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Monitoring and controlling oxygen therapy in preterm infants

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Dissertation

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Contents list

I

Chapter I

Introduction

Introduction

Preterm infants are born too early and they often require intensive care to survive. This care is mostly provided in dedicated neonatal intensive care units (NICU). Because the lungs of the preterm infants are immature, oxygen supplemental therapy is offered with a gas mixture with more than 21% oxygen. Oxygen therapy is however not without risk, because too much can result in oxidative stress by oxygen free radicals leading to organ damage, such as blindness, and too low blood oxygen levels can for example hamper organ development [1]. Oxygen therapy in preterm infants is therefore concerned with finding a balance between the need for additional oxygen and preventing damage due to oxidative stress. However, oxygen therapy is about more than providing additional oxygen only. It also includes the resuscitation setting, the monitoring of oxygen saturation and ventilation, and fitting oxygen delivery to the tissue's needs, to name a few [2-4]. All these aspects should be taken into account when provided oxygen therapy and ventilatory support to the vulnerable preterm infant (Fig. 1.1).

Figure 1: Preterm infant

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Resuscitation

Resuscitation, the immediate assessment and care after birth, is an excellent way to learn more about challenges involved with the measurements and physiological changes during the transition from intrauterine to extrauterine life in preterm infants. Fast acquisition of reliable measurements is needed, in order to be able to adjust the provided support effectively. The challenge of fast and reliable measurements becomes obvious when for instance using a pulse oximeter, measuring the heart rate and oxygen saturation levels right after birth. The time spend waiting to position the sensor, acquiring a signal, and getting the first reading can seem to last forever [5, 6]. Quick changes in measurements may immediately influence the therapy that is given. In this regard it is hard to beat an old-fashioned stethoscope to quickly check what the heartrate is.

When a health care professional uses a stethoscope to check the heart rate, it is up to him/her to determine if the first few beats represent heartrate accurately, or that (s)he needs to listen longer to get an adequate indication of the health condition. Manufacturers of electronic heartrate and oxygen saturation measurement systems take away some of this consideration, however, often by displaying averaged measurements. Filtering and averaging may improve reliability, but will almost inevitably slow down the response time [7-13]. Hence the measurements provided by these electronic measurements systems may not always result in the best treatment.

The targets for oxygen saturation, for example, are the normal values of older infants that did well and required little or no support [14]. An important question is: Should preterm infants reach the same targets and should they be expose to interventions to achieve them? Preterm infants have a less developed defense system against oxygen free radicals, less powerful perfusion, and likely different oxygen demands [1]. Should they receive higher fractions of oxygen in order to reach the same saturation? Or should it be e.g., slightly less as was the case in the mother's womb, reducing the amount of oxygen free radicals, but also reducing the amount of oxygen delivered to the cells? These are critical questions in determining the best oxygen treatment for preterm infants.

Measuring oxygen saturation

As said, oxygen therapy in preterm infants is mainly concerned with delivering of not more than the necessary amount of additional oxygen. Measuring cerebral oxygen saturation with near infrared spectroscopy (NIRS) can give an insight in the balance between oxygen delivery and usage. Measurements during the first 15 minutes after birth show that cerebral oxygenation can be extremely low in preterm infants, hinting towards a severe problem with either oxygen delivery or an extremely high oxygen usage [15, 16]. The first, an impairment of oxygen delivery, seems more likely and can be

treated by additional oxygen. However, it can also be that the problem is circulatory, for which current clinical practice offers only few solutions. In these cases, it still might be useful to use NIRS to get insight into the balance between oxygen delivery and consumption to fine tune the amount of oxygen given to preterm infant.

However, caution is needed when interpreting NIRS measurements. Studies have shown differences in outcome between the different techniques, different devices and different sensors [17-20]. There are methods developed to convert the measurement of one device and sensor combination to another, for instance when using a different device then the one used to develop a guideline. But these conversion methods are only validated in steady state situations [21]. How quick changes affect the measurements of the different techniques are less well known. During routine care on the NICU this is less of an issue, but during resuscitation this could be crucial when assessing therapy effectiveness.

Controlling oxygen saturation

Besides the uncertainties of the best oxygen saturation to aim for, there are also some uncertainties on how to control and adjust oxygen treatment. Clinical studies have shown that automated oxygen controllers are better than routine manual clinical adjustment in limiting the amount of time outside the defined target oxygen saturation range [22-27]. This usually comes at the cost of more frequent oxygen saturation dips, and many more fluctuations in the level of administered oxygen. Adequate gas exchange in the lungs is needed for these control schemes to work, because without the oxygen reaching the lungs, increasing the oxygen pressure up to high levels not necessary improves oxygen saturation. Most control systems rely on the assumption that ventilation is optimized, not taking into account the tradeoff between pressure, the resulting tidal volume and functional residual capacity, and the possible risk of lung tissue damage and amount of oxygen needed, and the risk of causing permanent organ damage due to oxygen free radicals due to high fractions of inspired oxygen (FiO2) [22, 24, 28].

Automated closed loop systems might be better than health care professionals in keeping the infant within a target range, because they are able to respond predictable and exactly the same, given the same circumstances [25]. Therefore, they are instrumental in research intended to find the optimal target range of oxygen saturation. Moreover, it is easier to find targets that are group or circumstance specific. However, without a direct and precise measurement of the oxygen needs and free radical exposure, large observational studies will still be needed to improve the ideal oxygen saturation targets [22]. Furthermore, in case the FiO_2 level is automatically controlled, it is not possible to find the optimal target for the individual patient without a measurement of the actual oxygen needs and potential damaging effect.

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The knowledge behind automated control systems are mostly hidden due to intellectual property protection [29]. This also holds for the algorithms that calculate saturation based on NIRS [17, 18]. To increase our understanding of when and how FiO_2 is titrated, it is desired that all these control schemes become part of public knowledge. Knowing the exact control mechanisms is not enough though. Still insight is required in the tradeoff between oxygen administration and delivery to the organs and hyperoxia, and damage caused by hypoxia.

Automated closed loop control of oxygen has yet to be proven during the resuscitation of neonates. In practice it should offer the same benefits as during routine clinical care on the neonatal intensive care unit (NICU). However, there is an increased risk of administering excessive FiO_2, due to poor respiratory support in the form of poor tidal volumes, due to high mask leaks, or due to potential circulatory/perfusion problems. These problems can potentially be solved by measuring the response to (a change in) the administered treatment, in the form of flow measurements or oxygen saturation changes. Although these checks might make oxygen delivery safer, they also make the system more complex, more prone to errors, and could also make the control system respond slower depending on how different parameters are measured and implemented. Where a stable setting could be assumed on the NICU, during resuscitation an unstable and dynamic situation must be assumed, and the control algorithm designed accordingly.

Challenges and goals

In order to improve oxygen therapy in the future, the technical solution for most of these problems seems to be to add more measurements, which is often the obvious answer of an engineer. However, preterm infants in general and the resuscitation period in particular put two restrains on adding more sensors. Preterm infants are very small, and their skin is fragile and during resuscitation sensor placement and signal acquisition must be quick, reliable and easy. Hence, just adding more measurements by itself is often not the best solution.

The goals of this PhD thesis are to improve oxygen treatment of preterm infants and to investigate the feasibility of new technology related to the measurement and control of oxygen.

Outline of the thesis

Chapter 2 provides an overview of the issues related to oxygen therapy, the methods to measure oxygen saturation and challenges that remain to be solved.

In **chapter 3** the resuscitation phase of very preterm infants after birth is observed to determine to what extent oxygen saturation levels are within the high and low limits of the European guidelines. **Chapter 4**, provides our findings on the cerebral hypoxia levels during resuscitation.

In **chapter 5** a fully automated closed loop control system for oxygenation saturation in initial mechanical ventilation directly after birth is presented. The control system was used in a study of preterm lambs to investigate the feasibility.

For oxygenation delivery to the cells the microvascular system plays a crucial role. It is unknown if the microcirculation of the fetus is different when pregnancy occur at high altitude (hypobaric hypoxia). In **chapter 6** the microvascular density of neonates born to mothers living at high altitude is investigated and compared to neonates born to mothers living at sea level.

Preterm infants have delicate and thin skin, making connection with sensors cumbersome. In **chapter 7** a new noncontact monitoring system of respiratory rate is presented using thermal imaging.

The thesis ends with a discussion and conclusion.

I

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2

Chapter 2

Optimizing oxygen therapy

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Oxygen therapy in preterm infants is mainly concerned with finding a balance between the need for additional oxygen and preventing damage due to oxygen free radicals [1]. But However, oxygen therapy is about more than providing additional oxygen. It also includes the transportation and delivery of the oxygen and in the end the extraction of oxygen fitting the tissue's needs should be the goal of the therapy.

Recent history of oxygen therapy and monitoring in neonatology

Pulse oximeter

Pulse oximetry was already invented in 1935 [2], but has gained popularity since the early nineties and is the golden standard for oxygen saturation measurement in NICU's. Because it also includes pulse rate measurement, in some NICU's it is the only continuous measurement performed on extreme preterm infants to ensure their wellbeing. Although pulse oximetry has many advantages, there are some pitfalls that should be acknowledged when using it. Although changes in the oxygen dissociation curve due to foetal haemoglobin, temperature and pH do not significantly affect SpO_2 measurements in one small study [3], it has been shown that ambient light and movement can cause inaccuracy in the measured oxygen saturation by pulse oximetry (SpO_2) [4]. To get reliable measurements pulse oximetry requires adequate perfusion and pulsation. Moreover, the measured saturation tells nothing about the quantity of the oxygen binding capacity, and we assume the measured SpO_2 is equal to the arterial oxygen saturation (SaO_2), which is not always the case [5].

Oxygen saturation targets

In practice, with the limitations of the pulse oximetry technique mentioned above, it is difficult to determine the perfect SpO_2 targets for preterm infants. Additionally, the difficulties of manual controlling the fraction of inspired oxygen (FiO_2) [6] and the variation in development of preterm infants, makes clear why large studies such as the SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial) [7], COT (Canadian Oxygen Trial) [8] and three BOOST II (Benefits of Oxygen Saturation Targeting) studies [9, 10] have failed to definitively determine the best target range (85%-89% or 91%-95%). The problems, such as inaccuracy of pulse oximetry, the adaption of the Masimo algorithm [11] and the difference between the prescribed targets versus actually achieved SpO_2 values [7] are summarised by Lakshminrusimha et al. [12]. The different trials leave us in doubt regarding the optimal oxygen saturation targets, and these doubts only increase when thinking about optimised targets based on gestational age (GA) and individual development [13, 14].

Resuscitation

100% vs room air

Multiple studies have made clear that resuscitating preterm neonates with 100% oxygen cause damage to the neonate [15-17]. Additional studies to find the optimal starting fraction have narrowed it down to somewhere between 30 and 60% for the extreme preterm infant [18, 19], and consensus has been reached that all infants past 28 weeks GA should be initially resuscitated with room air [20]. In the range between 30 and 60% also the specific conditions of the individual new-born starts to become a critical factor for the optimal concentration. The two studies performed in this area both speculate that a value between 30 and 40% is probably optimal in most cases, because this is the average FiO_2 for both groups cross [18]. However, lack of strong evidence and the fear of over administrating oxygen makes that a value between 21 and 30% is still the norm in most hospitals, as it is at Erasmus Medical Centre.

Titrating FiO_2 and oxygen targets during resuscitation

When resuscitation has commenced the FiO_2 is titrated against SpO_2 targets. The exact targets differ between different continents, but all are based on an observational study by Dawson et al. [21] describing the increase of SpO_2 in infants without the need of additional assistance. Obviously most of the infants included in this study are term born infants. Thus the question arises, how representative is their performance for what a(n extreme) preterm infant should achieve. The different resuscitation councils have picked different centiles to use as their targets. Most of them incorporate an upper and lower limit, giving an indication of the acceptable deviation that is accepted. But not all targets appear to be rational. The narrow section of the targets of the American Heart Association will prove to be a challenge to follow in practice. The European resuscitation guidelines contain single targets, with no clarification on if these are upper or lower limits, or what the acceptable deviation is. Working with the guidelines proves to be challenging but possible [22]. The targets of the Resuscitation Council of Australia and New Zealand are probably the most logical, with a broad range to start with, narrowing to the current upper and lower SpO_2 limits as seen in the NICU setting. A large international group of experts has since speculated on what would be the optimal SpO_2 target range, advising to use the 10th centile of Dawson et al. as the lower limit and the 50th centile as the upper [23]. The rational of this choice is that we accept that preterm infants doing a little worse than average, but that we want to keep them above the lowest 10 percent of what was found in term infants. There is, however, little to no evidence that these targets are the best for extreme preterm neonates.

Modern aids for monitoring oxygen therapy

Oxygen usage and need

The goal of oxygen therapy should be to ensure that sufficient oxygen is delivered to the tissue, without excess. In reality the saturation of the blood is continuously monitored while we know nothing about the actual quantity of oxygen that is delivered to the tissue and what the oxygen demand of that tissue actually is. More information is available in the form of blood test that provide information about the oxygen carrying capacity, and echocardiography can give a snap-shot of the cardiac output. But the holy grail remains a real-time continuous measurement of capacity, distribution, perfusion, flow, oxygen saturation and oxygen usage of tissue in multiple locations.

"New" techniques
NIRS

Near infra-red spectroscopy has been around since 1986 [24, 25], and is only recently been moving towards a clinical tool. Besides the many drawbacks of NIRS [26] there are two key features that make it interesting for optimizing oxygen therapy. Firstly it enables the continuous measurement of oxygen saturation of the brain, arguably the most important organ and secondly it gives an inside into the oxygen uptake by the tissue. Fractional Tissue Oxygen Extraction (FTOE) is calculated based on the difference between the SpO_2 and the regional cerebral oxygen saturation ($cSrO_2$), and indicates which percentage of the available oxygen is extracted by the tissue [27]. Initial results of the Safe Boost C trail indicate that it is a viable tool to check $cSrO_2$, and that it is possible to control those saturations [28, 29]. Measurements preformed during the transition from the foetal to neonatal situation immediately after birth show that extreme preterm infants have extremely low $cSrO_2$ values during the first minutes of life, while SpO2 values rose normally due to respiratory support and supplemental oxygen therapy [30]. This could indicate that there is a cardiac output or distribution problem in extreme preterm infants at birth.

Cardio circulatory monitoring

Although monitoring of the cardiac output is challenging [31], electrical cardiometry could be the solution for continous measurement. Trials are conducted with the Aesculon (Osypka Medical GmbH, Berlin, Germany) system, a non-invasive tool, showing promising results [32].

Microcirculation

Besides the brain another obvious important organ is the skin, the largest organ. There are strong indications that the microcirculation in the skin is the first to deteriorate in case of sepsis [33], and monitoring the perfusion would be of great help for fluid therapy [34]. The latest generation of microcirculation cameras using Incident Dark Field (IDF), such as the CytoCam (Braedius Medical B.V., Huizen, The Netherlands) enables (semi) quantitive evaluation of the microcirculation, but lack the ability to perform continuous monitoring. Devices based on Laser Doppler Flow measurements (LDF), such as the O2C (LEA Medizintechnik GmbH, Giessen, Germany), do allow for such continuous measurement, of both blood volume and flow in superficial tissue. Obvious drawbacks are the very localised and superficial measurement, and the assumption that the measured SpO_2 is representative of the SaO_2. But it does give an insight into the changes of both perfusion and oxygen consumption.

Advice

A more ***systematic and personalised approach to oxygen therapy*** is needed. By combining all the modern non-invasive tools with models and modern control techniques it should be possible to gain new insights in to the oxygen needs of individual patients, control the ventilation and FiO_2 based on multi input models and ensure that the targets that are prescribed are actually met. The inclusion of the area under the curve in oxygen saturation assessment instead of just number the number of incidence will give a better insight into the severity of the patient's condition [35]. Additionally analysis software and prediction models can aid with decision support by highlighting slow trends over longer periods of time and changes in the frequency domain that are hard to spot without these supporting systems.

Closed loop control

A technological innovation that can tie the new measurement techniques together is closed loop control. The ability to process multiple measurements, asses them and draw conclusions from them is a time consuming and tricky task. On a NICU there is lack of time and manpower to perform these tasks optimally. Modern control systems are however, perfectly capable of titrating the FiO_2 based on input parameters and guidelines that exist now [36-38]. Although a human controller might incorporate several individual characteristics better, automatic controllers are faster, more precise, and will free up the staff to perform other vital tasks. Till then it is important that the new measurement techniques are used, to gain expertise and familiarise with the drawbacks and pitfalls, and collect normative data.

Conclusion

Although large improvements in the administration of oxygen have been made, we are still far from giving the perfect oxygen therapy. New techniques have moved us to less invasive techniques, increasing comfort for the infants. And the insights that the studies have given have resulted in an improvement in the precision with which oxygen is administrated. The next step is to combine the current with the new techniques and use the combined data for the next step in oxygen therapy. However, the real challenge will be to personalize oxygen therapy, and automatically balance the individual oxygen need with his or her resistance to oxygen free radicals.

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Chapter 3

Observing the resuscitation of very preterm infants: Are we able to follow the oxygen saturation targets?

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Abstract

Background: Since 2010, the European Resuscitation Council (ERC) guidelines advise oxygen saturation (SpO_2) targets for the first 10 minutes of resuscitation after birth. Unfortunately, the control of SpO_2 in newborn infants is difficult.

Aim: To determine to what extent SpO_2 levels match the ERC targets during the resuscitation of very preterm infants, and how well the SpO_2 is kept within the high and low limits until the infants are transported to the NICU.

Methods: In a single-centre observational study, the SpO_2 and fraction of inspired oxygen (FiO_2) were collected during the resuscitation of very preterm infants with a gestational age (GA) ≤ 30 weeks.

Results: A total of 78 infants were included [median (IQR): GA $27^4/_7$ ($26-28^6/_7$) weeks, birth weight 945g (780-1140)]. During the initial 10 minutes after birth, large variations in SpO_2 were observed with deviations above the target [median (IQR)] of 4.4% SpO_2 (1.4-6.5), and below the target of 8.2% SpO_2 (2.8-16.0). After the first 10 minutes, the SpO_2 levels were respectively above and below the limit for 11% (0-27) and 8% (0-23) of the time.

Conclusion: During the resuscitation of very preterm infants, large deviations of the SpO_2 from the ERC targets are observed. During the first minutes of resuscitation the deviations were likely caused by an inability to control the SpO_2, whereas later deviations were due to weaning, pauses in respiratory support (i.e. intubation) and over exposure to oxygen. Changing the SpO_2 targets to a target range that depicts the acceptable deviation might be helpful in providing better respiratory support.

Introduction

During resuscitation of preterm infants, supplemental oxygen therapy is often used to reach and maintain adequate oxygenation. Adequate oxygenation is essential in preterm infants because both hypoxia and hyperoxia can have detrimental effects on the organs, and even fluctuations in oxygenation can be damaging.[1-3] The damage to the organs is caused by the formation of excessive oxygen free radicals.[4] The compromised anti-oxidative capacity of preterm infants and the need for a certain level of oxidative stress to initiate the adaptation from intra to extra uterine life make the control of oxygenation a delicate balance.[5]

To prevent negative outcomes due to under- or overexposure to oxygen in newborn infants, the European Resuscitation Council (ERC),[6] American Heart Association (AHA)[7] and Australian and New Zealand Resuscitation Council (ARC NZRC)[8] guidelines advise pulse oximetry oxygen saturation (SpO_2) targets for the first 10 minutes after birth. These targets are based on observational studies of healthy term and preterm infants not needing any intervention during their resuscitation.[9] To reach and maintain these SpO_2 targets, the fraction of inspired oxygen (FiO_2) is titrated manually according to the SpO_2 measurement. Unfortunately, none of the resuscitation guidelines specify how the FiO_2 should be titrated to make sure SpO_2 targets are reached.

Literature shows that manual control of the SpO_2 is difficult, reporting time spent outside the target range of approximately 50% in neonatal intensive care units (NICU).[10-13] Although the status of the infants and the tasks of the physicians in NICUs differ from that during resuscitations immediately after birth, it is likely that during DR resuscitation it is difficult for clinicians to keep SpO_2 within the recommended target range. It is unknown to what extent the SpO_2 targets are achieved. Therefore, the aim of this study was to determine to what extent SpO_2 levels matched ERC targets during the resuscitation immediately after birth of very preterm infants.

Materials and methods

An observational study was performed at the Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, the Netherlands, a level-III-c NICU with 33 beds.[14] The medical ethics committee of the Erasmus Medical Centre approved this study (ASM/hl/135583), and decided that informed consent was not needed because no interventions were imposed and no personal data was processed. Because of the observational nature of this study, there was no possibility to determine a sample size.

Subjects
Patients born with a GA ≤ 30 weeks in the study centre were eligible for inclusion in this study. Congenital or chromosomal defects were exclusion criteria.

