Temperature Instability Over Time and Respiratory Morbidity
in the Very Premature Infant

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy in Nursing
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ABSTRACT

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Abstract

Very premature infants are at risk for thermal instability due to thermoregulatory immaturity. Thermal instability upon neonatal intensive care unit admission has been associated with mortality and morbidity in these infants. Bronchopulmonary dysplasia (BPD), a developmental respiratory morbidity, is the most common complication of very premature birth. BPD is associated with admission temperature instability; however, its relationship with longitudinal temperature instability is poorly understood. An exploratory mixed-methods approach was used to examine the association between very premature infant temperatures over time and acute and chronic respiratory morbidities. The impact of daily care and respiratory care on infant body temperatures over time was also examined.

Research in the systematic literature review (Chapter 2) found that lower incubator temperatures can result in cold and dehumidified inspired air, and cold and dry inspired air can alter infant thermal stability. The studies in Chapter 3 and 4 found that infant temperatures (i.e., body, foot, abdominal-foot (temperature differential)) did not change significantly across the first five and 14 days of life, respectively. Daily care, respiratory care, and artificial respiratory support (i.e., MV, CPAP, RA) were associated with hypothermia. In addition, infants without chronic lung disease (CLD) had lower body temperatures and longer episodes of hypothermia compared to infants with CLD. Also, acute respiratory morbidities (i.e., bradycardia with desaturations and increases in supplemental oxygen and increased respiratory support) were associated with higher odds of hypothermia.

The relationships between hypothermia and both daily care and respiratory care support the need for bundling infant care, and potentially limiting care duration. The associations between hypothermia and respiratory support and acute and chronic respiratory morbidities should be explored further using advanced longitudinal methodologies. Ecological momentary assessment (EMA) can help delineate antecedent-consequence relationships to guide future intervention studies that are designed to reduce infant thermal instability over time and its associated morbidities.

Dedication

In loving memory of Joyce K. Harney

~Thank you for teaching my heart to care and my soul to never surrender.

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1. Introduction

1.1 Problem and Significance

1.1.1 BPD in Very Premature Infants

Approximately 55,000 very premature infants (≤1500 g) are born in the US each year (Martin, et al., 2018). The extremely immature pulmonary physiology of these infants predisposes them to the development of bronchopulmonary dysplasia (BPD). BPD occurs when there is an arrest of normal lung development following premature birth, resulting in large, sparse alveoli and dysmorphic pulmonary vasculature (Coalson, 1999; Martin, et al., 2015). BPD occurs in about half of very premature infants (Johnson, et al., 2013), making it the most common complication of very premature birth (Jobe, 2011). The incidence rate of BPD continues to rise due to the improved survival of the extremely premature infant (Stoll, 2015; Younge, et al., 2017), and additional morbidities such as asthma, developmental disability, pulmonary hypertension, and growth retardation have all been associated with BPD (Khetan, et al., 2016; Schmidt et al., 2003). Furthermore, a diagnosis of BPD can increase the cost of a very premature infant's neonatal intensive care unit (NICU) stay by two-fold, with about half of these infants requiring hospital readmission within their first year of life (Hong et al., 2016; Johnson et al., 2013).

Historically, BPD has been diagnosed clinically as oxygen dependency at ≥ 36 weeks postmenstrual age (PMA); however, to better capture the spectrum of the disease, severity based guidelines (i.e., mild, moderate, or severe) have been developed and adopted for diagnosis (Ehrenkranz et al., 2005; Kinsella, et al., 2006; McEvoy et al., 2014; Walsh et al., 2006). According to these guidelines, mild BPD is diagnosed by a supplemental oxygen (FiO_2) requirement of >21% for ≥ 28 days, with no FiO_2

requirement at 36 weeks PMA; moderate BPD is defined as a FiO_2 requirement of <30% at 36 weeks PMA; severe BPD is a FiO_2 requirement of ≥30% at 36 weeks PMA and/or positive pressure ventilation (i.e., mechanical ventilation (MV) or continuous positive airway pressure (CPAP) (Ehrenkranz et al., 2005).

The etiology of BPD is considered multifactorial, with a broad range of antecedents implicated in the development of the disease (Jobe, 2016). Artificial ventilation and supplemental oxygen are essential to the survival of the very premature infant yet are associated with pulmonary epithelial injury and reactive oxygen species (ROS), respectively, which can trigger a significant inflammatory response (Albertine, 2013; Jobe & Bancalari, 2001). If this inflammatory response persists, it can lead to pulmonary vasculature changes, characterized by smooth muscle proliferation and chronic vasoconstriction, thus resulting in a static reduction in the lumen of affected blood vessels (Wagenaar et al., 2014). Another risk factor identified in the development of BPD is inadequate thermoregulation (Lyu et al., 2015).

1.1.2 Thermoregulation in the Premature Infant

Although the ideal body temperature for a neonate is unknown, the World Health Organization (WHO) recommends maintaining infant body temperatures between 36.5°C to 37.5°C (World Health Organization, 2015). Very premature infants are highly susceptible to thermal instability due to the extreme immaturity of their thermoregulatory system (Guyton, 2016; Martin et al., 2015). These infants are also limited in their capacity for peripheral vasoconstriction during periods of hypothermia, which can lead to higher peripheral versus central temperatures (Knobel, et al., 2009; Knobel-Dail, et al., 2017). Temperature instability within the first hours of life has been strongly correlated with very premature infant morbidity, including BPD (Lyu et al., 2015). Further study has

shown that when body temperatures are maintained between 36.5° C to 37.2° C, the risk of morbidity is decreased (Lyu et al., 2015), thus suggesting a more narrow body temperature threshold for this population. To achieve and maintain these euthermic body temperatures, very premature infants receive auxiliary warming via controlled environments (i.e., incubators or radiant warmers); however, iatrogenic heat loss through conduction, convection, evaporation, and radiation can occur when these environments are disrupted during nursing care (Brandon, et al., 1999; Brandon, et al., 2007; Guyton, 2016; Martin et al., 2015). In addition, hyperthermia can occur if the incubator (or radiant warmer) exceeds the needs of the infant (Baumgart, 2008). While the WHO recommends that neonatal body temperatures not exceed 37.5° C (World Health Organization, 2015), the impact of hyperthermia on very premature infant outcomes is poorly understood, because thermoregulatory research in this population has historically concentrated on hypothermia associated outcomes (Ashmeade, et al., 2016; Castrodale & Rinehart, 2014; Lyu et al., 2015). After exploring the current literature, only one study was found that examined the potential association between hyperthermia and BPD. While a positive correlation was found, this cross-sectional study was limited to admission body temperatures (Lyu et al., 2015).

1.1.3 Respiratory Care Interventions

In addition to thermoregulatory system immaturity, a very premature infant's pulmonary-vascular system is significantly immature as well (Martin et al., 2015). This may result in dependence on positive pressure ventilation and/or supplemental oxygen for survival; however, these therapies have the potential to contribute to BPD directly by inducing an inflammatory response and/or indirectly by inducing body temperature instability (Jensen, & Schmidt, 2014; Kinsella et al., 2006; McEvoy & Aschner, 2015).

During normal respiration, the majority of the warming and humidification of inspired air is completed in the upper airway (Restrepo & Walsh, 2012). This process is interrupted or altered during artificial ventilation, so inspired air is routinely warmed and humidified to prevent complications (e.g., pulmonary epithelial damage, hypothermia, pneumothorax) associated with cold and dry gases (Restrepo & Walsh, 2012); however, studies have shown that conditioned gas temperatures and humidity levels can change significantly between the heater and the infant (Chang, et al., 2011; Davies, et al., 2004; Fassassi, 2007; Nagaya, et al., 2015; Yamada et al., 2008). Furthermore, if the inspired air temperature is outside current recommendations, it has the potential to alter infant body temperature (Lee & Lopez, 2002; te Pas, et al., 2010). Temperature instability can also occur when the infant receives artificial ventilation through positive pressure bag and mask ventilation, as the temperature and humidity of this air are significantly below recommended guidelines (Dawson, et al., 2014). Also, the simple act of entering the incubator to provide respiratory care can disrupt the well-controlled environmental temperature, which can lead to infant cooling (Mok, et al.,1991). This environmental cooling can also impact inspired air by causing the warmer inspired air to cool and dehumidify (Carter, et al., 2002; Davies et al., 2004; Nagaya, et al., 2009; Preo, et al., 2013; Yamada et al., 2008), thus placing the infant at risk for both pulmonary epithelial damage and body temperature instability.

1.1.4 Altered Temperatures on Respiratory Outcomes

Persistent body temperature instability in very premature infants results in ongoing oxygen consumption (Guyton, 2016); however, due to extreme pulmonary immaturity, these infants are unable to compensate for this increase in demand, so

hypoxemia/hypoxia and lactic/respiratory acidosis ensues (Martin et al., 2015). In response to hypoxemia and respiratory acidosis, supplemental FiO_2 and positive pressure ventilation are often increased. Reactive oxygen species (ROS) generated from supplemental FiO_2, and positive pressure ventilation have both been associated with pulmonary epithelial damage, which can trigger or sustain an inflammatory process that is strongly correlated with BPD (Jensen, & Schmidt, 2014; Kinsella et al., 2006; Martin et al., 2015; McEvoy & Aschner, 2015). While the association between acute temperature instability during the early hours of life and respiratory morbidity has been identified, the impact of longitudinal body temperature instability on the development of BPD has yet to be explored.

1.2 Study Design

The research in this dissertation was exploratory, mixed-methods, and correlational in design, using secondary analysis of recorded video, physiologic, and electronic health record data. The exploratory design provided an opportunity to gain insight into common problems and allowed for the examination of synchrony among variable variation (Bakeman, 2011). The small sample allowed for the collection of intensive longitudinal temperature and video data, and the use of mixed-methods supported the merging of multidimensional data (i.e., physiological, video, electronic health record) to examine the complex phenomenon of chronic lung disease. Therefore, this exploratory study allowed for an in-depth collection of data and intensive multi-level analysis that would not be feasible with larger studies (George, 2005). Although causation could not be inferred from this study design, it provided the opportunity to explore potential causal mechanisms within the very premature infant's natural

environment, thus allowing for the examination of relationships between longitudinal temperature instability and infant respiratory morbidity, as well as respiratory care events and body temperature instability over time (George, 2005).

1.3 Theoretical Framework: Inflammatory Systems Model

The Inflammatory Systems Model was created through the adaptation and integration of the Neuman Systems Model *(*Neuman*,* 2011*)*, the Decreased Temperature on Oxygenation Model (Knobel & Holditch-Davis, 2007) and the Human Inflammatory Response (Guyton, 2016) (see Figure 1).

The Neuman Systems Model provides a holistic framework that illustrates the interrelatedness between a very premature infant, his/her environment, and nursing in the maintenance or achievement of wellness (Neuman, 2011). The Inflammatory Systems Model expands this framework to include a study model derived from the Decreased Temperature on Oxygenation Model (Knobel & Holditch-Davis, 2007) and the Human Inflammatory Response (Guyton, 2016), which illustrates how longitudinal temperature instability (hypothermia and hyperthermia) can lead to BPD in very premature infants.

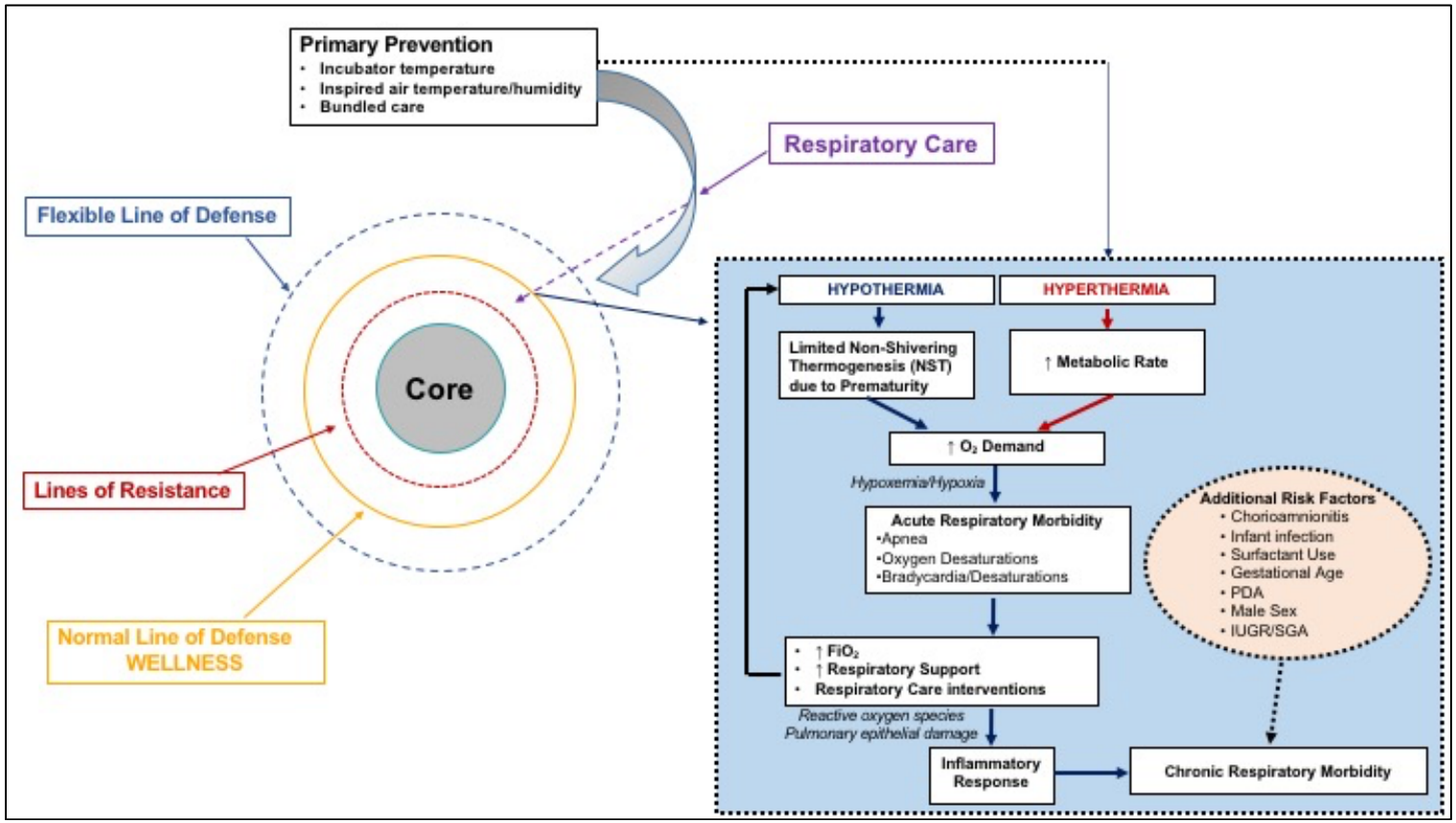

Figure 1: Inflammatory Systems Model

1.3.1 Modified Neuman Systems Model

The Inflammatory Systems Model contains several interrelated elements adapted from the Neuman Systems Model, including the client, the environment, the reaction, and nursing (see Table 1) (Neuman, 2011). The client system is the primary element of this model, and consists of several fundamental constructs: the basic structure/core, a flexible line of defense, a normal line of defense, and the lines of resistance (Neuman, 2011). This dissertation focuses on the very premature infant as the client system, with the core is defined as physiological stability, which is measured and operationalized by body temperature in Celsius (°C), heart rate (HR) in beats per minute, and oxygen saturation (SpO_2) in percentage.

1.3.1.1 Client

Several defensive mechanisms protect the basic core of a premature infant. The first line of defense that a stressor will encounter when trying to disrupt the physiological stability of an infant is the flexible line of defense. This flexible line expands or contracts based on the extent of infant balance. Respiratory, cardiovascular, and thermal stability are measures of infant balance. Respiratory stability is measured and operationalized by supplemental FiO_2, SpO2, and apnea; cardiovascular stability is measured and operationalized by HR and central-peripheral temperature difference (i.e., abdominal – foot temperature); thermal stability is measured and operationalized by abdominal temperature (°C). When respiratory, cardiovascular, and thermal stability is optimized, the infant is more resilient against stressors; however, if these are compromised, the infant's flexible line of defense shrinks, leaving her more susceptible to the impact of

Table 1: Theoretical Concepts and Variables

Construct	Concept	Variable	Operational Definition
Client (Very Premature Infant)			
Core	Physiological stability	Abdominal temp Heart rate Oxygen saturations	36.5 to 37.2 °C 120 to 160 beats per minute 90-100%
Flexible Line of Defense	Respiratory stability	Oxygen requirement Oxygen saturations Apnea	FiO_2 = 21% 90-100% None
	Cardiovascular stability	Central – peripheral temp Heart rate	Abd - foot temperature = 0 120 to 160 beats per minute
	Thermal stability	Abdominal temp	36.5 to 37.2 °C
Normal Line of Defense	Pulmonary growth & development	Respiratory support	MV; NIPPV; CPAP; HFNC; NC; RA
Lines of Resistance	Pulmonary inflammatory response	Atelectasis Pulmonary edema	Diagnosis on CXR Diagnosis on CXR
Environment			
Stressor	Healthcare interventions	Incubator air temp Respiratory air temp Respiratory care	<36.5°C or >37.2 °C <36.5°C or >37.2 °C ETT suctioning ETT saline instillation Taping of ETT Disconnection of ventilation circuit Bag & mask ventilation Intubation Removal of nasal prongs Surfactant administration Hands touching infant during care Portholes open during respiratory care
Nursing			
Primary Prevention	Prevention of illness	Respiratory air temp/humidity Abdominal temp Incubator temp Bundled care	36.5 to 37.2 °C/ 44mg/L 36.5 to 37.2 °C 36.5 to 37.2 °C
Secondary Prevention	Treatment of illness	Systemic steroids Bronchodilators Supplemental oxygen	 FiO_2 > 0.21
Tertiary Prevention	Re-adaptation & maintenance after illness	Caloric intake Fluid restriction Comfort measures	kcal/kg/day mL/kg/day

Abbreviations: temp=temperature; FiO_2= fraction of inspired oxygen; MV=mechanical ventilation; NIPPV=noninvasive positive pressure ventilation; CPAP=continuous positive pressure ventilation; HFNC=high flow nasal cannula; NC= nasal cannula; RA=room air; ETT=endotracheal tube

stressors. If this flexible line of defense is penetrated, the stressor will reach the infant's normal line of defense.

The normal line of defense refers to the infant's state of wellness, which occurs when more energy is available than used, and varies with time, development, and reconstitution following illness (Neuman, 2011). In this dissertation, wellness is measured in the very premature infant by pulmonary growth and development. Pulmonary growth and development are operationalized by the degree of respiratory support: MV, non-invasive positive pressure ventilation (NIPPV), CPAP, high flow nasal cannula (HFNC), nasal cannula (NC), or room air (RA). If the infant's wellness is compromised, the inner lines of resistance provide the final opportunity to protect their basic structure (Neuman, 2011). In this study, the inner lines of resistance are defined by the infant's pulmonary inflammatory response, which can contribute to and provide protection from invading and destructive forces. This response can be measured and operationalized by acute or chronic changes on CXR (e.g., atelectasis, pulmonary edema). If these mechanisms provide sufficient resistance to the stressor, the infant will regain wellness. However, if these final lines of resistance are ineffective or further perpetuate the impact of the stressor, significant morbidity or death will occur.

1.3.1.2 Environment

Another essential element in this model is the environment (see Table 1). This refers to any environmental stressor that has the potential to disrupt wellness (Neuman, 2011). The stressor in this dissertation refers to health care interventions, which are measured and operationalized by incubator and respiratory air temperatures (^{o}C), daily cares (e.g., diaper changes, oral care, nasogastric feedings) and respiratory care (e.g.,

ETT suctioning, removal of nasal prongs, disconnection of ventilation circuit). These stressors can impact infant temperature stability, which can stimulate the inflammatory response as described by the model. In addition, aberrant inspired air temperatures (i.e., cold/dry) can also stimulate the inflammatory response through direct pulmonary mucosal and ciliary damage (Restrepo & Walsh, 2012).

1.3.1.3 Nursing

The final element in this model is nursing, which is essential to the prevention and treatment of BPD and is categorized into primary, secondary, and tertiary prevention (see Table 1). Primary prevention refers to interventions that prevent illness or maintain wellness (Neuman, 2011). Interventions that focus on preventing hypothermia and hyperthermia are vital to premature infants' state of wellness and include maintaining optimal incubator and inspired air temperature/humidity levels, bundling care, and appropriate respiratory care. Primary prevention helps to protect the infant from environmental stressors by expanding the flexible line of defense. If these preventative measures fail, wellness is compromised, and the inflammatory response is triggered. This inflammatory response results in the initiation of secondary prevention. The goal of secondary prevention is to treat the illness and/or symptoms to regain wellness (Neuman, 2011). Secondary prevention of inflammatory lung disease often includes systemic steroids, which block the inflammatory response; an increase in total caloric goals in response to a high metabolic rate; bronchodilators due to an increase in airway tone; systemic antibiotics if mucosal damage results in infection; an increase in supplemental FiO_2 and/or respiratory support due to poor oxygen and carbon dioxide exchange (Baraldi & Filippone, 2007; Gomella, 2013; Martin et al., 2015). If secondary prevention is ineffective, death or significant morbidity will occur; however, if these

measures are effective, interventions will progress to tertiary prevention, which refers to re-adaptation and maintenance following lung inflammation. Tertiary prevention includes fluid restriction and scheduled diuretic therapy for the treatment or prevention of pulmonary edema, and comfort measures (e.g., minimal stimulation, bundled care, thermal stability, and adequate oxygenation) that decrease caloric consumption and the risk of bronchospasm, which promotes pulmonary growth and development (Gomella, 2013).

1.3.2 Study Model

The study model within the Inflammatory Systems Model was created from a modified version of the Decreased Temperature on Oxygenation Model (Knobel & Holditch-Davis, 2007) and the Human Inflammatory Response (see Figure 1) (Guyton, 2016; Martin et al., 2015). While the theory of inflammation continues to evolve and varies depending on the location and trigger for the process, this study used what is known regarding lung inflammation following the increased oxygen demands of body temperature extremes.

Due to the very premature infant's immature thermoregulatory system, it is dependent on auxiliary heat to maintain euthermia. When hypothermia occurs (due to inadequate auxiliary heating, aberrant inspired air, or respiratory care), non-shivering thermogenesis (NST) is activated (Knobel & Holditch-Davis, 2007). Because very premature infants are inefficient in generating heat through NST, hypothermia persists, thus increasing oxygen consumption (Guyton, 2016; Knobel & Holditch-Davis, 2007). Alternatively, if overheating through auxiliary means leads to hyperthermia, an increase in metabolic rate occurs, also leading to increased oxygen consumption (Guyton, 2016). The very premature infant's extremely immature pulmonary system is unable to

compensate for the increase in oxygen demand resulting in hypoxemia/hypoxia, lactic acidosis, oxygen desaturations, and eventually apnea (leading to respiratory acidosis) (Knobel & Holditch-Davis, 2007; Martin et al., 2015). Care providers compensate for this increase in oxygen demand and/or respiratory acidosis by providing/increasing supplemental FiO_2 and/or respiratory support, which can induce pulmonary epithelial damage from ROS and mechanical damage respectively (Martin et al., 2015; McEvoy & Aschner, 2015; McEvoy et al., 2014). Epithelial damage triggers an inflammatory response that precipitates further lung injury, resulting in chronic respiratory morbidity, including the structural and developmental abnormalities that define BPD (Jensen, & Schmidt, B., 2014; Jobe & Bancalari, 2001; Martin et al., 2015).

1.4 Purpose statement and dissertation aims

The purpose of this dissertation was to examine how daily respiratory care impacts very premature infant body temperature over time, and to examine the relationship between body temperature instability over time and acute and chronic respiratory morbidity in these infants. This dissertation addressed six aims in the following chapters:

1.4.1 Aim One

Introduction of the problem and significance of respiratory morbidity and body temperature instability in very premature infants (Chapter 1).

1.4.2 Aim Two

A systematic integrative review of the literature exploring the temperature and humidity levels of inspired air that very premature infants receive during artificial ventilation (Chapter 2).

