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Negative Temperature Differential in Preterm Infants Less Than 29 Weeks Gestational Age: Associations with Infection and Maternal Smoking

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Abstract

Background—Hypothermia is related to increased morbidity and mortality in very preterm infants; continuous temperature monitoring is necessary. Thermoregulation is limited in preterm infants.

Objectives—The purpose of the research was to assess describe negative temperature differential (NTD) and assess the associations of NTD with infant demographic characteristics, medical history, and clinical events.

Methods—An exploratory, case study design was used. Abdominal and foot temperature was measured every minute over the first two weeks of life in 22 preterm infants < 29 weeks GA.

Results—All infants experienced NTD. Daily NTD in all infants across all study days ranged from 0–70.7%; 2-week mean NTD over all infants ranged from 7.3–38.5%. Four infants treated for late onset of infection had a higher NTD than 18 infants without infection ($M = 27.8\%$, $SD = 9.52$ vs. $M = 16.4\%$, $SD = 5.34$, $p < .05$). Although not statistically significant, higher mean percent of NTD were noted in infants having early onset infection (24.1% vs. 16.4%), African-

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American race (20.0% vs. 15.3%) and/or being born to a mother who smoked during pregnancy (26.6% vs. 16.7%).

Discussion—A larger study is needed to examine associations between NTD and race, maternal smoking history, and infection. NTD might be used as a biomarker to guide acute clinical care and identify infants at risk for acute and chronic morbidity.

Keywords

infection; maternal smoking; neonatal intensive care; thermoregulation; very low birthweight

More than 63,000 very preterm infants (< 32 weeks gestational age [GA]), are born annually in the United States (Hamilton et al., 2015). Survival free from major morbidity is a significant problem in this population due to immature and underdeveloped physiological systems. Thermoregulation—regulation of thermal stability—either by the infant or the care provider, to achieve a heat gain/heat loss balance is important because hypothermia or hyperthermia contributes to increased mortality and morbidity in the very preterm infant (Bauer, Hentschel, Zahradnik, Karck, & Linderkamp, 2003; Buetow & Klein, 1964; Day, Caliguiri, Kamenski, & Ehrlich, 1964; Hazan, Maag, & Chessex, 1991; Vohra, Frent, Campbell, Abbott, & Whyte, 1999; Wilson et al., 2016). Despite over 50 years of research and standards of practice to improve thermoregulation of the preterm infant, hypothermia after birth (Mank et al., 2016) and during the neonatal period (Mok, Bass, Ducker, & McIntosh, 1991; Thomas, 2003) continues to be a problem. Research directed towards understanding the physiological processes of thermoregulation in the very preterm infant is necessary to better understand the links between thermoregulation and morbidity.

Human body temperature is regulated by balancing heat loss with heat production. This process is controlled through thermal sensors, afferent pathways, an integration system in the central nervous system, efferent pathways, and target organs (Gordon & Heath, 1986). Central and peripheral thermoreceptors sense temperature change and can modulate heat loss with physiological changes to generate heat. In humans over the age of 12 months, the hypothalamus causes motor neurons to signal the skeletal muscles to produce shivering—oscillating rhythmical muscle contractions and relaxations that generate heat. Infants less than a year in age generate heat through chemical thermogenesis—also called brown fat metabolism or nonshivering thermogenesis (NST) (Hull & Smales, 1978). All infants have some capacity to generate heat from NST. Once an infant is delivered and the umbilical cord is clamped, exposure to the cold extra-uterine environment will trigger NST (Asakura, 2004).

When an infant becomes cold and body temperature decreases, peripheral and central thermoreceptors detect temperature change (Figure 1). Immediately, peripheral skin receptors should respond through vasoconstriction of the peripheral vessels to diminish heat loss, increasing blood flow to the central body. In adults, the next physiological step is to inhibit sweating and increase shivering to increase body heat production. In a neonate, vasoconstriction is the predominant result of activation of peripheral skin receptors because they cannot inhibit sweating or increase shivering. While peripheral vasoconstriction is mediated through the autonomic nervous system (ANS) by sympathetic control (Bini,

Hagbarth, Hynninen, & Wallin, 1980), little research has examined maturation of the sympathetic nervous system. Maturation of the parasympathetic system is correlated with gestational and postnatal age and is immature in very preterm infants (Longin, Gerstner, Schaible, Lenz, & König, 2006). Therefore, when a very preterm infant becomes hypothermic, the first physiologic reaction should be peripheral vasoconstriction, whereby vessels in the feet and hands constrict to shunt blood to the central body to increase perfusion and warmth and protect the brain, heart, and gastrointestinal tract. However, this mechanism is not operative in most very preterm infants in the first hours after birth (Knobel, Holditch-Davis, Schwartz, & Wimmer, 2009; Lyon, Pikaar, Badger, & McIntosh, 1997). Instead, very preterm infants have been noted to exhibit a negative temperature differential (NTD)—a thermal pattern characterized by low central temperature and higher peripheral temperature. We define NTD as any occurrence of an abdominal (central) temperature lower by any amount than the foot (peripheral) temperature.