Local resuscitation protocol
The ERC guidelines were introduced 7 months prior to the start of this study. They were discussed amongst the staff prior to being adapted as the local resuscitation protocol, and are part of the education of resident physicians. A reminder of the SpO_2 targets was available in all resuscitation areas, together with a Dutch translation of the ERC 'Newborn life support algorithm'.[15]

According to the local protocol, preterm infants were transferred to the resuscitation unit immediately after delivery, where at least 2 clinicians start to stabilise the infant. Resuscitation of infants < 26 weeks GA are performed by a neonatologist or neonatal fellow. Measures were taken to prevent heat loss. Respiratory support was given, primarily with a T-piece resuscitator (Neopuff, Fisher & Paykel Healthcare, Auckland, New Zealand). A flow-inflating bag with pressure monitoring (Jackson Reese modification T-piece breathing system, Intersurgical, Wokingham, UK) was also available and could be used according to the physician's preferences. Contrary to the advice of the ERC guidelines to start all resuscitations with room air, local protocol advises to start resuscitation of infants with a GA ≤ 28 weeks with an FiO_2 of 0.30 (based on publications by Escrig et al., Vento et al. and Saugstad et al.[16-18]). Furthermore, FiO_2 should not be adjusted before an SpO_2 measurement is obtained, unless the heart rate, obtained from auscultation, drops below 100 beats per minute (bpm).[6] A pulse oximeter sensor (Nellcor OxiMax Max-N, Covidien, CO, USA) was placed on the right hand or wrist to measure preductal SpO_2.[19]

During the first 10 minutes after birth, the SpO_2 targets from the ERC guidelines were advised, i.e. 60%, 70%, 80%, 85%, and 90% at 2, 3, 4, 5, and 10 minutes after birth, respectively (Fig. 1A). From the 10th minute onwards, the target range of the

study centre's NICU were prescribed (85-93% SpO_2).[20] When respiration was absent or insufficient, ventilation was initiated with sustained inflations, i.e. 5 inflations of 3 seconds, after which respiratory support could be optimised by adjusting the positive end expiratory pressure (PEEP) and/or peak inspiratory pressure (PIP) (initially set to 5 and 20 cmH_2O respectively). When respiration of the infants remained insufficient or if the infants remained hypoxic, endotracheal intubation was performed.

Outcome parameters

The primary outcome was the deviation of SpO_2 from a trend line drawn through the ERC targets and, after the 10th minute, the target range for SpO_2. Deviation from the target was assessed by the time spent above and below the target and by calculating the average absolute deviation per infant.

$$average\ absolute\ deviation = \left(\frac{\Sigma_{measurements\ outside\ range} |\text{target } SpO_2 - \text{measured } SpO_2|}{number\ of\ measurements\ outside\ range} \right)$$

The deviation above the target was corrected for those moments when the SpO_2 was above the target while the infant was on room air (FiO_2 0.21). The secondary outcomes were the time to obtain SpO_2 measurement, total resuscitation time, administered FiO_2, and number of intubation attempts.

Data collection

Measurements were obtained from the pulse oximeter (Nellcor N-600x, Covidien, CO, USA) and recorded with a frequency of 0.5 Hz from the first measurement until the infant was disconnected for transfer to the transport incubator. The FiO_2 was obtained (1 Hz) through an oxygen monitor (MX300, Teledyne Technologies, City of Industry, USA) that was connected to an oxygen sensor (M-15 STD, IT Dr. Gambert GmbH, Wismar, Germany) in the blender's bleed port (Bird Ultrablender, Cardinal Health, Dublin, USA) . The time of birth was defined as the moment at which the APGAR timer was started. When the APGAR timer was not started, a time of 30 seconds prior to the infant being placed on the resuscitation unit was taken as the time of birth. In the 67 infants where the APGAR timer was started at birth it took a median (IQR) 30 (21-36) seconds for infants to be placed on the resuscitation unit. Data acquisition was performed on dedicated research computers, continuously running software specially written for this study (programmed in Labview 2011, National Instruments, Austin, USA).

Results

Seventy-eight infants were included during an 8-month period (see Table 1 for patient characteristics). The results are presented as median (IQR) unless stated otherwise. Of the 142 eligible infants, 42 were excluded [GA $27^3/_7$ ($25^4/_7$-$28^4/_7$) weeks, birth weight 870g (763-1050)] because they were included in one of two (interventional) studies that conflicted with the initial adjustment of the FiO_2.[21] The data of 21 patients [GA $27^4/_7$ ($26^3/_7$-$28^4/_7$) weeks, birth weight 955g (828-1186)] could not be used for analysis due to failure of the data acquisition. The failures of the data acquisition were purely technical; related to connections between the medical devises, the software, or the computer failing, which resulted in the data not being recorded. One infant was retrospectively excluded due to a congenital defect. There was a failure to start the APGAR timer in 11 cases (14%).

Table 1: Patient characteristics

Patients (N)	male: female	41 : 37
GA (weeks)		$27^4/_7$ (26-$28^6/_7$)
GA ≤28 weeks (N)		51
Birth weight (g)		945 (780-1140)
Mode of delivery (N)	vaginal : CS	33 : 45
Reason for elected preterm delivery	maternal : fetal	11 : 31
Received full course of corticosteroids (N)		43
Cord blood (arterial)	pH	7.31 (7.05-7.48)
	BE (mmol/l)	-2.4 (-4.0--1.4)
APGAR score at 5 min after birth		8 (7-9)

Data represented as number (N) or median (IQR). CS = caesarean section, GA = gestational age.

Deviation from the SpO_2 targets

During the first 10 minutes after birth, the time spent above [44% (12-66)] and below [51% (27-82)] the intended SpO_2 target was similarly distributed (Table 2), with an median deviation from the target of 8.2% SpO_2 (2.8-16.0). After the first 10 minutes, until the infant left the resuscitation area, 32% (14-46) of the time was spent outside of the NICU limits. The measured SpO_2 is plotted together with the ERC targets for SpO_2 and the NICU limits in Fig. 1A. Fig. 1 also shows the measured pulse rate (Fig. 1B), administered FiO_2 (Fig. 1C), and the number of infants that were on the resuscitation unit at that specific time after birth and contributed data (Fig. 1D) (a more detailed view of the SpO_2 during the first 10 minutes of the resuscitations can be seen in Fig. 3). There were 21 large drops in the SpO_2 (<60%), which were all the result of intubation attempts. In 41 infants (53%), the SpO_2 was at some point above the target, while the

FiO$_2$ was 0.21, for which the deviation was corrected. During the first 10 minutes after birth, this correction occurred for a total of 9% of the time (67 min) and for 3% of the time (64 min) during the remainder of the resuscitations. Only 6 infants (8%)remained inside the limits after the first 10 minutes.

Table 2: Primary results

SpO$_2$ deviation during the first 10 minutes after birth	
Time above ERC target (%)	44 (12-66)
Time below ERC target (%)	51 (27-82)
Average deviation above ECR target (% SpO$_2$)	4.4 (1.4-6.5)
Average deviation below ECR target (% SpO$_2$)	8.2 (2.8-16.0)
Average deviation (% SpO$_2$)	7.8 (5.8-12.5)
SpO$_2$ deviation after the first 10 minutes after birth	
Time above NICU limit (%)	11 (0-27)
Time below NICU limit (%)	8 (0-23)
Time outside NICU limit (%)	32 (14-46)
Average deviation above NICU limit (% SpO$_2$)	1.7 (0.3-2.5)
Average deviation below NICU limit (% SpO$_2$)	2.0 (0.0-5.1)
Average deviation (% SpO$_2$)	2.6 (1.3-4.5)
SpO$_2$ deviation during the entire resuscitation	
Total time above target (%)	25 (11-40)
Total time below target (%)	26 (14-39)
Average deviation above target (% SpO$_2$)	3.5 (2.4-5.4)
Average deviation below target (% SpO$_2$)	7.3 (3.2-13.3)
Average deviation (% SpO$_2$)	6.6 (4.6-9.6)
FiO$_2$ adjustments	
Number of adjustments (N)	7 (3-10)
Average FiO$_2$ (%)	33.5 (26.8-44.9)
Min FiO$_2$ (%)	21.0 (20.5-22.4)
Max FiO$_2$ (%)	59.0 (36.9-99.3)
FiO$_2$ at the end of resuscitation (%)	26.2 (22.2-33.0)

Data represented as median (IQR). ERC = European Resuscitation Council, FiO$_2$ = fraction of inspired oxygen, NICU = neonatal intensive care unit, SpO$_2$ = oxygen saturation.
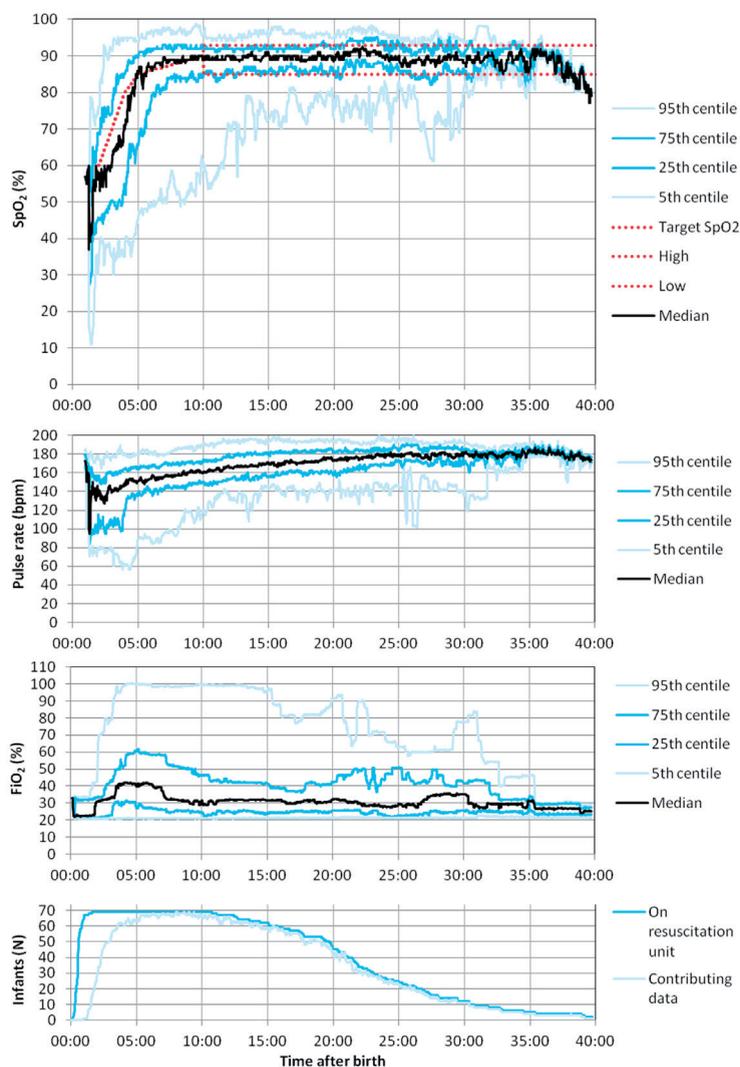
Fig. 1: Measured oxygen saturation (SpO$_2$) and fraction of inspired oxygen (FiO$_2$) during the resuscitation of preterm infants (N=78). (A) Median, 5th, 25th, 75th and 95th percentile of the SpO$_2$ measured during resuscitation, plotted together with the European Resuscitation Council (ERC), and high and low SpO$_2$ targets, as used at the Erasmus Medical Centre (Rotterdam, the Netherlands). (B) Median, 5th, 25th, 75th and 95th percentile of the measured pulse rate. (C) Median, 5th, 25th, 75th and 95th percentile of the FiO$_2$ administered during the resuscitation. (D) Number of infants that were on the resuscitation unit at specific times after birth, and number of infants that were contributing to the data set.

Secondary outcomes

The infants spent 22:24 (19:08-28:01) minutes on the resuscitation unit. The interval between the moment that the infant was placed on the resuscitation unit and the first

SpO_2 measurement was 1:29 (1:15-2:16) minutes. In 67 resuscitations (86%), the SpO_2 sensor was positioned on the extremity of the infant before the connector of the sensor was plugged into the monitor, which is the quickest method for obtaining an accurate measurement.[22] At the moment of the first ERC target (2 minutes after birth), the measurements from 33 infants were obtained (42%).

For infants with GA ≤ 28 weeks, the initial FiO_2 was 0.30 in 29 cases (57%), in one case it was set to 0.40, in the other cases room air was used. In one case the FiO_2 was corrected to 0.30 almost immediately. Two infants with a GA > 28 weeks (8%) received an initial FiO_2 of 0.30. The FiO_2 was increased before there was an SpO_2 measurement in 16 cases. In 9 of these 16 cases (56%), we could confirm that it was because of a low heart rate. When leaving the resuscitation area, the median FiO_2 of all infants was 26.2% (22.2-33.0). When an infant needed to be intubated (N=28, 36%), 2 (1-2) attempts were needed to do so successfully. Thirty-two infants (41%) left the resuscitation area with a nasal cannula, the others with mask ventilation (N=18, 23%).

Discussion

This study determined to what extent SpO_2 levels matched the ERC targets during the resuscitation of preterm infants in daily practice. While the median of the observed infants followed the ERC targets quite nicely, it did deviate below the targets during the first 5 minutes after birth. Overall the variation in the SpO_2 was large. The average deviation from the targets was 6.6% SpO_2 (4.6-9.6), whereas the deviation more than doubled in the worst cases (95th centile 19.3% SpO_2) (Fig. 1A and Fig. 3).
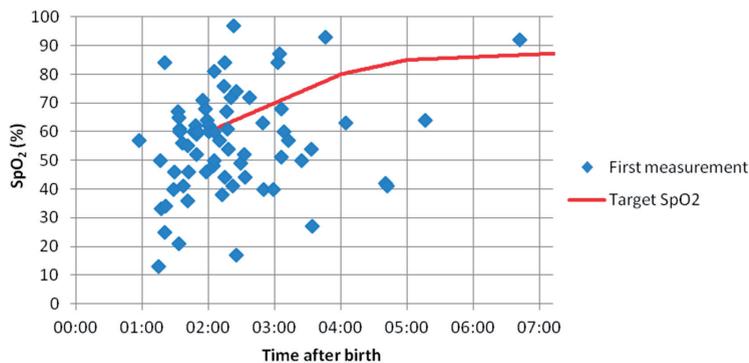
Fig. 2: First oxygen saturation measurement (SpO_2) of the resuscitated infants (N=78) at the time after birth the SpO_2 measurement was obtained.

There are several possible explanations for the large deviations during the first few minutes after birth. First, in some infants, the first SpO_2 measurement took longer to obtain (Fig. 2), which is most likely caused by poor perfusion, or problems with sensor placement.[23, 24] A longer time to obtain an SpO_2 measurement will increase the time until control over the SpO_2 is achieved, because the FiO_2 is not adjusted without an SpO_2 measurement unless the heart rate is below 100 bpm. Such a delay could cause a further deviation from the SpO_2 targets. Second, during the initial phase of resuscitation, ventilation of preterm infants is hampered by lung immaturity, resulting in inappropriate aeration of the lung, i.e. establishing functional residual capacity.[25] Other explanations for suboptimal ventilation could be mask leaks or airway obstructions.[26, 27]

The median of the administered FiO_2 rose sharply on two occasions, before 2 and shortly after 3 minutes after birth. The first rise is likely due to the initial assessment of the infant, the second rise because the SpO_2 measurement became available. Between 4 and 5 minutes after birth the median of the SpO_2 rose to follow the targets more closely and a reduction of the variation in pulse rate was observed. These combined results of respiratory support, improved lung recruitment and perfusion, indicates that in most infants control adequate respiratory support was obtained at this point.[27]

After the first 10 minutes, 32% (14-46) of the time was spent outside the SpO_2 limits. On average 36% (31-47) of the infants were outside the SpO_2 limits at any given time. Thus, even with adequate respiratory support, remaining between the high and low SpO_2 levels was challenging. Instability in the oxygenation was caused by, for example, a temporary halt in the respiratory support (i.e., tube placement or suctioning) but can also be caused by incomplete adaptation.[28] The time spent above the intended range was the result of the administration of a too high FiO_2 and could have been avoided by reducing the FiO_2. However, determining by how much the FiO_2 should be reduced is one of the major challenges in controlling the SpO_2, and the fear of low SpO_2 values might deter physicians from making rapid adjustments.

The APGAR time was not started in 14% of the resuscitations, indicating that the staff is not always fully focused on starting the timer. The not starting of the timer will make the following of the SpO_2 targets more difficult, because an exact time after birth is not readily available to the physicals. Compliance with the local protocol to start resuscitation of infants ≤28 weeks GA with a FiO_2 of 30% was low (57%).

The ERC guidelines prescribe single value SpO_2 targets, while the AHA and ARC guidelines advise a narrow SpO_2 target range.[7, 8] A target range provides physicians with information on what is considered to be an acceptable deviation, and could actually

reduce the observed variation. A group of experts on the resuscitation of preterm infants has suggested using the 10th and 50th centile of the study of Dawson et al.[9] (the same study as which the current guidelines are based on), as the SpO_2 target range, which is an significantly lower low target than the other SpO_2 targets (Fig. 3).[29]

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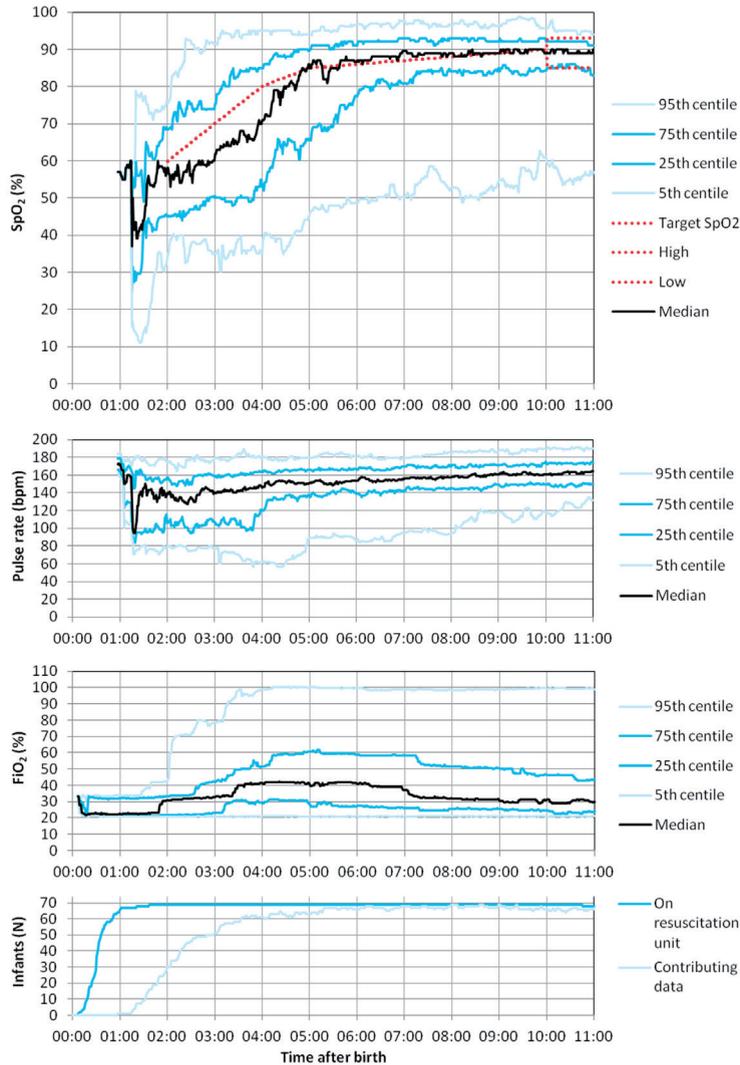
Fig. 3: Comparison of the median, 5th, 25th, 75th and 95th percentile of the oxygen saturation (SpO_2) measured during the first 10 minutes of resuscitation of preterm infants (N=78), to the median, 10th, 25th, 75th and 90th centile of preterm infants (<32 weeks gestational age, N=32) that did not receive any medical intervention after birth as observed by Dawson et al.[9] The number of infants on the resuscitation unit and the number that was contributing data can be found in fig. 3D.

When our results are compared to the observations of Dawson et al. of preterm infants (<32 weeks GA, N=39) who did not require medical intervention after birth, it seems likely that most infants were in a safe range with their SpO_2 values (Fig. 3).[9] However during the first 6 minutes after birth more than 25% of the observed infants had SpO_2 values that were below the 10th centile. Whether single value SpO_2 targets or target ranges result in more accurate control of the SpO_2 during routine clinical resuscitations needs to be determined. Furthermore, it remains unknown which SpO_2 targets, or target range provide the best compromise between exposure to oxygen and avoiding hypoxia. To determine the effects of the SpO_2 targets, long-term (follow up) studies are needed. However, to study the effects of different SpO_2 targets, current clinical practice must be able to control the SpO_2 adequately, and follow the targets with as little deviation as possible.

There are a few drawbacks to this study. Compliance with local protocol to start resuscitation of infants >28weeks GA was low (57%). It was performed in a single centre and it is unclear to what extent the results are representative of other centres. Patients stayed within the NICU limits 68% (54-86) of the time, which is similar to the results of studies with dedicated clinicians adjusting the FiO_2 in the NICU.[10, 11, 30]

Other new technological developments may help improve SpO_2 control. Providing the physician with constant feedback on deviations from the target SpO_2 could improve performance during resuscitation. With the improvement of pulse oximeters, which can provide measurements even when the infant has poor perfusion, comes a need to better understand how perfusion influences tissue oxygenation and how it changes after birth. But it will remain important to not overload the physician with information and devises to look at, as this takes the focus away from the infant. Closed loop SpO_2 control is available for use in a NICU setting (CliO$_2$, CareFusion, San Diego, USA).[31] Similar technology might be beneficial during resuscitation, as it would keep the physician free to focus on the infant, instead of fine-tuning the equipment.

Conclusions

In conclusion, in our institution, the SpO_2 targets were not always followed accurately during the initial minutes after birth. At the start of resuscitation, deviations were most likely caused by an inability to control the SpO_2, i.e., no lung aeration and/or no initial SpO_2 measurement, resulting in low SpO_2 values. Whereas after the infants were stabilised, the deviations were due to weaning, pauses in respiratory support (i.e., intubation), and/or overexposure to oxygen. The ERC advise acceptable SpO_2 targets, which leaves it to the individual physician to decide how much deviation is acceptable.

By changing the SpO_2 targets to a target range that depicts the acceptable deviation the targets could aid physicians in providing better respiratory support, and possibly reduce variation.

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3

Chapter 4

Cerebral hypoxia during the postnatal transition of very preterm infants directly after delivery by caesarean section.