1.4.3 Aim Three

Examination of the association between very premature infant body temperatures and respiratory care over the first five days of life (DOL). Specific research questions were: 1) What are the infant temperatures (i.e., body, foot, temperature differential) and incubator temperatures across the five DOL; 2) What is the association between the type of respiratory support an infant receives (i.e., MV, CPAP, and RA) and infant and incubator temperatures; 3) What is the association between care events and infant and incubator temperatures; 4) What is the association between care events and incubator temperatures while receiving different types of respiratory support; 5) What is the association between respiratory care events (e.g., suctioning, bag & mask ventilation) and infant and incubator temperatures; 6) What is the trajectory of infant body temperatures and incubator temperatures following the opening of the incubator portholes; 7) What is the trajectory of infant body temperatures an incubator temperatures following the closure of incubator portholes? (Chapter 3).

1.4.4 Aim Four

Examine the association between infant body temperatures over the first 14 DOL and symptoms of acute respiratory morbidity, as well as the outcome of chronic respiratory morbidity. Specific research questions included: 1) What is the association between infant temperature (i.e., body, foot, and temperature differential) and chronic respiratory morbidity; 2) What is the association between episodes of hypothermia and hyperthermia and chronic respiratory morbidity; 3) What is the association between infant temperature (i.e., abdominal, foot, and temperature differential) and concurrent biomarkers for acute respiratory morbidity (i.e., oxygen desaturations, bradycardia with

desaturations, apnea, increased FiO_2 requirement, and increased respiratory support)? (Chapter 4).

1.4.5 Aim Five

Synthesis of the findings from the chapters in this dissertation, present implications for nursing practice, and propose future research directions (Chapter 5).

2. Temperature and Humidity Associated with Artificial Ventilation: An Integrative Review of the Literature

Approximately 55,000 very low birth weight (VLBW) infants (≤1500 grams) are born in the United States each year (Martin, et al., 2018). Due to the extreme immature physiology of these infants, pulmonary morbidities like bronchopulmonary dysplasia (BPD) occur in about 50% of these infants (Stoll, 2015), making BPD the most common complication of the very premature infant (Islam, et al., 2015; Jobe, 2011). BPD is the abnormal development of alveoli and lung vasculature, and is broadly diagnosed by oxygen dependency beyond 36 weeks post menstrual age (Ehrenkranz et al., 2005; Walsh et al., 2006). A diagnosis of BPD increases the risk of additional morbidities, including growth retardation, developmental disabilities, asthma, and pulmonary hypertension (Khetan et al., 2016). In addition, a diagnosis of BPD has been shown to double the cost of an infant's initial hospital stay, and approximately 60% these infants will require readmission within the first year of life (Hong et al., 2016; Johnson et al., 2013).

Normal lung maturation requires a sequence of structural development, which is interrupted when an infant is born prematurely (Martin et al., 2015). BPD occurs when aberrant lung development results in large, sparse alveoli and dysmorphic vasculature, which results in a smaller surface area available for gas exchange (see Figure 2) (Coalson, 1999; Martin et al., 2015).

The etiology of BPD is considered multifactorial including the influence of both invasive and non-invasive artificial ventilation (Davies et al., 2004; Kinsella et al., 2006).

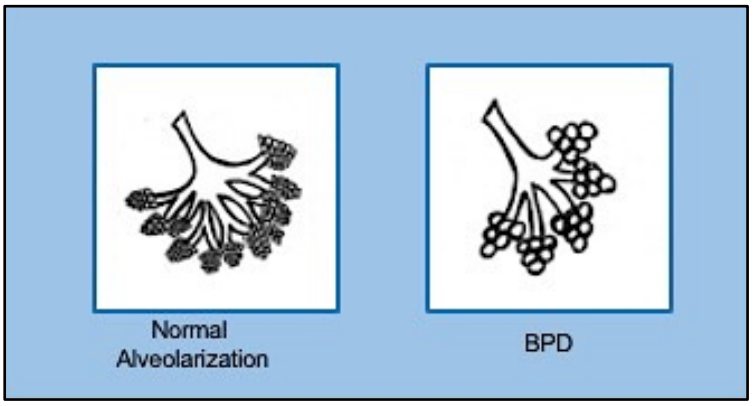

Figure 2: Abnormal Alveolarization Associated with BPD

The immature lung of the VLBW infant is unable to function adequately for survival (Martin et al., 2015), thus requires respiratory support and/or supplemental oxygen. Although these therapies are essential to survival, positive pressure ventilation has been associated with barotrauma, volutrauma, and atelectotrauma (see Table 2 for descriptions), which can result in epithelial damage that triggers an inflammatory response (Coalson, 1999; Martin et al., 2015; Walsh et al., 2006). This response is associated with an influx of white blood cells and inflammatory cytokines, which can precipitate further lung injury resulting in the structural and developmental abnormalities that define BPD (Jiang, et al., 2015; Jobe & Bancalari, 2001).

Table 2: Potential Lung Trauma from Invasive and Non-invasive Ventilation

Barotrauma	Volutrauma	Atelectotrauma
Injury resulting from excessive pressure exerting within the airways and alveoli.	Injury resulting from an excess of air volume within the airways and alveoli.	Injury resulting from repetitive collapse and reopening of alveoli.

Alterations in inspired air temperature/humidity from artificial ventilation have also been shown to cause pulmonary epithelial damage, thus inducing this same inflammatory response (Beam et al., 2014; Davies et al., 2004). The humidification of

inspired air is usually denoted as absolute or relative humidity. Absolute humidity (mg/L or g m^{-3}) is a measurement of water vapor in a gas while relative humidity (%) refers to the water vapor relative to 100% saturation of that gas (Schulze, 2007; Thompson, 2016). The relationship between absolute humidity (AH) and relative humidity (RH) is static, yet the values are dependent on air temperature: at 37.0°C, inspired air is fully saturated (RH of 100%) at an AH of 44mg/L; at 32°C, full saturation (RH of 100%) occurs at an AH of 30mg/L. Thus, warmer air is able to carry more water vapor (i.e. higher AH), and as saturated air cools, it loses water vapor (i.e. lower AH) (Schulze, 2007). The average temperature of unconditioned inspired air is closely associated with ambient room temperature (~23.0°C), and the average RH is extremely low at 5.4% (Dawson et al., 2014). Under normal conditions, inspired air is warmed and humidified as it passes through the upper airway, reaching almost full saturation within 0.5°C of body temperature at the level of the trachea (Guyton, 2016; Restrepo & Walsh, 2012); however, when the upper airway is bypassed during mechanical ventilation, the conditioning of the gas can be reduced by as much as 75% (Restrepo & Walsh, 2012). The consequence of noninvasive ventilation on the function of normal upper airway warming and humidification in the premature infant is unclear, which may be particularly significant when the mode of noninvasive ventilation utilizes a nasal apparatus that partially or completely bypasses the nasal conchae and septum (where the vast majority of warming and humidification occurs) (Guyton, 2016). Due to the potential lung injury from cold and dry gases, ventilator breaths are artificially warmed and humidified to the current national recommendations of 34° C to 41° C and 33 to 44 mg/L respectively (Restrepo & Walsh, 2012); however, recent animal studies described a significant decrease in lung pathology and inflammation with absolute humidity levels of >40 mg/L

during artificial ventilation (Jiang et al., 2015), thus supporting a humidification goal closer to physiological levels of 44 mg/L (full saturation at a core body temperature of 37.0^{o} C) (Schulze, 2007). In addition, neonatal research has shown that inspired air temperatures and AH levels below 36.5^{o} C and 37.0 mg/L respectively are associated with increased risk of pneumothorax, chronic lung disease (Lyu et al., 2015; Tarnow-Mordi, et al., 1989), and inadequate thermal stability in the very premature infant (Lee & Lopez, 2002; Meyer, et al., 2015; te Pas et al., 2010).

The consequences of aberrant inspired air temperatures on thermal stability can be significant, as hypothermic body temperatures have been associated with an increased risk of morbidity and mortality in VLBW infants (Chang et al., 2015; Laptook et al., 2018; Lyu et al., 2015), and very premature infants have limited capacity to respond effectively during periods of temperature instability due to the extreme immaturity of their thermoregulatory system (Guyton, 2016; Martin et al., 2015). While adults and children (≥12 months of age) rely on thermogenesis (i.e. shivering) for heat production during acute episodes of hypothermia, neonates are unable to generate heat through shivering, thus rely on nonshivering thermogenesis (NST) when hypothermic (Guyton, 2016). NST is the production of heat through the sympathetic stimulation of brown adipose tissue (i.e., brown fat) (Guyton, 2016; Knobel-Dail et al., 2017). The VLBW infant has limited ability to generate heat through NST due to insufficient brown fat (prior to 25 weeks GA), as well as limited quantities of essential components of fat metabolism: thermogenin and 5'-monodeiodinase (prior to 32 weeks GA) (Houstek et al., 1993; Knobel-Dail et al., 2017). Thus, as hypothermia persists due to ineffective NST, oxygen is consumed for heat production (Knobel & Holditch-Davis, 2007). Due to the extreme immaturity of the pulmonary system, VLBW infants are unable to compensate for this increase in oxygen

consumption, resulting in hypoxemia/hypoxia and lactic acidosis (Martin et al., 2015). In addition, acidosis, hypoxemia, and temperature instability can lead to apnea in the premature infant, resulting in respiratory acidosis and worsening hypoxemia due to ineffective respiratory gas exchange (Martin et al., 2015). Therefore, the impact of aberrant inspired air temperatures may extend beyond the VLBW infant's pulmonary system alone, potentially influencing their global physiological stability as well. Because altered temperature and humidity levels contribute to the development of BPD, and may contribute to thermal instability, further investigation into the temperature and humidity of neonatal ventilation is warranted.

2.1 Objective

The purpose of this literature review is to explore what is known regarding inspired air temperature/humidity levels from artificial ventilation (both invasive and noninvasive modalities) in very premature infants. This review examines the range of heated humidifier (HH) temperature settings used as standard of care for infants hospitalized in neonatal units, what temperature/humidity levels these infants actually receive, and what factors impact these levels. Synthesis of the literature will provide insight into the potential association between inspired air temperature/humidity levels from artificial ventilation and respiratory morbidity in the very premature infant. Future research can be designed to investigate these potential associations, as well as, the impact of inspired air temperature/humidity levels on VLBW infant body temperature, so measures can be taken to decrease morbid outcomes in this vulnerable population.

2.2 Method

PubMed, Scopus, CINAHL, and Web of Science search engines were used to retrieve articles associated with the inspired air temperature and/or humidity levels used in the artificial ventilation of premature infants. The initial search was delimited to the premature infant; however, this was expanded to include all infants less than 28 days of age during the final query on January 5, 2018, because little research was available within the premature infant population, and the heating and humidification practices in artificial ventilation are consistent across the neonatal population. Inclusion criteria was limited to articles written in English. No limits were placed on publication dates, because very few articles were retrieved with this delimiter. Initially, only human studies were to be utilized for this literature review; however, only eight substantially old (9 to 45 years since publication) human studies were retrieved, so studies utilizing artificial lung models (1 to 15 years since publication) were retained, because these more current studies were likely to employ current temperature/humidification practices. In addition, the artificial lung models allowed for the manipulation of both the HH and environmental (incubator, radiant warmer, or ambient room) temperature settings, which was limited in the human studies.

MESH terms were used in PubMed and Scopus to retrieve the most relevant citations. These MESH terms included: “infants, newborn,” “respiration, artificial,” “noninvasive ventilation,” “continuous positive airway pressure,” and “temperature.” The CINAHL search, which utilized subject terms, included: “infant, newborn,” “respiration, artificial,” “positive pressure ventilation,” “continuous positive airway pressure,” and “temperature.” The Web of Science search utilized subject terms with wild cards (*)

Table 3: Summary of Database Search

Database	Search Filters	Search Terms	Citations returned
PubMed	English	"Infant, newborn" [MESH] AND "Respiration, artificial" [MESH] OR "Noninvasive ventilation" [MESH] OR "Continuous Positive Airway Pressure" [MESH] AND "Temperature" [MESH]	336
Scopus	English, Article, & Review	"Infant, newborn" [MESH] AND "Respiration, artificial" [MESH] AND "Temperature" "Infant, newborn" [MESH] AND "Noninvasive ventilation" AND "Temperature" 'Infant, newborn" [MESH] AND Continuous Positive Airway Pressure" [MESH] AND "Temperature" [MESH]	197
CINAHL	English, & Academic journals	"Infant, newborn" AND "Respiration, artificial" AND "Temperature" "Infants, newborn AND "Positive pressure ventilation" AND "Temperature" "Infants, newborn" AND "Continuous positive airway pressure" AND "Temperature"	57
Web of Science	English, Article, & Review	"Neonat*" AND "Ventila*" "Neonat*" AND "Noninvasive ventilation" "Neonat*" AND "Continuous Positive Airway Pressure"AND "Temperature"	240

to increase the likelihood of retrieving relevant citations and included: "neonat*," "ventila*," "noninvasive ventilation," "continuous positive pressure ventilation," AND "temperature." Table 3 illustrates the PubMed, Scopus, CINAHL, and Web of Science search terms, and the results from each search.

These search engines identified 830 citations, which were imported into EndNote™ with 171 duplicates identified and removed. An additional four articles were identified through snowballing. After title or abstract review, 637 articles were discarded because they were not associated with the direct measurement of inspired air temperature or humidity. There were 26 articles assessed for eligibility by full-text review. One article was discarded, because it evaluated temperature/ humidity levels

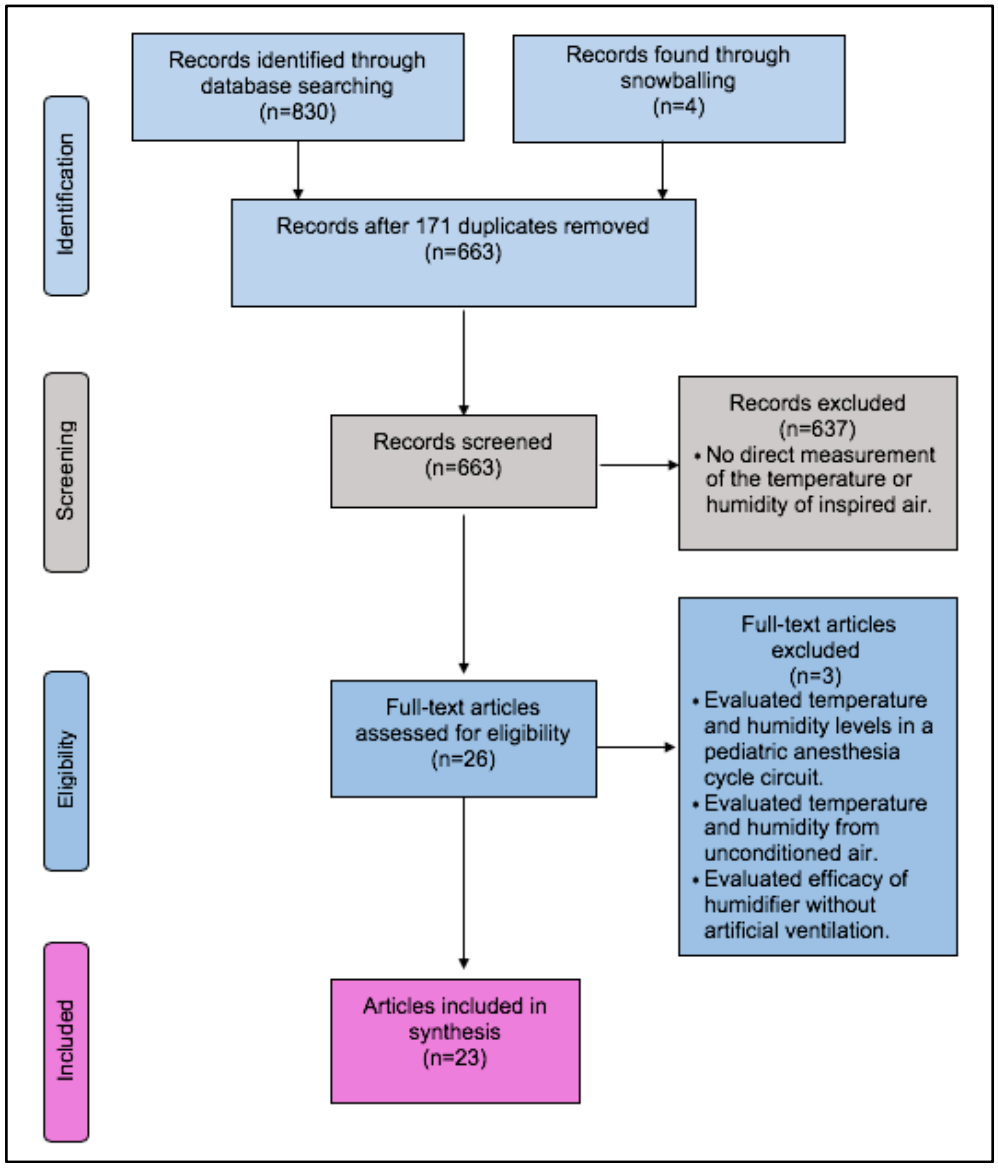

Figure 3: PRISMA© Flow Diagram

from a pediatric anesthesia cycle circuit. A second article was discarded because results only evaluated the temperature/humidity of unconditioned air, and a third article was discarded as it utilized a mathematical model to evaluate the efficacy of a HH without artificial ventilation. The PRISMA© (Moher, et al., 2010) flow process resulted in 23

articles (see Figure 3), which were organized using the Matrix Method and synthesized for review (Garrard, 2014).

2.3 Results

Data from these 23 studies were organized under several Matrix headings, including: year/author, study purpose, sample/study design, and temperature/humidity findings (Garrard, 2014) (see Appendix A). The studies used quantitative methods, focusing on the collection and analysis of recorded inspired air temperature and/or humidity measurements. Eight human studies were retrieved, which included six observational studies, one prospective randomized controlled study, and one retrospective study. The sample sizes ranged from 14 to 149 infants. The remaining 15 studies were observational studies performed on artificial lung models. Synthesis of the Matrix revealed several themes associated with the inspired air temperature and/or humidity from neonatal artificial ventilation, including changes from the humidifier to the infant, artificial ventilation settings, environmental temperature, and infant mouth position (Garrard, 2014). One article measured inspired air temperatures, but did not fit under any of the above themes.

2.3.1 Changes from Humidifier to Infant

Results from 13 of the 24 studies showed that the temperature and/or humidity of inspired air decreased when measured from the HH exit or HH temperature setting to the infant (see Appendix A) (Carter et al., 2002; Chang et al., 2011; Davies et al., 2004; Fassassi, 2007; Jardine, et al., 2008; O'Hagan, et al., 1991; Preo et al., 2013; Schiffmann et al., 1997; Tarnow-Mordi, et al., 1986; Tarnow-Mordi, et al., 1986; Todd, et al., 2001; Yamada et al., 2008). Researchers found inspired air changes between the

HH and the infant in six observational human studies (Davies et al., 2004; Fassassi, 2007; O'Hagan et al., 1991; Schiffmann et al., 1997; Tarnow-Mordi, et al., 1986; Tarnow-Mordi, et al., 1986) and seven artificial lung models (Carter et al., 2002; Chang et al., 2011; Jardine et al., 2008; Preo et al., 2013; Todd et al., 2001; Yamada et al., 2008). These studies documented a decline between inspired air temperatures exiting the HH (or HH temperature setting) and the infant of 1.4° C to 11.0° C, with air temperatures (proximal to the infant) ranging between 32.3°C to 36.8°C (Chang et al., 2011; Davies et al., 2004; Fassassi, 2007; Jardine et al., 2008; O'Hagan et al., 1991; Preo et al., 2013; Schiffmann et al., 1997; Yamada et al., 2008). In addition, seven studies measured absolute humidity, with mean levels declining to between 26.0mg/L to 37.9mg/L (G. Y. Chang et al., 2011; Fassassi, 2007; O'Hagan et al., 1991; Preo et al., 2013; Schiffmann et al., 1997; Tarnow-Mordi, Fletcher, et al., 1986; Tarnow-Mordi, Sutton, et al., 1986). In a similar study, the position of the HH air temperature probe (ATP) was found to impact the decline in temperature between the HH and the infant. The ATP is located at the end of the inspiratory circuit to help ensure stable air temperatures along the length of the circuit (see Figure 4). While these researchers found stable inspired air

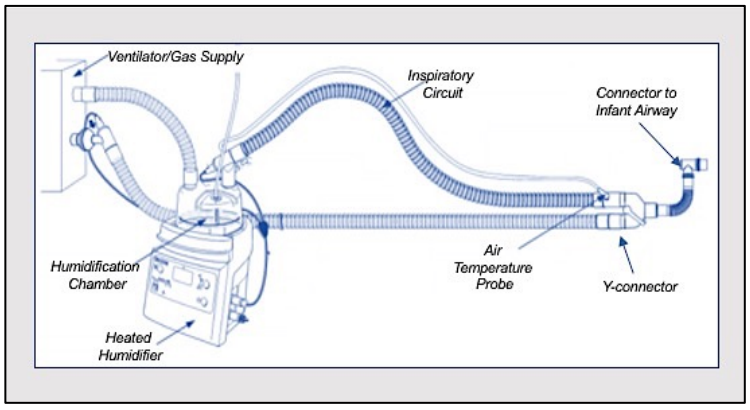

Figure 4: Heated Humidifier with Wire Circuit

temperatures when the ATP was within the incubator, inspired air temperatures as low as 30.8º C were measured prior to entering the infant when the ATP was located outside the incubator (Todd et al., 2001b). In addition to these findings, inspired air humidification was found to vary by HH model. A study of five different heater models recorded humidity levels ranging between 29.5 mg/L to 37.9 mg/L prior to it entering the infant (Tarnow-Mordi, et al., 1986). Overall, the findings from these studies revealed that the inspired air temperature and/or humidity levels from artificial ventilation were poorly controlled and frequently below levels shown to decrease morbidity in very premature infant (36.5ºC and 37mg/L respectively) (Tarnow-Mordi, et al., 1986; Tarnow-Mordi, Sutton, et al., 1986).

2.3.2 Artificial Ventilation Settings

Ten of the 23 studies retrieved from this literature review showed that ventilator settings may impact the temperature and/or humidity of inspired air (see Appendix A) (Chang et al., 2011; Chikata, et al., 2009; Epstein, 1971; Nagaya et al., 2009; Nagaya et al., 2015; Roberts et al., 2016; Schena, et al., 2013; Schiffmann et al., 1999; Tarnow-Mordi, et al., 1986; Yamada et al., 2008). Eight of these studies used artificial lung models in observational designs (Chang et al., 2011; Chikata et al., 2009; Nagaya et al., 2009; Nagaya et al., 2015; Roberts et al., 2016; Schena et al., 2013; Schiffmann et al., 1999; Yamada et al., 2008) and two were observational human studies (Epstein, 1971; Tarnow-Mordi, et al., 1986). Lower inspiratory temperatures were associated with lower minute volumes (MV) in two studies (Epstein, 1971; Yamada et al., 2008), and while these findings were not supported by Schena et al. (2013), they did document that an increase in both respiratory rate and MV were associated with a significant decrease in

inspired air humidity. Tidal volume was also noted to impact inspired air temperature/humidity levels (Chikata et al., 2009; Nagaya et al., 2009). A direct correlation between tidal volume and both inspired air temperature (with high frequency oscillatory & intermittent positive pressure ventilation) (Nagaya et al., 2015) and AH (with high frequency ventilation) (Chikata et al., 2009) were noted. In addition, flow rate was shown to impact inspired AH. One study found a direct correlation between flow rate and both inspired air temperature and AH (with HFV) (Nagaya et al., 2009), yet an inverse relationship between flow rate and AH during HFOV was noted in another study (Schiffmann et al., 1999). Other researchers found that the correlation between flow rate and AH was dependent on the HH model (Tarnow-Mordi, et al., 1986). Furthermore, investigation into noninvasive therapies documented variation in inspired air temperature/humidity levels between models, modes, and settings (Roberts et al., 2016). Overall, these studies demonstrate that significant variation in inspired air temperature/humidity can occur between artificial ventilation modalities, thus highlighting that control of temperature/humidity levels in neonatal ventilation requires not only the programming and management of therapeutic HH systems, but the understanding of how those systems interact with different artificial ventilation modes and settings.

