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A Pilot Study to Examine Maturation of Body Temperature Control in Preterm Infants

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Abstract

Objective—To test instrumentation and develop analytic models to use in a larger study to examine developmental trajectories of body temperature and peripheral perfusion from birth in extremely low birth weight (ELBW) infants.

Design—A case study design.

Setting—The study took place in a level four neonatal intensive care unit (NICU) in North Carolina.

Participants—Four ELBW infants, less than 29 weeks gestational age at birth.

Methods—Physiologic data were measured every minute for the first 5 days of life: peripheral perfusion using perfusion index by Masimo and body temperature using thermistors. Body temperature was also measured using infrared thermal imaging. Stimulation and care events were recorded over the first 5 days using video which was coded with Noldus Observer software. Novel analytical models using the state space approach to time series analysis were developed to explore maturation of neural control over central and peripheral body temperature.

Results/Conclusion—Results from this pilot study confirmed the feasibility of using multiple instruments to measure temperature and perfusion in ELBW infants. This approach added rich data to our case study design and set a clinical context with which to interpret longitudinal physiological data.

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Keywords

Neonatal; Hypothermia; Body Temperature Regulation; Physiological Processes; Pilot Projects

Extremely low birth weight (ELBW) infants with birth weights less than 1000 grams and gestational ages less than 29 weeks have little to no ability to maintain core body temperature by non-shivering thermogenesis because of an immature thermoregulatory system (Houstek et al., 1993; Hull & Smales, 1978). As a result, ELBW infants are prone to decreases in body temperature. Many common procedures and care expose these premature infants to cold environmental temperatures putting them at further risk for hypothermia until they are mature enough to regulate their own body temperatures effectively. When an infant's body temperature falls below normal, the first physiological response to conserve body heat should be via peripheral vasoconstriction achieved through constriction of vessels in the feet and sending blood to the core to protect vital organs lowering peripheral temperatures to 2°C below abdominal temperature (Lyon, Pikaar, Badger, & McIntosh, 1997; Mok, Bass, Ducker, & McIntosh, 1991; Wilson et al., 2007). In our previous studies of ELBW infants, we found that they exhibit minimal peripheral vasoconstriction during the first 12 hours of life (Knobel, Holditch-Davis, Schwartz, & Wimmer, 2009). We also found that ELBW infants often keep the temperature of the surface of the feet higher than the surface of the abdomen for the majority of the first 12 hours after birth.

Little is known about the maturation of the thermoregulatory system in ELBW infants, and it is not clear whether these infants are mature enough at birth to control central and peripheral temperature appropriately. Long periods of time with warmer peripheral than central temperatures may expose premature infants to cold central temperatures with possible perfusion damage, increasing the chance of developing pathological conditions such as necrotizing enterocolitis (NEC) (Boros, Takaichi, & Hatanaka, 1995; Nankervis, Giannone, & Reber, 2008; Neu & Walker, 2011).

Necrotizing enterocolitis (NEC) is a morbidity our team is exploring in relationship to central hypothermia. NEC has been found to be associated with poor central perfusion (Nankervis et al., 2008). It is unclear if hypothermic infants have adequate physiologic protective mechanisms to maintain consistent central organ perfusion. We believe that studies of hypothermia and control of central and peripheral temperature may lead to etiological hypotheses about the association between NEC and hypothermia and that periods of central hypothermia in ELBW infants make them vulnerable to acquiring NEC after feedings are begun. Before causal links can be made between bouts of hypothermia and NEC in ELBW infants, it is essential to understand normal developmental physiology of thermal control progresses in relationship to respiratory, cardiac, and gastrointestinal development after birth. Ways to study physiological maturation of systems in acutely ill, extremely premature infants in neonatal intensive care units (NICUs) with multiple providers and different modes of medical management are needed.

Methods to explore these relationships need to involve data triangulation, enabling the researcher to examine longitudinal relationships between physiological variables while taking into consideration the clinical context. We designed a study for 30 infants to examine body temperature over their first week of life to determine when an infant has a mature ability to regulate temperature centrally and peripherally. In this article, we describe the instrumentation tested and analytic models developed through pilot testing of four ELBW infants (see Table I) in a case study approach to refine methods for use in the subsequent, larger study. Study methods were examined for feasibility, acceptability, and some aspects of validity and reliability.

Pilot Testing

After approval from the University Medical Center Institutional Review Board, mothers and fathers were approached for consent for their infants to participate in the study while the mothers were patients in the labor and delivery unit but before delivery was imminent. Mothers were not in active labor and permission from the mother's care provider was obtained before parents were approached for consent. Infants were enrolled in the study if they were delivered prior to 29 weeks gestational age, the birth weight was less than 1000 grams, and they could be attached to the study instruments within 4 hours of birth. Physiological data were measured every minute for 5 days and clinical data were recorded until discharge from the unit.