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Reference ranges for regional cerebral tissue oxygen saturation ($crSO_2$) reported by Pichler et al. are an important step towards implementation of crSO2 monitoring during resuscitations.[1] At the Erasmus Medical Centre, Rotterdam, we found a surprising crSO2 observation in very preterm infants.

The first ten included infants ($26^4/_7$ weeks ($26^3/_7$-$27^1/_4$), birth weight 910g (705-960g)) had very low initial $crSO_2$ (15% (15-15%) (median (IQR))). Figure 1 shows the observed values in relation to the centiles published by Pichler et al.[1] Infants were resuscitated according to local guidelines, based upon European Resuscitation Council guidelines.[2] Arterial oxygen saturation (SpO_2) was measured with a Nellcor N600-x pulseoximeter, while $crSO_2$ was measured with an Invos 5100C (Covidien). During resuscitation SpO_2 and Apgar scores were similar to prior observations at our institution.[2] Infants left the resuscitation area with $crSO_2$ of 59% (47-64%).

The only other published observation of the $crSO_2$ in very preterm infants is by Fuchs et al. in infants <1500g.[3] They reported a median saturations of 37% (31-49%) at one minute after birth, but reported problems with the detection of $crSO_2$ in the more preterm infants.[3] The difference in ability to measure very preterm infants might be due to the Fore-sight (Casmed) that was used.

Preterm infants born before 28 weeks of gestation have about a 25% risk of surviving with a severe neurodevelopmental deficit.[4] Possible contributing factors are fluctuating cerebral blood flow during transitional in the first days of life, and misbalances between oxygen administration, use and need.[5] Two possible explanations for the observed $crSO_2$ could be the different adaptation of the circulation and perfusion of very preterm born infants, with low cardiac output, or specifically a difference in perfusion and/or activity in the frontal lobe. It is possible the observed low $crSO_2$'s is contributing to neurodevelopmental deficits observed in preterm before 28 weeks.
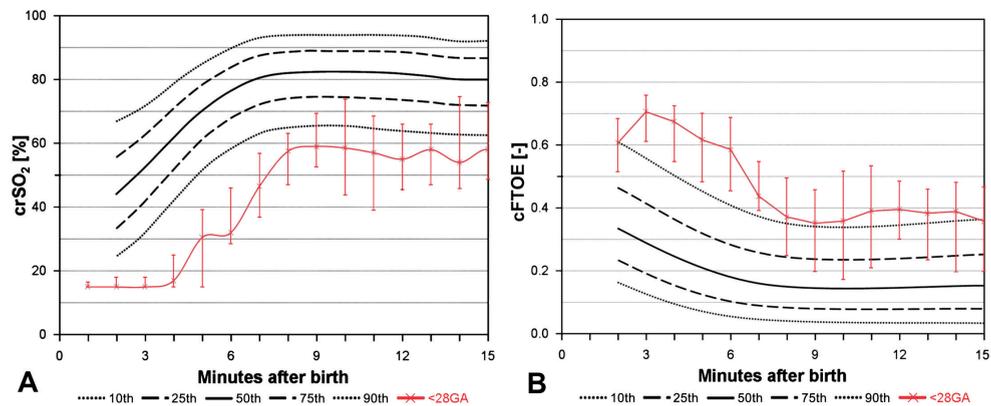
Figure1. crSo2 (A) and FTOE (B) of infants <28 weeks GA (median, IQR) compared to the preterm infants that required no medical support after birth (GA 34.9±1.4 weeks, 10th, 25th, 50th, 75th, and 90th percentiles) as published by Pichler et al.[1]

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Chapter 5

Fully automated predictive intelligent
control of oxygenation (PRICO)
in resuscitation and ventilation of
preterm lambs

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Abstract

Background: Hyperoxia and hypoxia influence morbidity and mortality of preterm infants. Therefore oxygen supplementation during resuscitation and ventilation of preterm infants has to be controlled within narrow saturation (SpO_2) targets. Automated closed-loop control of the fraction of inspired oxygen (FiO_2) has been shown to facilitate this difficult task in the NICU.

Hypothesis: We hypothesized that fully automated FiO_2 control based on predefined SpO_2 targets is applicable in both resuscitation and ventilation of preterm infants.

Study design: Twenty-two preterm lambs were operatively delivered and intubated in a modified EXIT procedure. They were randomized to receive standardized resuscitation with either automated or manual FiO_2 control, targeting SpO_2 according to the Dawson curve in the first 10 minutes and SpO_2 90-95% hereafter. Starting FiO_2 was either 0.3 or 0.6. Automated FiO_2 control was applied during surfactant replacement therapy and subsequent ventilation for 3 hours.

Results: Time within target range did not differ significantly between manual and automated FiO_2 control during resuscitation, however automated FiO_2 control significantly avoided hyperoxia. Automated FiO_2 control was feasible during surfactant replacement and kept SpO_2 within target range significantly better than manual control during subsequent ventilation.

Comment: In our model, fully automated FiO_2 control was applicable in rapidly changing physiologic conditions during postnatal resuscitation and surfactant replacement therapy and in stable conditions during subsequent ventilation. Although oxygenation in the first minutes of life is influenced by a multitude of parameters which need to be managed by experienced personnel, automated FiO_2 control might support preterm resuscitation.

Introduction

Oxygen supplementation is one of the most common therapeutic interventions in resuscitation and neonatal intensive care of term and preterm infants.[1] However, both hypoxia and hyperoxia must be avoided because of their detrimental effects on morbidity and mortality in these children. While hypoxia may lead to direct and indirect cellular damage, hyperoxia has been associated with oxygen toxicity, oxidative stress,[2] and chronic diseases of preterm infants such as bronchopulmonary dysplasia (BPD)[3] and retinopathy of prematurity (ROP).[4]

Increase in oxygenation after birth is a gradual process.[5] Measurement of oxygen saturation (SpO_2) by pulse oximetry in the delivery room is feasible in newborn resuscitation[6] and preterm infants within the first minutes of life.[7] SpO_2 reference values of preterm infants increase within the first 10 minutes of life.[5] This has led to SpO_2 target values incorporated in the current European Resuscitation Council (ERC) guidelines on resuscitation of newborns.[8] In order to avoid hyperoxia, current recommendations advice resuscitation of preterm infants with a mixture of air and oxygen, and to use fraction of inspired oxygen (FiO_2) between 0.21 and 0.30.[9] FiO_2 should subsequently be titrated according to SpO_2.[10,11] General use of pulse oximetry has been shown to extensively reduce O_2-derived toxicity in preterm infants.[12] However, keeping SpO_2 manually within changing saturation limits during a hectic period of resuscitation is a difficult task. Large deviations from SpO_2 targets during resuscitation of preterm infants have been observed in clinical studies.[13]

These deviations have also been described during routine NICU care, where SpO_2 target ranges are met during 50% of the time.[14,15] Meeting SpO_2 targets affects morbidity and mortality, depending on the target range chosen.[16,17,18] Besides overall SpO_2 targets, variability of oxygenation influences outcome of preterm infants.[4,19, 20] A promising solution to optimize oxygen therapy is the employment of an automatic „closed loop" system for regulation of FiO_2 based on SpO_2. Several clinical trials with different devices have proven feasibility of automated closed loop FiO_2 control in the NICU for various modes of ventilation, mixed populations, and by using different algorithms.[14,21,22,23,24,25,26] In addition, an overall reduction of manual interventions during automated control was found in these studies, indicating facilitation of caretakers and nursing staff in clinical routine.[27,28] However, at least one study raised concerns about safety, as time within target range was accompanied by an increase in time spent below target range.[25]

Automated FiO_2 control has not yet been tested in a delivery room setting.[28] We hypothesized that an algorithm developed for automated FiO_2 control during mechanical

ventilation is feasible in the delivery room setting with rapidly changing physiology of fetal transition to extra-uterine life and during surfactant replacement therapy. We further hypothesized that fully automated FiO_2 control conducted by this algorithm would keep SpO_2 within a predefined target range as good as a dedicated caretaker during stable ventilation conditions. We tested our hypotheses in an established lamb model of preterm respiratory distress syndrome (RDS).

Materials and methods

Experimental setup

An infant ventilator (Fabian HFO®, Acutronic, Hirzel, Switzerland) was prepared for digital control of the FiO_2. SpO_2 measurement was obtained via a Masimo pulse oximeter (Radical 7®, Masimo Inc., Irvine, CA). Both devices were linked to a laptop computer (Lenovo Thinkpad T500 with Microsoft® Windows 7®), containing control software with a user interface showing SpO_2, FiO_2, pulse and SpO_2 target ranges over time.[29] The algorithm used was a rule based control scheme that used both the current SpO_2 together with the trend in the SpO_2 measurement (Figure 1). The trend was used to fine tune the FiO_2 step size by recognizing larger and quicker changes. A prediction based on the trend was used to limit under- and overshoot. Different safety criteria were in place to ensure proper ventilation and reliable input before an automated adjustment was made. After each adjustment a 30 s time out followed to allow the effect of the adjustment to be observed.

Animal study

The lamb model of neonatal RDS allowed us a translational approach due to its physiologic similarities of lung development in humans.[30,31] Furthermore, anatomy and body size allowed us the use of the original equipment used in the neonatal intensive care units. The study design and the experimental protocol were in line with the institutional guidelines for animal experiments and were approved by the institutional Animal Ethics Research Committee, Maastricht University, The Netherlands.

One day before caesarean section, 22 date-mated ewes received an intra-muscular injection with betamethasone (12 mg, Celestone Chronodose®, Schering-Plough, North Ryde, New South Wales, Australia) to induce fetal lung maturation.[32] Before delivery, lambs were randomly assigned to four different treatment groups for resuscitation ("resuscitation") and independently for two different treatment groups for subsequent stable ventilation ("comparison"). This setup allowed us to separately analyse the algorithm during rapidly changing and stable conditions (Figure 2).
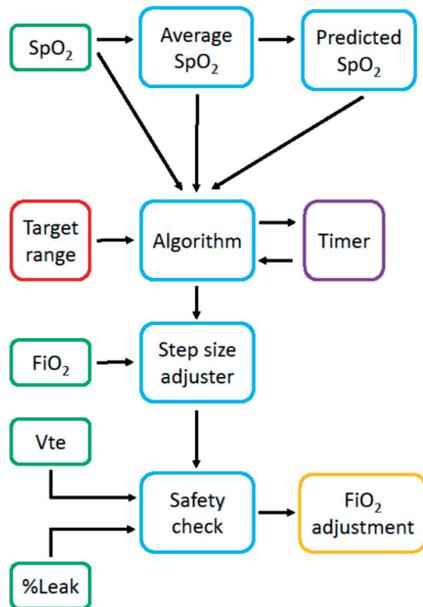
Figure 1: Flow scheme of algorithm
Green boxes indicate measured parameters, blue indicates software components, red indicates predefined
settings, yellow indicates output, violet indicates timer.
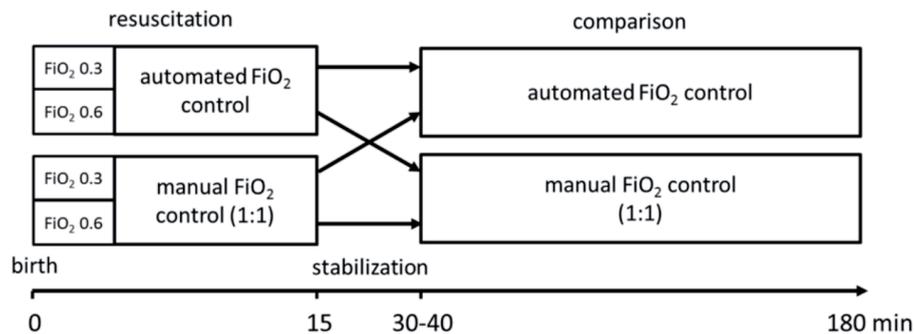
Figure 2: Experimental time line

Resuscitation

Lambs were operatively delivered prematurely at a gestational age of 128-132 days
(term ~150 d) via a modified EXIT procedure, equipped with umbilical artery and
vein catheters and intubated orally.[33] The arterial catheter was used to monitor heart
rate and blood pressure, and to frequently obtain blood for blood gas analysis. After
cord clamping, lambs were weighed, sedated and transferred to an infant radiator bed
(IW930 Series CosyCot™ Infant Warmer, Fisher & Paykel Healthcare, Auckland, New

Zealand). An adhesive pulse oximeter sensor (M-LNCS Neo™, MasimoSET®, Masimo Inc., Irvine, CA) was placed around the tongue and subsequently connected to the pulse oximeter. Resuscitation in the first 15 minutes was standardized to the greatest possible extend. This was achieved by connecting lambs to an infant ventilator set to volume-controlled mechanical ventilation (volume guarantee 6-7 ml/kg, max. PIP 45 cmH$_2$O, frequency 50/min). FiO$_2$ at start of resuscitation was randomized to either 0.3 or 0.6. FiO$_2$ was adjusted to keep the lamb within the 25th and 75th percentile of saturation in preterm infants according to Dawson[5] for the first ten minutes and subsequently between 90% and 95%. FiO$_2$ was either controlled by the algorithm alone, without manual interventions allowed, or by a caretaker with no other task than FiO$_2$ adjustment. Outcome parameters for the resuscitation part were time within, above and below target range, number of events outside the target range, and total number of FiO$_2$ adjustments.

Stabilization and surfactant replacement therapy

Resuscitation was followed by a short stabilization period. Animals which needed a fraction of inspired oxygen (FiO$_2$) above 0.8 at any time during resuscitation or stabilization were eligible to receive surfactant replacement therapy with Poractant alfa (Curosurf® 100mg/kg, Chiesi, Parma, Italy). Lambs were considered to be stabilized after 30 minutes, or if they received surfactant, 15 minutes after surfactant replacement therapy. We recorded SpO$_2$ and FiO$_2$ before and after surfactant replacement therapy.

Stable ventilation

After stabilization, stabilized lambs were mechanically ventilated with either automated or manual FiO$_2$ control for three hours. Automated FiO$_2$ control was performed without additional manual interventions. In the manual group, caretaker-lamb ratio was 1:1. Arterial blood gas analysis was obtained every 30 minutes and respiratory settings were adjusted to keep P$_a$CO$_2$ between 45 and 65 mmHg. Saturation target range was 90-95% according to current consensus guidelines from European neonatologists,[34] and the alarm range was set accordingly. Outcome parameters were time within and outside SpO$_2$ target range (90-95%), number and duration of episodes of hyperoxia (SpO$_2$ > 95%), hypoxia (< 85%) and severe hypoxia (< 75%), average variation from median target saturation and total number of FiO$_2$ adjustments. For analysis, we excluded times when animals showed saturation above the high target without a need for supplemental oxygen or when SpO$_2$ was below the low target despite a FiO$_2$ of 1.0, because oxygen targets could not be reached by FiO$_2$ control during these episodes.

Statistics

Normally distributed data are expressed as mean and standard deviation (SD), non-normally-distributed data are expressed as median and interquartile range (IQR).

Statistical analysis was performed using Student's t-test for normally distributed data and Mann- Whitney test for non-normally distributed data, using IBM® SPSS version 20. Graphs were drawn with GraphPad Prism® v5.0. Significance was accepted at $p < 0.05$.

Results

Animal characteristics

Preterm lambs did not vary significantly in baseline characteristics and ventilation parameters in both the resuscitation part (Table 1 A) and the stable ventilation part (Table 1 B) of the study. From 22 animals, 19 animals could be included for analysis of the resuscitation period. 2 animals were excluded because the control software was not activated as intended in the protocol, and one animal was excluded because of sensor malfunction. In all animals included, time until first SpO_2 measurement was about 2 minutes (median 106 s, IQR [80-148 s]) and time until pulse readout of the pulse oximeter correlated to the heart rate was 3 minutes on average (median 181 s, IQR [129-271s]). Fifteen animals underwent automated FiO_2 control during resuscitation, from which 9 started with a FiO_2 of 0.3 and 6 started with a FiO_2 of 0.6. In 4 animals FiO_2 was controlled manually (starting from FiO_2 0.3 in 3 and from FiO_2 0.6 in 1 animal).

5

Table 1 A: Animal characteristics (resuscitation)

		automated		manual		p
number of animals		15		4		
male : female [n]		5:10		1:3		
surfactant replacement		9		1		
gestational age [d]	median [IQR]	130	[128-132]	130	[129-131]	0.589
birth weight [kg]	mean (SD)	3.5	(0.8)	3.1	(0.8)	0.375
first blood gas analysis						
pH	mean (SD)	7.14	(0.10)	7.15	(0.08)	0.912
P_aCO_2 [mmHg]	median [IQR]	62.2	[55.0-70.7]	50.1	[49.1-50.1]	0.115
P_aO_2 [mmHg]	median [IQR]	43	[39-45]	39	[30-39]	0.411
blood gas analysis after resuscitation						
pH	mean (SD)	7.18	(0.15)	7.19	(0.11)	0.899
P_aCO_2 [mmHg]	median [IQR]	56.0	[44.2-85.3]	52.6	[47.8-58.3]	0.368
P_aO_2 [mmHg]	median [IQR]	51	[41-57]	44	[35-54]	0.342

SD standard deviation, IQR interquartile range

Table 1 B: Animal characteristics (stable ventilation)

		automated		manual		p
number of animals		11		11		
male : female [n]		4:7		4:7		
gestational age [d]	median [IQR]	130	[129-132]	130	[129-131]	0.401
birth weight [kg]	mean (SD)	3.7	(0.8)	3.2	(0.7)	0.545
average FiO$_2$	median [IQR]	0.60	[0.25-0.66]	0.35	[0.25-0.49]	0.243
PIP [mbar]	median [IQR]	24	[23-30]	25	[23-34]	1.000
PEEP [mbar]	median [IQR]	6.1	[5.7-7.3]	6.1	[5.6-7.2]	0.438
TVe [ml]	mean (SD)	21.9	(5.2)	20.6	(4.7)	0.519

IQR interquartile range; SD standard deviation
PIP: positive inspiratory pressure
PEEP: positive end expiratory pressure
TVe: expiratory tidal volume

Resuscitation

SpO$_2$ target during resuscitation was defined as 25th and 75th percentile over time for both groups (Figure 3 A). Relative time within target range did not differ significantly within groups (Figure 3 B). However, we observed significantly less time spent above the target range in the automated group, while time below the target range was similar (Figure 3 c-d).

Average time until first FiO$_2$ adjustment was below 3 minutes in both the automated and the manual group (median 160 s, IQR [134-208 s] vs. 149 s [81-1698 s], p=0.317). The average number of adjustments during resuscitation was similar in both groups (median 27, IQR [17-35] vs. 28 [20-36]; p=0.796).

Automated resuscitation with FiO$_2$ 0.3 vs. 0.6

Time within target range did not differ between animals receiving automated FiO$_2$ control with an initial FiO$_2$ of 0.3 compared to FiO$_2$ 0.6 (median 44.9%, IQR [24.2-48.5%] vs. 40.6% [30.5-45.9%], p=0.814). However, animals resuscitated with an initial FiO$_2$ of 0.3 showed significant less time above target range than animals resuscitated with FiO$_2$ 0.6 (3.7% [1.6-8.0%] vs. 14.9% [9.2-23.3%], p=0.008).

Automated FiO$_2$ control during stabilization and surfactant replacement therapy

Nine animals received surfactant replacement therapy in the stabilization period during automated FiO$_2$ control. FiO$_2$ was decreased from 97.4% [86.3-99.5%] to 45.5% [35.0-56.2%] in 14 [10-16] steps (Figure 4 A). The maximum number of steps the algorithm could make due to timeout restrictions of 30 s between steps was 20. In the 10 minutes after surfactant administration SpO$_2$ was subsequently kept close to target ranges, but was within the target range 44% of the time and above the range 54% (Figure 4 B). SpO$_2$, however, reached 100% in only 9% of the time.
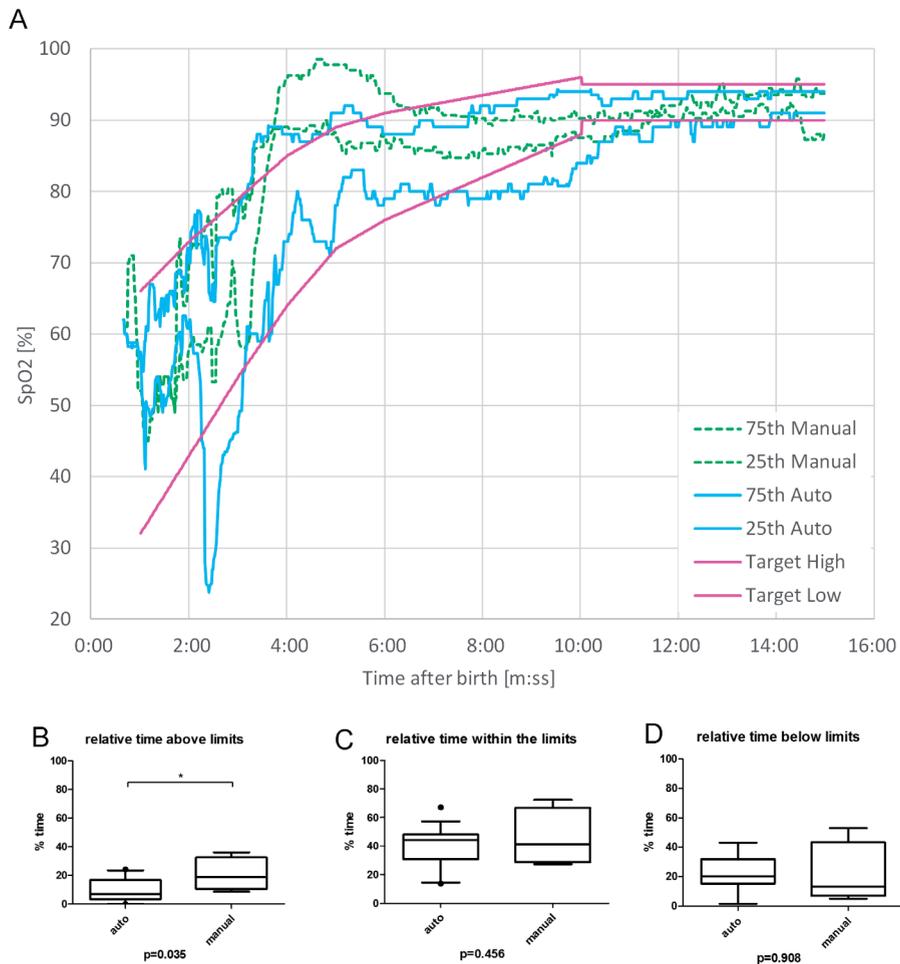
Figure 3: Resuscitation

(A) SpO2 during resuscitation is depicted as 25th and 75th percentile over time for automated (blue) and manual (dotted green) FiO_2 control. Boxplots depict (B) time above target range which was significantly higher in the automated group, (C) relative time within target range, and (D) time below target range which did not differ significantly between automated and manual control (whiskers represent +/- 1.5 IQR, *p<0.05).

