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Perfusion Index in Very Low Birth Weight Premature Infants During Their First 2 Weeks of Life

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Abstract

Background: Our program of research focuses on thermal and circulatory stability in extremely premature infants. In prior studies, we found that infants have long periods of time in which foot temperature (FT) is higher than central temperature. We thus wanted to determine whether blood flow in the foot is increased when FT is elevated. Perfusion index (PI) can be used as a clinical indicator of peripheral perfusion, but reports on use of PI in premature infants are lacking. We employed exploratory methodology to examine foot perfusion and temperature in very low birth weight infants. **Aims:** For premature infants after birth: (1) describe foot PI values for the first 2 weeks of life and (2) describe the relationship of longitudinal FT and PI. **Study Design:** Case study design with longitudinal FT and PI in 17 infants born at <29 weeks' gestation with birth weight < 1,200 g for 2 weeks after birth. **Results:** Infants averaged 851 g at birth and were 24–29 weeks' gestational age. The mean PI across all infants for 14 days was 1.04, $SD = 0.79$. Using a repeated measures multilevel model approach confirmed that FT and PI were positively related in these infants. **Conclusions:** These findings demonstrate that perfusion is increased in the periphery in extremely premature infants when FT is increased. PI measures can be used as a trend for peripheral perfusion, and these values increase over the first 2 weeks of life in infants weighing more than 750 g.

Keywords

perfusion index, body temperature, neonatal, preterm, hypothermia, thermoregulation

More than 56,000 very low birth weight (VLBW) infants, or infants weighing less than 1,500g, are born annually in the United States (Martin et al., 2011). Survival free from major morbidity is a challenge for these infants, and about 20% do not survive their first year of life. Extremely premature infants have circulation changes in the first few days of life related to maturation and clinical instability, and heat loss is a contributor to problems of instability. These infants have inefficient thermoregulation and are prone to hypothermia. Our program of research is dedicated to investigating thermal stability in premature infants to reduce morbidity and mortality related to central hypothermia. To optimally monitor thermal stability in this vulnerable population, clinicians should measure central and peripheral temperatures (Lemburg, 1995; Lyon & Freer, 2011). Abdominal skin temperature is a proxy for central temperature in extremely premature infants because their skin is very thin and there is little-to-no fat between the body core and abdominal skin (Simbrunner, 1995).

Surveillance of central (abdominal skin) and peripheral (foot) temperature can alert the clinician to very low central temperature that might be indicative of neonatal stress or illness (Messaritakis, Anagnostakis, Laskari, & Katerelos, 1990). Normally, an infant's central body temperature should be 36.5°C–37.0°C and the peripheral foot temperature (FT) lower. A classic study of infant thermal patterns found mean skin temperature to be 36.03°C, lower abdomen temperature to be 37.03°C, and FT to be 35.61°C in a study of 17 infant thermograms (Clark & Stothers, 1980). If an infant experiences hypothermic central body temperatures, peripheral vasoconstriction should be an early response, causing the foot vessels to constrict, sending blood centrally to increase central body temperature. Similar to the findings from other researchers (Horns, 2002; Lyon, Pikaar, Badger, & McIntosh, 1997; Thomas, 2003), in previous research, we found that peripheral (foot) temperatures were warmer than central (abdominal) temperatures in 8 of the 10 extremely low birth weight infants studied for the majority of their first 12 hr of life (Knobel,