Central thermoreceptors send signals to the hypothalamus which causes norepinephrine to be released from the nerve endings in the brown adipose tissue (BAT) due to sympathetic activity (Figure 1). BAT contains a high number of mitochondria and is rich in capillary blood supply, innervated with sympathetic nerve fibers making it ideal for thermogenesis. Simultaneously, thyroid stimulating hormone (TSH) increases (Hall, 2011). Increased TSH results in the release of thyroxine (T₄), which is converted to triiodothyronine (T₃) due to the presence of 5'-monodeiodinase (Power & Blood, 2011). The conversion of T₄ to T₃ is crucial for the thermogenic response (Sauer, 1995) because T₃ locally acts to upregulate thermogenin or uncoupling protein (UCP1) causing heat production through metabolism of fat.

BAT develops early in the fetal stage (Hatai, 1902). Only about 20–30 grams of BAT are necessary to produce heat by NST and (Hull & Smales, 1978) the structure of BAT is well developed in extremely preterm infants at 25 weeks GA (Sauer, 1995), with BAT comprising about 1–2% of body weight (Nechad, 1986). However, BAT is not the only component essential to generate heat through NST. Very preterm infants probably have limited abilities to generate heat through NST due to decreased content of UCP1 and 5'-monodeiodinase (Houstěk et al., 1993), which are essential components of NST. UCP1 increases from approximately 29.4 pmol/mg in infants at 25 weeks GA to approximately 62.5 pmol/mg in infants of 40 weeks GA (Houstěk et al., 1993). After 32 weeks gestational age, a major increase in UCP1 increases an infant's ability to generate heat. A major increase in the enzyme 5'-monodeiodinase also occurs at 32 weeks GA, with a fourfold increase by term gestation (Houstěk et al., 1993; Power & Blood, 2011). Thus, very preterm infants (< 32 weeks gestation) are born without these advantages, and can rapidly become hypothermic at any exposure to cold. Such infants have compromised abilities to send heat to essential central organs through peripheral vasoconstriction and to generate heat due to inefficient heat production, both of which increase an infant's risk for morbidity and mortality.

Acute and chronic morbidity can lead to extended hospitalizations in the neonatal intensive care unit (NICU) (Ertugrul et al., 2016; Kurek Eken, Tüten, Özkaya, Karatekin, & Karateke, 2017). Infection is one important cause of neonatal morbidity, which may contribute to increased mortality. Early onset neonatal sepsis (EONS) occurs within the first seven days of

life, whereas late onset sepsis (LOS) occurs after the first week of life and prior to hospital discharge. EONS confirmed by positive blood cultures is rare but frequently suspected due to high prevalence of prolonged rupture of membranes and chorioamnionitis (Dey et al., 2016). Diagnosis of EONS is difficult because clinical characteristics are nonspecific and there is usually no evidence of infection. EONS are caused most commonly by group B streptococcus and *Escherichia coli* (Bedford Russell & Kumar, 2015) and result most frequently from ascending bacterial transmission from the maternal genital tract. LOS usually results from the postnatal nosocomial hospital environment (Dong & Speer, 2015).

Determining if infection is present is difficult and care-providers largely depend on signs and symptoms such as respiratory distress, decreased activity, poor feeding, and poor perfusion (Johnson & Messier, 2016). Conclusive blood culture results determining LOS are more common, with incidence as high as 50% of very preterm infants (Agarwal, Sriram, & Rajadurai, 2015; Silva, Motta, Nunes, Schardosim, & Cunha, 2015; Stoll et al., 2015). Coagulase-negative staphylococci (CoNS) are the most common, accounting for approximately 50–75% of all neonatal infections in industrialized countries (Dong & Speer, 2015). Gram negative infections in neonates result from *E. coli*, *Klebsiella*, *Enterobacter*, and *Pseudomonas*. Fungi are also major pathogens, especially *Candida*.

