statistical significance was determined at the $p<0.05$ level. Two sided *t*-tests were used to compare mean differences in variables between the healthy and combined CHD physiology group and between each of the CHD physiology groups and healthy infants.

In addition, the mean difference between the SV and BV CHD physiology groups were compared using ANOVA. Possible linear relationships between all continuous variables were examined using Pearson's correlation coefficient. Additionally, Pearson's correlations were used to explore linear relationships between the continuous variables and REE kcal/day, and to determine the independent variables to be included in a model to predict REE kcal/day. Due to high correlation among many of the independent variables, the number of covariates in the regression model was restricted to minimize multicollinearity. ANCOVA models were constructed to examine the differences in REE kcal/day for each CHD physiology group and among healthy infants while controlling for particular continuous covariates. The least squares means and the difference of the means were used to evaluate differences among the healthy and the CHD physiology groups. The variance of inflation factor, a measure of the degree of multicollinearity present in the model was used to assess collinearity among the independent variables.[35] All models tested had a variance of inflation factor <10, indicating multicollinearity was minimal in the models constructed.

Results

The study group included 93 infants with REE and TOBEC measurements. Of the44 infants with CHD, 17 (18%) had SV physiology and27 (29%) had BV physiology. There were 49 (53%) healthy infants in the control group. The distribution of cardiac primary diagnoses is presented in Table 1. Characteristics of the study sample are presented in Table 2, and were similar between the control group, and the SV and BV groups. Mean age was similar between the groups at the 3-month visit (Table 3). Weight, length, head circumference (Table 3, Figure 1), and WHO z-score means were all significantly lower (p<0.05) in both the SV and BV physiology groups when compared to healthy infants, with the exception of length z-score of the BV physiology

group versus healthy infants (p=0.06). The SV and BV physiology groups only differed in head circumference z-score; infants with SV physiology had smaller head size (p=0.03).

The individual group means for REE kcal/day, %WHO REE, %Sch REE, FFM, FM, and % fat are shown in Table 3. Compared to healthy infants (27%), infants with SV (23.7%; p=0.04) or BV (22.7%; p<0.001) physiology had significantly lower % fat. REE as %WHO predicted was significantly higher in infants with CHD than in healthy infants (115, p=0.02). REE as %Sch predicted was higher in the BV group versus healthy infants (112, p=0.02) but not in the SV versus healthy group. There were no differences in REE or body composition between the SV and BV physiology groups.

From Pearson correlation analysis, REE kcal/day was significantly and positively correlated with FFM (r=0.71, p<0.0001), FM (r=0.44, p<0.0001) and age in days (r=0.31, p=0.003). From the multiple linear regression models, the best predictors of REE kcal/day were FFM and infant age in days. The model that best predicts REE kcal/day in this study sample includes FFM, age in days, and SV and BV physiology and has an adjusted r^2 =0.55 (Table 4). After adjusting for FFM and age in days, the differences in REE kcal/day between infants with either SV or BV physiology and healthy infants (reference group) were not significant. A model including FFM, FM, age in days and physiology was examined; however, FM was not significant in the presence of the other variables and did not contribute to the prediction of REE kcal/day for infants with CHD.

Age was a significant covariate in each model tested. When age was removed, retaining FFM, and SV and BV physiology, there was a decrease in variance from r^2=0.55 to r^2=0.53 for predictors of REE kcal/day. An interaction term for SV and BV physiology and FFM was tested but was not statistically significant, nor did these

interactions contribute to the prediction of REE kcal/day (data not shown). REE kcal/day increased significantly with increasing FFM (kg) in this study sample, with no significant difference found in the slope of this increase among the three groups (healthy, SV, and BV).

Discussion

In this study, we evaluated REE at 3 months of age in infants who underwent neonatal surgery for CHD compared to healthy infants. After adjusting for FFM and infant age in days, there was no difference in REE kcal in infants with SV or BV physiology compared to healthy controls. These findings do not support the clinically held hypothesis that post-operative cardiac physiology is a primary factor causing an increased REE kcal/day, contributing to delayed growth in infants with CHD. Instead, these data demonstrate that body composition; specifically FFM and infant age were strong predictors of REE kcal/day in our study sample.

As expected, the strongest and most consistent contributor to REE kcal in this study was FFM. As the metabolically active component of body composition, consisting of organs, muscles, skin, brain, bone, and supporting tissues, FFM is the major contributor to REE kcal.[36-38] An increased amount of FFM leads to an increased REE per kg of body weight. The development of FFM during fetal life and early infancy is environmentally regulated and is contingent on nutrient intake.[39] In our study sample, there was no difference in the mean FFM between the study groups. Despite its strong positive correlation (r=0.44, p=<0.0001) to REE kcal, total FM in kg, the most variable constituent of body composition in infancy was also not significant between the groups, nor did FM significantly contribute to the model predicting REE after adjusting for FFM and age.

The rapid weight gain, common in early infancy is due in large part to an increase in FM, which does not contribute significantly to REE kcal, likely related to the modest metabolic activity of fat tissue.[36,40] Although total FM in kg did not differ between groups, % body fat was significantly lower in infants with CHD when compared to healthy infants. At birth, full term neonates have approximately 14 - 15% body fat.[36] Fat accretion progresses rapidly in early infancy, and by 3 months of age, male infants have 25-30% body fat, and female infants have as much 32%. .[36,41] This rapid increase in the typically developing infant results from a positive energy balance, or energy intake that exceeds energy expenditure. Our data show the infants with CHD to be below the expected % fat gains for age. The decreased weight z-scores in the infants with CHD are primarily due to reduced FM rather than FFM suggesting inadequate energy intake continues after hospital discharge.[14] Insufficient energy intake to support a positive energy balance will lead to loss of FM and a decreased percentage of body fat per kg of body weight. This in turn commits a larger portion of the infant's body mass to metabolically active tissue, FFM, resulting in an increase in REE kcal. Since the accretion of FM is directly related to energy intake, inadequate caloric and nutrient intake in these infants was likely responsible for a reduced accretion of fat and the decrease in % body fat. Our data show the infants with CHD physiology to be below the expected % fat gains for age. Previous work reported poor weight gain at hospital discharge,[6,7] and findings of the current study demonstrate that poor weight gain persists between hospital discharge and 3 months of age. Modest improvement in caloric intake in infants with CHD will likely improve growth since there is no demonstrated burden of an excessive use of energy related to cardiac physiology.

Interestingly, we found infant age to be highly significant in the regression model (p=0.0006). The wide age range in this study sample across all groups (71 – 140 days) may account for the significance of age in the model. In multiple models tested, infant age was consistently a significant covariate. These findings are similar to those of Puhakka et al[19] who also found age to be a significant predictor of REE kcal, in their cohort of 25 subjects with CHD whose ages ranged from 2-months to 10 years.

In the last two decades, we identified nine studies examining REE kcal in infants with CHD.[15-23] A review of these studies and others by Nydegger and Bines[42] identified poor growth as a common occurrence in this patient population. Our study is unique in its approach to understanding energy expenditure in infants with CHD following neonatal surgical intervention. We compared a healthy control group to infants with CHD who underwent surgical intervention in the neonatal period, body composition was measured in all subjectsat 3 months of age, and all subjects with CHD were in their usual state of health at the time of study measurement.

Current clinical recommendations of energy requirements for healthy infants at 3 months of age are approximately 95 kcal/kg/day across gender irrespective of formula or human milk intake.[43] This recommendation is to provide a positive energy balance in an infant of appropriate size and body composition to support growth and activity compatible with good health.[44,45] Our data demonstrate statistically significant differences in kg weight and weight z-score at 3 months of age in infants with CHD compared to healthy infants, this difference is primarily due to reduced percent body fat. This deficit suggests that a moderate increase in caloric intake supporting the accretion of FM may increase the% body fat to meet energy requirements in infants with CHD, thus improving growth and development and decreasing the potential risks

of delayed neurobehavioral development, morbidity and mortality associated with poor growth in infancy.[45,46]

Study Limitations

Study limitations included this being a single center cohort study our results cannot be generalized. A major limitation of this study is lack of caloric and nutrient intake data. Birth weight was obtained from the transfer record or from parent report and are not as accurate or reliable as those obtained at 3 months of age in the research setting. Lastly, there may be bias in that the families of infants who were sicker did not return for testing.

Conclusion

Our findings refute the commonly held clinical view that postoperative cardiac physiology is a major factor in determining the energy expenditure of infants with CHD following neonatal surgical intervention. Infants with CHD had decreased weight z-scores and percent body fat at 3 months, which is attributable to inadequate energy intake and not post surgical cardiac physiology. These data suggest intermittent measurements of body composition to accompany incremental growth measures may provide better information on growth and have far-reaching implications for healthcare providers to intercede in the nutritional support of those infants with CHD at risk for growth failure.

References

1. Davis D, Davis S, Cotman K, et al. Feeding difficulties and growth delay in children with hypoplastic left heart syndrome versus d-transposition of the great arteries. *Pediatr Cardiol.* Mar 2008;29(2):328-333.

2. Forchielli ML, McColl R, Walker WA, Lo C. Children with congenital heart disease: a nutrition challenge. *Nutrition Review.* 1994;52(10):348-353.

3. Dooley KJ, Bishop L. Medical management of the cardiac infant and child after surgical discharge. *Critical Care Nursing Quarterly 2002 Nov; 25(3): 98-104 (15 ref).* 2002.

4. Black M, Dubowitz H, Krishnakumar A, Starr R. Early Intervention and Recovery Among Children With Failure to Thrive: Follow-Up at Age 8. *Pediatrics.* 2007;120(1):59 - 69.

5. Dykman R, Casey P, Ackerman P, McPherson W. Behavioral and Cognitive Status in School-Aged Children With a History of Failure to Thrive During Early Childhood. *Clinical Pediatrics.* 2001;40:63 - 70.

6. Anderson J, Marino B, Irving S, et al. Poor post-operative growth in infants with two-ventricle physiology. *Cardiology in the Young.* 2011(9):1 - 9.

7. Medoff-Cooper B, Irving SY, Marino BS, et al. Weight change in infants with a functionally univentricular heart: from surgical intervention to hospital discharge. *Cardiology in the Young.* 2011;21(2):136 - 144.

8. Menon G, Poskitt EM. Why does congenital heart disease cause failure to thrive? *Arch Dis Child.* December 1, 1985 1985;60(12):1134-1139.

9. Schwarz S, Gewitz M, See C, et al. Enteral Nutrition in Infants with Congenital Heart Disease and Growth Failure. *Pediatrics.* 1990;86(3):368 - 373.

10. Jackson M, Poskitt E. The effects of high-energy feeding on energy balance and growth in infants with congenital heart disease and failure to thrive. *British Journal of Nutrition.* 1991;65(131 - 143).

11. Unger R, DeKleermaeker M, Gidding S, Christoffel K. Improved Weight Gain With Dietary Intervention in Congenital Heart Disease. *American Journal of Diseases in Children.* 1992;146:1078-1084.

12. Hansen SR, Dorup I. Energy and nutrient intakes in congenital heart disease. *Acta Paediatr.* 1993;82:166 - 172.

13. Pillo-Blocka F, Adatia I, Sharieff W, McCrindle BW, Zlotkin S. Rapid advancement to more concentrated formula in infants after surgery for congenital heart disease reduces duration of hospital stay: A randomized clinical trial. *The Journal of Pediatrics.* 2004;145(6):761-766.

14. Schwalbe-Terilli C, Hartman D, Nagel M, et al. Enteral Feeding and Caloric Intake in Neonates After Cardiac Surgery. *American Journal of Critical Care.* 2009;18(1):52 - 57.

15. De Witt B, Meyer R, Desai A, Macrae D, Pathan N. Challenge of predicting resting energy expenditure in children undergoing surgery for congenital heart disease. *Pediatr Crit Care Med.* 2010;11(4):496 - 501.

16. Farrell AG, Schamberger MS, Olson IL, Leitch CA. Large left-to-right shunts and congestive heart failure increase total energy expenditure in infants with ventricular septal defect. *The American Journal of Cardiology.* 2001;87(9):1128-1131.

17. Avitzur Y, Singer P, Dagan O, et al. Resting energy expenditure in children with cyanotic and noncyanotic congenital heart disease before and after open heart surgery. *JPEN J Parenter Enteral Nutr.* January 1, 2003 2003;27(1):47-51.

18. Leitch CA, Karn CA, Peppard RJ, et al. Increased energy expenditure in infants with cyanotic congenital heart disease. *Journal of Pediatrics.* 1998;133:755 - 760.

19. Puhakka K, Rasanen J, Leijala M, Peltola K. Metabolic Effects of Corrective Surgery in Infants and Children with Congenital Heart Defects. *British Journal of Anaesthesia.* 1993;70:149 - 153.

20. Gebara B, Gelmini M, Sarnaik A. Oxygen consumption, energy expenditure, and substrate utilization after cardiac surgery in children. *Critical Care Medicine.* 1992;20(11):1550 - 1554.

21. Ackerman I, Karn C, Denne S, Ensing G, Leitch C. Total But Not Resting Energy Expenditure is Increased in Infants with Ventricular Septal Defects. *Pediatrics.* 1998;102(5):1172 - 1177.

22. Li J, Zhang G, Herridge J, et al. Energy expenditure and caloric and protein intake in infants following the Norwood procedure. *Pediatr Crit Care Med.* 2008;9(1):55 - 61.

23. Nydegger A, Walsh A, Penny DJ, Henning R, Bines JE. Changes in resting energy expenditure in children with congenital heart disease. *Eur J Clin Nutr.* 2007;63(3):392-397.

24. Rhodes L, Colan S, Perry S, Jonas R, Sanders S. Predictors of survival in neonates with critical aortic stenosis. *Circulation.* 1991;84:2325 - 2335.

25. Lohman TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Books; 1988.

26. World Health Organization. WHO Anthro (version 3.2.2, January 2011) and macros. *Child Growth Standards* 2011. Accessed 5/6/2011.