2.3.3 Environmental Temperature

The effect of environmental temperature (including incubator air temperature and the impact of a radiant warmer) on the temperature/humidity of inspired air was noted in 12 of the 23 studies, including nine artificial lung designs (Carter et al., 2002; Nagaya et al., 2009; Nagaya et al., 2015; Preo et al., 2013; Todd et al., 2001; Yamada et al., 2008; Yusuke, et al., 2017) and four human observational designs (see Appendix A) (Davies et al., 2004; Fassassi, 2007; O'Hagan et al., 1991; Schiffmann et al., 1997). Ten of these

studies revealed a direct correlation between the environmental air temperature and the temperature of inspired air (Carter et al., 2002; Davies et al., 2004; Fassassi, 2007; Nagaya et al., 2009; Nagaya et al., 2015; O'Hagan et al., 1991; Preo et al., 2013; Todd et al., 2001; Yamada et al., 2008; Yusuke et al., 2017), while three studies noted an inverse relationship between environmental temperature and the AH of inspired air (O'Hagan et al., 1991; Schiffmann et al., 1999; Todd et al., 2001). In addition, studies comparing the impact of incubators versus radiant warmers, documented significantly lower inspired air temperature (Davies et al., 2004) and AH (O'Hagan et al., 1991; Schiffmann et al., 1997) values when infants were nursed under radiant warmers. The findings from these studies demonstrate the potential impact that an infant's environment may have on the inspired air temperature/ humidity of artificial ventilation, thus warrants further investigation.

2.3.4 Infant Mouth Position

One study utilized an artificial mouth to evaluate the influence of an open versus closed mouth on oropharynx temperature during continuous positive airway pressure (see Appendix A). Results from this study showed a decrease in both oropharynx temperature (~2^{o}C) and AH (~6.9g m^{-3}) in an open versus closed mouth (Fischer, et al., 2017).

2.3.5 Limitations of Studies

The studies included in this literature review had several limitations, which threaten the internal and external validity of the findings, including: the use of artificial lung models, which do not accurately replicate the human lung or the thermoregulatory physiology of a neonate; all human studies were observational with small sample sizes

(14 to 48 neonates), and 17 of the 23 studies had publication dates greater than 5 years (6 to 45 years). Furthermore, due to the age of these studies, the equipment and measurement tools are likely outdated, which challenges their relevance in current neonatal care.

2.4 Discussion

The purpose of this literature review was to explore what is known regarding inspired air temperature/humidity in premature infant ventilation (invasive and non-invasive modalities), with a focus what levels these infants actually receive, and what factors impact these levels. Synthesis of the literature has shown that prevailing warming and humidification practices, used in neonatal ventilation, resulted in variable and inconsistent temperature/humidity levels. Results from existing research suggest maintaining inspired air temperatures >36.5° C and AH levels > 37.0 mg/L in VLBW infants (Tarnow-Mordi et al., 1989), yet eleven of these studies revealed that heating practices did not meet these standards (Chang et al., 2011; Davies et al., 2004; Fassassi, 2007; Jardine et al., 2008; O'Hagan et al., 1991; Preo et al., 2013; Schiffmann et al., 1997; Tarnow-Mordi, et al., 1986; Todd et al., 2001; Yamada et al., 2008). The validity of these findings is unclear as the human studies are quite old, and the new studies employed artificial lung models, which do not represent true neonatal respiratory physiology. It will be important for future studies to include current heating and humidification practices with human neonatal samples to increase the validity of the temperature and AH values obtained. Once this is complete, interventional studies, focusing on measures to obtain and maintain recommended inspired air temperature/humidity levels, can be conducted.

Findings from many studies in this review also showed an association between environmental air temperature, and the temperature/humidity of the inspired air (Carter et al., 2002; Davies et al., 2004; Dawson et al., 2014; Fassassi, 2007; Nagaya et al., 2009; Nagaya et al., 2015; O'Hagan et al., 1991; Preo et al., 2013; Schiffmann et al., 1997; Todd et al., 2001; Yamada et al., 2008; Yusuke et al., 2017). This may be attributed to the slower flow rates used in neonatal ventilation, which increases the exposure time of the air within the inspiratory circuit (and all tubing proximal to the infant) to the cooler environmental temperature. As the heat from the warmer inspired air is conducted to the cooler environmental air (incubator and/or ambient room) (Guyton, 2016), the inspired air temperature drops, and as a result its capacity to hold water vapor decreases (i.e., AH decreases), which is often illustrated by condensation in the inspiratory circuit (see Figure 5). This is an important finding, as incubator temperatures

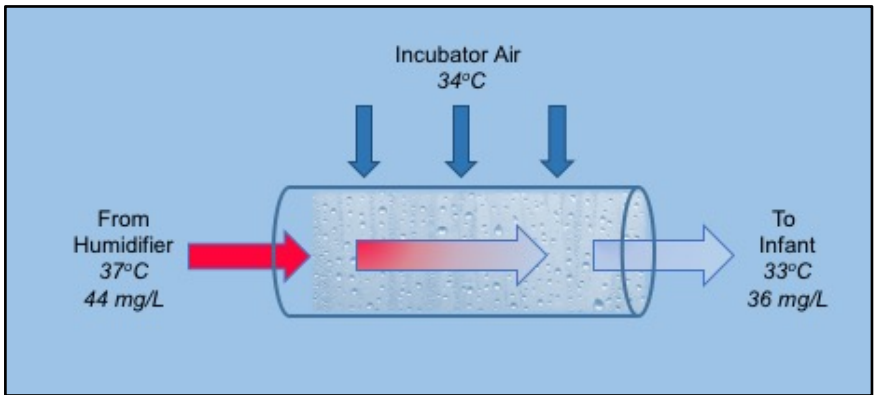

Figure 5: Inspired Air/Humidity Along Inspiratory Respiratory Circuit.

are routinely weaned over time, based on the skin and thermoregulatory development of the infant (New, et al., 2011). The potential impact of incubator air temperature on ventilation is rarely considered; however, incubators may contribute to the development of BPD if cooler incubator air results in inspired air temperature/humidity levels falling

below recommendations. In addition, as premature infants with ongoing respiratory requirements continue to grow and develop, they are transitioned from heated incubators to an open crib environment (Gomella, 2013; Knobel, 2014), thus increasing the chance of inspired air temperatures cooling toward ambient room temperature, which is a significant variant from current recommendations (Restrepo & Walsh, 2012; Tarnow-Mordi et al., 1989). This review also highlighted the difference in the inspired air temperature/humidity between infants nursed in incubators versus radiant warmers. This may be contributed to inspiratory circuit exposure to the cooler ambient room temperature, or radiant overheating of the ATP, thus resulting in falsely elevated temperature readings (signaling the humidifier to decrease heat output) (Schulze, 2002). Finally, research has shown that aberrant inspired air temperature/humidity levels can result in hypothermia in the very premature infant (Lee & Lopez, 2002; Meyer et al., 2015; te Pas et al., 2010). Since many of the studies included in this review documented inspired air temperature/humidity levels below recommendations, it raises the concern that current heating and humidification practices have the potential to contribute to hypothermia in this vulnerable population.

An additional goal of this literature review was to investigate what is known regarding the inspired air temperature and humidity levels of noninvasive neonatal ventilation; however, only two studies were retrieved that measured these parameters (Fischer et al., 2017; Roberts et al., 2016). These researchers documented a decrease in the temperature and/or humidity of the inspired air between the heater and the infant (Roberts et al., 2016) or a drop in temperature/humidity with mouth positioning (open vs. closed) (Fischer et al., 2017). How this may impact inspiratory air temperature/humidity levels beyond the oropharynx or the potential implications of these aberrant levels on

infant temperature is unclear. Since noninvasive ventilation has been shown to decrease the need for intubation, this therapy is used frequently in clinical practice (Goldsmith, 2017; Lemyre, et al., 2017; Roberts et al., 2016), thus this gap in the literature requires further investigation.

2.4.1 Implications for Practice

Based on the findings from this literature review, current heating and humidification practices are unlikely to maintain recommended temperature/humidity levels, thus it is essential for healthcare providers to take measures to minimize this change. The potential impact of environmental temperature on inspired temperature/humidity is a significant finding that healthcare providers can minimize. First, managing incubators to maintain air temperatures > 36.5^{o}C, for very premature artificially ventilated infants, will prevent cooler incubator air from causing inspired air temperatures to drop below recommended levels. While this may delay current incubator weaning guidelines, and associated blanket bundling, the benefit of this change is worth considering when possible. In addition, providing bundled care, thus minimizes the risk of disrupting the warm incubator environment, should be a priority. Furthermore, when infants are nursed under radiant warmers, it is important to block the ATP (with a reflective material) from the radiant heater or to move the ATP outside the radiant field, thus decreasing the risk of falsely elevated air temperature readings. It is also essential to closely monitor and maintain appropriate water levels within the HH chamber, because a dry HH not only provides significantly under humidified inspired air, this warm/dry air cools prior to substantially warming the pulmonary epithelium (Schulze, 2007). Finally, it is vital for practitioners to monitor infant body temperature closely while receiving artificial ventilation. Since aberrant inspired air temperature/humidity levels

have the capacity to impact infant body temperature (Lee & Lopez, 2002; Meyer et al., 2015; te Pas et al., 2010), and hypothermia increases the risk of mortality and morbidity in very premature infants (Chang et al., 2015; Laptook et al., 2018; Lyu et al., 2015), it is crucial that practitioners take measures to maintain stable infant body temperatures.

2.4.2 Limitations of this Literature Review

The main limitation of this literature review is that the database search was limited to the English language, which has the potential to exclude relevant untranslated studies.

2.5 Conclusion

Overall, this literature review underscores the need for further research examining the warming and humidification techniques of invasive and non-invasive ventilation in the premature infant population. With these data, the management of inspired air temperature and humidification can be standardized to optimize infant outcomes. Furthermore, researchers should examine the impact of environmental temperature and ventilator settings on inspired air temperature/humidity levels, as well as, the impact of aberrant temperature/humidity levels on premature infant body temperature. Without this valuable information, neonatal healthcare providers are limited in their ability to control for this known antecedent to BPD, as well as, it's potential to contribute to mortality and additional morbidity in the premature infant

3. Exploring the Association Between Very Premature Infant Body Temperatures and Respiratory Care

3.1 Introduction

Approximately 52,000 very premature infants (≤1500 grams) are born in the United States each year (Martin, et al., 2018). Due to their extreme prematurity, these infants have global body system immaturity (Martin et al., 2015). The immaturity of the very premature infant's thermoregulatory system inhibits their ability to achieve or maintain normal body temperatures (36.5^{o}C to 37.2^{o}C) independently (Knobel, 2014; Martin et al., 2015). Body temperature instability upon neonatal intensive care unit (NICU) admission has been associated with an increased risk of mortality and morbidity among these infants (Ashmeade et al., 2016; Castrodale & Rinehart, 2014; Lyu et al., 2015). The most common morbidity of very premature birth is bronchopulmonary dysplasia (BPD) (Jobe, 2011). BPD is the abnormal development of alveoli and pulmonary vasculature following premature birth (Jobe, 2011; Kinsella et al., 2006), and it is associated with admission temperature instability (Lyu et al., 2015).

The very premature infant's underdeveloped skin and reduced quantities of subcutaneous fat (Uthaya et al., 2005) contribute to heat loss, while autonomic immaturity impedes the normal process of thermoregulation (Knobel, et al., 2011; Knobel et al., 2009; Lyon, et al., 1997). Typically, during acute periods of hypothermia, the body generates heat through shivering (i.e., thermogenesis) (Guyton, 2016); however, neonates cannot generate heat through shivering, thus are reliant on nonshivering thermogenesis (NST) (Guyton, 2016). NST is the production of heat through the sympathetic stimulation of brown adipose tissue (i.e., brown fat) (Guyton, 2016; Knobel-Dail et al., 2017). The increased metabolic demand of NST stimulates glycolysis (Jeong,

et al., 2018), which can consume the limited energy stores of the very premature infant. These infants also have reduced quantities of essential components (i.e., thermogenin and 5'-monodeiodinase) of brown fat metabolism (Houstek et al., 1993; Knobel-Dail et al., 2017); thus, they are reliant on additional forms of heat production, including oxygen metabolism (Knobel & Holditch-Davis, 2007). However, due to the extreme immaturity of their pulmonary system, very premature infants are unable to compensate for an increase in oxygen consumption (Marks, et al., 1981). Therefore, hypothermia can persist as glucose and oxygen are depleted, leading to further physiological decompensation (e.g., hypoxemia, acidosis) (Knobel & Holditch-Davis, 2007).

Peripheral vasoconstriction is another normal physiological response to hypothermia. In the presence of peripheral vasoconstriction, body temperature is raised by increasing central perfusion (Lyon et al., 1997). However, very premature infants are unable to effectively peripherally vasoconstrict under hypothermic conditions due to poor vasomotor tone (Corbisier de Meautsart et al., 2016; Knobel-Dail et al., 2017; Knobel-Dail, et al., 2016; Lyon et al., 1997). Foot temperature has been shown to be a strong predictor of peripheral perfusion in these infants, with warmer foot temperatures associated with an increase in peripheral perfusion (Knobel-Dail et al., 2016); thus abnormal peripheral vasomotor tone can manifest as a positive or negative (> or < 0) abdominal-foot temperature differential (i.e., temperature differential) (Knobel-Dail et al., 2017; Knobel-Dail et al., 2016; Lyon et al., 1997).

In order to achieve thermal stability, very premature infants require auxiliary heat (e.g., incubator, radiant warmer) until their thermoregulatory system matures (Guyton, 2016). Because these infants are dependent on supplemental heat, they are at significant risk for thermal instability when these therapies fail to meet their needs.

Additionally, due to extreme pulmonary immaturity, these infants require respiratory support (e.g., mechanical ventilation (MV), continuous positive airway pressure (CPAP)) after birth. However, if the inspired air is inadequately warmed and humidified, it can impact infant thermal stability [Chapter 2] (Ralphe & Dail, 2018; te Pas et al., 2010). Furthermore, the daily nursing care (e.g., touching, stethoscopes, cleansing wipes) and respiratory care interventions (e.g., ETT suctioning, saline administration, nasal prong care) essential for very premature infant survival can impact body temperature through direct contact with the infant or indirectly by disrupting incubator temperature (Mok et al., 1991). While it is recognized that nursing care (Mok et al., 1991) and aberrant inspired air temperature and humidity from respiratory support [Chapter 2] (Ralphe & Dail, 2018) have the potential to induce heat loss through convection, conduction, evaporation, and radiation (Guyton, 2016; Martin et al., 2015), the impact of respiratory care on infant thermal stability is unclear. Therefore, the purpose of this study was to examine the association between respiratory care and infant body temperatures over time.

The overarching goal of this exploratory study was to examine the association between respiratory care and very premature infant body temperatures during the first five days of life. This study specifically examined: 1) infant temperatures (i.e., body, foot, and temperature differential) and incubator temperature trajectories across the first five DOL; 2) the association between infant temperatures and nursing care, type of respiratory support, and respiratory care; and 3) the trajectory of infant body temperatures and incubator temperatures following the opening and closing of the incubator portholes.

3.2 Method

3.2.1 Design

This exploratory, mixed-methods, correlational study was a secondary analysis of 12 very premature infants from the parent study (NIH/NINR: 1R15NR012157-01, RWJF: 68041), “Body Temperature and Vasomotor Tone in Preterm Infants” (Knobel et al., 2011; Knobel-Dail et al., 2016; Levy, et al., 2012). The parent study was designed to examine vasomotor tone maturation, as well as morbidity and mortality associated with this maturation in very premature infants. The current analysis using intensive longitudinal temperature and video data from the parent study focused on respiratory care, respiratory support, and infant body and incubator temperatures over the first five DOL.

3.2.2 Participants

The parent study enrolled very premature infants. Eligibility criteria for this study were infants <29 weeks gestational age (GA) at birth and a birth weight of <1200 grams. The parent study included 30 infants, with complete data collected on 22 infants. This secondary analysis included 12 infants from the parent study. Infants transferred before 34 weeks postmenstrual age (PMA) (two weeks prior to BPD diagnoses) (N=5), discharged before 36 weeks PMA (N=1), or with missing data (N=1) were excluded from this secondary analysis. A sample (N=12) similar to the parent study in birth weight, GA, race, and sex were chosen from the remaining infants (N=15).

3.2.3 Data Collection

This study included temperature data from the parent study, video data from the parent study coded specifically for this study's aims, and new data extracted from the electronic health record (EHR) (see Table 4).

Table 4: Data Collection

Data	Instrument	Definition	Time Collected
Temperature			
Abdominal	Thermistor	Abdominal skin temp in ^{o}C	Every min
Foot	Thermistor	Foot skin temp in ^{o}C	Every min
Incubator	Thermistor	Incubator air temp in ^{o}C	Every min
Servo set point	EHR	Servo temp setting in ^{o}C	Every min
Video Codes			
Open portholes	Video	Portholes open for ≥ 10 secs	Continuous
ETT suctioning	Video	ETT suctioning by catheter	Continuous
ETT saline instilled	Video	Saline instillation in ETT	Continuous
Bag/ETT ventilation	Video	Bag ventilation via ETT	Continuous
Circuit disconnect	Video	Ventilation circuit disconnected	Continuous
Taping ETT	Video	Initial taping or re-taping of ETT	Continuous
ETT maintenance	Video	Other ETT/circuit adjustments	Continuous
Extubation	Video	Removal of ETT	Continuous
Intubation	Video	ETT insertion or attempt	Continuous
Chest x-ray tray	Video	Chest x-ray with incubator tray	Continuous
Chest x-ray	Video	Chest x-ray directly under infant	Continuous
Bag/mask ventilation	Video	Bag ventilation via mask	Continuous
Removal of NP	Video	Removal of NP or nasal mask	Continuous
NP maintenance	Video	Any NP/mask adjustments except removal	Continuous
Oral/nasal suction	Video	Suctioning of mouth or nose	Continuous
Nasal saline	Video	Nasal saline instillation	Continuous
Hands touching	Video	Hands touching infant during respiratory care	Continuous
Completely blocked	Video	Infant view completely blocked	Continuous
Partially blocked	Video	Infant view partially blocked	Continuous
Electronic Health Record			
GA	EHR	GA at birth in weeks	At birth
Birth weight	EHR	Birth weight in grams	At birth
Chorioamnionitis	EHR	Maternal chorioamnionitis diagnosis	At birth
Infant infection	EHR	Sepsis or presumed sepsis	First 5 DOL
SGA or IUGR	EHR	Birth weight <10th percentile	At birth
Apgar Scores	EHR	Apgar score at 1 & 5 minutes	At birth

Abbreviations: temp= temperature; min= minute; ETT= endotracheal tube; NP= nasal prongs; EHR= electronic health record; SGA=small for gestational age; IUGR= intrauterine growth restriction

3.2.3.1 Temperature Data

As standard practice, infants were placed on servo-control mode (with a setting of 36.5°C to 37.2°C) in pre-warmed incubators upon admission to the neonatal intensive care unit (NICU) (Duke Intensive Care Nursery, 2018). Servo-control mode uses a skin temperature probe that continuously monitors the infant's skin temperature, regulating heat output to achieve and maintain the servo temperature setting (Deguines et al., 2012).

Abdominal and foot temperatures were measured by covered Y series Steri-Probe® skin temperature probes (Model 499B, Cincinnati Sub-Zero, Cincinnati, OH). With secure and appropriate placement, the skin temperature of a very premature infant is an adequate proxy for body temperature (Dollberg, et al., 2000; Okken & Koch, 2012). Incubator temperatures were also measured by a thermistor positioned inside the incubator. The three thermistors were attached to a data logger that recorded and stored temperatures to the nearest 0.1° C every minute for the study period.

3.2.3.2 Video Data

Video data were recorded with a Sony video camera attached to a single pod pole attached to the incubator (Knobel-Dail et al., 2017; Knobel-Dail et al., 2016). Using ®Noldus Observer 14 behavior software, the video file for each infant was coded using the video coding scheme described in Table 4.

3.2.3.3 Electronic Health Record (EHR) Data

Infant demographics and additional risk factors for thermal instability were extracted from the EHR (see Table 4). EHR data included: gestational age (GA), birth

weight, maternal diagnosis of chorioamnionitis, Apgar scores at 1 and 5 minutes, infant infection within the first five days of life, intrauterine growth restriction (IUGR), and small for gestational age (SGA) (Finken et al., 2018; Hofer, et al., 2012; Martin et al., 2015).

3.2.4 Data Preparation and Management

Temperature data were available in ®SAS case datasets (one data set per infant). EHR data, which was initially entered into Research Electronic Data Capture

Table 5: Analysis Variables

Variable	Definition
Temperature	
Body	Abdominal skin temp in °C
Foot	Foot skin temp in °C
TD	Abdominal temp – foot temp in °C
Incubator	Incubator air temp in °C
Servo set point	Servo temp setting in °C
Hypothermia	Abdominal temp <36.5° C, coded: 0=no, 1=yes
Hyperthermia	Abdominal temp >37.2° C, coded: 0=no, 1=yes
Respiratory Care Interventions (RCI)	
ETT suctioning	ETT suctioning by in-line catheter
ETT saline instilled	Saline instillation in ETT
Circuit disconnection	Circuit disconnected from ETT or NP
Taping/re-taping ETT	Initial taping or re-taping of ETT
ETT maintenance	Other ETT/circuit adjustments
Removal of NP	Removal of NP or nasal mask
NP/mask maintenance	Any NP/mask adjustments except removal
Hands touching infant	Hands touching infant during respiratory care
Care Event	Anytime portholes are open ≥ 10 seconds, coded: 0=no, 1=yes
Respiratory Care	Portholes are open ≥ 10 seconds and ≥ 1 RCI occurs, coded: 0=no, 1=yes
Respiratory Support	
MV	Receiving MV, coded: 0=no, 1=yes
CPAP	Receiving CPAP, coded: 0=no, 1=yes
RA	No respiratory support, coded: 0=no, 1=yes
Covariates	
GA	GA at birth in weeks
Birth weight	Birth weight in grams
Chorioamnionitis	Maternal diagnosis of Chorioamnionitis, coded: 0=no, 1=yes
Infant Infection	Sepsis or suspected sepsis DOL 1-5, coded: 0=no, 1=yes
SGA or IUGR	Birth weight <10% on growth curve, coded: 0=no, 1=yes
Apgar Scores	Apgar score at 1 & 5 minutes

Abbreviations: temp= temperature; TD=temperature differential; RCI=respiratory care intervention; *ETT= endotracheal tube; NP= nasal prongs; MV=mechanical ventilation; CPAP=continuous positive pressure ventilation; RA=room air; GA=gestational age; SGA=small for gestational age; IUGR= intrauterine growth restriction*

(REDCap™), were downloaded into ®SAS case datasets (one data set per infant). Once all video data were coded, ®Noldus Observer files were exported into Excel data files then converted into ®SAS case datasets (one data set per infant). Infant data sets were then concatenated into individual ®SAS datasets, which were then merged into a single ®SAS dataset using SAS statistical software version 9.4 (Cary, NC). Analysis variables derived from this single dataset included: temperature, respiratory care interventions, care event, respiratory care event, respiratory support, and covariates (see Table 5).

3.2.5 Data Analysis

Descriptive statistics were used to summarize infant characteristics, respiratory care events, and infant body temperature. Non-directional statistics tests were performed with the level of significance set at 0.05 for each test. The significance level was not adjusted for the multiple tests for this exploratory analysis of 12 very premature infants. Effect sizes and their 95% confidence intervals (CIs) were calculated to address clinical relevance.

Hierarchical multi-level, mixed-effects models for intensive longitudinal data were used to examine the association between respiratory care and infant temperatures during the first five DOL. Random coefficients regression models (RRMs), a type of multi-level, mixed-effect models for longitudinal data, were utilized for continuous outcomes, while Generalized Linear Mixed Model (GLMM) for conducted for binary outcomes. Importantly, a multi-level model approach was applied because level-3 of these models adjusted for nesting within each infant. Models also included 1) infant GA, 2) birth weight, 3) chorioamnionitis, 4) infection, and 5) Apgar scores at 5 minutes as fixed effect covariates due to their potential influence on thermal instability. SGA and

IUGR were merged and analyzed as a single covariate, as infants with IGUR in this study also met criteria for SGA (i.e., birthweight <10% on growth curve); however, this was omitted due to its collinearity with GA (Spearman rs = +0.66). Similarly, Apgar score at 1 minute was not included due to its relation with birth weight (Spearman rs = +0.52).

