Thermal Alterations in Premature Neonates

Master Thesis

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Thermal Alterations in Premature Neonates

By

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Preface

The present work has been performed thanks to the collaboration between the Erasmus Medical Center in Rotterdam and Delft University of Technology. I would like to thank my supervisors, Tom Goos and Jenny Dankelman for their support during the project and for giving me the opportunity of opening a new research line in the Neonatology Department of the Erasmus Medical Center. I would like to show my gratitude to the medical and nursing staff of the Erasmus Medical Center for their assistance during the study. Thanks to all the parents who gave consent to participate in the study and to all their babies, who without being aware of it, made this research possible. I would also like to show my gratitude to the Technical Department, and in particular to Fons Noordermeer, Arie Koedood and Leo Groenendaal. A special thanks to Katya Mauff and Willem van Weteringen for their help and support, and to Flor Abinzano for her friendly advice, encouragement and feedback.

Thanks to all my friends in Delft and to the ones that are around the world, for being my most treasured extended family. And last but not least, to my family: to my dad, my mum, my sister and my grandma, for always being there for me and for being the greatest support one could ever ask for, no matter the distance. Gracias.

Alba Pedrero
Delft, February 2017

Outline of Thesis

The present thesis is divided into two main sections, a general introduction and a pilot study in the form of a scientific paper. First, in the introductory chapter basic concepts are described and the context, motivation and goal of the project are presented. Then, the results belonging to the pilot study performed in the Neonatal Intensive Care Unit of the Erasmus Medical Center are presented in the form of a paper.

At the end of the document, there are 5 appendices. In the first one, a copy of the original Research Protocol is included. In the second one, problems encountered during data recording are illustrated and the filtering criteria, followed in the pilot study, are explained in detail. In the third one, additional results and observations from the study are included. The fourth one contains an overview of the instruments used for the study. In the last one, results from an additional experiment performed at the Erasmus Medical Center are presented.

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1

Introduction

Advances in technology and healthcare for the preterm neonates range from development of better nursing conditions and establishment of a neutral thermal environment to improvements in less invasive techniques to monitor vital constants continuously. This progress has allowed to decrease the number of neonatal deaths and increase survival of the most premature ones. However, despite all these improvements we are still facing challenges: most of the neonates admitted to Neonatal Intensive Care Units all around the world still experience high rates of thermal alterations, major morbidities and poor postnatal growth. Extremely low birth weight and preterm neonates present a limited ability to control their own temperature. However, very little is known regarding the moment in which maturation of thermal control occurs. In order to keep improving the current clinical practice and nursing conditions of the most preterm neonates, understanding of the thermal control progresses with postnatal age is needed.

1. Implications of Prematurity

The term "premature" or "preterm" neonate refers to all babies born before 37 weeks of gestational age (GA). Prematurity can be classified into 3 different levels according to the duration of the pregnancy [1]. *"Moderate to late preterm"* refers to neonates born within the 32 to 37 weeks of pregnancy. The term *"very preterm"* refers to neonates born within the 28 to 32 weeks of pregnancy. Finally, *"extremely preterm"* are those neonates born alive within less than 28 weeks of pregnancy.

The term "*low birthweight*" (BW) is used to describe the neonates that weigh less than 2500g at birth. Depending on the severity of the condition it can be classified as Very Low Birth Weight (VLBW, neonates weighing between 1500g and 1000g) and ELBW (Extremely Low Birth Weight, weighing <1000g) [2].

Preterm and low birthweight neonates present an immature system and compromised health status. Their organs have not been fully developed and may fail to complete their intended tasks. They require to be cared in specialized areas of the hospital called Neonatal Intensive Care Units (NICU).

Thermal Alterations

Thermoregulation is the ability of the human body to maintain its core body temperature steady when exposed to different environmental temperatures [3]. However, premature neonates are only able to maintain their temperature constant within a very limited range. This results in frequent variations in body temperature with that of the environment [4]. For instance, temperature of the neonate can drop at a rate of approximately 0.2°C per minute after birth [5]. Preterm neonates have a decreased muscular tone that does not allow them to independently move into a flexed position to minimize heat loss [7]. Their physical characteristics (large surface to volume ratio, immature skin, thin layer of insulating fat, and weak peripheral vasoconstriction among others) makes them prone to heat loss as they are unable to produce enough heat.

In order to counteract heat loss, neonates are cared in neonatal incubators, which provide additional thermal support and create a Neutral Thermal Environment (NTE). This ensures minimal energy expenditures (metabolic requirements and oxygen consumption), supporting neonatal growth and maturation. The maintenance of a NTE can influence the chances of survival of the very premature neonates [6, 7], decreasing the incidence of morbidity and mortality [8, 9].

- Neonatal Hypothermia & Hyperthermia

Hypothermia refers to the clinical condition in which the body temperature falls below normal. Temperatures ranging from 36°C to 36.4°C are considered as *cold stress* or *mild hypothermia* [10]. The incidence of hypothermia seems to be greater with lower GA and BW [4-6]. Hypothermia may result in acidosis [11], hypoglycemia, coagulation defects [3, 10, 12, 13], delayed readjustment from fetal to neonatal circulation [3, 13, 14], falls in systematic arterial pressure, decreased plasma volume, decreased cardiac output [15, 16] and brain damage [17, 18]. Hypothermia is significantly related to higher morbidity and mortality rates [19-23].

While treating hypothermia, the medical practitioners should pay attention not to overheat the body of the neonate, generating the reverse reaction: hyperthermia [10]. Hyperthermia refers to a state in which the temperature of the neonate rises above 37.5°C [9]. This may occur if the environment is too warm or if the neonate is overdressed. The main side effect of hyperthermia is dehydration [10], but severe hyperthermia may lead to acidosis, shock, seizures, neurological damage, coma and death [8, 10].

- Neonatal Sepsis

Sepsis is the response of the body to infection or inflammation and results in high fever. *"Approximately, 1 million deaths per year are caused by infection occurring in the neonatal period (0-28 days), accounting for over 25% of global neonatal deaths" [24, 25]*. Early Onset Neonatal Sepsis (*EONS*) is characterized by appearing during the first 4 days of life while Late Onset Neonatal Sepsis (*LONS*) refers to infections that occur after this period and up to 90 days of life approximately [26, 27]. Pathogens that trigger EONS are usually acquired from the mother before or during delivery while pathogens that characterized LONS are more likely to be acquired from the environment and conditions in the NICU, especially in cases with a long period of hospitalization [28, 29]. Not treating sepsis on time will result in aggravation of the system failures and eventual death of the neonate.

Among the clinical manifestations of a sepsis episode, one can find hypothermia, hyperthermia or temperature instability [8], feeding intolerance, listlessness and lethargy, pallor or grey skin color, apnea or tachypnea, increased need for respiratory support, abdominal distension, refusal to move a limb or seizures [8, 26, 30, 31]. However, these non-specific manifestations hinder the identification and early diagnosis of sepsis.

Additionally, hyperthermia and sepsis present the same clinical signs, making the diagnosis of sepsis a challenging task for the medical personnel [32]. Because of the fatal consequences of not treating the infection on time sepsis should be always suspected in the first place [10]. Even though blood samples are considered the gold standard for the diagnosis [33], they present long waiting times (not available within 48h [26]) and frequent false negative results, which hinders prompt sepsis diagnosis in the neonate [34]. There is also a limitation in the quantity of blood drawn from the neonate and the distress this may cause [26, 30]. There is a tendency to start too soon antibiotic therapy as a preventive measure. However, resistance against antibiotics or allergies may developed and gastrointestinal immunity may be compromised [10, 26]. Because of this, recent research has focused on finding the best combination of physiological parameters that might indicate a trigger of sepsis in the neonate.

Maturation of Thermal Control

With increasing postnatal age, neonates are able to increase their heat production and develop thermal control, depending less on the thermal support of the incubator [35, 36]. However, the point in time at which maturation of thermal control becomes evident is not clear. The main variable related to development in the first days of life is the ability to perform peripheral vasoconstriction. Vasoconstriction refers to the ability to limit blood flow to the peripheral limbs in order to maintain constant core body temperatures when exposed to a cold environment. It is estimated as the difference in thermal gradient (ΔT), i.e. the difference between central and peripheral temperatures. Exposure to cold environment usually refers to handling or medical interventions that requires the opening of the incubator, therefore decreasing the air temperature in which the neonate is nursed.

The reduced ability of the neonate to maintain heat, because of this immature vasomotor control, is associated with lower central to peripheral temperature differences [7, 37]. This is characterized by a decrease in abdominal temperature while the value of the peripheral temperature is kept close to the thermal support given by incubators (implying vasodilated extremities). As neonates develop thermal control, vasoconstriction allows them to decrease their peripheral temperature (restricting blood flow to the extremities) in order to keep the abdominal temperature constant when exposed to cold temperatures. Acquisition of vasomotor control results on stabilization of central (abdominal) temperatures over time and a gradual increase of ΔT.

Literature suggests that maturation of thermoregulation in terms of vasoconstriction occurs in the period of time between the third hour of life and the fifth postnatal day [7, 35, 37]. However, this broad range can lead to inconclusive results. Furthermore, definitions in the magnitude of ΔT associated to development of vasomotor control greatly vary among the different studies. There is no standard definition of the ΔT that characterizes vasomotor control. However, different studies consider alterations of ΔT as possible markers of sepsis [38-40] and hypovolemia [7].

- ΔT as an early diagnosis for neonatal sepsis

Signs and symptoms are not reliable if used in isolation to detect a sepsis episode. However, the combined use of different clinical signs could aid in providing an effective sepsis diagnosis that is cost-effective and non-invasive. In order to establish the use of temperatures as markers for early sepsis detection more research is needed to find reliable temperature limits and incidence of temperature alterations. Previous studies point towards alterations in central to peripheral temperature differences (ΔT) higher than 2°C and up to 3.2°C [38-40]. Further research is needed in this area in order to validate the magnitude of the thermal alterations according to the maturation of the neonate that can accurately be used to detect a trigger of sepsis on time [26].

2. Insights into the Erasmus Medical Center

The current work has been performed thanks to the collaboration between the Delft University of Technology and the Neonatology Department of the Sophia Children's Hospital. The Sophia Children's Hospital or *Sophia Kinderziekenhuis*, in Dutch, is located in the Erasmus Medical Center (MC) in Rotterdam.

Newborn Monitoring

Standard monitoring in the NICU in the Erasmus MC involves continuous measurements of physiological constants of the neonates. Figure 1 illustrates a nursing scenario of a neonate being cared under a radiant heater instead of an incubator. Multiple sensors are connected to the skin to obtain information of heart rate (with an electrocardiogram, ECG), blood pressure, body temperature and oxygen saturation levels, among others.

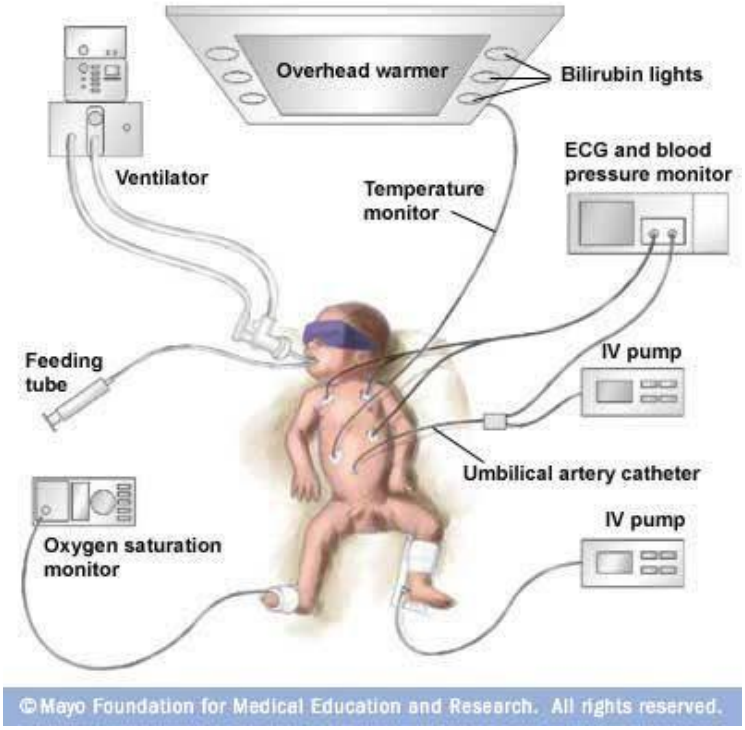

Figure 1 – Illustration of a neonate in the NICU [41]. The connection to different medical devices and sensors facilitate monitoring of the different physiological constants and early detection of alterations.

A patient monitor, located next to the neonatal incubator, provides an overview of the clinical variables being monitored. The patient monitor used in the NICU of the Erasmus MC is Infinity M540 (Dräger, Lübeck, Germany), as shown in Figure 2. Its small dimension facilitates transport and it can be also connected to a display monitor, Infinity C700 (Dräger, Lubeck, Germany), to ease visualization. Variables can be represented with a small graph over time with the actual value next to it.

Figure 2 – Example of the physical constants included in the display Infinity M540 (Dräger, Lübeck, Germany)[42].

Neonatal Incubators

Neonatal incubators consist of a transparent plastic hood or cover that encloses the neonate, as illustrated in Figure 3. Multiple portholes allow the medical personnel and parents to easily have access. Essentially, they create a microenvironment that allows the neonate to keep developing and growing without being exposed to sudden alterations in the surrounding environment. The temperature of the incubator can be regulated through servo-control or air temperature control (also known as manual control). Moreover, relative humidity can be added to counteract evaporative heat loses. Additionally, heat shields, plastic wraps or clothing can be used to reduce evaporative and non-evaporative heat loses of the neonate. Incubator covers (blankets) can be placed over the incubator to protect the neonate from the light of the room.

Figure 3 – Example of a neonatal incubator. It can be observed how this device can be easily used in combination with other equipment available in the NICU, such as mechanical ventilation, patient monitoring system and neonatal syringe pumps [43].

- Incubator Set Temperature

Incubators should be set to a temperature that ensures the NTE. It is recommended that the core temperature of the neonates is kept in the range of 36.5 to 37.5°C [10, 44]. However, there is a great variability in approaches and protocols for clinical practice among different medical centers [45]. In the Erasmus MC, the temperature of the incubator is controlled by the caregivers, who adjust the incubator temperature according to the needs of each individual neonate, influenced by GA, BW and postnatal age.

Deviations from the set incubator temperature are mainly due to medical and nursing procedures that involve the handling of the neonate. These procedures require the opening of the incubator (either one porthole, incubator sides or top cover) in order to gain proper access to the neonate, compromising the NTE. The port openings result in heat loss from the incubator and decrease in relative humidity, originating drops in the neonatal body temperature [36, 45].

With increasing postnatal age, neonates are able to increase their heat production and the incidence of alterations in temperature in the form of hypothermia decreases. Hence, lower incubator temperatures are needed to nurse the neonate. This maturation and less dependency on the incubator temperature should be carefully monitored by the nursing staff in order to avoid overheating the neonate, resulting in episodes of hyperthermia [35].

- Humidity

Evaporative heat loss is the main mechanism of fluid and heat loss in the preterm neonate, especially in ELBW neonates. The immature skin of the neonate and its low content of fat does not provide enough isolation. The introduction of humidity is associated with a reduction of trans-epidermal water losses from the skin of the neonate, better thermal stability and skin integrity [3, 46, 47]. The growth velocity when cared in humidified incubators has been shown to be significantly higher than for those neonates cared with no added humidity [6]. However, there is a lack of consensus regarding specific relative humidity levels that are adequate for nursing neonates [35, 37].

Kangaroo Care

When the health status of the neonate allows, the neonate can have periods of Kangaroo Care with the parents. It is a method of care that consists of skin-to-skin contact: the neonate will lie on the bare chest of one of the parents with only his diaper. The skin contact will keep him warm, at the same time that it helps establishing a bonding with the parents through breathing, smell and voice. The nurse in charge of the neonate will help the parents to take the neonate out of the incubator and position him comfortably.

3. Problem Statement & Objective

In the Erasmus MC approximately 20% of the neonates develop sepsis and 80% of the extreme preterm neonates have hyperthermia at least once during the first 3 days of life in the Erasmus MC [48]. The incubator set temperature is modified based on experience, as there is no specific protocol established for this practice.

In order to improve the current clinical practice and nursing conditions of the most preterm neonates, understanding of the developmental physiology of thermal control progresses with postnatal age is needed. More specifically, a clear definition of the magnitude of a stable and an altered relationship between central and peripheral temperatures (ΔT) characterizing the preterm neonates is needed.

The aim of this thesis is to study maturation of thermal control over time and investigate the potential of using peripheral temperatures or ΔT to help maintaining the NTE and avoid overheating the neonate. To do so, an observational pilot study was designed and performed in the NICU of the Erasmus MC. The alterations in ΔT for neonates that had sepsis during the study were investigated in comparison with the ΔT of healthy neonates. The percentage of time in which the neonates had hypothermia and hyperthermia was studied. The adjustments of the set incubator temperature were evaluated to study the possibility of reducing hypothermia and hyperthermia through careful monitoring of neonatal temperatures.

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2

Pilot Study

Thermal Alterations in the Preterm Neonates

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Keywords:
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Sepsis

A B S T R A C T

Introduction: Preterm neonates suffer frequent thermal alterations that result in increased morbidity and mortality rates. Thermal support is used to provide stability until thermal maturation is reached. The first manifestation of thermal control is peripheral vasoconstriction, estimated as the difference between central and peripheral temperatures (ΔT). However, very little is known regarding the point in time at which this maturation occurs and what values of ΔT characterize stability.

Aim: To study the maturation of thermal control and temperature trends over time. To assess the possibility of improving the temperature settings of the neonatal incubators to minimize hypothermia and hyperthermia. To evaluate the potential of using ΔT as an indicator of stability or marker for sepsis.

Methods: Very premature neonates (< 32 weeks of gestational age) admitted to the Neonatal Intensive Care Unit of the Erasmus Medical Center were included in the study. Peripheral and central body temperatures were recorded continuously for a maximum of 10 days were included. The temperature patterns were visually analyzed for possible trends over time. The percentage of time in which the neonates had hypothermia and hyperthermia was evaluated. The relation between adjustments in the incubator set temperature and the effects in the neonatal temperatures before and after the change were analyzed.

Results: Fifteen neonates were included in the pilot study. All the neonates presented stable body temperatures for at least 72.8% of the time. No maturation of thermal control could be observed over time. ΔT was observed to increase with gestational age. Extreme premature neonates kept a consistent ΔT < 2°C, with slightly altered values in cases with sepsis (20% of the neonates). Temperatures of the neonates were mostly outside the stable range before an adjustment in the set temperature was made.

Conclusions: ΔT might have the potential to help distinguishing between periods of stability, episodes of sepsis or hyperthermia. Preventive actions regarding adjustments of incubator set temperature could help minimizing episodes of hypothermia and hyperthermia.

1. Background

Disruptions in the body temperature threaten the health of preterm neonates and can lead to a variety of diseases and increased mortality [1-4]. Extremely low birth weight (ELBW, <1000g) and very preterm neonates (<32 weeks of gestational age, GA) present a limited ability to regulate their own temperature. This results in frequent temperature fluctuations and recurrent episodes of hypothermia (body temperatures < 36.4°C [5]). Preterm neonates are cared in neonatal incubators, which provide thermal support and establish a Neutral Thermal Environment (NTE). In this manner, metabolic requirements are minimized until the neonates reach thermal maturation. It is recommended that the core temperature (Tc) is kept in the range of 36.5 to 37.5°C [5, 6]. However, when the thermal support exceeds the actual heat requirements neonatal temperatures can rise above 37.5°C, a condition known as hyperthermia [5]. Hyperthermia should not be taken lightly, as it is *"as likely to occur and as dangerous as hypothermia"* [5]. A previous study showed that 80% of the preterm neonates (GA<26 weeks) had hyperthermia at least once during the first 3 days of life in the Neonatal Intensive Care Unit (NICU) of the Erasmus Medical Center (MC) [7].

When a raised body temperature is detected the distinction between hyperthermia and presence of sepsis becomes unclear. In the Erasmus MC approximately 20% of the neonates develop sepsis [7]. Sepsis is the response of the body to infection or inflammation, results in high fever and accounts for approximately 25% of global neonatal deaths [8, 9]. It presents non-specific manifestations that hinder its identification and early diagnose. Previous research suggests that the use of thermal alterations could be used as a non-invasive early diagnosis tool for neonatal sepsis [10-12].

The main variable related to development in the first days of life is peripheral vasoconstriction, the ability to limit blood flow to the peripheral limbs to maintain constant body temperatures when exposed to a cold environment. It is estimated as the difference between central and peripheral temperatures (ΔT). A lower ΔT is associated with the reduced ability to maintain heat because of the lack of vasomotor control, and will gradually increase over time [13-15]. There is no standard definition of the ΔT that characterizes vasomotor control although alterations in ΔT > 2°C

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and up to > 3.2°C haven been evaluated as possible markers of sepsis [10-12] and hypovolemia [13].

Therefore, even though thermal support is used in routine care, understanding the needs of the neonate through development of thermal control could help reducing the occurrence of hypothermia and hyperthermia. The goal of this pilot study is to assess the maturation of thermal control over time and to investigate the potential of using peripheral temperatures (Tp) or ΔT as an indicator of stability or as a marker for alterations. This could assist in adjusting the temperature of the incubator as the neonates mature, reducing the incidence of hyperthermia and therefore eventually making it easier to detect the trigger of an episode of sepsis in the NICU of Erasmus MC.

Nomenclature

ELBW	Extremely Low Birthweight
NICU	Neonatal Intensive Care Unit
NTE	Neutral Thermal Environment
BW	Birthweight
GA	Gestational Age
Tc	Central temperatures
Tp	Peripheral temperatures
ΔT	Difference between central and peripheral temperatures
Tinc	Incubator set temperature
Tin	Temperature inside the incubator

2. Methods

2.1. Protocol

The research protocol (included in Appendix A) involving 40 neonates was approved by the Medisch Ethische Toetsing Commissie (METC) from the Erasmus MC. This observational pilot study did not fall under the scope of the Medical Research Involving Human Subjects Act (not WMO-plichtig). Help from the statistician Katya Mauff (Department of Biostatistics of Erasmus MC) was requested while designing the protocol to estimate the sample size and the most convenient statistical methods for the data analysis. After approval was obtained, an additional appendix was submitted to request deferred consent.

Before approaching the parents for consent, the medical personnel was addressed to discuss the health status of the neonate and the adequacy of their inclusion in the study. Parents were approached after birth, once the neonate was admitted to the NICU. All instruments for the study had to be positioned no later than 48h after birth, in a moment of minimal distress for the neonate.

In the NICU of the Erasmus MC, core body temperatures are continuously monitored as part of standard care. A thermal probe (Mon-a-Therm™ 400TM, Covidien, US) is covered with plastic film (3M Tegaderm™ , 3M Health Care, St. Paul, US) and placed between the back of the neonate and the mattress. The same probe was used for peripheral temperatures. The foam of the peripheral probe was cut to avoid exceeding the size of the foot and covered with plastic film. It was positioned on the foot with a fixation band (Posey Paediatric Limb Holder 4733, Posey Company, Arcadia, US). For extreme premature neonates, the wire of the thermal probe was covered with soft tape to avoid any possible skin damage. Nurses were given the freedom to reposition the sensor in the opposite foot if needed. The extra thermal sensor was connected to the patient monitor (Infinity M540, Dräger, Lübeck, Germany) using a split cable. This monitor is in turn connected to a display screen, as shown in Figure 1. Labels were placed in both ends of the cables of the thermal probes to help preventing sensor misplacement. Central and peripheral temperatures were recorded every second by the patient monitor for a maximum of 10 days and updated into the network of the Erasmus MC. Decryption was handled by CapProcessor (Erasmus MC, Rotterdam, The Netherlands) and data was anonymized.

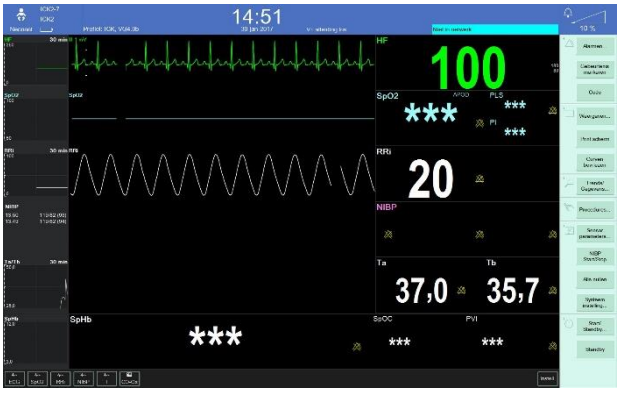

Figure 1 *– Patient monitor in simulation mode showing the readings of central and peripheral temperatures (bottom right corner)*

Two temperature data loggers HOBO® Pendant (Part #UA-002-64, Onset, US) were used for each neonate. One of them was positioned inside the Caleo® incubator (Dräger, Lübeck, Germany) and provided an estimation of the drops in incubator temperature during nursing procedures and medical interventions. The second sensor was fixed over the incubator display screen in order to have a reference of the room temperature. These sensors recorded temperature information every 30s for a maximum duration of 10 days.

The caregivers were responsible to adjust the incubator set temperature and relative humidity according to the needs of the neonate. Data of the incubator settings over time was collected from the records of the Patient Data Management System (PDMS). These values are manually recorded in the PDMS and updated every two hours by the nurse in charge of the neonate. Information regarding birth time, Apgar scores, gestational age, birthweight, weight and incidence of sepsis was obtained through the medical electronic health record (Elpado). Growth curves [16] were used to calculate whether the neonates were small for their gestational age and the percentiles to which they belong were estimated.

The neonates in the study were routinely monitored by the main researcher to check that the sensors were still in place and that the medical personnel did not encounter any problem. Once the neonates completed the study or before they were transferred to a secondary hospital or open bed the peripheral thermal probe was disposed and the rest of the instruments were collected.

2.2. Data Analysis

The central (Tc) and peripheral temperatures (Tp) recorded with the patient monitor were filtered to recover missing points in time (seconds) and to remove repeated points with Matlab R2016b (The MathWorks, Inc., Natick, MA, US). Temperature values of the missing seconds were filled with the average of the previous and following number. If the missing second was next to a not-a-number (NaN), but there was information before

or after, the value with the information was taken. If a NaN was present in any of the two seconds before or after, the number kept being a NaN (for more information, see Appendix B). Additionally, if the information of Tc or Tp was missing, both were deleted because the difference between Tc and Tp (ΔT) could not be computed in a later step. After filtering, the data was averaged per minute and ΔT was calculated. The information obtained with the HOBO® Pendant was also averaged over 1 minute.

If temperature data was missing for more than 24h the study was closed for that neonate at that point. For neonates that were transferred to an open cot, the temperature recordings of the HOBO® Pendant sensors were used to establish the point in time at which this transfer occurred. Information obtained with the different instruments was synchronized using Matlab and combined in an Excel file (Microsoft Excel, 2010).

Common encountered problems that led to abnormal temperature readings, indicating sensor detachment, were used to design a common criteria for filtering outliers (see Appendix B for more detailed information and examples). Recordings of Tc and Tp for which $|\Delta T| \geq 12°C$ were removed from the data. Any Tc lower than the incubator set temperature (Tinc) or than the measured temperature inside the incubator (Tin) was set to NaN ($Tc < Tinc$ or $Tc < Tin$). Any $Tp < Tin$ was set to NaN. Periods of time in which $Tp \geq Tc$ were analyzed; if in these periods $Tc \leq 35°C$, the values were set to NaN. Sudden drops and rises of temperature were not likely to occur unless the sensors were altered. Different magnitudes of reference for which these fluctuations were not physiologically possible were defined according to the variable (Tc and Tp) and duration of the observation (1 minute and 2 minute increment). If in a 1 minute increment any of the following increments were detected, the values were set to NaN: $Tc \leq -2.5°C$, $Tc \geq 3°C$, $Tp \leq -2°C$, $Tp \geq 1.4°C$. If in a 1 minute increment Tc or $Tp \leq -1°C$ and in a 2 minute increment Tc or $Tp \leq 1.9°$, NaN were assigned. If the data of a minute was missing and in the next 1 minute increment Tc or $Tp \leq -1.5°$ or ≥ 1.5 °C, NaN were assigned. If the data in a 1 minute increment was missing and in a 2 minute increment Tc or $Tp \leq -1.9°C$ or $\geq 1.9°C$, NaN were assigned.