A

B
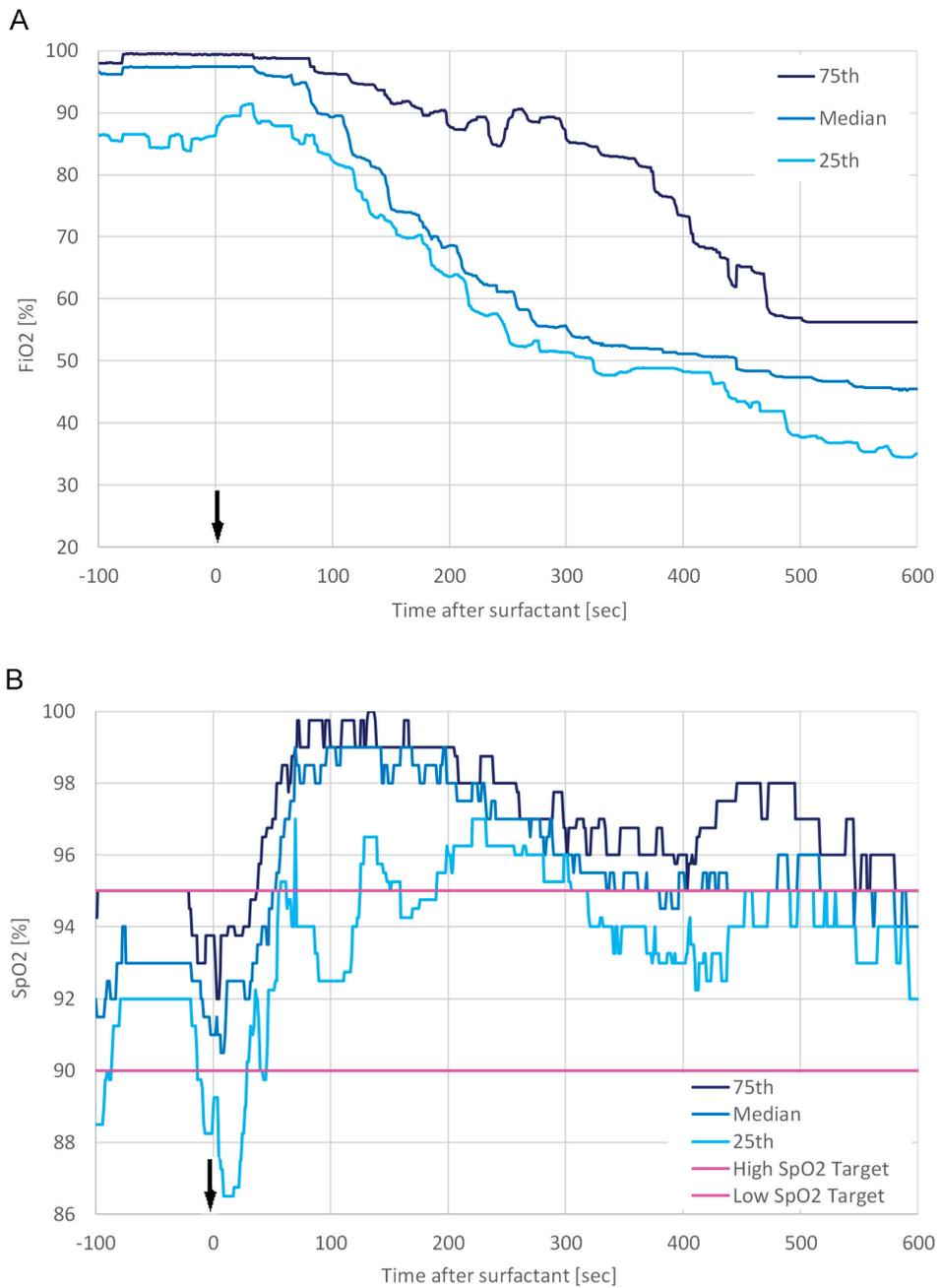
Figure 4: FiO$_2$ and SpO$_2$ after surfactant administration during automated FiO$_2$ control
After surfactant application (arrow), (A) automated FiO$_2$ adjustments reacted directly to changed oxygen needs and (B) kept SpO$_2$ close to the limits.

Stable ventilation

Animals were stabilized within the first half hour of life (median 33:11 min:sec, IQR [30:01-39:47 min:sec]). During the subsequent stable ventilation phase, time spend within the target range was significantly higher when the automated controller was used (93.2% [80.6-98.9%] vs. 84.0% [63.8-89.4%], p<0.05, Figure 5 A-B), and time outside the target range, depicted as area under the curve (SpO$_2$*sec per hour) was significantly lower (Figure 5 A, C). The number of episodes outside the target range per hour was also significantly lower in the automated group (2.2 [0.9-2.8] vs. 7.1 [4.0-18.6], p<0.01, Figure 5 D).
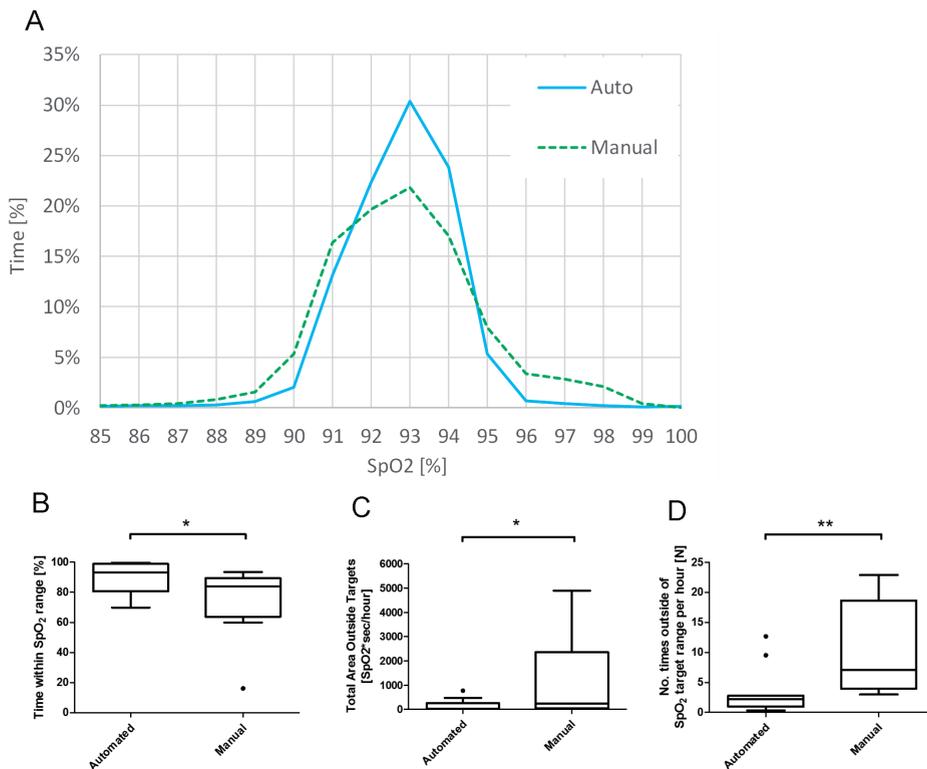
Figure 5: Stable ventilation

Distribution of oxygen saturation during stable ventilation in percentage of time (A) was more within predefined limits in the automated (blue) compared to the manual (dotted green) group. Boxplots depict (B) relative time within target range, which was significantly higher in the automated group, (C) time outside target range per hour as area under the curve [SpO$_2$*sec/hour] which was significantly lower in the automated group, and (D) episodes number of times outside target range, which were observed significantly more often in the manual group (*p<0.05, ** p<0.01).

When comparing hypoxic and hyperoxic episodes, animals ventilated with automated control had significantly less episodes below the lower target saturation of 90% and showed a trend towards less hyperoxic episodes per hour (p=0.065, Table 2). In our study, we observed only a small number of short hypoxic (< 85%) and severe hypoxic (<75%) episodes in our model, and number of these episodes did not differ between groups. This was also reflected in the low average deviation of saturation from the median target saturation in both groups (Table 2). The duration of hyperoxic, hypoxic and severe hypoxic episodes did no differ significantly between groups.

Compared to manual control, the number of FiO_2 adjustments per hour was 2.3 times higher in the automated group, although this difference was not significant (median 13.0, IQR [3.0-16.4] vs. 5.7 [2.3-9.8], p=0.243). Applied FiO_2 did not differ significantly between groups. However, animals in the manual group were outside target range longer with higher oxygen need, suggesting a moderate correlation between time outside target range and average FiO_2 ($R^2 = 0.614$), whereas in the automated group, average FiO_2 and time outside target range did not correlate ($R^2 = 0.229$, p= 0.276 vs. automated).

Table 2: Number and duration of hyperoxic, hypoxic and severe hypoxic episodes during stable ventilation

	automated		manual		p
No of episodes above 95% per hour	0.0	[0.0-1.4]	3.3	[0.6-10.3]	0.065
average duration of episodes above 95% [sec]	18.5	[7.5-51.1]	16.5	[13.1-57.7]	0.797
No of episodes below 90% per hour	1.4*	[0.9-2.2]	4.0	[1.7-6.4]	**0.010**
average duration of episodes below 90% [sec]	4.7	[1.0-27.5]	14.6	[6.3-49.4]	0.088
No of episodes below 85% per hour	0.0	[0.0-0.3]	0.0	[0.0-0.7]	0.748
average duration of episodes below 85% [sec]	16.5	[6.0-29.3]	36.3	[6.6-157.5]	0.686
No of episodes below 75% per hour	0.0	[0.0-0.0]	0.0	0.0-0.3	0,438
average duration of episodes below 75% [sec]	5.0		47.8	[1.0-75.0]	1.000
Average deviation from target saturation [SpO_2%]	1.0	[0.0-1.9]	1.7	[1.1-2.4]	0.171

Data is given as Median and [IQR].

Discussion

We tested in our study if fully automated FiO_2 control without manual interventions was feasible to keep lambs within a predefined SpO_2 target range under both rapidly changing conditions in a delivery room setting and under stable volume guarantee ventilation. Tailoring oxygen supplementation to the needs of preterm infants in the first minutes of life is difficult because of the gradual increase of oxygenation.[5] In our study, time within target range with both manual and automated FiO_2 control resembled clinical data obtained in the delivery room.[13]

Our data indicates that automated FiO_2 control avoided hyperoxia during resuscitation. This might have resulted from the algorithm following the target ranges in a stricter way than the human controller, although the number of adjustments and time until first FiO_2 adjustment did not differ between groups. However, we did not see significantly more time within target range in automated FiO_2 control during resuscitation. A possible explanation is that that the caretaker providing manual FiO_2 adjustments was able to see the changing SpO_2 target ranges depicted as Dawson's curve during resuscitation and therefore had more information about saturation trends than in a standard delivery room. This could have facilitated the decision for which FiO_2 to provide, and made it easier to achieve saturations within the limits than during routine clinical resuscitation where SpO_2 is presented only by pulse oximeter readout. However, we cannot rule out that the manual adjustments were based on additional clinical parameters, although heart rate increased adequately in both groups.

By basing the target range on Dawson's curve, the predefined range was broader during resuscitation than during subsequent ventilation. Closed loop FiO_2 control has been shown to maintain functionality in a setting of narrowed target ranges in the NICU,[35]Closed loop FiO2 control has been shown to maintain functionality in a setting of narrowed target ranges in the NICU,35 whereas in manual FiO2 control, changes in target range and oximeter alarm limits did not improve overall compliance with target range, but shifted actual SpO2 levels to potentially unfavorable levels.[36] Automated FiO_2 control might be further improved by allowing the algorithm to change FiO_2 more frequently, although the limitation of at least 30 seconds between two steps resembled clinical recommendations.[10]

Avoidance of oxygen overexposure is a major concern for implementing automated control in the delivery room.[28] In our study, animals resuscitated with an initial FiO_2 of 0.3 showed less SpO_2 above target range than animals initially resuscitated with FiO_2 0.6, although FiO_2 had to be increased during resuscitation in the first group.

The starting FiO_2 had an effect until about 5 minutes after birth. This observation is in accordance to a previous study where initial FiO_2 of 0.3 or 0.65 had a significant effect on the FiO_2 during the first 6 minutes of life.[37] Therefore resuscitation with initially low FiO_2 might be beneficial for preterm infants.[9]

Automated FiO_2 control was also feasible directly after surfactant replacement therapy. The automated controller showed immediate and adequate reaction on the altered needs for supplemental oxygen. In this scenario, a caretaker might have the advantage from knowing what to expect from the applied treatment. However, the small number of animals receiving surfactant during the study did not allow us a direct comparison between automated and manual control after surfactant replacement therapy.

During stable ventilation, animals receiving automated FiO_2 control spent significantly more time within the predefined target range. This advanced performance of the controller was striking, as manual control was performed in a 1-on-1 setting by a person without other tasks than ventilation control during the experiment. This dedicated FiO_2 control, which is different from the clinical situation, improved time within target range compared to routine control in a previous study.[23] In a clinical setting, meeting SpO_2 target ranges depends -amongst others- on patient-caretaker ratio[38]. Most closed loop studies compared automated to routine clinical care,[14,21,24,25,26] only one study could show a significant improvement comparing closed loop to dedicated manual control.[22] In addition, in our study alarm range was equal to target range, which created an ideal setting for dedicated manual control as caregivers are more effective in keeping SpO_2 within alarm limits then within target limits in preterm infants.[39] Interestingly, our data suggests that keeping animals manually within the limits was more difficult with high oxygen need, while individual oxygen need did not influence the performance of the automated control.

We therefore conclude that automated FiO_2 control is applicable both during rapidly changing physiologic conditions and during stable ventilation. Automated FiO_2 control has therefore the potential to facilitate delivery room management during resuscitation. On the NICU, automated FiO_2 control reduced the need for manual interventions during automated control by 33% to 90%.[23,24,25]. Only one study reported no manual interventions during automated control,[22] however the overall time within target range for both manual and automated control was lower and the target range was wider compared to our study. The potential of acting autonomously for at least a certain time is a prerequisite of safe use of automated FiO_2 control in this vulnerable patient population.

Nevertheless, automated control cannot outrun clinical experience, as therapeutic interventions in the delivery room have to be adapted to a multitude of parameters.[40] Early SpO_2 is related not only to FiO_2, but also to factors like adequate functional residual capacity (FRC)[41] and perinatal procedures like delayed cord clamping.[42] In addition, rising need for oxygen can be a symptom of a pathological condition as pneumothorax or ventilation related complication, e.g. tube dislocation. Automated control may mask these changes, at least for a short period of time. Therefore, adequate feedback about automated intervention to the caretaker must be ensured. Additional alarms for parameters like tidal volume should be routinely implemented.

Our model is limited by the fact that animals were mildly sedated for mechanical ventilation, partially preventing spontaneous breathing. Hypoventilation after episodes of active breathing during mechanical ventilation has been previously described as important contributor to desaturations in ventilated preterm children.[43] Automated FiO_2 control might be ineffective in prevention of hypoxic spells.[27] However, our data suggests that automated control prevented episodes below target and might therefore have an effect on these episodes, as hypoxic spells have been associated with lower average SpO_2 levels.[44] This highlights the need for additional studies investigating the influence of parameters defining the automated controller.

In summary, to the best of our knowledge this is the first study where we demonstrate that fully automated FiO_2 control is feasible during neonatal resuscitation in a near-clinical preterm delivery room setting, and that automated control prevents hyperoxia. We speculate that in a clinical scenario where not only SpO_2 but also clinical evaluation of the patient influence oxygen therapy, the combination of automated and manual control might even imply better results. However, this question may best be addressed in a clinical trial. In parallel, translational trials will help to improve closed-loop equipment.

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Chapter 6

Pregnancy at high altitude in the Andes leads to increased total vessel density in healthy newborns

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Abstract

The developing human fetus is able to cope with the physiological reduction in oxygen supply occurring in utero. However, it is not known if microvascularization of the fetus is augmented when pregnancy occurs at high altitude. Fifty-three healthy term newborns in Puno, Peru (3,840 m) were compared with sea-level controls. Pre- and postductal arterial oxygen saturation (SpO_2) was determined. Cerebral and calf muscle regional tissue oxygenation was measured using near infrared spectroscopy (NIRS). Skin microcirculation was noninvasively measured using incident dark field imaging. Pre- and postductal SpO_2 in Peruvian babies was 88.1 and 88.4%, respectively, which was 10.4 and 9.7% lower than in newborns at sea level (P < 0.001). Cerebral and regional oxygen saturation was significantly lower in the Peruvian newborns (cerebral: 71.0 vs. 74.9%; regional: 68.5 vs. 76.0%, P < 0.001). Transcutaneously measured total vessel density in the Peruvian newborns was 14% higher than that in the newborns born at sea level (29.7 vs. 26.0 mm/mm^2; P ≤ 0.001). This study demonstrates that microvascular vessel density in neonates born to mothers living at high altitude is higher than that in neonates born at sea level.

News and Noteworthy:

The natural hypoxic environment at high altitude results in reduced oxygenation, especially in the growing human fetus. Our prospective observational study on healthy term newborns in Peru (Puno at 3840m) that included novel non-invasive visualization of microcirculation demonstrates that vessel density is elevated by 14% in neonates born to women living at high altitude as compared to babies born at sea level, most likely revealing an adaptive mechanism to a highly hypoxic antenatal environment.

Introduction

It is estimated that in the South American Andes over 30 million people - most of them belonging to the Quechua or Aymara population and termed here "Andean" - permanently live above 2,500m (8,200ft), defined as high altitude (2, 10). At high altitude, the environmental conditions are extreme, including dramatic temperature changes and low atmospheric pressure leading to hypobaric hypoxia. The consequences of this are often exacerbated by low socio-economic status and negatively impact the health of infants (46). Of note, people living at high altitude not only show genetic adaptation but also plasticity in development in response to hypoxia (1, 17). Despite the harsh conditions at the high altitudes of the Andes, most fetuses develop well and are delivered at term (31). For that matter, it must be understood that the intrauterine environment already represents an extreme surrounding at sea level that is exacerbated in pregnancies at high altitude. In general, proper *in utero* development requires adequate oxygen delivery to the fetus, which is achieved by increased maternal ventilation rate and thus increased blood oxygen saturation (SpO_2) level (22, 25). Under conditions of chronic hypoxia, however, the utero-placental blood flow is lower (16) and, consequently, oxygen uptake by the fetus is reduced. This process can even be exacerbated by the presence of maternal preeclampsia (12). When pregnancy occurs at 3,100m, however, the placenta increases antioxidant capacity (38) while the fetus is able to adapt to maternal and placental hypoxemia by increasing nitric oxide production *in utero* and after birth. This adaptive response might be necessary to sustain placental blood flow but may also lead to improvement of microcirculatory blood flow (28).

It was shown, decades ago, that babies born to indigenous Andean women have a higher birth weight than non-Andean neonates both born at high altitude (9). A more recent study revealed that elevated uterine artery blood flow and thus increased oxygen delivery protect Andeans from fetal growth retardation when pregnancy occurs at high altitude (16). Perinatal Doppler and ultrasound studies in Andean fetuses performed at 3,600m showed reduced umbilical blood flow, compensated for, however, by the fetuses' elevated neonatal hemoglobin concentration and increased oxygen extraction capability (31). As a result, fetal oxygen delivery and oxygen consumption at high altitude do not differ from values measured at low altitude (31), supporting the notion that the fetus copes with the extreme *in utero* situation by increasing systemic blood flow and thus oxygen delivery. Note that the present study does not include the Tibetan population which is known to maintain better neonatal oxygenation than Andeans (reviewed in (24)).

Apart from vasodilation, an obvious strategy to increase blood and thus oxygen supply to the tissue is to increase microvascular density. Microcirculation studies in critically ill

neonates (40) found a low microvascular density to be a predictor for mortality in sepsis (39). However, no studies have reported on the effect of antenatal hypobaric hypoxia on fetal microcirculatory development. Thus, in the present prospective observational study the aim was to obtain microcirculatory profiles of term babies born at high altitude and compare these with the profiles of babies born at sea level. We postulated that the microvascularisation of the neonate born to mothers at high altitude is elevated and that this phenomenon reflects a general adaptive mechanism.