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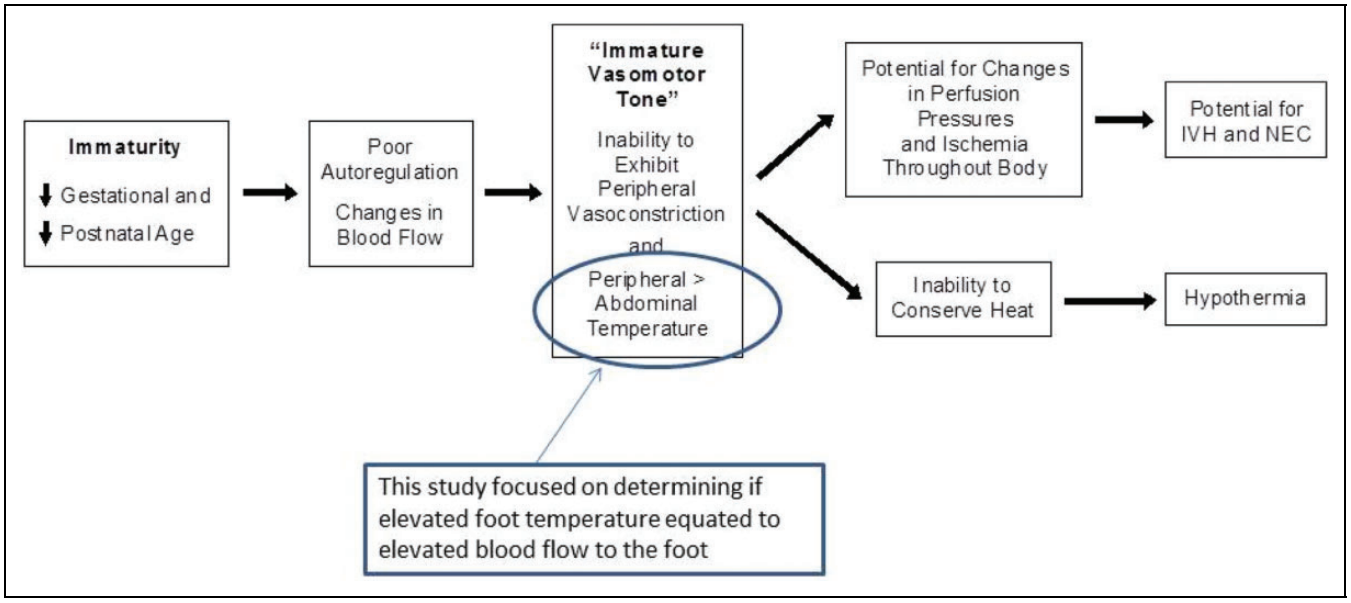

Figure 1. Conceptual framework for the Knobel-Dail program of research. IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; VLBW = very low birth weight.

Holditch-Davis, Schwartz, & Wimmer, 2009). From that study, we developed a conceptual framework that links alterations in thermal control with morbidity in premature infants of less than approximately 29 weeks' gestational age (see Figure 1). Infants in this vulnerable population are extremely immature and have poor autoregulation along with developmental circulation changes. We propose that the alteration in temperature control we have seen in our previous studies, including inefficient peripheral vasoconstriction and having long periods of time with an FT higher than a central temperature, leaves the infant in an altered stated of perfusion, which may lead to ischemia. Central ischemia may lead to morbidity such as necrotizing enterocolitis and brain ischemia manifested as intraventricular hemorrhage and ischemic brain changes. Before we can study the relationship between alterations in body temperature and morbidity and mortality in premature infants, however, it is imperative to rule out any iatrogenic causes of elevated FT such as a hot, humid incubator environment by answering the question: Is increasing FT associated with increasing blood flow to the foot? To study the relationship between FT and blood flow to the foot, we compared FT to a measure of foot perfusion index (PI) over time in 17 infants.

Monitoring extremely premature infants for adequate tissue perfusion is important to guide clinical care. PI is a clinical indicator of peripheral perfusion and serving as a noninvasive tool that measures the strength of pulsatile blood flow at the monitoring site. PI is calculated as the proportion of pulsatile to nonpulsatile blood flow of the tissue at the selected monitoring site, which is measured by the amount of infrared (940 nm) light that is absorbed on a pulse oximeter (Hales et al., 1989). The pulsatile signal is indexed against the nonpulsatile signal and expressed as a percentage. The Masimo Radical-7 (Masimo Corp., Irvine, CA) instrument displays a PI measure continuously, ranging from 0 to 20. According to the manufacturer, this measurement can be used for the detection of trends to provide sensitive information on slight changes in perfusion (Masimo Corporation, 2007). Masimo Radical-7 pulse oximetry set technology allows for accurate reporting of values due to its accuracy during motion (Workie, Rais-Bahrami, & Short, 2005). Foot PI has been positively correlated with calf blood flow and oxygen delivery ($r = .32$, $p = .03$) in term infants (Zaramella et al., 2005). Very few studies have measured PI in extremely premature infants; however, Kinoshita, Hawkes, Ryan, and Dempsey (2013) studied the reproducibility of PI values in 30 preterm infants. They concluded that the reproducibility of PI measurements in the same limb, the right upper extremity, is high ($p < .001$; Kinoshita, Hawkes, Ryan, & Dempsey, 2013) and found no correlation between median PI in the delivery room and gestational age (Hawkes, O'Toole, Kenosi, Ryan, & Dempsey, 2015). In addition, we pilot tested the use of PI in preterm infants with good performance in a previous study (Knobel, Levy, Katz, Guenther, & Holditch-Davis, 2013).