The following criteria was applied for all the neonates but one, who presented really low peripheral temperatures: if $Tp \leq 32.3°C$ and the minute next to it was NaN, the value was considered as NaN. In case this step generated more scenarios of $Tp \leq 32.3°C$ next to a NaN, data was not deleted for longer than 15 minutes. This criteria was used to solve periods for which the sudden drops and rises had been removed but the abnormal readings in between were still present in the data. Finally, if one or two data points in a row were surrounded with NaN these points were also deleted regardless the value of these data points. No automatic solution was found to fix periods of time in which the sensors had been accidentally reversed and data had to be rearranged manually.

Once filtering was completed, the excel file containing the full dataset was created. A copy of the dataset was converted to CSV to be further analyzed with RStudio (RStudio Team (2016), Integrated Development for R. RStudio, Inc., Boston, MA, US).

Graphs of the temperature trends over time were created with the built-in Matlab function MOVMEAN to provide a clear comparison between different neonates (window size specifies the number of points used to calculate the average, the windows size was reduced at the endpoints and NaN were omitted when computing the mean value). Despite a window of approximately 20h (1200 data points) could already provide a smooth distribution of Tc, a window of time of 48h (2880 points) was used to obtain a smooth trend of ΔT over time. Temperature trends using different window's size are included in Appendix B.

A dataset was created with Matlab to evaluate the changes in incubator set temperature over time. The averaged recorded central temperatures over one hour before and one hour after each change in incubator setting were computed. If more than 30 data points (equivalent to 30 minutes) were missing, the change in incubator temperature was not considered valid for the analysis. Data of the temperatures one hour before a change in the set temperature gave an estimation of how the neonate temperatures were before the change. Data of the temperatures at the moment of the change gave an estimation of what could have triggered the medical personnel to change the temperature settings. Data of the temperatures of the hour after the change gave an estimation of how much the change in temperature actually altered the temperature of the neonate. Once the data set was completed it was converted to CSV to be further analyzed with RStudio.

2.3. Statistical Analysis

Results were visually analyzed with the help of Katya Mauff with RStudio to evaluate trends in the temperature over time and the possibility of fitting the data with a non-linear mixed effect models.

Descriptive statistics regarding temperature distribution over the duration of the study, periods of hypothermia, hyperthermia and adjustments of the incubator set temperature were calculated with R studio. Matlab was used to filter the data, create the different datasets and generate the plots over time. The statistical data presented in this paper is expressed as median [IQR].

3. Results

Fifteen preterm neonates* were included in the study between 30 November 2016 and 14 January 2017. The parents of the first 7 neonates included in the study were approached before positioning the sensors. The parents of the remaining 8 neonates were approached after the sensor had been positioned (deferred consent). Five possible candidates were not included in the study, 3 of them by request from the medical personnel and 2 of them by decision of the parents.

The characteristics of the neonates (BW and GA), growth scores (expressed in percentiles), Apgar Scores (as estimated after 1, 5 and 10 minutes after birth), incidence of sepsis, duration of the study, percentage of data present before the outliers filter and percentage of data removed by the outliers filter are listed in Table 1.

The sample of 15 neonates was divided according to GA into very premature (<32 weeks and ≥ 28weeks, indicated with + in Table 1) and extreme premature neonates (<28 weeks, indicated with ● in Table 1). The sample of very preterm neonates (n=9) had a GA of 30 +4/7 weeks [30 + 2/7, 31 + 5/7] and BW 1010g [950, 1593]. The group of extreme premature neonates (n=6) had a GA of 25.5+ 4/7 weeks, [25 + 3/7, 27 + 5/7] and BW 835g [765, 1058].

Two of the extreme premature babies (neonates #13 and #14) were twins. Neonate #7 had a twin who was not included in the study as requested by the parents. Three of the neonates (equivalent to 20%) had sepsis during the study (one very preterm, #2, and two extreme preterm, #5 and #13) and one extreme premature had meningitis (#9). One of the extreme preterm neonates suffered a second trigger of sepsis after the study had been concluded (#5). One of the very premature babies (#1) was re-admitted in

* Because of the time constrain, only 15 neonates were analyzed (the study should continue for the sample size of 40 neonates).

Neonate	*BW(g)*	*GA (wks + d)*	*Growth Scores*	*Apgar Scores*	*Sepsis (Y/N)*	*Study Duration (Days)*	*Total Observations (minutes)*	*% Data before removing outliers*	*% of outliers that were removed*
1 +	950	31 + 0/7	P10	8,10	N	10.0	14462	98.6	1.3
2 +	1855	31 + 5/7	P50	5,8,10	**Y**	5.1	7348	89.8	3.0
3 +	1150	30 + 3/7	P20	6,8,8	N	7.0	10137	92.2	5.1
4 +	1730	30 + 4/7	P84	9,10,9	N	2.0	2857	99.4	3.3
5 ●	730	24 + 5/7	P20	6,8,9	**Y**	10.0	14441	99.0	3.3
6 +	1405	31 + 5/7	P20	5,7,10	N	3.0	4249	89.3	1.8
7 +	1593	30 + 2/7	P80	7,9,9	N	5.7	8270	98.5	2.6
8 +	1875	31 + 1/7	P84	9,9,10	N	4.9	7022	95.7	1.3
9 ●	1115	27 + 3/7	P50	6,8,9	N	8.3	11887	91.3	3.9
10 ●	765	27 + 6/7	P10	7,8,9	N	8.4	12074	98.3	0.4
11 ●	1058	26 + 5/7	P80	7,9,9	N	9.9	14320	97.9	2.2
12 +	905	28 + 5/7	P20	5,8,9	N	10	14461	99.1	1.4
13 ●	900	25 + 3/7	P80	5,8	**Y**	10	14391	96.7	1.7
14 ●	835	25 + 3/7	P50	6,8,9	N	10	14421	99.1	0.7
15 +	1010	28 + 6/7	P50	4,6,7	N	10	14453	98.1	1.7

Table 1 – *Characteristics of the neonates included in the study. Very premature neonates are indicated with + while extreme premature neonates are indicated with ●.*

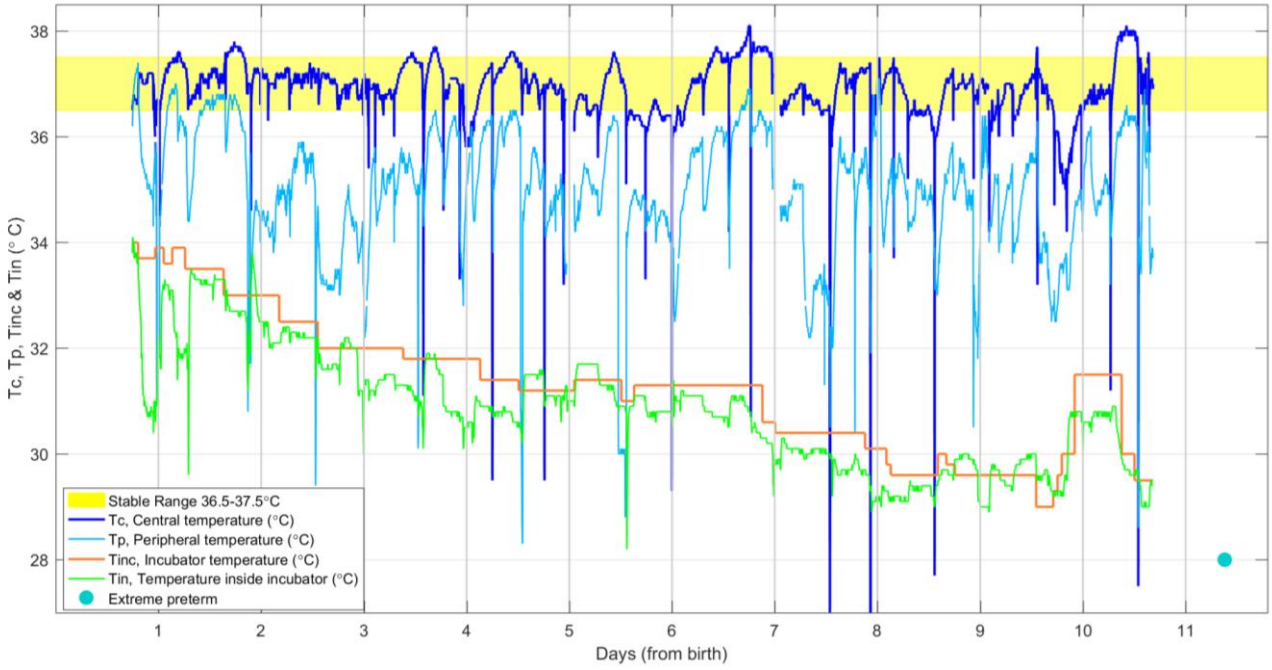

Figure 2 *– Example of the raw data from one extreme premature newborn (#11) with the distribution of central temperatures (shown in dark blue), peripheral temperatures (shown in light blue), incubator set temperatures (shown in orange) and the measured temperature inside the incubator (shown in green). The area shown in yellow correspond to the stable range in temperatures.*

the NICU after being transferred to a secondary hospital for 4 weeks. One of the neonates in the study (neonate #2) was nursed in High Care (HC) instead of in the NICU and neonate #1 was cared for the first 6 days of life in the NICU and then transferred to HC.

The incubator set temperatures registered during the study for the very premature neonates had a median of 31.0°C [29.8, 32.3] and of 32.0°C [31.0, 32.9] for the extreme premature neonates. The levels of relative humidity registered during the study for the very premature neonates had a median of 35% [0, 45] and of 60% [40, 80] for the extreme premature neonates.

The length of the recordings varied between a minimum and a maximum of 2857 minutes (2 days) and 14462 (10 days), respectively. The filter for outliers sought to keep as much data as possible, only removing periods in which the temperature readings were not physiologically possible. The maximum percentage of information removed (5.1%) corresponds to neonate #3, who had periods the sensors out of place for prolonged periods

	VERY PRETERM NEONATES (n=9, sepsis =1)				EXTREME PRETERM NEONATES (n=6, sepsis =2)			
	Time (%)	Tc (°C)	Tp (°C)	ΔT (°C)	Time (%)	Tc (°C)	Tp (°C)	ΔT (°C)
Stable	72.8	37.0 [36.7, 37.2]	35.2 [34.1, 35.8]	1.8 [1.2, 2.9]	75.8	37.0 [36.8, 37.2]	35.3 [34.8, 35.9]	1.6 [1.1, 2.2]
Tp > Tc	1.2	36.5 [36.0, 36.9]	36.8 [36.4, 37.1]	-0.2 [-0.4, -0.1]	0.6	36.7[36.4, 36.9]	37.1 [36.6, 37.4]	-0.3 [-0.6, -0.2]
Hyperthermia	8.5	37.7 [37.6, 38.0]	36.3 [35.1, 36.9]	1.5 [0.9, 2.6]	7.2	37.7 [37.6, 37.8]	36.4 [36.0, 36.7]	1.4 [1.1, 1.7]
No Sepsis	6.6	37.7 [37.6, 37.9]	36.4 [35.5, 36.9]	1.4 [0.9, 2.2]	4.3	37.7 [37.6, 37.9]	36.4 [36.2, 36.7]	1.3 [1.0, 1.6]
Sepsis	1.8	37.9 [37.6, 38.2]	35.5 [34.2, 37.0]	2.3 [1.0, 3.9]	2.8	37.7 [37.6, 37.8]	36.3 [34.5, 36,7]	1.5 [1.1, 3.2]
Hypothermia	18.7	36.2 [36.0, 36.3]	34.3 [33.3, 34.9]	1.8 [1.2, 2.8]	17.0	36.2 [36.1, 36.4]	34.3 [33.6, 34.9]	1.9 [1.4, 2.5]
Overall		36.9 [36.6, 37.2]	35.0 [33.9, 35.8]	1.8 [1.2, 2.8]		36.9 [36.6, 37.2]	35.2 [34.6, 35.9]	1.6 [1.2, 2.2]

Table 2 *– Temperatures (shown as Median [IQR]) for the two groups of neonates during periods in which the central temperatures were within the stable range, with Tp > Tc, hyperthermia (Tc > 37.5 °C), hypothermia (Tc < 36.5°C) and for the overall duration of the study.*

of time. An example of the raw data of an extreme premature neonate (#11) illustrating the fluctuations over time of Tc and Tp is included in Figure 2. These fluctuations are caused by incubator openings, which create drops in the measured incubator temperature (Tin) with respect to the set temperature (Tinc), followed by overshoots in temperature when the incubator is trying to recover the heat lost. The area shown in yellow corresponds to the stable range in temperatures, from 36.5°C to 37.5°C.

3.1. Hypothermia & Hyperthermia

Overall, central temperatures were kept within the same ranges, with 36.9°C [36.6, 37.2] for very premature and extreme premature neonates, as indicated in Table 2. The spread of peripheral temperatures was slightly larger in very premature (Tp 35.0°C [33.9, 35.8]) than in extreme premature neonates (Tp 35.2°C [34.6, 35.9]). The same pattern was observed in the distribution of ΔT. Very preterm and extremely preterm neonates presented temperatures within the stable range (36.5°C – 37.5°C) for 72.8% and 75.8% of the time. Peripheral temperatures exceeded central temperatures for only 1.2% and 0.6% of the time for very premature and extremely premature neonates, respectively.

The very preterm neonates presented cold stress or hypothermia (considered as Tc < 36.5°C) for 18.7% of the time with Tc 36.2°C [36.0, 36.3] and the extreme preterm neonates for 17% of the time with Tc 36.2°C [36.1, 36.4]. The lowest values of median Tp registered in the study belong to periods of hypothermia, with Tp 34.3°C [33.3, 34.9] and 34.3°C [33.6, 34.9] for very premature and extreme premature neonates, respectively. For the very premature neonates values of ΔT in cases of hypothermia did not differ from the ΔT in the overall observations while extreme preterm neonates the distribution of ΔT was slightly wider.

The very preterm neonates presented hyperthermia (Tc > 37.5°C) for a total of 8.5% of the time: 6.6% corresponding to hyperthermia due to overheating and 1.8% due to sepsis. The mean Tc for neonates with no sepsis was 37.7°C [37.6, 37.9] and 37.9°C [37.6, 38.2] in the case of sepsis. The incidence of hyperthermia in the group of extreme premature neonates was of 7.2%, divided into 4.3% for non-septic episodes and 2.8% for positive sepsis. The mean Tc for neonates with no sepsis was 37.7°C [37.6, 37.9] and 37.7°C [37.6, 37.8] in the case of sepsis.

The spread of Tp and ΔT was greater in periods of hyperthermia with a trigger of sepsis than in cases with no sepsis. Very premature neonates with no sepsis had ΔT 1.4°C [0.9, 2.2] and ΔT 2.3°C [1.0, 3.9] with sepsis. Extremely premature neonates with no sepsis had ΔT 1.3°C [1.0, 1.6] and ΔT 1.5°C [1.1, 3.2] with sepsis.

3.2. Trends in temperature

Tp fluctuated over a wider range with increased GA (see Figure 3). Very premature neonates exhibited lower temperatures than the group of extreme premature neonates. The opposite behaviour was observed for ΔT, which presented increased temperatures with GA. Slightly altered values in Tp correspond to the neonates with sepsis. Overall, extreme premature neonates presented a ΔT of 1.6°C [1.2, 2.2]. In neonates with sepsis (n=2, neonates # 5 and #13), the ΔT was slightly altered, with ΔT 1.3°C [0.9, 2.1] for neonate #5 and ΔT 1.8°C [1.4, 2.4] for neonate #13. This behaviour is not clearly seen in Figure 3 as the twins (one with sepsis and one without it) were grouped into the same box for having the same GA (25 + 3/7 weeks). In the group of very premature neonates, the range of the temperatures of the neonate with sepsis (#2) did not differ greatly from the rest of the neonates. This is also hindered in Figure 3, as neonates #3 and #6 had the same GA and were grouped (31 + 5/7 weeks). For the data that was grouped in Figure 3, the box was coloured indicating sepsis as soon as one of the neonates in the box had sepsis.

Figure 4 created with the built-in Matlab function MOVMEAN with a window of 48h, shows the evolution over time of the temperatures of all the neonates in the study (Tc, Tp and ΔT) and the temperature measured inside the incubator (Tin). Information of Tin was lost for neonate #8. Extreme premature neonates are represented with ● in the bottom right corner and very premature neonates are represented with +, neonates with sepsis are represented with a blue background. Despite the fact that this representation is an oversimplification of the results, it seemed that Tp follows Tc quite closely over time for extreme premature neonates, with an overall difference of less than 2°C, represented by ΔT. In the neonates with sepsis, this ΔT presented a higher value. For some very premature neonates, Tp fluctuated more over time and did not follow Tc, presenting variations in ΔT of up to 4.4°C. However, the sample size is too small to make a firm statement of whether these trends and differences in temperatures are representative. No maturation of thermal control or plateau in ΔT could be observed over time. Data could not be fitted with a non-linear mixed effect model because of the small sample size and the variability within the temperature patterns obtained for this group of 15 neonates.

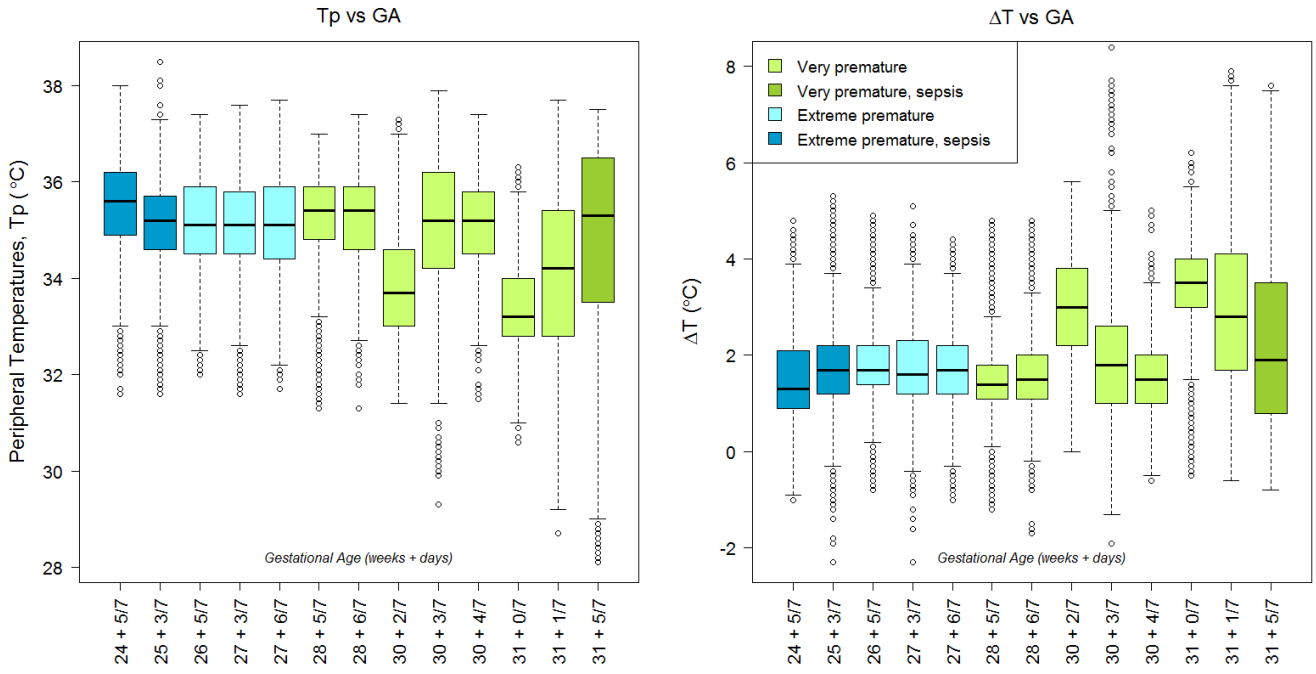

Figure 3 *– Distribution of peripheral temperatures and ΔT according to the gestational age (expressed in weeks + days) of the participants.*

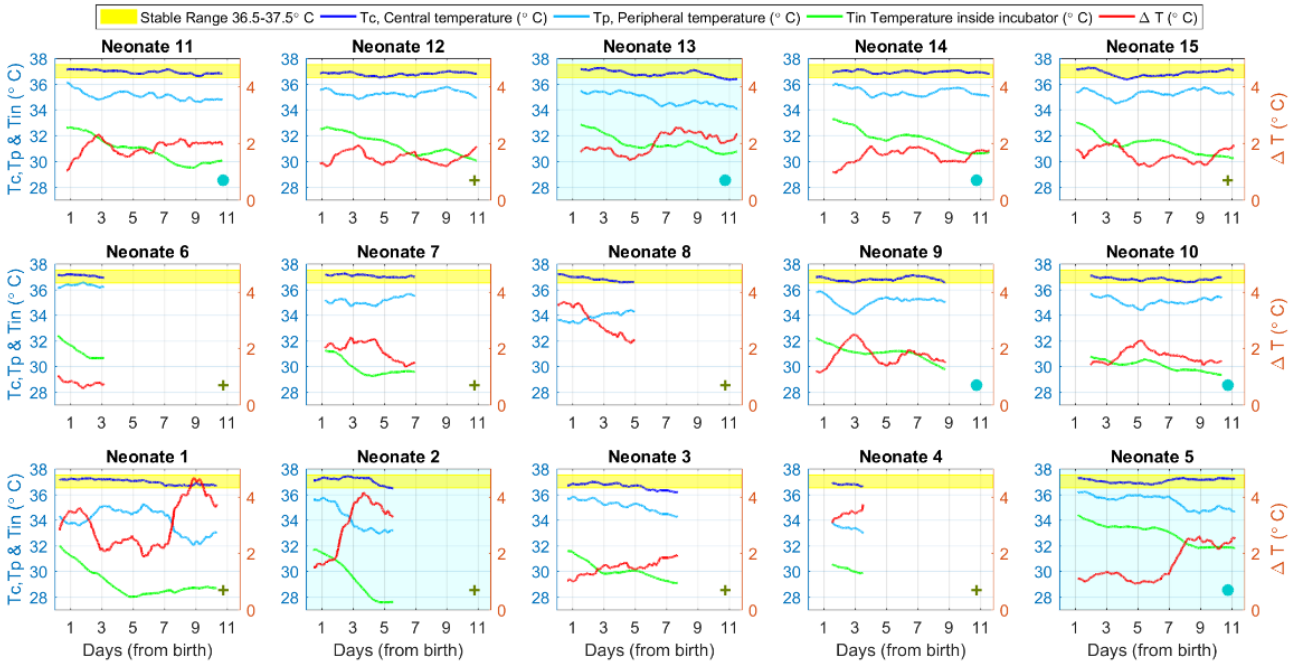

Figure 4 *– Temperature trends over time after using MOVMEAN to smooth the fluctuations in temperature. Temperatures corresponding to very premature and extreme premature neonates are illustrated with + and with a • in the lower right corner, respectively. In case a neonate had a trigger of sepsis, the background of the graph is represented in blue.*

3.3. Adjustments of the Incubator Set Temperature

Figure 5 illustrates possible patterns in temperature in relation to changes in the incubator set temperature before averaging the values over the previous and following hour. Examples marked with "a)" correspond to situations in which the change in incubator temperature prevented a decreasing or increasing tendency in the temperatures of the neonate. Examples marked with "b)" correspond to cases in which a change in set temperature was not effective and the temperature of the neonate remained outside the stable range. Examples marked with "c)" correspond to situations with incubator openings that caused a drop in central and peripheral temperatures. Because of the long stabilization times of neonatal temperatures, the change in incubator temperature did not have any apparent effect. The most common adjustment used by the nurses to modify the incubator set temperature were a decrease of 0.5°C and an increase of 0.3°C.

Figure 6 shows the ranges of temperature for each neonate corresponding to the average Tc 1 hour before a decrease in the incubator temperature was registered, the Tc at which the change in set temperature was done, and the average Tc 1h after the change. Four of the 15 neonates presented average central temperatures above the stable range ($Tc > 37.5°C$) for one hour before the incubator was set to a lower temperature (indicated by "-1h" in Figure 6). When the change in temperature setting was done (indicated by "Change" in Figure 6), the recordings of Tc continued raising or did not present changes. One hour after the incubator set temperature was changed, 7 neonates still presented temperatures above the stable range. Approximately the same patterns were observed regarding the increases in the incubator temperature. However, as the focus was to avoid hyperthermia to facilitate the diagnosis of sepsis, the results involving increases in incubator temperature are included in Appendix C.

4. Discussion

Extreme premature and very premature neonates showed an overall body temperature within the stable range of 36.5°C and 37.5°C, with Tc 36.9°C [36.6, 37.2], for 72.8% and 75.8% of the time as indicated in Table 2. Therefore, unless an altered Tc was encountered, ΔT was basically a mirror of the trends in Tp. Even though hypothermia and hyperthermia are recurrent problems in the care of premature neonates, the percentage of time of these episodes in the present study appears to be relatively low. The lowest values of Tp were registered during episodes of hypothermia, which could imply that the neonate was trying to perform vasoconstriction to reduce the blood flow to the extremities as a way of keeping the core temperature higher. During episodes of hyperthermia (with no trigger of sepsis) the neonates presented elevated peripheral temperatures, which might be an indicator of vasodilation, keeping peripheral temperatures higher in an attempt to dissipate heat from their body. However, as this is only a part of a pilot study, the sample size is too small and the percentage of time in which the neonates had hypothermia and hyperthermia is too low to make a firm statement of whether these could be representative and repeatable in a different sample of neonates.

For the very premature neonates, Tp was observed to fluctuate over a wider range than for extreme premature neonates, as shown in Figure 3. If the same increase in the distribution of Tp was observed with a larger sample size, the potential of using Tp or ΔT as indicator of an adequate nursing temperature according to GA could be investigated.