27. Reichman C, Shepherd R, Trocki O, Cleghorn G, Davies P. Comparison of measured sleeping metabolic rate and predicted basal metabolic rate during the first year of life: evidence of a bias changing with increasing metabolic. *European Journal of Clinical Nutiriton.* 2002;56:650-655.

28. Butte N, Wong W, Ferlic L, Smith E, Klein P, Cutberto G. Energy Expenditure and Deposition of Breast-Fed and Formula Fed Infants during Early Infancy. *Pediatric Research.* 1990;28(6):631-640.

29. Wells JCK, Joughin C, Crisp JA, Cole TJ, Davies PSW. Comparison of measured sleeping metabolic rate and predicted basal metabolic rate in the first year of life. *Acta Paediatrica.* 1996;85:1013 - 1018.

30. Weir J. New methods for calculating metabolic rate with special reference to protein metabolism. *The Journal of Physiology.* 1949;109:1 - 9.

31. Schofield W. Predicting Basal Metabolic Rate, New Standards and Review of Previous Work. *Human Nutrition: Clinical Nutrition.* 1985;39C(Suppl):1, 5 - 41.

32. World Health Organization. *FAO/WHO/UNU Expert Consultation. Energy and protein requirements: technical report series #724. pp 71-112.* Geneva1985.

33. de Bruin NC, Westerterp KR, Degehart HJ, Visser KHA. Measurement of Fat-Free Mass in Infants. *Pediatric Research.* 1995;38(3):411 - 417.

34. Fiorotto M, Klish W. Total body electral conductivity measurements in the neonate. *Clinical Perinatology.* 1991;18(3):611 - 627.

35. Robinson C, Schumaker RE. Interaction Effects: Centering, Variance Inflation Factor, and Interpretation Issues. *Multiple Linear Regression Viewpoints.* 2009;35(1):6-11.

36. Bechard LJ, Wroe E, Ellis K. Body Composition and Growth. In: Duggan C, Watkins JB, Walker WA, eds. *Nutrition in Pediatrics*. Shelton, Connecticut: People's Medical Publishing House; 2009:27 - 37.

37. Zemel BS, Barden E. Measuring Body Composition. In: Hauspie RC, Cameron N, Molinari L, eds. *Methods in Human Growth Research*. Cambridge, UK: Cambridge University Press; 2004:141 - 176.

38. Illner K, Brinkmmann G, Heller M, Bosy-Westphal A, Muller MJ. Metabolically active components of fat free mass and resting energy expenditure in nonobese adults. *Am J Endocrinol Metab.* 2000;278:E308 - E315.

39. Butte N, Wong W, Hopkinson J, Heinz C, Mehta N, Smith E. Energy requirements derived from total energy expenditure and energy deposition during the first 2 y of life. *American Journal of Clinical Nutrition.* 2000;72:1558-1569.

40. Bresson JL. Energy Metabolism and Requirements in Health and Disease. In: Duggan C, Watkins JB, Walker WA, eds. *Nutrition in Pediatrics*. Shelton, Connecticut: People's Medical Publishing House-USA; 2009:417 - 430.

41. Roche AF, Shumei SS. *Human Growth: Assessment and Interpretation*. New York: Cambridge University Press; 2003.

42. Nydegger A, Bines J. Energy metabolism in infants with congenital heart disease. *Nutrition.* 2006;22:697 - 704.

43. Joint FAO/WHO/UNU Expert Consultation. *Human energy requirements.* Rome: United Nations University; 2001.

44. Butte N. Energy requirements of infants. *Public Health Nutrition.* 2005;8(7A):953-967.

45. Butte N. Energy Requirements of Infants and Children. Paper presented at: Nestle Nutrition Workshop Series. Paediatric Programme2006.

46. Bjarnason-Wehrens B, Dordel S, Schickendantz S, et al. Motor development in children with congenital cardiac diseases compared to their healthy peers. *Cardiology of the Young.* 2007;17:487 - 498.

Table 1 Congenital Heart Disease diagnoses of study sample

	Single-Ventricular % of *n* = 17	Bi-Ventricular % of *n* = 27
Hypoplastic Left Heart Syndrome	76	
Double Outlet Right Ventricle	12	
Tricuspid Atresia	6	
Valvular Aortic Stenosis	6	
D-Transposition of Great Arteries		33
Coarctation of the Aorta		22
Tetralogy of Fallot		19
Valvular Pulmonary Atresia		7
Total Anomalous Pulmonary Venous Return		7
Interrupted Aortic Arch		4
Ventricular Septal Defect		4
Double Inlet Left Ventricle		4

Primary diagnoses with post-operative physiology classification, depicted in percent of total subjects for each category.

Table 2 Sample characteristics of healthy infants and infants with Congenital Heart Disease.

	Healthy Infants	Infants with Congenital Heart Disease		
		All	Single Ventricle	Bi-Ventricle
n	49	44	17	27
Gender (%)				
Male	63	61	71	56
Female	37	39	29	44
Race (%)				
African American	27	7	6	7
Asian	2	0	0	0
Caucasian	65	91	94	89
Other	6	2	0	4
Ethnicity (%)				
Latin/Hispanic	6	9	6	11
Non Latin/Hispanic	88	68	82	59
Other	6	23	12	30
Birth Weight				
kg	3.4 ± 0.5	3.4 ± 0.4	3.5 ± 0.3	3.3 ± 0.5
z-score	0.2 ± 1.0	0.2 ± 1.0	0.5 ± 0.6	0.0 ±1.0

Sample distribution for gender, race and ethnicity with birth weight.

Table 3 Growth, body composition and resting energy expenditure in all subjects at 3 months of age. *

	Healthy Infants	Infants with Congenital Heart Disease		
		All	Single Ventricle	Bi-Ventricle
n	49	44	17	27
Age at visit, days	95 ± 13	96 ± 13	99 ± 15	93 ± 11
Weight				
kg	6.1 ± 0.8	5.6 ± 0.9 **	5.6 ± 1.0 **	5.5 ± 0.7 **
z-score	-0.3 ± 1.0	-1.1 ± 1.1 ***	-1.1 ± 1.1 **	-1.0 ± 1.0 **
Length				
cm	61.4 ± 2.8	59.8 ± 2.3 **	60.1 ± 2.1	59.6 ± 2.5 *
z-score	0.0 ± 1.2	-0.7 ± 1.1 *	-0.8 ± 0.9 *	-0.6 ± 1.2
Head Circumference				
cm	40.8 ± 1.3	39.7 ± 1.5 ***	39.2 ± 1.6 ***	40.0 ± 1.3 **
z-score	0.3 ± 0.9	-0.6 ± 1.2 ***	-1.1 ± 1.3 ***	-0.2 ± 1.1 *§
Fat-free Mass, kg	4.4 ± 0.5	4.3 ± 0.5	4.2 ± 0.5	4.3 ± 0.5
Fat mass, kg	1.7 ± 0.5	1.3 ± 0.4	1.4 ± 0.5	1.3 ± 0.3
% Fat	27.0 ± 5.0	23.1 ± 5.1 **	23.7 ± 5.5 *	22.7 ± 4.9 **
REE Kcal/day	328 ± 52	324 ± 55	325 ± 59	322 ± 54
Schofield, % predicted	105 ± 13	112 ± 13 *	111 ± 14	112 ± 12 *
WHO, % predicted	104 ± 13	115 ± 14 **	115 ± 17 *	114 ± 12 *

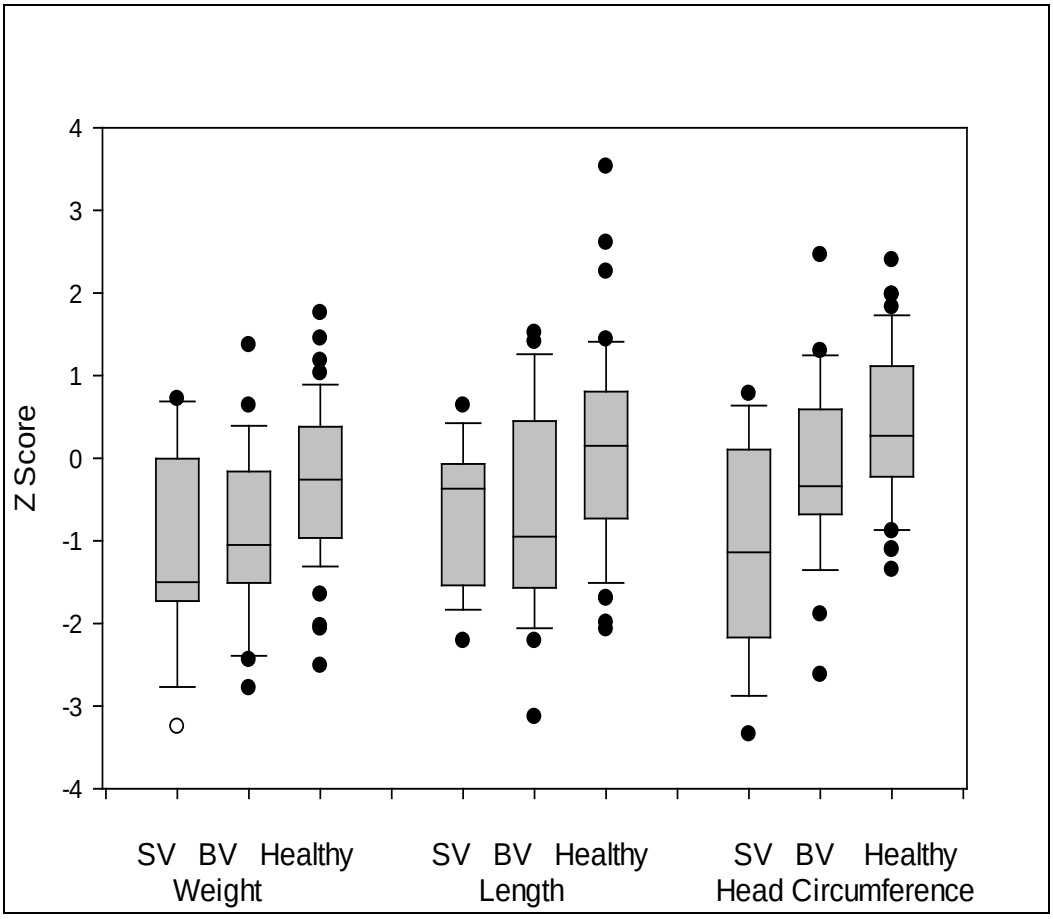
*Results shown are means ± SD. Significance levels *p<0.05, **p<0.01, ***p<0.001 show healthy infants compared separately to the combined and with each CHD physiology group; §p<0.05 depicts significance comparing the SV and BV CHD groups.

Table 4. Regression model of covariates with strongest contribution to REE kcal/day

	Parameter	Standard Error	*t* value	*p*	r^2
Intercept	-95.2	41.6	-2.3	0.02	0.55
FFM, kg	72.7	7.3	9.8	<0.0001	
Age, days	1.6	0.3	3.6	0.0006	
SV	7.6	10.3	0.7	0.5	
BV	8.3	8.7	1.0	0.3	
n = 93					

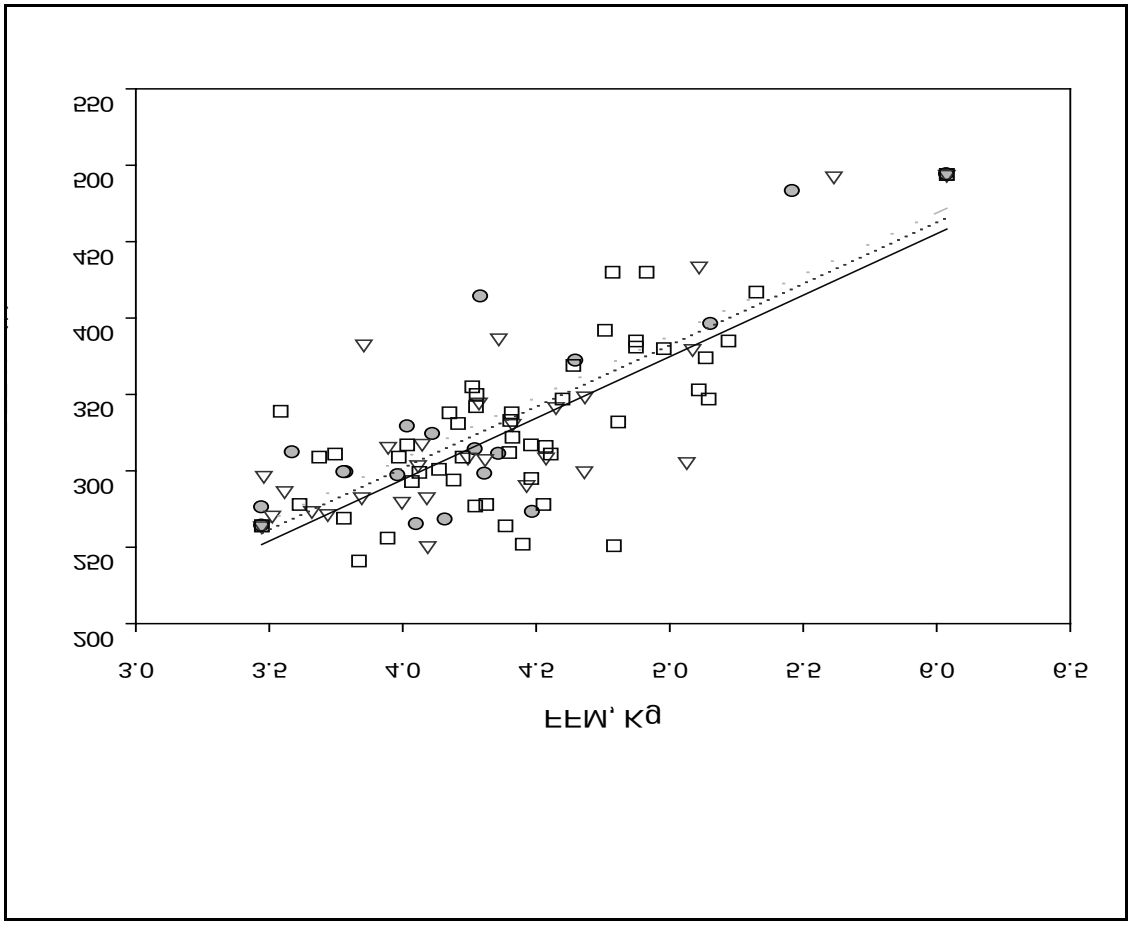
Model depicting contribution of FFM, age and cardiac physiology to REE kcal/day. Healthy infants are the reference group.