Materials and Methods

Subjects

This prospective observational study was performed in August 2014 at the pediatric department of the Hospital EsSalud III in Puno (Peru) located at 3,840m above sea level. The Peruvian microcirculatory measurements were compared to those performed at sea level in the maternity ward of the Erasmus MC - Sophia Children's Hospital in Rotterdam, The Netherlands (altitude: 0m) where measurements were performed by the same operator using identical instrumentation. Before any measurements were taken, all parents gave their written informed consent. The study protocol was approved by the Ethics Committee of the Universidad Peruana Cayetano Heredia (UPCH 180-17-14; 62794) as well as by the local Ethics Authorities represented by the Red Asistencial Puno EsSalud and the Erasmus MC Rotterdam Ethics Committee (NL48445.078.14). The measurements were carried out in accordance with the approved guidelines. Eligible for participation were healthy, singleton newborns of women either residing at high altitude (Puno and surroundings) or at sea level (Rotterdam and surroundings) at least during pregnancy, delivered either vaginally or by cesarean section, with Apgar scores of 8 or higher and not older than 30h at the time of measurement. Newborns were considered healthy if born at term to apparently healthy mothers not suffering from obvious pregnancy complications (no ante- or postnatal abnormalities). Maternal data on smoking was not collected. Babies delivered by cesarean section at high altitude (n=19), but not those at sea level, were placed in an incubator (33°C, 21% O_2) until the mother recovered. The latter babies were measured at a mean of 17 h after birth (similar to the vaginal-delivered ones: 14h) and 30 min after being taken out of the incubator. The room temperature at which the babies were measured was 22-23°C. Exclusion criteria included gestational age below 37 or above 42 wk, any known congenital, hematologic or cardiorespiratory disorder and refusal of written parental informed consent.

We intended to assign ancestry by analyzing the babies' parental surnames, a method that was validated by analyzing ancestry informative genetic markers (4, 45). Babies born

to Andean parents acquire both parental surnames that are not changed upon marriage. Accordingly, this custom yields four parental surnames for every child. By the method taking into account this tradition (16, 30), we considered a baby as "indigenous" if she or he had three or four Andean parental surnames. Babies with two Andean and two Hispanic surnames were considered of "mixed origin". If three or four parental surnames were of Hispanic origin, the baby was considered as "Hispanic". Classification was not possible in all other cases. Note that this classification is an approximation only as early reports show that it is not fully accurate to predict non-Andean ancestry using Hispanic surnames (34, 45). Accordingly, the "Hispanic" population cannot be classified as being of low-altitude but as of combined ancestry.

Data collection
Clinical data from 53 healthy term-born neonates born at high altitude, most of them born to Aymara parents, were retrieved from the medical files of the Hospital Puno EsSalud III and clinical data from 33 healthy term-born neonates born at sea level from the medical files of the Erasmus MC - Sophia Children's Hospital. Data included gender, gestational age, birth weight, mode of delivery, and rectal temperature. Additional data - only available in Peruvian newborns - included heart rate, respiratory rate, hematocrit, hemoglobin concentration as well as platelets and leukocyte count. For assessment of ancestry the surnames of the babies, the mothers and of the fathers (in 19 cases we obtained only one paternal surname instead of two) were collected.

Full microcirculatory profiles were obtained by the following measurements performed simultaneously: pre- and postductal arterial oxygen saturation (SpO_2), regional and cerebral tissue oxygen (rSO_2 and $crSO_2$) and total vessel density (TVD) using transcutaneous microcirculatory imaging. All newborns were asleep or awake but remain calm during measurements. While full microcirculatory profiles were obtained in Puno, in 33 newborns from Rotterdam only the transcutaneous microcirculation profiles were obtained.

Measurement methods
Pre- and postductal arterial oxygen saturation (SpO_2) levels were measured on the right and left wrist using two MASIMO RADICAL 7 pulse oximeters (Masimo, Irvine, CA).

Regional tissue oxygen saturation was measured by near infrared spectroscopy (NIRS) using the INVOS device (Somanetics, Troy, MI). This device uses near-infrared light at wavelengths of 730 and 810 nm to measure oxygenated and deoxygenated hemoglobin. Tissue oxygen saturation, defined as the percentage of oxygenated hemoglobin/total hemoglobin, was measured on the forehead to determine the cerebral oxygen saturation

(crSO$_2$) and on the skeletal calf muscle to determine the regional oxygen saturation (rSO$_2$). Fractional tissue oxygen extraction (FTOE) was calculated as (preductal arterial saturation -cerebral saturation) / preductal arterial saturation [(SO$_2$ - crSO$_2$)/ SO$_2$] for cerebral (crFTOE) and with the rSO$_2$ for the skeletal calf muscle measurements (rFTOE). Pulse oximetry and NIRS measurements of Peruvian newborns were compared with published reference values (13, 27, 29, 41).

Skin microcirculation was measured on the upper inner arm using incident dark field (IDF) technology (Braedius, Huizen, the Netherlands). This device (CYTOCAM) is a handheld microscope with an illumination unit (green light, 450nm) that allows optimal absorption of deoxy- and oxyhemoglobin thereby permitting visualization of the erythrocytes (44). The transcutaneous approach was chosen because sublingual measurement in newborns is not possible and a newborn's skin is thin enough to allow this (43). Identical instrumentation was used in Puno and Rotterdam and the measurements were performed by one and the same technical study operator present at both sites. A minimum of three video clips were recorded and those that did not met the quality criteria according to Massey *et al.* (21) were excluded from further analysis. TVD was automatically analyzed using CCTools (Version 1.7.12, brightness 500, sensibility level 95%). A distinction was made into small vessels, medium and large vessels: Ø ≤10, 10-20 and 20-100 μm, respectively. The automated analysis standardizes the process of analysis and thereby excludes inter-observer variability (42). Following standard guidelines, a minimum of three video clips per newborn was used for automated analysis (5).

The microvascular flow index (MFI) and the heterogeneity index (HI) semiquantitatively describe the velocity of microcirculatory perfusion (5). Each video image was divided in four equally sized quadrants. Each quadrant was scored manually by one experienced operator according to the predominant type of flow (continuous: 3, sluggish [e.g. continuous but very slow]: 2, intermittent: 1, or absent: 0). The MFI is represented by the mean score of the type of flow, and HI by the difference between the highest quadrant and the lowest quadrant score divided by the mean score of all quadrants for one measurement. The MFI and HI for small (Ø ≤10 μm) and non-small vessels (Ø 10 - 100 μm) were determined. This method shows good intrarater variability and is described in more detail elsewhere (3).

Statistical analysis

Continuous data are presented as median and range for non-normally distributed variables and as mean and standard deviation (SD) for normally distributed parameters. Non-continuous variables are presented as percentages of total and 95% confidence intervals (CI) of proportions.

Normally distributed continuous data were compared using an unpaired t-test. Pre- and post-ductal arterial saturation and cerebral saturation were compared with the aforementioned international reference values using a one-sample t-test. Median values were compared using a one sample Wilcoxon signed rank test. One way-ANOVA was used to compare means between more than two groups. Multivariable linear regression analyses adjusting for possible confounding variables were performed using SPSS version 21(IBM, Armonk, NY). The crude association between skin microcirculation parameters and country (Peru/Netherlands) was adjusted for sex, gestational age, birth weight z-score, Apgar score (5 min), mode of delivery, pregnancy (primigravida/multigravida) and rectal temperature. Collinearity analysis to explore correlation between all covariates using a correlation matrix was performed. A cut-off value of 0.7 was used for the exclusion of variables in the model. Residual plots were constructed to check for normality of the distribution of the residuals.

Results

Comparison of demographic data is shown in Table 1. Gender distribution was approximately even, and gestational age and birth weight were similar between Peru and Rotterdam. About one third of the Peruvian newborns were delivered by caesarean section, vs. circa 60% in Rotterdam. In Puno, 18 babies were classified as "indigenous", 6 as "mixed" and 19 as "Hispanic". The remaining 10 babies could not be classified by surnames. The birth weight of indigenous, mixed and Hispanic newborns was 3,374 (SD 315), 3,325 (SD 414) and 3,196 (SD 220) g, respectively. Comparison of birth weight between these groups, adjusted for sex and gestational age, showed no significant difference (the comparison between indigenous vs. Hispanic resulting in P = 0.1). Nevertheless, this trend of higher birth weight in indigenous newborns was in accordance to recent studies (8, 15) reporting that high altitude generally decreases birth weight but that birth weight of neonates of Andean descent was higher than that of neonates of combined origin.

Table 1. Clinical parameters of the newborns at high and low altitude

	High altitude: Puno (n=53)	Low altitude: Rotterdam (n=33)
Male gender (%, CI)	49.1 (27.1 – 51.0)	57.6 (40.8 – 72.8)
Caesarian section (%, CI)	35.9 (24.3 – 50.3)	60.6 (43.7 – 75.3)
Gestational age (weeks+days)	39+0 (37+0 – 40+0)†	39+5 (37+0 – 41+3) †
Birth weight (grams)	3310 (2590 – 4180) †	3353 (2475 – 4450) †
Rectal temperature (ºC)	36.8 (0.3)*	36.9 (0.3) *

Values are *mean (SD) and †median (range). Clinical data from babies born at high altitude (Puno, n = 53) and at sea level (Rotterdam, n = 33) that were compared for total vessel density (TVD; see Fig. 2). CI = 95% confidence interval.

Additional clinical data from the 53 healthy Peruvian newborns (3,840m above sea level) were the following: mean heart rate 145 (SD 13) n/min, mean respiratory rate 53 (SD 5) n/min, mean hematocrit 0.57 (SD 0.06), mean hemoglobin 19.0 (SD 1.9) g/dL, mean platelet count 247 (SD 53 x 10^{-9}) dL and mean leukocytes count 18.6 (SD 4.1 x 10^{-9} dL).
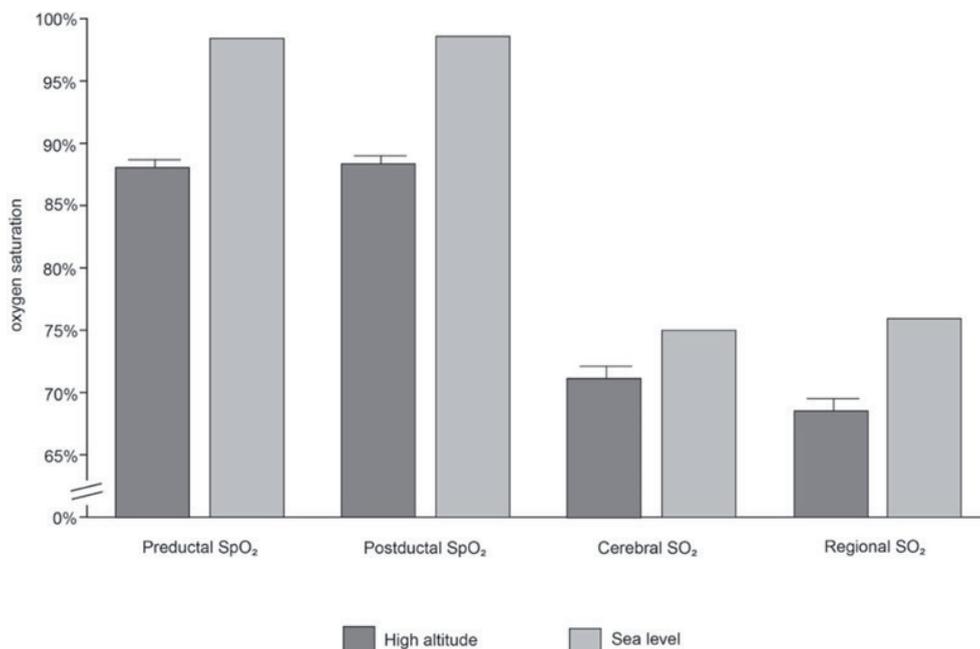
Fig. 1: Pre- and post-ductal arterial saturation (SpO_2) as well as cerebral and skeletal calf muscle (regional) oxygen saturation (SO_2) measured at high altitude are compared to sea level reference values. Pre- and postductal arterial saturation in newborns not older than 30 hours was measured as mentioned in Material and Methods. Skeletal muscle oxygen saturation was selected to mirror regional levels. The obtained data from high altitude babies (n = 52) were compared to the published one at low altitude (0-326 m, n = 13,714 for pre- and postductal SpO_2 (13) as well as n = 339 for cerebral (41). and n = 72 for regional SO_2 (29)). Error bars are SE

Mean pre- and postductal saturation in Peruvian newborns was 88.1% (SD 4.1%) and 88.4% (SD 4.6%), respectively (Fig.1). These values were significantly lower (p<0.001) than reference values (13) obtained from a total of 13,714 term newborns at sea-level, which are 98.5 and 98.7%, respectively. The relative difference between pre- and post-ductal saturation in high and low altitude born babies thus was 10.4 and 9.7%, respectively. The results of cerebral and regional NIRS measurements at high altitude are also shown in Fig. 1. These data were compared to published reference values of

term infants (cerebral n=339 and regional n=72), born at sea level and measured with the same NIRS device (27, 29, 41). Tissue oxygen saturation was significantly lower (cerebral 71.0 vs. 74.9%; calf muscle 68.5 vs. 76.0%, P < 0.001). Lower arterial and tissue saturation was not associated, however, with different tissue oxygen extraction (crFTOE 0.19 vs. 0.19, P = 0.610; rFTOE 0.22 vs. 0.24, P = 0.199).
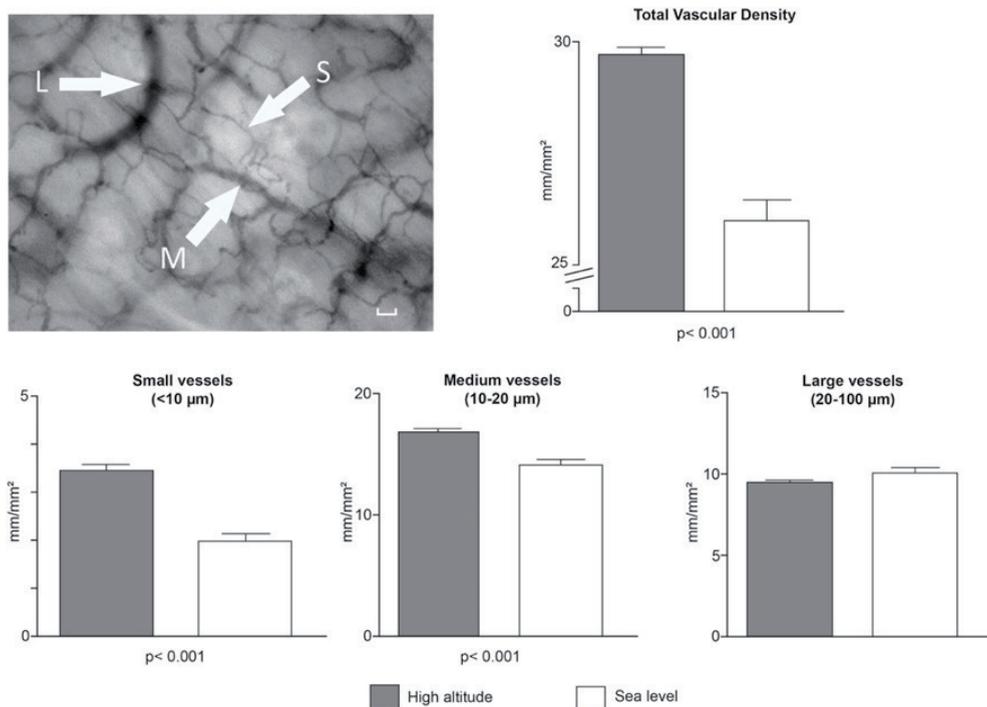
Fig. 2: Imaging and morphometric analysis of vessel density of the skin from newborns at high and low altitude. The image in the upper left shows a representative single shot of the video images obtained by a CYTOCAM. Small, medium and large vessels with Ø of <10, 10-20 and 20 -100 m, respectively, are labelled. Bar = 25μm. Top right: the unadjusted mean total vessel density (TVD) measured in babies born at high altitude (dark bars, n = 52) and at sea level (white bars, n = 32). Bottom: quantitation (unadjusted mean) of small, medium and large vessels. Error bars are SE

Regarding cutaneous microcirculation data, in only two cases (one from Puno and one from Rotterdam) microcirculation data could not be analyzed due to low quality video imaging and thus both were excluded from further analysis. As for the remaining cases, the mean TVD in the Peruvian babies born was 14% higher than that in the Rotterdam babies (Fig. 2, top right). Automated morphometric analysis revealed that both, small and medium sized vessels (but not large ones) were significantly longer in the Peruvian newborns (Fig. 2, bottom). To assess as whether ancestry might have an impact on increased microvascularisation in newborns at high altitude, TVD was

calculated for the three groups mentioned above: indigenous, mixed and Hispanic (n = 18, 6 and 19, respectively). No statistical differences in TVD were found between any two groups tested. Moreover, there was a remarkable difference in incidence of caesarian sections between the Rotterdam and Puno group (60.6 vs. 35.9%) but we observed no differences in TVD between the two delivery modes (Rotterdam: cesarian section vs. vaginal delivery: mean TVD 25.86 and 26,18 mm/mm^2, respectively, P = 0.761; Puno: cesarian section vs. vaginal delivery: mean TVD 29.55 and 29.72 mm/mm^2, respectively, P = 0.728).

Multivariable linear regression analysis adjusted for possible confounding variables between countries showed no collinearity between the independent variables used in the model and normal distribution of the residuals. Table 2 shows the corresponding crude and adjusted differences for microcirculatory parameters: after adjustment the difference between the Peruvian and Rotterdam groups remained significant. Moreover, both the MFI and HI were not altered in either group.

Table 2. Crude and adjusted difference between Puno and Rotterdam for microcirculatory parameters

| Variable | Difference between high altitude and sea-level (95% CI) | | | |
	Unadjusted difference (95% CI)	p-value	Adjusted* difference (95% CI)	p-value
Total Vessel Density (mm/mm^2)	3.67 (2.68 – 4.66)	<0.001	3.57 (2.37 – 4.77)	<0.001
TVD small (mm/mm^2)	1.46 (1.02 – 1.91)	<0.001	1.14 (0.64 – 1.64)	<0.001
TVD medium (mm/mm^2)	2.79 (1.91 – 3.66)	<0.001	3.08 (2.00 – 4.16)	<0.001
TVD large (mm/mm^2)	-0.58 (-1.26 – 0.10)	0.129	-0.64 (-1.49 – 0.20)	0.132
MFI small (au)	-0.02 (-0.14 – 0.09)	0.688	-0.08 (-0.21 – 0.06)	0.261
MFI non-small (au)	0.03 (-0.04 – 0.09)	0.381	0.02 (-0.06 – 0.09)	0.646
HI small (au)	0.001 (-0.08 – 0.09)	0.854	0.02 (-0.08 – 0.13)	0.640
HI non-small (au)	0.03 (-0.04 – 0.09)	0.367	0.04 (-0.04 – 0.11)	0.368

Crude and adjusted differences between microcirculatory parameters obtained from neonates born at high altitude and sea level. Crude data from the babies mentioned in Table 1 (Puno n = 52; Rotterdam n = 32) were adjusted (*) for country, sex, gestational age, birth weight z-score, Apgar score (5 min), mode of delivery, pregnancy (primigravida/multigravida) and rectal temperature as described in MATERIALS AND METHODS. Small, medium, and large vessels have Ø <10, 10–20, and 20–100 µm, respectively. MFI, microvascular flow index; HI, heterogeneity index; CI, 95% confidence interval; AU, arbitrary units.

Discussion

Reduced oxygenation of the placenta is linked to severe complications including intra-uterine growth retardation and preeclampsia (12, 23, 36). Of note, despite reductions in systemic oxygen supply, such as occurs at high altitude, the fetus is able to cope with this extreme but still physiologic hypoxic condition. While many studies have addressed the hypoxic placenta's vascular remodeling and metabolic changes (reviewed in (19, 36)), data on the mature fetus's adaptation to a hypoxic environment are scarce. The present study is the first, to our knowledge, to examine microvascular density in healthy term neonates born to mothers that were living at high altitude during pregnancy (3,840 m). Our major finding was that their TVD was 14% higher than in neonates born at sea level, pointing towards a possible adaptive fetal strategy to cope with reduced oxygenation. In addition, based on our surname assessment, we suspect that the increase in TVD was independent of the babies' ancestry. The microcirculation is defined as vessels equal to or smaller than 100 μm in diameter that form the capillary network (11). The above-mentioned difference in TVD was still significant when the crude data were adjusted for the following predefined, potentially confounding variables: country, gender, gestational age, birth weight, Apgar score (5 min), mode of delivery, primigravida/multigravida, and rectal temperature. Increased vascularization was observed in small (Ø ≤ 10 μm) and medium (Ø 10-20 μm) vessels but not in larger ones. This implies that vessel density is only increased at the level of gas exchange (i.e. capillaries and small arterioles). In a study of healthy adults with no high altitude ancestry (20) a 10.9% increase in TVD was found in subjects first measured at sea level and thereafter at high altitude (5,300 m). Also, in preterm infants born small for gestational age, most often caused by more extreme hypoxic conditions, TVD was significantly higher soon after birth (van Elteren HA, de Jonge RC, and Reiss IK unpublished observations).

Considering that blood flow in the umbilical vein is reduced at high altitude (31) and that vascularization seems to be independent of ancestry, it is plausible to speculate that enhanced microvascularisation is a general adaptive mechanism that might be induced by hypoxia-driven stabilization of the a-subunits of the hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2) (reviewed in (7, 37)). In turn these heterodimeric regulatory transcription factors upregulate hypoxia-dependent genes including those that trigger angiogenesis such as the vascular endothelial growth factor (VEGF) (26, 36). In contrast to the Andean population, evolution has selected a blunted erythropoietic response for Tibetans as an adaptive strategy to high altitude: a missense mutation in the EGLN1 gene that encodes for the main cellular oxygen sensor results in increased HIF degradation under hypoxic conditions (18) but this observation has been challenged recently (33).

6

Nevertheless, it would be of interest to determine TVD in healthy babies born to Tibetan mothers at high altitude. Apart from such mutations epigenetic modifications may also support adaptation to exogenous factors such as hypoxia, which can be transmitted to next generations. As such, Julian *et al.* (14) recently provided evidence that unique DNA methylation patterns occur in genes known to influence vascular development and integrity in offspring of hypertensive pregnancies.