From the simplified tendencies over time shown in Figure 4, it appears that Tp had a tendency to gradually decrease over time generating a progressive increment in ΔT. The decrease in Tp could be due to fluctuations over a wider range of temperatures which could be an indication of vasoconstriction or vasodilation in response to cold or warm

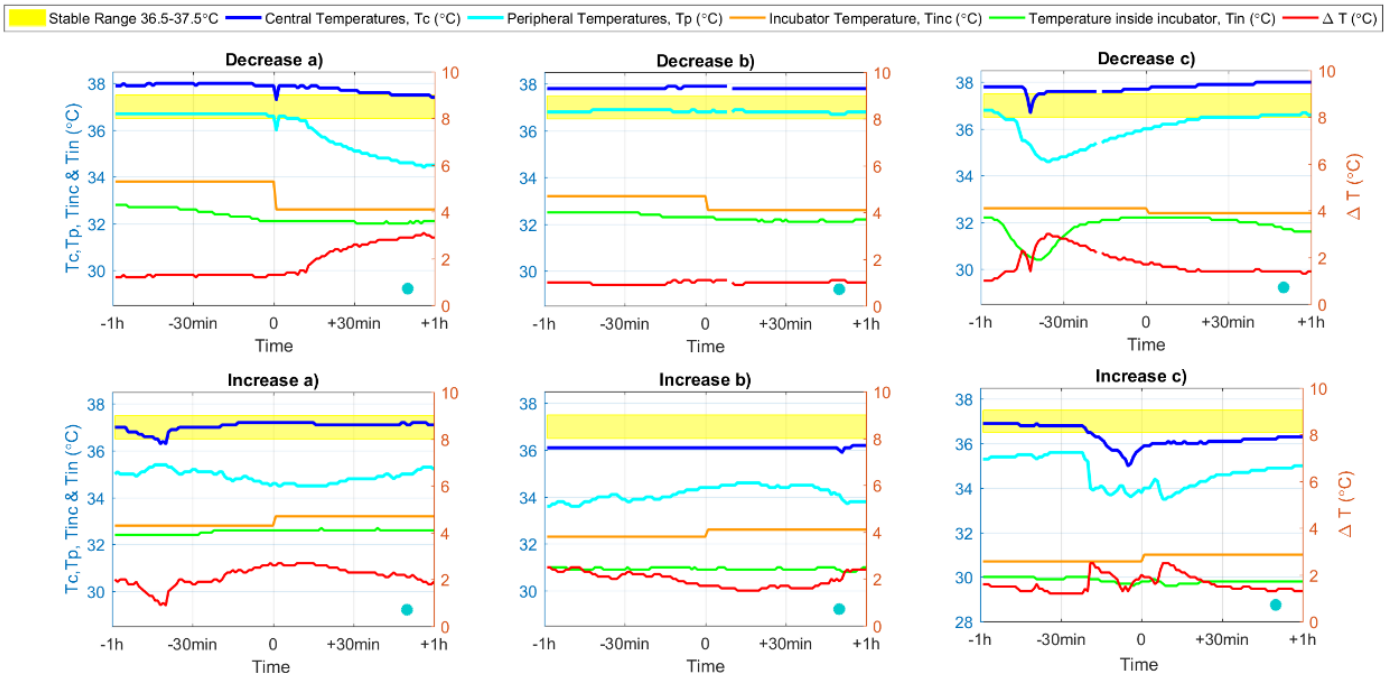

Figure 5 *– Illustration of moments in which the settings of temperature of the incubator were adjusted, before the averages in central temperatures were calculated for further analysis (raw data). The first row corresponds to decreases and the second row to increases in the incubator temperature. The point of time "0" corresponds to the moment in which the temperature of the incubator was either increased or decreased. The trends in central, peripheral temperatures, ΔT and measured temperature inside the incubator before and after the change in incubator temperature are illustrated.*

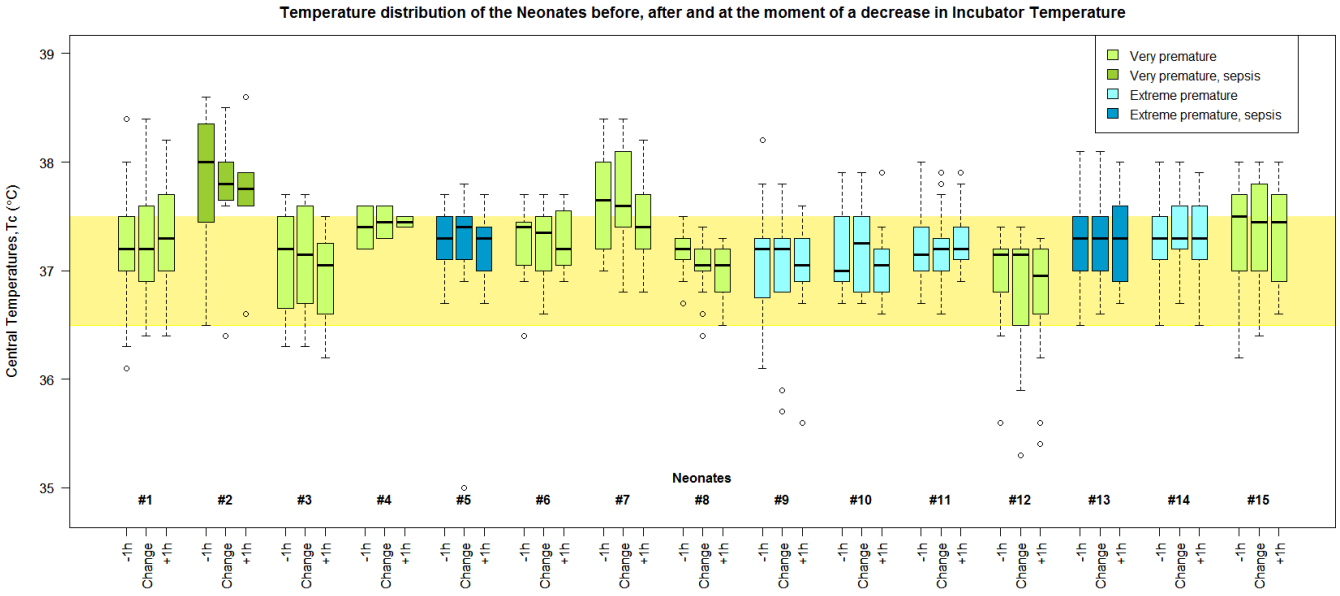

Figure 6 *– Distribution of the central temperatures of the neonates over one hour before a decrease in incubator set temperature was made (indicated by-1h), the temperature they exhibit at the moment of change (indicated by Change), and the temperature over one hour after the decrease in temperature was made (indicated by +1). The stable temperature range (36.5°C – 37.5°C) is shown in yellow.*

environments. The ΔT of some of the extreme premature neonates seemed to increase over the first 3 days of life and then stabilize. Nevertheless, no maturation of thermal control or clear plateau in ΔT could be observed over time. Back in 1997, Lyon et al. [13] studied a group of 83 neonates (BW <1000g, GA not specified) whose ΔT stabilized in a plateau over time. However, Tp was found to progressively decrease over time while Tc increased. Tp was higher than Tc for 18.9% of the time and progressively decreased over time. In 2009, Knobel et al. [15], studied a group of 10 ELBW neonates (GA <27 wks) during the first 12 hours after birth. Neonates exhibited low abdominal temperatures (ranging from 35.2°C to 36.7°C) and 7 of them had for at least 50% of the time Tp > Tc. Hence, the absence of the plateau might have also be due to the stability of Tc over time of all the neonates included in the present study. The percentage of time in which the value of peripheral temperatures exceeded the central temperatures is only of 1.2% and 0.6% for very premature and extremely premature neonates, respectively. Because Tc was stable when admitted to the NICU and when admitted to the study, the temperature plateau might be present but not be as pronounced as in previous research. This, together with the continuous incubator openings and medical interventions may have hidden the plateau, if present. Moreover, it might have been the case that by the time the neonates were included in the study the plateau had already been reached. However, the comparison with previous research also implies that the technique followed in the Erasmus MC during resuscitation procedures and transport to the NICU is indeed effective in keeping the neonates warm after birth.

Nevertheless, the temperature patterns of all the neonates (shown in Figure 4) not only varied with time according to GA, but they could also have been influenced by the health status of the neonate, incubator openings, medical interventions or weight loss. Because of trans-epidermal water loss after birth and compromised skin integrity, premature neonates lose weight during the first days of life until they stabilize and start to progressively gain weight. The extent to which these parameters might influence the temperature trends is not clear (a comparison of the values of Tp and ΔT with weight is included in Appendix C). For instance, the small ΔT in neonate #6 could be due to the baby being cared with a warmer incubator temperature than needed, as other neonates with approximately the same gestational age (neonates #1, #2, #7 and #8) were nursed with lower incubator temperatures over time. On the other hand, it could also be the case that the incubator temperatures of the other neonates were slightly low for them, which could have resulted in their wider ΔT. Neonate #1 was small for gestational age (belonging to the 10th percentile in the growth curves) but there is not a clear reason of why he presented the widest variations in temperature**.**

Overall, neonates with sepsis presented slightly different temperature in patterns in ΔT than the rest. Previous research has shown that alterations in temperature could have the potential to be used as an early diagnosis tool for sepsis [10-12]. Results of different studies point towards alterations in ΔT > 2°C and up to > 3.2°C [10-12]. However, further research is needed in this area in order to narrow the magnitude of ΔT that can accurately be used to detect a trigger of sepsis [17]. In the present work, the temperature patterns for both groups of neonates appear to be different in episodes of hyperthermia with presence or absence of sepsis. Neonates who had sepsis presented lower Tp than neonates who had hyperthermia from being overheated, which in turn resulted in higher values of ΔT. This could indicate that in cases with no sepsis, both very preterm and extreme preterm babies were trying to dissipate heat through their extremities, which resulted in a higher Tp. Neonates with sepsis presented a lower Tp which could be an indication of vasoconstriction as a natural response of the organism against fever [18]. Both of these situations would imply that the neonates had achieved thermal control and were able to perform vasodilation or vasoconstriction. However, because of the small sample size no solid conclusions can be drawn from these results and further research is needed to examine whether these patterns also occur in a bigger sample size.

The changes in the incubator set temperature performed by the nurses ranged from increments of 0.1°C up to 2.3°C. In most of the cases, the

neonates already had temperatures outside the limits of the stable range during the hour before a change in set temperature was done. It should be kept in mind that the response of the neonate's body to a change in external heat is relative low and gradual over time. Hence, before the neonatal temperatures fall considerably outside the stable range (36.5°C to 37.5°C), an adjustment of the incubator's temperature should be done to prevent episodes of hypothermia and hyperthermia. Avoiding or reducing the episodes of hyperthermia could also contribute to detect a trigger of sepsis. Additionally, if with a large sample size the tendencies in Tp are considered significant in episodes of hypothermia and hyperthermia, variations in Tp could be used to adjust more efficiently the temperature of the incubator. Peripheral vasoconstriction would imply the need of a higher nursing temperature, while vasodilation would imply the need of a reduction of thermal support.

It should also be considered that neonatal incubators can gain heat relatively fast. However, when kept closed and with relative added humidity, neonatal incubators are slower at reducing the set incubator temperature [19]. Moreover, incubators in the Erasmus MC are covered by a blanket that protects neonates from the light. This blanket also reduces radiative heat loss, helping the incubator to keep its warm temperature but making harder to dissipate heat when the set temperature of the incubator is decreased by the operator [19]. Overall, the duration of the openings of the incubator should be minimized [20]. This would not only reduce the magnitude by which the temperature of the neonate's body and of the incubator drops, but it will also help minimize the overshoot in temperature and humidity that occurs once the incubator is trying to recover its set values [19, 21].

4.1. Limitations of the study

The main limitation of the present pilot study is the lack of more precise information regarding caregiving procedures, medical interventions and moments of Kangaroo Care. These procedures may vary in duration and aggressiveness for the neonate, therefore creating a decrease in body temperature. Moreover, it is also likely that the skin thermal probes were not properly attached during these periods of time. This lack of information hinders the distinction between readings indicating hypothermia and a sensor being detached. Therefore, the incidences of hypothermia found in the present paper might be biased by these periods. Despite the fact that main outliers were removed by filtering the data according to the established criteria, there were periods of time where it remains unclear whether the sensor was in placed or not. In order to assess the validity of the data, further research should be carried out where all caregiving procedures are documented (nature of the intervention, duration, degree of opening of the incubator, whether the sensors were still in place). Visual information could also be essential to distinguish variations in temperature due to the repositioning of the peripheral thermal probe from one foot to another [21, 22].

Neonates were divided according to GA because of their variability in temperature patterns. However, this resulted in two groups with a very small sample size (n=9 for very preterm babies and n=6 for extreme premature babies) that limits the degree to which the findings can be generalized. Therefore, further research is needed to obtain a more conclusive result regarding the possibility of using Tp as an additional indicator to adjust the temperature of the incubator.

Although there is a tendency showing that neonates presented an altered ΔT during sepsis, the sample size is too small to draw any definitive conclusions. Among these neonates (n=1 for very preterm and n=2 for extreme preterm) ΔT showed relatively larger values than for the rest of neonates. However, an altered ΔT was also observed in older (increased GA) neonates who did not present any pathological medical condition.

Regarding the experimental setup, the HOBO® Pendant sensors positioned inside and outside of the incubator gave an estimation of the drops in temperature of the incubator. However, they fail to differentiate the opening modalities (1, 2, or 4 port holes or incubator top wall being removed). Additionally, when the top wall of the incubator was removed the information about the nursing environment was lost, as the sensor placed inside the incubator was attached to it. Placing additional HOBO® Pendant sensors distributed inside the incubator in combination with details of caregiving procedures would give a better estimation of the drops and overshoots in temperature experienced by the incubator. The readings of the additional HOBO® Pendant sensors located outside the incubator greatly differed between neonates who were nursed in incubators approximately located one or two meters apart and were therefore not used in the analysis. This could have been influenced by the sunlight or air flows in different points in the NICU. The present study fails to monitor the drops in relative humidity of the incubator over time. Further research should consider recording the information of incubator's temperature and humidity continuously from its display by connecting a computer to the neonatal incubator. This would also improve the reliability of the recordings over time at which the incubator set temperature was adjusted. This is currently updated by the nurses every 1 or 2h. However, the time at which they adjust the temperature of the incubator and the moment when they update this change into the system may differ. For instance, this appears to be the case in the example shown in Figure 6 "increase a), as the temperature of the incubator (Tin, green line) starts increasing before a change in incubator temperature (Tinc, orange line) was "indicated". Additionally, multiple incubator openings and the different levels of openings may have compromised the validity of the data for the comparison of the neonatal temperatures before and after a change in incubator set temperature.

This study is also limited by the number of split cables available, which restricted the number of neonates that could be measured at the same time to a maximum of 5. Labels were placed to prevent sensor misplacement but sensors were found to be reversed in 3 neonates. This did not seem to alter the way in which the incubator temperatures were adjusted over time. The HOBO® Pendant sensors of one of the neonates (#8) were lost at the end of the study. Temperature recordings from the first 47h of one of the neonates (#10) were lost as the patient monitor broke and data was not saved into the system.

Finally, it should also be considered that neonates in the study did not have the same routine care procedures. This implies that every medical practitioner followed their own preferred techniques regarding the handling of the neonate and adjustments of the settings in the incubator. For instance, for some of the neonates in the study, the peripheral sensor was still attached to the neonate during periods of Kangaroo Care while for other neonates the peripheral sensor was disconnected before Kangaroo Care started. Nurses were given the freedom to reposition the sensor from one foot to another. However, when removing one of the sensors of the neonates (#15) the thermal probe was found attached to the lower part of the neonate's leg.

5. Conclusion

Tp was found to fluctuate over a wider range with increasing GA, resulting in overall larger values of ΔT. In periods of hyperthermia, alterations in Tp with a trigger of sepsis presented lower values of Tp,

which might have indicated that the neonates were trying perform vasoconstriction as a response to fever. In cases of hyperthermia with no sepsis, the values of Tp seemed to be slightly higher, which might have implied vasodilation. Results suggest that Tp could have the potential to help distinguishing between periods of stability, episode of sepsis and hyperthermia. However, because of the small sample size, the few number of neonates with sepsis and the small percentage of time in which hyperthermia was detected (7.2 % to 8.5%) these tendencies should be evaluated in a larger group of neonates.

Most of the neonates presented altered Tc for approximately one hour before actions were taken and their temperatures were still outside the stable range one hour after the adjustment in incubator temperature. In order to prevent episodes of hypothermia and hyperthermia, any deviation from the stable range of temperatures (36.5°C to 37.5°C) should be carefully monitored in order to modify the incubator settings as soon as possible.

Further research should be done to establish what a normal value of ΔT (indicator of stability) is according to the GA of the neonate. Additionally, the viability of using alterations in Tp or ΔT as a non-invasive early diagnosis tool of sepsis and as a tool to adjust the temperature of the incubator in the Erasmus MC needs to be evaluated.

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Appendix A Research Protocol

RESEARCH PROTOCOL

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics

Monitoring Alterations in the Thermal Gradient of Preterm Newborns

Protocol ID	**MEC-2016-567**
Short title	**Monitoring Alterations in the Thermal Gradient of Preterm Newborns**
Version	**2**
Date	**18th of October, 2016**
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Independent expert (s)	***Dr. Enno D. Wildschut*** Room SK-3234 Wytemaweg 80 3015 CN Rotterdam tel: 010 70 36189

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: ***Prof. Dr Irwin K.M. Reiss*** ***Professor of Neonatology*** ***Head division of Neonatology*** **Head of Department:** ***Prof. Dr Edmond H.H.M. Rings*** ***Head of Paediatrics***		
Coordinating Investigator/Project leader /Principal Investigator Rogier C.J. de Jonge Neonatologist		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BW	**Birthweight**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CSF	**Cerebro Spinal Fluid**
ΔCV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GA	**Gestational Age**
GCP	**Good Clinical Practice**
H_{inc}	**Humidity of the neonatal incubator**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
L_{in}	**Light inside the incubator**
L_{out}	**Light outside the incubator**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NICU	**Neonatal Intensive Care Unit**
NTE	**Neutral Thermal Environment**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
ΔT	**Central to peripheral Temperature Difference**

T_c	**Central (abdominal) temperature**
T_{in}	**Temperature inside the incubator (as measured by the light sensor)**
T_{inc}	**Incubator Air Temperature (given by the Caleo display monitor)**
T_{out}	**Outside temperature (temperature of the room, NICU)**
T_p	**Peripheral temperature**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Preterm newborns are those babies born before 37 weeks of pregnancy. Because of their immature physiological metabolism their heat loss is higher than the heat they are able to generate. They are prone to suffer thermal alterations, such as hypothermia or hyperthermia, which result in higher morbidity and mortality rates [1]. Neonatal Intensive Care Units (NICUs) are specifically equipped to care for neonates with a compromised health status but, unfortunately, newborns still present frequent temperature fluctuations. Very little is known regarding the development of thermal control processes with postnatal age. There is evidence in the literature suggesting that understanding the development of the ability to perform vasoconstriction could improve the current nursing conditions. Vasoconstriction can be assessed through alterations in the thermal gradient (central to peripheral temperature differences or ΔT) and could help preventing adverse effects in the preterm newborns [2-4].

Objective: To study the maturation of thermal control in preterm newborns with postnatal age. To assess the development of the ability to perform vasoconstriction by monitoring alterations in the thermal gradient, ΔT and determine the value of a stable ΔT.

Study design: A single center, prospective observational pilot study at the Erasmus MC-Sophia Children's Hospital.

Study population: 40 very preterm neonates admitted to the NICU in the Erasmus MC, Rotterdam and cared in incubators with < 32 weeks of gestational age (GA).

Intervention (if applicable): Measuring of central and peripheral temperatures with the application of two thermal probes. One of these thermal probes belongs to the current clinical practice and the other one is added for the study purposes. It is attached with a bandage to the sole of the foot, providing an estimation of peripheral temperatures. There will be no changes in the current nursing protocol. Temperature measurements are taken every second for 10 days or until discharge from the unit.

Main study parameters/endpoints: The main parameter during the study is ΔT and its relation with maturation of thermal control. The relation of ΔT with GA and birthweight (BW), postnatal age and weight, surface to volume ratio, temperature and humidity of the incubator (T_{inc} and H_{inc}) will be studied.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Newborns participating in the study are cared in the NICU using the same nursing protocol as in routine care, with the addition of one thermal sensor. As this study has an observational character, there are no additional risks. The study needs to be performed on this specific group of preterm newborns in order to study how the maturation of thermal control occurs in newborns with limited intrauterine maturation and what can be considered as a normal and stable ΔT.

1. INTRODUCTION AND RATIONALE

According to the World Health Organization, *"15 million babies are born too soon every year"* and the tendency is rising [1, 5]. The term premature or preterm refers to babies born before 37 weeks of pregnancy. In 2010, 14600 preterm births were registered in The Netherlands [6]. Low birthweight (BW) and very premature newborns present higher chances of suffering cold stress or hypothermia, characterized by body temperatures lower than 36°C [7]. These alterations in temperature in turn result in higher morbidity and mortality rates [1].

Episodes of hypothermia or cold stress are common in the newborns, mainly because of the physiological adaptations to extrauterine life, exposure to sudden lower temperatures in the delivery room, stabilization and resuscitation procedures if needed, and further transfer and admission to the Neonatal Intensive Care Unit (NICU) [8, 9]. As a result, the newborns' heat loss is higher than what their immature physiological metabolism is able to generate. NICUs are specifically equipped to care for neonates with a compromised health status or prematurity. Preterm newborns are cared in neonatal incubators, which provide thermal support in order to counterbalance heat loss, creating a Neutral Thermal Environment (NTE). NTE ensures minimal metabolic requirements until the neonates reach maturity to independently control their own temperature.

However, despite the thermal support provided by incubators, newborns still develop frequent temperature fluctuations and recurrent episodes of hypothermia. Moreover, when the thermal support exceeds the actual heat requirements the newborns may become hyperthermic, presenting body temperatures higher than 37.5°C [7]. This condition should not be taken lightly, as hyperthermia is *"as likely to occur and as dangerous as hypothermia"* [7]. In Erasmus MC, 80% of the most preterm newborns is hyperthermic during the first 3 days of life. Therefore, even though thermal support is used in routine care, understanding the needs of the newborn through development of thermal control could help reducing these adverse events of hypothermia and hyperthermia.

It is known that with increasing postnatal age, infants are able to increase their heat production and develop thermal control. However, the point in time at which maturation of thermal control becomes evident is not clear. The main variable related to development in the first days of life is the ability to perform vasoconstriction. Vasoconstriction refers to the ability to limit blood flow to the peripheral limbs in order to maintain constant core body temperatures when exposed to a cold environment. Vasoconstriction in the preterm newborns is estimated by the differences in thermal gradient (ΔT), i.e. central to peripheral temperature differences, represented by abdominal and foot skin surface temperatures respectively. Exposure to cold environment usually refers to handling or medical interventions that requires the opening of the incubator, therefore decreasing the air temperature in which the newborn is cared for. Lower central to peripheral temperature differences are associated to the reduced ability of the neonate to maintain heat [3] because of immaturity or the lack of vasomotor control [10]. This is characterized by a decrease in abdominal temperatures while keeping their vasodilated extremities (peripheral temperatures) close to the incubator temperatures. As newborns develop their vasomotor tone, vasoconstriction allows them to decrease their peripheral temperature in order to keep their abdominal temperature higher when exposed to cold temperatures. Therefore, the ability to vasoconstrict also results on stabilization of central (abdominal) temperatures. Literature suggest that thermoregulation occurs in the period of time between the third hour of life and the fifth postnatal day [3, 4, 10]. However, this really broad range that can lead to inconclusive results. Furthermore, it has been observed that definitions in the magnitude of ΔT associated to development of vasomotor control greatly vary among the different studies in the literature.

This study focuses on quantifying the (limited) ability to perform peripheral vasoconstriction through variations in the ΔT and determining when vasomotor control develops with postnatal age. Maturation of thermoregulation mechanisms is associated with less dependency on the incubator [4, 11]. In the Erasmus MC the temperature of the incubator (T_{inc}, heater output) is controlled manually by the caregiver. Hence, the caregiver is responsible for adjusting the incubator temperature according to the needs of each individual neonate, which are usually influenced by gestational age (GA), birthweight (BW) and postnatal age. However, there is no protocol for this practice and incubator air temperature is modified based on experience.

Careful monitoring of neonatal temperatures and alterations in the ΔT in the NICU can help maintaining the ideal NTE and avoid overheating the newborn [4]. Therefore, in order to improve the current clinical practice and nursing conditions of preterm newborns an understanding of the developmental physiology of thermal control progresses with postnatal age is needed. More specifically, a clear definition of the magnitude of a stable and an altered ΔT characterizing the preterm newborns is needed. Once an alteration in the ΔT is detected, pertinent measures can be taken to modify the intensity of thermal support until the newborn achieves stability.

It should also be considered that when a raised temperature is detected in the newborn it could be both, an episode of hyperthermia or sepsis. In the Erasmus MC 20% of the newborns develop sepsis. Sepsis is the response of the body to infection or inflammation and results in high fever. Neonatal sepsis is a major cause of morbidity and mortality in infants [12], accounting for approximately 25% of global neonatal deaths [13, 14]. Neonatal sepsis presents genuinely non-specific manifestations that hinder the identification and early diagnose of failure in different systems or organs of the body. Not treating sepsis on time results in aggravation of the system failures and eventual death of the infant. This makes of an early diagnosis and antibiotic treatment the best tools to fight the infection. However, early application of antibiotic therapy without confirmation of sepsis represents a hazard as well. Resistance against antibiotics may be developed, gastrointestinal immunity of the neonate may be compromised and allergies may appear [15].

To detect the possible presence of infection and confirm the sepsis diagnosis, medical analysis primarily in the form of blood samples, Cerebrospinal Fluid (CSF) or urine are needed [16]. Even though blood samples are considered the gold standard for the diagnosis [17], they present long waiting times (not available within 48h [15]) and frequent false negative results, which hinders prompt sepsis diagnose in the newborn [18]. There is also a limitation in the quantity of blood drawn from the newborn and the distress this may cause [15, 16]. Because of this, in the last few decades, research has focused on identifying changes in clinical signs that might indicate the development of sepsis in the newborn. Among the clinical manifestations of a sepsis episode, one can find hypothermia, hyperthermia or temperature instability [2, 15, 19, 20]. There is evidence in the literature that alterations in temperature have a great potential as an early marker for sepsis diagnose. However, there is not a clear definition of the magnitude of alterations in ΔT that are a marker for sepsis. Results of different studies point towards alterations in $\Delta T > 2°C$ and up to $> 3.2°C$ but further research is needed in this area in order to narrow the magnitude of ΔT that can accurately be used to detect a trigger of sepsis on time [2, 21].

Therefore, the knowledge of development of thermal control and alterations in the ΔT could shed some light to evaluate the viability of using alterations in the ΔT as a non-invasive early diagnose of sepsis in

the Erasmus MC. Alterations in ΔT could eventually overcome current challenges in preventive measures, eventually increasing newborn's survival rates in the Erasmus MC.

2. OBJECTIVES

Primary Objective:

To study the ΔT and its relation with maturation of thermal control through development of vasomotor control. To stablish a relation between the gestational age, birthweight, postnatal age, weight, temperature and humidity of the incubator at which this maturation of thermal control takes place.

Secondary Objective(s):

- To stablish the time (postnatal days) or relative growth (weight or volume increment) required to obtain stable abdominal temperatures.
- To monitor the differences in duration of hypothermic and hyperthermic episodes with postnatal age.
- To make a distinction, when possible, between stable ΔT and alterations indicating a possible trigger of sepsis.

3. STUDY DESIGN

The proposed study is an observational prospective pilot study at the Sophia Children's Hospital. The goal is to include 40 preterm newborns in the study, with written informed consent obtained from the parents or legal representatives.

A list of all the recorded parameters can be found in **Table 1**. Preterm newborns cared in Caleo® incubators (Dräger, Germany) in the NICU according to current clinical practice. Data is collected from the newborn using 2 skin temperature probes (Mon-a-Therm™ 400TM, Covidien, US). One of the thermal probes is already used in routine care and the second thermal probe is introduced for the study purposes. Data of the nursing environment is obtained by placing temperature and light data loggers HOBO® Pendant (Onset, US) inside and outside the incubator. L_{in} and L_{out} are the light measured inside and outside the incubator, respectively, and T_{in} and T_{out} the temperatures inside and outside the incubator. Additionally, a computer is connected to the incubator in order to obtain continuous readings of the incubator air temperature and humidity (T_{inc} and H_{inc}) during the study period (as displayed in the monitor of the Caleo incubator). This allows to distinguish periods of time in which medical interventions or nursing procedures are being performed on the newborn from stable moments in which no alteration of the incubator microenvironment is present. Additionally, the patient characteristics listed in **Table 1** are collected. If available, culture positivity or culture negativity for sepsis is recorded. That is, if any of the newborns under study is suspected to have developed sepsis. This data is used to look for alterations in the ΔT that could be related to a trigger of sepsis.

Hence, only one additional sensor is placed on the newborns and no changes are introduced in the routine care. This additional sensor is a thermistor that is positioned on the newborn's foot in order to obtain a reading of peripheral temperatures. The foam of the thermistor is cut so that it never exceeds the size of the newborn's foot. The thermistor is not stuck to the patient's skin. Instead, a bandage is used to wrap it around the newborn's foot to position it in place. This allows an easy and quick detachment and no damage to the skin.

The data of all the patients will be recorded every 1 second. Data recording starts as soon as possible after admission to the NICU, obtaining consent of the parents and positioning of the sensors. Each subject will be monitored during 10 days or until discharge from the neonatal unit. Data from all the subjects under study will be compared. Subjects will be stratified according to GA. The gestational age will be considered as the estimated by the obstetrician.

3.1. Experimental Setup

A complete list of all materials used in the experiment can be found in Table 2. There is only one additional sensor placed on the newborn compared to routine care (an additional thermal probe to monitor peripheral temperatures). No modifications in routine care are introduced. The temperature/light data loggers are currently used in another observational study on the NICU *"Monitoring Oxygen Transport in preterm infants during the first week of life".* The entire experimental setup is checked by the Department of Medical Technology at the Sophia children's hospital, and will only be used after their approval.

Parameter	Abbrev.	Obtained with
Patient Characteristics		
Gestational age	GA	
Birthweight	BW	
Postnatal age		
Weight		Caleo® (Dräger, Germany)
Body Length		
Recorded during the Study		
Central temperature	T_c	Mon-a-Therm™ 400TM (Covidien, US)
Peripheral temperature	T_p	Mon-a-Therm™ 400TM (Covidien, US)
Air Temperature of the incubator	T_{inc}	Caleo® (Dräger, Germany)
Humidity of the incubator	H_{inc}	Caleo® (Dräger, Germany)
Light inside the incubator	L_{in}	HOBO® Pendant (Onset, US)
Temperature of the incubator	T_{in}	HOBO® Pendant (Onset, US)
Light of the room (NICU)	L_{out}	HOBO® Pendant (Onset, US)
Temperature of the room (NICU)	T_{out}	HOBO® Pendant (Onset, US)
Additional Parameters, if available		
Culture positivity of Sepsis		
CRP		

Table 1 – Recorded parameters in the study

Device	Brand and Version
Thermal Probe (x2)	Mon-a-Therm™ 400TM (Covidien, US)
Light Sensors (x2)	HOBO® Pendant (Onset, US)
Neonatal incubator	Caleo (Dräger, Germany)

Table 2 – Devices used for data acquisition

4. STUDY POPULATION

4.1. Population (base)

All preterm infants admitted into the NICU of the Sophia Children's Hospital in the Erasmus Medical Center.