Figure 1 Box plot graph of growth measures at 3 months of age.



Legend:
N for each group: SV – 17, BV – 27, Healthy – 49.

Figure 2 Regression line of REE kcal/day for fat-free mass (FFM), kg from TOBEC



Legend:

Single Ventricle Biventricle Healthy

The predicted line is calculated from an ANCOVA model using REE kcal/day as the dependent variable with FFM and physiology as independent variables.

CHAPTER 3

The Use of Indirect Calorimetry (IC) to Measure Energy Needs in Mechanically Ventilated Children with Acute Lung Injury

(Submitted as NIH Director's Early Independence Award Application)

Abstract

Acute Lung Injury (ALI) is associated with significant morbidity and mortality in critically ill children. Annually, between 2,500 and 9,000 children are diagnosed with ALI, a condition of lung injury marked by diffuse pulmonary inflammation that leads to hypoxemia and respiratory failure. Characterized by acute onset, severe arterial hypoxemia, and diffuse bilateral pulmonary infiltrates, ALI can quickly progress, requiring mechanical ventilation for respiratory support and inciting a metabolic stress response. If not halted, these physiologic reactions to stress prolong healing and increase the risk for complications. In a critical illness such as ALI, optimal nutrition support is essential to diminish the metabolic response, support immune function, promote tissue repair, prevent loss of lean muscle mass, and eliminate weight loss. Current clinical practice uses prediction equations derived from measurements of healthy children and adults. These equations tend to over- or underestimate energy needs and risk over- or underfeeding, threatening clinical outcomes. We purport that the use of Indirect Calorimetry (IC) to measure energy needs is superior to prediction equations and in fact, can help improve current nutrition management for critically ill, mechanically ventilated children with ALI. Our study will test the efficacy of using IC to accurately measure energy needs to the current practice of prescribing caloric needs based on the use of prediction equation calculations in critically ill, mechanically ventilated children with ALI. We hypothesize that compared to the use of standard prediction equations, energy requirements derived from IC measurements will improve

clinical outcomes, measured by increase in ventilator-free days, decreased weight loss, decreased loss of lean body mass, and decreased length of pediatric intensive care admission with an overall reduction in the length of hospitalization.

Specific Aim

ALI is associated with significant morbidity and mortality in critically ill children. Annually between 2500 and 9000 children are diagnosed with ALI,[1] a condition of lung injury marked by diffuse pulmonary inflammation that leads to hypoxemia and respiratory failure.[1-6] Characterized by acute onset, severe arterial hypoxemia, and diffuse bilateral pulmonary infiltrates, ALI can quickly progress, requiring mechanical ventilation for respiratory support and inciting a metabolic stress response.[1] This metabolic response uses endogenous energy stores to provide for basic metabolic needs and support the ongoing stress response.[7-10] If not halted, these physiologic reactions prolong healing and increase the risk for complications. In a critical illness such as ALI, optimal nutrition support is essential to diminish the metabolic response, support immune function, promote tissue repair, prevent loss of lean muscle mass, and eliminate weight loss.[7,11] Research suggests that 16–20% and as high as 50% of critically ill children demonstrate significant protein energy malnutrition (PEM) within 48 hours of admission, with continued deterioration during hospitalization.[10-14] Current clinical practice using prediction equations derived from measurements on healthy children[15,16] will likely over or underestimate energy needs, risking over or underfeeding and threatening clinical outcomes.[15] We propose the use of IC to measure energy needs, which research suggests is superior to prediction equations to assess energy requirements and improve current nutrition management for critically ill, mechanically ventilated children with ALI. To improve clinical outcomes and decrease length of hospital stay providing specific caloric goals are vital to counter the metabolic response

to critical illness, increase ventilator-free days, minimize loss of lean muscle mass, and diminish weight loss for critically ill, mechanically ventilated children with ALI.[17]

Innovation and Impact

The caloric needs of critically ill children with ALI are related to the energy burden imposed by the metabolic response to the inflammatory process and the severity of illness.[7,18] We suggest that measurement of energy expenditure by IC will prove to be an accurate method to assess energy needs of critically ill children with ALI. Current practice, the use of standard prediction equations with or without a stress factor, are likely to over or underestimate energy requirements in critical illness,[14,19-23] with the potential to prolong mechanical ventilation, increase the risk of infection, and extend hospitalization due to prolonged recovery.[24] To date, we are not aware of clinical investigation assessing energy requirements for a specific disease in critically ill, mechanically ventilated children in an intensive care unit. This study may reveal energy requirements not previously acknowledged by critical care providers for critically ill children with ALI. Indirect Calorimetry can provide precise information about energy needs for children with ALI to optimize nutrition support and minimize the caloric imbalances often incurred from use of prediction equations. This approach to energy needs assessment has high potential for clinical implementation and has the capability to shift clinical practice paradigms of nutrition management in the Pediatric Intensive Care Unit (PICU) environment. Our study will test the efficacy of IC in critically ill, mechanically ventilated children with ALI to assess energy requirements and inform prescription for caloric goals. IC will be assessed during the acute, plateau, and weaning phase of mechanical ventilation. In contrast to prediction equations, accurate measurement of energy expenditure can provide more precise information to determine specific caloric needs, inform clinical practice and assist decision-making for

nutrition support. This randomized, controlled clinical trial will compare IC measurements to the current clinical practice, use of prediction equations to determine energy needs, and examine outcomes specifically related to critical illness and mechanical ventilation in children with ALI.

Primary Aim

To compare the effect of using Indirect Calorimetry to determine energy requirements in critically ill, mechanically ventilated children with Acute Lung Injury to the current clinical practice of prescribing energy needs by the use of prediction equation calculations.

Hypothesis

Compared to the use of standard prediction equations, energy requirements derived from Indirect Calorimetry measurements for critically ill, mechanically ventilated children with Acute Lung Injury will improve clinical outcomes as evidenced by:

1) Increase in ventilator-free days
2) Decreased weight loss
3) Decreased loss of lean body mass
4) Decreased length of Pediatric Intensive Care Unit hospitalization

Background and Significance

Acute Lung Injury

Acute lung injury (ALI) is a condition marked by diffuse pulmonary inflammation that leads to hypoxemia and respiratory failure in both children and adults.[1-6] It is associated with high mortality, morbidity, and an increased use of intensive care resources with significant financial burden.[1-3] Characterized by acute onset, severe arterial hypoxemia resistant to oxygen therapy, and diffuse bilateral pulmonary infiltrates without evidence of left atrial hypertension, ALI has a variety of triggers and risk factors, the most

common being infection in the pulmonary airways and parenchyma.[1,25] In the United States, between 2,500 and 9,000 children are diagnosed with ALI annually, constituting between 1– 4% of all Pediatric Intensive Care Unit (PICU) admissions.[1,26] The high volume of children with ALI, severity of the disease, and potential for increased morbidity make this a suitable illness to investigate energy needs for a subgroup of critically ill children requiring mechanical ventilation. Approximately 63% of children have more than one risk factor for developing ALI, a rate similar to that found in adults.[25] These factors include direct lung injury (51% pulmonary infection, 12% pulmonary aspiration, 3% near drowning) and indirect lung injury (43% sepsis syndrome, 40% multiple transfusions in close proximity, 10% post-bone-marrow transplantation, 8% non-thoracic trauma). Mortality associated with ALI is reported to be as high as 18–35% in children.[5] Due to the severity of the pulmonary disease, children with ALI often quickly progress to respiratory failure requiring endotracheal intubation and mechanical ventilation. The disease process and respiratory failure activate an acute alteration in metabolic status and trigger initiation of the stress response and the ensuing catabolism inherent in the process. Characteristics of the disease, the ensuing respiratory failure requiring mechanical ventilation, the metabolic stress response, and decreased energy intake put these children at risk for alterations in energy balance, PEM and its consequences leading to a prolonged PICU stay and extended hospitalization.[1,4] Despite its frequency as a diagnosis in the PICU population and its severity, we have not found an investigation specifically designed to assess the energy needs of critically ill, mechanically ventilated children with ALI. The severity of illness, metabolic response to lung injury, alterations in caloric requirements, and decreased energy intake are dynamic factors that potentially make the use of standard prediction equations inconsistent with actual energy needs; the use of IC is a more

accurate method to assess energy needs and prescribe appropriate caloric intake. It follows that children with ALI requiring mechanical ventilation and supportive care will benefit from early, accurate assessment of energy needs and nutrient prescription for appropriate caloric goals to decrease the harmful effects of catabolism resulting from the metabolic response to critical illness.

Metabolic Alterations in Critical Illness

Metabolic alterations that accompany critical illness occur in proportion to the magnitude of the illness and the pre-illness nutrition status. It is not always possible to predict the child's response to illness owing to the range of illness onset, its intensity, and its duration. The metabolic response to critical illness is variable, and includes hormonal and cytokine profiles that influence the overall energy burden.[7,10,27] Characterized by an elevation of serum hormone levels of insulin, glucagon, growth hormone, and cortisol and combined with the release of catecholamines and cytokines, the stress response results in catabolism of endogenous supplies of protein, fat, and carbohydrates. This process provides energy for both basal metabolism and the metabolic requirements incited by the presenting illness.[10] Typically, the metabolic response to stress induces muscle protein breakdown that results in increased circulation of free amino acids, some of which are used for tissue repair. Those free amino acids not used in repair are redirected through the liver and become involved in the production of glucose through gluconeogenesis. The increase in circulating serum glucagon levels may deplete the limited endogenous stores, increasing reliance on gluconeogenesis from non carbohydrate substrates (e.g. lactate).[10,27] In addition, cytokines mediate fat metabolism, causing increased fatty acid oxidation, resulting in hypertriglyceridemia and lipid intolerance. Ketone production results from lipolysis to provide energy and protection for the brain to maintain its uninterrupted and large

supply of glucose.[27] It is common for children to have a delayed response to nutrition support, this predisposes them to develop malnutrition from the metabolic response to stress faster than adults.[8] The administration of exogenous substrate of glucose does not stop gluconeogenesis, and alteration in carbohydrate metabolism continues;[27] however, the combined provision of glucose and protein may blunt the process by supporting protein synthesis.[7] The ability to utilize exogenous energy substrate and synthesize new proteins is a critical aspect of recovery from critical illness and resumption of normal metabolic processes. The capability to accurately assess caloric needs and prescribe appropriate energy goals may facilitate early protein synthesis. Given these alterations in the metabolic process with critical illness, and the severity of illness seen in children with ALI requiring mechanical ventilation, it is conceivable that PEM would complicate the disease process, delay recovery, and increase the length of hospitalization.[15] Overall, the metabolic response in ALI results in increased protein breakdown and lipid and glucose intolerance. This combination of reactions, along with suboptimal nutrition support, puts the critically ill child at high risk for weight loss, loss of lean body mass, and an exacerbation of malnutrition that can worsen disease progression.[10,27]

Suboptimal Nutrition Support in Pediatric Critical Illness

Nutrition support during critical illness such as ALI is challenging. The potential risk of malnutrition and caloric imbalance can lead to PEM, which is associated with altered physiologic response(s), impaired cell-mediated immunity, and loss of lean body mass.[9,22] Acute PEM in critical illness is multifactorial, owing to the dynamic range of metabolic alterations, the child's age, and severity of illness.[7,12,28] It is difficult to determine if the degree of illness contributes to a poor nutrition status or if a poor nutrition status contributes to the severity of illness. The metabolic response to critical

illness cannot be prevented solely by nutrition support; however, suboptimal nutrition accompanied by critical illness may contribute to prolonged alterations in metabolism and exacerbate the stress response.