The purpose of this report is to (1) describe peripheral PI in VLBW infants over their first 2 weeks of life and (2) describe the relationship of FT and foot PI in these infants. We hypothesized that we would find evidence of a strong positive association between foot PI and FT and that this association would not change over time.

Method

Design and Sample

For this exploratory, descriptive research study, we used a case study design to examine premature infants' body temperature and perfusion over their first 2 weeks of life. After institutional review board approval at a North Carolina university hospital,

we approached parents who were not in active labor but expected to deliver infants at less than 29 weeks' gestation between August 2010 and December 2013 in order to enroll 30 infants after birth and before 6 hr in age. Because most infants deliver at unknown times and mothers in nonactive premature labor may be hospitalized from days to months, obtaining consent prior to infants' delivery was necessary. For this reason, we consented many more parents than there were infants delivered during the enrollment window who qualified by weight to be in the study. Infants were eligible if their birth weight was greater than 500 g and less than 1,200 g and if there were no visible anomalies or medical complications initially after birth. We obtained permission from each infants' attending neonatologist to include them in the study.

Procedures

We enrolled infants in the study after their admission to the Level 3 neonatal intensive care unit. As standard of care in this unit, infants are initially stabilized on a warming table and then moved to a Draeger Caleo incubator on incubator servo control, which means their body temperature is controlled by skin temperature at a desired 36.5°C. If the skin temperature is too cold, the incubator increases environmental heat, and if the skin temperature is above 36.5°C, the incubator limits heat production. A research assistant attached FT and PI probes as soon as the infant was stabilized. All instrumentation was synchronized to the time on each infant's cardiopulmonary monitor. Peripheral FTs were measured every minute using Y series Steri-Probe® skin temperature probes (Model 499B, Cincinnati Sub-Zero, Cincinnati, OH) applied to the sole of each infant's foot and attached to a four-channel data logger, model SP-1400-44Y (Veriteq Instruments; Vaisala, Richmond, British Columbia, Canada). Peripheral PI was measured every 10 s in each infant's foot with a Masimo Radical Set 7 pulse oximeter (Masimo Corp.). The pulse oximeter probe and the skin temperature probes were secured on opposite feet. We used opposite feet for measurement because FT may not be valid if it is obtained from the same foot being used for PI measurement because the light from the PI probe may distort the FT. Unless there is an obvious sign of decreased perfusion, it can be assumed that perfusion is approximately equal to both feet.

Infants' nurses repositioned all probes at least every 6–8 hr as needed, as they assessed and documented standard care and skin condition using a research study form kept at the bedside. Signage instructed nurses where to place FT probes and how to secure them. The probe we used for measurement of PI was a standard pulse oximeter probe, thus nurses required no additional education. We measured PI and FT in these infants over their first 2 weeks of life. The research assistant visited each study infant's nurse daily to ensure there were no problems with study data loggers, the pulse oximeter, or probes. Data loggers and the pulse oximeter continuously stored FT and PI until the infant was discontinued from data collection after 2 weeks. Because we did not download data loggers or PI data during the 2 weeks, it was impossible to know if all 20,000 measures had been collected continuously until we examined the downloaded data.

Data Analysis

We downloaded the PI data, with measures every 10 s by instrument default, onto a laptop computer into an Excel file using TrendCare software (TrendCom MFC Applications® 2007, Irvine, CA). We downloaded FT data from the data loggers as text files with measures every minute and then imported the files into a SAS (SAS, Cary, NC) data set for each infant every minute for each infant's first 2 weeks of life. We averaged PI measurements into 1-min measures in order to synchronize with FT measurements. Within the SAS data sets for each infant, we synchronized all instrumentation times to be expressed as minutes elapsed since infant's birth. We cleaned the data to eliminate temperature outliers that were thought to be representative of nonvalid data collection (such as when the probe was lying in the bed or not on the foot), deleting FTs below 33.0°C and above 39.0°C. We visually inspected longitudinal plots of FT and foot PI for each infant and calculated descriptive statistics within infants as well as between infants using 1-min measures. We attempted to run multilevel models to describe the relationship between foot PI and FT using 1-min measures, adding all infants into the model; however, there was too much variation in minute-to-minute measures and statistical models would not converge or provide results after we attempted to run them for 24 hr. Therefore, we used the lowest level of averaging (4-hr averages) that would provide results, which still provided 84 measures for each of the 17 infants.