A type of infection related to inflammation of the gastrointestinal (GI) track called necrotizing enterocolitis (NEC) occurs in 5–15% of premature infants (Stoll et al., 2010; Yee et al., 2012) and has a mortality rate as high as 41% (Qian et al., 2017). Incidence increases with decreasing GA. Hypothermia after birth is associated with incidence of NEC in preterm infants (Lyu et al., 2015; Yu, Joseph, Bajuk, Orgill & Astbury, 1984). Abnormal postnatal circulation can lead to problems with feeding intolerance and intestinal motility, both of which are associated with NEC (Robel-Tillig, Knüpfer, Pulzer, & Vogtmann, 2004).

Most NICUs use one monitoring point for central body temperature measurement as standard of care, which may be assessed on an infant's abdominal/flank area, back, or axillae. However, one single time point for measurement gives no information about the infant's use of energy to maintain thermal stability (Lyon & Freer, 2011). Continuous surveillance of central (abdominal) and peripheral (foot) temperature is the optimal method for monitoring thermal stability in very preterm infants because low central temperatures and/or a widening central peripheral temperature difference may alert clinicians to neonatal stress or illness (Lyon & Freer, 2011; Messaritakis, Anagnostakis, Laskari, & Katerelos, 1990). Normally, in a stable preterm infant, the abdominal temperature is about 0.5° to 1°C above the foot temperature (Lyon & Freer, 2011). Monitoring thermal stability through continuous temperature measurement is crucial to preventing hypothermia in very preterm infants and we believe it can be used as a biomarker for guiding care.

Previously, we examined abdominal temperature (AT) and foot temperature (FT) in 10 premature infants < 29 weeks GA every minute over their first 12 hours of life (Knobel, Holditch-Davis, et al., 2009). Only one infant briefly exhibited peripheral vasoconstriction by showing AT higher than FT by a 2°C temperature difference. More importantly, 7 of 10 infants showed NTD, with their AT lower than their FT for most of the first 12 hours of life.

The NTD thermal pattern suggests that perfusion is decreased centrally due to decreased warmth and blood flow, and increased in the feet. Very little published research has described this finding. Messaritakis et al. (1990) found that in sick infants with a mean birthweight of 1,300 grams, FT remained elevated while AT became very low. However, in the entire sample, the AT averaged higher than the FT. These researchers postulated that the sicker infants did not have the ability to muster a vasoconstrictive response because of the severity of their illnesses; the group that showed this abnormal thermal pattern had the highest mortality. Lyon et al. (1997) examined 83 infants less than 1000 g at birth over their first five days of life and found that infants experienced NTD 18.3% of the time on the first day of life. They found the abnormal temperature pattern was largely associated with handling and found the infants with NTD had a higher mortality rate; however, noted they were the sickest infants. Because of these previous findings, we wanted to examine thermal patterns beyond the first day of life in this vulnerable population.

Purpose

The purpose of the overall study was to examine longitudinal body temperature in 30 preterm infants less than 29 weeks GA over their first two weeks of life in relationship to hypothermia and morbidity outcomes. (A pilot study of five infants was completed to evaluate methods prior to initiating enrollment in the larger study [Knobel, Levy, Katz, Guenther, & Holditch-Davis, 2013].) The three-year parent study assessed body temperature using measured thermistor skin temperatures, infrared thermal imaging (Knobel-Dail, Holditch-Davis, Sloane, Guenther, Katz, 2017), and compared foot temperature to perfusion index in the foot (Knobel-Dail, Tanaka, Holditch-Davis, & White, 2016). Perfusion index analysis confirmed that foot temperature is elevated due to increased perfusion in the foot, which rules out this abnormal temperature pattern as being due to external factors, such as high incubator heat. Longitudinal temperatures were also compared to care events and procedures assessed using continuous video observation over each infant's first five days of life, with the results paper in progress. This data-rich study has taken two years to analyze and because of the large amount of data to report, results are being disseminated by aims and methodology. The purpose of this report is to describe results examining skin AT and FT in 22 preterm infants less than 29 weeks GA over their first two weeks of life in relationship to morbidity and mortality.

Methods

Design and Sample

This was an exploratory, descriptive study using a case study design to examine body temperature and perfusion in preterm infants over their first two weeks of life. A case study design allows researchers to consider data obtained from mixed methods, enriching the data from several different methodologies to allow for synthesis to address the specific aims (Zainal, 2007). In our study, each infant had data from several different sources, as described in our purpose, which informed the case. This study analysis considered longitudinal body temperature from instrumentation in relationship to clinical context variables obtained from the electronic health record over the hospital course to generate hypotheses for further

exploration in our program of research. The study was conducted from 2010–2013. The protocol was approved by the Institutional Review Board approval at a North Carolina university hospital.