Measuring Body Temperature with Thermistors

Initial approach—Each participating infant's abdominal skin temperature was controlled by incubator servo control (ISC) determined by the bedside nurse. Abdominal (central), hand (peripheral), and foot (peripheral) surface temperatures were measured with skin surface temperature probes. One thermistor was attached to the exposed trunk area, one to the palm of a hand, and one to the sole of a foot using skin care tape, which is a soft, silicone retention fabric. The abdominal probe was covered with a reflective cover. Patient care nurses recorded any issues with probes affecting the skin and documented changes to probe position.

Thermistors were connected to a 4-channel data logger that was placed in the incubator (see Figure 1). Data loggers were calibrated by the manufacturer to meet requirements of measurement variability of 0.03°C upon calibration. A separate data logger was used to measure environmental temperature and was positioned at the bottom of the incubator mattress between the infant and the end of the mattress.

Each infant was evaluated for episodes of hypothermia. Because there are no published definitions of hypothermia for infants cared for with ISC in heated incubators, we defined hypothermia as the abdominal surface temperature decreasing at least 0.5° C below the ISC set point. An episode of hypothermia was defined beginning when the abdominal temperature reached the hypothermic point and ending when the abdominal temperature returned to the ISC set point.

Findings—For the infants studied, the set ISC temperature varied from day to day in the range of 36.0°C to 37.0°C. Nurses made frequent changes to the ISC set point, usually in response to variable body temperature. There was no strict unit standard as to where to keep the ISC. We noted that when the thermistor became detached from the body or when the nurse changed the thermistor position, a lower or higher than normal temperature was measured from the bed surface or air for a period of time until the thermistor was reattached to the body. Therefore to increase validity in the data, data were cleaned by removing any body temperatures less than 33°C or greater than 39°C to account for these periods. Temperatures between these limits are more physiologic and likely to occur; outside these ranges, temperatures are most likely non-physiologic.

No incidences of skin irritation due to the study probes were reported, making it feasible to use thermistors for measurement of study temperature. However, occasionally thermistor probes were found in the wrong body location because the probe became detached from the body, and a nurse reattached it in a different area. We found several ways to improve the reliability and validity of the temperature measures obtained. Placing labels on each probe indicating the extremity on which it should be attached was a good way to clearly identify the intended location for the study probe. We also found that keeping the probe location

(abdomen, hand or foot) associated to the same data logger channel for each subject was necessary to reduce confusion for the research assistant and bedside nurse. We noted that the connection between the thermistor probe and the data logger channel connector, a telephone jack type connection, needed to be checked frequently to prevent loose connections that could result in lost data.

We attempted to attach the foot thermistor probe to the sole of the foot on the first study infant using the pulse oximeter adhesive tape that wrapped around the foot. However, it became dislodged from the foot resulting in lost data. We eliminated this problem by using skin care tape to attach the thermistor probe on the sole of the foot and by attaching the pulse oximeter to the opposite foot. In this way, we also increased the reliability and validity of temperatures obtained from the foot, insuring a secure connection. After examining body temperatures from all four pilot infants, we determined that very little additional information was obtained from measuring two peripheral sites: hand and foot. We felt that parental and staff acceptability of the research could be improved by eliminating the thermistor on the hand. Having three thermistors attached to the infant seemed to impose an unnecessary burden on the infant and parents; therefore, we eliminated measurement of body temperature from the hand after the pilot study was complete. We decided the parents' ability to hold their infants' hands without research probes attached was more important than collecting data on hand temperature.

Over the 5 days of study, abdominal, hand, and foot temperature varied greatly for the four pilot infants with enough data available to allow analyses (see Table 2). Mean daily abdominal temperatures for the four infants ranged from 35.1°C to 36.9°C. Foot temperature means ranged from 35.3°C to 37.1°C. Hand temperature was very close to foot temperature in each infant, with means ranging from 35.8°C to 36.8°C. The mean central (abdominal) - peripheral (foot) temperature difference for each day for each infant varied but trended upward as the infants matured. The range of mean central-peripheral (CP) temperature differences was 0.550 to 1.160. Infants did not keep at least a 1°C difference between their abdomen and foot temperatures until day 5. Previous researchers found that a central temperature above peripheral temperature by 1-2°C was within an optimal range (Simbrunner, 1995). Body tissue that is highly metabolic and with a high blood flow in central areas such as the heart, liver, and gastrointestinal system should have a higher temperature than areas of low metabolic rate and low blood flow such as the feet.

We computed descriptive statistics for episodes of hypothermia, finding the coldest temperature that the abdomen reached during that episode then computing the maximum level of peripheral vasoconstriction (as measured by the maximum value of the CP temperature difference) the infant reached in response to that episode of hypothermia. A visual plot was created for these episodes. The plot in Figure 2 depicts data for the only infant to have a consistent level of peripheral vasoconstriction at 2°C. All other infants exhibited peripheral vasoconstriction at intermittent levels between 0.5°C and 2°C.

Our pilot study showed that it was feasible to measure central and peripheral temperature using thermistors attached to the abdomen, hand and foot. We found ways to improve the reliability and validity of the measures. We also found a way to improve the acceptability of these research methods for the parents and care providers by eliminating one research probe, improving methods for nurses to follow, and streamlining procedures.