4.2. Inclusion criteria

Preterm neonates born at a GA < 32 weeks that are admitted to the NICU and cared for in closed incubators are included if informed consent can be obtained within 48 hours after birth.

4.3. Exclusion criteria

Infants with any known congenital or chromosomal defects will be excluded from this study.

4.4. Sample size calculation

The proposed study is a pilot study in which a population of 40 preterm babies will be used to obtain an understanding of how the incubator settings (temperature and humidity) and patient characteristics (postnatal age and growth) are actually influencing the maturation of thermal control. This study will allow determining the most relevant variables to be monitored in future studies, which will require a considerably bigger population.

5. TREATMENT OF SUBJECTS

Not applicable

5.1. Investigational product/treatment

Not applicable

5.2. Use of co-intervention (if applicable)

Not applicable

5.3. Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

6.1. Name and description of investigational product(s)

Not applicable

6.2. Summary of findings from non-clinical studies

Not applicable

6.3. Summary of findings from clinical studies

Not applicable

6.4. Summary of known and potential risks and benefits

Not applicable

6.5. Description and justification of route of administration and dosage

Not applicable

6.6. Dosages, dosage modifications and method of administration

Not applicable

6.7. Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8. Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1. Name and description of non-investigational product(s)

Not applicable

7.2. Summary of findings from non-clinical studies

Not applicable

7.3. Summary of findings from clinical studies

Not applicable

7.4. Summary of known and potential risks and benefits

Not applicable

7.5. Description and justification of route of administration and dosage

Not applicable

7.6. Dosages, dosage modifications and method of administration

Not applicable

7.7. Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8. Drug accountability

Not applicable

8. METHODS

8.1. Study parameters/endpoints

8.1.1. Main study parameter/endpoint

The main study parameter is the ΔT in relation to maturation of thermal control with increasing postnatal age. A relation is sought between thermal control and the GA, BW, postnatal age, weight, T_{inc} and H_{inc} at which this maturation of thermal control takes place.

8.1.2. Secondary study parameters/endpoints (if applicable)

Secondary parameters are the time (postnatal days) required to obtain stable T_c and the differences in duration of hypothermic and hyperthermic episodes with postnatal age.

To make a distinction between stable ΔT and alterations that could indicate a critical condition, such as sepsis, in case results of blood analysis are available.

8.2. Study procedures

The newborns are nursed in the NICU using the current routine care protocols. There is only one additional sensor used on the patient, a thermal probe positioned on the foot. As the study has an observational character, this additional sensor does not involve any change in the routine care or extra procedures. The additional devices in the experimental setup are used to record data from the nursing environment. The light sensors store information about the level of light and temperature inside the incubator and of the room (NICU). The principal investigator will be present to prepare the experimental set up. The additional thermal sensor will be positioned in placed by the nurse or physician in charge.

8.3. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if the parents wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

9. SAFETY REPORTING

9.1. Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the parents of the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

9.2. Adverse events and serious adverse events

As the intervention performed is minimal (introduction of one additional sensor which is not stuck to the foot but just positioned in placed with a bandage), there are no expected adverse events (AEs) or serious adverse events (SAEs). However, in case an adverse event occurs, it will be recorded by the investigator or nursing staff.

9.3. Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached.

10. STATISTICAL ANALYSIS

Demographic characteristics of the study population will be described. The gestational age, birthweight, weight, postnatal age and the trigger of any critical condition such as sepsis will be documented. Any other information that could have an influence on the temperature readings such as periods of kangaroo care (skin to skin contact with the mother), transport due to surgical needs or MRI analysis will be documented. Information given by the light sensors and readings of temperature and humidity of the neonatal incubator will be used to discern periods of time in which nursing or medical interventions were being performed.

In this pilot study a relation or tendency in time of thermal control is sought between the initial BW and GA, and postnatal age, weight, T_{inc} and H_{inc} at which the maturation of thermal control takes place. A statistician of the Erasmus MC, Katya Mauff, was contacted to plan the best way to proceed with the data analysis. She provided consultation on a variety of advanced statistical models that could be used for the proper fitting and interpretation of the results. The influence of the variables will be studied using longitudinal analysis, more specifically, fitting the data in a non-linear mixed effect model that correlates the within-group most relevant variables. This model will allow evaluating the fixed and random effects of the recorded variables and their influence on the time to reach a stable ΔT (plateau). Model comparisons including different covariates will help discerning the variables with the highest impact on maturation of thermal control. This will help defining the most relevant parameters for further studies. The number of episodes of thermal alterations will also be recorded and the percentage of time in which the newborns presented hypothermic or hyperthermic temperatures will be calculated.

11. ETHICAL CONSIDERATIONS

11.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki version 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2. Recruitment and consent

Preterm babies undergo a lot of medical interventions or resuscitation procedures from delivery until the first day after admission to the NICU, which can greatly influence the drop in body temperature of the neonate. Additionally, for the study of the maturation of the thermal control and stabilization of the newborn it is important to have access to the temperature data from the first hours of life. For all these reasons, central and peripheral temperatures should start being recorded as soon as the newborn is admitted to the NICU.

However, for some parents or care givers it is not possible to be present when their newborn is admitted to the NICU. And if they are present, approaching the parents to ask for consent during this moment is not desirable. It may increase their worries, nervousness and concerns about their baby.

Because of the non-invasive character of this study, minimum disturbance and absent risk represented by the peripheral thermometer (Mon-a-Therm^{TM} 400TM, Covidien, US) deferred consent is requested. With deferred consent, if parents are not available, the peripheral thermometer will be placed on the sole of the foot when the newborn is admitted to the NICU. When parents are available, they are informed about the study, otherwise information about the research will be given as soon as the parents are available. A member of the research team will answer any questions they may have about the study. At this point, parents can decide whether to join or withdraw from the study, or take as much time as they need in order to decide. In case any or both of the parents do not agree to participation in the study, the peripheral temperature sensor from the foot of the newborn as well as the light and temperature sensors attached to the incubator walls will be removed during the next time the nursing staff attend to the neonate, and all data will be deleted. Only the thermometer located between the back of the baby and the mattress will remain as it is part of the current normal routine care.

11.3. Objection by minors or incapacitated subjects

The Code of conduct relating to expressions of objection by minors participating in medical research is applicable. Both parents, care givers and all legal representatives must give consent for the inclusion of the neonate into this study.

11.4. Benefits and risks assessment, group relatedness

For the infants enrolled in this study there is no added benefit or risk.

11.5. Compensation for injury

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

Handling and storage of data and documents

The recorded data will be accessible for the investigators. In the recorded data the patient's information is anonymous and patients can be identified by an identification number. Forms and data will be kept for 15 years.

12.1. Monitoring and Quality Assurance

Not applicable

12.2. Amendments

Not applicable

12.3. Annual progress report

Not applicable

12.4. End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient born and monitored.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC. In case the final study report will not be available within one year, another term should be defined including the reasons.

12.5. Public disclosure and publication policy

Not applicable

13. STRUCTURED RISK ANALYSIS

Not applicable

13.1. Potential issues of concern

Not applicable

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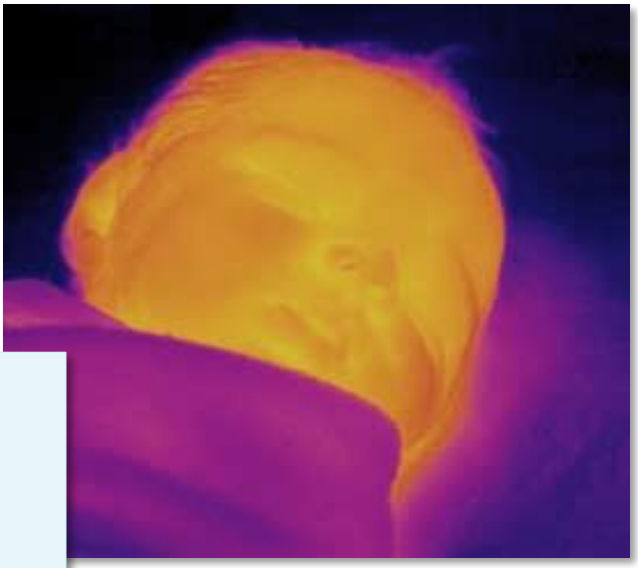

Appendix B
Data Filtering

This appendix is divided into 4 sections. First of all, the problem of the missing data from the patient monitor will be presented and the filter used to recover information will be described. Second of all, some of main problems encountered that led to abnormal temperature readings will be illustrated. The filtering criteria for outliers will be explained and examples of the effect of the filter will be presented. Then, the moving average filter used to create the simplified trends of temperature over time included in the research paper will be clarified and different levels of the filter will be illustrated. Finally, recommendations for future work will be given.

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1. Missing data from the patient monitor

Core and peripheral temperatures were recorded every second patient monitor (Infinity M540, Dräger, Lübeck, Germany). However, in some cases seconds were doubled or missing from the timeline. Additionally, sometimes the system failed to record the temperatures and a line of zero values for Tc and Tp was obtained. Periods of time in which one of the sensors were disconnected were analyzed as a Not-a-Number value (NaN) because the value was misisng. *Table 3* illustrates the missing data from the patient monitor in comparison with the total number of seconds that corresponded to the duration of the observations (reference value). The number of total missing seconds is calculated as the sum of the number of seconds that contained a NaN and the number of seconds missing.

The value of ΔT was included among the variables recorded by the monitor. However, it was automatically computed as the absolute value of the difference between central and peripheral temperatures. To avoid introducing uncertainties in the periods in which the peripheral temperatures were higher than central temperatures (with a negative value of ΔT), the ΔT from the monitor was not included in the dataset. Instead, it was computed using Matlab R2016b (The MathWorks, Inc., Natick, Massachusetts, United States) after filling in the missing seconds and averaging.

Neonate	*Days*	*Total # seconds*	*# Seconds (patient monitor)*	*# NaN*	*# Missing seconds*	*# Total Missing seconds*	*% Total Missing seconds*
1	10.0	867720	850737	4150	18153	22303	4.5
2	5.1	440880	434442	42530	7178	49708	12.7
3	7.0	608220	597475	38811	11737	50548	10.1
4	2.0	171420	168097	40	3610	3650	4.1
5	10.0	866460	852990	2150	14842	16992	3.5
6	3.0	254940	248576	22733	6684	29417	14.0
7	5.7	496200	486679	3746	10234	13980	4.7
8	4.9	421320	413051	10144	8704	18848	6.4
9	8.3	713220	700897	57180	13436	70616	11.6
10	8.4	724440	710289	3888	15203	19091	4.6
11	9.9	859200	843188	1083	17326	18409	4.0
12	10.0	867660	851773	2856	17231	20087	4.1
13	10.0	863460	849341	23141	15488	38629	6.1
14	10.0	865260	851000	512	15665	16177	3.5
15	10.0	867180	849100	960	19360	20320	4.4

Table 3 – Illustration of the data from the patient monitor per neonate. "Total # of seconds" refers to the number of seconds corresponding to the duration of the study. "# Seconds (patient monitor" corresponds to the number of seconds of information given by the patient monitor during the same period of time. "# NaN and #missing seconds" corresponds to the number of observations in which the sensors got disconnected and the missing seconds from the patient monitor, respectively. "# Total missing seconds" corresponds to the sum of the last two values. "% Total missing seconds corresponds to the # of missing seconds in relation with the 2nd column, expressed in %.

Filtering and averaging data from the patient monitor

The points 00:00:00 (HH:MM:SS) and 23:59:59 of the timeline of the patient monitor were the target starting and end values to filter the data per day. However, sometimes these seconds were missing and the recoding of a certain day started or finished after these pre-established periods. If these markers were missing they needed to be added to the excel file before applying the filter and a value of NaN was assigned.

Then, using Matlab R2016b (The MathWorks, Inc., Natick, Massachusetts, United States), the data of temperature was matched with a reference timeline (going from 0:00:00 to 23:59:59h) to find all the missing or double data points (seconds). Zeroes recorded by the patient monitor were rewritten as NaN. Afterwards, the missing data points were filled with the average value of the temperatures in the previous and following second, unless a NaN was registered:

- If the seconds before and after were also a NaN, the value kept being a NaN.
- If the second before had a value of NaN but the second after did not, the value of the temperature in the second after was applied. However, if two seconds before had a value of NaN, the value remain as NaN, regardless the reading found in the following second.
- If the second after had a value of NaN but the second before did not, the value of the temperature in the second before was applied. However, if two seconds after had a value of NaN, the value remain as NaN, regardless the reading found in the previous second.

Additionally, central and peripheral temperatures were deleted from the dataset as soon as one of the two readings in temperature was missing. As explained before, the disconnection of one of the sensors was an indication of something happening that disturb the stability of the neonate (Kangaroo Care or medical intervention). Moreover, the value of ΔT (difference between central and peripheral temperatures) could not be computed if one of the values was missing.

Lastly, the data was averaged every 60 seconds. If a value of NaN still remained after the filtering, the whole minute was cancelled (NaN value). Once the data was averaged, the value of ΔT was calculated.

Example of Filtered Data

Because of the amount of information missing from the raw data of the patient monitor the filter increased the amount of data. Table 4 illustrates how the percentage of data after filtering is greater than the percentage of raw data from the monitor. The percentage of recovered data is given as the difference between these two, as indicated in. Table 4 by "% data recovered by the filter". After averaging, a small part of the information is lost and the % of data that remained is included in the last column of Table 4. The differences in data percentage per neonate basically give an estimation of what neonates had the sensors connected without problems for most of the time.

		Filtering Raw data (seconds)				*After averaging*	
Neonate	***Total # seconds***	***# Seconds (patient monitor)***	***% Data from monitor***	***% Data after filtering***	***% Data recovered***	***Total # minutes***	***% Data kept***
1	867720	850737	95.5	99.4	3.9	14462	98.6
2	440880	434442	87.3	90.2	2.9	7348	89.8
3	608220	597475	89.9	92.9	3.0	10137	92.2
4	171420	168097	95.9	100.0	4.0	2857	99.4
5	866460	852990	96.5	99.7	3.2	14441	99.0
6	254940	248576	86.0	89.7	3.8	4249	89.3
7	496200	486679	95.3	99.2	3.9	8270	98.5
8	421320	413051	93.6	96.1	2.5	7022	95.7
9	713220	700897	88.4	91.8	3.5	11887	91.3
10	724440	710289	95.4	98.7	3.3	12074	98.3
11	859200	843188	96.0	98.5	2.5	14320	97.9
12	867660	851773	95.9	99.6	3.8	14461	99.1
13	863460	849341	93.9	97.3	3.4	14391	96.7
14	865260	851000	96.5	99.9	3.4	14421	99.1
15	867180	84910	95.6	98.8	3.2	14453	98.1

Table 4 – Illustration of the % of data recovered after filtering with respect to the raw data from the patient monitor before and after averaging, per neonate.

2. Filtering Outliers in Central and Peripheral Temperatures

One of the main limitations of the present work is the uncertainties regarding whether the sensors were in contact with the skin of the neonate and whether the neonate was inside the incubator. A filtering criteria was designed based on the problems encountered during the study. The observed problems were used to find patterns in the data in which abnormal readings were being recorded, indicating that the sensor was out of placed. A not a number value (NaN) was assigned to the data points of Tc, Tp and ΔT in the data point specified by the filter, while keeping the information of the rest of the variables. No solution was found to determine if the neonate was

It should be considered that outliers are already considered as such in the computation of, for instance, boxplots, and do not influence the final results. However, moments in which the sensor was out of place for really long periods of time could influence the computation of the percentage of time in which the neonates had hypothermia. Also abnormal low readings could be introduced in the moving average filter, as it will be shown a continuation. When designing the filtering criteria the intention was to keep as much data as possible and only remove extreme alterations known to be not possible. As this is a pilot study, no previous background knowledge could be used. For the filtering criteria of peripheral and central temperatures the data of all the patients was contrasted to check that all of them met the conditions and that there were no exceptions to the rule. Temperature ranges and intervals of each condition were adjusted to fit all the neonates. There was only one criteria in the filter for which a patient was omitted, as it will be explain a continuation.

Only one Thermal Sensor or Sensors Reversed

For some medical interventions one of the sensors was disconnected to get a better access to the neonate's body and minimize the number of cables. It was also observed that after some medical interventions the peripheral sensor was not placed back into the proper position or reversed with the central one or it simply took longer to reposition.

Figure 1 shows a period of time in which the sensors were reversed (indicated with a red line). The moment in which the sensors started being misplaced is indicated with red arrows. It can be seen how the light colored line (corresponding to peripheral temperatures) is unexpectedly above the central temperatures (dark blue line). Then, at a certain moment the temperature reading of the peripheral sensor suddenly plummeted and kept a low value for about 1h and 45 minutes (as pointed out by a red arrow). Both sensors were disconnected for 8 minutes and when they were connected again the temperatures were back into the proper position. Moreover, it can be seen how the peripheral sensor took longer to reposition after connecting it, characterized by low temperature readings followed by a sudden increase and further stabilization.

Periods of Kangaroo Care were somehow more deceptive and delicate to work with. There is a great variability in the procedure followed by the nurses in periods of Kangaroo Care. In some cases, the peripheral sensor was disconnected and the neonate was place in contact with the skin of the mother with only the central thermal probe connected. On the other hand, in some occasions it was not clear whether the baby was in Kangaroo Care with both central and peripheral sensors connected or if the peripheral sensor was left inside the incubator.

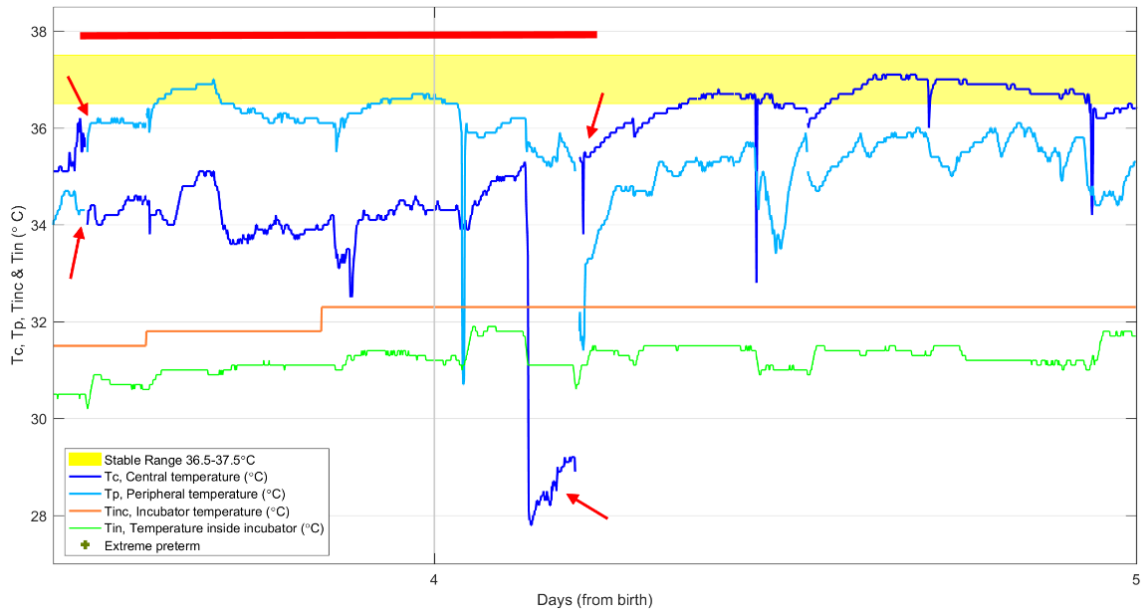

Figure 1 – Example showing a moment in which central and peripheral sensors were reversed.

Filtering Criteria for Outliers

1. Regarding moments of Kangaroo Care, the initial intention was to remove the temperature recordings of all known (observed) periods. However, the technique followed in every Kangaroo Care was different depending on the nurse in charge and unknown to the researchers. Therefore, to avoid increasing the variability of the results all Kangaroo periods were kept, unless the temperature readings of the peripheral temperature were missing.

2. No automatic solution could be found to account for moments in which the temperatures had been reversed and the information was fixed manually.

Sensor Detached

In some occasions the thermal probes became detached by movements of the neonate or after medical interventions. It could take really long for the nurses to reposition the thermal probes back in place. The decision of not repositioning the sensor was probably postponed in order to reduce the distress of the neonate. However, if periods of hypothermia or hyperthermia would have occurred, the medical personnel would not have been able to detect them. Peripheral sensor detachments were really difficult to identify, unless the temperature readings fell below the temperature measured inside the incubator. A detachment for the central probe was observed in one of the visits to the NICU and it is illustrated in *Figure 2*. It can be seen how the sensor was progressively detached and the temperature drop accordingly.

Filtering Criteria for Outliers

1. Periods of time with the condition Tp ≥ Tc were analyzed in the data. A value of Tc ≤ 35°C indicated that the sensor was out of place and the values were set to NaN. No other condition could be used to solve this problem as it could have implied deleting periods of hypothermia.

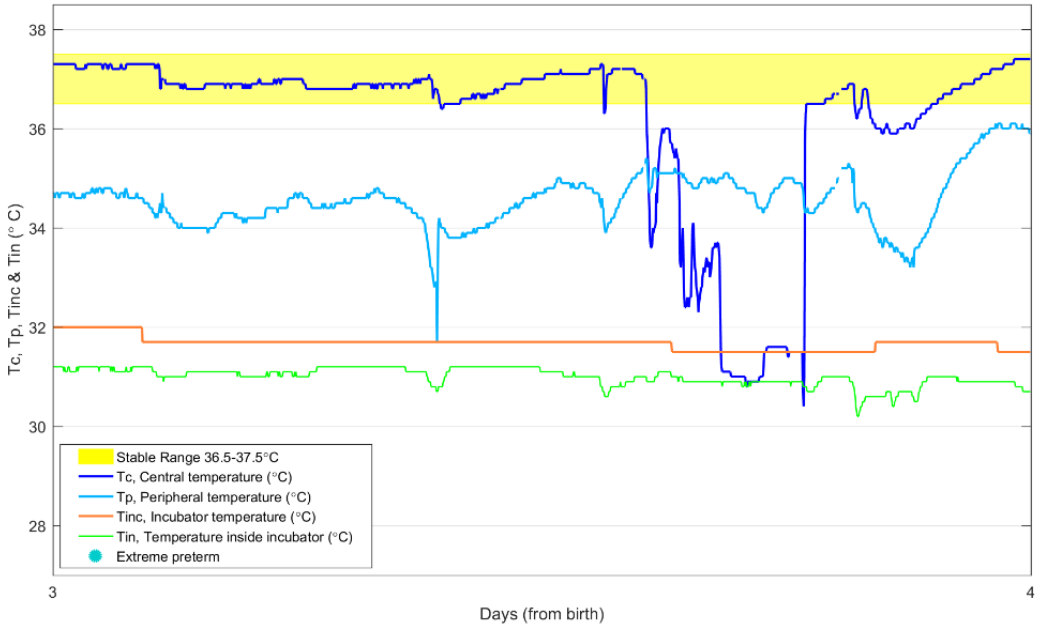

Figure 2 – Example of a central thermal probe getting progressively detached.

Sudden Drops & Rises in Temperature

Neonatal temperatures used to decreased and increased gradually over time. Incubator openings could lower down the temperature of the neonate but sudden drops in temperature were due to probe repositioning or detachment. Sudden drops and rises could also occur in the moment that the neonate was being weighted. Neonatal incubators are designed with a built in weighting scale, so that the thermal environment of the neonate is kept as constant as possible during routine care. In order to weight the neonate, the neonate needs to be lifted from the matress of the incubator (tare) and then placed back on top again. Therefore, as the central thermal probe is placed between the back of the neonate and the mattress, the sensor will give an abnormal false reading. However, the neonates were only weighted once per day and sometimes every 2 or 3 days.

Moreover, two of the five cables used in the present study were new and more problems were encountered in the neonates to whom these cables were randomly assigned. The connection with the disposable thermal probe was too tight, making really difficult for the medical personnel to disconnect the cable. In some cases the wire from the thermal probe broke while trying to detach them and the thermal probe had to be replaced. However, in other cases, the cable did not break completely but the connection was damaged. This resulted in invalid temperature readings in which sudden peaks were successively recorded. *Figure 3* illustrates these problems. The graph on the left corresponds to the

start of a period of Kangaroo Care. The peripheral sensor broke when it was trying to be disconnected. It can be seen how the temperature progressively dropped as the nurse was trying to detach it and moments after the signal was lost. A sudden drop can be also observed in the central temperatures, corresponding to the moment in which the neonate was lifted from the incubator. The temperature reading went back to 'normal' (previous values) as soon as the sensor is placed back in contact with the neonate. It should be considered that the information of central temperature during Kangaroo Care has been already cancelled from this graph since the connection with the peripheral sensor was lost. The graph on the right of *Figure 3* corresponds to a defective wire connection. Sudden ups and downs appeared in the peripheral temperature readings, with peripheral temperatures as low as 3.5°C, inconceivable to the registered in a neonate nursed with an incubator.

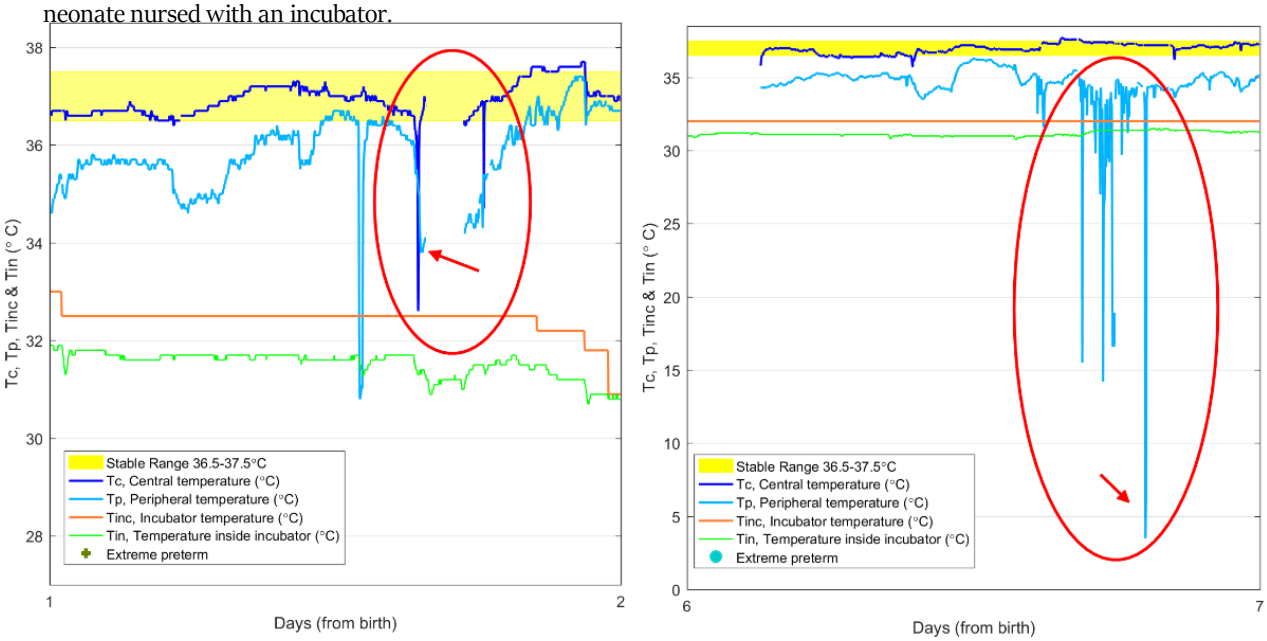

Figure 3 – Examples of drops in the temperature readings and problems with the cables.

Filtering Criteria for Outliers

1. Any recording of central and peripheral temperatures for which a $|\Delta T| \geq 12°C$ was detected was removed from the data as it clearly indicated that one of the sensors was out of place. In order for a ΔT of 12°C to occur, neonatal temperatures would have to be in a range of approximately 27 to 29°C for peripheral temperatures and 38 to 41°C for central temperatures. Such a wide alterations in the ΔT are really unlikely to occur in neonates, especially when cared in an incubator. These alterations were not observed in any of the neonates unless the sensor was out of place.

2. Any central temperature lower than the set incubator temperature or than the measured temperature inside the incubator was set to NaN (Tc<Tinc, Tc<Tin). Any peripheral temperature lower than the measured temperature inside the incubator (Tp<Tin) was considered as NaN. The reason why this criteria was not also stablish for the set incubator temperature (Tinc) is because for the most preterm babies it wasn't uncommon that the peripheral temperatures dropped a bit below the incubator temperature. However, because of the small sample size of extreme premature neonates included in this study no condition was set on a specific value of Tinc.