The effects of PEM in critically ill children were noted over two decades ago by Pollack et al,[29] who demonstrated acute PEM in 16% of their heterogeneous sample of 50 children admitted to the PICU; the condition was associated with clinical instability, increased use of PICU resources, and higher rates of mortality. More recently, Hulst and colleagues[30] demonstrated a cumulative energy deficit of 100 kcal/kg and a cumulative protein deficit of 10 gm/kg, which explained 39% and 40% of the respective change in kilogram weight and lean body mass in their cohort of 98 mechanically ventilated children. Despite advances in clinical care, the challenges of nutrition support for children during critical illness identified in the 1980s persist.[7-9,29,31,32]

The lack of recognition and knowledge by care providers to the unique and complex energy needs of the critically ill child add to the challenges of providing adequate caloric intake during critical illness.[7,29] In a recent study of 33 PICU subjects with various diagnoses, Mehta and colleagues[15] demonstrated failure of physicians to accurately predict the metabolic status of the children studied, supporting the idea that providers are unaware of metabolic requirements in critical illness. The researchers deduced this was a contributing factor to overestimation of energy needs and subsequent overfeeding in their study sample.[15] This lack of accuracy in energy assessment puts critically ill children such as those with ALI at risk for overfeeding or underfeeding, either of which can contribute to acute PEM and potentiate infectious and non-infectious complications, alterations in normal physiologic response to illness, additional use of PICU resources, increased financial burden and can add to morbidity and mortality.[7,12,13,15,33,34]

Lack of energy intake or underfeeding has been associated with gastrointestinal mucosal atrophy, heightening the subject's susceptibility to infection, delayed wound healing, muscle weakness prolonging the need for mechanical ventilation, diminished cardiac reserve, and immune system dysfunction.[7,9,12,14,33,35,36] Alternatively, overfeeding can result in increased carbon dioxide production prolonging mechanical ventilation, alteration in hepatic function, and variation in glycemic control.[7,8,12,17,33,36] Either condition can be potentially life threatening for the mechanically ventilated child with ALI who has a compromised respiratory status. Studies suggest that critically ill children who receive adequate nutrition support experience early physiologic stability and improved outcomes.[8,35] The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) acknowledges that investigations specific to critically ill children are necessary to guide nutrition support.[18,22] Recently published guidelines for nutrition support in critically ill children concede the inaccuracy of predictive equations to estimate energy needs and suggest further investigation on the use of IC as a method to accurately assess energy expenditure and guide energy prescription for critically ill children.[15,22]

Determining Energy Needs: Predictive Equations and Indirect Calorimetry

Energy requirements in children are derived from standard prediction equations. The equations frequently used in pediatrics include those developed by Harris-Benedict, Talbot, Schofield, the Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU), and the Recommended Dietary Allowance (RDA) predictions.[6,17,37,38] The Harris-Benedict equation was based on measurements in 97 infants under one month of age and more than 200 adolescents.[20,39] Talbot developed energy estimates from data obtained through repeated measures on healthy infants and children (the same participants) combined

with previously published studies.[40] Schofield refined the initial predictive equations, including those developed by Talbot, and constructed equations using weight, height, and gender across age groups.[41-43] The RDA is an estimate of the minimum average daily intake necessary to meet nutrient requirements of healthy individuals across gender and age.[38]

Studies conducted in heterogeneous PICU populations have shown incongruence between measured energy expenditure and prediction equations. Thomson et al[44] demonstrated inaccuracies between the Harris-Benedict and Schofield equations when compared to measured energy expenditure in both healthy and ill infants. Coss-Bu et al[45] found large differences between the Harris-Benedict and Talbot equations, with and without use of a correction stress factor, when compared to IC measurements in critically ill, mechanically ventilated children. Briassoulis and colleagues[17] found energy expenditure measured by IC to be significantly lower than energy expenditure derived from prediction equations. Other researchers have found under and overestimation of energy needs when using prediction equations and endorse the use of IC to accurately assess energy needs and prescribe realistic caloric intake goals for critically ill children.[1,9,19,23,24,33,46,47] Many of the studies cited do not address assessment of body composition as part of IC measurement. However, determination of body composition is necessary for the judicious interpretation of prediction equations and IC measurement. It is the variation in fat-free mass that may explain a large component of energy needs, in that energy expenditure may be decreased in children with a higher percentage of fat-free mass per kilogram of body weight.[48] The respiratory quotient (RQ) is another important marker obtained from IC measurement. The RQ thought to be indicative of substrate use is a ratio derived from carbon dioxide production (VCO_2) to oxygen consumption (VO_2) with an acceptable

range of 0.85 to 1.0 in children. Used to substantiate the validity of IC measurements, an RQ above 1.0 may indicate overfeeding, while less than 0.85 may be a sign of suboptimal energy intake. Applicability of the RQ in critical illness is limited owing to alterations in metabolism, a compromised respiratory status, and its reported low sensitivity and specificity in both adults and children.[28,49] De Klerk et al[35] found the RQ in mechanically ventilated, critically ill children to indicate underfeeding in 45% of their study sample and overfeeding in 15%. These researchers suggest RQ measurements combined with IC measurements may be a better approach to assessment of energy needs in critically ill children.[35]

Current Practice for Derived Energy Requirements

Investigations into energy requirements in critically ill children overwhelmingly suggest inaccuracy of prediction equations to estimate energy needs.[17,22-24,33,46,47,50] In a recent study by Mehta and colleagues[19] there was poor agreement between equation derived energy needs and IC measured energy expenditure, resulting in a high incidence of overfeeding and underfeeding, in their study sample, based on the equations alone. Challenges with the use of these equations lie in the fact that they are based on demographics from healthy children under conditions of usual environment and physical activity[16] and they do not account for the shifts in energy requirements that accompany critical illness. Energy normally used for tissue accretion and growth is used for tissue repair and glucose generation in critical illness; there is minimal physical activity; and there is a transient cessation of growth during critical illness that alters energy requirements.[7,16,17,30] The metabolic response that is proportional to the severity of illness can trigger changes in energy metabolism that work to counteract the stress response while simultaneously lending support to basal metabolic function[7]; prediction equations cannot adjust for these changes. This is particularly true for

critically ill children with ALI whose energy needs may be significantly altered, and in whom inaccurate assessment of needs may lead to overfeeding or underfeeding and affect an already compromised metabolic and respiratory status. In the PICU at The Children's Hospital of Philadelphia (CHOP), energy requirements are derived by prediction equations. Dedicated PICU nutritionists primarily use the RDA for children less than 1 year of age and the World Health Organization (WHO) equation for children over 1 year. If the child is overweight and a length or height measurement is available the Schofield equation is applied, lastly, in the case of an older adolescent or young adult the Harris-Benedict equation is used to calculate energy requirements (personal communication: M. Nagel RD, LDN, CNSD, S. Seiple, RD, LDN, CNSD; January 12, 2011). Based on calculations derived by one of the aforementioned equations, prescriptions for caloric intake are generated. The child's progress is followed and adjustments for energy needs are made based on clinical status, laboratory results, and respiratory progress. The decision to increase calories by use of a stress factor is made by the clinical nutritionist in discussion with the critical care team based on age, history,and severity of illness. Using IC to determine specific energy requirements and prescribing such for critically ill, mechanically ventilated children with ALI can achieve optimal nutrition support and avoid caloric imbalances often incurred with the use of prediction equations.

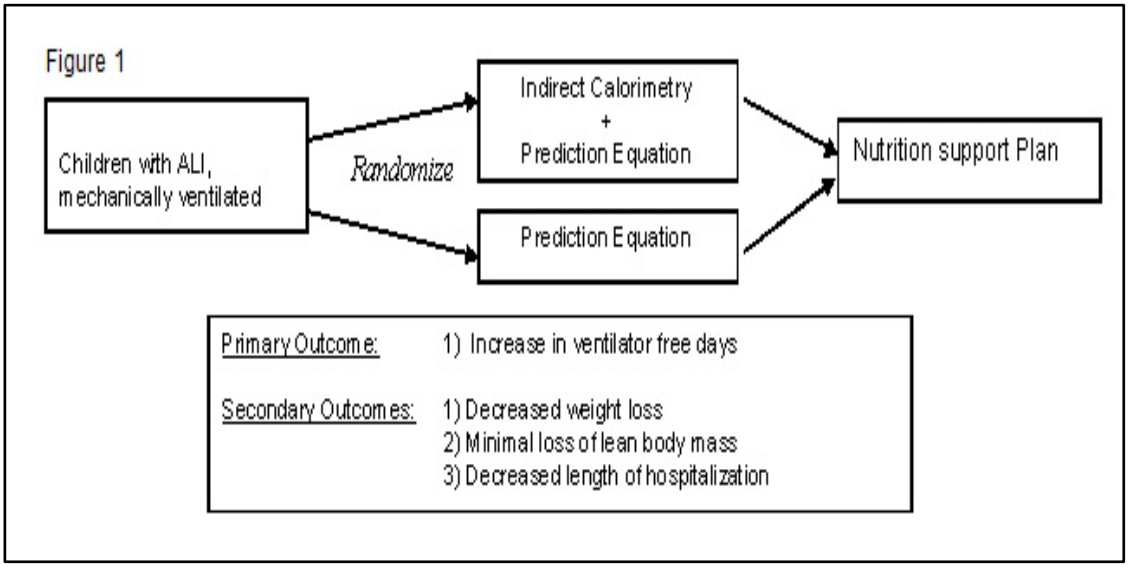
Research Design and Methods

Study Overview

This study is a two-group randomized, controlled clinical trial that compares energy requirements derived from IC measurement of energy expenditure to the current practice of energy requirements derived from standard prediction equations. After obtaining informed consent, subjects diagnosed with ALI will be randomized to

either the study or control group. The study group will receive IC measurements in addition to prediction equation calculation for energy requirements, versus the control group who will maintain the current practice of sole use of prediction equation calculations to derive energy needs. Prediction equations, as described above, will be calculated for all study participants to evaluate differences between IC measured energy needs and energy needs derived from prediction equations. Those participants who receive IC measurements will have their prescription for energy intake based on the IC measurement and will receive caloric intake based on this measurement for the duration of the study period. Participants whose energy needs are assessed by prediction equation will have energy intake prescriptions generated accordingly. All intake will be recorded and assessed daily for caloric content and total fluid volume for each child participating in the study. This will include all intravenous fluids, glucose containing base solutions for medications (enteral or intravenous), and enteral or parenteral nutrition. All participants will have anthropometric measurements of weight, supine length, and head circumference (if 5 years of age or younger). In addition, 4 skinfold measures including subscapular, tricep, bicep, suprailiac, and a mid upperarm circumference will complete the anthropometric data set. These measurements will be obtained upon study enrollment, prior to each IC measurement and at PICU discharge or day 28 of study participation, whichever occurs first. Study participation will end at 28 days regardless of whether the participant remains mechanically ventilated or remains in the PICU. The Acute Respiratory Distress Syndrome network defines ventilator-free days (VFD) as the number of days from study enrollment to day 28 during which there is unassisted spontaneous breathing for 48 consecutive hours.[51] All participants will receive usual PICU care for ventilator and supportive management. Usual PICU care includes extubation readiness testing (see appendix).

Figure 1 Randomization Schema



Eligibility and Recruitment

Study Setting

The sample will be drawn from children admitted to the PICU at CHOP. This is an internationally recognized clinical, critical care research center with a 54-bed multidisciplinary intensive care unit that admits more than 3,000 critically ill children annually. Age of children admitted to the PICU ranges from neonatal (28 days) to 18 years. The *RESTORE* clinical trial (U01HL086622; U01HL086649; Principal Investigator: Martha A. Q. Curley, RN, PhD) is currently recruiting intubated and ventilated participants with acute respiratory failure from the PICU at CHOP. In the most recent 18 months, 108 participants consented and enrolled, 37% of whom had a diagnosis of ALI. These data support the feasibility of recruitment for the current proposal.

Study Sample

Children admitted to the PICU and diagnosed with ALI will be screened for study eligibility and participation. Parents or legal guardians will be approached for consent if their child meets study criteria. All participants will be children with a diagnosis of ALI requiring mechanical ventilation, who are at least 44 weeks post conceptual age but have not yet reached their 19th birthday. Given that all participants will be intubated and mechanically ventilated, it is anticipated that subjects will not be able to provide assent to participate in the study. The exclusion criteria are designed to eliminate potential participants with conditions known to alter basal metabolism and/or conditions that can lead to inaccurate IC measurement results. Study exclusion criteria include infants less than 44 weeks post conceptual age owing to typical physiologic changes of the premature newborn that require increased energy, children with chronic pulmonary disease and those with known chromosomal abnormalities. In addition, children with illnesses that result in a compromised respiratory or pulmonary status known to have alterations in energy requirements at baseline or the presence of air leak through chest tube(s) causing inaccurate IC measurements are ineligible for enrollment.[52] Table 1 specifies inclusion and exclusion criteria.

Randomization

Once informed consent is obtained, study participants will be randomized at enrollment to receive IC measurements in addition to having energy needs calculated with prediction equations (intervention group) versus current practice for use of prediction equations alone. Randomization will be performed using a permuted block design with random block sizes[53] to ensure an equal allocation of participants to both the intervention and control groups throughout the study. Allocation will be concealed

using serially numbered, opaque sealed envelopes containing study assignments. The randomization schema is presented in Figure 1.

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• At least 44 weeks postconceptual age but have not yet had their 19th birthday • Diagnosis of acute lung injury: Intubated and mechanically ventilated with a ratio of partial pressure of arterial oxygen((PaO2) to the fraction of inspired oxygen (FIO2) of 300), bilateral pulmonary infiltrates, and no clinical evidence of left atrial hypertension • Intubated with a cuffed or uncuffed entdotracheal tube with negligible air leak ≤ 5% difference between inspired and expired tidal volumes	• Chromosomal abnormalities (known or suspected) • Metabolic disorders (known or suspected) • Congenital heart disease • Severe brain injury (Glasgow coma scale ≤8) • Presence of chest tube(s) with air leak • Supported on extracorporeal membrane oxygenation (ECMO) or High Frequency Oscillatory Ventilation (HFOV) • History of/presence of oxygen and/or diuretic dependent chronic lung disease • Upper airway diseases (e.g. bronchial / tracheomalacia, • Neuromuscular respiratory failure (e.g. spinal muscular atrophy) • Chronic ventilator dependence • Agreement that continued treatment is futile • Concurrent participation in any other clinical trial

Power Analysis

Based on preliminary data, we estimate the overall median numbers of ventilator-free days (VFD) in the control group to be 21, recognizing that these data are skewed consequential to assigning zero VFD to participants censored at the end of their stay. As such, group sample sizes of 50 each will achieve 80% power to detect a difference of 3 days between the groups (21 verses 24 VFD). The estimated group standard deviations are assumed to be 4.0, along with a significance level (alpha) of 0.01 to account for multiple outcomes. This calculation is based on a two-sided Mann-Whitney U test.

Attrition

Although attrition is expected to be minimal in this study, we will enroll 10 additional participants in each group to accommodate for participant dropout. Some parents may opt to withdraw their child from the study. In addition, some participants may improve rapidly and not provide 3 data points while other participants may become too ill for 3 data points, or may not be able to tolerate the recommended calories prescribed from IC measurement. Data will be analyzed with an intention-to-treat analysis. Based on these assumptions, a completed data point is defined as one completed IC assessment, with anthropometric measures and participant capability to tolerate the caloric load recommended by the IC measurement. Nutrition support can be delivered via either the enteral or the parenteral route; either route may be used for the IC recommended caloric load to meet study completion criteria.

Study Procedures

The following section includes a discussion of the research protocol for the proposed study. The major variables, their measurement, and the data analysis plan are presented. Study measurements are outlined in Table 2.