Parents of infants expected to be born at < 29 weeks GA were approached for consent for their infant to participate, if the mother was not in active labor. We limited the upper GA to target infants that would be only housed in incubators and in need of thermal support and because our last study focused on this GA limit. Infants greater than 29 weeks GA may not need care in heated incubators and many times are admitted directly to open bassinets. Obtaining consent prior to birth was necessary because most infants were delivered at unknown times and mothers in nonactive premature labor might be hospitalized from days to months. More parents were approached for consent than were needed for study during the enrollment window because only a fraction of infants born qualified to be enrolled in the study. Infants were eligible if their birth weight was > 500 g and < 1200 g and if they were determined to be < 29 weeks GA by obstetrical ultrasound or maternal obstetrical dates. They were not included if there were any visible anomalies or medical complications initially after birth such as cardiac or pulmonary decompensation requiring resuscitation. We obtained permission from each infant's attending neonatologist to include them in the study prior to initiating data collection.

Procedures

Study enrollment—Enrollment of infants occurred once they were admitted to the NICU. This NICU used Draeger Caleo incubators in servo mode as standard of care; skin temperature of the abdominal area was controlled to the NICU standard of 36.5°C using the incubator servo control. Infants were stabilized on warmer tables under radiant heat, then transferred to an incubator within approximately 4–6 hours. A research assistant attached Y series Steri-Probe skin temperature probes (Model 499B, Cincinnati Sub-Zero, Cincinnati, OH) to the infant after stabilization. One skin probe was attached to the abdominal/liver/flank area with a fabric tape (Mepitac, Molnlycke Health Care, Gothenberg, Sweden) and the second probe was attached to the sole of a foot and covered with the same fabric tape. The abdominal probe was covered by a reflective cover; when used in this population with inherent thin skin, it provided a temperature very close to central temperature (Simbrunner, 1995). A third thermistor was positioned in the ambient space of the incubator, close to the study infant, to measure minute-to-minute ambient air temperature. All three temperature probes were connected to a 4-channel data logger, model SP-1400-44Y (Veriteq Instruments; Vaisala; Richmond, British Columbia, CA), which sampled and stored temperatures every minute for 2 weeks (20,000 measures).

Nursing responsibilities—Nurses repositioned infants and examined skin at probe sites throughout each day according to standard care. Probe positions were changed at least every 6–8 hours as needed, keeping the probe on the same general area of the skin. Each infant's nurse documented skin condition on the infant's study log. Study probes were labeled with the location (foot vs. abdomen) to prevent probes from being moved to the wrong position.

Data collection—Once the infant reached two weeks of age, temperatures were downloaded to a secure server—in data text files—and then imported into a SAS (Cary, NC) data set for analysis. The research nurse recorded maternal history data, infant demographics, infant medical history and clinical events obtained from the infant electronic medical record. Infant records were followed for morbidity and outcome data until discharge.

Variables and Measurement

Negative temperature differential—The NTD was calculated by quantifying the number of minutes when the AT was less than FT, out of each day and week, converting it to a percentage. The mean percentage of minutes for each study day and over the entire 2-week study period were assessed for each infant.

Infant characteristics—Infant characteristics were collected from the electronic medical chart of the mother and infant, including birth weight, GA, gender and race. Race was assigned by mother's declared race and was assessed as being African American or non-African American for purposes of analysis.

Medical conditions—The research nurse followed the electronic medical record for all diagnoses as well as laboratory and radiology results by searching progress notes and history notes. The infant conditions we explored in analyses were NEC and infection and the maternal conditions were smoking during pregnancy and chorioamnionitis. We defined infants born to mothers with chorioamnionitis if the mother's medical record indicated this diagnosis, or there was indication in the record of foul smelling amniotic fluid, or there was prolonged rupture of membranes AND the infant was treated with antibiotics for early EONS. NEC was defined as a diagnosis made in an infant's medical chart from an x-ray reading or diagnosis in the progress notes. LOS was operationalized as bacteria or fungi cultured from the blood, urine or skin after the first five days of life that was considered pathogenic and treated with antibiotics.

Clinical events—The research nurse also surveyed the medical record for clinical events—interventions that occurred during the 14 days of study, such as blood transfusions, central catheter placement, continuous positive airway pressure (CPAP) respiratory management, and endotracheal intubation. We selected these particular events because they were procedures or treatments that may have an impact on thermoregulation and the medical conditions that we were exploring.