Results

We obtained study consent from 107 parents prior to their infants' births. Of those, 76 infants were not eligible for data collection because they did not meet birth weight or gestational-age inclusion requirements or the mother left the hospital to return at term for delivery. The remaining 31 infants were eligible for data collection; 17 of these infants had complete FT and PI data for a 14-day period for analysis (see Table 1), and the remaining 14 infants were excluded from this analysis because they had incomplete PI or FT data collected for the majority of 1 or more days or no data for 1 of the first 3 days of life. The infants included had 20,000 measurement points for two variables, providing a large enough sample for analyses for this exploratory study. Infants' birth weights ranged from 590 to 1,090 g (mean = 851.2, SD = 145.4 g) and gestational ages ranged from 24 to 29 weeks (mean = 26.76, SD = 1.34 weeks). We conducted case study analyses within infants and also analyzed data between infants. To add descriptive information to the science around this exploratory method, we compared infants in post hoc birthweight cohorts: low, n = 4 (500–750 g); mid, n = 10 (751–1,000 g); and high, n = 3 (1,001–1,200 g). We used birth weights to split infants

Table 1. Infant Demographics.

ID	Birth Weight (g)	Gestational Age (Weeks)	Sex	Ethnicity	Apgar Scores[a]
1	850	26	M	AA	6, 9
2	880	26	F	AA	8, 8
3	660	26	F	His	4, 7
4	900	27	F	AA	4, 6, 7
5	1,040	27	M	AA	6, 8
6	820	28	F	AA	5, 6
7	590	27	F	W	2, 6, 8
8	760	26	M	AA	6, 7
9	1,090	28	F	AA	8, 9
10	850	28	F	AA	5, 9
11	730	27	M	W	3, 7
12	950	28	F	W	9, 9
13	880	26	M	AA	4, 6, 7
14	850	26	M	AA	3, 6, 7
15	640	27	F	W	1, 9
16	1,090	29	M	His	5, 7
17	890	24	F	AA	6, 6

Note. AA = African American; His = Hispanic; W = White.
[a]Apgar score at 1, 5, and, if warranted, 10 min of age.

Table 2. Perfusion Index (PI) and Foot Temperature (FT) Over 2-Week Study Period for All Infants ($N = 17$) and by Birth Weight Cohort.

		PI			FT (°C)		
Group	*n*	*M* (*SD*)	Min	Max	*M* (*SD*)	Min	Max
All	290,519	1.04 (0.79)	0	20	35.93 (0.89)	33.01	38.99
Low	68,831	0.93 (0.79)	0	20	35.85 (0.90)	33.01	38.99
Mid	177,276	1.04 (0.78)	0	20	35.95 (0.88)	33.01	38.99
High	44,412	1.20 (0.79)	0	20	35.95 (088)	33.01	38.93

Note. *n* = number of observations; low = low birth weight group (<750 g); mid = mid birth weight group (751–1,000 g); high = high birth weight group (1,001 > g).

into groups because gestational-age dating is not as exact and can be off by as much as ± 2 weeks.

Table 2 shows descriptive statistics of PI and FT across all infants over their first 2 weeks of life and by birth weight cohort. Even though the instrument was capable of displaying a PI from 0 to 20, visual inspection of data revealed that minute measures remained mostly less than 2, were occasionally 2–5, and were rarely above 5 for all of the 17 infants. The mean PI across all infants for all 14 days was 1.04, $SD = 0.79$. Figure 2 shows a plot of the range of PI measures for each weight group. Although the numbers of infants in the smaller and larger weight groups are small, these data give clinicians an idea of what to expect for the weight range and are comparable to results from a previous study of term and preterm infants (Hakan, Dilli, Zenciroglu, Aydin, & Okumus, 2014). Indeed, our results on PI were similar to those of all prior studies we reviewed, in which mean and median PI values were less than 2.0 and mostly less than 1.5 (Cresi et al., 2010; DeFelice, Latini, Vacca, & Kopotic, 2002; Hawkes et al., 2015; Jardim, Rocha, Silva, & Guimaraes, 2014; Vidal et al., 2013).