3. The speed at which the temperature increases or decreases was an indicator of the sensor being out of place as sudden drops and increases in temperature are not physiologically possible. The magnitudes of extreme drops and increases in temperature within 1 and 2 minutes are listed a continuation with the reasoning behind them.
   a) **Decreases and increases in temperature in 1 minute increments:**

Because Tc and Tp did not follow the same response in time, different values were used to filter them within 1 minute. First of all, drops in central temperature were observed to occurred, in most of the neonates, faster than drops in peripheral temperatures. Only when the sensor was not in place the magnitude of the drop was lower than -2.5°C. As drops in peripheral temperature occurred slightly slower, the magnitude of the drop was set to -2°C, based on the observations of the neonatal temperatures. Regarding increases in temperature, Tc was characterized by recovering its value faster after repositioning the sensor (as can be observed in *Figure 3*). Tp recovered more slowly and gradually over time, and the increment was set to 1.4°C.

These conditions can be summarized as follows:

- If in a 1 minute increment there was a drop in Tc ≤ -2.5°C or Tp ≤-2, a NaN was assigned to the minute of the drop.
- If in a 1 minute increment there was an increase in Tc ≥ 3°C or Tp ≥1.4, a NaN was assigned to the minute previous to the increase.

b) **Decreases in temperature in 1 and 2 minute increments, with no missing information:**
After removing the biggest drops in magnitude within one minute, the values of the patterns in decreases over two minutes were considered. No common pattern was found for rises in temperature and therefore no criteria was applied.

- If in a 1 minute increment there was a drop in Tc ≤ -1°C and in a 2 minute increment there was a drop in Tc ≤ -1.9°, NaN were assigned to these increments. The same principle was applied for Tp.

c) **Decreases and increases in temperature in one minute, when the minute before or after the increase is missing:**
When the temperature data in a minute was missing, it indicated the presence of an alteration:

- If the data of a certain minute was missing and in a 1 minute increment there was a drop or increase in Tc or Tp ≤ -1.5° or ≥ 1.5 °C, respectively, NaN were assigned to the minute of the drop or previous to the increase.

d) **Decreases and increases in temperature in a 2 minute increment, when the information in the increment of 1 minute is missing:**
As in the previous point, when the temperature data in a minute was missing, it was a marker of an alteration. In this case the magnitude to filter the temperatures is slightly bigger than in the previous point because it involves drops and rises within a 2 minute interval, instead of 1 minute.

- If the data in a 1 minute increment is missing and in a 2 minute increment there was a drop or increase in Tc or Tp ≤ -1.9°C or ≥ 1.9°C, respectively, NaN were assigned to the minute of the drop or the minute previous to the increase.

Removing Regions of Unconnected data:

Once the sudden drops and rises had been removed, the following criteria were applied to avoid having regions with unconnected abnormal temperature readings:

1. **The following criteria was applied for all the neonates but the first one:** If peripheral values were found with a value ≤ 32.3°C and the previous or following minute was NaN, the value in that minute was considered as NaN. In case this step generated more scenarios of Tp≤ 32.3°C preceded or followed by a NaN a counter was introduced so that data was not deleted for longer than 15min. This criteria was used to solve periods for which the sensor was out of place for which the "sudden drops" and "rises" in temperatures had been removed but the readings in between were still present in the data.
2. If a certain minute or two minutes in a row were surrounded by data that had already been deleted (NaN) these points were deleted regardless the value of these data points.

Example of Filtered Data

Table 5 illustrates the percentage of data kept and removed by the outliers filter, per neonate. The maximum number of information removed corresponds to neonate 3, whose sensors were out of place for more than half a day, as illustrated in *Figure 4*.

	Data before the outliers filter		*Data after the outliers filter*	
Neonate	***# minutes***	***% Data***	***% Data kept***	***% Removed***
1	14462	98.6	97.3	1.3
2	7348	89.8	86.8	3.0
3	10137	92.2	87.1	5.1
4	2857	99.4	96.1	3.3
5	14441	99.0	95.7	3.3
6	4249	89.3	87.4	1.8
7	8270	98.5	96.0	2.6
8	7022	95.7	94.4	1.3
9	11887	91.3	87.3	3.9
10	12074	98.3	97.9	0.4
11	14320	97.9	95.7	2.2
12	14461	99.1	97.6	1.4
13	14391	96.7	95.0	1.7
14	14421	99.1	98.4	0.7
15	14453	98.1	96.4	1.7

Table 5 – Illustration of the percentage of data kept and removed by the outliers filter per neonate.

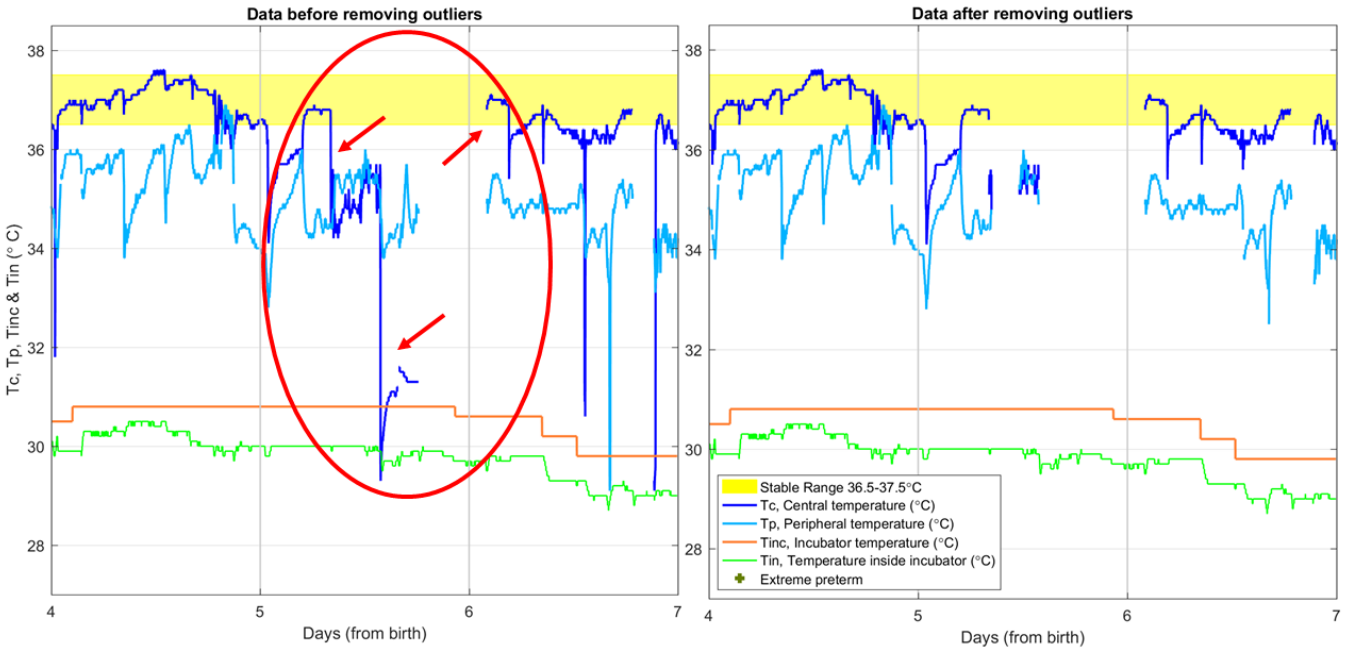

Figure 4 – Example of a sensor being out of placed (left), characterized by the low readings in central temperatures and sudden drop, and how the filter removed these outliers (right). Data corresponds to neonate #3.

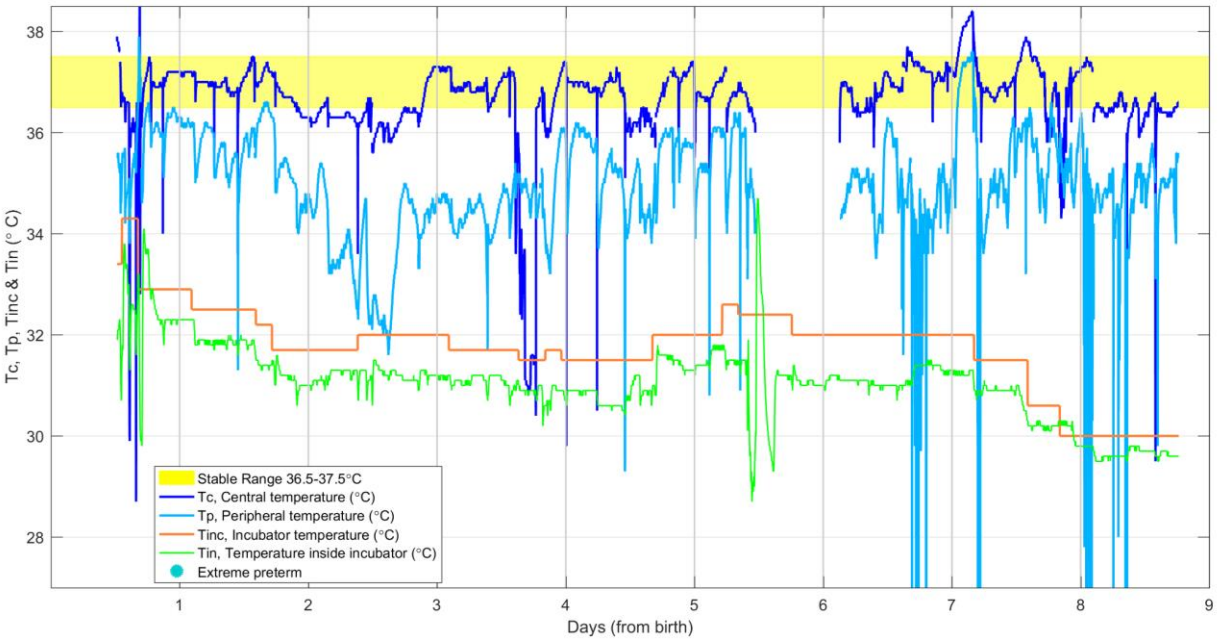

Figure 5 – Example of the raw temperature data of neonate #9 before applying the outliers filter.

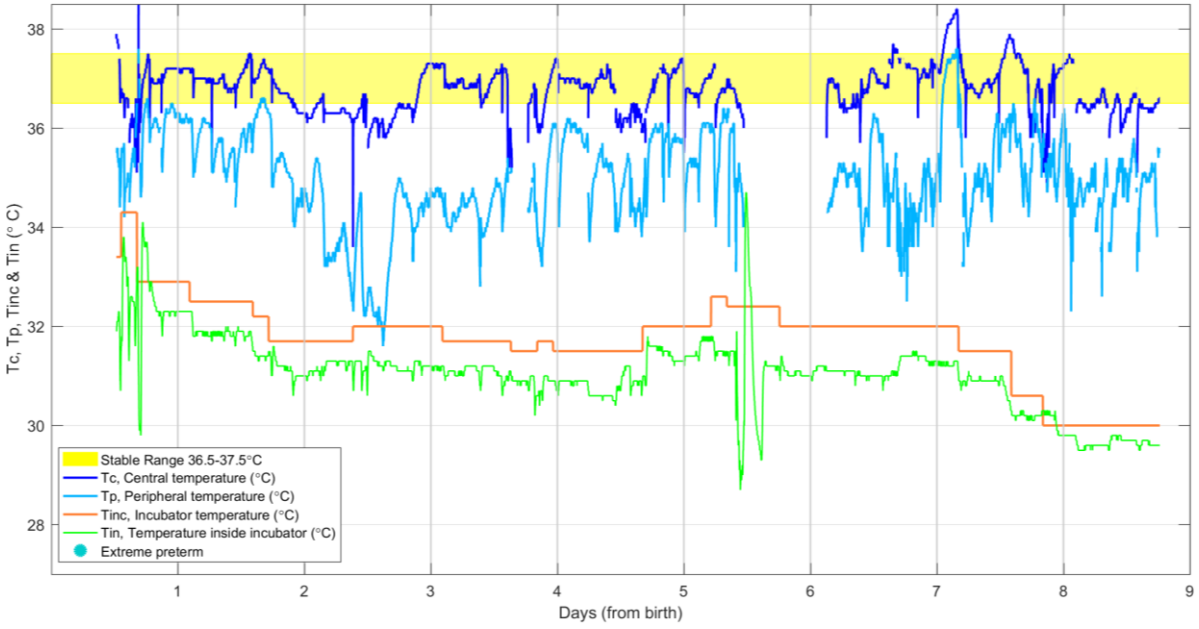

Figure 6 – Example of the temperature data of neonate #9 after filtering the outliers.

3. Moving Average Filter

First and foremost, it should be considered that the output of the moving average was solely used for visualization purposes of trends in temperature over time. The size of the filtering window (size over which the mean values are computed) used in the research paper (48h) results in an oversimplification of the results and cannot be used in clinical practice. However, in order to look for trends in ΔT over time it was necessary to smooth the signal. The reason for this is that the wiggles in the data (both with and without the filter for outliers) did not give a clear idea of how the temperatures evolved over time. Examples with different filtering windows are included in this section to illustrate the problem and justify the choice of the 48h window.

The built-in Matlab function "MOVMEAN" was used to create the graphs of the trends in temperature over time. The setting 'omitnan' worked in such a way that a NaN was only obtained if all the elements in the window were NaN, otherwise it will skip the NaN and calculate the mean within the remaining values in the filtering window. The setting to specify the behavior of the averaging at the endpoints of the data was left as default, 'shrink'. This setting automatically reduced the size of the windows at the start and end of the temperature recordings so that the length of the observations was not altered.

Moving Average with and without removing Outliers:

Figure 7 shows the influence of the sensors out of place when applying the moving average. When outliers are removed, the NaN in the temperature readings are replaced with the mean values of the readings in the specified window, avoiding false drops in the averaged signal (indicated with read circles).

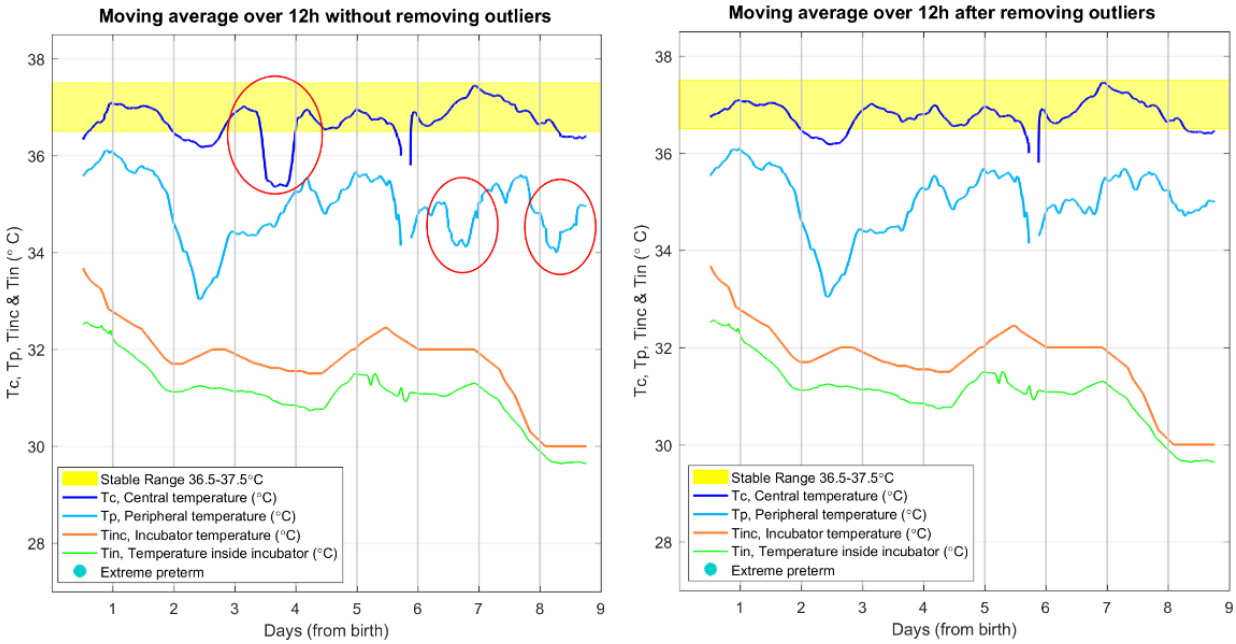

Figure 7 – Example of the effect of the effect in the moving average created by keeping or removing the outliers.

Example of Averaging over different time windows

The moving average filter was used to get a better idea of how the trends of ΔT over time. *Figure 8* to *Figure 11* show examples of the moving average over different windows (periods of time). In all these examples the outliers have already been removed:

- *Figure 8* corresponds to a window of 6 hours (equivalent to 360 minutes or data points).
- *Figure 9* corresponds to a window of 12 hours (720 data points).
- *Figure 10* corresponds to a window of 24 hours (1440 data points).
- *Figure 11* corresponds to a window of 48 hours (2880 data points).

It can be observed how at first the wiggles in the complete data set smooth out quite fast with increments of 6 hours (from no averaging (not shown here), to averaging over 6 hours, to averaging over 12h). However, starting from 24 hours the changes in the signal are smaller. With windows of 6 and 12 hours drops in the temperatures and periods of missing data are still present. When the window is increased to 24h all the data points are connected and Tc and Tp are quite steady. However, there are still some wiggles. Increasing the window to 36 hours did not make a difference but with 48h the distribution of ΔT is smoother and gives a better idea of its the evolution over time. Therefore, a smaller time windows could have been used to visualize trends in Tc and Tp, but a 48h windows was chosen in preference to ΔT.

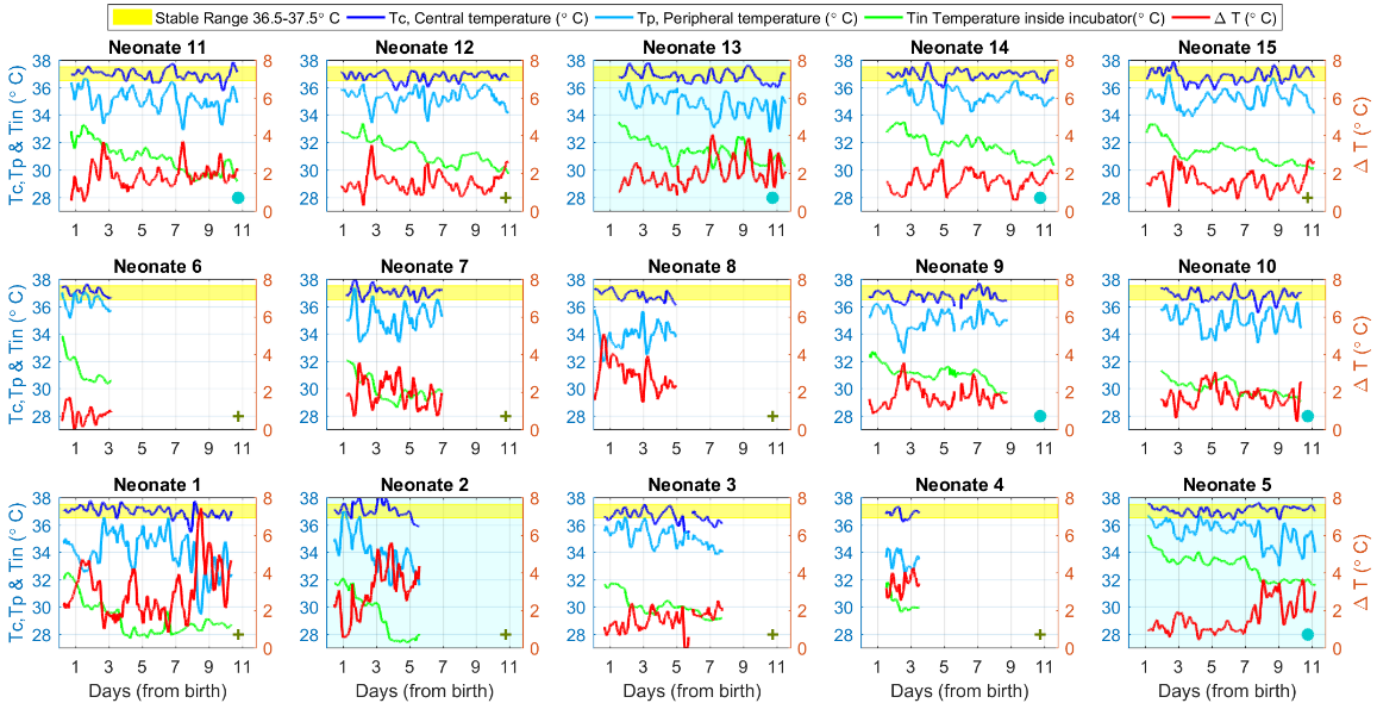

*Figure 8 – Example of the moving average filter with a window of **6 hours**. Neonates that had sepsis are shown with the background in blue. Very premature neonates are shown with + and extreme premature neonates are shown with ●.*

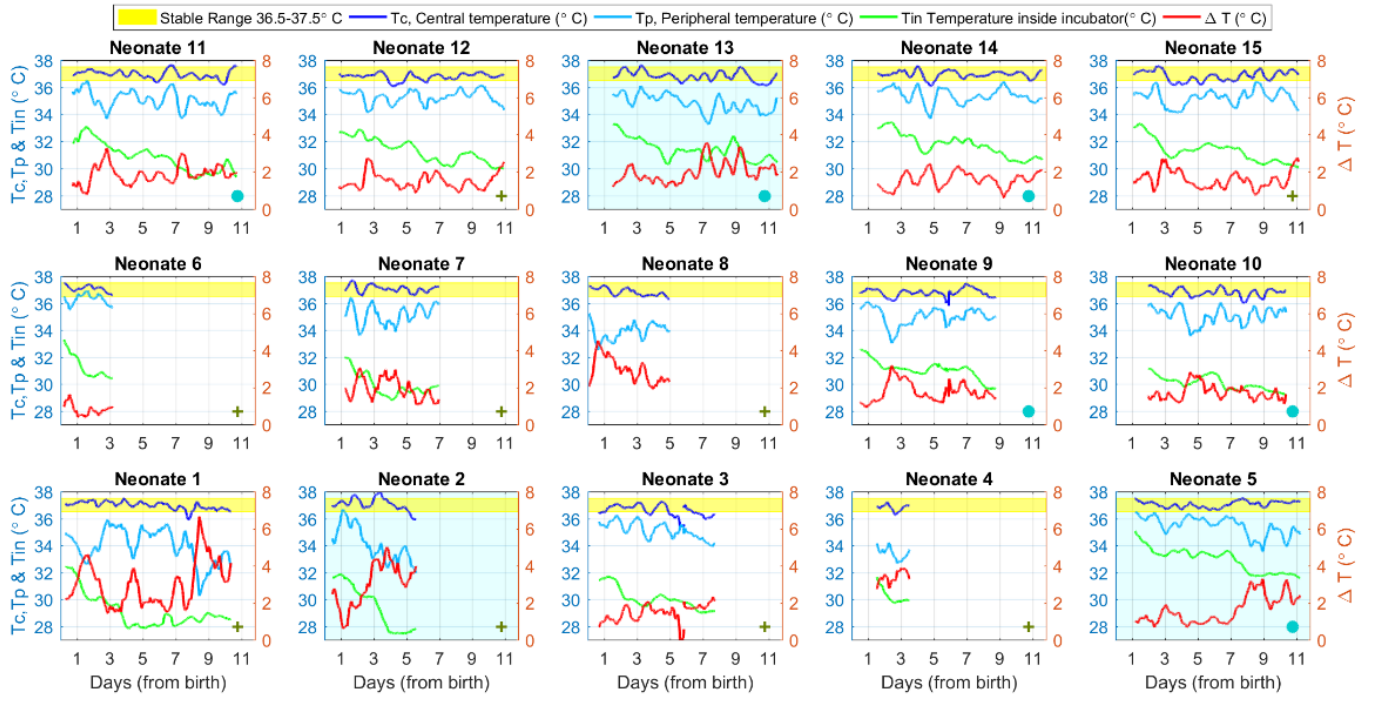

*Figure 9 - Example of the moving average filter with a window of **12 hours**. Neonates that had sepsis are shown with the background in blue. Very premature neonates are shown with + and extreme premature neonates are shown with ●.*

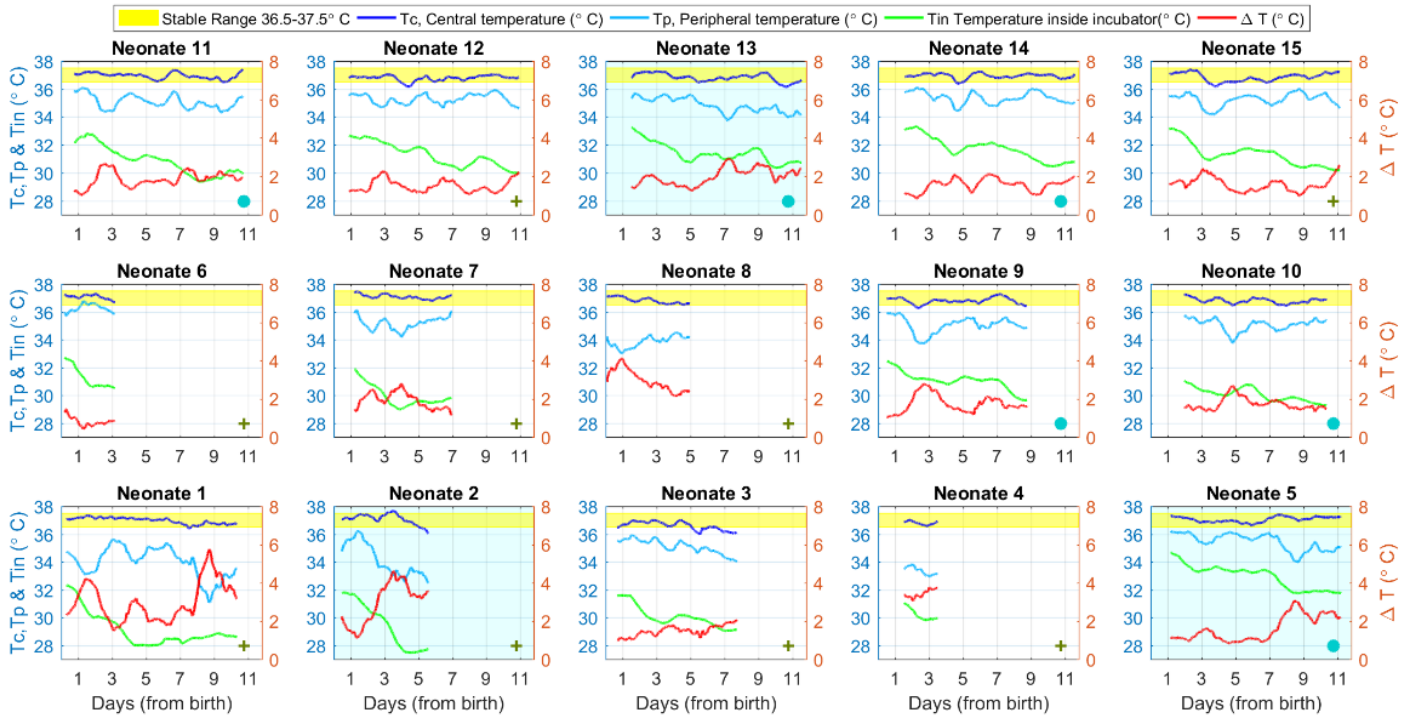

*Figure 10 - Example of the moving average filter with a window of **24 hours**. Neonates that had sepsis are shown with the background in blue. Very premature neonates are shown with + and extreme premature neonates are shown with ●.*

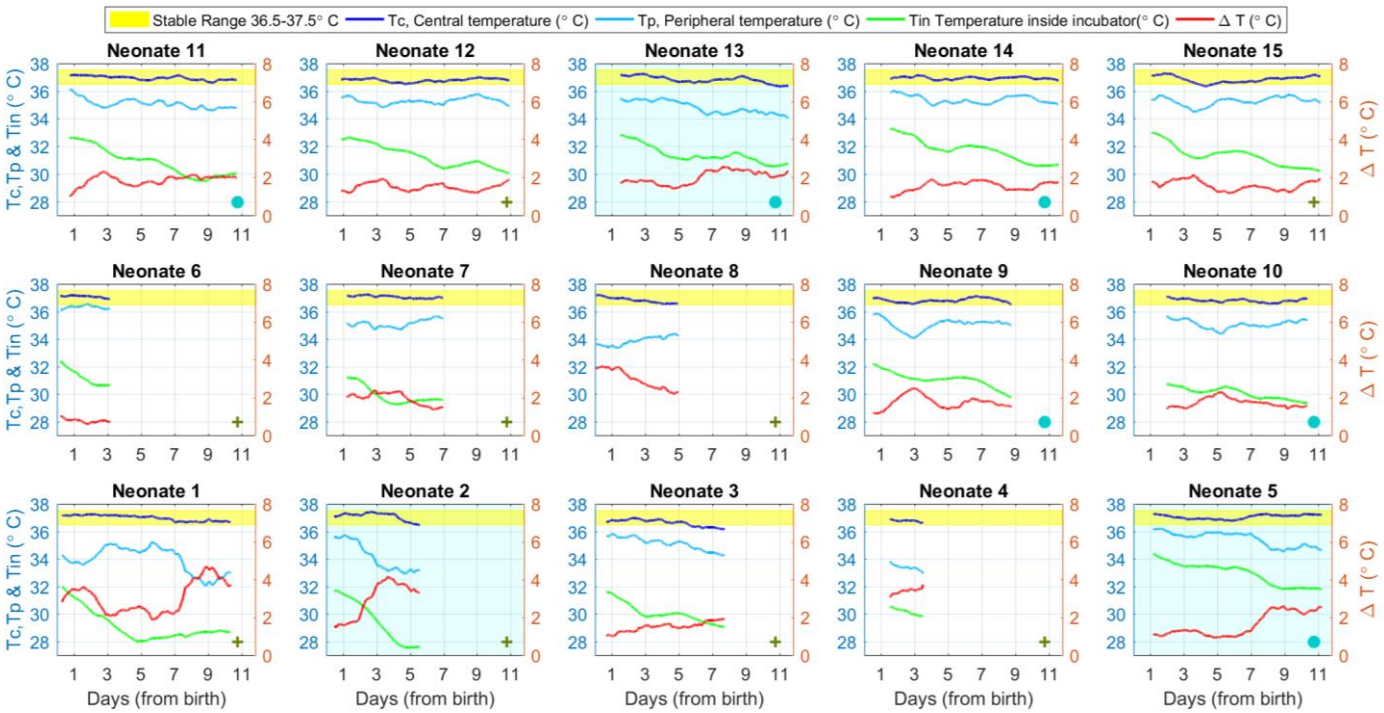

*Figure 11 - Example of the moving average filter with a window of **48 hours**. Neonates that had sepsis are shown with the background in blue. Very premature neonates are shown with + and extreme premature neonates are shown with ●.*

4. Recommendations for Future Work

Different filters could be applied according to the level of noise or pattern of outliers of a temperature profile. For example, consider that one of the neonates did keep his peripheral temperatures quite elevated and homogeneous during the study. If at a certain point the temperatures suddenly plummeted and then the sensors got disconnected, we could be almost certain that the sensor was out of place right before being disconnected. This could be easily fixed with the present filter by changing the temperature limit bellow which the temperature readings become suspicious (this value is currently set to 32.3°C). Additionally, different levels can be assigned to the variable *count* to remove more or less minutes around the given temperature limit. Consider that these levels are "low", medium" and "high". The filter used in the present work would correspond to the "low" level (maximum of 15 minutes), as it needed to be common for all the neonates. By setting this variable to a higher value, more outliers would be removed.