Participant PICU Measurements

Measurements of weight, length, and head circumference are obtained by the Principal Investigator (PI) and /or Research Assistant (RA), the results will be shared with the clinical staff. Weight measured in kilograms will be obtained on all potential participants on admission to PICU in weigh bed scales (Stryker Medical, Portage, MI) or infant weigh cribs (Hard Manufacturing Company, Buffalo, NY). If not admitted to a weigh bed or crib, a weight will be obtained on the appropriate infant pan scale (Scaletronix, White Plains, NY) or sling scale (Scaletronix, White Plains, NY) for age and size. Head circumference is measured on subjects 5 years of age or less (protocol of CHOP Nutrition and Growth Lab) using a non stretch, fiberglass tape measure. Three measures are taken repositioning the tape between each measure; the mean of the measures is recorded and used in analysis. Supine recumbent heel-to-crown length will be measured on all subjects using flexible, non stretch measuring tape and a stabilization board at the foot to optimize measurement.

Anthropometric Measures

Body composition, total fat-free mass, fat mass, and percent body fat will be assessed by 4 skinfolds and a mid upper-arm and mid calf circumference using prediction equations adapted for children and adolescents.[54,55] All anthropometric techniques will follow those described by Lohman et al[56] and be performed by a trained research anthropometrist. Anthropometric measurements will be assessed prior to or following each IC measurement. Skinfold thickness to 0.1 mm will be measured at the subscapular, tricep, bicep, and suprailiac sites with a skinfold caliper (Holtain, Crymych, UK) to assess subcutaneous fat stores. Mid upper-arm and mid-calf circumference will be measured with a non-stretch fiberglass tape to 0.1 cm (McCoy, Maryland Heights, MO). All measurements will be taken and recorded in triplicate with

the mean used in analysis. Lange and Holtain skinfold calipers, sliding calipers, abdominal caliper, and anthropometer, and a knee-height measuring device for assessment of short-term growth are used for measurements. Anthropometric equipment is checked and calibrated before every assessment to assure proper operation.

Table 2 Study Measurements

All Enrolled			Study Intervention Group			All Enrolled
Measurement	Baseline with Enrollment	Daily	1st IC Measurement (within 24 hours of Intubation)	2nd IC Measurement (at Plateau Ventilation Support)	3rd IC Measurement (De-escalation of care prior to extubation)	Protocol End (PICU Discharge **OR** Study Day 28)
Demographic Data	X					
Past and Current Medical History	X					
Assessment of Organ Function	X	X	X	X	X	X
Ventilation Parameters	X	X	X	X	X	X
Weight	X		X	X	X	X
Supine Length	X		X	X	X	X
Head Circumference (≤ 5 years)	X					X
Anthropometric Skinfold Measurements	X		X	X	X	X
Prediction Equation Calculation	X					X
Total Intake	X	X	X	X	X	X

Prediction Equation Calculation

The PI and the clinical nutritionist will calculate energy needs based on an appropriate equation for the participant's age, gender, weight, stature and clinical status. The Schofield,[41] WHO,[57] and RDA[58] equations are used most often in our PICU at CHOP and will be used for this study Parameters to use in the calculations are specified by the equation.

Fluid and Nutrient Intake

All nutritional and non-nutritional intake will be retrieved from the clinical flow sheet as documented by the bedside nurse and recorded daily for each enrolled participant. Caloric and fluid intake and fluid balance will be followed daily for the 28-day study period. Prescriptions for nutrient intake based on the recommendations of the clinical nutritionist and prescribed by the provider clinically responsible will be checked in the electronic medical record order system and documented by the RA in the study clinical database. With few exceptions, nutrition support can be delivered to critically ill children by either the enteral or the parenteral route or both. The enteral route is preferred as it is the most physiologic, allowing stomach and bowel digestion and absorption of nutrients. In the critically ill child, however, enteral intake may not be possible for various reasons. Following IC measurements, the clinical nutritionist will reassess the initially prescribed intake and make adjustments as indicated for participants in the study group. The adjusted recommendations for energy intake made in accordance with the IC measurements

will be communicated to the responsible prescriber and prescription changes made accordingly. All energy intake inclusive of changes will be recorded daily for all participants.

Indirect Calorimetry Measurement

Using IC, resting energy expenditure (REE) and the respiratory quotient (RQ) will be assessed during the participant's acute phase, plateau phase, and weaning to extubation phase of illness. Individual time points allow the intervention to be driven by the participant's clinical status. In the acute phase of ALI, which commences with the onset of respiratory insufficiency, measured by an increasing ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PF ratio), equal to 300 mmHg or less and requires ventilator support, is when alterations in metabolism may be heightened. During this time, accurate assessment of energy requirements is necessary to provide adequate calories to minimize loss of lean body mass and minimize the catabolic effects that can occur with the metabolic stress response. During the plateau phase, when ventilator settings have not escalated in the previous 24 hours, metabolic requirements may change and adjustment of caloric goals will minimize the potential to over- or underfeed. At the point of weaning ventilator support (the weaning phase) characterized by a progressive reduction in ventilator settings in the preceding 24 hours, energy needs may again change, and an adjustment in calories may be necessary.[59]

IC measurements will be obtained using a portable computerized metabolic cart (Vmax SPECTRA (29s), Viasys Healthcare/Sensormedics, Yorba Linda, CA). The PI, a pediatric critical care nurse practitioner, or a critical care trained physician will assess the participant for hemodynamic and respiratory stability prior to initiation of IC measurements. For the purposes of this study, respiratory stability is defined as no escalation in ventilation within 4 hours of IC measurement, no ventilation changes within 1 hour prior to IC measurement, acceptable oxygen saturation and end tidal carbon dioxide levels (based on preceding 4-hour trend), equal bilateral breath sounds with equal aeration and chest rise, absence of retractions, and no overt signs of

respiratory distress (cough, excessive movement, pain, etc). Participants will be assessed for a leak in the ventilator circuit that is 5% or less between measured inspiratory and expiratory tidal volumes. Pain will be assessed by the PI using the Faces, Legs, Activity, Cry and Consolability (FLACC) scale,[60] cross-checked with the bedside critical care nurse and both scores recorded. A score of 0–3 indicating none to mild pain is necessary for the IC measurement to commence. If the FLACC scale score is 3 or greater, the IC measurement will be postponed until the participant is in a resting, comfortable state.

A registered respiratory therapist (RRT) trained in the care of critically ill, mechanically ventilated children at CHOP will be present for the duration of each IC measurement. In mechanically ventilated participants, an adapter is used to attach the flow sensor of the metabolic cart to the exhalation outlet of the ventilator. This adapter will be secured by the RRT and the participant will be reassessed for continued stability and any changes in respiratory or ventilation status. Anticipating the possibility of lung volume loss with attachment of the adapter, usual PICU procedures for managing lung volume loss will be instituted and followed. For the entirety of each IC measurement on each participant, a respiratory therapist, a critical care nurse specially trained in the care of critically ill children requiring mechanical ventilation, the PI, and/or a critical-care-trained physician will be in attendance. Should the participant exhibit any sign of distress or clinical instability during IC measurement, the assessment will be immediately aborted. Usual PICU care for safety will be maintained during IC measurement, including but not limited to checking security and patency of the endotracheal tube, continuous electronic hemodynamic monitoring and continuous observed patient assessment. During each IC measurement, the environment will be controlled in the usual manner as that used during an invasive or high-risk procedure in

the PICU. Previous studies have not reported any serious adverse events associated with IC measurements in mechanically ventilated children or adults.[17,19,35,45,61]

Following a well-established protocol from the Nutrition and Growth Laboratory of Dr. Virginia Stallings at CHOP, an age-appropriate fast according to institution standards will be instituted prior to each IC measurement. Every attempt will be made to perform IC measurements between 6 a.m. and 10a.m. with the participant resting and pain-free. Once the specified assessments are complete and the participant determined clinically stable for IC testing, a 60-minute test will be performed. In accordance with Dr Stallings' protocol, 60 minutes is necessary to allow collection of an adequate number of time points to ensure technical quality of the test, allow a period of steady-state to commence, and have enough time measurements to assure quality data collection for each IC measurement. Steady-state is defined as a period of time after the start of the measurement with 10% or less variation in VO_2 and VCO_2 and a 5% or less variation in RQ measurements.[62-64] Data from the first 10 minutes and during periods of significant physical movement, coughing or agitation are eliminated, with the remaining data averaged for the mean REE and RQ. REE is then electronically calculated using the modified Weir equation and expressed in kilocalories. REE from IC is then compared to values derived from prediction equation calculations. The WHO equation adjusts for age, gender and weight,[57] while Schofield adjusts for age, gender, weight, and height.[41] Fat-free mass will be assessed from skinfold measures to determine its contribution to the REE.

Study Burden

We anticipate minimal study burden as all measurements are planned during admission in the PICU. The degree of burden will be in a family's decision to participate. The study procedures will not interfere with any usual PICU care or

procedures nor will it prevent participants transferring out of the intensive care unit once they are clinically stable.

Study Safety

Safety of study procedures will be monitored for all study participants. There will be strict adherence to study protocol with continuous electronic hemodynamic monitoring in addition to continuous observation during the IC measurement by a critical care provider (PI or critical-care-trained physician), critical care RRT, and the critical care nurse. PICU precautions for maintenance of lung volume will include the use of inline adapters and all usual maneuvers to minimize loss of lung volume when the participant is disconnected from the ventilator circuit. Should a decrease in lung volume occur, usual PICU maneuvers for re-recruitment will be employed. Participants are monitored for respiratory and hemodynamic stability as well as environmental safety throughout each IC measurement and throughout the study period.

Measurement of Study Outcomes

Study outcome is to compare the effect of using IC to determine energy requirements in mechanically ventilated children with ALI to the current practice of prescribing energy needs by the use of prediction equations. IC measurements as proposed are useful for directing prescriptions for energy intake. This, we propose, will result in:

1) Increase in ventilator-free days(VFD)

Ventilator-free days, is a composite outcome that reflects duration of mechanical ventilation. For this investigation, VFD will be used to reflect appropriateness of energy intake prescription. The numbers of consecutive days after the endotracheal tube has been removed up to study day 28 constitute the absolute number of VFD. Removal of the endotracheal tube will be calculated from the first time the tube is continuously

absent for a minimum of 48 hours, with success defined as spontaneous breathing for 24 hours without support of mechanical ventilation.[61] We expect to see a difference between those nutrient prescriptions derived from IC measurements compared to prescriptions derived from prediction equation calculations. The difference we propose will manifest in a 20% increase in ventilator-free days in the study group compared to the control group.

2) Decreased weight loss

Adequate caloric intake should minimize weight loss. There is an association between cumulative energy deficit and decrease in weight-for-age z-score (0.06; 95% CI: 0.01 – 0.1).[30] Participant weight is obtained on admission to the PICU and followed throughout the study period. Although it is difficult to obtain weights during the course of acute, critical illness, we will follow the trend and determine change from admission through PICU discharge or study day 28, whichever occurs first.

3) Decreased loss of lean body mass

Appropriate energy intake should minimize loss of lean muscle mass. We expect that sustained, appropriate intake will result in minimal breakdown of endogenous protein stores. Hulst and colleagues[30] demonstrate an association between cumulative energy deficit and decrease in mid-upper arm circumference z-score (0.07; 95% CI: 0.009 – 0.1). We will follow anthropometric measurements to determine change in muscle mass during the 28-day study period.

4) Decreased length of PICU hospitalization

With the use of IC to direct prescription for energy needs, participants should receive appropriate intake during the PICU stay and experience a decrease in overall length of hospitalization. Research has demonstrated that critically ill children who receive appropriate nutrition support demonstrate increased physiologic stability and an earlier

return to baseline health status, shortening the duration of the illness and decreasing the length of hospitalization.[35] We hypothesize that critically ill children with ALI requiring mechanical ventilation who have energy needs assessed through the use of IC and nutrient prescription based on IC data will demonstrate improved physiologic status due to optimization of nutrition support, resulting in improved clinical outcomes and decreased length of hospitalization in comparison to those children whose nutrition was determined using standard prediction equations.

Overall Analysis Plan

Preparation of the Analysis Data Set

All primary and secondary outcomes will undergo 100% data audit against the medical record. The data audit includes visual screening for missing data and inconsistencies. All out-of-range values, inconsistencies, and missing data will generate a query that will require examination of the participant's medical record for resolution. Preplanned construction of new variables will be conducted in accordance with the study hypotheses and analysis plans. Variable transformation may be required for interpretation and statistical analysis purposes.

Analysis Plan

The primary outcome for this study is the number of VFD in the two groups. Secondary outcomes include a decreased loss of lean body mass (LBM) with weight maintenance (baseline to day 28) and length of hospitalization. The median number of VFD will be compared using the nonparametric Wilcoxon rank-sum (Mann-Whitney U) test. Categorical demographic variables will be analyzed using the Chi-square test, while differences in continuous demographic and secondary outcome variables (loss of lean body mass and length of hospitalization) will be assessed with the two-sample

Student t test (for normally distributed data) or the Wilcoxon rank-sum test (non-normal data). Baseline analysis will include the following:

1. Comparison of the two groups using descriptive statistics (measures of central tendency [means and medians] and dispersion [standard deviations and interquartile ranges] for continuous variables with frequency counts and marginal percentages for categorical variables) will be computed for all study variables and examined for marked skewing, outliers, and any systematic missing data. Transformations will be undertaken as required.
2. Pearson product intercorrelations will be computed and examined for multicollinearity.

   Statistical significance will be set at the 0.05 level based on the two-tailed alpha test. Data analysis will be performed using SPSS (SPSS Inc., Chicago, IL) and SAS (SAS Institute, Inc., Cary, NC) statistical programs.

Training of Study Personnel

In the start-up phase (first 9 months of study year 1), all members of the study team will be trained on the study protocol. In addition, the PI will be trained and quality tested for reliability on use of the metabolic cart to perform the REE measurements. Both the PI and the RA will be trained and tested for reliability and reproducibility in obtaining skinfold measurements, overseen by Dr. Stallings. Procedures for screening of potential participants, family approach, and the consent and enrollment process will be developed and evaluated for completeness with support from Drs. Medoff-Cooper, Curley, and Srinivasan. The RA will be trained in participant screening, confirmation of eligibility, family approach and consent, data abstraction, and data entry into a password-secured database. RA activities will be directed and supervised by the PI. Table 3 depicts the proposed training and study timeline.