Visual inspection of each study infant's plot of FT and foot PI, measured every minute for their first 2 weeks of life, indicated a large amount of minute-to-minute variation. Figure 3 shows the plots of PI and FT for one study infant. It is not appropriate to assess the correlation between FT and foot PI within infants by pooling all the repeated measures together and using a Pearson's correlation because the repeated measures are highly correlated within each individual (Raudenbush & Bryk, 2002). Therefore, we assessed FT as a predictor of the log of PI across infants using a repeated measures multilevel model (Goldstein, Healy, & Rasbash, 1994; see Tables 3 and 4). Multilevel modeling of repeated measures, also known as hierarchical linear modeling, variance component modeling, or mixed effects modeling, is more robust than conventional analysis of variance because it solves the problems of sphericity, hierarchical sampling, and missing data (Quene & van den Bergh, 2004). We log-transformed PI values because of concerns about the nonnormality of this variable and residuals from a linear model. Level 1 of the multilevel model included the time-based measures of FT and PI. Level 2 was the infant level, which included birth weight. We selected a multilevel, repeated measures model to account for correlation between the residuals of individual subjects, so that they could be related to one another due to proximity in time. Foot PI and FT measures would be more related to each other the closer together they were in time. Therefore, we used an autoregressive covariance structure. In the multilevel model, there was a statistically significant random intercept indicating differences among the infants, which can explain some of the differences seen in PI. Differences among infants can be related to weight, gestation, sex, clinical condition, respiratory status, and so on. The variance component was 0, suggesting that there were no differences in the relationship between FT and PI among the different infants, therefore, we removed the component from the model. The model indicated that FT was a statistically significant predictor of PI (see Table 3). Adding weight or gestational age was not statistically significant in the model because we were already accounting for the random variation among infants. Using a repeated measures multilevel model approach with this sample confirmed that, as FT increased in these infants, foot PI also increased (see Table 4).

Because very little of the literature describes PI trends over time in extremely premature infants, we examined PI longitudinal trends among our participants. PI increased over the first few days of life in the mid and high birth weight groups (see Figure 4). The infants who were the most immature and smallest (small birth weight group) had lower PI levels over the entire 2 weeks, and trends were very flat with no evidence of increase over time ($y = 0.8958 + 0.00061 \times$ 4-hr blocks). When we compared 4-hr PI means over time for infants in the mid and high birth weight groups to those for infants in the small birth weight group, we found that the PI in the heavier groups increased significantly as days of life increased ($t = 4.15$, $p < .0001$ mid group; $t = 3$, $p = .0027$ high group),