Analysis

The primary aim of this analysis was to describe longitudinal body temperatures and daily and two-week NTD and to explore associations with infant characteristics, medical conditions, and clinical events within and between infants. We began by visual inspection of plots of all longitudinal temperature trajectories, including abdominal, foot and inside incubator temperature which was plotted over timelines on the x-axis by week; Figure 2 shows an example. First, we assessed for the expected normal peripheral vasoconstriction response whereby the FT decreases below AT by at least 2°C in response to hypothermia

(Lyon et al., 1997). (Our previous studies have not confirmed a peripheral vasoconstriction response in this population.) Next, we assessed the association between NTD mean minutes with infant characteristics and medical conditions and events. Medical conditions and clinical events were analyzed between infants using a two-week mean NTD for each infant. The medical conditions and events were used as binary classification variables. The *t*-test was used when residuals were normally distributed; the Wilcoxon rank-sum test for very small class sizes. Daily events were analyzed using daily mean minutes of NTD within and between infants. Nominal *p*-values of .05 were used. Because this was a small sample of 22 infants, *p*-values were interpreted with caution; our main goal was to generate hypotheses to be used to design a larger clinical trial. All analyses were conducted using SAS v9.4 (SAS, Cary, NC).

Results

Sample

We obtained informed consent from 107 parents; of these, 76 were not eligible for data collection because they did not meet inclusion requirements or the mother left the hospital before delivering the infant. The remaining 31 infants were eligible; of these, 22 (66.7%) had complete AT and FT data for a 14-day period and were used for the analysis. The mean GA of the 22 infants was 26.9 weeks (*SD*=1.2). Mean birthweight was 860.0 g (*SD*=135.6). Most were female (68%) and African American (68%; the remainder were White [27%] or Hispanic [5%]). Infants were housed in heated, humidified incubators and although the standard of care dictated infants to be kept on servo control at 36.5°C; when electronic records were searched, we found that nurses had actually set servo temperatures ranging from 36.0°C to 37.0°C.

Body Temperature

Over all infants under servo controlled conditions, the mean AT was 36.5°C (*SD*= 0.19; range of means: 36.09°C–36.81°C). The mean FT was 35.9°C (*SD*= 0.28; range of means: 35.10°C–36.40°C). To examine body temperature in each infant over time, we began with a visual inspection of abdominal, foot, and environmental temperatures over each day of the 2-week study period (Figure 2). We identified bouts of hypothermic temperatures within each infant, looking for a peripheral vasoconstriction response.). All infants had intermittent AT below their servo control point (usually 36.5°C)—indicating low central body temperature; however, none of the 22 infants had a consistent peripheral vasoconstriction response reaching 2°C which is no different from our previous findings.

In contrast, all infants had some periods of NTD (AT lower than their FT) into their second week of life. Time with a NTD ranged from 0 to 70.7% mean minutes on any given day for any infant, with a 2-week mean over all infants ranging from 7.3 to 38.5% (Table 1).

Factors Associated with NTD

Table 1 provides a display for examination of relationships between 2-week mean NTD and maternal factors (maternal smoking, chorioamnionitis) and infant factors (demographics, infection, NEC,) for each infant. For easier inspection of relationships, we arranged the NTD

percentage in ascending order. Visually, it is apparent that higher levels of NTD were associated with medical conditions and maternal factors.

Infection—Three of the 22 infants (13.6%) were diagnosed with NEC (Figure 3, Panel A). NTD was more common among the three infants who developed NEC ($M = 26.9\%$, $SD = 10.56$; Range: 17.9–38.5%) than among the 19 infants who did not develop NEC ($M = 17.2\%$, $SD = 6.3$; Range: 7.3–32.7%).

Four infants had infections during their hospital course. Two infants had CoNS infections (at 9 days and 33 days), and one had methicillin-resistant *Staphylococcus aureus* (MRSA) at 23 days. The fourth infant had frequent signs of infection, testing, and treatment with antibiotics at days of life (DOL) 1, 5, 7, 30, 45, and 52, although all blood cultures were negative. However, a skin culture was positive for *Candida* on the abdomen at DOL 5 and *E. coli* was in the urine at DOL 45. The four infants who acquired an infection or UTI had more NTD than the 18 infants without infections ($M = 27.8\%$, $SD = 9.52\%$, Range: 17.6–38.5% vs. $M = 16.4\%$, $SD = 5.34\%$, Range: 7.3–27.3%, $p < .05$; Figure 3, Panel B).