Table 3 Estimated Timeline of Study Activity

	Year 1				Year 2				Year 3				Year 4				Year 5			
Hire RA; Develop databases, operations manual, case report forms; Complete IRB process	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
PI, RA training																				
Participant screening, enrollment, initiate protocol, data collection, data entry																				
Complete data entry, data cleaning; Preliminary data analysis																				
Final Data analysis																				
Dissemination of results																				

Responsible Conduct of Research

The PI has received and will continue to receive training on the ethical conduct of research through various resources available at the University of Pennsylvania. The University recognizes and takes responsibility for training the applicant in the area of responsible conduct of research. The format for the education in the responsible conduct of research will vary. Members of the training team will be available for formal and informal problem-focused meetings. The applicant will meet face-to-face monthly with Dr. Barbara Medoff-Cooper, to assure the understanding of informed consent, have the opportunity to observe and debrief the deliberations of two different IRBs and observe the peer review process. In addition, the applicant will have face-to-face meetings with Dr. Medoff-Cooper regarding the conduct of research with families and

vulnerable populations and to ensure protection of human subjects. The PI will continue to participate in the University of Pennsylvania School of Nursing weekly Research Colloquia, which is conducted though the Office of Nursing Research. In addition, the PI will have access to monthly meetings in the Divisions of Family and Community Health and Biobehavioral Research at the School of Nursing. Topics of these hour-long sessions include, but are not limited to: conflict of interest (personal, professional, and financial), policies regarding human subjects, mentor/mentee responsibilities and relationships, collaborative research (including collaborations with industry), peer review, data acquisition and laboratory tools, scientific integrity, research misconduct (and policies for handling misconduct), responsible authorship and publication, contemporary ethical issues in biomedical research, the scientist as a responsible member of society, Federal Assurances, Internal Review Board (IRB) basics, monitoring grant spending research with vulnerable populations, and academic integrity.

The PI has completed on-line education on HIPAA certification and Protection of Human Research Subjects- Biomedical, which satisfies the university's requirement for human subjects' research training in the biomedical sciences. In addition, the PI has completed the Subject Oriented Training in the School of Medicine. These modules include information on informed consent, vulnerable populations, records research, FDA regulated research, and conflicts of interest. In addition, the PI has completed courses in clinical and research ethics. Issues of responsible conduct are included in coursework of two research methods courses (quantitative and qualitative methods). These courses are required of the applicant during doctoral education.

Protection of Human Subjects

The study will seek recruitment of a representative proportion of males and

females indicative of the ethnic and racial distribution common to the PICU at CHOP. All participants will be children who are at least 44 weeks post-conceptual age, but have not yet had their 19th birthday, with a diagnosis of ALI and require mechanical ventilation. The entire primary research team is trained and has extensive experience in the care and clinical management of critically ill infants, children and adolescents. A member of the research team will be available to communicate with enrolled families and the PICU staff at all times to answer questions and explain procedures as necessary. Weekend and off-hours coverage will be on a rotating basis.

Potential risks which would involve loss of lung volume during the IC measurement, will be minimized by strict adherence to the study protocol. Should the participant exhibit signs of distress during IC measurement, the assessment will be aborted immediately. A critical care provider, RRT and critical care nurse will be present at all times during IC measurement. The patient will be continuously monitored by observation and electronic hemodynamic monitoring.

Potential benefit to the participants randomized to the study group include precise prescription of energy needs to meet actual energy requirements with the potential to increase ventilator free days, decrease loss of lean muscle mass, maintain weight through critical illness, improve overall outcomes and decrease length of hospitalization. These potential benefits hold promise for clinical implementation and shift of clinical practice paradigms related to nutrition management for critically ill children with ALI requiring mechanical ventilation. Participants randomized to the control group will receive usual PICU care. The alternative to IC measurements to determine energy needs is usual PICU care and families can opt to withdraw from the protocol at any time, however all effort to maintain participation will be employed. There are no financial or legal risks for participation in this study.

Confidentiality

To protect against any risk to participant confidentiality, all printed data forms will be coded with a unique anonymous identifier. This unique identifier will be stored separately from files with personal health information (PHI) to maintain confidentiality. As part of the of the consent process, participants will be made aware that circumstances exist (regulatory or legal) where the research team will have to provide subject information to others. Signed consent forms and other participant specific forms and documents will be labeled with the participant's name, these forms along with a master list of participants will be secured separate from any information with PHI and identification numbers in locked cabinets away from the PICU. Access will be limited to those directly involved with this study. Databases will be maintained on a secured, password-protected research quality network drive and maintained by the PI in accordance with the standards of the School of Nursing at the University of Pennsylvania and CHOP. The scheduled back up procedures in accordance with each institution will be followed. Every effort to maintain participant information confidentiality will be employed. All identifying data will be removed from files prior to electronic transfer to the biostatistician. No individual subjects will be identifiable from written or oral dissemination of the results of this study.

Data Safety Monitoring

There will be two levels of data and safety monitoring. The first level will be on-site, a study monitor (PI or other member of the study team) will verify data integrity, compliance to the protocol and review source data and medical records, case report forms and regulatory documents for completeness, accuracy and legibility. Discrepancies will be discussed between the PI and study team as appropriate. The study team will collect all data and perform initial data entry. A verification of data entry

will then be performed by another member of the team. The second level of data and safety monitoring will be the establishment of a Data and Safety Monitoring Board (DSMB), which consists of individuals responsible for study oversight. The DSMB members will be appointed by the PI with approval of the funding agency. The Research Institute at CHOP and the University of Pennsylvania will be provided names, and a summary of the background and expertise of the DSMB board members. The DSMB members will consist of three faculty members independent of the research team, two with expertise in pediatric critical care and one with expertise in interpretation and analysis of energy expenditure measurements.

All DSMB members will be appointed for the five study years. They must disclose any conflict of interest with the present study. The DSMB board will have a Chair and Executive Secretary appointed. The DSMB will monitor study regulatory files, enrollment tracking logs, informed consent forms, case report forms and overall study protocol. The board will meet at least annually for these activities. The PI will be responsible for scheduling the meetings and selecting items to be reviewed.

Inclusion of Women, Minorities, and Children

All participants in the study are children between post-conceptual age of 44 weeks and prior to their 19th birthday. The anticipated sample will be racially diverse as CHOP serves a large local, regional, national and international community. Bi-weekly meetings with the research team will include discussions surrounding recruitment and retention of minority children. Concurrently, the PI and RA will participate in the University of Pennsylvania, School of Nursing's Culture and Diversity seminars. In the over 3000 annual admissions in the PICU at CHOP in the preceding year, the diversity distribution was 54% non-Hispanic White, 6.4% Hispanic, 28% African-American, 1.7%

Asian/Pacific Islanders, < 1% Native American and 10% Other / Unknown / Decline to Claim. Gender distribution was 58% to 42% male to female respectively.

Consortium Agreement

The Pediatric Intensive Care Unit (PICU) at The Children's Hospital of Philadelphia (CHOP) is a clinical, research facility were this randomized clinical trial would be conducted.

Invertebrate Animals

There is no use of animals or collection of data from animals in this study.

References

1. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med.* 2009;37(8):2448 - 2454.

2. Artigas A, Bernard GR, Carlet J, et al. The American-European Consensus Conference on ARDS, part 2. Ventilatory, pharmacologic, supportive therapy, study design strategies and issues related to recovery and remodeling. *Intensive Care Med.* Apr 1998;24(4):378-398.

3. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* Mar 1994;149(3 Pt 1):818-824.

4. Priestley MA, MA H. Approaches in the management of acute respiratory failure in children. *Current Opinion in Pediatrics.* 2004;16:293 - 298.

5. Santschi M, Joumet P, Lederc F, et al. Acute lung injury in children: Theraputic practice and feasibility of international clinical trials. *Pediatric Critical Care Medicine.* 2010;11(6):681 - 689.

6. Verger JT, Bradshaw DJ, Henry E, KE R. The pragmatics of feeding the pediatric patient with acute respiratory distress syndrome. *Critical Care Nursing Clinics of North America.* 2004;16:431 - 443.

7. Mehta NM, Duggan CP. Nutritional Deficiencies During Critical Illness. *Pediatr Clin N Am.* 2009;56:1143 - 1160.

8. Briassoulis G, Zavras N, T H. Malnutrition, Nutritional Indices, and Early Enteral Feeding in Critically Ill Children. *Nutrition.* 2001;17:548 - 557.

9. Hulst J, Joosten K, Zimmermann L, et al. Malnutrition in critically ill children: admission to 6 months after discharge. *Clinical Nutrition.* 2004;23:223 - 232.

10. Mehta NM, Castillo L. Nutrition in the Critically Ill Child. In: Bradley P. Fuhrman, Jerry J. Zimmerman, eds. *Pediatric Critical Care*. Third ed. Philadelphia: Mosby Elsevier; 2006:1068 - 1084.

11. Meyer R, Harrison S, Sargent S, Ramnarayan P, Habibi P, Labadarios D. The impact of enteral feeding protocols on nutritional support in critically ill children. *The Journal of Human Nutrition and Dietetics.* 2009;22:428 - 436.

12. Hulst JM, Joosten KF, Tibboel D, van Goudoever JB. Causes and consequences of inadequate substrate supply to pediatric ICU patients. *Current Opinion in Clinical Nutrition and Metabolic Care.* 2006;9(3):297 - 303.

13. Sermet-Gaudelus I, Poisson-Salomon AS, Colomb V, et al. Simple pediatric nutritional risk score to identify children at risk of malnutrition. *Am J Clin Nutr.* 2000;72:64 - 70.

14. De Neef M, Geukers VGM, Dral A, Lindeboom R, Sauerwein HP, AP B. Nutritional goals, prescription and delivery in a pediatric intensive care unit. *Clinical Nutrition.* 2007;27:65 - 71.

15. Mehta NM, Bechard LJ, Dolan M, Ariango K, Jiang H, Duggan C. Energy imbalance and the risk of overfeeding in critically ill children. *Pediatric Critical Care Medicine.* 2011;12(4).

16. Kaplan AS, Zemel BS, Neiswender KM, Stallings V. Resting energy expenditure in clinical pediatrics: Measured versus prediction equations. *Journal of Pediatrics.* 1995;127(2):200 - 205.

17. Briassoulis G, Venkataraman S, Thompson AE. Energy expenditure in critically ill children. *Critical Care Medicine.* 2000;28(4):1166 - 1172.

18. Joffe A, Anton N, Lequier L, et al. Nutritional support for critically ill children. *Cochrane Database of Syst Rev 2009*. Art. No.: CD005144 ed2009.

19. Mehta NM, Bechard LJ, Leavitt K, Duggan C. Cumulative Energy Imbalance in the Pediatric Intensive Care Unit: Role of Targeted Indirect Calorimetry. *JPEN J Parenter Enteral Nutr.* 2009;33(3):336 - 344.

20. Butte NF. Energy Requirements of Infants and Children. Paper presented at: Nestlé Nutrition Workshop Series. Paediatric Programme, 2006.

21. Chwals WJ, Bistrian BR. Predicted energy expenditure in critically ill children: Problems associated with increased variability. *Crit Care Med.* 2000;28(7):2655-2656.

22. Mehta NM, Compher C. A.S.P.E.N. Clinical Guidelines: Nutrition Support of the Critically Ill Child. *JPEN J Parenter Enteral Nutr.* 2009;33(3):260 - 276.

23. White MS, Shepherd RW, JA M. Energy expenditure in 100 ventilated, critically ill children: Improving the accuracy of predictive equations. *Crit Care Med.* 2000;28(7):2307 - 2312.

24. Hardy CM, Dwyer J, Snelling LK, Dallal GE, Adelson JW. Pitfalls in Predicting Resting Energy Requirements in Critically Ill Children: A Comparison of Predictive Methods to Indirect Calorimetry. *Nutr Clin Pract.* 2002;17(182 - 189).

25. Timmons OD, Havens PL, Fackler JC. Predicting death in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. Extracorporeal Life Support Organization. *Chest.* Sep 1995;108(3):789-797.

26. Curley MAQ, Thompson JE, Arnold JH. The effects of early and repeated prone positioning in pediatric patients with acute lung injury. *Chest.* Jul 2000;118(1):156-163.

27. Cook RC, Blinman TA. Nutritional support of the pediatric trauma patient. *Semin Pediatr Surg.* 2010;19:242 - 251.

28. Hulst JM, van Goudoever JB, Zimmermann LJ, et al. Adequate feeding and the usefulness of the respiratory quotient in critically ill children. *Nutrition.* 2005;21:192 - 198.

29. Pollack MM, Wiley JS, Holbrook PR. Early nutritional depletion in critically ill children. *Crit Care Med.* 1981;9(8):580 - 583.

30. Hulst JM, van Goudoever JB, Zimmermann LJ, et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. *Clin Nutr.* 2004;23:1381 - 1389.

31. Pollack MM, Wiley JS, Kanter R, Holbrook PR. Malnutrition in Critically Ill Infants and Children. *JPEN J Parenter Enteral Nutr.* 1982;6(1):20 - 24.

32. Hendricks KM, Duggan C, Gallagher L, et al. Malnutrition in Hospitalized Pediatric Patients. *Arch Pediatr Adolesc Med/Vol.* 1995;149:1118 - 1122.

33. Taylor RM, Cheeseman P, Preedy V, Baker AJ, Grimble G. Can energy expenditure be predicted in critically ill children? *Pediatr Crit Care Med.* 2003;4(2):176 - 180.

34. White MS, Shepherd RW, JA M. Energy Expenditure Measurements in Ventilated Critically Ill Children: Within-and Between-Day Variability. *JPEN J Parenter Enteral Nutr.* 1999;23:300 - 304.

35. De Klerk G, Hop WCJ, De Hoog M, Joosten KFM. Serial measurements of energy expenditure in critically ill children: useful in optimizing nutritional therapy. *Intensive Care Med.* 2002;28:1781 - 1785.