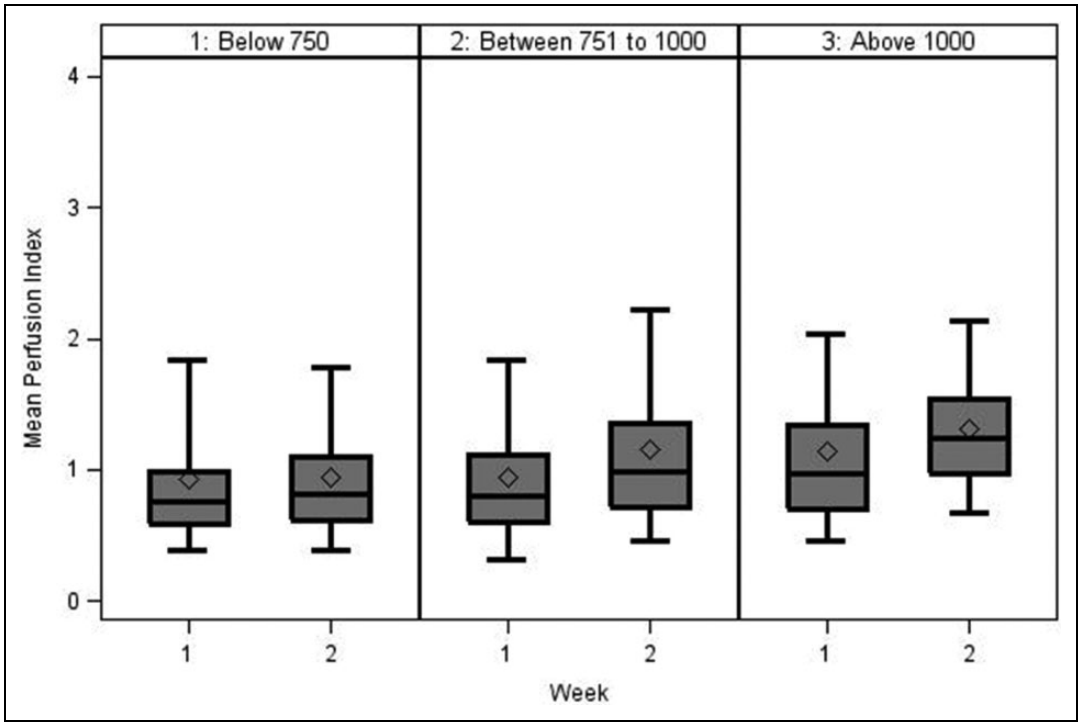

Figure 2. Boxplot of perfusion index (PI) means for all infants in the study by birth weight group in grams for their first and second weeks of life. The top of each box is the 75th percentile and bottom is the 25th percentile, middle line is the median with a diamond showing the skew when the mean is different than the median. Top tail is the 95th percentile and bottom tail is the 5th percentile.

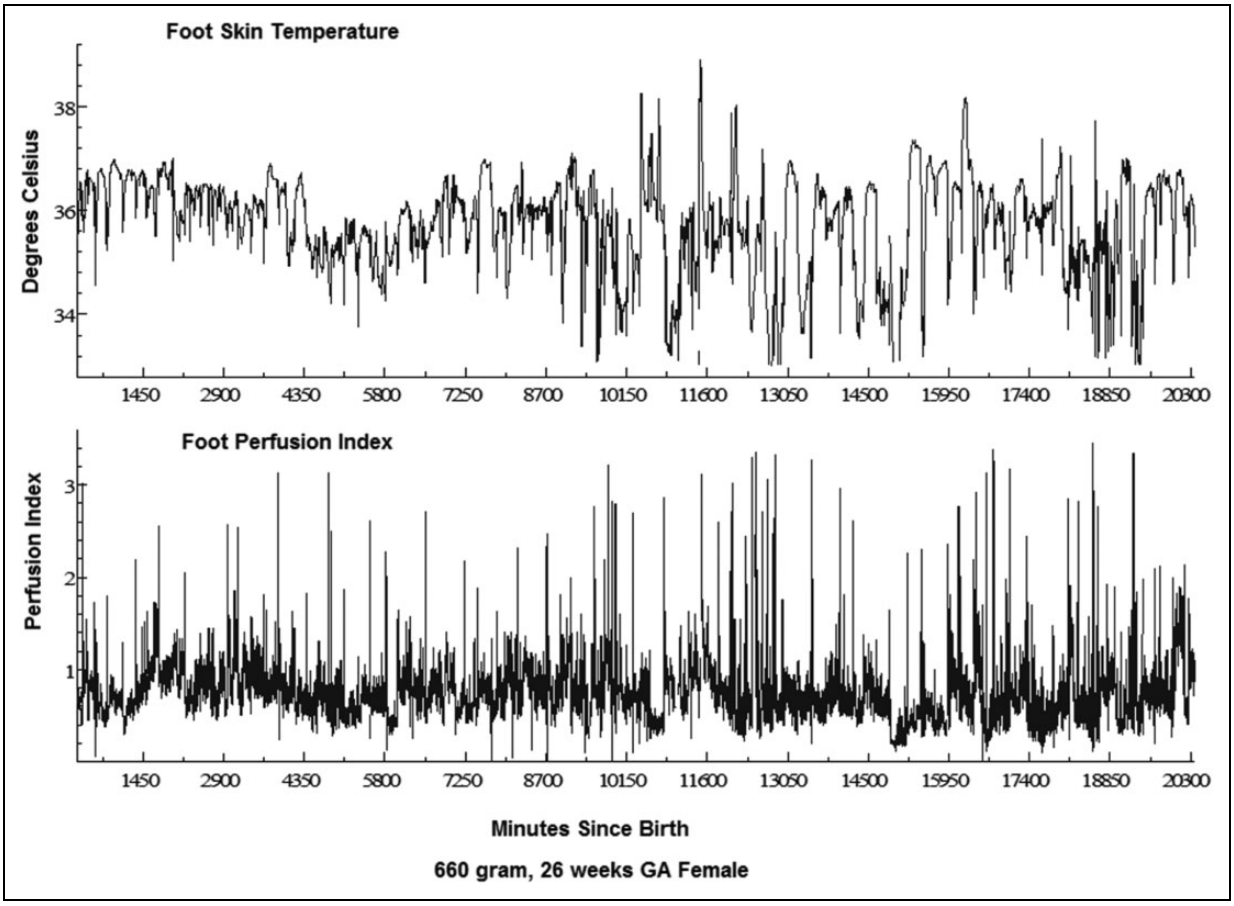

Figure 3. Exemplar plots of foot temperature and foot perfusion index measures over the first 2 weeks of life in one infant. GA = gestational age.