Recommendations for future study—When using thermistors to study body temperature in the neonate, we recommend that each thermistor be attached using skin care tape. The minimal number of thermistors needed should be attached to the infant and redundant collection of data avoided. Spurious temperature measures can be obtained when

probes become detached from the body; therefore, data should be eliminated by statistical cleaning for non-physiologic temperatures. We also recommend checking all study probe connections and locations often and using clear labels to identify intended locations for probes.

Measuring Body Temperature with Infrared Imaging

Initial approach—To explore an additional method of measuring central and peripheral temperature simultaneously, we conducted thermal imaging with an infrared camera. Through this pilot study, we assessed the feasibility of using an infrared camera with infants housed in plexiglass incubators. We also wanted to assess the acceptability of this instrument in the clinical area. Our detailed methodology and experience utilizing infrared thermography in infants was described previously (Knobel, Guenther, & Rice, 2011). The infrared camera is capable of taking thermal images that are stored on a card inside the camera, and each pixel of the image displays a temperature in degrees Celsius. Dark areas on the image represent cooler temperatures and whiter images are warmer (see Figure 3). Emissivity of skin is 0.98, which allows accurate surface temperatures to be recorded of all skin types, regardless of pigment (Steketee, 1973). When viewing a thermal image on a computer screen, the operator can compare temperatures in central areas of the abdomen adjacent to the visible temperature thermistor probe to temperatures on the foot surface.

The principal investigator trained two research assistants to take thermal images of the study infants daily during their morning care for comparison to thermistor temperatures (Knobel et al., 2011). Our engineering department cut a rectangular opening in the top of an incubator, and a truncated monopod was fitted to a rolling IV pole in order to position the camera over the incubator cutout.

Findings—Initially, in order to prevent heat loss, a sheet of polyurethane was placed over the cutout and secured in place with a rubber ring. However, this ring did not keep the sheet taut, so images through the polyurethane were blurred. We changed to securing the plastic sheet with tape, which improved the quality of the images. One patient care nurse related that the time taken to conduct infrared imaging for the first pilot infant was too long. For the first several images, we spent extra time learning the appropriate techniques, but afterwards we were able to complete imaging in about 3 minutes per session. Another challenge was that water droplets accumulated on the underside of the polyurethane sheet similar to accumulation on the inside walls of an incubator when adding water for humidity. When we tried to image through the sheet, water droplets distorted the image. Since we had decreased imaging time, we decided to briefly lift the sheet from the cutout and image directly through the opening. This method greatly improved the quality of the images.

We used the camera connected to a laptop computer on the first infant; however, the software failed to control the camera adequately. We recorded measures 20°C higher than actual temperatures on the first day, but this problem resolved on the second day for the first infant. The program also did not allow good focus control. We changed to using manual focus control on the camera, which greatly improved the quality of the images.

After the cutout hood could not be located in NICU storage for another pilot infant, we submitted an amendment to the IRB to use any incubator for our study, which prompted us to image through the porthole, greatly improving imaging methods by eliminating the barrier between the infant and the camera. Moving imaging from above the incubator to in front of the incubator allowed the research assistant to have better control of the camera and images being captured. This method worked well; however, the infant's entire body could not be imaged because of the lens depth of field. We attempted to record central and peripheral areas of the body, which could be accomplished by imaging from the neck to the feet.

Quality images can be taken of smaller areas of the body. Imaging of infants inside the incubator was much more feasible and acceptable using the method of briefly opening the port hole to conduct the image. There were too many problems trying to image through the cut out in a particular study incubator, with water droplets, increased imaging time, and being unable to find that incubator at times.

We were able to record infrared images in three infants and compare skin thermistor body temperature in the abdomen and foot with infrared measurements in the same areas (see Figure 3). Temperature differences between infrared measurement and skin thermistor measurement ranged between 0.2 and 1°C, with the mean difference of 0.4°C, showing promise for *valid* and *reliable* measures. We will be able to assess validity and reliability in the larger study by imaging 30 infants, once a day for 5 days, for 150 images. This methodology is exploratory and in early stages of use with premature infants in incubators. Our pilot measurements showed that the technology is feasible with infants weighing 600-1000 grams inside heated/humid incubators.

Recommendations for future study—Since this pilot was started, many smaller infrared cameras that may be better suited to use in the NICU have been produced. These cameras can be easily used without a computer, and many of the newer cameras can send images over the internet to an iPad or PC based tablet for immediate viewing. We strongly recommend the research and development course given by the FLIR Corporation, which can be found on FLIR's website. This two day course will give the principal investigator the knowledge needed to conduct imaging, train others to image, and conduct analyses. We also recommend exploring other options for smaller, less expensive cameras that could yield the same temperature measurements. We recommend imaging through the port hole of the incubator and focusing on the area of the infant needed measurement.