36. Reid C. Frequency of under- and overfeeding in mechanically ventilated ICU patients: causes and possible consequences. *J Hum Nutr Diet.* 2006;19:13 - 22.

37. World Health Organization. *WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index for age: Methods and development*. Geneva, Switzerland: World Health Organization; 2006.

38. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.* Washington, DC: The National Academies Press; 2005.

39. Briassoulis G, Venkataraman S, Thompson A. Energy expenditure in critically ill children. *Crit Care Med.* 2000;28(4):1166 - 1172.

40. Talbot F. Basal Metabolism Standards for Children. *Am J Dis Child.* 1938;55(3):455 - 459.

41. Schofield W. Predicting Basal Metabolic Rate, New Standards and Review of Previous Work. *Human Nutrition: Clinical Nutrition.* 1985;39C(Suppl):1, 5 - 41.

42. Reichman CA, Shepherd RW, Trocki O, Cleghorn G, Davies PSW. Comparison of measured sleeping metabolic rate and predicted basal metabolic rate during the first year of life: evidence of a bias changing with increasing metabolic rate. *Eur J Clin Nutr.* 2002;56:650-655.

43. Sentongo TA, Tershakovec AM, Mascarenhas MR, Watson MH, Stallings VA. Resting energy expenditure and prediction equations in young children with failure to thrive. *J Pediatr.* 2000;136:345-350.

44. Thomson MA, Bucolo S, Quirk P, RW S. Measured versus predicted resting energy expenditure in infants: A need for reappraisal. *J Pediatr.* 1995;126:21 - 27.

45. Coss-Bu JA, Jefferson LS, Walding D, David Y, Smith EO, WJ K. Resting energy expenditure in children in a pediatric intensive care unit: comparison of

Harris-Benedict and Talbot predictions with indirect calorimetry values. *Am J Clin Nutr.* 1998;67:74 - 80.

46. Verhoeven JJ, Hazelzet JA, van der Voort E, KFM J. Comparison of measured and predicted energy expenditure in mechanically ventilated children. *Intensive Care Med.* 1998;24:464 - 468.

47. Hardy Framson CM, LeLeiko NS, Dallal GE, Roubenoff R, Snelling LK, Dwyer JT. Energy expenditure in critically ill children. *Pediatr Crit Care Med.* 2007;8(3):264 - 267.

48. Illner K, Brinkmann G, Heller M, Bosy-Westphal A, Muller MJ. Metabolically active components of fat free mass and resting energy expenditure in nonobese adults. *American Journal of Physiology Endocrinology and Metabolism* 2000;278:E308 - E315.

49. McClave SA, Lowen CC, Kleber MJ, McConnell W, Jung LY, Goldsmith LJ. Clinical Use of the Respiratory Quotient Obtained From Indirect Calorimetry. *Journal of Parenteral and Enteral Nutrition.* 2003;27(1):21 - 26.

50. Martinez JLV, Martinez-Romillo PD, Sebastian JD, Tarrio FR. Predited versus measured energy expenditure by continuous, online indirect calorimetry in ventilated, critically ill children during the early postinjury period. *Pediatr Crit Care Med.* 2004;5(1):19 - 27.

51. Curley MAQ, Arnold JH, Thompson JE, et al. Clinical trial design - effect of prone positioning on clinical outcomes in infants and children with acute respiratory distress syndrome. *J Crit Care.* 2006;21:23 - 37.

52. McArthur CD. AARC Clinical Practice Guidelines Metabolic measurements using indirect calorimetry during mechanical venitlation - 2004 Revision & Update. *Respir Care.* 2004;46(9):1073 - 1079.

53. Vickers AJ. How to randomize. *J Soc Integr Oncol.* 2006;4(4):194 - 198.

54. Brook CGD. Determination of Body Composition of Children from Skinfold Measurements. *Arch Dis Child.* 1971;46(246):182 - 187.

55. Slaughter MH, Lohman TG, Boileau RA. Skinfold Equations for Estimation of Body Fatness in Children and Youth. *Hum Biol.* 1988;60(5):709 - 723.

56. Lohman TG, Roche AR, Martorell R. *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics; 1988.

57. FAO/WHO/UNU, Expert Consultation. *Energy and protein requirements: technical report series. #1985724.* Rome, Italy. 2001.

58. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press; 2005.

59. Curley MAQ, Fackler JC. Weaning from mechanical ventilation: patterns in young children recovering from acute hypoxemic respiratory failure. *Am J Crit Care.* Sep 1998;7(5):335-345.

60. Voepel-Lewis T, Merkel S, Tait AR, Trzcinka A, Malviya S. The Reliability and Validity of the Face, Legs, Activity, Cry, Consolability Obervational Tool as a Measure of Pain in Children with Cognitive Impairment. *Anes Analg.* 2002;95(1224 - 1229).

61. Knebel AR, Shekleton ME, Burns S, Clochesy JM, Hanneman SK, Ingersoll GL. Weaning from mechanical ventilation: concept development. *Am J Crit Care.* 1994;3(6):416 - 420.

62. Mehta NM, Bechard LJ, Leavitt K, Duggan C. Severe Weight Loss and Hypermetabolic Paroxysmal Dysautonomia Following Hypoxic Brain Injury:

The Role of Indirect Calorimetry in the Intensive Care Unit. *JPEN J Parenter Enteral Nutr.* 2008;32(3):281 - 284.

63. Branson RD, Johannigman JA. The Measurement of Energy Expenditure. *Nutr Clin Pract.* 2004;19:622-636.

64. Bines JE, Truby HD. Measurement of resting energy expenditure in infants. *J Paediatr Child Health.* 2004;40:380-383.

Chapter 4

Summary and Conclusions

There is abundant evidence associating growth failure and infants with Congenital Heart Disease (CHD). This body of work further examines this relationship through an investigation of growth velocity and energy expenditure in a sample of infants with CHD following surgical intervention in early infancy. Although there is debate clinically and in the literature on what constitutes growth failure in these infants, the studies presented in this dissertation illustrate a negative statistical difference in growth between infants with CHD and healthy infants. In addition, this data offers one potential explanation – inadequate energy intake. Use of the newly developed World Health Organization (WHO) child growth and growth velocity standards,[1,2] make the studies presented here novel in their approach to investigate growth in these infants. Illustrating a difference in growth velocity compared to healthy infants and demonstrating that energy expenditure in infants with CHD is not different from healthy infants of the same age and gender, make this work is timely and important to the clinical care of these infants. The following is a summation of the research findings and their contribution to better understand growth failure in infants with CHD following surgery in the neonatal period.

Specific Aims and Manuscript Review

Growth Monitoring

Growth Velocity

Growth velocity is the change over time in a given measure of physical development. It can have high variability reflecting a naturally occurring pattern of saltatory growth and catch-up or slow-down to account for a normal pattern of attained growth reflected on standard growth charts.[2] The first study of this dissertation, “Growth

Velocity over the First Year of Life Following Neonatal Surgery for Congenital Heart Disease" is a descriptive study describing the pattern of growth velocity for weight, length and head circumference in a sample of infants with CHD following neonatal surgery compared to healthy infants of similar age and gender. These data demonstrate decreased growth velocity in infants with CHD compared to healthy infants. Calculating and monitoring growth velocity growth is a more accurate way to assess short and long-term changes in growth measures based on the time intervals instead of a point in time.[2,3] Using the WHO standards, which define growth based on international child health standards, weight, length and head circumference, z-scores and velocity z-scores were calculated. The standardized z-score measures clearly exhibited a difference at 3-months of age, depicting lower z-scores and a decreased rate of growth in infants with CHD. Despite the decreased rate of growth seen at 3 months of age, there was no difference in velocity z-scores for weight, length or head circumference for the remaining time intervals, suggesting that the growth disparity of early infancy is modifiable and that improved growth in infants with CHD is attainable. These data provide a foundation on which to build a definition of growth failure in infants with CHD. However, small sample size and missing data prevent development of a definition based on this sample.

Although we measured growth velocity in 3-month intervals, the WHO growth velocity standards allow for surveillance in weekly intervals in early infancy.[2] The use of these standards with close observation beginning at birth of attained growth and the rate of change in growth parameters are a means for early identification of infants at risk for poor growth. With early identification, early intervention is possible which can prevent or minimize the degree of growth failure and decrease the potential for long-term morbidities that can result from poor growth in infancy.

These data provide the platform for the design of strategies and interventions aimed at increased caloric intake to assess if growth failure demonstrated in this study by poor growth velocity is in fact modifiable. A program of feeding strategies that supports an increase in energy intake may be the not so simple solution to this persistent problem.[4-8] Ongoing concentrated efforts in nutrition support aligned with medical and nursing care may improve the rate of growth in infants with CHD to mirror that of healthy infants. Further, this study may be the prologue of an intervention study to develop and longitudinally test an intervention aimed at providing increased caloric intake and monitoring infant response through feeding tolerance and attained growth and growth velocity patterns. This may be a step at mitigating growth failure in infants with CHD following neonatal surgery.

Energy Expenditure

The identification of differences in growth between infants with CHD and healthy infants demonstrated in the study on growth velocity, presents a logical progression to identify predictors of poor growth in these infants. Increased energy expenditure related to cardiac physiology and the associated hemodynamic and metabolic status is hypothesized to be a contributing factor in growth failure in infants with CHD. This is the focus of the second study presented in chapter 2, "Resting Energy Expenditure at 3-Months of Age in Infants Following Neonatal Surgery for Congenital Heart Disease". The primary aim of the study was to determine differences in resting energy expenditure (REE), body composition and weight at 3-months of age in infants with CHD compared to healthy infants. A secondary aim was to identify predictors of REE in the same population.

Findings from this investigation reject the hypothesis that post surgical cardiac physiology is the primary component driving energy expenditure. Further, no difference

in REE was demonstrated between infants with CHD compared to healthy infants. In fact, fat free mass (FFM) and infant age were the strong predictors of REE Kcal/day in the study sample. Not only was cardiac physiology was not a primary causal factor, it was not a major contributor to REE kcal in this study sample.

As expected, data from this study demonstrate FFM to be the primary predictor of REE kcal. There was no difference in REE kcal between infants with CHD and healthy infants, eliminating it, FFM, as contributing to poor growth in infants with CHD. Instead, this study demonstrated % body fat to be lower in infants with cardiac disease, which like accounts for their lower body weight in this study. This finding suggests energy intake is inadequate in infants with CHD since FM and therefore % body fat is directly related to caloric intake. Studies have shown poor nutrient intake during hospitalization, poor weight gain at hospital discharge, and reports of inconsistent feeding tolerance once home.[4,9-11] The decreased accretion of fat demonstrated in this study at 3-months of age suggests that poor weight gain continues post hospital discharge. This was an interesting finding as it further supports the hypothesis that consistent energy and nutrient intake are a challenge for infants with CHD and may be the basis for poor weight gain and subsequent growth failure. It was striking that the infants with CHD showed an increased REE difference of only 8 kcal/day compared to healthy infants, however, kg weight and WHO weight z-scores were significantly different between the groups. This is most likely explained by the significantly lower % body fat these infants exhibited. Clinically, these findings suggest poor attained weight at 3-months of age is related to inadequate caloric intake and the inability of these infants to attain and sustain a positive energy balance that is necessary for fat and lean body mass accretion.

It is important to note that these findings did not indicate cardiac physiology to be a predictor for REE kcal in infants with CHD. This dispels the commonly held view that cardiac disease is the basis for growth failure these infants often exhibit. In addition, these findings support that idea that with focused concentrated nutrition support along with medical and nursing care, growth failure seen in early infancy is reversible and it is possible for these infant to attain their genetic growth potential. Similar to the study on growth velocity, these findings present a platform for a program of research investigating the unique feeding, energy and nutrient intake needs of infants with CHD. Further, this study supports the idea of incremental measurements of body composition in these infants to assess their nutrition status by the amount of lean body mass compared to body fat mass, which can direct prescriptions for energy and nutrient intake.

These studies examined questions focused on growth and nutrition status in infants with cardiac disease following neonatal surgery. They present important data that can be used as a platform for further inquiry and clinical practice. The introduction of the WHO growth and growth velocity standards for infants and children, provide excellent tools to further the inquiry surrounding growth and nutrition in clinical practice and research endeavors.[12] The WHO standards have indices for weight, length, head circumference and growth velocity that have proven successful in the studies presented to evaluate growth. [1,2] The child growth and growth velocity standards can be useful for designing protocols and to identify specific parameters that can be used to define growth failure in infants with chronic illness such as CHD, however the studies presented suggest poor growth seen in early infancy is reversible and normal growth patterns for infants with CHD attainable.

These investigations of growth and growth failure in infants with CHD are important not only for somatic growth and its association with child health, but also for the sequela that is associated with poor growth. Numerous associations exist between cognitive, neurodevelopmental and neurobehavioral deficits in children who have experienced poor growth in infancy. In both the general pediatric literature and the pediatric cardiac literature, poor growth in infancy has the potential to have residual effects well into childhood. The work of this dissertation has elucidated information that potentially can intervene in growth failure in early infant and may in turn thwart the associated untoward cognitive and neurologic outcomes seen in childhood.

Study Limitations

The limitations presented here are relevant to both studies presented in Chapter 2. These include both studies are single center cohorts. This limits the generalizability of the findings but lays the groundwork for replication of each of the study protocols as larger clinical trials to determine reproducibility and generalizability of the study results. The study setting, The Children's Hospital of Philadelphia (CHOP), may have a higher acuity of cardiac disease than that seen and treated in other centers. Therefore, study findings may not be applicable in all pediatric cardiac settings. Recruitment for both studies occurred approximately 8 years prior, with the changes in surgical approach and technology these study findings may have a decreased impact in the research community. Assessment of dietary intake was attempted but the Neither investigation had reliable dietary intake data available for analysis, which would have strengthened the results. Birth data was extracted from the transport record that accompanied the infant to CHOP leaving question to its reliability, and reducing any inference that can be made regarding growth and growth velocity between birth and 3-months of age. Information learned from the 3-month data in both

studies, indicate the time between hospital discharge and 3 months of age in infants with CHD may be crucial to better understanding growth issues in these infants. There may be bias in that the families that enrolled and participated were motivated and actively participated in the rigorous research protocol. Data is not available to address familial educational or socioeconomic status and whether this reflects or impacts study enrollment. Lastly, the study sample may not completely represent families with infants that had the most challenging hospital course and were therefore not willing to consent to study participation. These issues singularly or in combination, they may influence study results.