The same reasoning could be applied to sudden increases in temperature. However, these events are less likely to occur and would only correspond to invasive procedures for long periods of time, such as encountering problems when placing a line.

The sudden drops in peripheral temperatures fell below the temperature of the incubator quite frequently. However, this condition was not imposed in the filtering criteria because the extreme premature babies were sometimes an exception to the rule. These group of babies were nursed with incubator temperatures higher than the very premature neonates. Because of this, it is possible that the peripheral temperature was simply bellow the incubator temperature without indicating any alteration. As such, it would be interesting to explore the possibility of applying different filtering criteria to extreme premature and very premature neonates.

Appendix C Additional Results

This section covers additional results and trends of different parameters recorded during the study. First of all, the overall distributions of the neonatal temperatures will be presented. The settings of the neonatal incubators (set relative humidity and temperature) will be shown to illustrate the different routine care according to GA, BW and health status of the neonates. Then, the relation of peripheral temperatures and ΔT with birthweight and weight over time will be displayed. Finally, the increases performed to adjust the incubator set temperatures will be discussed according to the behavior of central and peripheral temperatures.

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1. Overall distribution of the neonatal temperatures

The overall distribution of the central temperatures, peripheral temperatures and ΔT for all the neonates is included in *Figure 12*. However, it should be considered that data of some neonates was only recorded for a few days, such as neonate #4 with 2 days and #6 with 3 days. Therefore, the small spread in their temperatures is likely to be due to the small number of recordings.

As already discussed in the pilot study, the medical staff kept the core temperatures within the stable temperature range (delimited by the red lines in *Figure 12*) for the majority of the time. Preterm neonates kept central and peripheral temperatures (and hence ΔT) within a narrower interval than very preterm neonates. Neonates with sepsis presented a wider spread in temperatures.

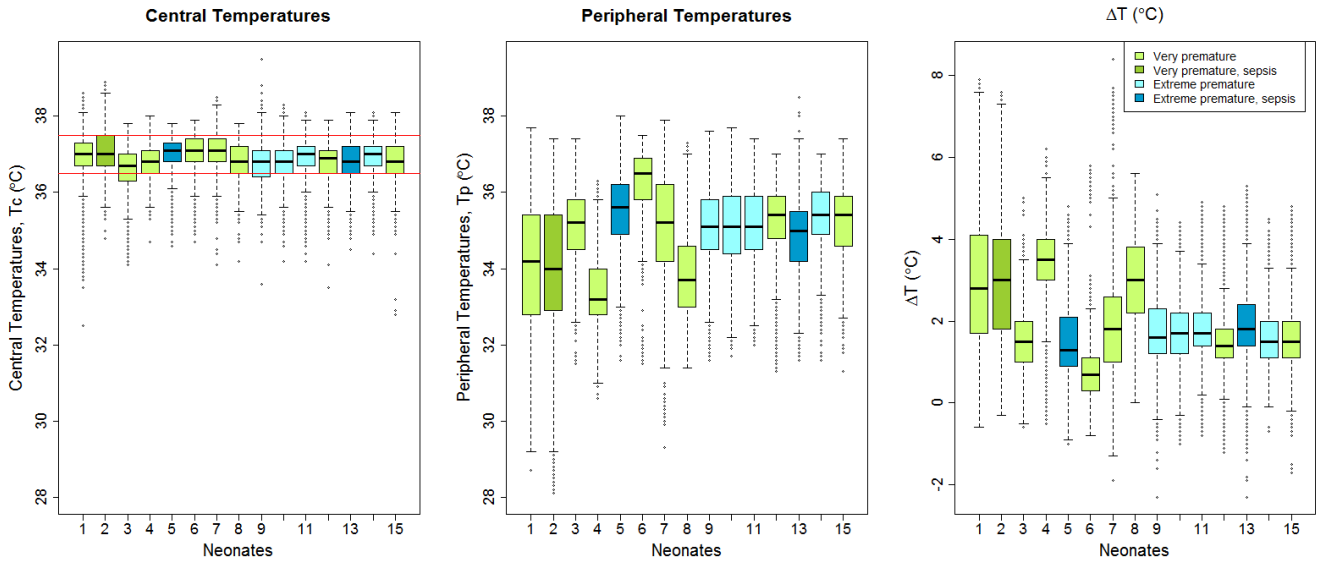


Figure 12 – Overall distribution of the temperatures of the neonates during the study.

2. Incubator Set Temperature & Humidity

The incubator settings over the duration of the study (raw data) are shown in Figure 13. The moving average has not been used to generate Figure 13, in order to clearly see the true (raw) adjustments done by the nurses. For instance, in the case of the twins (neonates #13 and #14) the relative humidity of one of them (#14) was set to a lower value on the 4th postnatal day, while for the other one (#13) the starting value was kept constant until approximately the 8th postnatal day. It should be considered that even though the settings of relative humidity were sometimes set to zero as the neonates mature, the humidity was never absolute zero because of the warm environment inside the incubator.

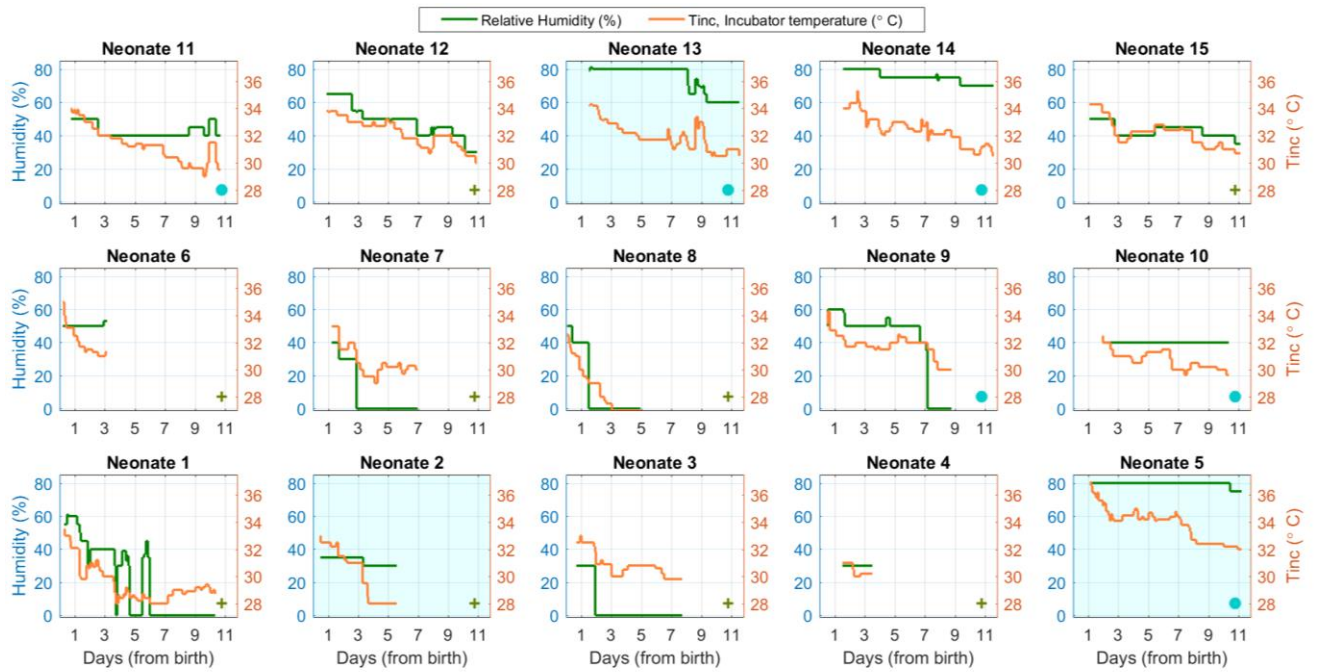


Figure 13 - Incubator settings (relative humidity and temperature) over the duration of the study. Neonates that had sepsis are shown with the background in blue. Very premature neonates are shown with + and extreme premature neonates are shown with ●.

3. Peripheral Temperatures and ΔT vs Birthweight

With the exception of the neonate weighting 950g (neonate #1, who was small for gestational age, belonging to the 10th percentile in the growth curves), it appeared that ΔT increases with birthweight (BW), as shown in *Figure 14*. ΔT seems to be slightly smaller for the neonate weighting 1405g (neonate #6). However, the temperatures of this neonate were only recorded for 3 days, which may explain the small variability and low values of ΔT after birth. The number of recordings for each neonate according to the days after birth is included in *Table 6*. *Figure 15* shows the distribution of Tp with birthweight of the neonates. The spread appears to increase with birthweight, with the same exceptions for neonates #1 and #6 (950g and 1405g) as in *Figure 14*.

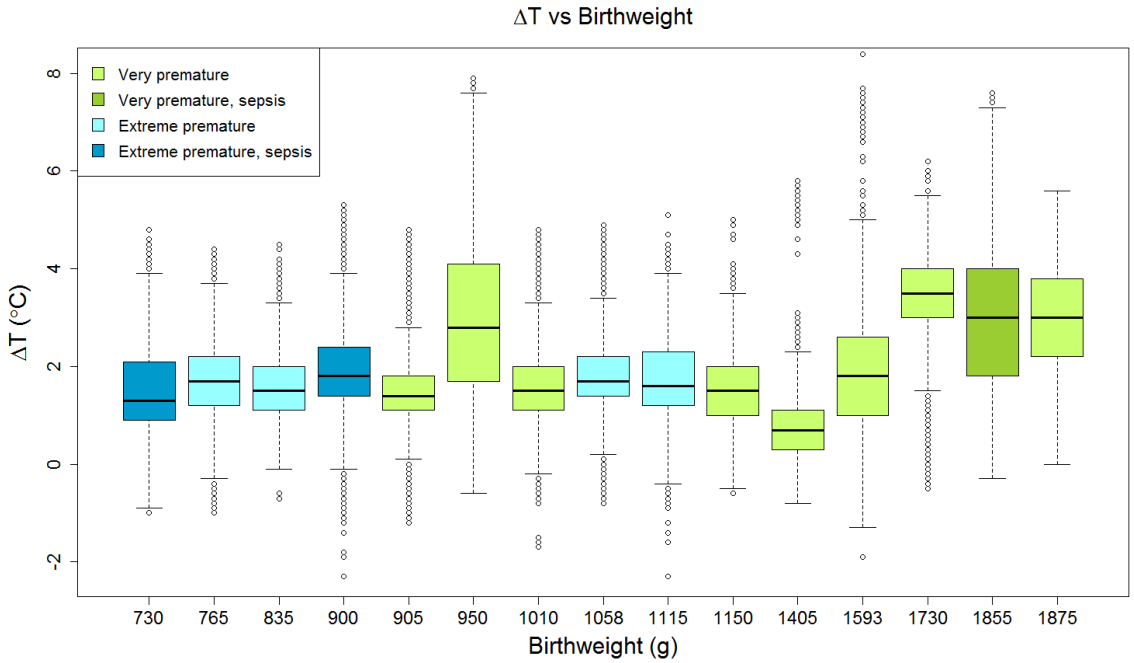


Figure 14 – Boxplot showing the relation between ΔT and the birthweight of the neonates in increasing order.

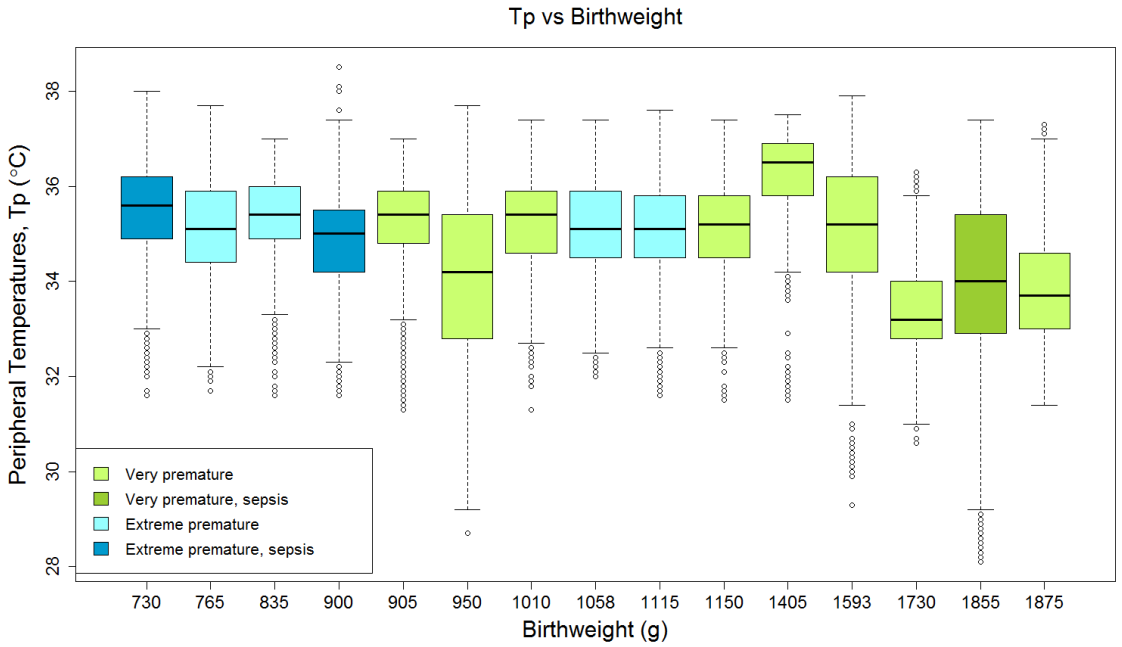


Figure 15 - Boxplot showing the relation between peripheral temperatures and the birthweight of the neonates in increasing order.

	Very premature neonates (no sepsis, sepsis)	*Extreme premature neonates (no sepsis, sepsis)*
Day 0	n=6 (5, 1)	n=2 (2, 0)
Day 1	n=9 (8, 1)	n=6 (4, 2)
Day 2	n=9 (8, 1)	n=6 (4, 2)
Day 3	n=9 (8, 1)	n=6 (4, 2)
Day 4	n=7 (6, 1)	n=6 (4, 2)
Day 5	n=6 (5, 1)	n=6 (4, 2)
Day 6	n=5 (5, 0)	n=6 (4, 2)
Day 7	n=4 (5, 0)	n=6 (4, 2)
Day 8	n=3 (5, 0)	n=6 (4, 2)
Day 9	n=3 (5, 0)	n=5 (3, 2)
Day 10	n=3 (5, 0)	n=5 (3, 2)
Day 11	n=1 (5, 0)	n=3 (1, 2)

Table 6 – Number of neonates in the study according to the postnatal age (days).

4. ΔT vs Weight

Premature neonates lose weight during the first few days after birth because of trans-epidermal water loss and compromised skin integrity. Relative humidity added to the incubator tries to compensate these losses. Then, after this initial drop in weight, the neonates slowly stabilize and start gradually gaining weight. *Figure 16* illustrates the progressive weight loss and gain of the neonates together with ΔT. The moving average filter has been used with a time windows of 48 hours to smooth tendencies in ΔT. It is unclear how much weight influences in the maturation of thermal control. ΔT does not appear to follow the tendencies in weight. However, it is interesting to see how for neonate # 15 the fluctuations in ΔT seemed to be related with variations in weight.

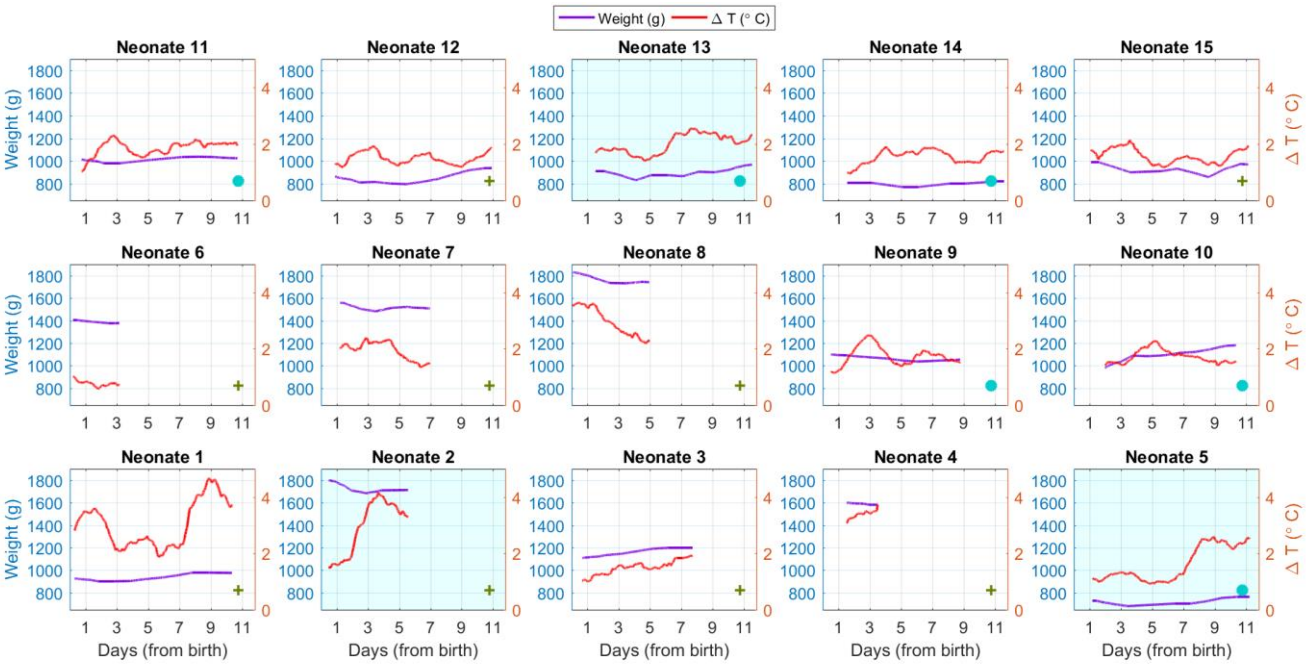


Figure 16 – Trends over time of weight of the neonates and ΔT (moving average filter with a window of 48 hours). Neonates that had sepsis are shown with the background in blue. Very premature neonates are shown with + and extreme premature neonates are shown with ●.

5. ΔT vs Days

The distribution of ΔT according to the days of life of the very premature and extreme premature neonates with no sepsis is included in *Figure 17* and *Figure 18*, respectively. Ideally, a plateau or a progressive increase in the values of ΔT should be seen over time. However, no solid conclusions can be drawn from the distributions of ΔT as the neonates were included in the study within 48h after birth and therefore the starting point of the recordings and number of neonates per day vary (as illustrated in *Table 6*). For instance, only 2 extreme premature neonates had been included in the study the day they were born (day 0). However, it seems that for the extreme premature neonates the ΔT over the 1st day of life (n=6) was slightly lower than for the following postnatal days. The distribution of the very premature and extreme premature neonates with sepsis is shown in separate figures, not to influence the results (*Figure 19*, *Figure 20* and *Figure 21*).

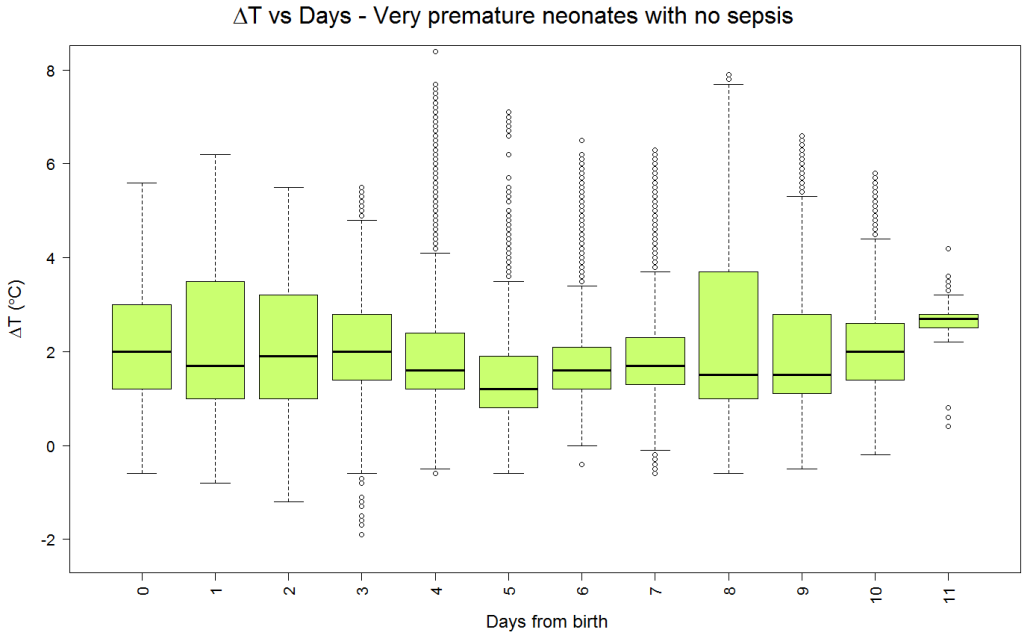


Figure 17 – Distribution of ΔT with postnatal age of the group of very premature neonates with no sepsis (for the number of neonates included in the study per day, see Table 6).

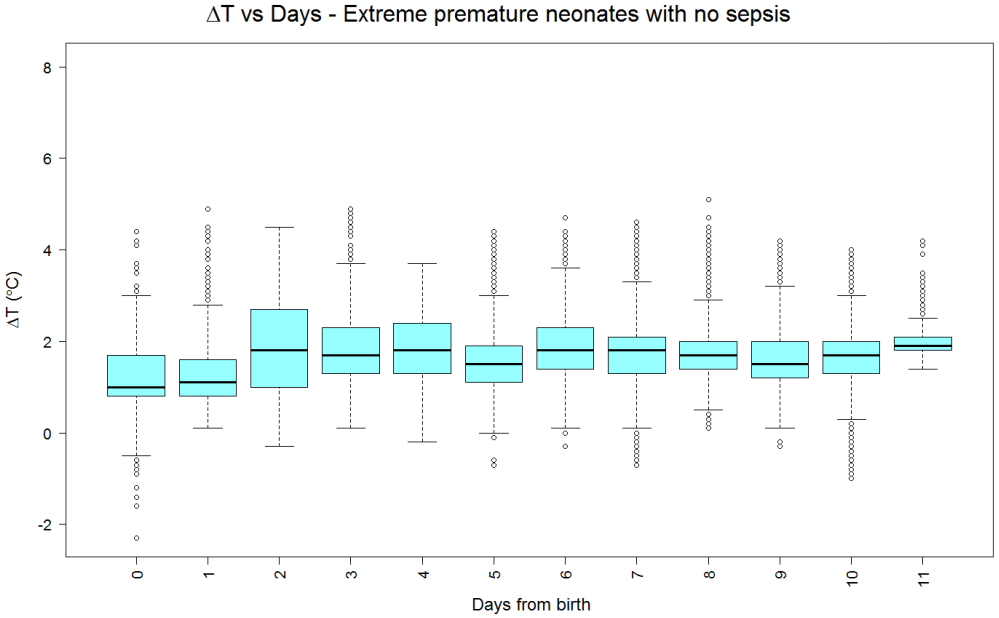


Figure 18 - Distribution of ΔT with postnatal age of the group of extreme premature neonates with no sepsis (for the number of neonates included in the study per day, see Table 6).

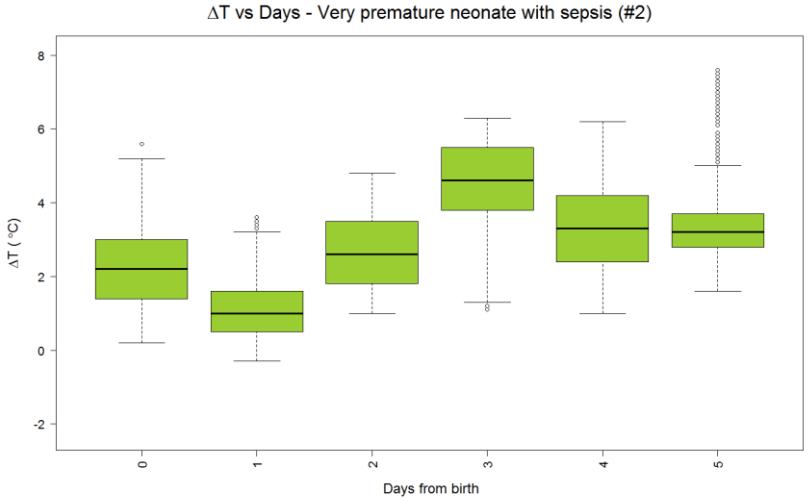


Figure 19 - Distribution of ΔT with postnatal age of the very premature neonate that had a trigger of sepsis.

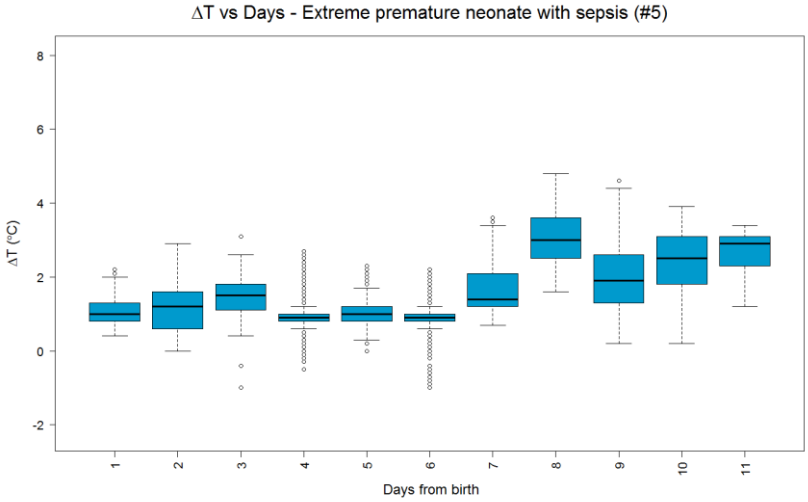


Figure 20 - Distribution of ΔT with postnatal age of one of the two extreme premature neonates that had a trigger of sepsis.