Environmental Temperature

Initial approach—In order to discern whether hypothermia in ELBW infants was related to an infant's inability to control body temperature or to decreased environmental temperature inside the incubator, we needed to find a good way to measure continuous internal incubator temperature. Initially, we used a separate humidity/temperature data logger to measure continuous environmental temperature inside the incubator.

Findings—We found that having two data loggers in the bed increased the chances that the data logger not attached to the infant would be moved to various locations in the bed, including under the mattress. It also appeared that there was great error in the environmental temperature measures. Therefore, we changed the procedure to measure environmental temperature with the body temperature data logger. A thermistor was attached to the 4th channel of the data logger and coiled against the data logger so that the thermistor tip was secured and extended into the air (see Figure 1). Environmental temperature varied for each infant on each day (see Table 2). As expected, environmental heat requirements generally decreased over time as infants matured and required less heat to maintain set ISC points.

Recommendations for future study—It is important to minimize instrumentation inside the infant's environment. By using one data logger to measure thermistor temperatures and environmental temperature, the researcher can minimize the number of data loggers inside the incubator. It is also important to frequently check data logger position inside the incubator to minimize error. This measure is important to know when evaluating episodes of hypothermia in ELBW infants.

Peripheral Perfusion Index

Initial approach—Because infants in our previous studies had higher foot temperatures than abdominal temperatures during their first 12 hours of life, we needed an instrument to compare perfusion in the foot to surface temperature of the foot. A pulse oximeter with perfusion index (PI) trending capability was attached to each infant's hand and foot to record a PI. By measuring the infrared (940 nm) light absorbed in the extremity, an index is computed from the pulsatile strength (during arterial blood flow) against the non-pulsatile strength in the hand or foot (De Felice et al., 2005; Goldstein et al., 2005; Workie, Rais-Bahrani, & Short, 2005). Perfusion index has been used in a few studies with premature infants, but not in relationship to body temperature (Cresi et al., 2010; De Felice et al.; Granelli & Östman-Smith, 2007; Zaramella et al., 2005). This methodology has not been used widely in research with ELBW infants and good reliability and validity data are lacking; therefore use of this instrument was exploratory. If higher foot temperatures were due to increased perfusion, the trend in the PI should have been elevated with warmer temperatures as peripheral temperature correlates with peripheral perfusion (Martin & Norman, 1997).

Findings—The standard of care in this NICU is pulse oximetry integrated into the cardio-pulmonary monitor but without PI measurement. Initially, two free-standing pulse oximeters were attached to each study infant, one on the hand and one on the foot. We were able to measure continuous PI in four pilot infants; however, one infant's data were lost during download due an interrupted internet connection. Several problems were encountered during the pilot. We learned that if the pulse oximeter was kept plugged into an electrical current during storage between study infants, data would accumulate and it took as long as 30-45 minutes to download data measured during storage. Additionally, in the same way that temperature probes had been moved to different extremities, pulse oximeter probes were moved to the wrong extremity during data collection inadvertently by the nursing staff. This problem was also eliminated once labels were applied specifying the pulse oximeter probe was for research.

A major problem occurred during transition to daylight savings time with the pulse oximeter dumping data during the time change, then either cutting off or starting over with storage of data. This problem occurred randomly. We eliminated the problem of missing data by downloading data before and after the time changes.

Finally, several unanticipated small problems with downloading data from the pulse oximeter occurred. Initially, it was difficult to match serial ports on the computer to the cable for download from the pulse oximeter. Each pulse oximeter may match to a different serial port, depending on the computer. If the computer used for download is changed, most likely serial ports will change. It is necessary to specify a serial port when setting up the software for download. We also attempted to download the data directly to an internet supported secure server; however, once during download the internet connection was lost for a second, causing the download to be interrupted and the entire 5 days of data to be lost. We learned to download to a stable hard drive instead. The PI records measures every 10 seconds making it necessary to take the mean for all six measures over one minute in order to compare with other physiologic data measured each minute.

Perfusion index can be measured from 0 to 20 using a monitor. The range of PI measurements in these infants was also from 0 to 20; however, the trended daily means were much lower (see Figure 4). Trends in PI increased over time, as they have in other studies of premature infants (Cresi et al., 2010). When we examined Pearson's correlations between foot perfusion and foot temperature, all infants had little to no correlation using data within

each day ($-.05$ to $.22$). For one pilot infant, a moderate correlation was seen between hand temperature and PI on day 4 of $.34$ and day 5 of $.35$.

Recommendations for future study—Results from this study confirmed that PI can be measured and entered into analysis with temperature measures. There seems to be a maturational trend to measures of PI over time. Many more infants are needed to determine the nature of the associations between longitudinal PI and peripheral temperature in ELBW infants, and if this instrument produces valid perfusion measures in the ELBW population

Context Data through Video Observation

Methods-initial approach—In order to evaluate episodes of hypothermia over time in relationship to care events that may be the cause of hypothermia in ELBW infants, video observation was evaluated as a source of data collection. A Sony® handheld video camera was attached to the study infant's incubator using an adapted, straight tripod arm so that the video camera recorded the infant inside the incubator through the back corner of the incubator. The camera was capable of recording continuously for a maximum of 12 hours, once the record button was activated. The video camera had low light recording capability, making it useful with incubator drapes in place. Each infant's nurse was instructed to turn the camera off around 2200 each night, and then restart the recording so that another 12 hours of video could be recorded enabling download of video once each day at 1000.