NIH Director's Early Independence Award Application

To move the science forward and to 'translate' the knowledge and skills obtained over the course of this dissertation work, a grant proposal was prepared and submitted to the National Institutes of Health (NIH) as a candidate for an Early independent Investigator award. This proposal entitled: "The Use of Indirect Calorimetry (IC) to Measure Energy Needs in Mechanically Ventilated Children with Acute Lung Injury", represents a modified approach to translational research, addressing the adoption of best practice.[13] As part of this dissertation, this proposal serves to demonstrate the importance of translation of knowledge to support the idea of best practice in the care of children. Through knowledge gained from the testing and analysis of energy expenditure in postsurgical infants with complex CHD, this application, designed as a clinical trial proposes to measure energy expenditure in critically ill children requiring mechanical ventilation. The goal of this proposed trial was to assess energy needs through the use of indirect calorimetry in children with acute lung injury requiring mechanical ventilation. The specific aim of the proposed study is to measure energy expenditure using indirect calorimetry to assess and prescribe

caloric intake specific to energy needs as compared to standard current practice of prescribing energy intake from the use of prediction equation calculations. Research has shown that prediction equations often under or overestimate energy requirements, which can threaten clinical outcomes[14-16]. In this dissertation work, the investigation of energy expenditure in infants with cardiac disease demonstrated the inaccuracy of prediction equations to estimate energy needs when compared to measured energy expenditure. This proposal exemplifies the need to further study measurement of energy expenditure and its impact on participant outcomes versus the use of equations.

Many of the current therapies and much of our understanding of disease progression and appropriate treatment for children are derived from adult science. This practice can be challenging as knowledge is gained about differences between

adults and children in their presentation and response to illness and treatment. This proposal exemplifies the importance of conducting research specific to infants and children to better understand pediatric response to illness, treat the unique needs of the pediatric population and improve care delivery and overall outcomes. This is particularly true in regards to energy needs, which can influence response to illness and has long-reaching consequences for optimal health.

Future Research

The current body of work can move forward in two directions. The first would be to replicate the research presented to a larger sample and follow the cohort for a longer period. This would allow serial monitoring of growth measures, and the collection of more data points to better examine and understand growth and growth velocity in both healthy infants and those with CHD. Data on nutrient intake during the study period will also improve understanding of growth and growth failure and can provide for

recommendations for caloric and nutrient intake, improve prescriptions for energy needs based on actual energy intake and expenditure, and provide for a better assessment of growth measures. This will better define growth, growth velocity and growth failure in infants with complex CHD relating their nutrient intake, nutrition status and growth parameters. This trajectory of research will establish a foundation to develop nutrition support programs for infants are at risk for growth failure. Initiating nutrition support programs can establish another tier of continued research to monitor program success with incremental assessments of growth, growth velocity, body composition and energy expenditure.

A second direction for future research would parallel the ideas outlined in the grant proposal. There is much to understand the nutritional needs of infants and young children during critical illness. With ongoing evidence that the prediction equations are inadequate, it follows that a more accurate method is necessary to address energy needs and prescription of appropriate energy and nutrient intake during critical illness. Measurement of caloric needs with prescription and delivery specific to those needs can be an adjunct to care in critically ill children and has potential to improve outcomes. In pediatric critical care, appropriate provision of energy and nutrients remains a challenge, both researchers and clinicians acknowledge meeting nutrition needs to be an important aspect of care during and immediately following hospitalization. Accurate nutrition prescriptions based on measured energy expenditure can decrease complications associated with inadequate nutrient intake in critical illness, i.e. weight loss, alteration in body composition, and length of hospitalization.

Based on work throughout this dissertation, the conceptual model introduced at the outset can be modified. This work suggests energy balance is modifiable, and that modification can effect growth in infants with cardiac disease who have undergone

surgical intervention in the neonatal period. The possibilities for future nutrition and growth research born from this dissertation work abound and provide an exciting outlook for the direction of investigations in the care of infants and young children.

References

1. World Health Organization. *WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index for age: Methods and development*. Geneva, Switzerland: World Health Organization; 2006.

2. World Health Organization. *WHO Child Growth Standards. Growth Velocity based on weight, length and head circumference: Methods and development*. Geneva, Switzerland: World Health Organization; 2009.

3. Nommsen-Rivers LA, Dewey KG. Growth of Breastfed Infants. *Breastfeed Med.* 2009;4(Supplment 1):S45 - S-49.

4. Medoff-Cooper B, Irving SY. Innovative Strategies for Feeding and Nutrition in Infants with Congenitally Malformed Hearts. *Cardiol Young.* 2009;19(Suppl. 2):90 - 95.

5. Owens JL, Musa N. Nutrition Support After Neonatal Cardiac Surgery. *Nutr Clin Pract.* Apr-May 2009;24(2):242-249.

6. Pillo-Blocka F, Adatia I, Sharieff W, McCrindle BW, Zlotkin S. Rapid advancement to more concentrated formula in infants after surgery for congenital heart disease reduces duration of hospital stay: A randomized clinical trial. *J Pediatr.* 2004;145(6):761-766.

7. Natarajan G, Anne SR, Aggarwal S. Enteral Feeding of Neonates with Congenital Heart Disease. *Neonatology.* 2010;98:330 - 336.

8. Braudis NJ, Curley MAQ, Beaupre K, et al. Enteral feeding algorithm for infants with hypoplastic left heart syndrome poststage I palliation. *Pediatr Crit Care Med.* 2009;10(4):460 460 466.

9. Schwalbe-Terilli C, Hartman DH, Nagel ML, et al. Enteral Feeding and Caloric Intake in Neonates After Cardiac Surgery. *Am J Crit Care.* 2009;18(1):52 - 57.

10. Medoff-Cooper B, Irving SY, Marino BS, et al. Weight change in infants with a functionally univentricular heart: from surgical intervention to hospital discharge. *Cardiol Young.* 2011;21(2):136 - 144.

11. Anderson JB, Marino BS, Irving SY, et al. Poor post-operative growth in infants with two-ventricle physiology. *Cardiol Young.* 2011;21:421 - 429.

12. Van den Broeck J, Willie D, Younger N. The World Health Organization child growth standards: expected implications for clinical and epidemiological research. *Eur J Pediatr.* 2008;168:247 - 251.

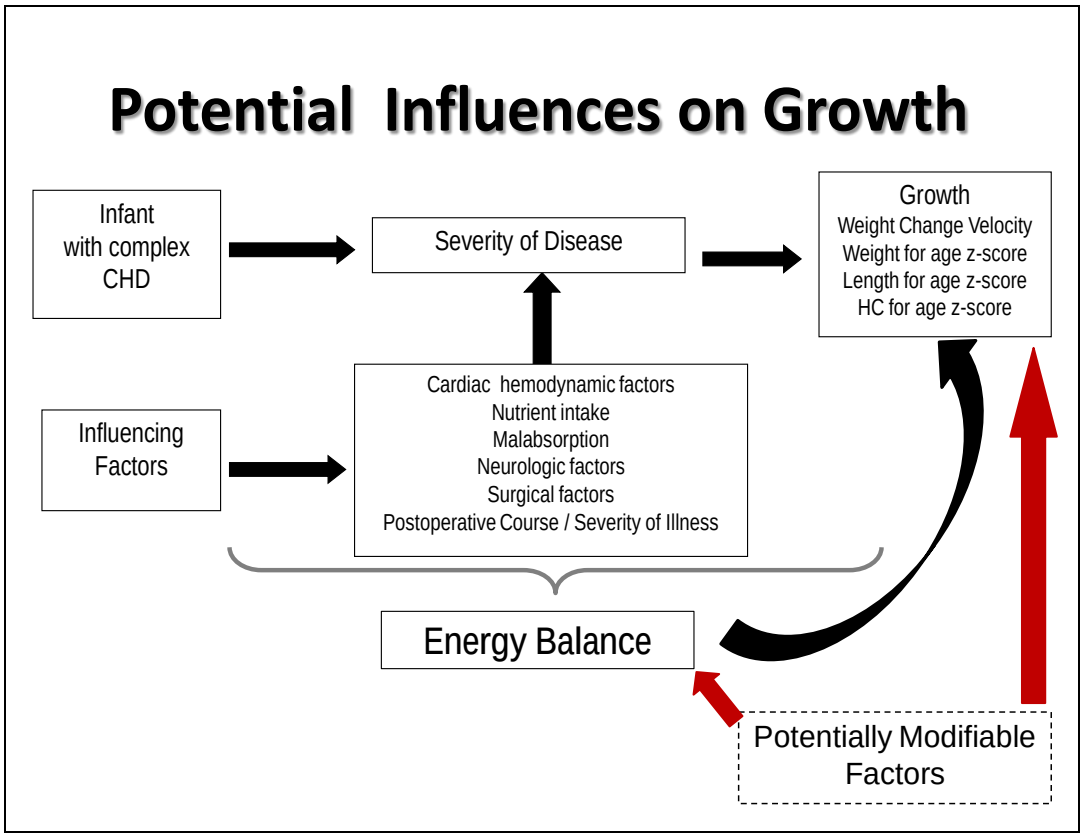
13. What is Translational Research. 2007; http://ccts.uth.tmc.edu/what-is-translational-research. Accessed May 3, 2011, 2011.

14. De Neef M, Geukers VGM, Dral A, Lindeboom R, Sauerwein HP, AP B. Nutritional goals, prescription and delivery in a pediatric intensive care unit. *Clin Nutr.* 2007;27:65 - 71.

15. Mehta NM, Bechard LJ, Dolan M, Ariango K, Jiang H, C D. Energy imbalance and the risk of overfeeding in critically ill children. *Pediatr Crit Care Med.* 2011;12(4).

16. Kaplan AS, Zemel BS, Neiswender KM, Stallings VA. Resting energy expenditure in clinical pediatrics: Measured versus prediction equations. *The Journal of Pediatrics.* 1995;127:200-205.

Figure 1 Modified Conceptual Model



Modified schematic of the concept of potential influences on growth in infants with CHD following surgical intervention in the neonatal period

CLOSING

Commencement May 16, 2011
PhD Student Speaker Address:
University of Pennsylvania,
School of Nursing
Kimmel Center, Philadelphia, PA

LOOK AT US NOW

Good Afternoon. To Dean Meleis, Ms Greco, Dr Savard, Dr Shalala, esteemed faculty, honored guests, fellow graduates, family and friends:

LOOK AT US NOW

LOOK AT US. To my graduating colleagues, you remember year "1". We were all sitting in Dr Julie Fairman's class on the "Philosophy of Science in Nursing". You remember – we were told that we were about to have our brains unpacked, scrambled and then by graduation – sometime in the future, we would re-packed our brains with some of the same but also with enhanced and new knowledge. Who knew we would learn the language of post-modernism, empiricism, feminism, relativism and the like…Well – LOOK AT US NOW, the repacking has been a journey, but much easier than we thought…

LOOK AT US NOW. Remember - "Concept Analysis" – some of us had to stretch, because to conceptualize we thought, was well beyond our reach, we provided care, it was tangible, not a concept… but, concept building, it was a part of the unpacking and the scrambling; we had yet to reach the repacking stage, so we needed a *concept*, a *model* on how to do it...

LOOK AT US NOW. We have poked proteins; examined phthalates; uncovered properties of skin elasticity; cared for the elderly; scrutinized kidney disease; held heart to heart talks with immigrants; used history to explore our nursing identity; examined symptom clusters in cancer; followed mothers and children with HIV; wacked on a few mice; probed into psychiatric assessment; thought about sleep – while we were losing it; investigated the impact of vitamin D in diabetes; examined school performance in ex- preemies and studied the expenditure of energy in infants with congenital heart disease… In essence, we have repacked our brains and in doing so, we have added to the knowledge of nursing science, we are becoming epistemologists…LOOK AT US NOW!

LOOK AT US – now we initiate and we lead the conversations on: "the literature tells us", "the research is lacking" and "recent data suggests"…that's us talking and us saying those words! LOOK AT US NOW!

LOOK AT US – while we repack of our brains, we also pack tools…tools to pioneer new thought processes, tools to formulate new questions, tools to be a new wave of nurse scientist...tools with which we will build new knowledge – epistemologically speaking…

LOOK AT US NOW… to everyone here, go-ahead look around - remember these names and these faces for we are a generation of nurse scientists who are multi-talented, and the world has just become our playground.

So, everyone, take a look…look at this class of PhD graduates of the University of Pennsylvania, School of Nursing for 2011… But don't blink or look away, because once you do, you will miss the continuation of the repacking, you will miss epistemology in the making… because along the way, we found out, the unpacking and repacking – it doesn't end, it just changes. We will forever unpack and repack – it is through that process that tools for continued growth and advancement develop, it is through that process that innovations and innovators – my graduating colleagues, are discovered…

LOOK AT US NOW…I am humbled, proud and so very honored to have been nominated by you, my classmates to represent the 2011 PhD class…We walk out as newly graduated nurse scientists who have the ability to teach, to practice, to question and disseminate findings (please don't forget to publish!)…and through the process we will continue to add to the knowledge of the science of nursing

So, Dean Melesis, Ms Greco, Dr Savard, Dr Shalala, esteemed faculty, honored guests and friends – keep your eyes on us, WE ARE A FORCE!

LOOK AT US NOW!!!

Thank you.

The Acquisition of Knowledge

"The acquisition of knowledge is always of use to the intellect, because it may thus drive out useless things and retain the good. For nothing can be loved or hated unless it is first known."

Leonardo da Vinci