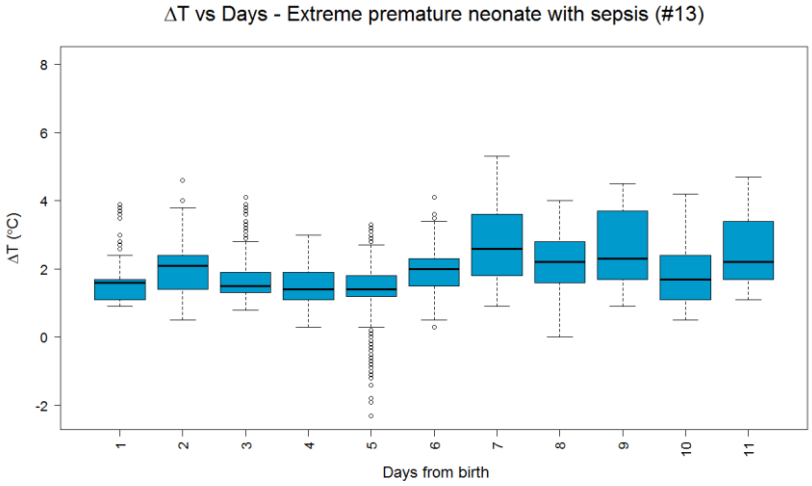


Figure 21 - Distribution of ΔT with postnatal age of one of the two extreme premature neonates that had a trigger of sepsis.

6. Adjustment of the Incubator Set Temperature

Two neonates did not have any registered increase in incubator set temperature (neonate #2 and #8). Nine of the neonates had Tc lower than 36.5°C during one hour before the change in incubator temperature, as shown in *Figure 22*. At the time of the change in temperature, the overall Tc of the neonates had decreased. An hour after the increase in incubator temperature the Tc slightly increased although the median Tc of 8 of the neonates still fell below 36.5°C.

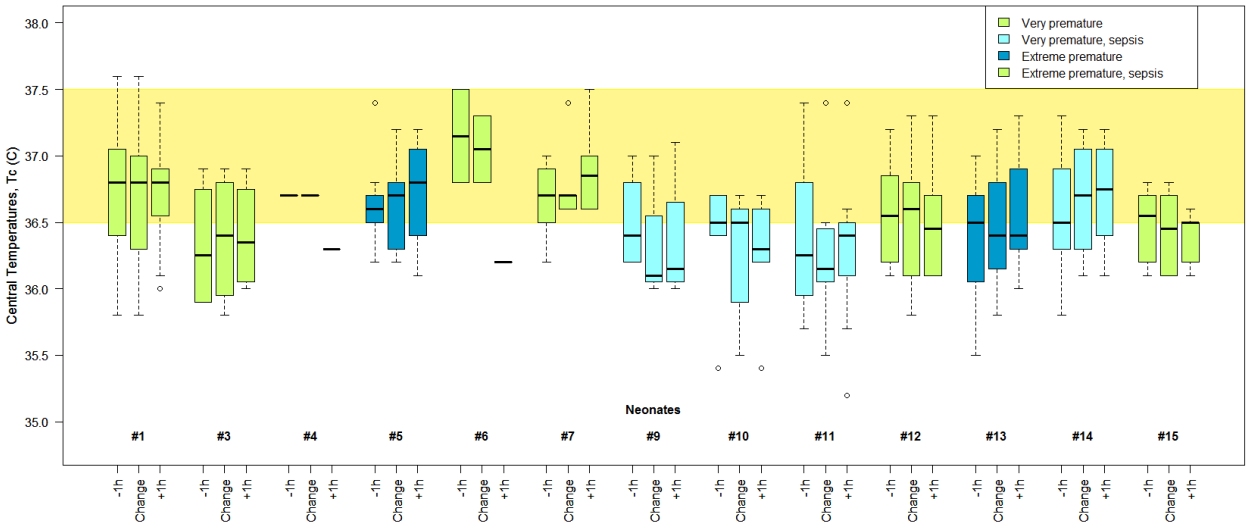


Figure 22 - Distribution of the central temperatures of the neonates over one hour before (indicated by "-1h"), at the moment of an increase in the temperature of the incubator (indicated by "Change"), and one hour after the increase (indicated by +1).

Figure 24 was already shown in the research paper and is including here for comparison. *Figure 23* and *Figure 25* show the patterns of Tp over one before, at the time of the change in incubator temperature and during the following hour. *Figure 22* and *Figure 23* correspond to an increase in temperature of the incubator and *Figure 24* and *Figure 25* correspond to a decrease. By comparing *Figure 22* and *Figure 23* it can be seen how the values of Tp were really close to Tc in the extreme premature neonates when an increase in incubator temperature was needed. When an increase in temperature was needed Tp values were overall lower than when a decrease was needed. When a decrease in incubator was needed, only the Tp of some of the very premature neonates presented values closer to Tc.

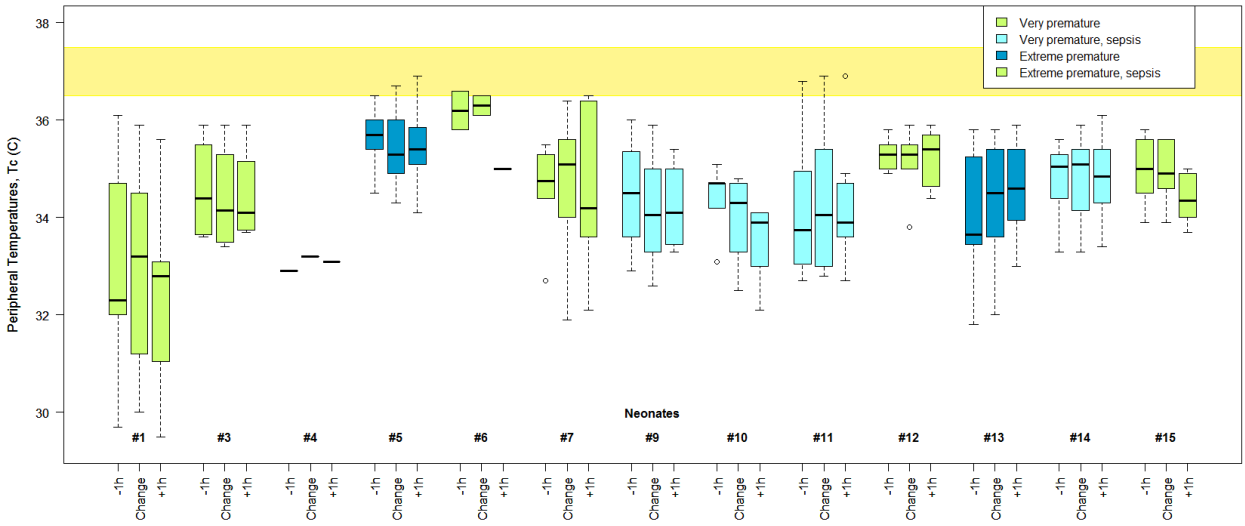


Figure 23 - Distribution of the peripheral temperatures of the neonates over one hour before (indicated by "-1h"), at the moment of an increase in the temperature of the incubator (indicated by "Change"), and one hour after the increase (indicated by +1).

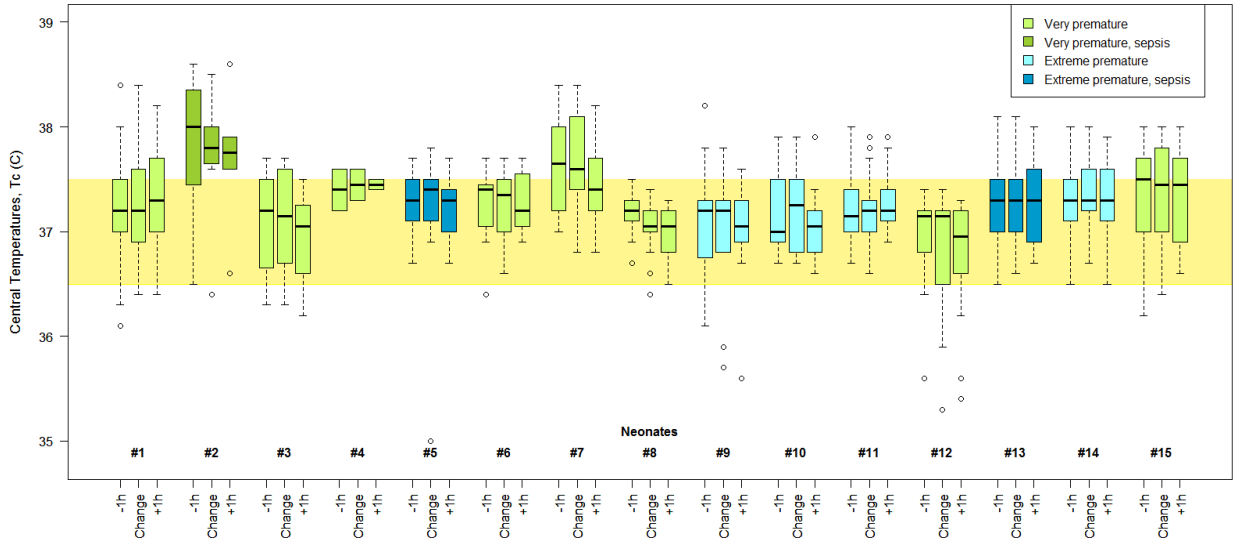


Figure 24 - Distribution of the central temperatures of the neonates over one hour before (indicated by "-1h"), at the moment of a decrease in the temperature of the incubator (indicated by "Change"), and one hour after the decrease (indicated by +1).

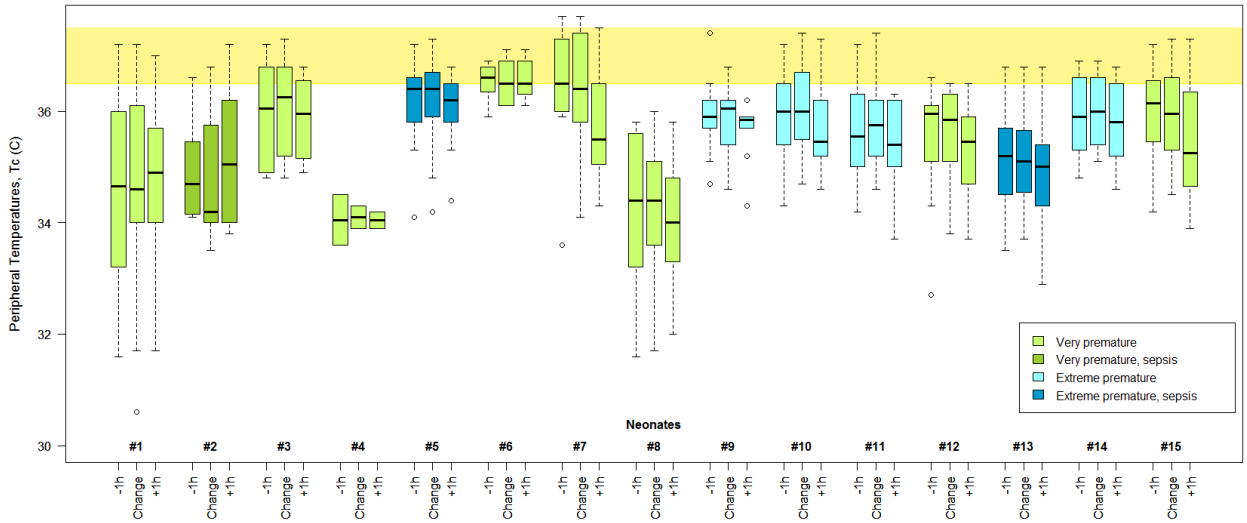


Figure 25 - Distribution of the peripheral temperatures of the neonates over one hour before (indicated by "-1h"), at the moment of a decrease in the temperature of the incubator (indicated by "Change"), and one hour after the decrease (indicated by +1).

The minimum and maximum magnitude registered in the changes in incubator temperature with respect to the previous setting was a decrease in temperature of 0.1°C and 2°C, respectively. The minimum and maximum in the case of increments in incubator temperature were 0.3°C and 2.3°C, respectively.

Appendix D Instruments Used

This section contains observations regarding the interaction with the medical personnel during the study and a small summary and illustration of all the instruments used in the study and problems encountered with them.

1. Interaction with the Medical Personnel

Before starting the research a small description about the study was sent in the research newsletter of the Erasmus MC. Nevertheless, at the start of the study not all the nurses were aware of the new research and the addition of one extra thermal sensor. Some difficulties were initially encountered and preventive measures were sought to avoid problems in the future. For instance, as the thermal probes used were hard to be distinguished, labels were included to make it easier for the nurses to reposition the sensors. Nurses were approached during the coffee break for 3 weeks so that they could become acquainted with the study. Nurses in charge of the neonates included in the study were personally approached during the day and night shift to let them know about the study and to discuss any problem encountered.

It should also be considered that the interaction with the medical personnel was in English instead of Dutch. This did not represent a problem when communicating with the nurses, as most of them were fluent in English. When a candidate for the study was born (<32 weeks GA), before approaching the parents the health status of the neonate, skin integrity and the possibility of inclusion in the study was discussed with the medical staff. The health status of the neonate was monitored during the study and the possible transfers to a secondary hospital. This information was available in Dutch.

However, the language difference was a great limiting factor when communicating with the parents. Multiple research lines are being performed in the Erasmus MC. Parents are continuously approached for consent of different studies during the pregnancy and after birth. In order to reduce parental distress, it was better that consent was asked in Dutch rather than in English. For the study of maturation of thermal control neonates needed to be included in the research as soon as possible after birth. However, when a potential candidate for the study was born it was necessary that someone

was available to talk with the parents and ask for consent before positioning the sensors and, of course, the parents needed to be in the hospital and available. When deferred consent was obtained, sensors could be positioned before approaching the parents, which speeded up the process. A special thanks to Tom Goos and Willem van Weteringen for their help with the parents.

2. Instruments Used & Their Limitations

Dräger Monitors

The patient monitor Infinity M540 (Dräger, Lübeck, Germany) and the display monitor, Infinity C700 (Dräger, Lubeck, Germany) used in the NICU of the Erasmus MC are shown in *Figure 26*. Variables are represented with a small graph over time with the actual value next to it both of these monitors. On the left of *Figure 26* it can be seen how the neonatal temperatures were displayed on the screen (two white numbers shown in the bottom right corner). Ta represents central temperature readings while Tb corresponds to peripheral temperatures (numbers shown in the left and right, respectively). The nurses could see both temperatures in the monitor during the study. This was an advantage in case the sensors were reversed as if they would had only have access to one of the temperature readings maybe the adjustment of the incubator temperature would have been altered. However, if in periods in which the sensors were reversed the peripheral temperatures would have been really elevated (Tp ≥ Tc), the nurses would not have been able to differentiate both temperature readings.

Figure 26 – Patient monitor and display monitor used in Erasmus MC (right, [22]) and an example of the screen display in simulation mode showing the central and peripheral temperatures (right).

As explained in Appendix B and in the limitations of the study, the main problem when working with the patient monitor was the missing seconds while recording data, and the information that was lost for almost 48h of the neonate #10 because of a defective monitor.

Split adapter & Cable

A split adapter (5592154 D9, Dräger, Lübeck, Germany) was used to obtain the reading of both thermal probes in the patient monitor. The cable connected to the thermal probe (Mon-a-Therm™ Cable 400TM , Covidien, US) of the central temperatures corresponded to the "Ta" port and the one of the peripheral temperatures corresponded to the "Tb" port. Five split adapters were used in the study. Four of them were purchased before starting the study as only one was available in the Erasmus MC. Therefore, this instrument limited the number of neonates that could be measured at the same time to 5.

When a neonate was admitted in the study the central thermal probe was disconnected for a few seconds to position the split connector and reconnect again the central temperatures and add the peripheral temperatures. The same procedure was followed at the end of the study to remove the peripheral thermal probe and split connector.

Thermal Probes

The thermal probe currently used in routine care in the Erasmus MC to measure central body temperatures is Mon-a-Therm™ 400TM (Covidien, US), as shown in *Figure 27*. It is provided sterile and will be disposed of after use. The thermal probes consist of two different layers: a thin hypoallergenic adhesive layer that will be placed in contact with the skin and a thicker foam layer which protects the thermistor from the environmental temperature influences [23]. The thermistor is placed between these two layers to obtain the most optimal temperature reading. The same thermal probe was used for peripheral temperatures. However, the weight and size of the neonates included in the study were quite different. For the smallest neonates, the foam of the sensor needed to be cut so that it did not exceed the size of the foot of the neonate. *Figure 27* shows a normal-size thermal probe (first probe on the left), which has a width of 2.5 cm and a length of 5 cm. The second thermal probe starting from the left in *Figure 27* has been cut to fit a foot of an extreme premature neonate with the least disturbance as possible. The sensors were cut, when needed, to a width of approximately 1.5 cm.

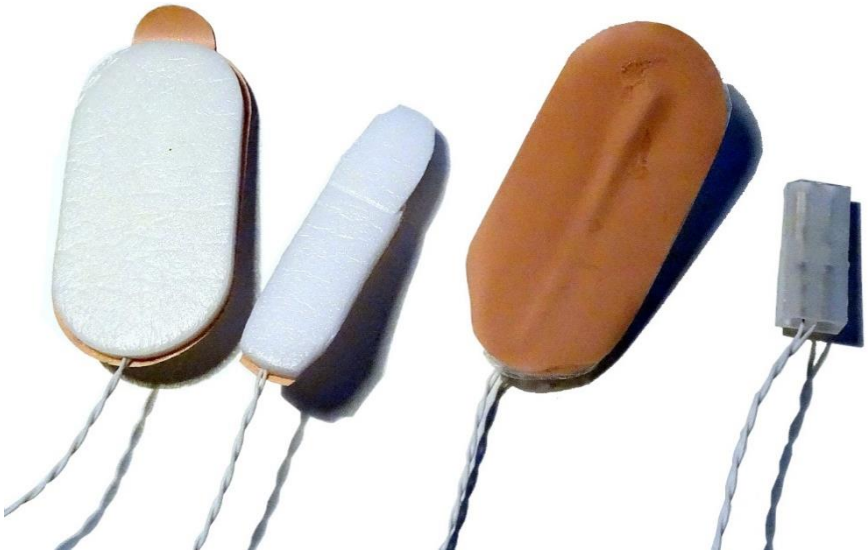


Figure 27 – Illustration of the thermal probes used for very premature and extreme premature neonates included in the study.

In the Erasmus MC the adhesive layer is not used to hold the sensor in contact with the skin of the neonates. Instead, it is covered with a thin plastic film to protect the skin of the neonate (3M Tegaderm™, 3M Health Care, St. Paul, US), as shown in the second sensor on the right of *Figure 27*. The first element on the right of *Figure 27* corresponds to the connection at end of the wire of Mon-a-Therm. This connection is the one that broke or was damaged for some of the neonates, resulting in false temperature readings, as explained in Appendix B. The thermistors are connected through this long and thin white wire to another cable, as explained before, that connects to the patient's monitoring system, where there is a conversion into digital numbers.

Labels

As explained in the previous section, not all the nurses were aware of the start of the study and some difficulties were initially encountered. During the first hours of data recording, two types of problems occurred with the first neonate included in the study. First of all, the peripheral sensor was found to be repositioned in the back of the neonate. Therefore the neonate had two thermal probes measuring the same central temperatures. The nurse in charge of the neonate (night shift) did not know about the study and thought someone misplaced the central sensor in the foot. The main researcher realized about the problem within minutes and the sensors were repositioned. On the other hand, a few hours later the central and peripheral sensors were reversed and the recordings were altered for a total of 15 hours. The nurse seemed to be aware that the higher temperature in the display monitor corresponded to central temperatures and no abnormalities were found in the adjustments of incubator set temperature.

Preventive measures were sought to avoid sensor misplacement or removal in the future. Two thermal probes were used in the study, which were hard to distinguish unless the peripheral one was cut. Additionally, neonates are

surrounded by sensors, wires and cables inside the incubator, which hindered the two white wires of the thermal probes. Labels were used to make it easier for the nurses to identify and distinguish both probes (see *Figure 28*). Labels were placed at the end of the wire of the thermal probes and at the start and end of the connecting cable to the patient monitoring system. One label indicated "Foot temperature" and the other one "Central Temperature".

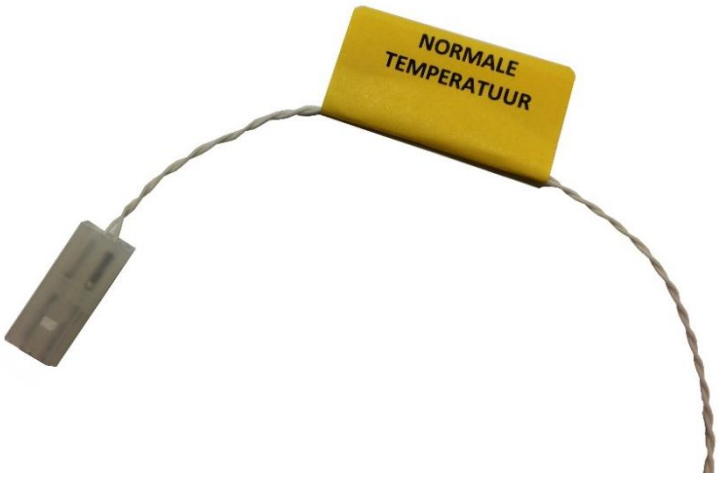


Figure 28 – Example of one of the wires of the thermal probes with a label indicating the proper connector.

The solution of using labels was found to be relatively effective. No problems of misplacement were found until the 9th neonate included in the study. This neonate had the most altered temperature readings because the connection of the cable was damaged, originating really low-temperature readings. Moreover, for the last 2 days in the study only peripheral temperatures were recorded, without any record of central ones. The last neonate included in the study, #15, also had the sensors reversed for 17 hours the central temperatures were kept within the stable range. More careful monitoring of the positioning of the sensors should be done to avoid altered temperature readings that could lead to misinterpretation, endangering the neonate.

Fixation bands

The fixation bands used in the study (Posey Paediatric Limb Holder 4733, Posey Company, Arcadia, US) are used in routine care to hold different sensors in contact with the skin of the neonates. As the medical personnel already had experience with these bands no problems were encountered. The soft foam of the band avoids damaging the skin of the neonate (dimensions 14 cm x 3 cm). The band is wrapped around the foot of the neonate, easily adjusting to the size of the foot, and closed with Velcro (as illustrated in *Figure 29*).

Figure 29 – Posey fixation band used in the NICU of Erasmus MC to hold sensors in place without damaging the skin of the neonates.

Data loggers HOBO® Pendant

Two light and temperature data loggers HOBO® Pendant temp/light (Part #UA-002-64, Onset, US) were used for each neonate (see Figure 30, green data loggers). Even though these data loggers recorded both light and temperature, light measurements were not related to the neonatal temperatures and were not included in the final data analysis. These sensors have a size of 58 x 33 x 23 mm and an accuracy of ± 0.53ºC [24]. Their waterproof housing protects them from wet environments, such as the humidity of the neonatal incubators [24]. The memory is of 64K bytes (approximately 28K combined temperature and light readings or events) [24]. The recordings of the data loggers are obtained through a base station (HOBO® Pendant Optic USB Base Station, Part #BASE-U-1, Onset, US), connected to a PC through a USB (see Pendant coupler on Figure 30, with one arrow pointing towards "logger" and another one towards "base station").

Figure 30 – Data logger for temperature and light used in the Erasmus MC with the base station to read the recorded data [24, 25].

One of the data loggers was positioned inside the Caleo® incubator (Dräger, Lübeck, Germany), attached to one of the lateral sides with a suction pad. The location was chosen by the nurses, in the most appropriate place so that it did not impede proper visualization and access to the neonate. It provided an estimation of the drops in incubator temperature during nursing procedures and medical interventions. The main problem with this sensor was encountered when the medical interventions required the removal of the incubator top wall. As the sensor was attached to the incubator cover, it was moved with it to a different part of the room. Therefore, abnormal temperature readings were recorded during these periods. It is true that if the incubator cover was removed the incubator was losing a lot of heat. However, the neonates were not exposed to a lower temperature because the additional thermal support of a radiant heater was used. The second sensor was fixed with tape over the incubator display screen in order to have a reference of the room temperature. Great variability was found in room temperatures were even for neonates that were nursed approximately 2 meters apart. Air flows in the room or being positioned closer to windows may have influenced the temperature readings.

These sensors recorded temperature information every 30 seconds for a maximum duration of 10 days. They were set to 30 seconds so that they did not require to be read out before the end of the study. This minimized the amount of data that was lost and the need of disturbing the neonates to remove and reposition the sensors several times during the study. If further research increases the frequency of the recordings to once a second (as the information from the patient monitor), the sensors will need to be replaced every 3 days approximately.

Neonatal Incubators

The neonatal incubators (Caleo, Dräger, Lübeck, Germany) used in the study consisted of a transparent plastic hood or cover that encloses the neonate and multiple portholes. The port openings resulted in heat loss from the incubator and a decrease in relative humidity, originating drops in the neonatal body temperature. The drops in incubator temperature were estimated by the light sensor placed inside the incubator. However, the positioning of the sensor inside the incubator only gave an approximate temperature reading of that small area of the incubator and not on the temperature in the complete volume of air. Furthermore, the area in which the sensor was located

(on the side wall next to the neonate's head) appears to be the coldest spot in the incubator, as illustrated in *Figure 31*. Drops in incubator temperature could also be slightly influenced by the removal of the blanket that covers them, as the radiative heat loss increases (*Figure 32* shows how these blankets are placed on the incubators).

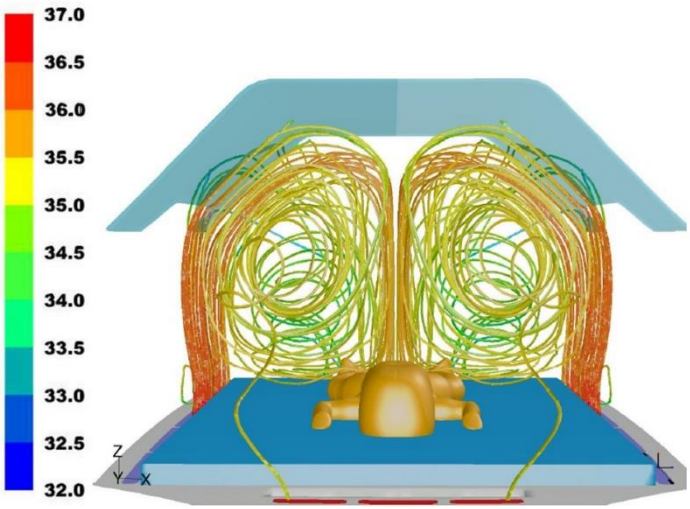


Figure 31 – Example of the path lines of temperature flow in a Caleo incubator as calculated by Ginalski et al. [26].