3.3 Results

3.3.1 Infant Characteristics.

Infant characteristics are described in Table 6. The median GA was 27.1 weeks, and the median birth weight was 865 grams. Infants were 58% female and 67% non-Hispanic Black. The remaining infants were non-Hispanic White (35%) and Hispanic (8%). While only two infants met the clinical criteria for BPD, an additional six infants were receiving diuretics for symptoms of chronic lung disease at or beyond 36 weeks PMA.

Table 6: Infant Characteristics

Infant	GA	BW	Sex	Race	CLD	
					BPD	*Diuretics*
1	25.9	880	M	B	Mild	Yes
2	26.1	660	F	H	No	Yes
3	26.1	850	M	B	No	Yes
4	26.3	760	M	B	No	Yes
5	27.1	820	F	B	Severe	Yes
6	27.1	880	F	B	No	No
7	27.1	940	F	W	No	No
8	27.1	1040	F	W	No	No
9	27.1	1040	M	B	No	Yes
10	27.6	730	M	W	No	Yes
11	27.6	1050	F	B	No	No
12	27.9	740	F	B	No	Yes

GA= gestational age in weeks; BW= birth weight in grams; B=non-Hispanic Black; W=non-Hispanic White; H=Hispanic; CLD= chronic lung disease at 36 weeks; BPD= bronchopulmonary dysplasia

Servo setpoint values, adjusted by the bedside nurse, were examined over the five DOL using RRMs to determine whether changes in servo setpoint should be included as a time-dependent covariate in subsequent analyses. The results indicated no significant change in servo set point over time (p=0.5082) and that younger GA tended to be associated with increased servo set point (p=0.0804). Thus, servo setpoint values were not incorporated as a time-dependent covariate in subsequent analysis.

3.3.2 Infant and Incubator Temperatures

RRMs were used to determine the trajectory of change in infant temperatures (i.e., body, foot, temperature differential) and incubator temperatures across the five days (See Figure 6). Fixed effects were DOL and the five infant covariates, while

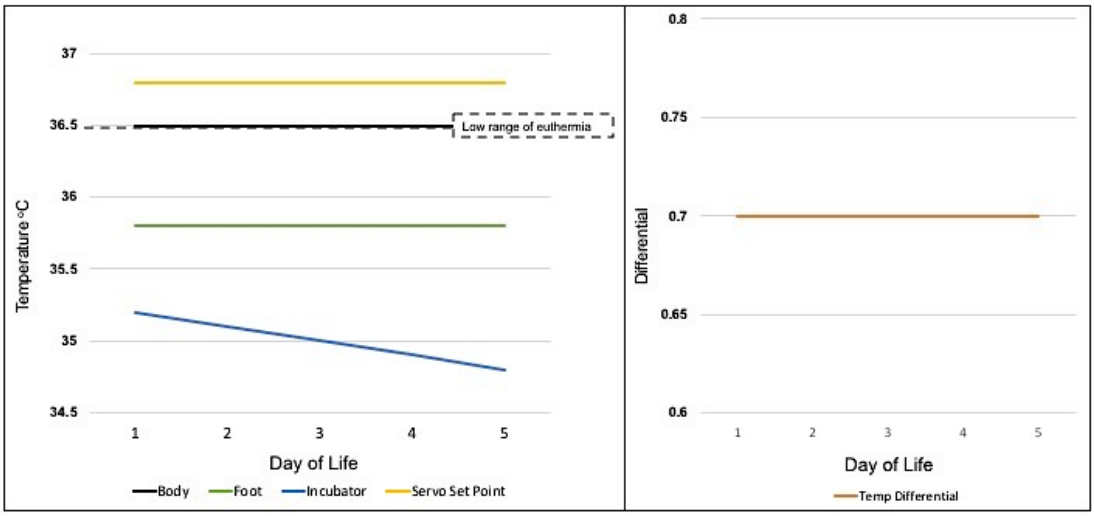

Figure 6: Mean Temperatures Across Five Days

random effects were infant and the infant-by-DOL interactions. Outcomes were the four temperatures across the five days. Temperature outcomes did not significantly change across the first five DOL (all p>0.05). Covariates were not significantly associated with any temperatures, with the exception that younger GA was significantly related to

increased incubator temperature (p=0.0544). Appendix B presents the RRM results and adjusted means for the temperature outcomes.

3.3.3 Respiratory Support and Temperatures

Multi-level models were used to determine whether the type of respiratory support infants received was associated with infant temperatures (i.e., body, foot, temperature differential, hypothermia, and hyperthermia) and incubator temperature. Since there was not a significant change in any measures of temperature across days, DOL was not included as an explanatory variable in the models. Respiratory support included three types: MV, CPAP, and RA (see Table 7). While only one infant was on RA during the first 5 DOL, this analysis was conducted for exploratory purposes as a large number of temperature points (n= 4215) were available from this infant. The respiratory support type and five infant covariates were fixed effects, and infant was a random effect.

Respiratory support type was significantly associated with temperature outcomes (all $p<0.0001$). Table 7 presents the adjusted means for temperature outcome and pairwise comparisons of each type of respiratory support. Pairwise contrasts indicated significant differences between MV vs. CPAP, MV vs. RA, and CPAP vs. RA on body, foot, and incubator temperatures; however, a significant temperature differential was only found between MV vs. CPAP and CPAP vs. RA. The lowest body and foot temperatures and the largest temperature differentials occurred during MV. The lowest incubator temperatures were noted during RA. Younger GA was significantly associated with higher incubator temperatures (p=0.0246), while the other four covariates were not statistically significant (all $p>0.05$). For the statistically significant relationships, very small effect sizes were observed (all $d< \pm 0.20$).

Table 7: Relationship Between Respiratory Support and Temperature

Temp	Explanatory Variable	F *p*-value	Adjusted Mean ± SE[1]	Pairwise Contrast	Contrast *p*-value	Cohen *d*[2]	Cohen *d* 95% CI[2]
Body	RS Type	<0.0001					
	MV		36.45 ± 0.10	MV vs RA	<0.0001	-0.02	-0.05, -0.01
	CPAP		36.50 ± 0.10	CPAP vs MV	<0.0001	0.002	-0.01, 0.02
	RA		36.74 ± 0.10	CPAP vs RA	<0.0001	-0.01	-0.04, 0.02
Foot	RS Type	<0.0001					
	MV		35.63 ± 0.09	MV vs RA	<0.0001	-0.03	-0.06, 0.01
	CPAP		35.90 ± 0.09	CPAP vs MV	<0.0001	0.02	0.00, 0.03
	RA		35.97 ± 0.09	CPAP vs RA	0.0008	0.004	-0.04, 0.03
TD	RS Type	<0.0001					
	MV		0.82 ± 0.08	MV vs RA	0.0713	--	--
	CPAP		0.61 ± 0.08	CPAP vs MV	<0.0001	-0.01	-0.03, 0.00
	RA		0.78 ± 0.08	CPAP vs RA	<0.0001	-0.01	-0.04, 0.02
Incubator	RS Type	<0.0001					
	MV		35.07 ± 0.20	MV vs RA	<0.0001	0.03	0.00, 0.06
	CPAP		35.03 ± 0.20	CPAP vs MV	0.0250	-0.01	-0.03, 0.01
	RA		34.17 ± 0.20	CPAP vs RA	<0.0001	-0.03	-0.06, 0.00
Temp Outcome	Explanatory Variable	F p-value		Pairwise Contrast	Contrast p-value	aOR[3]	aOR 95% CI[3]
Hypo	RS Type	<0.0001					
	MV			MV vs RA	<0.0001	2.59	2.29, 2.93
	CPAP			CPAP vs MV	<0.0001	1.17	1.11, 1.24
	RA			CPAP vs RA	<0.0001	3.05	2.73, 3.40
Hyper	RS Type	<0.0001					
	MV			MV vs CPAP	0.9707	1.00	0.88, 1.15
	CPAP			RA vs CPAP	<0.0001	7.46	5.86, 9.50
	RA			RA vs MV	<0.0001	7.44	5.64, 9.81

Abbreviations: temp=temperature; RS=respiratory support; MV=mechanical ventilation; CPAP=continuous positive pressure ventilation; RA=room air; SE=standard error; CI=confidence interval; Hypo=hypothermia; Hyper=hyperthermia

[1] Mean and SE adjusted for adjusted for fixed, random, and within-infant nesting effects

[2] Cohen d effect sizes: small= ±0.20, medium= ±0.50, large = ±0.80

[3] aOR=adjusted odds ratio and 95% CI for specified pairwise contrast; aORs effect sizes: small=1.44,medium=2.47, large=4.25

Table 7 also presents the results for hypothermia and hyperthermia, each coded as 0=no and 1=yes at each temperature collection point. Respiratory support type was significantly associated with both outcomes (both $p<0.0001$). The adjusted odds of hypothermia were three times higher during CPAP compared RA, 2.6 times higher during MV compared to RA, and 1.2 times higher during CPAP vs. MV (all $p<0.0001$). In terms of hyperthermia, the adjusted odds of hyperthermia were 7.4 greater in the RA compared to MV and 7.5 times greater compared to CPAP (both $p<0.0001$); however, the odds were similar for the MV and CPAP comparison ($p<0.9707$). Covariates were not significantly related to hypothermia (all $p>0.05$). However, hyperthermia was associated with younger GA ($p=0.0296$) and higher Apgar score at 5 minutes ($p=0.0396$).

3.3.4 Care Events and Temperatures

The impact of care events on infant temperatures was also examined. A care event occurred any time the portholes were open for ≥10 seconds, coded as 0=no, portholes closed and 1=yes, portholes open for ≥10 seconds (see Table 5). Care event and the five infant covariates were fixed effects, while infant was a random effect. Care events were significantly associated with all temperatures outcomes (all $p<0.0001$). Adjusted mean body, foot, and incubator temperatures were significantly lower, and temperature differential was significantly larger (i.e., body temperatures warmer relative to foot temperature) during care events compared to when the portholes were closed. Younger GA was significantly associated with higher foot temperatures ($p=0.0339$) and warmer incubator temperatures ($p=0.0382$), while higher Apgar score at 5 minutes was also significantly associated with higher foot temperatures ($p=0.0298$). The remaining covariates were not statistically significant predictors of the outcomes (all $p>0.05$). For

the statistically significant relationships, very small effect sizes were observed (all $d < \pm 0.20$). Table 8 presents the adjusted means of care events on temperature outcomes.

Care events were also significantly associated with hypothermia and hyperthermia (both $p<0.0001$) (see Table 8). The adjusted odds of hypothermia were 2.6 times greater during a care event than when the portholes were closed. In comparison, the adjusted odds of hyperthermia was 2.5 times lower during a care event than when the portholes were closed. Covariates were not significantly related to hypothermia (all $p>0.05$); however, hyperthermia was associated with younger GA ($p=0.0482$) and higher Apgar score at 5 minutes ($p=0.0333$). For the statistically significant relationships, very small effect sizes were observed (all $d < \pm 0.20$).

Table 8: Relationship Between Care Events and Temperature

Temperature	Explanatory Variable	*F* p-value	Adjusted Mean ± SE[1]	Cohen *d*[2]	Cohen *d* 95% CI[2]
Body	Care Event	<0.0001		-0.01	-0.03, 0.01
	Yes		36.28 ± 0.10		
	No		36.51 ± 0.10		
Foot	Care Event	<0.0001		-0.02	-0.04, 0.01
	Yes		35.58 ± 0.07		
	No		35.88 ± 0.07		
TD	Care Event	<0.0001		0.01	-0.02, 0.03
	Yes		0.72 ± 0.07		
	No		0.63 ± 0.07		
Incubator	Care Event	<0.0001		-0.01	-0.03, 0.01
	Yes		34.71 ± 0.22		
	No		35.12 ± 0.22		
Temperature Outcome	Explanatory Variable	*F* p-value		aOR[3]	aOR 95% CI[3]
Hypothermia	Care Event	<0.0001		2.56	2.43, 2.69
Hyperthermia	Care Event	<0.0001		0.40	0.35, 0.47

Abbreviation: TD= temperature differential; SE=standard error
[1] Mean and SE adjusted for fixed, random, and within-infant nesting effects
[2] Cohen d effect sizes: small= ±0.20, medium= ±0.50, large= ±0.80
[3] aOR=adjusted odds ratio and 95% CI; aOR for care event relative to no care event); <1 aORs effect sizes: small=0.69, medium=0.40, large=0.23; >1 aORs effect sizes: small=1.44, medium=2.47, large=4.25

3.3.5 Care Events and Temperatures by Respiratory Support

The impact of care events on infant temperatures during each type of respiratory support (i.e., MV, CPAP, and RA) was examined. A separate analysis was conducted for each type of respiratory support, with care event and five infant covariates as fixed effects and infant as random effect. Care events for each type of respiratory support were significantly associated with all temperatures outcomes (all $p<0.05$), except for temperature differential during MV ($p=0.4931$). Table 9 presents the adjusted means and pairwise comparisons of care events by respiratory support on temperature outcomes.

The adjusted mean body, foot, and incubator temperatures were significantly lower during care events compared to between care (i.e., portholes closed) regardless of the type of respiratory support the infant was receiving. Younger GA was significantly associated with warmer incubator temperatures ($p=0.0466$), while the remaining four covariates were not statistically significant (all $p>0.05$). For the statistically significant relationships, very small ($d< \pm 0.20$) to medium ($d= \pm 0.50$) effect sizes were observed.

Table 9 also presents the association between care events during each type of respiratory support and hypothermia and hyperthermia. Care events, regardless of the type of respiratory support, were significantly associated with hypothermia (all $p<0.0001$). The adjusted odds of hypothermia was 3.5 times greater during a care event while an infant was on MV than when the portholes were closed, 2.3 times greater while on CPAP, and 2.7 times greater while on RA. Chorioamnionitis was associated with hypothermia during MV ($p=0.0080$), while higher Apgar score at 5 minutes was associated with a decreased probability of hypothermia ($p=0.0467$). Remaining covariates were not significantly related to hypothermia (all $p>0.05$). The adjusted odds of hyperthermia was three times higher during CPAP and two times higher during RA

Table 9: Relationship Between Care Events and Temperature by Respiratory Support

Temperature	Explanatory Variables	F *p*-value	Adjusted Mean ± SE[1]	Cohen *d*[2]	Cohen *d* 95% CI[2]
Body	Care Event & MV	<0.0001		-0.01	-0.06, 0.03
	Yes		36.34 ± 0.14		
	No		36.54 ± 0.14		
	Care Event & CPAP	<0.0001		-0.01	-0.04, 0.01
	Yes		36.20 ± 0.10		
	No		36.44 ± 0.10		
	Care Event & RA	<0.0001		-0.5	-0.62, -0.40
	Yes		36.62 ± 0.02		
	No		36.88 ± 0.01		
Foot	Care Event & MV	<0.0001		-0.01	-0.05, 0.03
	Yes		35.55 ± 0.24		
	No		35.76 ± 0.24		
	Care Event & CPAP	<0.0001		-0.02	-0.05, 0.01
	Yes		35.60 ± 0.09		
	No		35.95 ± 0.09		
	Care Event & RA	0.0267		-0.13	-0.23, -0.02
	Yes		36.04 ± 0.05		
	No		36.17 ± 0.02		
TD	Care Event & MV	0.4931		--	--
	Yes		0.79 ± 0.21		
	No		0.78 ± 0.21		
	Care Event & CPAP	<0.0001		0.01	-0.02, 0.04
	Yes		0.62 ± 0.12		
	No		0.49 ± 0.12		
	Care Event & RA	0.0117		-0.13	-0.23, -0.02
	Yes		0.58 ± 0.05		
	No		0.71 ± 0.02		
Incubator	Care Event & MV	<0.0001		-0.02	-0.06, 0.03
	Yes		34.99 ± 0.22		
	No		35.33 ± 0.22		
	Care Event & CPAP	<0.0001		-0.01	-0.04, 0.02
	Yes		34.75 ± 0.27		
	No		35.15 ± 0.27		
	Care Event & RA	<0.0001		-0.52	-0.62, -0.41
	Yes		34.07 ± 0.03		
	No		34.83 ± 0.03		
Temperature Outcome	Explanatory Variables	F *p*-value		aOR[3]	aOR 95% CI[3]
Hypothermia	Care Event & MV	<0.0001		3.46	3.11, 3.86
	Care Event & CPAP	<0.0001		2.26	2.11, 2.41
	Care Event & RA	<0.0001		0.47	0.34, 0.65
Hyperthermia	Care Event & CPAP	<0.0001		0.33	0.26, 0.41
	Care Event & RA	<0.0001		0.47	0.34, 0.65

Abbreviations: MV=mechanical ventilation; CPAP= continuous positive pressure ventilation; RA=room air; SE=standard error

[1] Mean and SE adjusted for fixed, random, and within-infant nesting effects

[2] Cohen d effect sizes: small= ±0.20, medium= ±0.50, large= ±0.80

[3] aORs effect sizes: <1 small=0.69, medium=0.40, large=0.23; >1 aORs effect sizes: small=1.44, medium=2.47, large=4.25

when the portholes were closed versus during care. Due to the infrequency of hyperthermia during MV, we were unable to analyze the odds of hyperthermia during MV and care events.

3.3.6 Respiratory Care Events and Temperature

The impact of respiratory care events on infant and incubator temperatures was evaluated using multi-level models. Respiratory care events were significantly associated with body and foot temperatures (p<0.0001*)*; however, they were not associated with temperature differential and incubator temperature (p>0.05) (see Table 10). Younger GA was significantly associated with warmer foot temperatures (p=0.0462) and lower incubator temperatures (p=0.0448), while the other four covariates were not statistically significant (all p>0.05).

Table 10: Relationship Between Respiratory Care Events and Temperature

Temperature	Explanatory Variable	F p-value	Adjusted Mean ± SE[1]	Cohen d[2]	Cohen d 95% CI[2]
Body	Respiratory Care	<0.0001			
	Yes		36.23 ± 0.10	-0.01	-0.07, 0.05
	No		36.31 ± 0.10		
Foot	Respiratory Care	<0.0001			
	Yes		35.51 ± 0.09	-0.02	-0.08, 0.05
	No		35.63 ± 0.09		
TD	Respiratory Care	0.5746		--	--
	Yes		0.71 ± 0.05		
	No		0.70 ± 0.04		
Incubator	Respiratory Care	0.3745		--	--
	Yes		34.77 ± 0.23		
	No		34.73 ± 0.22		
Temperature Outcome	Explanatory Variable	F p-value		aOR[3]	aOR 95% CI[3]
Hypothermia	Respiratory Care	<0.0001		1.52	1.30, 1.77
Hyperthermia	Respiratory Care	0.0027		0.28	0.12, 0.65

Abbreviations: TD=temperature differential; SE=standard error
[1] Mean and SE adjusted for fixed, random, and within-infant nesting effects
[2] Cohen d effect sizes: small= ±0.20, medium=±0.50, large = ±0.80
[3] aOR=adjusted odds ratio and 95% CI; aOR for respiratory care to other daily care; aORs effect sizes: <1 small=0.69, medium=0.40, large=0.23; >1 aORs effect sizes: small=1.44, medium=2.47, large=4.25;

Respiratory care events were significantly associated with hypothermia and hyperthermia (both $p<0.0001$) (see Table 10). The adjusted odds of hypothermia was 1.5 times greater during respiratory care events than during no respiratory care events (i.e., portholes open but no respiratory care), while the adjusted odds of hyperthermia was 3.5 times lower during respiratory care events than during no respiratory care. Covariates were not significantly related to hypothermia (all $p>0.05$); however, hyperthermia was associated with younger GA (p=0.0060). For statistically significant relationships, very small effect sizes (all $d< \pm 0.20$) were observed.

3.3.7 Open Port Holes on Body Temperature Trajectory

RRMs were used to examine the body temperature trajectory following the opening of incubator portholes (see Figure 7). The first 15 minutes following the

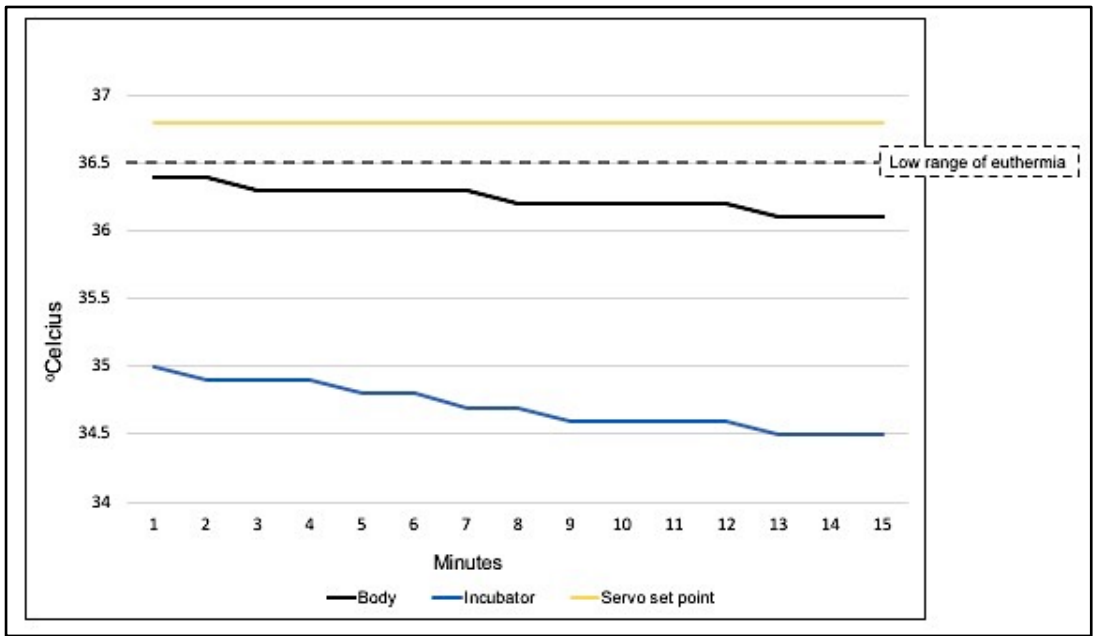

Figure 7: Temperatures Over the First 15 Minutes Following Porthole Opening

opening of incubator portholes were examined. Fixed effects were time (minutes), and the five infant covariates were, the random effect was infant, and models were adjusted for within-infant nesting effects. Time was significantly related to body (p<0.0001) and incubator (p=0.0100) temperatures, with both temperatures decreasing across the 15 minutes. Body temperatures began decreasing three minutes following portholes opening, while incubator temperatures began decreasing at 2 minutes. Both temperatures followed a stepwise decrease over the 15 minutes. All covariates were nonsignificant factors, except younger GA was significantly associated with warmer incubator temperatures (p=0.0337). Appendix D presents the RRM results and adjusted means for temperature outcomes.

RRMs were also utilized to examine temperature recovery following porthole closure. The first 15 minutes following the closure of the incubator portholes were examined (see Figure 8). Time was significantly associated with body temperature (p=0.0005), but not with incubator temperature (p=0.1280). Body and incubator

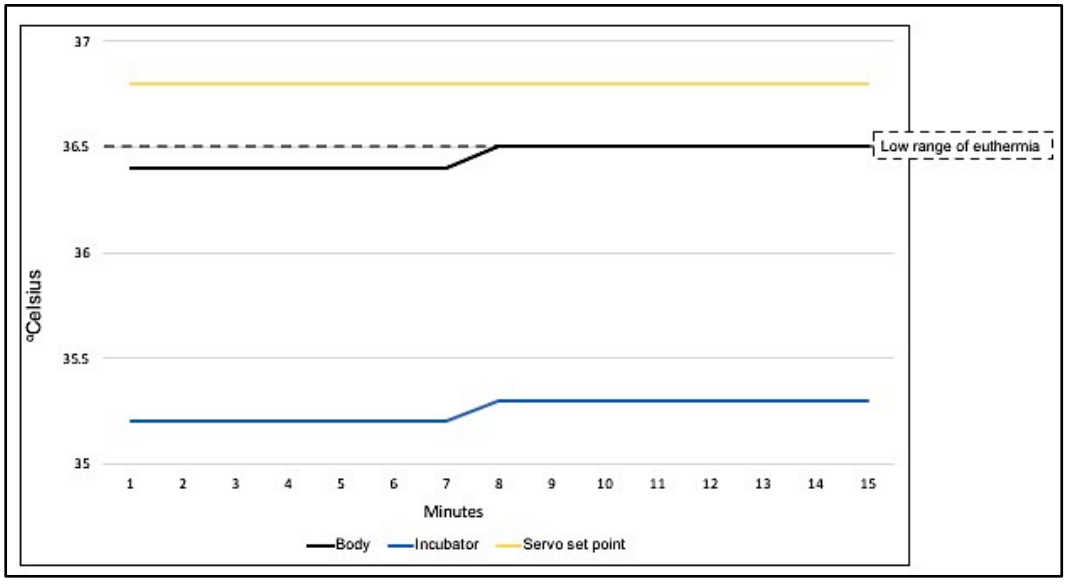

Figure 8: Temperatures Over the First 15 minutes Following Porthole Closure

temperatures began to rise eight minutes after porthole closure, with body temperatures plateauing at the bottom range of euthermia (36.5° C) despite adjusted mean servo setpoint temperatures consistent at 36.8° C (see Figure 8). All covariates were not significantly related to temperatures during this period ($p>0.05$). Appendix E presents the RRM results and adjusted means for temperature outcomes.