Methods-findings—Regardless of where the video camera was positioned, some missing data occurred in each 12 hour video recording because care givers unknowingly bumped the camera and did not realize it was no longer aimed on the infant. We had much better luck with high quality, continuous video recording when the camera was mounted to the incubator. The incubator was draped with a quilt to decrease light from shining on the infant. This drape was not a problem as the corner of the drape was secured so that the lens of the camera was between the edges of the drape. We also learned that after continued use, the camera would no longer hold a charge on the battery and if the power cord became dislodged, the video would stop recording and data would be lost.

Each morning, a research assistant removed the video camera from the bedside and replaced it with another video camera. This download took approximately 45-90 minutes each day. Each 12 hour video required 14 to 50 GB of storage space depending on the video camera that was used to capture the video. High definition recording resulted in larger files of up to 50GB. It became necessary to store data on separate 500 GB hard drives instead of computer servers due to large file size. The large amount of storage needed for data increases costs for the study.

Initially, we used Mangold coding software to identify the start and stop times of 12 different stimulation and care event codes. After attempting to become proficient with this software, we had to find a more user friendly software. Mangold software was produced in Germany, making technical support difficult and sometimes translation of written help guides was difficult to understand. We now use Noldus Observer 10.5 (Noldus, Wageningen, Netherlands), which has an American technical support team and local sales support. A detailed description of the observational methods using continuous video and statistical analyses will be reported in a separate paper in preparation.

Coding of each 12 hour video file was completed in 4-8 hours of time by student research assistants, depending on their experience with coding software and their previous NICU experience. Using coded video files, we were able to capture the relationship between the presence of stimulation and hypothermia in three of four infants. For each infant, we cross tabulated each minute as (1) stimulation present or absent and (2) hypothermic or not

depending on the infant's abdominal temperature. We could then construct 2 by 2 tables of counts for each day for each infant. We quantified the relationship between stimulation and hypothermia by an odds ratio (Agresti, 2002) derived directly from each table of counts. In this analysis, the odds ratio had a possible range from 0 to positive infinity. A strong relationship between stimulation and hypothermia was indicated by an odds ratio near zero or very far from 1. Odds ratio were different in each infant, ranging from 1.2 to 5.4 times, based on pooled data over all days. Each infant had varying odds ratios over their five days of data observation, with two of the three infants having particularly large odds ratios on their first day of life; 6.2 and 7.5.

Recommendations for future study—We found video observation to be *feasible* and an excellent source of qualitative data to create a context around bouts of hypothermia in these pilot infants. With proper instruction and clear written directions, video recording can be carried out to maximize data *validity*. We recommend that researchers should estimate storage space needed for video data and this expense be computed into a study budget. Storage requirements can be large. We also highly recommend Noldus Observer 10.5 Software (Noldus, Wageningen, Netherlands) for use in coding video data.

Context Data from Medical Chart Review

Initial approach—A research assistant reviewed each infant's electronic medical record for demographic and clinical data until discharge or transfer from the NICU. These data were entered into a data base program created for this study. Medical data and disease information were collected on each infant to determine the context around each case, in order to understand ongoing body temperature and perfusion changes. The demographic data for each infant could be merged with the large set of physiological data for each infant. Each demographic and clinical variable could then be exported into the data set for each infant to evaluate it in relationship to physiological and observational data.

Findings—Our first pilot infant had an unstable course and required multiple procedures including multiple peripherally inserted central catheter insertions and blood transfusions. We described these types of events over the plot of central peripheral (CP) temperature difference trends using software and demographic/medical information (see Figure 5). This type of data triangulation was very helpful in identifying the context of the longitudinal physiological data. This infant died from NEC at 18 days of age. Interestingly, this infant had more episodes of hypothermia and abnormal perfusion states (where the foot was warmer than the abdomen) than any of the other pilot infants over the 5 days of data collection. Another infant had the least variable CP temperature difference over the 5 days, with minimal variability which possibly represented immaturity. This male infant was the largest in birth weight, but had a gestational age of 26 weeks. One infant appeared the most mature from analysis of body temperature. The infant appeared to have mature control over peripheral blood flow at 66 hours of age, with the ability to exhibit peripheral vasoconstriction to episodes of hypothermia.

Recommendations for future study—We found that demographic data and clinical disease context information were essential to frame each case study. The clinical context data included episodes of feeding intolerance, presence of a patent ductus arteriosus, and procedures being performed. Analyzing longitudinal physiologic data without this frame of reference decreases *validity* to interpretation of data.