Table 3. Covariance Parameter Estimates From the Repeated Measures Multilevel Model.

Parameter	Subject	Estimate
Intercept	Infant	0.05112
AR (1)	Infant	0.5157
Residual		0.09178

Note. AR (1) = first-order autoregressive.

Table 4. Fixed Effects From the Repeated Measures Multilevel Model, Indicating the Average Relationship Between Foot Temperature (FT) and the Log of Perfusion Index With and Without Birth Weight.

Effect	Estimate	*SE*	*df*	t	*p*
Without birth weight					
Intercept	−1.8849	0.4626	1,297	−4.07	<.0001
FT	0.0491	0.01278	1,297	3.84	.0001
With birth weight					
Intercept	−2.291	0.5765	1,296	−3.85	.0001
FT	0.04911	0.01279	1,296	3.84	.0001
Birth weight	0.000392	0.000404	1,296	0.97	.3313

Note. Birth weight is not statistically significant in the model. *df* = degrees of freedom; *SE* = standard error.

while the values in the low group remained relatively flat. For every 4-hr-block increase in time, infants in the mid-weight group experienced an increase in the mean PI of .00525.

Discussion

Our results in the present study provide evidence that FT and foot PI may be used as proxies to monitor for decreased peripheral perfusion in extremely premature infants. Findings indicate that when FT increases, perfusion is also increased.

Like others, we found that foot PI is best used for illustrating trends in peripheral perfusion because one measure provides very little information and there is great variation from minute to minute. According to our literature search, ours is the first study in which foot PI was measured every minute continuously over a long period of time (2 weeks). Most studies have recorded PI for a short period of time using a single value (Granelli & Östman-Smith, 2007; Takahashi et al., 2010) or a few seconds to 15 min of data (Cresi et al., 2010; DeFelice et al., 2002; Jardim et al., 2014; Kinoshita et al., 2013). In one prior study, investigators measured PI for 6 hr continuously (Sahni & Schulze, 2011).

The values for foot PI that we obtained in our study were very similar to those previous researchers have obtained, as all means were less than two (Cresi et al., 2010; Hawkes et al., 2015; Jardim et al., 2014; Vidal et al., 2013). In a recent review of nine studies examining PI in term and preterm infants, authors found that median values for all infants studied were less than 2.5 (Piasek, Van Bel, & Sola, 2014). Our analysis in the present study further showed that the mean PI values of infants with birth weights were greater than 750 g over time (see Figure 4). Vidal et al. (2013) found the same trend in 45 infants with gestational ages of 25–28 weeks and birth weights of 750–1,080 g. Specifically, these authors found that PI significantly increased between Days 1 and 7 after birth. They also found that PI was not influenced by ductal flow pattern, meaning that, regardless of whether the ductus arteriosus was open or closed, infants' PI values increased over time. Because our study was focused on the relationship between FT and foot PI, we did not assess right-hand PI for a preductal differential. In a previous pilot study of five infants, we did find that overall hand and foot PI were very similar, but keeping probes on both hand and feet placed a large research burden on the parents because they were unable to touch infant extremities that did not have research probes attached (Knobel et al., 2013).

In the present study, the infants weighing less than 750 g had flat longitudinal mean PI values or even, in some cases, values that decreased over time. This finding underscores the vulnerability of smaller infants. Low perfusion indicates low blood flow and possible ischemia if there is low perfusion to other areas of the body. Having low perfusion may make them more susceptible to perfusion injury. Granelli and Ostman-Smith (2007) found that PI values <0.7 may indicate illness and that values <0.5 do indicate illness. Another team found significantly lower PI (0.86 ± 0.26 vs. 2.02 ± 0.7; $p < .0001$) in infants with increased severity of illness as indicated by Swanson, Nolan, and Pelham (SNAP) scores (DeFelice et al., 2002). Future studies should examine PI in relationship to morbidity and mortality, both as a concurrent factor and as a predictor of outcomes.

In the present study, we used an exploratory methodology to confirm that FT is elevated when there is increased blood flow to the foot, as measured by PI. We were able to confirm a positive, linear relationship between FT and foot PI over time across 17 infants and have evidence using aggregate data that PI and FT had a statistically significant positive association when controlling for age and birth weight. With this study, then, we solved one research question related to an important area in our program of research dedicated to studying the relationship between abnormal body temperature and morbidity and mortality in premature infants. We found that increased FT does occur with increased perfusion in the foot. In future studies, we will attempt to understand the physiological significance and possible etiological pathways leading to morbidity when FTs remain greater than abdominal temperatures over long periods of time (hours to days) in extremely premature infants.