3.4 Discussion

This exploratory study found that adjusted mean temperatures (i.e., body, foot, and temperature differential) did not change significantly over the first five DOL. On each day, the adjusted mean body temperature was borderline euthermic (36.5°C); however, infants continued to experience episodes of body hypothermia across each day, particularly during periods of daily care; a finding consistent with previous research (Mok et al., 1991). In contrast, adjusted mean foot temperatures were hypothermic (<36.0°C) each day. This disparity between body and foot temperatures may be attributed to abnormal vasomotor tone due to autonomic dysfunction (Corbisier de Meautsart et al., 2016), or given the adjusted mean body temperatures were borderline euthermic, and infants continued to experience episodes hypothermia, this disparity may represent peripheral vasoconstriction in response to ongoing thermal instability (Corbisier de Meautsart et al., 2016; Lyon et al., 1997). In addition, incubator temperatures did not change significantly over the first five DOL; however, a steady decline was noted over the five days. This decline is consistent with previous research in which very premature infants maintained consistent body temperatures at slightly cooler incubator temperatures over time (Dollberg, Demarini, Donovan, & Hoath, 2000).

Respiratory support type (i.e., MV, CPAP, RA) was associated with infant body temperatures. MV and CPAP were associated with lower body temperatures, while

temperatures during RA were significantly warmer. MV bypasses the normal process of heating and humidifying inspired air (Restrepo & Walsh, 2012); thus, it can impact infant thermal stability when the inspired air is inadequately heated and humidified (Meyer et al., 2015; te Pas et al., 2010). These results are consistent with previous studies linking MV to lower very premature infant body temperatures (Meyer et al., 2015; te Pas et al., 2010). Since the inspired air temperatures of MV and CPAP in this study are unknown, it is unclear if this association is a result of aberrant inspired air temperatures. However, previous studies have found a significant correlation between incubator temperatures and inspired air temperatures (Preo et al., 2013; Todd et al., 2001). Therefore, given that the adjusted mean incubator temperatures during MV and CPAP were both 35.0° C, these cooler temperatures could have influenced inspired air temperatures to fall below-recommended levels (≥36.5° C) (te Pas et al., 2010), thus influencing infant body temperature.

While the impact of CPAP on infant body temperature is poorly understood (Ralphe & Dail, 2018), this study found that infants receiving CPAP were more likely to experience hypothermia than infants receiving MV. Although the effect size for this relationship was very small, any increase in hypothermia risk may be clinically significant due to the associated complications of ongoing oxygen and glucose consumption (Knobel & Holditch-Davis, 2007). This study also found that the odds of an infant experiencing hyperthermia while in RA were significantly higher than infants receiving MV or CPAP. This may be a reflection of the cooling potential of aberrant inspired air temperatures, or an indicator of greater physiologic stability among RA infants, thus increasing their susceptibility to iatrogenic overheating. This body temperature variability noted between respiratory support groups cannot be attributed to infant environment,

because incubator temperatures were lowest during RA, while similar during MV and CPAP.

A significant decline in infant body and foot temperatures, as well as incubator temperatures, was seen during periods of care. Although the effect sizes for these changes were very small, this decline resulted in body and foot temperature hypothermia despite servo control temperatures set within the euthermic range. These results support previous findings (Mok et al., 1991), and highlight the vulnerability of these infants to thermal instability despite efforts to create a stable, neutral thermal environment. Trajectory analysis also found that infant body temperatures and incubator temperatures began to fall two minutes after the portholes were opened, with the initial rise in body and incubator temperatures occurring eight minutes after porthole closure. These results are consistent with previous research, which showed that infant temperature recovery could take up to two hours following nursing care (Mok et al., 1991). This extended recovery time illuminates the very premature infant's ongoing susceptibility to hypothermia throughout episodes of care. Therefore, these results support the bundling of infant care; however, limiting the duration of bundled care may also prevent extreme and/or prolonged episodes of hypothermia. Otherwise, very premature infants may not have adequate time to recover to a stable euthermic state between care.

This was the first study to examine very premature infant temperatures (i.e., body, foot, and temperature differential) during respiratory care. As reported earlier, infant body temperatures fell to hypothermic range during daily care. This study also found that infant body and foot temperatures were even lower during episodes of respiratory care. Although a very small effect size was noted, this decline may represent

clinical significance, because previous research found that mortality and morbidity risk continues to rise as infant body temperatures continue to decline (Laptook et al., 2018; Lyu et al., 2015). In addition, worsening hypothermia during respiratory care (e.g., ETT suctioning) compared to other types of daily care (e.g., diaper changing), may indicate that the kind of activities within a bundled care event should be limited, and/or the duration of bundled care should be limited by the types of included activities.

The associations between temperature differential and respiratory support, care events, and respiratory care were also examined. While previous studies have found that very premature infants have poor vasomotor tone during the early hours of life, demonstrated by episodes of foot temperatures > body temperatures (Knobel et al., 2009; Lyon et al., 1997; Troiani et al., 2017), this study found a mean increase in peripheral vasoconstriction across all five days of life (i.e., body temperatures > foot temperatures). Temperature differential was the largest (i.e., body temperatures were warmest relative to foot temperatures) during MV compared to CPAP; during care events compared to porthole closure, and during care events while receiving MV compared to care events during CPAP or RA. Whether these larger temperature differentials are associated with dysfunctional vasomotor tone, or if they reflect peripheral vasoconstriction in response to infant body hypothermia (Lyon et al., 1997) is unclear.

3.5 Conclusion

This was an intensive descriptive study with a small sample size; however, results from this study are consistent with previous findings and provide direction for future research. While an incubator's servo control mode uses skin temperature to adjust to the needs of the infant, these changes are not made until a decline in temperature

occurs, making this therapy reactive versus proactive. Also, the rapid decline in infant temperature after care begins, and the prolonged recovery following porthole closure, highlights how the disruption of the neutral thermal environment can result in significant thermal instability. This provides further support for bundling infant care. However, it is unclear if bundled care should be limited in duration to prevent extreme episodes of hypothermia, and/or if the activities within it should dictate the duration of care. Furthermore, the association between infant temperatures and CPAP highlights a potentially meaningful relationship between a conventional NICU therapy and thermal instability. Overall, results from this study reveal the need for larger studies with advanced longitudinal analysis that can assess the causal impact of care, respiratory care, and respiratory support modalities on infant temperatures over time, as well as the implications of longitudinal thermal instability on infant outcomes. If a causal relationship is determined, intervention studies can be implemented, and clinical guidelines can be adapted to optimize thermal stability over time, thus decreasing very premature infant mortality and morbidity risk.

4. Association Between Body Temperature Instability and Respiratory Morbidity in the Very Premature Infant

4.1 Introduction

Approximately 10% of all infants in the United States are born prematurely, a statistic that includes over 50,000 very premature infants (≤1500 g) (Martin, et al., 2018). The most common complication of very premature birth is bronchopulmonary dysplasia (BPD) (Horbar et al., 2012; Jobe, 2011), which occurs in approximately 50% of these infants (Johnson et al., 2013; Stoll, 2015). BPD is the abnormal development of alveoli and lung vasculature following premature delivery and is diagnosed clinically as oxygen dependency at ≥ 36 weeks postmenstrual age (PMA) (Ehrenkranz et al., 2005; Jobe & Bancalari, 2001; Kinsella et al., 2006; McEvoy et al., 2014). This clinical definition has been refined by the NIH to include very premature infants with an oxygen requirement at 28 days of life (DOL), as well as a severity assignment (mild, moderate, or severe) based on oxygen requirement at 36 weeks PMA (McEvoy et al., 2014). The definition of BPD continues to be a topic of debate since it manifests differently across infants (Jobe & Steinhorn, 2017; McEvoy et al., 2014), and because this diagnosis does not capture all infants diagnosed with chronic pulmonary insufficiency of prematurity (Mandell, et al., 2019; Steinhorn et al., 2017). Chronic pulmonary insufficiency of prematurity is a global concept that includes chronic respiratory morbidities diagnosed during the infant's NICU hospitalization through early childhood (e.g., reactive airway disease) (Steinhorn et al., 2017). Although advances in neonatal care have reduced the rate of severe BPD and its associated mortality, the incidence of BPD has risen due to the improved survival of extremely premature infants (≤1000 grams) (Stoll, 2015; Younge et al., 2017). In addition, BPD complications are not limited to respiratory sequelae (e.g., hypoxia,

bronchospasm, and carbon dioxide retention) as this disease is associated with additional morbidities, including developmental disabilities, growth retardation, right ventricular hypertrophy, and pulmonary hypertension (Khetan et al., 2016; Schmidt et al., 2003). A diagnosis of BPD can also result in significant financial implications, as it is associated with a two-fold increase in initial hospitalization costs, and many infants have respiratory sequelae that require ongoing healthcare utilization (Hong et al., 2016; Johnson et al., 2013; Schmidt et al., 2015). The prevention and treatment of BPD are complicated due to its multifactorial etiology, and because only a portion of infants with shared risk factors develop this morbidity (Johnson et al., 2013).

Hypothermia and hyperthermia, in the early hours of life, have been associated with the development of BPD in very premature infants (Ashmeade et al., 2016; Castrodale & Rinehart, 2014; Lyu et al., 2015). While the ideal body temperature for these infants is unclear, temperatures <36.5^{o} C and >37.2^{o} C have been associated with an increased risk of mortality and morbidity, including BPD (Lyu et al., 2015). Due to extreme thermoregulatory system immaturity, the very premature infant is unable to maintain euthermic body temperatures independently (Knobel, 2014; Knobel & Holditch-Davis, 2007; Martin et al., 2015). Both autonomic dysfunction (Knobel et al., 2011; Knobel et al., 2009; Lyon et al., 1997) and skin immaturity (Martin et al., 2015) contribute to thermal instability in these infants.

While shivering (i.e., thermogenesis) is a normal autonomic response to hypothermia (Guyton, 2016), neonates are unable to generate heat through shivering, thus are reliant on nonshivering thermogenesis (NST) (Guyton, 2016; Knobel & Holditch-Davis, 2007). NST produces heat through sympathetic stimulation of brown adipose tissue (i.e., brown fat) (Guyton, 2016; Knobel-Dail et al., 2017); however, NST is

ineffective in very premature infants because elements essential to brown fat metabolism (e.g., thermogenin and 5'-monodeiodinase) are limited, thus oxygen (O_2) is metabolized for heat production (see Figure 9) (Houstek et al., 1993; Knobel & Holditch-Davis, 2007; Marks et al., 1981). However, due to the extreme immaturity of the pulmonary system, very premature infants are unable to compensate for an increase in O_2 consumption, therefore if hypothermia persists, hypoxemia and acidosis can ensue (Knobel & Holditch-Davis, 2007). Hyperthermia can also lead to an increase in O_2 consumption due to the rise in metabolic demand associated with elevated core temperatures (Guyton, 2016; Knobel & Holditch-Davis, 2007).

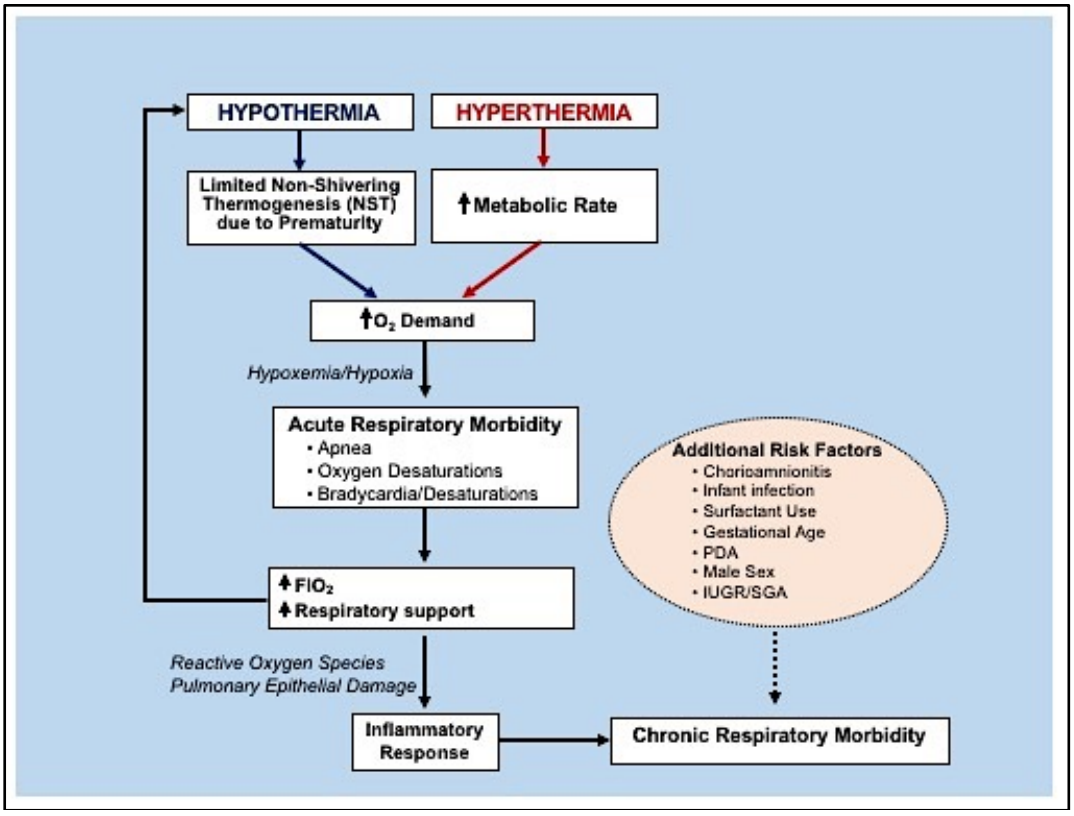

Figure 9: Study Model

Temperature instability, acidosis, and hypoxemia can also induce apnea (cessation of breathing ≥ 15 seconds) in very premature infants, which can lead to ineffective respiratory gas exchange and subsequent respiratory acidosis and advancing hypoxemia (Martin et al., 2015; Mathew, 2003). This hypoxemia can manifest as O_2 desaturations (SpO_2 <90%) and/or O_2 desaturations with bradycardia (i.e., brady/desat) (SpO_2 <90% and HR <100) (Mathew, 2003) (see Figure 9). Recent studies have found an association between O_2 desaturations and long-term morbidity and mortality in very premature infants, including chronic respiratory disease (Di Fiore et al., 2019; Poets et al., 2015). Supplemental oxygen (FiO_2 >21%) and increased respiratory support (e.g., positive inspiratory pressure (PIP), positive end-expiratory pressure (PEEP)) are used to treat hypoxemia and respiratory acidosis, respectively. Reactive oxygen species (ROS), a product of supplemental FiO_2, and positive pressure from respiratory support can result in pulmonary epithelial damage, which can stimulate and/or sustain the inflammatory process that is strongly associated with the development of BPD (Jensen, & Schmidt, 2014; Kinsella et al., 2006; Martin et al., 2015; McEvoy & Aschner, 2015) (see Figure 9). Diuretics are often prescribed to treat the pulmonary edema associated with pulmonary inflammation and capillary leak (Mandell et al., 2019). However, the efficacy of diuretics in BPD prevention and treatment is debated; therefore, its use varies significantly across institutions, yet it remains one of the most utilized medications in the care of very premature infants, with over 50% of infants receiving dosing during their neonatal intensive care unit (NICU) stay (Bamat et al., 2019; Greenberg et al., 2019).

Peripheral vasoconstriction is another normal physiological response to hypothermia, which can increase body temperature by increasing central perfusion (Lyon et al., 1997). However, the very premature infant is unable to effectively

peripherally vasoconstrict under hypothermic conditions due to poor vasomotor control (Corbisier de Meautsart et al., 2016; Knobel & Holditch-Davis, 2007; Knobel-Dail et al., 2016; Lyon et al., 1997). This poor vasomotor control is associated with autonomic dysfunction and can manifest through peripheral temperature change (Knobel & Holditch-Davis, 2007; Lyon et al., 1997). Because foot temperature is a predictor of peripheral perfusion in very premature infants, warmer foot temperatures are associated with an increase in peripheral perfusion. In comparison, cooler foot temperatures are associated with a decrease in perfusion (Knobel-Dail et al., 2016). Therefore, abnormal peripheral vasoconstriction can be depicted by a differential (> or < 0) in body-foot temperature (i.e., temperature differential) (Knobel-Dail et al., 2017; Knobel-Dail et al., 2016; Lyon et al., 1997).

While NICU admission temperature instability has been implicated in the development of BPD in very premature infants (Ashmeade et al., 2016; Castrodale & Rinehart, 2014; Lyu et al., 2015), only a portion of infants with admission temperature instability develop this morbidity. In addition, recent studies have been unable to validate this relationship, thus adding confusion to the influence of this potential risk factor (Jensen et al., 2017; Ting, et al., 2018). Although very premature infants are susceptible to thermal instability for weeks following NICU admission, few studies have examined the impact of longitudinal body temperature instability on acute or chronic respiratory morbidity. Therefore, the purpose of this study was to examine the relationship between infant body temperature instability over the first 14 days of life and respiratory morbidity in very premature infants. This study specifically examined the association between 1) infant temperature (i.e., body, foot, and temperature differential) and chronic respiratory morbidity; 2) episodes of hypothermia and hyperthermia and

chronic respiratory morbidity; and 3) infant temperature (i.e., abdominal, foot, and temperature differential) and concurrent biomarkers for acute respiratory morbidity (i.e., oxygen desaturations, brady/desats, apnea, increased FiO_2 requirement, and increased respiratory support).

4.2 Method

4.2.1 Design

This descriptive, correlative study applied a mixed-methods approach to explore the association between body temperature instability and respiratory morbidity in very premature infants. A secondary analysis of data from 12 very premature infants enrolled in the parent study, "*Body Temperature and Vasomotor Tone in Preterm Infants*,"(NIH/NINR: 1R15NR012157-0; RWJF: 68041), an exploratory study that examined vasomotor tone maturation and associated morbidity and mortality was conducted. The current analysis, using intensive longitudinal physiological data from the parent study, focused on body temperature, heart rate, and oxygen saturation data during the first 14 days of life (DOL).

4.2.2 Participants

The parent study enrolled very premature infants. Eligibility criteria for this study were infants <29 weeks gestational age (GA) at birth and a birth weight of <1200 grams. The parent study included 22 infants. This secondary analysis included 12 infants from the parent study. Infants transferred before 34 weeks PMA (two weeks prior to BPD diagnoses) (N=5), discharged before 36 weeks PMA (N=1), or with missing data (N=1) were excluded from this secondary analysis. A sample (N=12) similar to the parent study in birth weight, GA, race, and sex were chosen from the remaining infants (N=15).

4.2.3 Data Collection

Temperature, cardiovascular, respiratory, and additional infant health data were retrieved from the electronic health record (EHR) (see Table 11). Temperature, heart rate, and oxygen saturation data were recorded continuously over the first 14 DOL.

4.2.3.1 Temperature Data

Infants were stabilized under radiant heat, then transferred to a pre-warmed Draeger Caleo incubator within 4-6 hours of life (Knobel-Dail et al., 2017). Per standard of practice, infants were placed on servo-control mode with a setting of 36.5°C to 37.2°C, with a humidity setting based on birth weight (≤750 grams= 75-80%; >750 grams= 40%) (Duke Intensive Care Nursery, 2018). Using a skin temperature probe, servo-control mode continuously monitors skin temperature, adjusting heat output to achieve or maintain the servo temperature setting (Deguines et al., 2012). The servo temperature setting (i.e., servo set point) was retrieved from the EHR.

Minute to minute abdominal and foot temperatures were measured by covered Y series Steri-Probe® skin temperature probes (Model 499B, Cincinnati Sub-Zero, Cincinnati, OH) (Knobel-Dail et al., 2017). With secure and appropriated probe placement, the skin temperature of a very premature infant is an adequate proxy for infant body temperature (Dollberg, Rimon, et al., 2000; Okken & Koch, 2012). A thermistor was also placed inside the incubator to measure minute to minute air temperatures. These three thermistors were attached to a data logger that recorded and stored temperatures to the nearest 0.1^{o}C.

Table 11: Data Collection

Data	Instrument	Definition	Time collected
Temperature			
Abdominal	Thermistor	Abdominal skin temp in °C	Every minute
Foot	Thermistor	Foot skin temp in °C	Every minute
Servo set point	EHR	Servo temp setting in °C	Every minute
Cardiovascular			
Heart Rate	GE Monitor	Heart rate in beats per min	Every minute
Respiratory			
Oxygen sats	GE Monitor	Peripheral capillary oxygen sats (SpO_2)	Every minute
Apnea	EHR	Cessation of breathing ≥ 15 sec	First 14 DOL
FiO_2	EHR	Supplemental oxygen requirement	First 14 DOL
PIP	EHR	Peak Inspiratory Pressure	First 14 DOL
Peep	EHR	Positive End Expiratory Pressure	First 14 DOL
RR	EHR	Respiratory rate of MV	First 14 DOL
Surfactant	EHR	Received surfactant dosing	First 14 DOL
SD	EHR	Scheduled diuretic dosing	36 wks PMA
Mild BPD	EHR	FiO_2 >21% for ≥ 28 days;no FiO_2 at 36 wks PMA	36 wks PMA
Moderate BPD	EHR	FiO_2 30% at 36 wks PMA	36 wks PMA
Severe BPD	EHR	FiO_2 ≥30% and/or PPV at 36 wks PMA	36 wks PMA
Infant Health			
GA	EHR	Gestational Age at Birth	At birth
Birthweight	EHR	Birthweight in grams (g)	At birth
Sex	EHR	Male or Female	At birth
Chorioamnionitis	EHR	Maternal diagnosis of chorioamnionitis	At birth
Infant Infection	EHR	Diagnosis of infection	First 14 DOL
SGA/IUGR	EHR	Birthweight <10^{th} percentile on growth curve	At birth
Apgar Scores	EHR	Apgar score at 1 & 5 minutes	At birth
PDA	EHR	Diagnosis of PDA	36 wks PMA

Abbreviations: Temp=temperature; sats=saturations; PMA=post menstrual age; EHR=electronic health record; MV=mechanical ventilation; FiO_2=fraction of inspired oxygen; SD=scheduled diuretic dosing; PDA=patent ductus arteriosus; BPD=bronchopulmonary dysplasia; PMA=post-menstrual age; GA= gestational age; SGA=small for gestational age; IUGR= intrauterine growth restriction

4.2.3.2 Cardiovascular and Respiratory Data

Heart rate (HR) and oxygen saturations (SpO_2) were monitored continuously with the infant's GE cardiopulmonary monitor. Minute-to-minute measurements were downloaded into a laptop computer. Additional respiratory data, including apnea episodes, FiO_2 requirement, respiratory support settings (PIP, PEEP, RR), surfactant and diuretic dosing, and BPD diagnoses were extracted from EHR review.

4.2.3.3 Infant Health Data

Infant demographics and additional risk factors for acute respiratory distress and chronic respiratory morbidity were extracted from the EHR. Additional infant data included: gestational age (GA), birth weight, sex, maternal diagnosis of chorioamnionitis, Apgar scores at 1 and 5 minutes, infant infection (i.e., sepsis or presumed sepsis) during DOL 1-14, small for gestational age (SGA), intrauterine growth restriction (IUGR), and diagnosis of patent ductus arteriosus (PDA).