While the babies' heart rate at high altitude (mean 145, SD 13 n/min) did not deviate from published data, levels of hematocrit (0.57 vs. 0.49-0.50) and hemoglobin concentration (19.0 vs. 16.8 -17.1 g/dl) values in our Peruvian population were higher than those reported in a study performed at 3,600 m (31). We cannot explain this difference as the hospital in which our study was conducted was located only about 300 m higher. Nevertheless, in the present study the flow-related parameters MFI and HI did not differ between the high-altitude and sea level groups despite a physiological higher hematocrit level in the high-altitude group. However, hematocrit values measured in arterial or venous blood differ greatly from hematocrit at a microcirculatory level. Known as tube hematocrit, it is significantly lower and highly variable in the presence of a constant systemic hematocrit (6). Systemic hematocrit is therefore not correlated to viscosity and blood flow at a microcirculatory level. Moreover, it should be noted that MFI values are often lower in disease states, especially in individuals suffering from septic shock (32).

Previously, a study on NIRS measurements in 24 children reported a significant decrease in cerebral tissue oxygen saturation on ascent from 1610 to 3109 m (78 to 67%, P < 0.001) (47). In another study, reporting NIRS measurement in 17 children during emergency helicopter transport, NIRS decreased from 69.2 to 66.3% in patients transported to altitudes higher than 5000 ft (1524 m) above sea level (35). Although these two studies measured the response to acute hypoxia, these observations are in line with our results showing that exposure to high altitude significantly lowers cerebral tissue oxygenation.

Limitations

Due to unforeseen administrative delays in Peru, measurements could not be performed in the local sea level control group that of note is mainly represented by a Hispanic population. Therefore, measurements at high altitude were compared with sea-level values either found in the literature (pulse oximeter and NIRS data) or by own data obtained from our Rotterdam cohort (determination of TVD). Although a control

group of babies born at sea level in Peru is also not completely similar to the neonates in Puno, the use of a Dutch control group might have introduced additional unknown confounding factors. The number of participants in the referred studies exceeded the number of participants in our control group, thereby serving as a reliable comparison group unless ancestry plays an important role. This was assessed and despite the fact that all four parental surnames of the neonates were not always obtained, it was possible to classify a significant number as indigenous (n = 18) or Hispanic (n = 19). Although ancestry classification by surname is not as precise as genetic analysis, this strategy - first being described and validated back in 1989 (4) - has been successfully applied recently (30, 34). Considering that elevated TVD was observed in all analyzed neonates who consisted of Andean and combined ancestry, we propose that comparison of our data obtained in neonates born at high altitude to sea level neonates from the literature is sound.

The automated computer IDF technology used for microcirculatory analysis has, just like its predecessor methods (sidestream darkfield imaging and orthogonal polarization spectral imaging), only been validated against its predecessor. However, given that the same method was used in both the Peruvian and the Rotterdam group, under supervision of the same experienced operator, any limitation of the software should be equally reflected in both groups. Thus, the data provided are comparable within this study but cannot be extrapolated to other studies.

To conclude, in this study, microvascular vessel density measured using IDF imaging was higher in babies born at high altitude than in babies born at sea level. Neonatologists are often confronted with hypoxemia in their little patients. Visualizing the cutaneous microcirculation represents a new, non-invasive and fast diagnostic tool in neonatal intensive care helping to understand the balance between macrocirculation and peripheral perfusion and newborns.

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Acknowledgments

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Chapter 7

Noncontact Monitoring of Respiratory Rate in Newborn Infants Using Thermal Imaging

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Abstract

Monitoring of respiratory rate (RR) is very important for patient assessment. In fact, it is considered one of the relevant vital parameters in critical care medicine. Nowadays, standard monitoring relies on obtrusive and invasive techniques which require adhesive electrodes or sensors to be attached to the patient's body. Unfortunately, these procedures cause stress, pain and frequently damage the vulnerable skin of preterm infants. The current paper presents a "black-box" algorithm for remote monitoring of RR in thermal videos. "Black-box" in this context means that the algorithm does not rely on tracking of specific anatomic landmarks. Instead, it automatically distinguishes regions of interest in the video containing the respiratory signal from those containing only noise. To examine its performance and robustness during physiological (phase A) and pathological scenarios (phase B), a study on twelve healthy volunteers was carried out. After a successful validation on adults, a clinical study on eight newborn infants was conducted. A good agreement between estimated RR and ground truth was achieved. In the study involving adult volunteers, a mean root-mean-square error (RMSE) of (0.31 ± 0.09) breaths/min and (3.27 ± 0.72) breaths/min was obtained for phase A and phase B, respectively. In the study involving infants, the mean RMSE hovered around (4.15 ± 1.44) breaths/min. In brief, this paper demonstrates that infrared thermography might become a clinically relevant alternative for the currently available RR monitoring modalities in neonatal care.

I. Introduction

RESPIRATION is an important physiological process which ensures oxygen supply to the human body and removal of carbon dioxide from the circulation. Each respiratory cycle consists of two phases: inspiration of oxygen-rich air necessary for metabolism, and expiration of carbon dioxide generated during energy-producing reactions [1]. Thus, monitoring of respiratory function, and especially, respiratory rate (RR) is very important for patient assessment [2-4]. Indeed, RR is considered a crucial vital parameter in critical care medicine [3, 5].

Respiratory rate, usually measured in breaths per minute (breaths/min), describes the rate of the respiratory cycles. Normal values for this vital sign vary according to age. While RR of adults normally ranges between 12 to 20 breaths/min, RR of preterm infants may vary between 40 to 60 breaths/min [6]. Diverse diseases contribute to breathing disorders, which are commonly identified either by abnormal RRs, respiratory sounds, or by an atypical waveform (altered breathing depth and/or rhythm) [7-9]. Tachypnea (increased RR), for example, can be an early indicator for heart and lung diseases. Bradypnea (decreased RR), in turn, may be caused by hypothermia, certain medications (e.g. narcotics) or by diseases affecting the central nervous system [10]. Other pathological breathing patterns such as Kussmaul's breathing or Cheyne-Stokes respiration are commonly associated e.g. with cerebral ischemia [11, 12] and metabolic disorders [13]. In context with preterm neonates, the continuous surveillance of the respiratory rate and its variations is mandatory, since apneas and bradycardia occur frequently. If not detected early, they may lead to oxygen-depletion in the organs, resulting e.g. in deficits in their neurodevelopmental outcome [14]. Furthermore, tachypnea is one of the leading clinical signs for bacterial pulmonary infection [15]. Finally, this vital sign contributes to an early identification of sudden infant death syndrome, which is one of the major causes for death in children younger than one year [16].

However, RR is still one of the most clinically undocumented and underestimated vital signs, mostly due to shortcomings of current clinical monitoring techniques [3, 17]. These modalities rely on the attachment of sensors to the patients body, which induce stress and discomfort [18]. In preterm and very low birth weight (VLBW) infants, placement and removal of adhesive electrodes frequently lead to epidermal stripping and skin disruption because the electrode-dermis junction is stronger than the bond between the epidermis and dermis. In fact, removal of adhesive electrodes is the major cause of skin breakdown in neonatal intensive care units (NICUs) [19, 20].

In recent years, there has been a great effort to develop non-contact RR monitoring techniques. Their major aim is to improve patients quality of life [5]. One of the first techniques for contactless measurement of vital signs was the Radar Vital Signs Monitor (RVSM) developed by Greneker et al. in 1997 [21]. Steffen et al. [22] proposed in 2008 a multichannel simultaneous magnetic induction measurement system (MUSIMITOS) capable of monitoring heart and lung activity unobtrusively. In 2013, Marchionni et al. used a laser Doppler vibrometer, which measures vibrations of a surface, for contactless monitoring of respiration and heart rate in preterm infants [23]. Recently, the focus has broadened to encompass imaging technologies: visible and near-infrared [24-26], mid-wave infrared [16] as well as long wave infrared [27] imaging systems. Infrared thermography (IRT), also known as thermal imaging, is a very promising approach for unobtrusive and non-contact monitoring of both heart rate and RR [28]. In contrast to visible and near-infrared imaging systems, IRT does not require any active illumination. It is a completely passive technology which works in total darkness. Therefore, it is well suited for very sensitive patients such as neonates [29].

Most imaging approaches for RR monitoring [16, 30] including our previous works [27, 28, 31] are based on the detection and tracking of certain feature points or anatomic landmarks such as the nose. Abbas et al. [27] presented in 2011 an algorithm which estimated the RR using a continuous wavelet transform of the temperature modulation around the nostrils. The region of interest (ROI) was defined in the first frame and no tracking algorithm was used. They validated their approach using video data from seven premature infants. In 2017, our research group improved this approach by implementing a tracking algorithm. To estimate the instantaneous respiratory frequencies, three estimators were computed for each position of the short adaptive analysis window: adaptive window autocorrelation, adaptive window average magnitude difference function, and adaptive maximum amplitude pairs [32]. To the best of our knowledge, there aren't any other approaches in the literature, which use thermal imaging to monitor RR in infants. Further research groups (such as [16, 30]) tested their methods in video data from adult volunteers. Fei and co-authors [16] used a coalitional tracking algorithm to track motion. Posteriorly, the respiratory temperature waveform was normalized and wavelet analysis was applied to the re-sampled signal. Lewis et al. [30], in turn, tested a tracking method based on the Piecewise Bezier Volume Deformation model. The thermal signal, computed from both nostrils, was dynamically filtered and the breath interval was calculated using its first derivative.

The former techniques work well when the nose is clearly visible in the image, however they fail when the nose is outside the camera's field of view (patient lying on the side). In this paper, we present a new "black-box" approach which does not rely on tracking of

anatomic landmarks, but instead automatically detects respiration in image sequences.

For a proof-of-concept, the approach was firstly validated in a study involving healthy adult human subjects. Here, its ability to accurately measure RR during challenging conditions (simulated breathing disorders) was analyzed. A second study with newborn infants was performed at the division of Neonatology of the Sophia Children's Hospital (Erasmus MC, Rotterdam, The Netherlands); the aim was to evaluate the outcome of the algorithms in this particular group as well as in a clinical scenario.

In this paper, Sec. II presents the proposed algorithm. Section III describes the experimental protocol and setup of both studies. The results are presented in Sec. IV and discussed in Sec. V. Finally, Sec. VI concludes the paper and gives future perspectives.

II. Methodology

In this paper, a "black-box" or grid-based approach was used. This means that instead of defining a ROI based on anatomic landmarks (e.g. the nose [16, 30]), a grid was laid over the image with each grid cell representing one ROI. The respiratory signal and RR were extracted for each ROI and afterwards analyzed with regard to its quality. Finally, suitable ROIs were automatically selected and information was fused in order to get robust estimations for RR. The above-mentioned steps are illustrated in Fig. 1 and are described below in detail. The algorithm was programed and tested in MATLAB (MATLAB 2017a, The MathWorks Inc., Natick, MA, USA) using a 64-bit Windows 7 computer with a quad-core Intel® Core™i5-3450 3.10 GHz processor, 16 GB RAM and a solidstate drive. Data were analyzed offline.
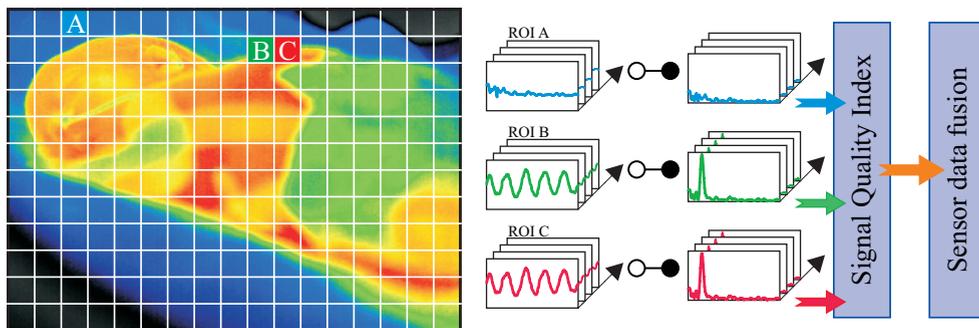
Figure 1: Schematic representation of the major steps used to estimate RR.

A. Extraction of respiratory signal and estimation of signal quality

For the kth ROI, the signal sROIk (t) at timestamp t was extracted by calculating the 2-dimensional mean value of all pixels within the ROI according to

$$s_{ROI_k}(t) = \frac{1}{mn} \sum_{i=0}^{m-1} \sum_{j=0}^{n-1} I_{ROIk}(i,j,t) \tag{1}$$

The width and height of ROIk are denoted by *m* and *n*, while I_{ROIk} *(i,j,t)* denotes the intensity at pixel *i,j* at time stamp *t*. For further analysis, a hamming window was applied to the most recent 15 seconds of $sROI_k(t)$, resulting in the analysis window $s_w ROI_k(t)$. As known, a rectangular window applied to a signal in the time domain can lead to distortions in the frequency domain. To minimize these distortions, a smoother window shape (Hamming window) was applied. When used, this de-emphasizes the edges and reduces their effects [33]. The length of 15s was used because the resulting trade-off between time- (15s) and frequency resolution (4 breaths/min) seemed reasonable to track changes in respiratory rate fast enough while maintaining sufficient accuracy. Posteriorly, the analysis window was mean centered and transformed into the frequency domain using a Fourier transform. Each window's spectrum $S_w ROI_k(f)$ was normalized to its maximum value.

In subsequent steps, three different frequency bands were considered:
- Low-Pass (LP): f < 0:1Hz,
- Band-Pass (BP): 0:1Hz ≤ f ≤ 3Hz,
- High-Pass (HP): f > 3Hz.

While the LP-Band contains low-frequency noise (e.g. baseline drift), the HP-Band contains high-frequency noise components (e.g. sensor noise or motion artefacts). The BPBand is the frequency range of respiration. It ranges between 0.1 and 3 Hz in order to increase the number of applications of our approach. It can be used not only for monitoring RR in newborn infants (normal RR ranges between 40 and 60 breaths/min) but also for monitoring RR in adult patients (normal RR ranges between 12 and 20 breaths/min). Additionally, in the future, we plan to test the capability of the current approach to detect heart rate. The mean heart rate for adults ranges from 60 to 100 beats per minute (bpm) and that for preterm infants ranges from 120 to 170 bpm [6, 34, 35].

In order to determine whether the current analysis window of a ROI actually contains a respiration-related signal or only noise, a signal quality index (SQI) was empirically developed:

$$\begin{cases} 1 - \left[\frac{1}{2} \cdot F3 + \frac{1}{4} \cdot (F1 + F2)\right], & if\ F4 \geq 2 \\ 1 - \frac{1}{2} \cdot (F1 + F2), & otherwise. \end{cases} \tag{2}$$

It was based on four features (F1 - F4) of the normalized spectrum, see Fig. 2. The first feature (F1) corresponds to the maximum within the HP-band. The second feature, F2, stands for the percentage of values in the HP-band larger than a given threshold. The third feature, F3, denotes the difference between maximum in the BP-band and maximum in the LPband. The last feature, F4, refers to the ratio between the maximum in LP-band and maximum in BP-band.
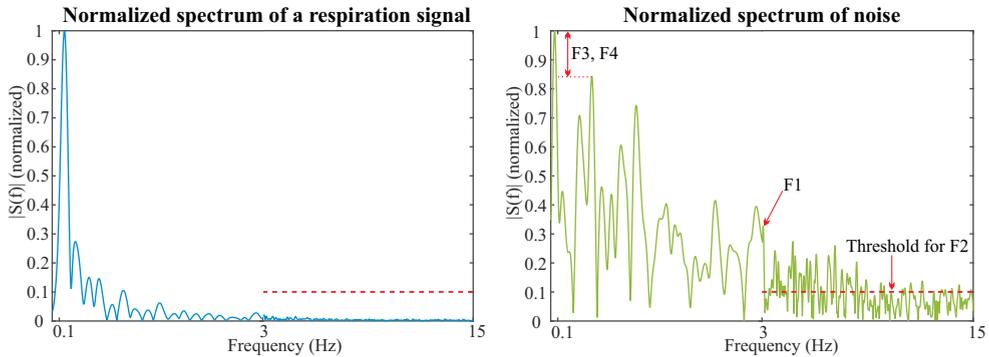
Figure 2: Left: normalized spectrum of a representative respiratory signal resulting in a SQI of 0.98. Right: normalized spectrum of noise (SQI = 0.71)

The SQI takes both high frequency noise (features F1 and F2) as well as low frequency noise (features F3 and F4) into account. Due to its definition, possible values of the SQI are limited to [0,1]. While a SQI of 1 indicates a very good signal quality, a SQI of 0 points towards a very poor signal quality.

B. Selection of grid cells and estimation of RR using information fusion

For each ROI's current analysis window, the RR was defined as the frequency within the BP-Band with the maximum amplitude in the normalized spectrum. However, ROIs with an actual respiratory signal must be distinguished from those which do not contain a respiratory signal (e.g. background noise). This was accomplished by only accepting ROIs with a SQI higher than a threshold of 0:75, which was empirically defined. All other ROIs were excluded from further analysis.

Three different sensor fusion techniques were applied to the RRs of the ROIs RR_{ROIk}, in order to estimate the instantaneous RR. The following paragraphs describe the three algorithms in detail.

a)   *Median:* This first approach computes the median frequency of all valid ROIs. The fused RR at time point t is governed by the following equation:

Chapter 7

$$RR_t^{fus} = 60 \cdot f_t^{fus},$$ (3)

with

$$f_t^{fus} = median(f_t^i).$$ (4)

Here, stands for the fused frequencies at time point *t*. The variable represents, in turn, the frequency at which the normalized power spectrum of the ROI *k* assumes its maximum:

$$f_t^i = \arg\max_{f_{min} \leq f \leq f_{max}} S_{ROIk,norm}(f).$$ (5)

The frequency boundaries f$_{min}$ and f$_{max}$ correspond to the boundary respiratory rates of the HP-band, i.e. 6 breaths/min and 180 breaths/min, respectively.

b)   *Best SQI:* The second approach consists in selecting the RR of the ROI with the highest SQI.

c)   *Bayesian fusion:* The Bayesian fusion is based on the well-known Bayes' law, which allows the estimation of a system state variable x (posterior probability distribution) using observations (measurements) from different sensors (ROIs in this case) s. In order to apply Bayesian fusion to the presented algorithm, current observations (current analysis window) needed to be separated from previous observations (previous analysis windows):

$$p(x|s_t^m) = \frac{p(s_t^m|x, s_{t-1}^m) \cdot p(x|s_{t-1}^m)}{p(s_t^m|s_{t-1}^m)}.$$ (6)

While is the likelihood function, denotes the prior distribution. The denominator is a normalization factor for integrating the probability density function to one. The *m* available sensors (ROIs) *s¹… sᵐ* are denoted by *sᵐ*. In this work, we considered the sensors to be independent from each other, therefore

$$p(s_k^m|x, s_{k-1}^m) = \prod_{i=1}^{m} p(s_k^i|x, s_{k-1}^i).$$ (7)

Under this assumption, the Bayesian fusion can be calculated according to

$$p(x|[s_k^1 ... s_k^m]) = p(x|s_{k-1}^1 ... s_{k-1}^m) \cdot \prod_{i=1}^{m} \frac{p(x|s_k^i)}{p(x|s_{k-1}^i)}.$$ (8)

In this work, the system state variable x stands for the RR and represents the RR of each

valid ROI. Based on the probability function after Bayesian fusion, the RR was defined as the RR with the highest probability within the frequency boundaries of the BP-band (6 breaths/min and 180 breaths/min):

$$RR_{fus} = \arg\max p\left(x\big|\left[s_k^1 \dots s_k^m\right]\right), RR_{min} \leq RR_{fus} \leq RR_{max}. \tag{9}$$

The analysis window was updated in steps of 1 second resulting in a temporal resolution of 1 Hz for the RR.

III. Experimental protocol and setup

The first aim of this work was to validate the feasibility of the proposed "black-box" algorithm. To achieve this, data of healthy volunteers collected in a previous study [31] was used. The second aim was to examine the capability of our approach to accurately estimate RR in newborn infants. For that, a second study was carried out with newborns at the division of Neonatology of the Sophia Children's Hospital (Erasmus MC, Rotterdam, Netherlands).