Developing Analytic Models

Initial approach—At the end of 5 days, all physiologic data and video were downloaded by the research nurse. Raw temperature data were saved in a text file and later cleaned and

exported. Perfusion index data were downloaded, and raw data were saved then cleaned and exported into each infant's data set. Each infant had approximately 10 video files for as much as 500 GB of data. Coded video data were exported into spreadsheet files and imported into each infant's data set. Infrared images were downloaded from the card to the secure server and analyzed (Knobel et al., 2011). Demographic and clinical data were exported into each infant's data set.

Each infant's data were analyzed using a case study approach, combining physiological, observational, and qualitative data to construct a picture of the infant's maturation in regard to the ability to constrict and dilate peripheral blood vessels in relationship to variations in central and peripheral temperature. Data plots and descriptive statistics were used to obtain a general overview of each variable over time.

To examine peripheral vasoconstriction in relation to hypothermic episodes associated to care events, observational data (5 days of video recordings) were viewed by student research assistants and coded for 12 care events. Coded events were analyzed in comparison to physiologic data by examining segments of time with hypothermic temperatures in relationship to the presence or absence of stimulation within each infant.

The statistical approach used to examine research questions related to maturation of control over central and peripheral body temperature was developed with the pilot data over approximately 1 year, with trial attempts at modeling data. Temperature data were modeled initially with logistic regression and then subsequently with the state space approach to time series analysis (Durbin & Koopman, 2001; Levy, Elser, & Knobel, 2012). The resulting statistical methods identified long term trends in maturation as well as shorter periods of abnormal perfusion.

Findings—Initially, we modeled longitudinal changes in the CP temperature difference assuming that the difference would be monotonically increasing to some age of maturity after which variation would hover over an essentially straight line. This type of pattern is well modeled by a logistic S shaped curve. However, only one infant exhibited this trend in CP temperature differences over time. As a consequence, logistic type models did not adequately fit these data. Instead, CP temperature differences exhibited a variety of patterns as infants aged. For some infants, this metric appeared to increase then return to values near zero or even below zero, only to return to positive values at a later time. For this reason, we chose a statistical method which would not impose a preconceived pattern over the way in which the CP temperatures varied over time. We needed an approach which would model the long term trend in a way dictated by the data. For this reason, we selected the state space approach to time series analysis (Durbin & Koopman, 2001).

In the state space framework, time series data are decomposed into either fixed or time varying levels called trends and cycles. We were particularly interested in fitted trends that via a well-known process called the *Kalman filter* (Durbin & Koopman, 2001) are estimated and adjusted as each data element is examined from first to last, then smoothed. Trends estimated by this approach reflect the data as they naturally unfold over time. We examined the CP temperature difference over the 5 day course for each infant (see Figure 5). With this approach, we were able to estimate the long-term trend in the data after removing shorter term cyclical variation. Consequently, we were able to more clearly discern time periods where the infant kept the foot warmer than the abdomen, which is representative of an abnormal perfusion state—either due to immature neural control over blood flow, or physiologic instability causing an abnormal perfusion state. The analysis provides an excellent way to view the data and examine CP temperature differences over time (Levy et al., 2012).

Recommendations for future study—When studying maturation of physiologic processes, analyzing longitudinal data using the state space approach to time series analysis provides a way to visualize the data without interference from cyclic or error measures. This approach allows the natural trend of the data to unfold over time and enables the researcher to see inconsistent patterns that may represent aberrations from normal physiological patterns.

Conclusion

Results from this pilot study showed that adding multiple instruments to measure temperature and perfusion adds rich data to a case study approach. We were able to analyze data with statistical models that allowed trends to unfold. Our data suggest that measuring PI gives a trend over time to add information to the trajectory of maturation of control of peripheral perfusion and temperature. Other researchers (Cresi et al., 2010) have shown that PI trends increase over time, which suggests that as peripheral perfusion increases with age, the index is capable of detecting trends. As infants' ability to control peripheral body temperature matures, PI measures increase. More infants are needed to discern significant correlations between changes in peripheral body temperature and perfusion index trends.

The PI and skin thermistor body temperature combined with simultaneous measure of infrared central and peripheral body temperature provided a method for evaluating correlations between central and peripheral perfusion. Infrared imaging revealed body temperatures in peripheral and central areas of the body simultaneously, allowing us to visualize a temperature differential between these areas. Researchers have successfully used infrared thermal imaging to locate areas of peripheral body temperature differentials to diagnose limb trauma with altered perfusion in pediatric patients (Silva et al., 2012). This exploratory technology may be useful in determining why infants have periods with increased peripheral temperature while keeping their central temperature cold. Our future study will apply this technology in a case study design of 30 infants. This will be one step in our program of research to explore causal links between hypothermia and increased morbidity (Miller, Lee, & Gould, 2011).

Lastly, we were able to examine development over control of central and peripheral temperature using state space approach to time series analysis (Durbin & Koopman, 2001), which differentiates between maturation and random periods of instability. Through analysis of these pilot data we realized that the appropriate statistical model for the development of CP differences must be flexible enough to allow an infant's natural course of development of temperature control to emerge. Based on these four infants, this natural course appears to be irregular, with periods of growth followed by plateaus or downward trends. Traditional longitudinal methods impose a mathematical structure on the trajectory of growth (Diggle, Heagerty, Liang, & Zeger, 2002). We selected a more flexible set of models allowing the growth in temperature control to be studied as it naturally unfolds over the first few weeks of life (Durbin & Koopman, 2001).