4.2.4 Data Preparation and Management

Infant identifiers were removed from data files, and each infant was assigned a unique and anonymous subject ID number used to link temperature, cardiovascular, respiratory, and additional EHR data. The temperature, HR, and SpO_2 data along with EHR data initially entered into Research Electronic Data Capture (REDCap™) for each infant were merged and archived in a SAS case dataset (one dataset per infant) using ®SAS statistical software version 9.4 (Cary, NC). The 12 infant datasets were then combined into a final analysis dataset. Analysis variables in this final dataset included measures of temperature, acute respiratory morbidity, chronic respiratory morbidity, and covariates (see Table 12). The covariates SGA and IUGR were combined into a single covariate during analysis as infants with IGUR in this study also met criteria for SGA (i.e., birth weight <10% on growth curve).

Table 12: Analysis Variables

Variable	Definition
Temperature	
Body	Abdominal skin temp in ^oC
Foot	Foot skin temp in ^oC
Temp Differential	Abdominal temp – Foot temp in ^oC
Hypothermia	Abdominal temp <36.5^oC: coded, 0=no, 1=yes
Hyperthermia	Abdominal temp >37.2^oC: coded, 0=no, 1=yes
Euthermia	Abdominal temp 36.5^oC to 37.2^oC
Hypothermic Episode	Begins when Abdominal temp <36.5^oC and ends when abdominal temp >36.5^oC (in minutes), coded, 0=no, 1=yes
Hyperthermic Episode	Begins when Abdominal temp <37.2^oC and ends when abdominal temp >37.2^oC (in minutes), coded, 0=no, 1=yes
Acute Respiratory Morbidity	
Desaturation	SpO_2 <90%: coded, 0=no, 1=yes
Brady/Desaturation	Heart rate <100 & SpO_2 <90%: coded, 0=no, 1=yes
Apnea	Apnea start plus 15 min prior & 5 min after: coded, 0=no, 1=yes
FiO_2 rise	Increase in FiO_2 plus 15 min prior & 5 min after: coded, 0=no, 1=yes
RS increase	Increase in PIP, PEEP, or RR plus 15 min prior & 5 min after: coded, 0=no, 1=yes
Chronic Respiratory Morbidity	
CLD	Diagnosis of BPD or SD: coded, 0=no, 1=yes
BPD	BPD diagnosis (mild, moderate or severe): coded, 0=no, 1=yes
SD	No diagnosis of BPD, but receiving scheduled diuretic dosing for respiratory symptoms at 36 weeks PMA: coded, 0=no, 1=yes.
Covariates	
Chorioamnionitis	Maternal diagnosis of chorioamnionitis, coded: 0= no, 1= yes
GA	Gestational age at birth in weeks
Birth weight	Birth weight in grams
SGA/IUGR	Birth weight <10^{th} percentile on growth curve, coded: 0=no, 1=yes
Sex	Female=0; Male=1
Apgar Scores	Apgar score at 1 & 5 minutes
Surfactant	Received at least one dose of surfactant, coded: 0=no, 1=yes
Infection	Sepsis/presumed sepsis during the first 14 days of life, coded: 0=no, 1=yes

Abbreviations: temp= temperature; SpO_2= peripheral capillary oxygen saturation; min=minute; RS= respiratory support; BPD= bronchopulmonary dysplasia; SD= scheduled diuretic dosing; CLD= chronic lung disease; GA=gestational age; SGA=small for gestational age; IUGR=intrauterine growth restriction

4.2.5 Data Analysis

Descriptive statistics were used to summarize infant characteristics and analysis variables during the first 14 DOL. Non-directional statistical tests were performed with the level of significance set at 0.05 for each test. The significance level was not adjusted for the multiple outcomes and tests for this exploratory analysis of 12 very premature

infants. Effect sizes and their 95% confidence intervals (CIs) were calculated to address clinical relevance.

Hierarchical multi-level, mixed-effects models for intensive longitudinal data were used to examine the association between the infant temperatures during the first 14 DOL with acute and chronic respiratory morbidity. Random coefficients regression models (RRMs), a type of multi-level, mixed-effects model for intensive longitudinal data, were used for continuous outcomes, while Generalized Linear Mixed Models (GLIMMIX) were applied for binary outcomes. A multi-level approach was applied because level-3 of such models allowed us to adjust for nesting within each infant. The multi-level models also included 1) infant GA, 2) birth weight, 3) Apgar score at 5 minutes, 4) infection, 5) sex, and 6) surfactant dosing. SGA/IUGR was omitted as a covariate due to its collinearity with GA (Spearman $r_s = 0.66$). Similarly, Apgar score at one minute (Spearman $r_s = -0.68$), chorioamnionitis (Spearman $r_s = 0.55$), and PDA (Spearman $r_s = -0.52$) were excluded due to collinearity with surfactant.

4.3 Results

4.3.1 Infant Characteristics

Infant characteristics are described in Table 13. The median GA was 27.1 weeks, and the median birth weight was 865 grams. Infants were 58% female and 67% non-Hispanic Black. The remaining infants were non-Hispanic White (35%) and Hispanic (8%). While only two infants met the NIH criteria for BPD, six additional infants were receiving scheduled diuretic dosing for symptoms of chronic lung disease at or beyond 36 weeks PMA. The two infants with BPD were dissimilar in sex and race; however, they were both extremely low birth weight (<1000grams), received surfactant, and were treated for infection during the first 14 DOL. The four infants without CLD (i.e.,

BPD or scheduled diuretics) were all female and greater than 27 weeks' gestation, and only one of these infants was treated for infection during the study. GA, birth weight, sex, race, maternal chorioamnionitis, and surfactant dosing varied by infant in the CLD group.

Table 13: Infant Characteristics and Respiratory Outcome

Respiratory Outcome		GA	BW	Sex	Race	Chorio	Surfactant	Infection
CLD	BPD	25.9	880	M	B	No	Yes	Yes
	BPD	27.1	940	F	W	No	Yes	Yes
	SD	26.1	660	F	H	No	Yes	Yes
	SD	26.1	850	M	B	No	Yes	No
	SD	26.3	760	M	B	Yes	No	Yes
	SD	27.1	1040	M	B	Yes	No	Yes
	SD	27.6	730	M	W	No	Yes	Yes
	SD	27.9	740	F	B	No	Yes	Yes
No CLD		27.1	880	F	W	Yes	Yes	Yes
		27.1	940	F	W	No	Yes	No
		27.1	1040	F	W	No	Yes	No
		27.6	1050	F	B	No	No	No

Abbreviations: chorio=chorioamnionitis; CLD=chronic lung disease at 36 weeks; BPD=bronchopulmonary dysplasia; SD=scheduled diuretic dosing; GA=gestational age; BW=birthweight in grams; B=non-Hispanic Black; W=non-Hispanic White; H=Hispanic

4.3.2 Temperature Instability and Chronic Lung Disease

4.3.2.1 Body Temperatures and Chronic Lung disease

Multi-level models were used to examine the association between infant body temperatures and respiratory morbidity (i.e., CLD, BPD, or scheduled diuretics). Infants diagnosed with BPD were excluded from the scheduled diuretics group during analysis. Respiratory morbidity and the six infant covariates were fixed effects, and infant was a random effect. Table 14 presents the adjusted means and details of RRM.

Table 14: Relationship Between Infant Temperatures and CLD

Temperature	Respiratory Outcome	*p*-value	Adjusted Mean ± SE[1]	Cohen *d*[2]	Cohen *d* 95% CI[2]
Body	CLD	0.2765		0.01	0.00, 0.02
	Yes		36.69 ± 0.14		
	No		36.23 ± 0.25		
	BPD	0.5743		0.002	-0.01, 0.01
	Yes		36.64 ± 0.19		
	No		36.52 ± 0.07		
	SD	0.5260		0.004	-0.01, 0.01
	Yes		36.70 ± 0.26		
	No		36.23 ± 0.38		
Foot	CLD	0.2540		0.01	0.00, 0.02
	Yes		35.76 ± 0.11		
	No		36.15 ± 0.20		
	BPD	0.8520		0.001	-0.01, 0.01
	Yes		35.92 ± 0.15		
	No		35.88 ± 0.06		
	SD	0.2768		-0.01	-0.02, 0.00
	Yes		35.63 ± 0.17		
	No		36.21 ± 0.25		
TD	CLD	0.0250		0.02	0.01, 0.02
	Yes		0.95 ± 0.09		
	No		0.05 ± 0.18		
	BPD	0.7283		0.00	-0.01, 0.01
	Yes		0.74 ± 0.23		
	No		0.64 ± 0.09		
	SD	0.0718		0.02	0.01, 0.03
	Yes		1.10 ± 0.13		
	No		-0.02 ± 0.20		

Abbreviations: temp= temperature; TD=temperature differential; CLD= chronic lung disease at 36 weeks; BPD= bronchopulmonary dysplasia; SD=scheduled diuretic dosing
[1] Mean and Standard error (SE) adjusted fixed, random, and nesting effects
[2] Cohen d effect sizes: small=±0.20, medium=±0.50, large= ±0.80

Infant body and foot temperatures were not significantly associated with the outcomes of CLD, BPD, or scheduled diuretics (all $p > 0.05$). However, the adjusted mean body temperatures in the CLD and scheduled diuretics groups were euthermic, while the temperatures of the four infants without CLD were hypothermic. The adjusted mean body temperatures of infants with and without BPD were euthermic, yet temperatures in the BPD group were lower. Infant foot temperatures were not significantly associated with the outcome of CLD, BPD, or scheduled diuretics

(all p>0.05); however, the adjusted mean foot temperatures of infants without CLD were higher than those with CLD. A significant association was also noted between temperature differential and infants with CLD (p= 0.0250), as these infants had larger differentials (i.e., warmer abdominal temperatures relative to foot temperatures). However, this relationship had a very small effect size (<0.20). The associations between temperature differential and the scheduled diuretics and BPD groups were not significant (p>0.05), although the differentials were larger in those with BPD and scheduled diuretics. The absence of infection was associated with warmer abdominal relative to foot temperatures in the infants with CLD (p=0.0118) and scheduled diuretics (p=0.0488). The remaining covariates were not statistically significant.

4.3.2.2 Hypothermia and Hyperthermia and Chronic Lung disease

Descriptive statistics were used to examine the association between episodes of hypothermia and hyperthermia with the outcome of CLD. Minute-by-minute data with missing temperatures were excluded from the analysis. Hypothermic and hyperthermic episodes were analyzed by infant case, then merged for group analysis (N=12). The median and the 25th, 75th percentiles (lower and upper quartiles of the interquartile range [IQR]) are reported due to the small sample size (see Table 15).

Following removal of missing abdominal temperatures, an average of 22.3 hours (20.3 - 23.1 hours) per infant per day were assessed over the 14 days. As a group (N=12), infants spent almost one-third of the assessed time hypothermic (Median=30.5%, IQR= 26.7% - 49.1%), and the median duration of each hypothermic episode was 26.8 minutes (IQR= 20.2 - 38.7). The incidence of hyperthermia was significantly less (Median=6.3%, IQR= 4.4% - 9.9%), yet the duration of hyperthermic episodes was longer (Median=40.6 minutes, IQR= 32.5 - 51.7). Infants without CLD

(N=4) spent more time hypothermic (Median=51.8%, IQR= 35.7- 63.6%) than infants with CLD (N=8) (Median=27.6%, IQR= 26.7 - 34.2%), and the duration of hypothermic events were longer in infants with CLD (Median=42.4, IQR= 26.1 - 62.7) than infants without CLD (Median=22.4, IQR= 20.2 - 34.4). This trend was similar when infants were assessed by CLD type (i.e., BPD and scheduled diuretics). The rate of hyperthermia was infrequent and comparable among infants with and without respiratory morbidity (Median=6.3-6.6%); however, the duration of hyperthermic events was shorter in infants with respiratory morbidity (Median= 30.1-43.6 minutes) compared to those without (Median= 47.2 minutes).

Table 15: Relationship Between Thermal Stability and Chronic Respiratory Morbidity

Respiratory Outcome	Hypothermia		Hyperthermia	
	Percent (%) Median (IQR)	Duration (min) Median (IQR)	Percent (%) Median (IQR)	Duration (min) Median (IQR)
All Infants (N=12)	30.5 (26.7 - 49.1)	26.8 (20.2 - 38.7)	6.3 (4.4 - 9.9)	40.6 (32.5 - 51.7)
CLD				
Yes (8)	27.6 (26.7 - 34.2)	22.4 (20.2 - 34.4)	6.3 (4.4 - 10.5)	36.3 (30.6 - 55.7)
No (4)	51.8 (35.7 - 63.6)	42.4 (26.1 - 62.7)	6.5 (3.4 - 9.5)	47.2 (39.1 - 50.9)
BPD				
Yes (2)	26.7 (26.2 - 27.2)	21.6 (20.7 - 22.6)	6.3 (6.3 - 6.3)	30.1 (24.0, 36.2)
No (10)	34.2 (27.3 - 50.4)	32.3 (19.7 - 39.5)	6.5 (4.3, 11.1)	47.2 (33.3, 52.4)
SD				
Yes (6)	30.5 (27.3 - 35.3)	26.6 (19.7 - 37.8)	6.6 (4.3 - 12.4)	43.6 (31.8 - 60.3)
No (4)	51.8 (35.7 - 63.6)	42.4 (26.1 - 62.7)	6.5 (3.4 - 9.5)	47.2 (39.1 - 50.9)

Abbreviations: CLD=chronic lung disease; BPD=bronchopulmonary dysplasia; SD=scheduled diuretic dosing

4.3.3 Infant Temperatures Across 14 Days

RRMs were used to determine and describe the trajectory of change in infant temperatures (i.e., body, foot, and temperature differential) and incubator temperatures across the 14 days (see Figure 10). The fixed effects were DOL and the six covariates, while random effects were infant and the infant-by-DOL interaction trajectories. Outcomes were the three temperatures across the 14 days. Infant temperature

outcomes (i.e., body, foot, and temperature differential) did not significantly change across the 14 days (all *p>0.05*), and all covariates were not significantly associated infant temperatures (all *p>0.05*). Since there was not a significant change in any measures of temperature across days, DOL was not included as a predictor in the analysis models. Appendix C presents the RRM results and adjusted means for each temperature outcome.

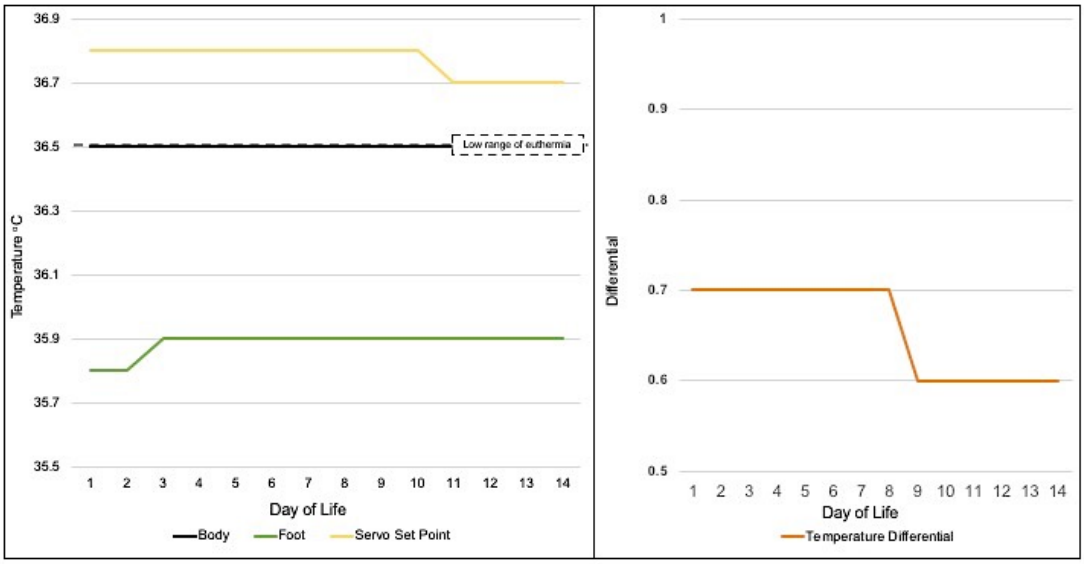

Figure 10: Mean Temperatures Across 14 Days

4.3.4 Desaturations and Temperatures

Multi-level models were used to examine the association between oxygen desaturations and infant temperatures (i.e., body, foot, and temperature differential). Desaturations included episodes where SpO_2 was <90%. Desaturations and infant covariates were fixed effects, while infant was a random effect.

Desaturations were significantly associated with body and foot temperatures (p<0.001), with both temperatures lower during episodes of desaturation. Very small

effect sizes for these statistically significant relationships were observed (both d< ±0.20). No significant association was seen between temperature differential and desaturations (p=0.1148), and all covariates were non-significant (all p>0.05). Table 16 presents the adjusted means and details of RRM.

Table 16: Relationship Between Oxygen Desaturations and Temperature

Temperature Outcome	Explanatory Variable	F *p*-value	Adjusted Mean ± SE[1]	Cohen *d*[2]	Cohen *d* 95% CI[2]
Body	Desaturation	<0.0001		-0.01	-0.02, 0.01
	Yes		36.49 ± 0.05		
	No		36.59 ± 0.05		
Foot	Desaturation	<0.0001		-0.003	-0.02, 0.01
	Yes		35.82 ± 0.06		
	No		35.91 ± 0.06		
TD	Desaturation	0.1148		--	--
	Yes		0.68 ± 0.06	-0.0004	-0.01, 0.01
	No		0.69 ± 0.06		
Temperature Outcome	Explanatory Variable	*F* *p*-value		aOR[3]	aOR 95% CI[3]
Hypothermia	Desaturation	<0.0001		1.29	1.24, 1.34
Hyperthermia	Desaturation	<0.0001		0.85	0.80, 0.92

Abbreviations: temp=temperature; TD=temperature differential; SE=standard error
[1] Mean and SE adjusted for adjusted for fixed, random, and nesting effects
[2] Cohen d effect sizes: small= ±0.20, medium= ±0.50, large = ±0.80
[3] aOR=adjusted odds ratio and 95% CI for the specified pairwise contrast; <1 aORs effect sizes: small=0.69, medium=0.40, large=0.23; >1 aORs effect sizes: small=1.44, medium=2.47, large=4.25

Desaturations were significantly associated with hypothermia and hyperthermia (both p<0.0001); however, the adjusted odds of desaturation during hypothermia or hyperthermia were very small (see Table 16). Infant covariates were not significantly associated with hypothermia or hyperthermia (all p>0.05), except a lower Apgar score at 5 minutes, which was associated with hyperthermia (p=0.0170).

4.3.5 Bradycardia/Desaturations and Temperatures

The associations between bradycardia with desaturations (brady/desats) and infant temperatures (i.e., body, foot, and temperature differential) were also examined. Brady/desats included episodes when HR was <100, and SpO_2 was <90%. Brady/desats, and the six infant covariates were fixed effects, while infant was a random effect.

Brady/desats were significantly associated with body temperature, foot temperature, and temperature differential (all $p<0.001$). Body and foot temperatures were lower, while temperature differential was smaller during brady/desat episodes. All covariates were non-significant (all $p>0.05$). Very small effect size was observed for each statistically significant relationship. Table 17 presents the adjusted means and details of RRM.

Table 17: Relationship Between Bradycardia with Desaturations and Temperature

Temperature Outcome	Explanatory Variable	F *p*-value	Adjusted Mean ± SE[1]	Cohen *d*[2]	Cohen *d* 95% CI[2]
Body	Brady/ Desat	<0.0001		0.03	0.02, 0.04
	Yes		36.29 ± 0.06		
	No		36.58 ± 0.06		
Foot	Brady/Desat	<0.0001		0.05	0.04, 0.06
	Yes		35.86 ± 0.05		
	No		35.89 ± 0.05		
TD	Brady/Desat	<0.0001		-0.01	-0.02, 0.00
	Yes		0.43 ± 0.07		
	No		0.70 ± 0.07		
Temperature Outcome	Explanatory Variable	F *p*-value		aOR[3]	aOR 95% CI[3]
Hypothermia	Brady/Desat	<0.0001		2.22	2.16, 2.28
Hyperthermia	Brady/Desat	<0.0001		0.70	0.66, 0.75

Abbreviations: temp=temperature; TD=temperature differential; SE=standard error
[1] Mean and SE adjusted for adjusted for fixed, random, and nesting effects
[2] Cohen d effect sizes: small= ±0.20, medium= ±0.50, large = ±0.80
[3] aOR=adjusted odds ratio and 95% CI for specified pairwise contrast; <1 aORs effect sizes: small=0.69, medium=0.40, large=0.23; >1 aORs effect sizes: small=1.44, medium=2.47, large=4.25

Results for predicting the presence of hypothermia and hyperthermia during brady/desats are also presented in Table 17. Brady/desats were significantly associated with hypothermia and hyperthermia (p<0.0001). The adjusted odds of hypothermia was 2.2 times higher during brady/desats, while the adjusted odds of hyperthermia was 1.4 times lower during brady/desats. Increased GA was associated with hypothermia (p=0.0057), and increased Apgar score at 5 minutes was associated with hyperthermia (p=0.0170). The remaining covariates were not significantly related to hypothermia or hyperthermia (all p>0.05).

4.3.6 Apnea and Temperatures

Bivariate regression and GLIMMIX were used to examine the association between documented apnea episodes (cessation of breathing ≥15 seconds) and infant temperatures (i.e., body, foot, temperature differential). Apnea included the 15 minutes preceding the start time of each recorded apnea episode, as well as the five minutes following to assess the association of preceding temperatures. Apnea and the six infant covariates were fixed effects, and infant was a random effect.

Apnea was significantly associated with warmer body temperatures (p=0.0318) and foot temperatures (p<0.0001), and smaller temperature differential (p <0.0001). All covariates were significantly associated with all infant temperatures (see Table 18). Higher birth weight and Apgar scores, as well as male sex, were associated with higher body and foot temperatures (all p<0.0001). Surfactant dosing was associated with higher body (p<0.0001), yet lower foot temperatures (p=0.002), while infection was associated with lower body, yet higher foot temperatures (both p<0.0001). Greater gestational age, smaller birth weight, male sex, higher Apgar score, surfactant dosing,

and absence of infection were associated with increasing temperature differential (i.e., warmer body temperatures relative to foot temperatures) (all $p<0.0001$). Apnea was not significantly associated with hypothermia ($p=0.2039$) or hyperthermia ($p=0.6552$), and no covariates were significant (all $p>0.05$) (see Table 18).

Table 18: Relationship Between Apnea and Temperatures

Temperature Outcome	[1]*b*	SE	*B*	*t*	*p*	[2]Adj R^2
Body						0.0426
Apnea	0.02545	0.01185	0.00454	2.15	0.0318	
Birthweight	0.00012	0.00001	0.02055	8.26	<0.0001	
Sex	0.24922	0.00385	0.17219	64.68	<0.0001	
GA	-0.06721	0.00269	-0.05936	-25.03	<0.0001	
Apgar	0.08391	0.00129	0.14671	65.29	<0.0001	
Surfactant	0.08200	0.00458	0.05038	17.92	<0.0001	
Infection	-0.07055	0.00412	-0.04626	-17.11	<0.0001	
Foot						0.0351
Apnea	0.15564	0.01505	0.02198	10.34	<0.0001	
Birthweight	0.00058	0.00002	0.08115	32.48	<0.0001	
Sex	0.14100	0.00489	0.07703	28.82	<0.0001	
GA	-0.15954	0.00341	-0.11142	-46.79	<0.0001	
Apgar	0.03881	0.00163	0.05366	23.79	<0.0001	
Surfactant	-0.01794	0.00581	-0.00872	-3.09	<0.0001	
Infection	0.22794	0.00524	0.11819	43.53	<0.0001	
TD						0.0188
Apnea	-0.13019	0.01611	-0.01732	-8.08	<0.0001	
Birthweight	-0.00046	0.00002	-0.06113	-24.27	<0.0001	
Sex	0.10822	0.00524	0.05569	20.66	<0.0001	
GA	0.09232	0.00365	0.06073	25.29	<0.0001	
Apgar	0.04510	0.00175	0.05873	25.81	<0.0001	
Surfactant	0.09994	0.00622	0.04574	16.07	<0.0001	
Infection	-0.29849	00561	-0.14578	-53.25	<0.0001	
Temperature Outcome		aOR[3]	aOR 95%[3]		F *p*-value	
Hypothermia		1.05	0.9735, 1.1338		0.2039	
Hyperthermia		1.11	0.9936, 1.2330		0.0655	

Abbreviations: GA=gestational; temp=temperature; TD=temperature differential
[1] b= unstandardized trajectory slope
[2] Adj R^2=R-squared for the model adjusted for number of explanatory variables
[3] aOR=adjusted odds ratio and 95% CI for specified pairwise contrast; aORs effect sizes: small=1.44, medium=2.47, large=4.25

4.3.7 Increase in FiO_2 and Temperatures

Bivariate regression and GLIMMIX were also used to examine the association between the rise in FiO_2 requirement (documented increase in FiO_2) and infant temperatures (i.e., body, foot, and temperature differential). FiO_2 rise included the 15 minutes preceding each increase in FiO_2, as well as the five minutes following to assess the association of preceding temperatures. FiO_2 rise and the six infant covariates were fixed effects, while infant was a random effect.