Study Limitations

Generalizability of our results is limited by the sample size of 17 infants who had complete data. Our study results and conclusions are limited in external validity in that data were obtained within one clinical setting, with infants having varied clinical courses in a highly complicated intensive care environment. Infants did not have the same medical management in that they were managed by multiple attending physicians, residents, neonatal nurse practitioners, and nurses. Data collection

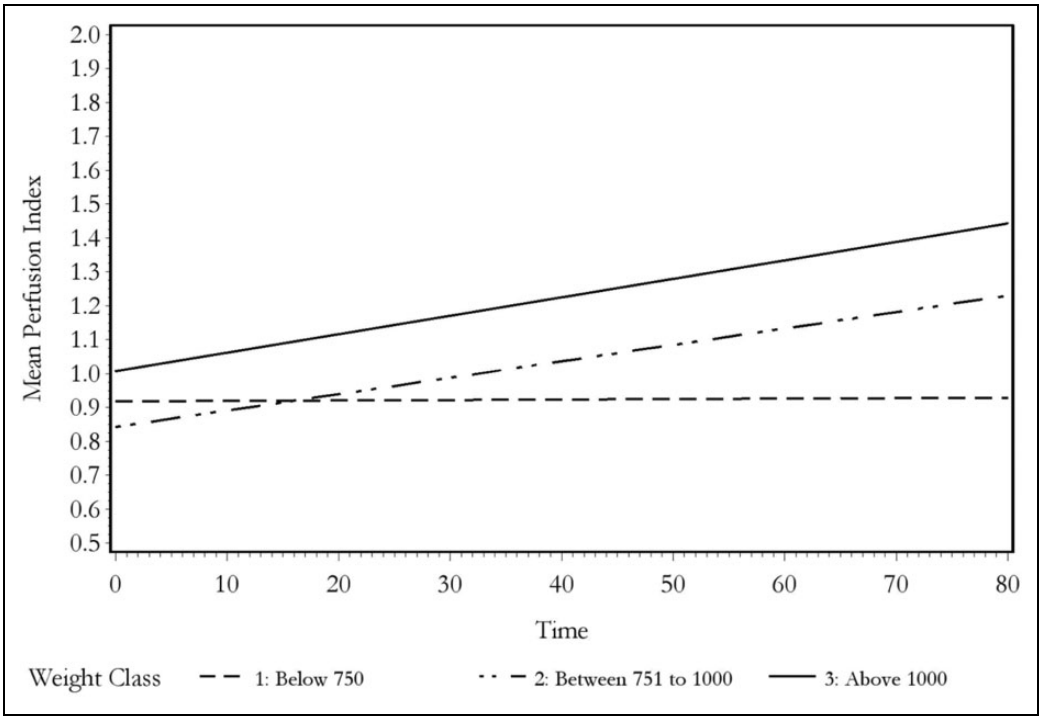

Figure 4. Regression lines of average perfusion index values by infant birth weight group over the first 2 weeks of life. Time = Each point on the *x*-axis represents a 4-hr block of time.

methods were embedded in a clinical environment, which may introduce error into the data collected. For example, attending nurses changed locations of the thermistors according to the effect on the skin and nursing routines. Knowing when a skin temperature probe was dislodged or off for site rotation over the entire study period would have improved our ability to analyze these data. In future studies, we will develop a way for nurses to indicate when the probes are off for repositioning, so that we can exclude those time periods. Because this protocol was not in place a priori, we attempted to clean data to exclude times when thermistors were not attached by deleting all skin temperature values less than 32°C.

Conclusion and Clinical Implications

The present study provides evidence that the PI reading can provide information about peripheral perfusion in premature infants. According to our findings, PI trend values should increase over time in infants with birth weights greater than 750 g. If peripheral PI values remain low after the first few days of life in these infants, clinicians should investigate potential problems with stability and low perfusion. Our results and results from other studies confirm that PI measures are appropriate for illustrating trending peripheral perfusion in infants but should not be used as a point-to-point measure clinically.

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Author Contribution

R. B. Knobel-Dail contributed to conception and design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. D. Tanaka contributed to design, analysis, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. D. Holditch-Davis contributed to conception, design, and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. J. White contributed to analysis and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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