Our methodology was able to measure the intended parameters. There were limitations to each method, but solutions were devised to improve the monitoring for future studies. Methodological triangulation of data is helpful in that multiple sources of data are used to explore phenomena and interpret findings (Bekhet & Zauszniewski, 2012). We were able to use our analysis of longitudinal temperatures on one pilot infant along with data collected on procedures performed to interpret periods of abnormal temperature and perfusion with possible etiologies and suggest possible hypothetical pathways to the eventual diagnosis of NEC in this infant. Using data integration with a case study approach on infants with a continuum of gestational ages between 24-29 weeks and birth weights between 400-1000

grams should enable researchers to build maturational trajectories of development and control over body temperature and perfusion. Such trajectories, when evaluated in context with physiological systems variation, should help researchers determine etiologies that link hypothermia to morbidities such as NEC. Neural control of body temperature regulation matures over the gestational and postnatal age, but can change with clinical instability. A better understanding of this pathophysiology in neonates may provide a tool for early detection, treatment and reduction in morbidity from such disease processes as necrotizing enterocolitis. Future research is needed in this area.

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REFERENCES

- Agresti, A. Categorical data analysis. 2nd ed. John Wiley & Sons; Hoboken, New Jersey: 2002.
- Bekhet AK, Zauszniewski JA. Methodological triangulation: an approach to understanding data. *Nurse Researcher*. 2012; 20:40–43. [PubMed: 23316537]
- Boros M, Takaichi S, Hatanaka K. Ischemic time-dependent microvascular changes and reperfusion injury in the rat small intestine. *Journal of Surgical Research*. 1995; 59:311–320. [PubMed: 7637347]
- Cresi F, Pelle E, Calabrese R, Costa L, Farinasso D, Silvestro L. Perfusion index variations in clinically and hemodynamically stable preterm newborns in the first week of life. *Italian Journal of Pediatrics*. 2010; 36:1–6. [PubMed: 20180944]
- De Felice C, Del Vecchio A, Criscuolo M, Lozupone A, Parrini S, Latini G. Early postnatal changes in the perfusion index in term newborns with subclinical chorioamnionitis. *Archives of Disease in Childhood: Fetal and Neonatal Edition*. 2005; 90(5):F411–414. [PubMed: 15863488]
- Diggle, P.; Heagerty, P.; Liang, K.; Zeger, S. Analysis of longitudinal data. 2nd ed. Oxford University Press; Oxford: 2002.
- Durbin, J.; Koopman, S. Time series analysis by state space method. Oxford University Press; New York: 2001.
- Goldstein MR, Pernia ML, Yang LL, Lawas-Alejo P, Furman GI, Ochikubo CG, Martin GI. Decreased perfusion index (PI) predicts neonatal therapeutic intervention scoring system (NTISS) identified sick neonates and correlates with decreases in heart rate variability (HRV). *Proceedings of the 2005 Annual Meeting of the Pediatric Academic Societies*. 2005; 57:569.
- Granelli A, Óstman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. *Acta Pædiatrica*. 2007; 96(10):1455–1459.
- Houstek J, Vizek K, Pavelka S, Kopecky J, Krejcova E, Hermanska J, Cermakova M. Type II iodothyronine 5 -deiodinase and uncoupling protein in brown adipose tissue of human newborns. *Journal of Clinical Endocrinology Metabolism*. 1993; 77(2):382–387. [PubMed: 8393883]
- Hull, D.; Smales, O. Temperature regulation and energy metabolism in the newborn. Grune & Stratton; New York, New York: 1978.
- Knobel R, Guenther BD, Rice H. Thermoregulation and thermography in neonatal physiology and disease. *Biological Research for Nursing*. 2011; 13:274–282. [PubMed: 21586499]
- Knobel RB, Holditch-Davis D, Schwartz T, Wimmer JE. Extremely low birth weight preterm infants lack vasomotor response in relationship to cold body temperatures at birth. *Journal of Perinatology*. 2009; 29:814–821. [PubMed: 19626030]
- Levy JA, Elser HA, Knobel RB. The promise of the state space approach to time series analysis for nursing research. *Nursing Research*. 2012; 61:388–394. [PubMed: 23090442]
- Lyon AJ, Pikaar ME, Badger P, McIntosh N. Temperature control in very low birthweight infants during first five days of life. *Archives of Disease in Childhood: Fetal and Neonatal Edition*. 1997; 76(1):F47–50. [PubMed: 9059187]