Infants with the highest NTD were all born to mothers with presumed chorioamnionitis (presumed EONS). We compared the six infants born with presumed EONS with the 16 infants who were not treated for EONS (Figure 3, Panel C). NTD was higher in the infants of mothers with chorioamnionitis ($M = 24.0$; $SD = 10.59$; Range: 10.2–38.5%) than the infants who were not treated due to no known maternal history of infection ($M = 16.4\%$; $SD = 4.9$; Range: 7.3–25.3%), but the difference was not significant ($p = .13$).

Maternal smoking—Four infants born to mothers with a smoking history had a higher NTD ($M = 26.6\%$; $SD = 25.75$; Range: 20.3–32.9%) compared to 18 infants born to mothers who did not smoke during pregnancy ($M = 16.7\%$; $SD = 16.99$; Range: 11.6–8.2%) but the difference was not significant ($p = .06$) (Figure 3, Panel D).

Race—The eight infants (5 females and 3 males) having the highest NTD (all $M > 18.2\%$) over the first two weeks were born to mothers who self-reported race as African American. The 14 infants with lower NTD ($M = 17.9\%$) included eight (57%) who were African Americans five (36%) who were White, and one (7%) who was Hispanic. When we examined this relationship statistically, 15 African American infants had a higher mean NTD ($M = 20.0\%$; $SD = 8.54$; Range: 7.3–38.5%) compared to seven nonAfrican American infants ($M = 15.3\%$; $SD = 2.82$; Range: 11.5–17.9%); $p = .07$); however, the relationship was not statistically significant (Figure 3, Panel E).

Clinical events—There was no clear relationship between NTD and central catheter placements but there was a higher NTD associated with having a blood transfusion ($p < .05$) on any particular day (Table 2). Infants having CPAP respiratory management appeared to differ from infants not on CPAP, but difference was not statistically significant ($p < .08$). Infants with an endotracheal tube managed with mechanical ventilation differed from infants who were not intubated (i.e., they were either on room air without ventilation or on CPAP ($p < .004$); infants with endotracheal tubes and mechanical ventilation had lower NTD than those who did not.

Infants with the highest mean NTD over the first two weeks of life had more risk factors than infants with lower mean percentage of minutes with NTD. The infant with the highest NTD was an 880 g, 27 week GA, African American female infant who was born to a mother who smoked and used drugs during her pregnancy (by self-report). Maternal history was positive for prolonged rupture of membranes with probable chorioamnionitis. This infant developed an infection of CoNS and was diagnosed with NEC at 33 days of age (Figure 4). The infant had two blood transfusions and two central catheter placement attempts; she was fed on days 4–11 and 14. The infant was also on dopamine and epinephrine for the first four days of life. She had a mean NTD of 38.5% over the first two weeks of life. Figure 4, Panels A, B, and C show her NTD over the 2-week study period with clinical course annotations.

The only other infant with NTD in the 30% range over their first two weeks of life was an 890 g, 23 week GA African American female infant with 32.7% minutes. This infant was born to a mother who had chorioamnionitis and admitted to drug use during her pregnancy. The infant had presumed EONS at birth and was diagnosed with a MRSA infection at DOL 23. This infant also received two blood transfusions and three attempts at placement of peripherally-inserted central catheters in the first two weeks of life, and was noted to have three episodes of abdominal distention. She was fed from DOL 4–14.

Discussion

NTD may be an important biomarker that can be used in clinical care to identify infants with abnormal thermal patterns. This association needs to be examined in a larger sample to determine if the biomarker may be used to identify infants with acute morbidity. It is not clear if having body temperature with NTD is a sign of acute stress (infection or other local stressors) or a result of prior pathology (such as smoking during pregnancy, chorioamnionitis), or multifactorial with combined etiology. Our sample consisted of preterm infants < 29 weeks GA during their first two weeks of life, which is a very unstable and vulnerable population at a critical time period. We found NTD was associated with early and late onset sepsis. However, a study with larger samples is necessary to confirm this association. Researchers have shown that having a greater central-peripheral temperature difference is associated with late onset of neonatal sepsis (Leante-Castellanos et al., 2012) and that lower central temperatures with a decreased central-peripheral temperature difference are related to extremely sick infants with infection (Messaritakis et al., 1990). In all of our studies, we have not seen preterm infants < 29 weeks GA able to muster a peripheral vasoconstriction response of a positive difference (AT > FT) of 2°C to hypothermic central temperatures; therefore, we believe this population is unable to achieve such a response and using the goal of this level may not be realistic to show a response to hypothermia. We cannot find published literature verifying that this is a consistent response to hypothermia in the very preterm population.