A. Study in Healthy Subjects
Twelve healthy subjects (5 females and 7 males), between the ages of 21 and 31 (25.25 ± 2.83 years) voluntarily accepted to participate in the study. During the experiments, a long-wavelength infrared (LWIR) camera [VarioCAM® HD head 820S/30 mm (InfraTec GmbH, Dresden, Germany)] was sat atop a tripod located 2m away from the subjects and at their height. The thermal camera has an uncooled infrared microbolometer focal plane array with a spatial resolution of 1024 x 768 pixels and detects infrared wavelengths in the spectral range of 7.5 μm to 14 μm. At 30°C, its thermal sensitivity is better than 0.05K. In addition, the thermal videos were acquired with a frame rate of 30 frames per second (fps). The study protocol comprised two phases: A and B. In phase A, a nine minutes recording was carried out; the volunteers were instructed to sit still and breathe normally. In phase B, they were advised to simulate in a period of ten minutes the sequence represented in Fig. 3. It was composed of normal (eupnea) and diverse altered respiratory patterns (e.g. tachypnea, apnea, Kussmaul breathing and Cheyne-Stokes respiration). Thoracic effort (piezoplethysmography) was the ground truth (GT) used to validate the results. It was measured simultaneously with the data recording system SOMNOlab 2 (Weinmann GmbH, Hamburg, Germany). In order to simplify signal synchronization, the volunteers were advised to hold their breath 15 s before beginning and 15 s after ending of each phase. The study design and protocol were approved by the Ethics Committee of RWTH Aachen University Hospital (EK

081/16).
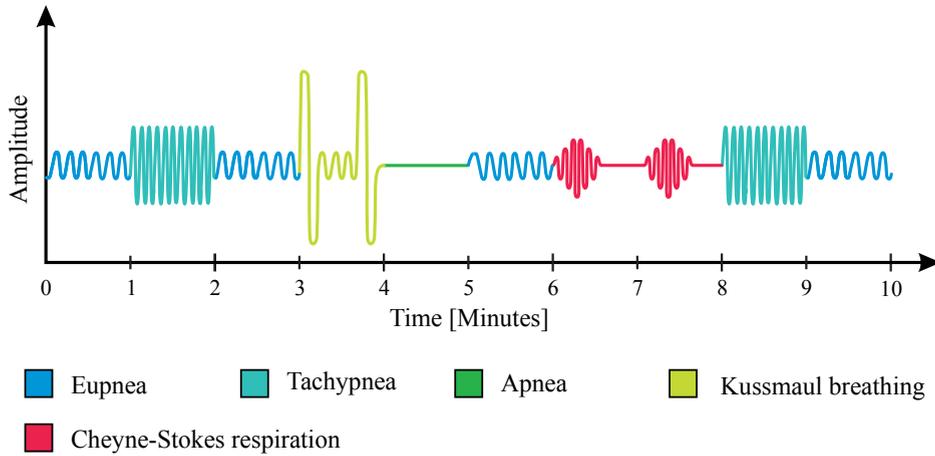
Figure 3: Respiratory sequence simulated by the healthy volunteers in phase B. It consists of normal and altered breathing patterns: tachypnea, apnea, Kussmaul breathing and Cheyne-Stokes respiration.

B. Study in Newborn Infants

To investigate the performance of the algorithms under real conditions, a feasibility study was carried out at the division of Neonatology of the Sophia Children's Hospital, Erasmus University Medical Center (Erasmus MC). Its design and protocol were approved by the Ethics Committee of the Erasmus MC (MEC 2017-042). In order to be eligible to participate in this study, the subjects must meet all of the following criteria:

1)   admitted to the Sophia Childrens hospital;
2)   gestational age between 24 and 42 weeks;
3)   be in control of their breathing frequency (either non-invasive, synchronized, flow, or no respiratory support);
4)   stable health condition.

Patients with time-dependent respiratory support were excluded from participation.

After obtaining informed consent from the parents/caregivers, two 5-minutes thermal recordings per patient (one on each side of the incubator/open bed) were carried out. For each recording of patients lying in incubators, a different door (left or right) was opened (note that it is not possible to record through the polycarbonate hood of the incubator due to its non-transparency for thermal radiation).

When the patient was in an open bed, the curtain was slide aside slightly. The thermal

camera [VarioCAM® HD head 820S/30 mm (InfraTec GmbH, Dresden, Germany)] was sat atop a tripod in front of the open door. As a matter of fact, patients were not moved for the recording, thus all sleeping positions were considered. Fig. 4 illustrates the study setup. In general, the observational study included eight newborn infants (6 males and 2 females) with the following characteristics: gestational age (GA) - 32 ± 4 weeks, postnatal age (PA) - 27 ± 19 days. Table I shows the patient data. To validate the results, the RR derived from body surface electrocardiography (ECG), measured with the M540 patient monitor (Dräger AG, Lübeck, Germany), was used. RR was acquired with a sampling rate of 1 Hz.

Figure 4: Illustration of the study setup for an open bed.

IV. Results

This section firstly describes the performance of our approach in thermal videos of healthy adult subjects (Sec. IVA). Section IV-B, in turn, presents the results of the validation in newborn infants. The whole evaluation was performed in MATLAB (MATLAB 2017a, The MathWorks Inc., Natick, MA, USA).

Table 1: Patient data

Infant	Gender	Gestational age [weeks + days]	Postnatal age [days]	Weight [g]	Sleeping position	Respiratory Support	Type of bed
I1	M	33 3/7	46	1705	Supine	O$_2$ therapy	Open bed
I2	M	33 3/7	46	1690	Lateral	O$_2$ therapy	Open bed
I3	F	32 6/7	29	1125	Prone	O$_2$ therapy	Incubator
I4	M	34 2/7	52	1850	Lateral	SIMV and PSV	Open bed
I5	M	27 3/7	6	950	Supine	CPAP	Incubator
I6	M	27 3/7	6	955	Supine	CPAP	Incubator
I7	F	40	26	3100	Supine	SIMV and PSV	Incubator
I8	M	30 2/7	3	1570	Lateral	CPAP	Incubator

SIMV: Synchronous Intermittent Mandatory Ventilation; PSV: Pressure Support Ventilation

CPAP: Continuous positive airway pressure

A. Study in Healthy Subjects

a)   *Phase A:* Table II shows the performance of the algorithm for phase A. The best results were obtained using the fusion method median. The root-mean-square error (RMSE) hovered around (0.31 ± 0.09) breaths/min. On average, 97.53% and 99.55% of the absolute errors did not transcend 1 breath/min and 2 breaths/min. By using the best SQI, similar results were achieved; the RMSE averaged (0.32 ± 0.15) breaths/min. In addition, 97.82% and 99.53% of the absolute errors between both monitoring technologies (IRT and GT) were smaller than 1 breath/min and 2 breaths/min. Finally, with Bayesian fusion the RMSE was (0.51 ± 0.15) breaths/min. In comparison with the two previous fusion methods, the percentage of errors smaller than 1 breath/min and 2 breaths/min decreased to 92.19% and 99.39%, respectively. Additionally, the results showed similar mean correlation coefficients for the three fusion methods: 0.98 for both median and best *SQI*, and 0.95 for Bayesian fusion (all p-values were smaller than 0.05). Note, that the previous values were calculated by averaging the correlations calculated for each single subject.

Table 2: Performance of the approach for phase A.

Subject	Gender	Age	RMSE [breaths/min]		
			Median	best SQI	Bayes
S1	F	24	0.3	0.24	0.35
S2	F	24	0.27	0.24	0.79
S3	M	31	0.4	0.7	0.54
S4	M	27	0.38	0.39	0.34
S5	M	29	0.2	0.21	0.49
S6	M	25	0.22	0.22	0.34
S7	F	22	0.45	0.44	0.47
S8	M	25	0.47	0.47	0.56
S9	F	26	0.26	0.21	0.47
S10	M	26	0.2	0.2	0.56
S11	M	21	0.38	0.33	0.45
S12	F	23	0.24	0.22	0.79
Mean ± SD			0.31 ± 0.09	0.32 ± 0.15	0.51 ± 0.15

Fig. 5 displays a Bland-Altman plot comparing both measurement techniques (IRT and GT). Using median for data fusion, a mean difference of 0.026 breaths/min was achieved and the limits of agreements ranged from –0.82 breaths/min to 0.87 breaths/min.
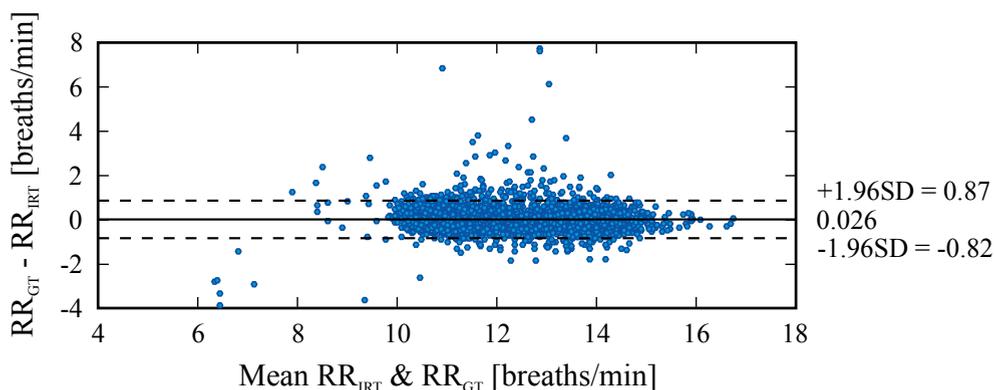
Figure 5: Bland-Altman plot comparing both measurement methods, IRT (RR_{IRT}, fusion method median) and GT (RR_{GT}). The bias averages 0.026 breaths/min (solid line) and the 95% limits of agreement vary between –0.82 breaths/min and 0.87 breaths/min (dashed lines).

b)   *Phase B:* Table III shows, in turn, the performance of the algorithm for phase B. Also here, the best results were obtained using the fusion method *median;* the RMSE hovered around (3.27 ± 0.72) breaths/min. On average, 88:60% of the absolute errors between IRT and GT did not exceed 2 breaths/min (81.09% were smaller than 1 breath/min). Using the *best SQI*, the following results were achieved: RMSE averaged (3.39 ± 0.86) breaths/min, and the absolute errors between both techniques were smaller than 1 breath/min and 2 breaths/min in 81.33% and 88.75% of the cases. Lastly, with the third fusion algorithm (Bayesian fusion), a RMSE of (3.41 ± 0.63) breaths/min was obtained. In this case, 79.76% and 88.82% of the absolute errors did not transcend 1 breath/min and 2 breaths/min. Also in phase B similar mean correlation coefficients were obtained for the three fusion methods: 0.95 for median and 0.94 for both best SQI and Bayesian fusion (all p-values were smaller than 0.05).

Table 3: Performance of approach for phase B.

Subject	RMSE [breaths/min]		
	Median	best SQI	Bayes
S1	2.36	2.27	2.7
S2	4.35	4.23	4.41
S3	3.17	3.19	3.26
S4	2.2	2.32	2.6
S5	2.49	2.46	2.75
S6	3.33	3.42	3.32
S7	4.36	5.34	4.18
S8	2.71	3.22	2.8
S9	3.63	3.78	3.67
S10	3.98	3.19	4.26
S11	2.96	3.01	3.04
S12	3.73	4.22	3.87
Mean ± SD	3.27 ± 0.72	3.39 ± 0.86	3.41 ± 0.63

Fig. 6 shows the RR estimated with thermal imaging (solid blue line) as well as the GT signal (green dashed line). This illustrative example displays the signals correspond to subject S5 (phase B). In Fig. 7, a Bland-Altman plot comparing both monitoring techniques is presented. In this example, median was the method used for data fusion. In general, the Bland-Altman demonstrates a bias of 0.78 breaths/min and limits of agreement range from –6.4 breaths/min to 8.0 breaths/min. Outliers are highlighted by the grey shading regions (more details in Sec. V - Discussion).

Figure 6: Estimated RR correspondent to subject S5 (blue solid - IRT, green dashed line - GT). Median approach was used for data fusion. The grey shading regions show the transitions between different respiratory patterns.
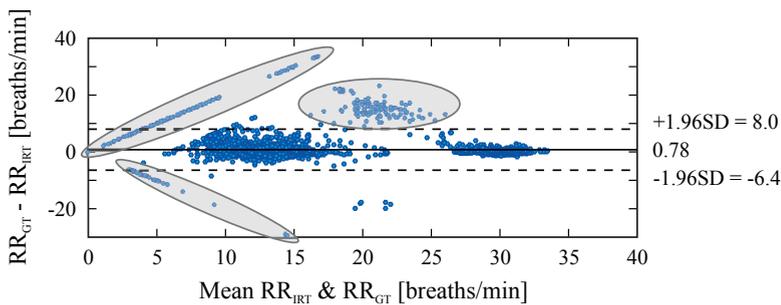
Figure 7: Bland-Altman plot comparing both measurement methods, IRT (RR_{IRT}, fusion method median) and GT (RR_{GT}). The bias averages 0.78 breaths/min (solid line) and the 95% limits of agreement vary between –6.4 breaths/min and 8.0 breaths/min (dashed lines). Outliers are highlighted by the grey shading regions.
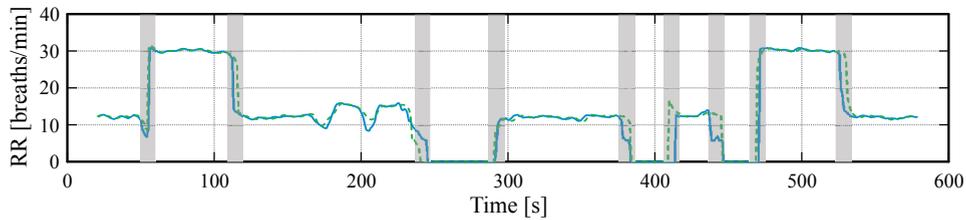
B. Study in Newborn Infants

Table IV demonstrates the performance of the proposed algorithm for each infant and video sequence (1 and 2). Unfortunately, during the first video recording the infant I3 became agitated (due to reasons not related with this study). As the signals only contained movement artifacts, the sequence was not considered for evaluation. Using the median for signal fusion, a mean RMSE of (4.15 ± 1.44) breaths/min was obtained. In addition, the mean RR error was (3.36 ± 1.25) breaths/min and the spread of the error, calculated using the 90th percentile of the errors , reached (6.53 ± 2.39) breaths/min. On average, the RR of the newborn infants hovered around (54.19 ± 6.23) breaths/min. The results showed a mean correlation of 0.79 (all p-values were smaller than 0.05).

Table 4: Performance of the approach on the thermal videos of newborn infants.

Infant	Sequence	RR_{GT} [breaths/min]	RR_{IRT} [breaths/min]	RMSE [breaths/min]	[breaths/min]	$_{90}$ [breaths/min]
I1	1	62.05	59.41	4.79	4.17	7.71
	2	53.86	51.2	6.11	5.16	8.96
I2	1	46.45	46.88	4.53	3.49	7.69
	2	50.24	52.86	6.75	5.14	11.68
I3	1	-	-	-	-	-
	2	47.49	46.99	4.29	3.43	6.86
I4	1	53.03	52.08	1.95	1.48	2.97
	2	55.63	56.07	1.53	1.15	2.97
I5	1	53.35	56.51	3.98	3.29	5.53
	2	49.6	47.96	2.86	2.42	4.59
I6	1	69.56	68.17	5.02	4.06	8.62
	2	61.84	62.35	5.91	5.31	8.83
I7	1	49.38	51.88	3.56	3.06	5.83
	2	49.91	51.34	2.67	2.02	4.58
I8	1	59.5	57.15	4.42	3.76	7.03
	2	51.02	50.96	3.86	2.44	4.09
Mean ± SD		54.19 ± 6.23	54.12 ± 5.72	4.15 ± 1.44	3.36 ± 1.25	6.53 ± 2.39

Fig. 8 depicts a Bland-Altman plot comparing both measurement techniques, IRT and GT. According to the results, the estimated mean difference was 0.24 breaths/min and the limits of agreement ranged from −8.1 breaths/min to 8.6 breaths/min. Lastly, Fig. 9 shows the RR estimated with thermal imaging (solid line) as well as the GT signal (dashed line). This illustrative example displays the signals of infant I7 (video sequence 2).
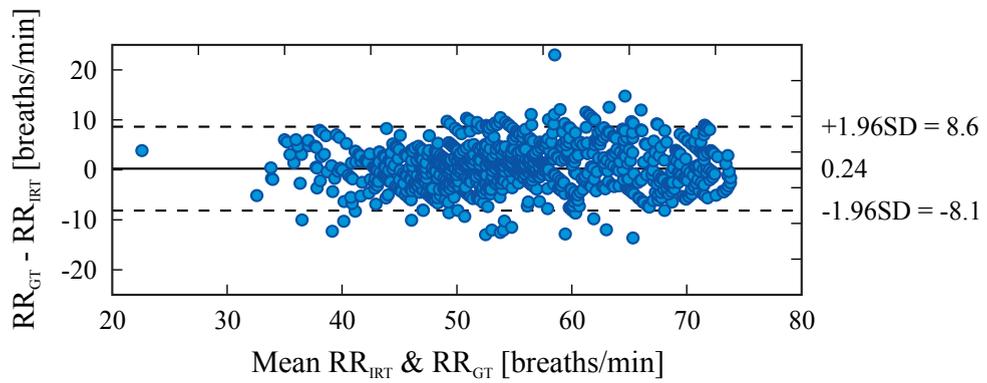
Figure 8: Bland-Altman plot comparing both measurement methods, IRT (RR_{IRT}, fusion method median) and GT (RR_{GT}). The bias averages 0.24 breaths/min (solid line) and the 95% limits of agreement vary between –8.1 breaths/min and 8.6 breaths/min (dashed lines).
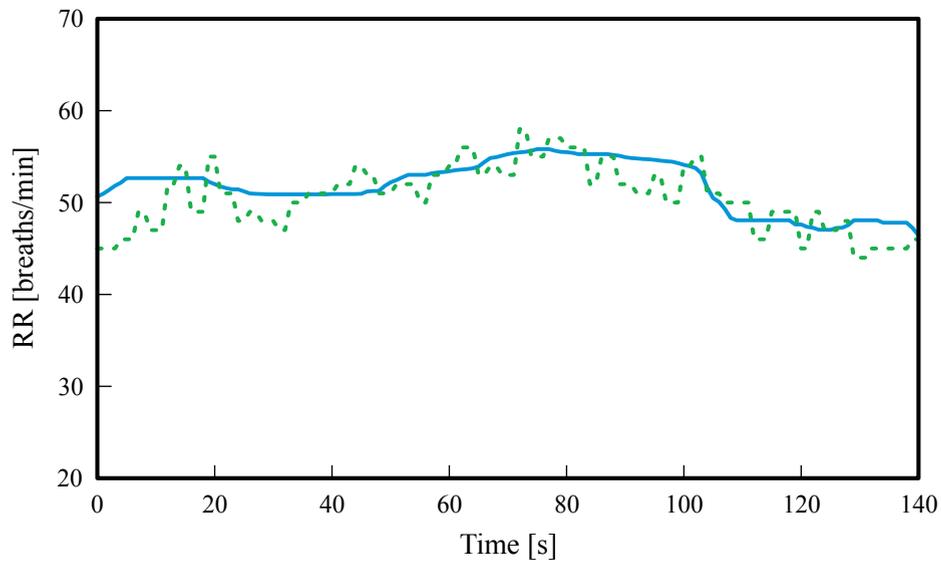
Figure 9: Illustrative example showing estimated RR. Whereas the dashed line corresponds to the GT, the solid line stands for the RR estimated with IRT. The signals correspond to subject I7 (video sequence 2).

V. Discussion

Respiratory rate is a primary vital sign in critical care. However, it is also one of the major undocumented parameters. This is mainly due to the drawbacks of current monitoring techniques, which rely on cables as well as on the attachment of sensors. In neonatal care, cables and electrodes contribute significantly to stress and discomfort. Especially preterm and VLBW infants have a very thin and sensitive skin, thus adhesive electrodes often damage their skin when being removed. To overcome all these issues, scientists seek for new reliable and unobtrusive monitoring alternatives.

The current paper proposed a novel approach for noninvasive and passive assessment of RR in newborn infants using IRT. As a proof-of-concept, its performance was firstly validated in a study involving twelve healthy adult human subjects. Here, the robustness of the algorithm under challenging conditions (e.g. variable RR and simulated respiratory disorders) was investigated. A second study was carried out in eight newborn infants hosted in an incubator under real conditions.

A. Study in Healthy Subjects

The presented approach was firstly validated using thermal videos of twelve healthy adults. In phase A (subjects were advised to breath normally), a good agreement between GT (piezoplethysmography) and thermal imaging was observed. By using the median for sensor fusion, the best results were achieved, with a mean RMSE of (0.31 ± 0.09) breaths/min. The Bland-Altman plot of Fig. 5 together with the mean correlation coefficient and the percentage of errors smaller than 1 and 2 breaths/min (92.19% and 99.39%) corroborate the good agreement between both monitoring technologies. To examine clinically relevant scenarios within the study, a wide range of physiological and pathological respiratory patterns (including eupnea, tachypnea, apnea, Kussmaul breathing, and Cheyne-Stokes respiration) were simulated in phase B. Table III together with the Bland-Altman plot of Fig. 7 show higher RR errors in Phase B (compare with Table II and Fig. 5 of phase A). In this phase, abrupt changes in RR were simulated (e.g. from 0 breaths/min to 30 breaths/min), as illustrated in Fig. 3 and Fig. 6. Therefore, small delays between GT and IRT in these transitions caused higher temporal errors, which negatively influenced the RMSEs displayed in Table III. These errors correspond to the outliers illustrated by the grey shading regions of Fig. 7. The great discrepancies occurred in transitions such as eupnea to tachypnea, tachypnea to eupnea, apnea to tachypnea, tachypnea to eupnea, etc. The previous statements together with Fig. 6 prove that the errors between IRT and GT outside these passages were actually quite small. Indeed, as described in Sec. IV-A, the percentage of absolute errors smaller than 1 and 2 breaths/min hovered around 81.09% and 88.60%, respectively. In addition, two techniques based on different measurement principles were compared, which may have

contributed to small lags or different reaction times in the transitions between distinct respiratory patterns.

In 2017, our group proposed another approach to estimate RR from thermal videos of adult volunteers [31]. Note that the video sequences were used in the current paper to test the feasibility of the "black-box" algorithm. The approach presented in 2017 used the information of four different ROIs to compute RR ("multiple regions of interest" approach): nose (temperature modulation), mouth (temperature modulation), and shoulders (movement). To measure RR, the ROIs were automatically identified in the first frame of the video sequence and, afterwards tracked. In a further step, the four respiratory waveforms were extracted. Lastly, the RR from the four ROIs were fused to minimize the detection error probability and to achieve a higher reliability. Despite of the good results, it presented a major drawback. For an automatic detection of all ROIs, the subjects must lay in supine position. To overcome this issue, we developed a novel algorithm, presented in this paper, which does not use any anatomical region to estimate RR; it regards thermal videos sequences as blackboxes. In brief, similar results between the two approaches were obtained. By applying the "black-box" algorithm, a mean RMSE of 0.31 breaths/min and 3.27 breaths/min was obtained for phase A and B, respectively. Using the approach "multiple regions of interest", the mean RMSEs averaged 0.28 breaths/min and 3.36 breaths/min. In sum, the results indicate that the proposed approach is capable of accurately estimating RR in thermal videos even during challenging conditions.