- Martin H, Norman M. Skin microcirculation before and after local warming in infants delivered vaginally or by caesarean section. *Acta Paediatrica*. 1997; 86(3):261–267. [PubMed: 9099315]
- Miller SS, Lee HC, Gould JB. Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. *Journal of Perinatology*. 2011; 31:S49–56. [PubMed: 21448204]
- Mok Q, Bass CA, Ducker DA, McIntosh N. Temperature instability during nursing procedures in preterm neonates. *Archives of Disease in Childhood*. 1991; 66(7):783–786. [PubMed: 1863124]
- Nankervis C, Giannone P, Reber K. The neonatal intestinal vasculature: Contributing factors to necrotizing enterocolitis. *Seminars in Perinatology*. 2008; 32:83–91. [PubMed: 18346531]
- Neu J, Walker A. Necrotizing enterocolitis. *The New England Journal of Medicine*. 2011; 364:255–264. [PubMed: 21247316]
- Silva CT, Naveed N, Bokhari S, Baker KE, Staib LH, Ibrahim SM, Goodman TR. Early assessment of the efficacy of digital infrared thermal imaging in pediatric extremity trauma. *Emergency Radiology*. 2012; 19(3):203–209. [PubMed: 22362422]
- Simbrunner, G. Thermoregulation of sick and low birth weight neonates. Springer-Verlag; Berlin / New York: 1995.
- Steketee J. Spectral emissivity of skin and pericardium. *Physics in Medicine and Biology*. 1973; 18(5): 686–694. [PubMed: 4758213]
- Wilson T, Sauder C, Kearney M, Kuipers N, Leuenberger U, Monahan K, Ray C. Skin-surface cooling elicits peripheral and visceral vasoconstriction in humans. *Journal of Applied Physiology*. 2007; 103:1257–1262. [PubMed: 17673561]
- Workie FA, Rais-Bahrami K, Short BL. Clinical use of new-generation pulse oximeters in the neonatal intensive care unit. *American Journal of Perinatology*. 2005; 22(7):357–360. [PubMed: 16215921]
- Zaramella P, Freato F, Quaresima V, Ferrari M, Vianello A, Giongo D, Chiandetti L. Foot pulse oximeter perfusion index correlates with calf muscle perfusion measured by near-infrared spectroscopy in healthy neonates. *Journal of Perinatology*. 2005; 25(6):417–422. [PubMed: 15915164]

Callouts

1. Ways to study maturational physiology in extremely premature infants having multiple providers and different modes of medical management are needed.
2. We determined that parents' ability to hold their infants' hands without research probes attached was more important than collecting hand temperature.
3. Results showed that adding multiple instruments to measure temperature and perfusion adds rich data to a case study approach.

Figure 1.
Data logger and thermistors used on infants for measuring body temperature.

Figure 2.

Needle plot for infant showing episodes of hypothermia and peripheral vasoconstriction response. Line 1 with circles: hypothermic episode. Level indicates maximum degrees abdomen decreased below ISC. Line 2 with stars: Level indicates the difference between the abdominal temperature and the foot temperature, or peripheral vasoconstriction level.

Figure 3.
Infrared image on an infant on Day 4 of life.

Figure 4. Daily means for perfusion index readings for three pilot infants. Infant 1: 830 gms birth weight; Infant 2: 990 gms birth weight; Infant 3: 610 gms birth weight.

Figure 5.

Plot of central (abdominal), peripheral (foot) temperature difference for one infant using Stamp program (OxMetrics) and the state space approach. $\text{Abdtp} - \text{ftp}$ = abdominal temperature - foot temperature; Level: trend as defined by state space analysis.

Table 1

Demographic characteristics of the four pilot infants.

Pilot Infants	Birth Weight	Gestational Age	Gender	Race
1	830 gms	27 5/7 weeks	Male	African American
2	990 gms	26 3/7 weeks	Male	African American
3	770 gms	26 6/7 weeks	Female	African American
4	610 gms	23 6/7 weeks	Female	African American

Table 2

Ranges of daily mean temperature measurements for the four pilot infants.

	Daily Mean Temperature (°C)				
	Day 1	Day 2	Day 3	Day 4	Day 5
Abdomen	36.1 - 36.7	36.0 - 36.8	35.1 - 36.7	35.9 - 36.9	35.9 - 36.9
Foot	35.8 - 36.8	35.3 - 36.7	35.9 - 36.3	36.1 - 37.0	35.7 - 37.1
Hand	36.1 - 36.7	35.8 - 36.8	36.5 - 36.5	36.1 - 36.7	36.2 - 36.4
Environmental	34.8 - 36.6	35.3 - 36.7	34.7 - 36.2	34.6 - 36.2	33.7 - 34.8
ISC	36.1 - 37.0	36.3 - 36.9	36.6 - 36.9	36.4 - 36.9	36.6 - 36.9
Central-Peripheral ^a	-0.17 to 0.24	0.05 to 0.57	-0.50 to 0.77	-0.18 to 0.45	-0.54 to 1.16

Note. Environmental=inside incubator temperature; ISC=set servo control for abdominal temperature;

^a Central-Peripheral : Temperature difference between abdomen and foot (with positive numbers meaning abdomen was warmer than foot, negative numbers meaning foot was warmer than abdomen).