Our findings confirmed that a much smaller central-to-peripheral temperature difference (sometimes being negative) in these preterm infants was associated with diagnosis of infection. Very preterm infants are unable to effectively control vasomotor tone; therefore, these infants as expected, could not muster the same circulatory response to a stressor such as infection by widening their central-to-peripheral difference (Lyon et al., 1997).

Our findings showed infants born to mothers who smoked during pregnancy had a higher mean percentage of minutes with NTD during their first two weeks, signifying an abnormal thermal pattern. We did not expect to examine this relationship a priori and we are interpreting these results with caution due to the small sample; however this relationship needs to be explored further. Environmental exposure to tobacco smoke potentiates morbidity and mortality in infants (Bjornholt, Leite, Albieri, Kjaer, & Jensen, 2016; Jeppesen, Nielsen, Ersboll, & Valerius, 2008; Lanari et al., 2015) and approximately 12% of pregnant women smoke in the United States (Tong et al., 2013). Smoking during pregnancy is related to fetal growth restriction (Akahoshi et al., 2016; Blatt, Moore, Chen, Van Hook, & DeFranco, 2015), preterm delivery (Wallace, Aland, Blatt, Moore, & DeFranco, 2017) and infant death, with 23–34% of infant deaths from Sudden Infant Death Syndrome (SIDS) (Friedmann, Dahdouh, Kugler, Mimran, & Balayla, 2016). Maternal smoking also increases the risk for postnatal infections (Jeppesen et al., 2008; Metzger, Halperin, Manhart, & Hawes, 2013; Sochaczewska, Czeszynska, Konefal, & Garanty-Bogacka, 2010). Therefore, our findings may point to potential relationships amongst these factors.

We also found differences of NTD percentages between infants having certain clinical factors and those without those factors. It is not clear if higher NTD indicates a stressful event or perhaps an infant that is sicker during the day that NTD is measured. Usually, infants in a NICU are deemed sicker if they are intubated versus on CPAP; however, in our study infants who were intubated had less NTD than those that were not intubated and infants on CPAP had higher NTD. We believe that infants who are intubated are more protected and are having less respiratory distress with an easier time ventilating; therefore, may have a more normal thermal pattern due to less energy spent breathing. This is speculation and a larger study would need to examine this relationship.

We now believe that the ANS and hypothalamic-pituitary-adrenal (HPA) axis (Chiang, Taylor, & Bower, 2015) are likely part of the etiological mechanisms leading to abnormal thermal patterns in preterm infants as seen in our study. Premature birth delays ANS maturity (Patural et al., 2014) and being born to a mother who has received antenatal steroids can cause suppression of the HPA axis for up to six weeks (Davis et al., 2006). Dysregulation of the ANS and HPA axis can be related to maternal infection and maternal smoking (Stéphan-Blanchard et al., 2016) and can lead to infection in the infant (Rees, 2014). Dysregulated ANS is also associated with morbid conditions related to the GI tract, connective tissue and immunological system, as well as neurological development (Rees, 2014). Therefore, this mechanism should be studied in detail.

Our plans for future research will extend these findings. A mechanistic study will examine the NTD in very preterm infants in relationship to heart rate variability (HRV). A second study will be large multicenter study of very preterm infants over the course of their hospitalizations will examine continuous central and peripheral temperature examine body temperature, morbidity and mortality, maternal risk factors, and infant demographics. A third possible study should examine the epigenetic factors associated with methylation that occurs in the fetus during pregnancy in a tobacco filled-environment.

Limitations

This exploratory, case study design was implemented with a small sample in one NICU. Due to the small sample size, any relationships found in this study are not generalizable to the general neonatal population. The study was conducted in one NICU using a particular management style, with one specific type of incubator, which also decreases generalizability. Future studies will include several sites and a much larger sample. We also found infants that were diagnosed with NEC had more NTD in their first two weeks compared to infants who did not; however, the occurrences were small—there were not enough NEC cases for statistical comparison. A larger sample will capture more NEC cases. Additionally, we found it was difficult to determine the exact time that nurses changed probe positions and momentarily lowered temperature readings, which artificially decreased skin temperature. We controlled this variable by cleaning data and eliminating temperatures below certain limits. By doing so, it is possible that we removed valid temperatures that represented extreme hypothermia. In the future, a method for determining time periods when the thermistor is not attached to the skin needs to be incorporated in study methods. Lastly, this study population is an acutely ill population due to extreme prematurity. Many factors can affect each infant's physiological outcomes; therefore, it is difficult to make any causal inferences.