Table 19: Relationship Between Increase in FiO_2 and Temperatures

Temperature Outcome	*b*[1]	SE	*B*	*t*	*p*	[2]*Adj* R^2
Body						0.0427
FiO_2	-0.01368	0.01315	-0.00221	-1.04	0.02980	
Birthweight	0.00098	0.00001	0.01738	6.99	<0.0001	
Sex	0.24711	0.00383	0.17091	64.54	<0.0001	
GA	-0.07002	0.00267	-0.06218	-26.20	<0.0001	
Apgar 5	0.08435	0.00128	0.14836	65.75	<0.0001	
Surfactant	0.08782	0.00460	0.05369	19.10	<0.0001	
Infection	-0.07337	0.00416	-0.04803	-17.65	<0.0001	
Foot						0.0349
FiO_2	-0.21021	0.01668	-0.02688	-12.60	<0.0001	
Birthweight	0.00056	0.00002	-0.07881	31.55	<0.0001	
Sex	0.14198	0.00486	0.07771	29.23	<0.0001	
GA	-0.16598	0.00339	-0.11664	-48.95	<0.0001	
Apgar 5	0.04096	0.00163	0.05701	25.16	<0.0001	
Surfactant	-0.00635	0.00584	-0.00307	-1.09	0.2762	
Infection	0.21575	0.00527	0.11175	40.91	<0.0001	
TD						0.0180
FiO_2	0.19653	0.01784	0.02371	11.02	<0.0001	
Birthweight	-0.00046	0.00002	-0.06137	-24.36	<0.0001	
Sex	0.10513	0.00519	0.05428	20.24	<0.0001	
GA	0.09596	0.00363	0.06362	26.47	<0.0001	
Apgar 5	0.04339	0.00174	0.05698	24.93	<0.0001	
Surfactant	0.09418	0.00624	0.04298	15.09	<0.0001	
Infection	-0.28912	0.00564	-0.14128	-51.28	<0.0001	
Temperature Outcome		aOR[3]	aOR 95%[3]		*F* p-value	
Hypothermia		1.23	1.13, 1.33		<0.0001	

Abbreviations: GA=gestational; temp=temperature
[1] b= unstandardized trajectory slope
[2] Adj R^2=R-squared for the model adjusted for number of explanatory variables
[3] aOR=adjusted odds ratio and 95% CI for specified pairwise contrast; aORs effect sizes: small=1.44, medium=2.47, large=4.25

FiO_2 rise was significantly associated with decreased body temperature (p=0.02980*)* and foot temperature (p<0.0001), and increased temperature differential (p<0.0001) (i.e., warmer abdominal temperatures relative to foot temperatures). All covariates were significantly associated with all infant temperature outcomes (all p<0.0001), except surfactant and foot temperature (p=0.2762) (see Table 19). Higher birth weight and Apgar scores, as well as male sex, were associated with higher body and foot temperatures. Surfactant dosing was associated with higher body temperatures, while infection was associated with lower body, yet higher foot temperatures. Greater gestational age, smaller birth weight, male sex, higher Apgar score, and surfactant dosing, and absence of infection were associated with increasing temperature differentials (i.e., warmer body temperatures relative to foot temperatures).

FiO_2 rise was significantly associated with hypothermia (p<0.0001) (see Table 19); however, the adjusted odds were very small (aOR<1.44). Lower Apgar score was associated with the presence of hypothermia (p=0.0220), while all other covariates were non-significant (all p >0.05). Episodes of FiO_2 rise during hyperthermia were too few to analyze.

4.3.8 Increase in Respiratory Support and Temperatures

Bivariate regression and GLIMMIX examined the association between increases in respiratory support (i.e., documented increase in PIP, PEEP, and/or RR) and infant temperatures (i.e., body, foot, and temperature differential). Each respiratory support increase included the 15 minutes preceding each documented increase in respiratory support, as well as the five minutes following to assess the association of temperatures preceding respiratory support increases. Respiratory support increase and the six infant covariates were fixed effects, and infant was a random effect.

Bivariate regression indicated that respiratory support increase was significantly associated with decreased body and foot temperatures and increased temperature differential (i.e., warmer abdominal temperatures relative to foot temperatures) (all $p<0.0001$) (see Table 20). All covariates were significantly associated with all infant temperature outcomes (all $p<0.0001$), except the association between surfactant and foot temperature ($p=0.3115$). Higher birth weight and Apgar scores, younger GA, and

Table 20: Relationship Between Increase in Respiratory Support and Temperatures

Temperature Outcome	*b*[1]	SE	*B*	*t*	*p*	[2]*Adj* R^2
Body						0.0416
Increase in RS	-0.07666	0.02014	-0.00809	-3.81	0.0001	
Birthweight	0.00011	0.00001	0.01880	7.51	<0.0001	
Sex	0.24595	0.00385	0.17029	63.95	<0.0001	
GA	-0.06794	0.00268	-0.06037	-25.35	<0.0001	
Apgar 5	0.08229	0.00129	0.14460	63.97	<0.0001	
Surfactant	0.08740	0.00461	0.05357	18.97	<0.0001	
Infection	-0.07418	0.00417	-0.04865	-17.80	<0.0001	
Foot						0.0338
Increase in RS	-0.22639	0.02558	-0.01890	-8.85	<0.0001	
Birthweight	0.00055	0.00002	0.07760	30.88	<0.0001	
Sex	0.14230	0.00488	0.07788	29.13	<0.0001	
GA	-0.16235	0.00340	-0.11404	-47.70	<0.0001	
Apgar 5	0.04023	0.00163	0.05588	24.62	<0.0001	
Surfactant	-0.00592	0.00585	-0.00287	-1.01	0.3115	
Infection	0.21192	0.00529	0.10989	40.05	<0.0001	
TD						0.0173
Increase in RS	0.14972	0.02734	0.01179	5.48	<0.0001	
Birthweight	-0.00045	0.00002	-0.05919	-23.36	<0.0001	
Sex	0.10366	0.00522	0.05353	19.85	<0.0001	
GA	0.09442	0.00364	0.06257	25.95	<0.0001	
Apgar 5	0.04207	0.00175	0.05513	24.08	<0.0001	
Surfactant	0.09332	0.00626	0.04266	14.92	<0.0001	
Infection	-0.28610	0.00566	-0.13996	-50.58	<0.0001	
Temperature Outcome		aOR[3]	aOR 95%[3]		F *p-value*	
Hypothermia		1.23	1.09, 1.39		0.0009	
Hyperthermia		0.45	0.31, 0.65		<0.0001	

Abbreviations: GA=gestational; RS=respiratory support
[1] b=unstandardized trajectory slope
[2] Adj R^2=R-square for the model adjusting for the number of explanatory variables
[3] aOR=adjusted odds ratio and 95% CI for specified pairwise contrast; <1 aORs effect sizes: small=0.69, medium=0.40, large=0.23; >1 aORs effect sizes: small=1.44, medium=2.47, large=4.25

male sex were associated with higher body and foot temperatures. Surfactant dosing was associated with higher body temperatures, while infection was associated with lower body, yet higher foot temperatures. Greater gestational age, smaller birth weight, male sex, higher Apgar score, surfactant dosing, and absence of infection were associated with increasing temperature differentials (i.e., warmer body temperatures relative to foot temperatures).

Increases in respiratory support were significantly associated with hypothermia (p=0.0009) and hyperthermia (p= <0.0001) (see Table 20). However, the adjusted odds of hypothermia was during respiratory support were very small (aOR<1.44). In contrast, the adjusted odds of experiencing hyperthermia was 2.2 times lower during a respiratory support increase, which is a medium effect. Smaller birth weight was associated with hypothermia (p=0.0390) and hyperthermia (p=0.0051). The remaining covariates were non-significant (all p>0.05).

4.4 Discussion

This exploratory study found that adjusted mean temperatures (i.e., body, foot, and temperature differential) did not change significantly over the first 14 DOL. On each day, the adjusted mean body temperature was borderline euthermic (36.5^{o}C). However, infants spent almost one-third of the 14 days hypothermic (Median=30.5%, IQR 26.7%-49%), with each hypothermic episode lasting almost 27 minutes (Median= 26.8, IQR= 20.2-38.7). Therefore, while the adjusted mean body temperatures fell within the normal range, the high frequency and extended duration of hypothermic episodes demonstrate an increased risk of hypothermia associated morbidity among these infants. In addition, the adjusted mean foot temperatures per day were hypothermic (<36.0^{o}C). This disparity

between body and foot temperatures may be a reflection of peripheral vasomotor dysfunction associated with prematurity, which is consistent with previous research (Corbisier de Meautsart et al., 2016). However, given the significant percentage of time that these infants were hypothermic, this disparity could also be an indicator of compensatory peripheral vasoconstriction in response to frequent body hypothermia (Corbisier de Meautsart et al., 2016; Lyon et al., 1997). While this would be contrary to previous descriptive studies, which describe episodes of dysfunctional peripheral vasodilation in very premature infants, especially during the early hours of life (Knobel et al., 2009; Lyon et al., 1997), this study examined adjusted mean temperatures over time. In addition, the foot temperature (as it relates to abdominal temperature) that indicates a true peripheral vasoconstrictive response to hypothermia is unclear (Knobel-Dail et al., 2017). Given that foot temperatures were consistently hypothermic, while abdominal temperatures were borderline euthermic, results from this study may demonstrate the potential for very premature infants to peripherally vasoconstrict in response to hypothermia over time.

Only two infants met the NIH criteria for BPD, yet an additional six infants were receiving diuretics for respiratory symptoms at 36 weeks PMA. Given that many premature infants without a BPD diagnosis are later diagnosed with chronic pulmonary insufficiency (Mandell et al., 2019; Steinhorn et al., 2017), the use of diuretics at 36 weeks PMA may be an indicator of chronic lung disease risk. Also, supplemental oxygen (the essential factor of BPD diagnosis) may have been required to manage respiratory symptoms if diuretics (or other forms of fluid management) were not utilized. All four infants without CLD (i.e., BPD or scheduled diuretics) were female. In addition, eight infants (67%) in the CLD group were treated for infection during the first 14 days of

life, while only one infant (25%) without CLD was treated for infection. Although this is a very small sample, these results are consistent with previous findings that link male sex (E. A. Jensen & Schmidt, 2014) and infant infection (Lahra, Beeby, & Jeffery, 2009; Schlapbach et al., 2011) with respiratory morbidity.

Infants without CLD had lower body temperatures than those with CLD. Although this association was not statistically significant, the adjusted mean body temperature of those without CLD was hypothermic, while the adjusted mean body temperature of those with CLD was euthermic. Infants without CLD also spent more time hypothermic, and the episodes of hypothermia were longer than infants with CLD. While these findings contradict previous studies linking admission hypothermia and CLD (Lyu et al., 2015), this study assessed infant temperatures beyond admission. In addition, these results are consistent with animal models that found hypothermia to be protective against inflammatory mechanisms associated with BPD (Altinsoy et al., 2014; Ball et al., 2010). When individual infant temperatures were examined over time, the infant with the lowest median body temperature (Median=35.8°C, IQR=35.8-36.6 °C) across the 14 days did not have CLD. Yet, this infant developed necrotizing enterocolitis (NEC): a morbidity also associated with hypothermia (Lyu et al., 2015). Given the exploratory nature of this study, an association between hypothermia beyond admission and decreased CLD risk cannot be concluded. However, if hypothermia is protective against CLD, establishing a body temperature range that minimizes CLD risk over time, without increasing the risk of mortality and other morbidities (e.g., NEC) should become a priority.

Consistent with previous research, this analysis showed an association between apnea and rising infant body temperatures (Daily, et al., 1969; Perlstein, et al., 1970).

These findings further demonstrate the significance of body temperature extremes and the importance of maintaining infant thermal stability. The number of apnea events occurring during episodes of hyperthermia were insufficient to assess the odds of this association.

Hypothermia has also been associated with respiratory depression, which can result in oxygen desaturations, brady/desats, and the need for increased respiratory support (R. J. Martin et al., 2015; Mathew, 2003); however, to our knowledge, this is the first study to assess the association between oxygen desaturations and very premature infant body temperatures over time. While a significant association between body temperatures and oxygen desaturations was not found, the odds of oxygen desaturation during hypothermia was significantly greater than when the infants were euthermic. This was also the first study, to our knowledge, to examine the association between brady/desats and body temperatures over time, with a significant association between brady/desats and decreased body temperatures noted. While the effect size between body temperatures and brady/desats was small, the odds of experiencing a brady/desat were significantly higher during hypothermia (medium effect size) and significantly lower (small effect size) during hyperthermia. It is important to delineate if oxygen desaturations and/or brady/desats are accurate biomarkers for hypothermia, or if hypothermia is a biomarker for physiological instability that may cluster with these symptoms.

Consistent with previous research, this study found a significant association between increasing respiratory support and body temperature instability (Jost et al., 2017). Lower body temperatures were associated with an increase in both FiO_2 requirement and respiratory support (i.e., PIP, PEEP, RR). While these changes

represented only 4% of the variance in body temperatures, the odds of hypothermia associated with those changes was significantly higher as well. Several infant characteristics contributed to the prediction of increases in FiO_2 requirement and respiratory support; birth weight was associated with lower body temperatures, while male sex and higher Apgar score at five minutes were associated with higher body temperatures. This finding is important given that male infants have an increased risk of CLD (Ambalavanan et al., 2008; Costeloe et al., 2012), and this analysis found an association between increased body temperatures and CLD, as well as an association between male sex and increased body temperature. Analysis from this study also showed an inverse relationship between GA and body temperature. Per the study site standard of care, infants ≤750 grams were placed in 75-80% humidity, while infants >750 grams were placed in 40% humidity during the first 14 days of life. Given smaller infants in this study had warmer body temperatures over time, these results support previous findings that environmental humidity protects very premature infants from heat loss via insensible water loss (Flenady & Woodgate, 2003).

To our knowledge, this was the first study to assess the association between symptoms of acute respiratory distress (i.e., apnea, desaturations, brady/desats, and increased respiratory support) and temperature differential over time. An important finding was the association between larger temperature differentials (i.e., body temperature warmer relative to foot temperature) and increases in FiO_2 and respiratory support. While these changes only represent about 2% of the variance, this increase in temperature differential could represent autonomic dysfunction association with prematurity or could represent peripheral vasoconstriction. Given that increases in FiO_2 and respiratory support were also associated with decreased infant body temperatures,

as well as increased odds of hypothermia, these larger temperature differentials could represent peripheral vasoconstriction in response to hypothermia.

4.5 Conclusion

Results from this study support previous findings, provide direction for future study and have clinical relevance. The relationship between infant temperatures and CLD was not statistically significant, yet infants without CLD had hypothermic body temperatures, while infants with CLD had euthermic temperatures across the 14 days. While these results are contradictory to previous research, this study examined temperatures beyond admission, and this relationship may be attributed to the anti-inflammatory mechanisms associated with hypothermia demonstrated in animal models. However, due to the increased risk of mortality and other system morbidities (e.g., NEC), the therapeutic use of hypothermia is contraindicated in the very premature infant.

Results from this study examined associations between adjusted mean temperatures and acute and chronic respiratory morbidity over the first 14 days of life; however, to examine causal relationships, larger longitudinal studies are needed. These studies should examine the temporal relationships between temperature instability and desaturations, brady/desats and increasing FiO_2 and respiratory support requirements. Advanced longitudinal analysis can assist in delineating if thermal instability is the causative factor in these symptoms or if thermal instability is a biomarker of physiological instability that manifests concurrently with these respiratory symptoms. The temporal relationship between abdominal temperatures and foot temperatures over time should also be examined. This type of longitudinal analysis would help determine the timing between the start of abdominal temperature change and the start of foot temperature

change (and vice versa), thus providing additional clarity to the nature of this relationship, as this is a potential biomarker of infant instability. Also, these types of studies are needed to adequately explore the relationship between temperature instability over time and the development of CLD. Finally, the ideal temperature range that minimizes morbidity risk as very premature infants grow and develop over time should be determined. If a true causal relationship between longitudinal temperature instability and CLD is found and an ideal body temperature range that reduces infant risk is delineated, intervention studies can be developed, and clinical guidelines can be adapted to reduce infant risk.

5. Conclusion

This dissertation examined the significance of very premature infant temperature instability over time, and its association with respiratory care, symptoms of acute respiratory morbidity, as well as the outcome of chronic lung disease. The literature review conducted in Chapter 2 stemmed from a recent multidimensional clinical initiative that included the warming and humidification of inspired air used during extremely premature infant resuscitation (Vermont Oxford Network, 2017). The goal of this initiative was to improve extremely premature infant outcomes across institutions. The information gained from this literature review informed the aims of both Chapter 3 and Chapter 4. An exploratory mixed-method approach was used, given the intensive multidimensional data collection over time. This method provided an opportunity to explore the associations between minute-to-minute physiological data and respiratory care (Chapter 3), as well as acute and chronic respiratory morbidity (Chapter 4). The specific and relevant findings of each Chapter are summarized below, followed by future research and clinical practice recommendations.

5.1 Summary of Findings

5.1.1 Chapter 2: Temperature and Humidity Associated with Artificial Ventilation: An Integrative Review of the Literature

The integrative review of the literature analyzed the findings of published research regarding the inspired air temperature and humidity from very premature infant ventilation. These findings highlighted factors that can contribute to aberrant inspired air temperature and humidity levels, as well as gaps in the literature that should be addressed to inform clinical care. Importantly, the majority of research was conducted

on artificial lung models, while the few human studies were at least ten years old and conducted on small (N ≤ 48) sample sizes.

A primary finding from this review was that the inspired air temperature and humidity levels decreased significantly between the heater and the infant. This change is an important outcome, as cold and dry inspired air has been associated with pulmonary epithelial damage and inflammation, as well as temperature instability in very premature infants (Tarnow-Mordi, et al., 1989; te Pas, et al., 2010). Also, different artificial ventilation settings resulted in significant variation in inspired air temperature and humidity levels; therefore, adding a level of complexity to the proper management of heating and humidifying artificially inspired air. Furthermore, this review revealed that an infant's environmental temperature (i.e., incubator or radiant warmer) had a significant effect on inspired air temperature and humidity. These studies found that lower environmental air temperatures could cool and dehumidify the inspired air, thus increasing the risks associated with cold and dry gases (Tarnow-Mordi, et al.,1989; te Pas, et al., 2010). It also highlighted a significant gap in the literature, as only two studies examined inspired air temperature and humidity in noninvasive ventilation (e.g., CPAP). Given that noninvasive respiratory support decreases the need for intubation and its associated risks, these therapies are frequently used in clinical practice; thus, a better understanding of inspired air temperature and humidity levels in these therapies is needed.

In summary, inadequately heated and humidified inspired air has the potential to induce lung pathology and temperature instability in these infants. This literature review highlighted the inadequacies of neonatal heating and humidification practices. However, research studies in this review were performed primarily on artificial lung models, the

human studies were old with small sample sizes, and only two studies examined noninvasive ventilation. Therefore, extensive human studies are needed to examine the efficacy of current heating and humidification practices used in invasive and noninvasive ventilation.

5.1.2 Chapter 3: Exploring the Association Between Very Premature Infant Body Temperatures and Respiratory Care

This study described the relationships between very premature infant temperatures (body, foot, and abdominal-foot (i.e., temperature differential)) and daily care, respiratory care, and respiratory support type (i.e., MV, CPAP, RA) over this first five days of life. This intensive analysis of 12 very premature infants found that adjusted mean temperatures (i.e., body, foot, and temperature differential) did not change significantly over the first five days of life. On each day, infant body temperatures were borderline euthermic, foot temperatures were hypothermic, and temperature differentials were greater than zero (i.e., warmer body temperatures relative to foot temperatures). Also, recurrent episodes of hypothermia over the five days of life demonstrated the ongoing risk of morbidity associated with thermal instability.

Because aberrant inspired air temperature and humidity levels can impact very premature infant thermal stability and can increase the risk of respiratory morbidity [Chapter 2] (Ralphe & Dail, 2018), the association between respiratory support type (i.e., MV, CPAP, RA) and very premature infant temperatures was examined in this Chapter. A significant relationship between respiratory support type and infant temperatures was identified. Infant temperatures while receiving MV or CPAP were borderline euthermic, while temperatures during RA were significantly warmer. In addition, infants were more likely to experience hypothermia during CPAP compared to MV, and more likely to

experience hyperthermia while in RA versus MV or CPAP. While the inspired air temperatures were unknown, previous studies found a strong correlation between inspired air temperatures and incubator temperatures (Preo et al., 2013). Therefore, the lower incubator temperatures (35.0^{o} C) noted during MV and CPAP could have cooled inspired air temperatures to below optimal levels (≥36.5^{o} C). Thus, the lower body temperatures noted during MV and CPAP versus RA could be associated with aberrant inspired air temperatures. However, the higher body temperatures in the RA infant could also be a reflection of improved thermal stability in a more physiologically stable infant.

Infant body and foot temperatures, as well as incubator temperatures, declined during care. Body temperatures became hypothermic, while foot hypothermia worsened. Also, infant body and foot temperatures were lower during respiratory care than during other types of daily care. Trajectory analysis found that infant and incubator temperatures began to fall two minutes after the portholes were opened, with the initial rise in these temperatures not occurring until eight minutes after the portholes were closed. These findings further support the need for bundling infant care, as well as the potential benefit of limiting the duration of care, so the disruption of the infant's neutral thermal environment is minimized. In addition, the lower body temperatures noted during respiratory care versus other types of daily care may indicate the kinds of activities within a single bundled care event should be limited, and/or the duration of bundled care should be determined by the activities included.

Temperature differential was associated with respiratory support type and care events. This study found that the adjusted mean temperature differentials were significant and larger (i.e., body temperatures warmer relative to foot temperatures) during MV versus CPAP and care versus porthole closure. This positive temperature

differential may represent autonomic dysfunction associated with prematurity, or it may represent peripheral vasoconstriction. Given that infant body temperatures were hypothermic during MV and care events, and episodes of hypothermia continued throughout the five days of study, these larger temperature differentials may be a reflection of thermal instability over time as the infants attempt to compensate for it via peripheral vasoconstriction.

This study highlighted the potential impact that incubator air temperatures may have on infant temperatures over time. Incubator temperatures during this study were significantly below recommended infant body temperatures. Due to the extreme thermoregulatory immaturity of very premature infants, they are highly susceptible to their environmental temperature; consequently, their body temperature will assume the temperature of their environment (Guyton, 2016). It is common practice to place these infants in a pre-warmed incubator on servo-control mode upon NICU admission, with supplemental humidity added for the extremely immature (≤1000g) (Deguines et al., 2012; Duke Intensive Care Nursery, 2018). The humidification is typically weaned off over the first several weeks of life, yet servo-control mode is continued per unit protocol as the infant continues to grow and develop (Deguines et al., 2012; Duke Intensive Care Nursery, 2018). In the interim, the infant is progressively swaddled and dressed, until she is eventually "weaned" to air temperature control (Deguines et al., 2012; Duke Intensive Care Nursery, 2018). While the servo-control mode is designed to adjust heat output to achieve and/or maintain the servo temperature setting, infants in this study became hypothermic during periods of care, with an extended duration of recovery following porthole closure, thus challenging the efficacy of this mode. Given incubator air temperatures were significantly below recommended infant body temperatures, and very

premature infants will take on the temperature of their environment, using air temperature control mode, set at recommended infant body temperature (i.e., 36.5^{o}C to 37.2^{o}C), may provide a more consistent, optimal environmental temperature for these infants. In addition, this incubator air temperature range would assist in maintaining the recommended inspired air temperatures identified in Chapter 2, thus reducing the risk of respiratory morbidity associated with cold and dry gases.