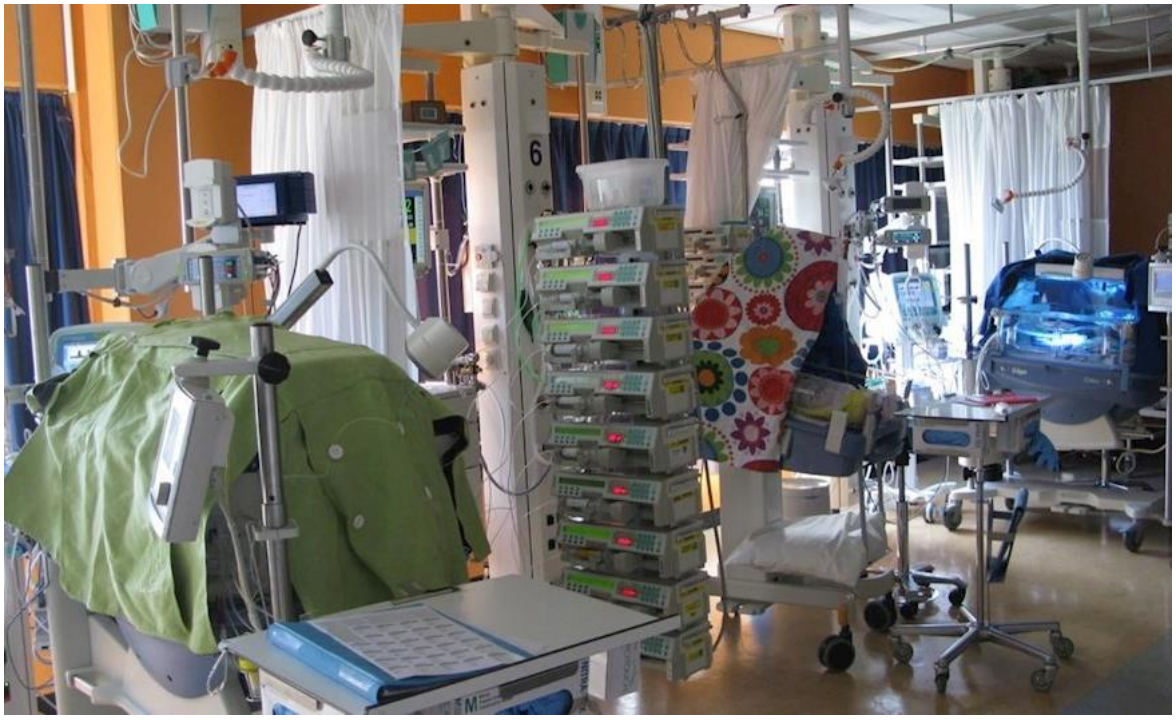
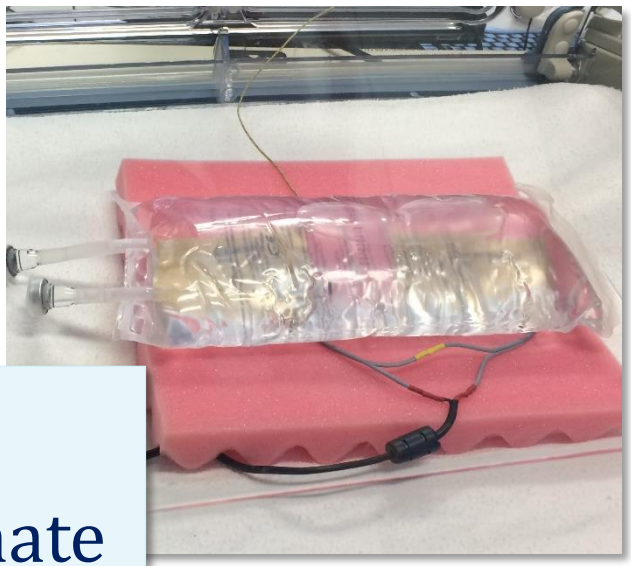


Figure 32 – Part of a NICU in the Erasmus MC [27]. From left to right: neonatal incubator covered with a green blanket to protect the neonate from the light, open bed with a blanket with flowers to protect the neonate, neonatal incubator with a blue blanket partially open and with a lamp switched on to obtain a better view of the neonate.

Drops in the relative humidity were not measured continuously. As already discussed in the pilot study, further research should consider recording the information of incubator's temperature and humidity directly from its display by connecting a computer to the neonatal incubator. This would also improve the reliability of the recordings over time at which the incubator set temperature was adjusted.



Appendix E
Simulating a Neonate

Simulation of a Neonate under Standard Nursing Conditions

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Keywords:
Nursing Environment
Simulation
Neonate
Incubator
Set Temperature
Power

A B S T R A C T

Introduction: Disruptions in the body temperature threaten the health of the preterm neonates and can lead to a variety of diseases and increased mortality. Preterm neonates are nursed in neonatal incubators, which provide thermal support to counteract heat loss as the neonates mature. The incubator temperature needs to be adjusted over time according to the needs of the neonates. A better understanding of the nursing environment created by the incubator and the response of the neonates to changes in the environment could help adjusting the incubator temperature of the most preterm neonates.

Aim: To quantify the level of variation in simulated neonatal temperatures after controlled changes in the incubator set temperature. To study the effect of the room temperature and light levels on the incubator performance and neonatal temperatures.

Methods: The body of a neonate was simulated with a water bag. The neonatal heat production (temperature of the water bag) was adjusted with the use of heat pads. Thermal probes were attached to the water bag in order to give an estimation of the central and peripheral temperatures. The nursing conditions were reproduced with a neonatal incubator. Light and temperature sensors were positioned inside and outside the incubator to study the effect of the surrounded environment on the incubator and water bag. An energy data logger was used to measure the power consumption of the incubator over time. The incubator set temperature was decreased in controlled periods and the time to achieve stabilization of the incubator power consumption and temperatures of the water bag was analyzed.

Results: After a decrease of 1°C in the set temperature the power consumption of the incubator achieved stabilization within 25 minutes. For the water bag, the time to stabilize to the new incubator temperature was approximately 10 hours. Changes in the environment in the neonatal intensive care unit greatly influenced the temperature of the water bag and incubator. Sudden drops in the power consumption of the incubator were registered after increases in the incubator set temperature or increases in the room temperature caused by sunlight.

Conclusions: The response in the simulated neonatal temperatures to a change in incubator temperature appears to be relatively slow. Careful monitoring is needed in order to adjust the set temperature of the incubator to keep neonatal temperatures within the stable range (36.5°C – 37.5°C) before deviations occur.

1. Background

Extremely low birth weight (ELBW, <1000g) and very preterm neonates (<32 weeks of gestational age) present a limited ability to regulate their own temperature. This results in frequent temperature fluctuations that can lead to increased morbidity and mortality rates [28-31]. The temperature of a neonate can drop at a rate of approximately 0.2°C per minute after birth if no preventive actions are taken [32]. Their physical characteristics (large surface to volume ratio, immature skin, thin layer of insulating fat, and weak peripheral vasoconstriction among others) makes them prone to heat loss, as they are unable to produce enough heat [4, 7, 33, 34]. There are four modes of heat exchange with the environment by which the neonates can lose heat: evaporation, convection, conduction, and radiation [7, 35]. In order to counteract the different mechanisms of heat loss, preterm neonates are nursed in neonatal incubators, which provide thermal support, establishing a Neutral Thermal Environment (NTE). In this manner, energy expenditures (metabolic requirements and oxygen consumption) are minimized until the neonates reach thermal maturation. It is recommended that the core or central temperature is kept in the range of 36.5 to 37.5°C [7, 36]. The temperature of the incubator is modified by the caregivers according to the needs of the neonate over time. With increasing postnatal age, neonates are able to increase their heat production and lower incubator temperatures are needed. Moreover, relative humidity can be added in neonatal incubators in order to counteract and minimize the trans-epidermal water loss from the skin and provide better thermal stability, as evaporation

*

is the main mechanism of fluid and heat loss in the premature neonates during the first days after birth. In the Erasmus MC, the humidity of the incubator is modified according to the "Treatment Protocol for Extreme Premature Neonates". Changes in incubator temperature are performed based on experience, as there is no specific protocol established for this practice. However, the degree of effectiveness of the adjustments in incubator temperature is unclear because it depends on the speed at which the body of the neonates assimilates the change and adjust to the new incubator temperature. Moreover, it is greatly influenced by incubator openings and medical interventions. The goal of this experiment was to simulate a neonate under standard nursing conditions in order to estimate the stabilization times in neonatal temperatures after controlled changes in the incubator set temperature (nursing environment).

2. Materials and Methods

2.1. Materials

A neonatal incubator (Caleo, Dräger, Lübeck, Germany) was used to create a nursing environment that could resemble routine care. The power consumption of the neonatal incubator was measured using an energy monitor data logger 4000 (VOLTCRAFT, Germany). Values of the apparent and active power consumption were recorded per minute. Active power corresponds to the amount of power consumed by the resistive components of the system and it is measured in watts. Apparent power, measured in VA, is the product of the root mean square of the voltage and current of a circuit and is therefore a function of the circuit's total impedance (Z). It value gives an estimation of what is occurring in the overall system, not only in relation with the resistive components.

Data of the nursing environment was obtained by placing two data loggers HOBO® Pendant temp/light (Part #UA-002-64, Onset, US) inside and outside the incubator, as already explained for the pilot study. Information was recorded every 10 seconds. The body of a premature neonate, mainly made of water, was simulated with a water bag because of its similarities and availability in the hospital. This water bag is used in routine care as an input to the incubator to create relative humidity (see Figure 33). In order to simulate the heat production of a neonate, two heating pads connected in series were placed in contact with the water bag (see Figure 33). Different voltages could be set to regulate their heat production (watts). A soft foam (shown in pink in Figure 33) was placed between the incubator mattress and the heat pads in order to protect the mattress from any possible damage.

Two thermal probes Mon-a-Therm™ 400TM (Covidien, US) were used to estimate "central and peripheral temperatures of the neonate" (water bag). One of the thermal probes was positioned between the soft foam and the water bag, avoiding direct contact with the heating pads. The second heating pad was placed on the upper part of one of the shorter sides of the plastic bag and it was hold in place with a rubber band. As already explained in the pilot study and in Appendix D, these thermal probes were connected to the patient monitor Infinity M540 (Dräger, Lübeck, Germany) with two cables (Mon-a-Therm™ Cable 400TM, Covidien, US) and one split adapter (5592154 D9, Dräger, Lübeck, Germany). Temperatures were displayed in the monitor Infinity C700 (Dräger, Lubeck, Germany). The temperatures were recorded every second by the patient monitor and updated into the network of the Erasmus MC. Decryption was handled by CapProcessor (Erasmus MC, Rotterdam, The Netherlands).

Figure 33 *– Initial experimental setup showing the water bag and heat pads and how they were positioned inside the neonatal incubator.*

A raspberry pi with a custom python script was configured by Tom Goos. It allowed to have continuous information of the incubator set temperature and measured temperature inside the incubator as displayed on the screen of the incubator. Information was recorded per second in an excel file and stored in a USB.

2.2. Methods

Initially, the first experiments were done to test that the water bag did not burst with the heat generated by the heating pads. These experiments were done without an incubator. Then, once it was ensured that the integrity of the water bag was not compromised by the added heat, the water bag and heating pads were placed in a neonatal incubator with additional thermal support. This was performed in the Technical Department of the Sophia Children's Hospital in the Erasmus MC. However, the environmental conditions (light and temperature) of the Technical Department were not ideal for the experimental setup. These conditions greatly differed from a standard NICU environment and led to continuous instabilities in the power consumption. Large variations in temperature were mainly caused by the air conditioning and heating system (periods of time in which it was on or off) and by sunrise and sunset, which also influenced the light levels. The room temperature of the NICU is approximately kept between 24.5°C and 27.5°C, in order to reduce radiative and convective heat losses from the incubator and from the body of the neonates during periods of kangaroo care. Additionally, the light level of the room is kept low to minimize disruptions to the neonate. In order to simulate a consistent working environment for the present experiment, the incubator was placed in the NICU of the Erasmus MC, Unit III.

According to Brück [37], a neonate between 500g and 1kg could produce approximately 1.65 Watts during the first day of life. During the second day of life, this value would rise up to 1.74 Watts and up to 1.90 Watts for the fifth day of life for a neonate of 1kg. This heat production was simulated as followed by modifying the voltage of the heating pads: 1.57 Watts (19V), 1.74 Watts (20V) and 1.92 Watts (21V).

Different combinations of incubator set temperature and heat production were studied to find the settings that could keep the central temperatures of the water bag between the range of 35°C and 38°C. These corresponded to

incubator temperatures between 34°C and 32°C. Based on this, the changes in incubator temperature that were analyzed corresponded to decreases from 34°C to 33°C, from 33°C to 32°C and from 32°C to 31°C. These decreases were performed with the heat pads set to a heat production of 1.57 Watts (19V), 1.74 Watts (20V) and 1.92 Watts (21V). Every experiment was repeated twice and the averaged in active and apparent power, central and peripheral temperatures was computed. No added relative humidity was used in the experiments as there could not be any evaporative losses from the water bag that needed to be "compensated" by the nursing environment.

Experiments were only performed when the incubator was stable. Stability was defined in terms of a power consumption with no sudden fluctuations and the ability of the incubator to keep the set temperature. Each experiment consisted of modifying the set temperature of the incubator 1°C and waiting for the incubator and temperature of the water bag to stabilize again. The stabilization times in the neonatal incubator were assessed based on power consumption. The stabilization times for the "simulated neonate" were calculated as the time to reach temperature stabilization after a change in the incubator set temperature was done.

The analysis of the data was performed with Matlab R2016b (The MathWorks, Inc., Natick, MA, US). Data recorded with the thermal probes and with the light and temperature sensors was averaged over a minute to match the readings of the power consumption. The influence of the environment (light and room temperature) on the power consumption and temperature of the incubator and central and peripheral temperatures was visually analysed.

3. Results

3.1. Influence of the Environment

Changes in the environment of the NICU greatly influenced the temperature of the water bag. Overall, a greater room temperature resulted in slightly higher peripheral and central temperatures. When the curtains of the window next to the incubator were not closed and there was clarity outside, the temperature of the incubator increased and slightly differed from the incubator set temperature. However, when incubator was under direct sunlight, the readings of the light sensor could be altered by up to 3°C while the incubator temperature registered was about 0.5°C higher than what it should. This also generated an increased in room temperature of up to 2°C, approximately. More importantly, the sudden increase in incubator temperature generated a drop in the power consumption of the incubator.

3.2. Stabilization of the Central and Peripheral Temperatures

The stabilization curves of central and peripheral temperatures are included in Figure 34. The recordings of the temperatures start one hour before the change in incubator temperature was done (as a reference). The change in temperature was done at 1:00h. Immediately after a change in incubator temperature was done there was a sudden drop in peripheral temperatures while central temperatures decreased more gradually over time. The time to achieve stabilization (temperature plateau) varied between 9h and 12h for central temperatures and approximately between 7h and 9h for peripheral temperatures. It can be observed how central temperatures spread quite evenly, while peripheral temperatures were grouped into 3 differentiated clusters according to the change in incubator temperature. In the case of central temperatures, there only seemed to be 2 clusters, one

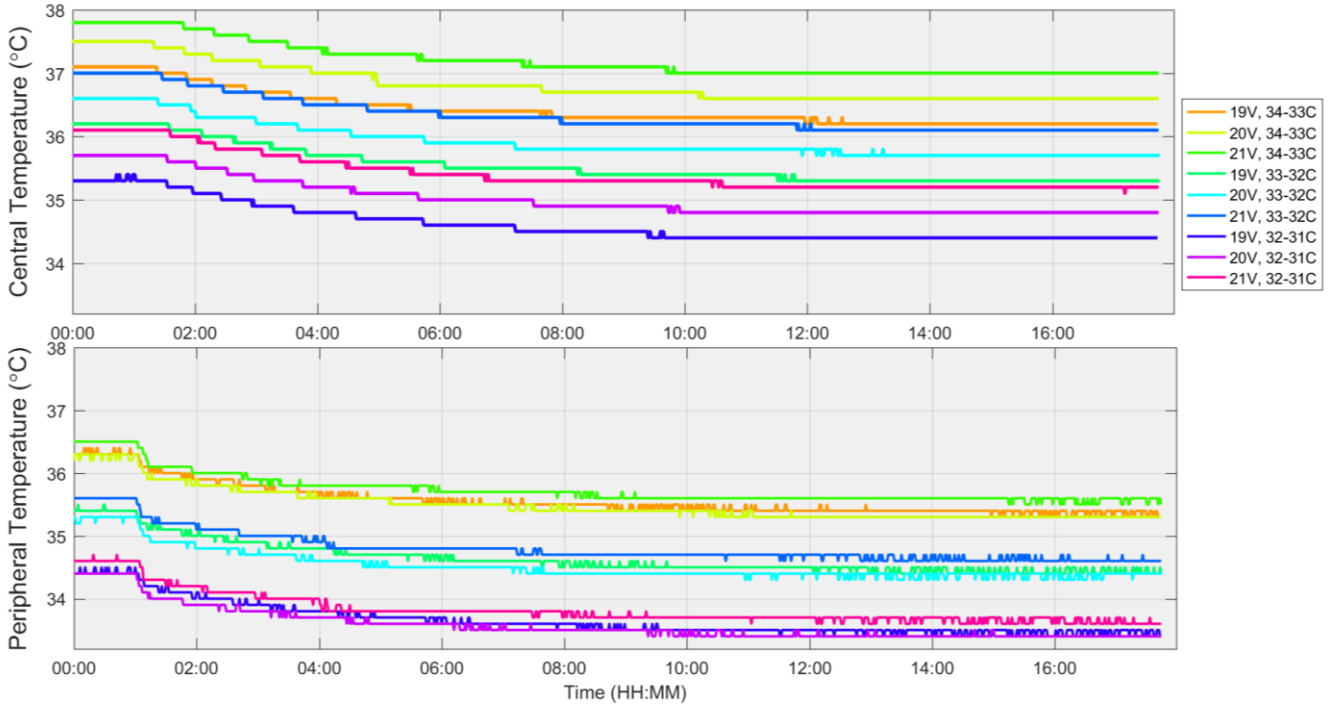

Figure 34 *– Progressive decrease in central and peripheral temperatures after a decrease in incubator temperature of 1°C.*

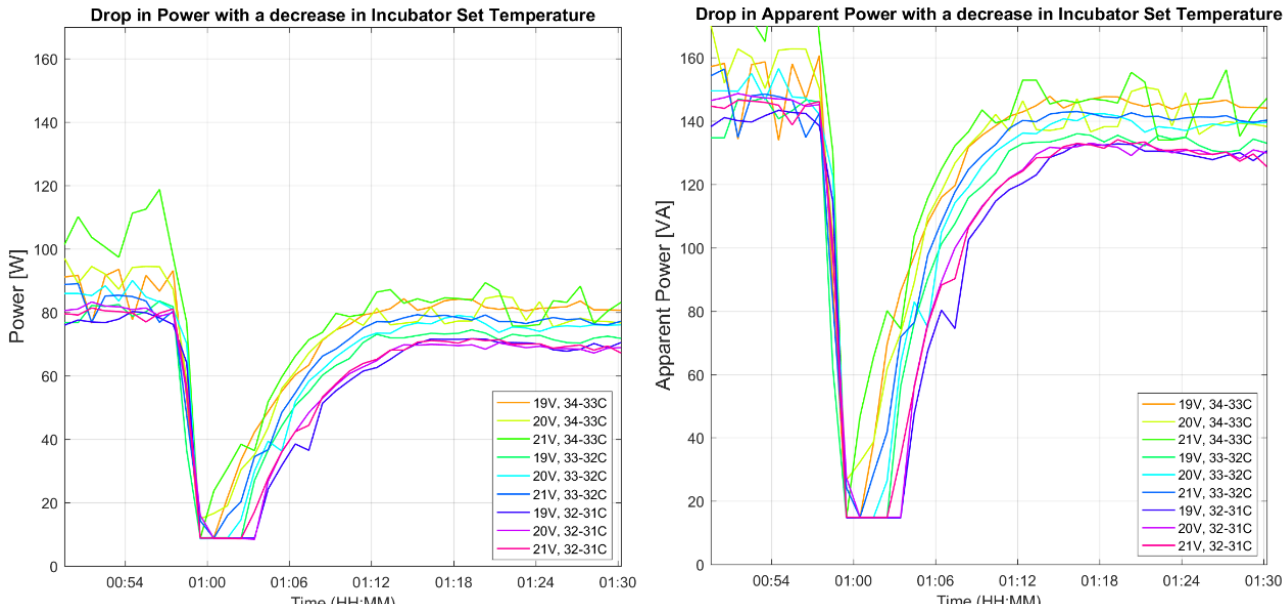

Figure 35 *- Drops in the power consumption after a decrease in incubator set temperature followed by a rise and stabilization as the incubator reached the new set temperature.*

formed by the change 19V, 34-33°C and 21V, 33-32°C and another one created by the change 19V, 33-32°C and 21V, 32-31°C. It can also be seen how peripheral temperatures fluctuated more than central temperatures. This could be explained by the fact that they the thermal sensor was more exposed and not isolated as the ones for central temperatures. Therefore, it could have been influenced by small deviations from the incubator temperature (heater output) that might have been caused by differences in the room temperature and light levels.

3.3. Stabilization of Active and Apparent Power

Overall values in apparent power consumption of the incubator were greater than those of the active power. The same pattern was observed for the drops in power consumption during a change in incubator set temperature, as shown in Figure 35. The recordings of the power consumption start one hour before the change in incubator temperature was done (reference value). With higher incubator temperatures the power consumption increased faster after dropping than with lower incubator temperatures, for which the power of the incubator seemed to be minimum for approximately 4 minutes. In about 20-25 minutes the incubator seemed to have achieved stability.

4. Discussion

The intention of the present research was to give a first approximation of the behaviour of the incubator and water bag in response to controlled changes in incubator set temperature.

The time for the temperatures of the water bag to stabilize to the new incubator set temperature was of approximately 10 hours. However, it should be kept in mind that the experimental setup did not represent the reality. The water bag was an oversimplification of the body of a neonate. It had an inert metabolism, did not perform vasoconstriction or vasodilation in response to changes in the environment and did not suffer evaporative heat losses, among many others.

Immediately after a change in incubator temperature was done there was a sudden drop in peripheral temperatures while central temperatures decreased more gradually over time. This would not be the case of a neonate cared in the NICU of Erasmus MC. In routine care, neonates are covered by a blanket, which would limit the sudden decrease in peripheral temperatures.

The experimental results show that incubators reached stabilization in the power consumption within 25 minutes after a decrease of 1°C in the set temperature was done. It should be considered that neonatal incubators can gain heat relatively faster than losing it. When kept closed, neonatal incubators are slower at reducing the set incubator temperature, especially if relative humidity is added [38]. Hence, stabilization times may vary when an adjustment to increase the incubator temperature is done. Moreover, in routine care incubators in the Erasmus MC are covered by a blanket that protects the neonates from the light. This blanket also reduces radiative heat loss, helping the incubator to keep its warm temperature, and therefore decreasing the power consumption, but making harder to dissipate heat when the set temperature of the incubator is decreased by the operator [38].

The independent variables (incubator set temperature and heat production of the heat pads) were selected based on the adequacy to simulate a nursing environment as realistic as possible. However, it should be considered that it is recommended that the core or central temperature is kept in the range of 36.5 to 37.5°C [7, 36]. For the adequacy of the experiments, central temperatures could vary between 35°C and 38°C although this range is certainly ample. Moreover, the simulated neonatal heat production is just an approximation as basal metabolism changes with age and is influenced by the health status of each individual [37, 39].

Additionally, it should be noted that while performing the experiments with the incubator certain disturbances were observed in the power

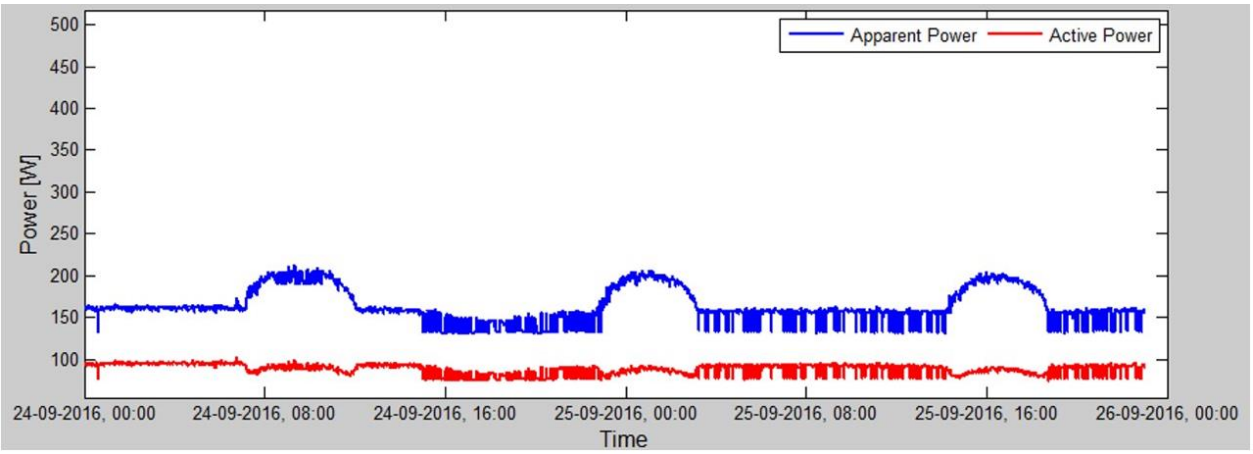

Figure 37 *- Rises and Drops in Power Consumption of the neonatal incubator while running under stable conditions.*

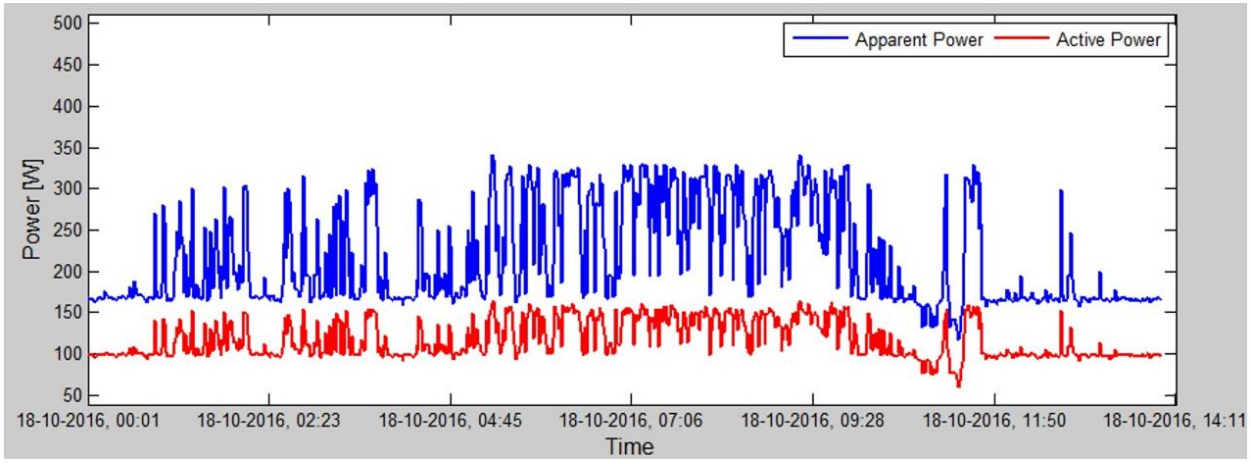

Figure 36 *– Periods of instabilities in the power consumption of the neonatal incubator.*

consumption. Periodic cycles were found in which the power consumption of the incubator was suddenly rising (about 30-50 VA higher for the apparent power) and then decreasing again, as shown in Figure 37. The duration of every periodic increment in power was of approximately 4-5 hours and the time between the cessation of one rise and the start following of approximately 11-12 hours. Figure 36 illustrates periods of instabilities in the neonatal incubator in which experiments could not be carried out. These pattern of power instabilities could have been generated by an altered environment in the NICU, which is most likely to occur during the day (such as, for instance, if the incubator was placed under direct sunlight or if there was an increase in the room temperature). However, the instabilities shown in Figure 36 occurred during the night, when the environment in the NICU was stable and no explanation could be found regarding the occurrence of these alterations in the power consumption. Further evaluation of the power consumption would be needed in order to assess its reliability and relevance for future studies and to get a better understanding of the working principles of the incubator.

4.1. Limitations of the study

The data recorded during one day was lost because the nurses set the patient monitor to standby, automatically cancelling the recording of central and peripheral temperatures. The incubator was disconnected twice during the study. The first time it was moved to a different part of the NICU and reconnected again, resulting in no loss of information. On the other hand, the second time the incubator and corresponding sensors were not plugged again. The incubator lost the set temperature, water bag became cold because the heating pads stopped working and central and peripheral temperatures were not recorded.

The difference between active and apparent power could imply that the system is not efficient, in the sense that the current is circulating but not delivering useful power to the load. However, the neonatal incubators are quite a complex system and no solid conclusions can be drawn without further knowledge regarding the complete control mechanisms included in the system.

Additionally, it should be considered that if the change in the incubator set temperature was not accurately synchronized with the energy data logger, the drop in incubator temperature was progressive over two minutes. The timer of the data recorded by the raspberry did not work and the researcher attempted to synchronize the data of all the sensors. This could have resulted in an uncertainty of ±1 minute in the measurements.

5. Conclusion

The results presented here correspond to the first attempt to quantify the level of variation in a simulation of neonatal temperatures to get a better understanding of the environment created by the incubator. This could eventually help improving the nursing environment of the most preterm neonates. The experimental results showed that incubators achieved stabilization within 25 minutes after a decrease of 1°C in the set temperature. However, the time for the temperature of the water bag to stabilize to the new incubator setting was of approximately 10 hours. The medical personnel should be aware of the fact that when a change in incubator temperature is done, it could take very long for the neonates to assimilate it. Therefore, careful monitoring of the neonatal temperatures (within the stable range, 36.5°C – 37.5°C) is needed in order to modify the incubator set temperature before an alteration occurs. Furthermore, knowing the magnitude of the drops and rises in power and temperature in an empty incubator could eventually help distinguishing the contribution to the heat production of the body of a neonate, leading to a further study of their postnatal maturation.

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