Conclusions

Preterm infants < 29 weeks GA with NTD (i.e., colder central temperatures and discordant warmer peripheral temperatures) in their first two weeks of life were more likely to experience early and late onset infection; however, a larger, multi-site study needs to confirm this association. Infants in our study who were African American or born to a mother who smoked during pregnancy had increased NTD over the first two weeks of life. A larger study is needed to examine central and peripheral temperature in very preterm infants (up to 32 weeks GA) during the neonatal period in relationship to racial background, maternal smoking, infection, and NEC as well as risk for morbid conditions after hospital discharge. Continuous monitoring of AT and FT may guide acute clinical care in the future to decrease acute morbidity and identify infants at risk due to abnormal thermoregulation.

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FIGURE 1.

Model of immature thermoregulation in very preterm infants. Dashed lines indicate processes that are immature in preterm infants. BAT = brown adipose tissue; TSH = thyroid stimulating hormone; UCP1 = uncoupling protein 1. Copyright, Robin Knobel-Dail. Used with permission.

FIGURE 2.

Temperature plot for day of life 1, for the infant with highest mean negative temperature differential. AT = abdominal temperature; ET = environmental temperature (inside incubator); FT = foot temperature; ISC = incubator servo control (temperature on incubator to maintain infant skin temperature).

FIGURE 3.

Negative temperature differential (NTD; abdominal temperature [AT] < foot temperature [FT]; mean percentage of minutes during the two-week study period) by groups. Panel A: Necrotizing enterocolitis [NEC]; Panel B: Infection; Panel C: Maternal chorioamnionitis; Panel D: Maternal smoking; Panel E: Race/ethnicity (African-American vs. Other).

FIGURE 4.

Negative temperature differential for one infant. $AT > FT$ is plotted above the 0 line; $AT < FT$ is plotted below the 0 line. Panel A: First five days of life; Panel B: Days of life 6–10; Panel C: Days of life 11–14. Missing data occurred when temperature probes were removed for procedures. AT = abdominal temperature. FT = foot temperature.

TABLE 1
Negative Temperature Differential, Infant Demographics and Infection, and Maternal Factors

NTD ^a	Infant demographics and infection						Maternal factors	
	GA ^b	BW ^c	Sex	R/E	NEC	Infection	Smoking	Chorioamnionitis
38.5	27	880	F	AA	yes	yes	yes	Yes
32.7	23 3/7	890	F	AA		yes		Yes
27.3	25 3/7	950	M	AA			yes	Yes
25.3	27 4/7	1050	F	AA				
24.3	25 6/7	850	M	AA	yes		yes	
22.3	26	850	M	AA		yes		
19.3	27 5/7	850	F	AA				
18.2	27 1/7	900	F	AA				
17.9	27 1/7	640	F	W				
17.9	28 1/7	950	F	W				Yes
17.9	27 4/7	820	F	AA	yes			Yes
17.6	27 3/7	730	M	W		yes		
16.4	27 4/7	1090	F	AA			yes	
16.3	27	820	F	AA				
15.6	26 1/7	660	F	H				
14.7	27 3/7	590	F	W				
12.8	25 6/7	880	M	AA				
11.6	27	1040	F	W				
11.6	27 6/7	740	F	AA				
11.5	27	940	F	W				
10.2	27 3/7	1040	M	AA				Yes
7.3	26 2/7	760	M	AA				

Note. Cases are sorted in descending order of NTD. AA = African American; BW = birth weight (g); F = female; GA = gestation age; H = Hispanic; M = male. NEC = necrotizing enterocolitis; NTD = negative temperature differential; R/E = race/ethnicity.

^aPercentage of minutes over two-week study period with NTD

^bWeeks.

^cGrams.

TABLE 2

Negative Temperature Differential by Clinical Events

Clinical event	Yes			No			<i>p</i> ^a
	<i>n</i>	<i>M</i>	(<i>SD</i>)	<i>n</i>	<i>M</i>	(<i>SD</i>)	
Blood transfusion	25	25.1	(17.4)	281	17.9	(17.8)	.05
Central catheter insertion	33	20.6	(14.7)	273	18.2	(18.2)	.48
CPAP respiratory management	185	19.9	(17.4)	121	16.3	(18.3)	.08
Endotracheal tube/ventilation	99	14.3	(16.7)	207	20.5	(18.0)	.004

Note. CPAP = continuous positive airway pressure.

^aFrom *t*-tests for difference in clinical event on patient-day units, based on the 22 subjects for each day for a maximum of 14 per subject.