5.1.3 Chapter 4: Exploring the Association Between Body Temperature Instability and Respiratory Morbidity in the Very Premature Infant

Chapter 3 highlighted how the very premature infant's environment and clinical management might contribute to thermal instability over time. The study in Chapter 4 explored the association between these episodes of thermal instability and symptoms of acute respiratory morbidity, as well as the outcome of chronic lung disease. This study expanded the five days of intensive analysis in Chapter 3 to the first 14 days of life in the same 12 very premature infants. Similar to the results in Chapter 3, the adjusted mean temperatures (body, foot, and temperature differential) did not change significantly over the first 14 days of life. Each day, infant body temperatures were borderline euthermic, foot temperatures were hypothermic, and temperature differentials were greater than zero (i.e., warmer body temperatures relative to foot temperatures). Also, recurrent episodes of hypothermia over the 14 days of life again demonstrated the very premature infant's ongoing risk of thermal instability associated morbidity.

A total of eight infants (67%) met the study criteria for chronic lung disease. This included two infants with NIH defined BPD, and six infants receiving scheduled diuretics for the management of respiratory symptoms at 36 weeks PMA. BPD is a complex

disease with a spectrum of histological and clinical presentations (Jobe & Steinhorn, 2017; Kinsella et al., 2006). Given that BPD is a diagnosis made by oxygen dependence, and does not always predict future respiratory sequelae, the utilization of additional criteria (like diuretic use) may assist in delineating true respiratory morbidity. This recognition and clustering of symptoms beyond just oxygen requirement could assist in the development of individualized prevention and treatment plans that optimize outcomes.

A significant finding in this study was that the four infants without CLD had lower body temperatures than those with CLD. Also, these infants without CLD spent more study time hypothermic, and episodes of hypothermia were longer than those with CLD. This contradicts previous research that found an association between BPD and admission hypothermia (Lyu et al., 2015). However, this study examined temperatures beyond admission, and animal models have found hypothermia to be protective against the inflammatory process that leads to BPD (Altinsoy et al., 2014; Ball et al., 2010). Therefore, while the results from this study highlight the potential protective mechanism of hypothermia, they also contribute complexity to the body of knowledge regarding BPD development and prevention.

This was the first study to explore the association between very premature infant body temperatures over time and symptoms of acute respiratory morbidity. Therefore, the significant associations between lower body temperatures and symptoms of acute respiratory morbidity (i.e., bradycardia with desaturations and increased FiO_2 and respiratory support (i.e., PIP, PEEP, RR)) are valuable findings that requires further exploration. In contrast, apnea was associated with higher infant body temperatures, a finding supported by previous studies.

All of the covariates were significant in many of these models, thus illuminating their influence on infant body temperatures over time. A relatively unexpected finding was that higher birth weight was associated with lower body temperatures. Incubator humidity could be a factor in this study finding, as all infants were placed in incubators with similar servo temperature settings. However, infants >750 grams received lower environmental humidity (40%) compared to infants ≤750 grams (65-80%). Another important covariate finding was the association between male sex and higher infant body temperatures. Previous studies have found male infants at higher risk for CLD, yet the etiology of this increased risk is unclear (Ambalavanan et al., 2008; Castrodale & Rinehart, 2014). If male infants have higher mean body temperatures over time, and higher temperatures are found to increase the risk of CLD, this illuminates a potential association that has yet to be examined.

Another important finding in this study was the associations between adjusted mean temperature differentials (i.e., abdomen – foot temperatures) and acute respiratory symptoms. An increase in both FiO_2 requirement and respiratory support were associated with larger temperature differentials (i.e., abdominal temperature was warmer relative to foot temperature). While previous studies have found and examined episodes of dysfunctional vasodilation (i.e., foot temperature warmer than abdominal temperature) in very premature infants, this was the first study to examine adjusted mean temperature differentials over time (Lyon, et al., 1997). These larger temperature differentials could indicate autonomic dysfunction associated with prematurity. However, given FiO_2 and respiratory support increases were also associated with decreased body temperatures, these larger temperature differentials could represent peripheral vasoconstriction in response to ongoing cold stress.

5.2 Limitations

This was an intensive exploratory study; thus, the sample size was small. Also, the sample was somewhat homogenous, lacking ethnic and racial representation. Given the physiologic and video data were previously collected, data analysis was limited by the parent study design. Also, the sample represented a single neonatal intensive care unit; therefore, the generalizability to other very premature infants may be limited, as the infant temperatures and respiratory outcomes may be associated with the standard of care and institutional guidelines.

5.3 Future Directions

5.3.1 Nursing Implications

Nursing care is essential to very premature infant growth and development. Providing optimal care without increasing the risk of temperature instability in this vulnerable population can be a challenge. Results from this study further support the need for bundling infant care, as well as potentially limiting the duration of care to minimize the disruption of the infant's neutral thermal environment. Their vulnerability to thermal instability is highlighted by the frequency of hypothermia across the 14 days, the occurrence of hypothermia during care, and the time required for temperature recovery following porthole closure. These findings also illuminate the limitations of servo control mode in maintaining very premature infant thermal stability. Furthermore, the higher body temperatures noted in smaller infants may reflect the protective effects of higher humidity on evaporative heat loss. Thus, results from this study support clinical practice adaptations that create a more stable, consistent thermal environment, which may be achieved through bundled care, limiting bundled care duration, shifting incubator setting

from servo control to air temperature control mode, and increasing humidity levels for very premature infants >750 grams.

5.3.2 Research Implications

This dissertation was the first step in my program of research. Although this was an exploratory study with a small sample size, findings from this study will inform prospective research that will utilize ecological momentary assessment (EMA) methodology. EMA provides a framework for longitudinal research that promotes appropriate data collection and advanced statistical analysis. It also allows for rigorous case examination, which may uncover within-subject variability at any point in time; thus, research is not limited to the inferences that aggregate measurement analysis can provide (Dunton, 2017). EMA methodology can also evaluate for the temporal sequence: variables leading to behavior and outcomes after the behavior occurs (i.e., antecedent-consequence relations) (Dunton, 2017; Shiffman et al., 2008). Therefore, EMA can assist in delineating the relationships between very premature infant temperatures over time and acute and chronic respiratory morbidity and could be expanded to examine relationships between other types of physiological data and infant outcomes.

Neonatal care is dictated by the external interpretation of objective and subjective symptoms. However, these infants are unable to self-report, so neonatal care is poorly represented in symptom science. The use of EMA methodologies can assist in identifying causal relationships between infant symptoms and chronic morbidity. The development of a neonatal symptom science model would assist in delineating infant symptom clusters into phenotypes, as well as identify associated biomarkers; therefore, laying the groundwork for precision medicine to prevent or attenuate chronic morbidity.

5.4 Conclusion

Very premature infants are a highly vulnerable population. The consequences of premature birth can bring lifelong morbidity and associated financial implications. Research has identified temperature instability as a risk factor for chronic morbidity in very premature infants. This study has also identified a relationship between temperature instability and symptoms of acute respiratory morbidity. Despite efforts to create a neutral thermal environment, the daily care and respiratory support essential for very premature infant survival can result in thermal instability. However, research has been unable to declare a causal relationship between daily care and thermal instability, or thermal instability and acute and chronic respiratory morbidity. Given that very premature infants have global body system immaturity, it is also unclear if acute and chronic morbidities are a consequence of thermal instability, or if thermal instability is a symptom of physiological instability that clusters with these outcomes. The use of EMA methodologies in future prospective studies may help delineate if these associations are antecedent-consequence relationships. If these relationships are identified, large, prospective studies can be developed to validate these findings and delineate clinical practice change that can be adapted to reduce infant risk.

Appendix A. Matrix Table of Retrieved Articles

Year/ Authors	Purpose	Sample/ Study Design	Temperature (°C) /Humidity (mg/L) Findings
Changes from Humidifier to Infant			
1986 Tarnow-Mordi, W.O., *et al.*	Evaluate AH from AV	14 neonates/ Obs	HH temp setting: 32.0 to 38.0 AH: 63% of values less than 33 Correlation between AH & FR dependent on HH model
1986 Tarnow-Mordi, W.O., *et al.*	Evaluate AH from AV with 5 different HH & different temp settings	Size NR neonates/ Obs	HH temp setting: *32.4 to 35.5 *AT: 32.4 to 35.5 *AH: 29.5 to 37.9
1991 O'Hagan, M., *et al.*	Evaluate relationship between AH & HH temp settings.	48 neonates/ Obs	HH temp setting (°C): 37.0 *AT: 35.3 *AH: 37.4 (*Incb*); 33.8 (*RW*) Direct correlation: AH & AT (**34.1°C* incb) Inverse correlation: AH & AT (**32.9°C* incb)
1997 Schiffmann, H., *et al.*	Evaluate efficiency of HH & HME during AV	40 infants/ Obs	HH temp setting: *NR* AT: 31.9 (HH) *(**HME was NR*) *AH: 34.0 (*HH*); 33.8 (*HME*) *AH with HME: 35 (*Incb*); 33.9 (*RW)*; 33.4 (*Crib*) (***HH was not reported)*
2004 Davies, M.W, *et al.*	Evaluate & compare AT from AV in Incb vs RW	25 neonates/ Obs	HH temp setting: 36.0 & circuit 37.0 *AT: 34.9 (*Incb*) & 33.1 (*RW*) Direct correlation: AT & Incb temp
2007 Fassassi, M., *et al*.	Evaluate & compare AT/AH from AV with HH vs HME	14 neonates/ PRC	HH temp setting: 37.0 *AT: 34.6 (*HH*); 33.8 (*HME*) Direct correlation: AT & Incb temp *AH: 36.6 (*HH*); 32.1(*HME*)
2001 Todd, D.A., *et al*.	Evaluate AT from AV with different HH & ATPs	Artificial lung/ Obs	HH temp setting: 36.5 & circuit 39.0 *AT: 36.2 to 40.0 (ATP inside Incb); 33.9 to 40.6 (ATP outside Incb) Direct correlation: AT & Incb temp when ATP outside Incb
2001 Todd, D.A., *et al.*	Evaluate AH from AV with different HH & ATP placement	Artificial lung/ Obs	HH temp setting: 36.5 & circuit 39.0 Inverse correlation: AH & Incb temp AH: Higher when ATP outside the Incb
2002 Carter, B.G., *et al.*	Evaluate impact of the air temp entering HH on AH	HH/ Obs	HH temp setting: 37.0 & 40.0 Inverse correlation: AH & air temp entering HH
2008 Jardine, L.A., *et al*.	Evaluate AT from AV	Artificial lung/ Obs	HH temp setting: 37.0 & circuit 40.0 *AT: decreased from 36.9 (*ETT connector*) to 33.9 (*1cm into ETT*)
2008 Yamada, Y., *et al.*	Evaluate AT from AV with built-in HH	Artificial lung/ Obs	HH temp setting: 39.0 *AT: 32.3 to 34.1 (*ETT*) Direct correlation: AT (*ETT*) & Incb temp Direct correlation: AT (*ETT*) & MV

2011 Chang, G., *et. al.*	Evaluate impact of FR on AT/RH & resistance during CPAP, HFNC, & NC	Artificial lung/ Obs	HH temp setting: 36.2 (CPAP); 39.0 (HFNC); 24.9 (NC) *AT: 34.5(*CPAP*); 34 (*HFNC*); 35.9 (*NC*) Direct correlation: AT & FR *RH(%): 77 (*CPAP); 82 (HFNC);* 57 (*NC)* Direct correlation: AH & FR (HFNC) Inverse correlation: AH & FR (NC/CPAP)
2013 Preo, B., *et al.*	Evaluate AT/AH from AV with built-in HH & different: temp settings, circuit length/insulation, ATP position, & Incb temp	Artificial lung/ Obs	HH temp setting: 37.0 & 39.0 *AT: 32.9 to 36.8 Direct correlation: AT & Incb temp *AH short circuit: 26.0 to 32.3 *AH long circuit: 33.1 to 33.8 Insulation improved AH with short circuit
Artificial Ventilation Settings			
1971 Epstein, R.A[7]	Evaluate AT from AV with new HH	15 Infants/ Obs	HH temp setting(ºF): *98-100* *AT(ºF): 94.0 Direct correlation: AT & MV
1986 Tarnow-Mordi, W.O., *et al.*	*See Above*		
1999 Schiffmann, H., *et al.*	Evaluate & compare AH from HFOV with HH vs HME	Artificial lung/ Obs	HH temp setting: 33.0 to 37.0 *AT: 34.6 to 38.6 (*HH*); 36.1(*HME)*. Direct correlation *(HH)*: AH & FR Inverse correlation *(HME)*: AH & Amplitude
2008 Yamada, Y., *et al.*	*See Above*		
2009 Nagaya, K., *et al.*	Evaluate & compare AT/AH from HFV vs IPPV	Artificial lung Obs	HH temp setting: 37.0 & circuit 40.0 Direct correlation: AT & Incb temp Direct correlation: AT/AH & HFV FR. *AH: 43.5 *(IPPV*); <35mg/L (*HFV*)
2009 Chikata, Y., *et al.*	Evaluate AH from HFOV with different circuits & HFOV settings	Artificial lung/ Obs	HH temp setting: 37.0 & circuit 40.0 Inverse correlation: AT/AH & circuit length AH: higher with embedded vs inner wire Direct correlation: AH & TV (inner wire)
2011 Chang, G., *et. al.*	*See Above*		
2013 Schena, E., *et al*.	Evaluate impact of MV & RR on circuit condensation during AV	Artificial lung/ Obs	HH temp setting: 37.0 & circuit 40.0 Condensation increased over time (*all vent settings*). Direct correlation: condensation & RR/MV
2015 Nagaya, K., *et al.*	Evaluate & compare AT from HFV vs IPPV	Artificial lung/ Obs	HH temp setting: 37.0 & circuit 40.0 Direct correlation: AT & Incb temp Direct correlation: AT & TV
2016 Roberts, C., T., *et al*	Evaluate AT in oropharynx during CPAP/HFNC/LFNC	Manikin/ Obs	HH temp setting: 37.0 AT: 34.2 to 38.3 (*CPAP*); 33.7 to 36.3 (*HFNC*); 33.4 to 34.1 (*LFNC*)
Environmental Temperature			

1991 O'Hagan, M., *et al.*	*See Above*		
1997 Schiffmann, H., *et al.*	*See Above*		
2001 Todd, D.A., *et al*	*See Above*		
2001 Todd, D.A., *et al.*	*See Above*		
2002 Carter, B.G., *et al.*	*See Above*		
2004 Davies, M.W., *et al*.	*See Above*		
2007 Fassassi, M., *et al.*	*See Above*		
2008 Yamada, Y., *et al.*	*See Above*		
2009 Nagaya, k., *et al*.	*See Above*		
2013 Preo, B., *et al.*	*See Above*		
2015 Nagaya, K., *et al.*	*See Above*		
2017 Yusuke, C., *et a*l. (Yusuke et al., 2017) (Yusuke et al., 2017) (Yusuke et al., 2017) (Yusuke et al., 2017) (Yusuke et al., 2017)	Evaluate impact of environmental temp on AH during HFNC	Artificial lung/Obs	HH temp setting: 40.0 Direct correlation: AH & Incb temp AH: 16.5 (*Incb temp *26.1°C*) AH: 35.6 (*Incb temp *37.0°C*)
Infant Mouth Position			
2017 Fischer, H.S., *et al.*	Evaluate impact of open (*op*) vs closed (*cl*) mouth on oropharynx AT/AH ($g\ m^{-3}$) during CPAP	Mouth model/ Obs	HH temp setting: *invasive mode* AT (maximum): 36.4 *(cl*); 34.4 *(op*) *AH with HH: 42.6 (*cl); 35.7(op*) *AH with dry HH: 23.2 (*cl*); 4.3 *(op*) *AH w/o *HH*: 23.2 (cl); 3.0 (*op*)
Did Not Fit Under Theme			
1989 Tarnow-Mordi, W.O., *et al.*	Evaluate relationship between AT & CLD	149 neonates/ Retro	HH temp setting: 34.0 to 38.0 *AT: 34.5 to 37.6

Abbreviations*: AV: artificial ventilation; HH: heated humidifier; HME: heat moisture exchanger; AT: air temperature; temp: temperature; RH: relative humidity; AH: absolute humidity; ATP: air temperature probe; Obs: observational; Retro: retrospective; PRC: prospective randomized control; Incb: incubator; RW: radiant warmer; CPAP: continuous positive airway pressure; HFNC: high flow nasal cannula; LFNC: low flow nasal cannula; HFOV: high frequency oscillatory ventilation; IPPV: intermittent positive pressure ventilation; HFV: high frequency ventilation; TV: tidal volume; FR: flow rate; CLD: chronic lung disease*

Appendix B. Temperatures Over First Five Days of Life

Temperature	Adjusted Mean ± SD[1]	Slope Coefficient[2]	Standard Error (SE)	*p*-value
Body		0.01214	0.0193	0.5426
DOL 1	36.5 ± 0.4			
DOL 2	36.5 ± 0.3			
DOL 3	36.5 ± 0.3			
DOL 4	36.5 ± 0.3			
DOL 5	36.5 ± 0.3			
Foot		0.0061	0.0512	0.9069
DOL 1	35.8 ± 0.5			
DOL 2	35.8 ± 0.4			
DOL 3	35.8 ± 0.3			
DOL 4	35.8 ± 0.3			
DOL 5	35.8 ± 0.4			
Temp Differential		0.0059	0.0421	0.8911
DOL 1	0.7 ± 0.5			
DOL 2	0.7 ± 0.4			
DOL 3	0.7 ± 0.3			
DOL 4	0.7 ± 0.2			
DOL 5	0.7 ± 0.3			
Incubator		-0.1056	0.0878	0.2542
DOL 1	35.2 ± 1.1			
DOL 2	35.1 ± 0.9			
DOL 3	35.0 ± 0.8			
DOL 4	34.9 ± 0.7			
DOL 5	34.8 ± 0.8			

Abbreviations: DOL=day of life; temp=temperature
[1] Mean and Standard deviation (SD) adjusted for fixed, random, and within-infant nesting effects
[2] Slope coefficient= unstandardized trajectory slope

Appendix C. Temperatures Over First 14 Days of Life

Temperature	Adjusted Mean ± SD[1]	Slope Coefficient[2]	Standard Error (SE)	*p*-value
Body		0.001743	0.0109	0.8759
DOL 1 - DOL 4	36.5 ± 0.3			
DOL 5 - DOL 12	36.5 ± 0.2			
DOL 13- DOL 14	36.5 ± 0.3			
Foot		0.0081	0.0133	0.5545
DOL 1- DOL 2	35.8 ± 0.3			
DOL 3	35.9 ± 0.3			
DOL 4 -DOL 10	35.9 ± 0.2			
DOL 11- DOL 14	35.9 ± 0.3			
Temp Differential		-0.0058	0.0151	0.7097
DOL 1 – DOL 3	0.7 ± 0.3			
DOL 4 – DOL 8	0.7 ± 0.2			
DOL 9	0.6 ± 0.2			
DOL 10 - DOL 11	0.6 ± 0.3			
DOL 12 – DOL 14	0.6 ± 0.4			

Abbreviations: DOL=day of life; temp=temperature
[1] Mean & Standard deviation (SD) adjusted for fixed, random, & within-infant nesting effects
[2] Slope coefficient=unstandardized trajectory slope

Appendix D. Temperatures Following Porthole Opening

Temperature	Adjusted Mean ± SD[1]	Slope Coefficient[2]	Standard Error (SE)	*p*-value
Body		-0.02082	0.00295	<0.0001
1 minute	36.4 ± 0.3			
2 minute	36.4 ± 0.3			
3 minute	36.3 ± 0.3			
4 minute	36.3 ± 0.3			
5 minute	36.3 ± 0.3			
6 minute	36.3 ± 0.3			
7 minute	36.3 ± 0.3			
8 minute	36.2 ± 0.3			
9 minute	36.2 ± 0.3			
10 minute	36.2 ± 0.3			
11 minute	36.2 ± 0.3			
12 minute	36.2 ± 0.3			
13 minute	36.1 ± 0.3			
14 minute	36.1 ± 0.3			
15 minute	36.1 ± 0.3			
Incubator		-0.04029	0.01288	0.0100
1 minute	35.0 ± 0.8			
2 minute	35.0 ± 0.8			
3 minute	34.9 ± 0.8			
4 minute	34.9 ± 0.8			
5 minute	34.8 ± 0.8			
6 minute	34.8 ± 0.8			
7 minute	34.7 ± 0.8			
8 minute	34.7 ± 0.8			
9 minute	34.6 ± 0.8			
10 minute	34.6 ± 0.7			
11 minute	34.6 ± 0.7			
12 minute	34.6 ± 0.7			
13 minute	34.5 ± 0.7			
14 minute	34.5 ± 0.7			
15 minute	34.5 ± 0.7			

Abbreviations: DOL=day of life; temp=temperature
[1] Mean and Standard deviation (SD) adjusted for fixed, random, and within-infant nesting effects
[2] Slope coefficient= unstandardized trajectory slope

Appendix E. Temperatures Following Porthole Closure

Temperature	Adjusted Mean ± SD[1]	Slope Coefficient[2]	Standard Error (SE)	*p*-value
Body		0.00835	0.00175	0.0005
1 minute	36.4 ± 0.3			
2 minute	36.4 ± 0.3			
3 minute	36.4 ± 0.3			
4 minute	36.4 ± 0.3			
5 minute	36.4 ± 0.3			
6 minute	36.4 ± 0.3			
7 minute	36.4 ± 0.3			
8 minute	36.5 ± 0.3			
9 minute	36.5 ± 0.3			
10 minute	36.5 ± 0.3			
11 minute	36.5 ± 0.3			
12 minute	36.5 ± 0.3			
13 minute	36.5 ± 0.3			
14 minute	36.5 ± 0.3			
15 minute	36.5 ± 0.3			
Incubator		0.01018	0.00614	0.1280
1 minute	35.2 ± 0.7			
2 minute	35.2 ± 0.7			
3 minute	35.2 ± 0.7			
4 minute	35.2 ± 0.7			
5 minute	35.2 ± 0.7			
6 minute	35.2 ± 0.7			
7 minute	35.2 ± 0.7			
8 minute	35.3 ± 0.7			
9 minute	35.3 ± 0.8			
10 minute	35.3 ± 0.8			
11 minute	35.3 ± 0.8			
12 minute	35.3 ± 0.8			
13 minute	35.3 ± 0.8			
14 minute	35.3 ± 0.8			
15 minute	35.3 ± 0.8			

Abbreviations: DOL=day of life; temp=temperature
[1] Mean and Standard deviation (SD) adjusted for fixed, random, and within-infant nesting effects
[2] Slope coefficient= unstandardized trajectory slope

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Biography

Jane Lynne Harney-Ralphe graduated from the University of Iowa in 1995 with a Bachelor of Science in Nursing, then in 2002 with a Master of Science in Nursing, Pediatric Nurse Practitioner. Ms. Ralphe received a University of Iowa Graduate Tuition Scholarship from 2001-2002, which funded her graduate studies. She then completed a postmaster's Neonatal Nurse Practitioner program at the University of Missouri—Kansas City in 2015. Ms. Ralphe worked as a staff nurse, then as a nurse practitioner in the neonatal intensive care unit for over 20 years before enrolling at Duke University School of Nursing Ph.D. program. During her doctoral studies, she was awarded a research grant from Sigma Theta Tau/Council for Advancement in Nursing Science, first-authored a peer-reviewed systematic literature review and Abstract, and presented at several academic conferences and workshops. Ms. Ralphe completed the Certificate in College Teaching at Duke's Graduate School, served as a member of Duke's judicial advisory board, and was a student facilitator in the Ph.D. program. She was inducted into Sigma Theta Tau International Honor Society in 1995, was inducted into Sigma's Gamma Chapter at Duke University in 2016, and continues to serve as a member of several nursing and neonatal professional organizations.