B. Study in Newborn Infants

After a successful validation on thermal videos of healthy adults, the performance of the "black-box" algorithm was examined on data from newborn infants under incubator care. For the two recordings, the camera was placed first on the left and then on the right side of the medical device. One aim of the study was to discover whether the position of the infants affects the analysis technique. Thus, patients were not moved for video acquisition.

Table IV and the correlation analysis show the good agreement between the proposed method and reference, with a mean RMSE of (4.15 ± 1.44) breaths/min and a mean correlation coefficient of 0.79. The Bland-Altman plot of Fig. 8 shows a very good accuracy (ability to measure RR close to its true value) between thermal imaging and GT as corroborated by the small bias (0.24 breaths/min). The 95% limits of agreement (−8.1 breaths/min, 8.6 breaths/min), on the other hand, indicate a higher spread of the errors. There are some reasons that justify these higher errors. First, RR derived from ECG is very prone to motion artifacts, to physiologic events which induce thoracic movements unrelated to respiration (e.g. crying), and to poor ECG electrode placement. Second, the monitoring modalities as well as the algorithms (e.g. filtering, averaging)

used to compute this vital parameter are different. Lastly, the RR from newborn infants varies constantly and is also characterized by abrupt changes. Therefore, small delays between thermal imaging and GT may lead to high errors.

In 2011, Abbas et al. [27] evaluated the capability of their approach to estimate RR in eight preterm neonates. This algorithm tracks a ROI enclosing the nose in order to detect temperature fluctuations during the respiratory cycle. Despite of the outstanding results, this approach is impracticable during respiratory support via face masks and it strongly depends on sleeping position, since the nostrils must be always in the field of view of the thermal camera. In our paper, we demonstrated that our algorithm is capable of detecting this vital parameter without being affected by the (1) sleeping position, (2) position of the head and (3) by the oxygen delivery method (e.g. face masks, nasal cannulae, nasal prongs).

The major drawback of the proposed algorithm is the sensitivity to motion artifacts. Therefore, the next aim should be to integrate a motion analysis algorithm capable of detecting motion noise inside the incubator, including patient movement, nursing interventions or maternal touch. In the clinical study, the recordings were performed with the door of the incubator opened, since its polycarbonate hood is not transparent for thermal radiation. In a real setting, the camera should be integrated inside of the incubator, or the setting proposed by Villarroel et al. [25] should be adopted, where a 3 cm hole was cut in the top of the incubator canopy.

Thermal imaging is still an expensive technology, especially when compared with other techniques, such as radar or visible imaging systems, which are relatively affordable. However, IRT has peculiar specifications that make it very attractive for diverse medical applications, especially in neonatology. First, thermal imaging is a passive technique, i.e. it measures the radiation emanated by the body. In contrast, radar is an active system, which irradiates the patient with electromagnetic radiation. Regarding safety aspects and a future product approval, such characteristics are particularly valuable, as the eligibility criteria for neonatal medical equipment are very rigorous. Secondly, contrary to other technologies, thermal imaging is also capable of "seeing" in total darkness. Near infrared and visible imaging systems, in turn, require at least a small amount of light to produce an image. Thus, a 24 hours monitoring would require an active radiation of the patients, at least during the night. Thirdly, IRT also allows the monitoring of body temperature and body temperature distribution.

Until a few years ago, thermal cameras were mostly used for military applications. Nevertheless, in the last decade, thermal imaging cameras are finding their way in more

and more consumer-oriented applications, like driver vision enhancement and home security, leading to an increase in production volumes and, consequently, to a decrease in prices. As other technologies, we believe that IRT systems will become affordable, compact and, image quality will even further improve.

The calibration of an uncooled IRT camera is still a very complex process. Therefore, their use for applications that require a very accurate temperature measurement might not be meaningful. In our case, absolute accuracy is not a crucial parameter, since we do not intend to measure absolute temperatures. Instead of accuracy, a good thermal sensitivity and resolution is mandatory for RR assessment, since the acquired videos must have a good contrast.

VI. Conclusions

Unobtrusive and non-contact monitoring of RR and other vital signs have become increasingly important during the last years. Doppler radar, magnetic impedance and camera technologies (visible, near-infrared, mid-wave infrared, and LWIR imaging systems) can be an important contribution to unobtrusive vital signs monitoring. In this paper, a novel approach to unobtrusive and non-contact RR monitoring using a LWIR camera was presented. Instead of tracking anatomic landmarks, a grid of regions of interest was laid over the image and an algorithm was developed in order to automatically select ROIs suitable for detection of respiration. Such an approach enables to monitor RR independent of the subject's position and anatomic landmarks in the camera's field of view. In order to further improve accuracy, different methods were used to fuse the information available from the different ROIs. Initially, the validation of the algorithm demonstrated its high accuracy compared to a clinical gold standard using data from a lab experiment. Afterwards, the algorithm was validated using clinical data recorded during a study with preterm neonates. Again, the algorithm showed very good results (mean RMSE of (4.15 ± 1.44) breaths/min). In conclusion, this approach was able to robustly extract RR from LWIR video sequences not only in lab settings, but also under real clinical conditions. Therefore, IRT may be a very promising and clinically relevant alternative for current monitoring technologies in neonatal care.

Acknowledgment

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Chapter 8

Discussion

Discussion

The aim of these studies was to improve oxygen treatment of preterm infants after birth during treatment in the delivery room and to investigate the feasibility of new technology related to the control of oxygen saturation. The discussion below focusses on oxygen saturation measurements during delivery room management and the development of a new monitoring system that provides easier access to relevant parameters. Moreover, it takes automatic control of oxygen saturation into account, as well as some new advancements that are expected in the future.

Resuscitation

Resuscitation, the assessment and care in the delivery room immediate after birth, is challenging. Guidelines, especially the European guidelines, do not provide practical targets for SpO_2 for the first minutes after birth[1]. Tailoring the fraction of inspired oxygen (FiO_2) to the needs of preterm infants in the first minutes of life is challenging because of e.g., the gradual aeration of the lungs. We studied SpO_2 levels during resuscitation of preterm infants in daily practice and found that the median of the observed infants followed the European RC targets quite nicely [2], but the variation in the SpO_2 in the first 5 minutes was large. These large deviations could have several possible explanations. Sometimes it takes time before the first SpO_2 measurement could be obtained. This could be due to poor perfusion, which is difficult to prevent, but it can also be due to problems with sensor placement [3, 4]. Such a delay could cause a further deviation from the SpO_2 targets. Second, during the initial phase of supportive care, ventilation of preterm infants is hampered by lung immaturity, resulting in inappropriate aeration of the lung, i.e. establishing functional residual capacity [5]. Other explanations for suboptimal ventilation could be mask leaks or airway obstructions [6, 7]. During this entire process, the transition from foetal to a neonatal ventilation can cause additional problems for the perfusion, oxygen extraction and correctly measuring the SpO_2 [8].

Around 5 minutes after birth, the median of the SpO_2 rose to follow the targets more closely. Hence, the result of respiratory support, improved lung recruitment and perfusion[7] is that in most infants adequate respiratory support was obtained [7]. However, as found in Chapter 3 although the median indicates adequate respiratory support, more than 30% of the infants were still outside the SpO_2 limits at any given time. Hence, even with adequate respiratory support, it is challenging to remain between the high and low SpO_2 levels, especially during e.g., tube placement or suctioning. These interventions are necessary and hence will remain a cause of variations in SpO_2 levels. Furthermore, it remains unknown which SpO_2 targets, or target range, provide the best compromise between exposure to oxygen and avoiding hypoxia. It is clear however that

a target *range* provides physicians with more practical information than a target value, because it also includes information about an acceptable deviation.

Compliance with the local protocol to start resuscitation was low (57%). The study of van Eijk et al., showed that low compliance can also be caused by protocols that are not up to date or do not fit to clinical practice. An example of this is that sometimes before an intervention, FiO_2 is shortly set to 100 so that a dip in saturation is diminished during the intervention [9]. This can be an advantage for the infant, but it is often not included in protocols. Hence, a critical discussion on current protocols was advised. How to deal with these interventions still needs to be included in the resuscitation protocol.

Closed loop control

In chapter 5, it was shown that automated FiO_2 control is applicable both during rapidly changing physiologic conditions in a delivery room setting and during stable ventilation. Fully automated FiO_2 control without manual interventions was feasible to keep lambs within a predefined SpO_2 target range [10]. We also found that the time SpO_2 is within target range with manual and automated FiO_2 control resembled clinical data obtained in the delivery room and that automated FiO_2 control resulted in less hyperoxia during resuscitation [11].

In the study with lambs, the study alarm range was equal to target range, which created an ideal setting for dedicated manual control as caregivers are more effective in keeping SpO_2 within alarm limits then within target limits [12]. Interestingly, our data suggests that keeping animals manually within the limits was more difficult with high oxygen needs, while individual oxygen need did not influence the performance of the automated control. The caretaker providing manual FiO_2 adjustments was able to see the changing SpO_2 target ranges depicted as Dawson's curve during resuscitation and therefore had more information about saturation trends than in a standard delivery room. Seeing the SpO_2 values relatively to the Dawson curve helps in deciding which FiO_2 to provide, as we have shown in a previous study where a graphical interface was used to do exactly this [13, 14]. Thus providing an improved scenario for the manual control of the FiO_2.

8

Automated control cannot outperform clinical experience, as therapeutic interventions in the delivery room have to be adapted to a multitude of parameters [15, 16]. Early SpO_2 is related not only to FiO_2, but also to factors like adequate functional residual capacity (FRC) [17] and perinatal procedures like delayed cord clamping [18]. In addition, an increasing need for oxygen can be a symptom of a pathological condition as pneumothorax or ventilation related complication, e.g. tube dislocation. Automated control may mask these changes, at least for a short period of time. Therefore, adequate feedback to the caretaker on the automated interventions must be ensured and additional

alarms for relevant parameters like tidal volume should be routinely implemented.

Studies before and after the development of PRICO, including the first clinical trials with PRICO, have largely shown the same results; an improved time within the SpO_2 target range, less hyperoxia, but often with an increase in the frequency and or duration of hypoxia. In the studies where this did occur, this was related to the fact that when a patient is lower in the target range(more in the middle then at the top), any event that will cause a drop in the saturation is more likely to cause hypoxia and severe hypoxia [19, 20]. Highlighting the fact that the main benefit is using closed loop control, and that the differences between the different controllers is much smaller than the difference between manual and closed loop control. Because of the difficulties of achieving the prescribed target SpO_2 ranges during routine manual control, it is not well known what the balance is between damage due to hyperoxia and hypoxia [9, 21-26]. Any long term benefit of closed loop control of the FiO_2 is yet to be shown. The hope is that the effect on outcome will be shown in the FiO_2-C study, where neonates receive oxygen fine tuned through closed loop control for the entire time they need supplemental oxygen [27].

Addaptation
By studying a sample of the population in Puno, Peru, the hope was to gain more insides into the ability of neonates to adapt during the pregnancy to a low oxygen environment. Unfortunately, we were not able to include a Peruvian control population study in the fashion we had intended, because the observations in Lima at sea level could not be performed due to delays at customs. However, the study did show that adaptation is likely taking place [28]. The problem is that we are currently not actively trying to predict which neonates are likely to be born prematurely, let alone treat mother and child proactively to prepare them in case it does occur. Improvements in modelling and artificial intelligence should be able to provide us with a better insight into who is at risk of delivering prematurely, making it feasible to develop treatments so they can be prepared in advance.

Future developments
Improvements in the administration of oxygen have been made, however, we are still far away from the ideal oxygen therapy. New techniques should provide more patients specific treatments, be quicker to apply and acquire a measurement and be less obtrusive, increasing patient comfort.

New insights in factors that influence oxygen delivery to infants are needed to improve the precision with which oxygen is administrated. A good example of this is physiological

based cord clamping, during which the umbilical cord is only clamped after the lungs are aerated [29-31]. This is more inline with a natural uncomplicated birth, where a term neonate starts to cry before the umbilical cord is clamped. Although the first large multi centre randomised control study did not show a significant improvement in survival without major cerebral injury or necrotizing enterocolitis, or a reduction in mortality. The study did show lower rates of blood transfusions in the group that underwent physiological based cord clamping [29]. An improvement in the blood volume and especially the red blood cell count will aid in the transportation of oxygen, thus improving oxygen delivery.

It is unavoidable that choices that optimise oxygen for one specific organ, like brain or eyes, are not always optimal for other parts. The need for oxygen is dependent on the oxygen consumption that is directly related to the activity of that specific organ. But the oxygen saturation is the same for all arterial blood and the cardiac output controls the overall oxygen transport. Only the circulation can finetune the actual oxygen delivery, but that is a system that might not be developed to the point that it can regulate the oxygen delivery in an extreme preterm neonate. At the same time, it is a system that is faced with large internal and external changes during the initial neonatal period. And currently there is no way to manipulate the circulation as part of the care provided to the neonate. Hence, the real challenge will be to measure the need for consumption of oxygen and personalize oxygen therapy, and automatically balance the individual oxygen delivery to his or her specific needs. This type of adjustment will require additional computational power, not available in the current generation of mechanical ventilators and will pose a regulatory challenge, requiring more extensive validation to obtain medical certification.

Several non-invasive measurement options already exist and although the overall trend in the last decade has been to move to wireless sensors, this is not as useful for neonates as it is for other patient groups. New and improved options have however emerged for non-contact physiological measurements to measure heartrate, respiratory rate, and oxygen saturation, e.g., using infrared thermography and radar [32-35]. Although they are less intrusive, thus far they come with the tradeoff of reduced accuracy and reliability. Another non-invasive option is to measure respiratory effort or to approximate tidal volumes through impedance changes [36, 37]. These techniques have the potential to provide more information more quickly and provide more insight into how the premature baby is doing and how he or she is responding to therapy. However, there is also a high risk of overwhelming the medical professional with too much information. Therefore, these new techniques must not only be good enough to truly replace the old, they also should provide decision support to limit the number of parameters that are

8

presented to the medical professionals. Moreover, more efforts could be made to look at extracting as much information as possible from the measurements that are already performed, for example by combining routine physiological measurements to asses sleep [38].

Implementing and making sure that the newly developed algorithms and techniques become part of routine clinical care is as challenging as developing them. Making sure it works in all cases, all patients and all the time, and making sure that all clinical and technical staff are up to speed on all the ins and outs, is both challenging and time consuming. Efforts have been made to describe the differences between the different closed loop algorithms currently on the market. In a study by Salverda et. al., bench top simulations were performed, using a computer controlled SpO_2 simulator and a simple test lung, to feed standardized scenarios to different algorithms to compare how they react [39]. The problem that remains with this type of test is that the result is only the change in FiO_2 and it is left to the readers interpretation to determine which response is the best. More advanced simulation models will aid in comparing and validating different algorithms. Simulators like the "LuSi Physiological Model" by NeoSim AG (Chur, Switzerland) go beyond the simulation of lung mechanics, but include the physiological responses, enabling to see the full effect of changes [40]. These types of models enable users to compare different algorithms, testing them on the same scenario. As the formulas on which the models are based are published, it enables the scientific community to adapt and improve the models to fit their needs and specific patient population. This is contrary to the closed loop control algorithms which are not public, probably due to them being sold or funded by medical device manufacturers.

It will be interesting to see if these advanced physiological models can also contribute to a better understanding of the damage that is caused by oxygen free radicals. Currently it is not known what causes how much damage and how quickly; the peak oxygen tension in the blood to which an organ is exposed, or the cumulative exposure over time (area under the curve). And neither is it known what the exact optimal point is to minimize damage due to over exposure to oxygen, or damage due to a lack of oxygen. Again, all of these might be different for each individual, depending on their ability to regulate their circulation, (metabolic) activity and development of their defense against oxygen free radicals.

With the new Medical Device Regulations [41], the speed at which new developments are brought to the market will slow down further. This will increase the gap between devices used for clinical research and routine clinical use, which could, among others, lead to long running "trials", bad implementation and less frequent updates. Advanced simulation models or digital twins will likely take over some of the role of patient data

to validate new developments [42]. The need for device manufacturers to perform post market surveillance will likely improve the quality and quantity of patient data that is available for developments and improvements. But that data will come at a cost, which might make it more difficult for startups to enter the market. Catching up to manufacturers that already have a closed loop controller for the FiO_2 will be difficult, also because the best data source for developing a better closed loop algorithm is a similar patient population on a closed loop algorithm. This affirms that frequent comparable and well controlled changes will take place, and that all the measurements available are similar to the final implementation.

Conclusion

The studies in this thesis show that oxygen therapy given to preterm infants can be improved. Changing and showing the SpO_2 targets during resuscitation to a target range that depicts the acceptable deviation, aided the physicians in providing better respiratory support. Moreover, it is demonstrated that fully automated FiO_2 control is feasible during neonatal resuscitation in a near-clinical preterm delivery room setting, and that automated control prevents hyperoxia. I expect that the combination of automated and manual control might even result in further improvement of oxygen therapy in infants. However, this question needs to be further addressed in a clinical setting.

In the end, it is a balance of taking up innovations and using them in a deliberate way for either research or routine care, and making sure that the innovations either improve knowledge and care or comfort of patient, parents and medical staff.

8

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Summary

The focus of oxygen therapy in preterm infants is to strike a balance between the need for additional oxygen and preventing damage due to oxygen free radicals. Beyond merely providing extra oxygen, therapy should encompass the transportation, delivery, and extraction of oxygen tailored to the organs and tissue needs. This thesis explores the challenges that are related to optimizing oxygen therapy, and some of the advancements in automated control and non-invasive measurement techniques that could be used to improve the optimization.

"Optimizing oxygen therapy" (Chapter 2) discusses the challenges arising from factors such as the limitations of pulse oximetry, difficulties in manual control of the fraction of inspired oxygen (FiO2), and variations in preterm infant development. Existing studies, like SUPPORT, COT and BOOST, have not definitively determined optimal oxygen saturation targets for preterm infants. This has led to doubts, especially concerning the interaction between gestational age and the oxygen saturation targets.

In an observational study done at Erasmus Medical Center, the challenges in achieving oxygen saturation (SpO2) targets during resuscitation of very preterm infants, born before 30 weeks of gestational age, were quantified by focusing on the first 10 minutes after birth. Despite European Resuscitation Council guidelines recommending SpO2 targets, the control of SpO2 in newborns proves difficult. The study reveals significant variations in SpO2 levels during the initial 10 minutes and highlights the struggle to maintain the SpO2 within the target range during resuscitation (Chapter 3).

Measurements made during resuscitation of very preterm infants reveal surprising observations when compared to reference ranges for regional cerebral tissue oxygen saturation (crSO2). Initial crSO2 values were notably lower than the reference values, potentially indicating cardiac output or oxygen distribution problems in extreme preterm infants at birth. The study emphasizes the need for further understanding the adaptation of circulation and perfusion in very preterm infants and its impact on neurological outcomes (Chapter 4).

"Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs" (Chapter 5) investigates the application of fully automated FiO2 control based on predefined SpO2 targets in resuscitation and ventilation of preterm lambs. The hypothesis is that automated control can effectively manage oxygen supplementation within specified saturation targets during various physiological conditions. Results indicate that automated FiO2 control is feasible and

helps avoid hyperoxia during resuscitation, suggesting its potential to support preterm resuscitation.

Examining the impact of high-altitude pregnancy on newborns, the study in Puno, Peru, observes elevated microvascular vessel density in neonates born to mothers living at high altitude. Despite lower arterial oxygen saturation in Peruvian babies, increased vessel density is identified as a potential adaptive mechanism to a highly hypoxic antenatal environment (Chapter 6).

"Noncontact monitoring of respiratory rate in newborn infants using thermal imaging" (Chapter 7) introduces a "black-box" algorithm for noncontact monitoring of the respiratory rate in newborns through thermal imaging. The algorithm distinguishes respiratory signals from noise without relying on specific anatomical landmarks. Results from studies on healthy volunteers and newborn infants demonstrate good agreement between estimated respiratory rate by the algorithm and traditional measurements, highlighting the potential of infrared thermography as a nonintrusive alternative for respiratory rate monitoring in neonatal care.

The results of the presented studies highlight the need for improvements in oxygen therapy for preterm infants, emphasizing the importance of personalized approaches and the integration of innovative technologies into routine clinical care. Challenges in compliance with protocols, the application of fully automated control, and the future landscape of non-invasive monitoring technologies were explored. Thus, despite advancements, achieving the ideal oxygen therapy remains a challenge, with the balance between adopting innovations and ensuring effective implementation being crucial for improved neonatal care.

Samenvatting

De focus van zuurstoftherapie bij premature neonaten is het vinden van een balans tussen de behoefte aan extra zuurstof en het voorkomen van schade als gevolg van zuurstofvrije radicalen. Naast het eenvoudigweg verschaffen van extra zuurstof, zou de therapie het transport, de levering en de extractie van zuurstof moeten omvatten, afgestemd op de behoeften van organen en weefsels. Deze scriptie onderzoekt de uitdagingen die verband houden met het optimaliseren van zuurstoftherapie, en enkele vooruitgangen in de geautomatiseerde controle en niet-invasieve meettechnieken die kunnen worden gebruikt om de optimalisatie te verbeteren.

" Optimizing oxygen therapy in the year 2015" (hoofdstuk 2) bespreekt de uitdagingen die voortkomen uit factoren zoals de beperkingen van pulsoximetrie, moeilijkheden bij de handmatige controle van het fractioneel geïnspireerde zuurstofgehalte (FiO2), en variaties in de ontwikkeling van premature neonaten. Bestaande studies, zoals SUPPORT, COT en BOOST, hebben niet definitief bepaald wat de optimale zuurstofsaturatiedoelen (SpO2) zijn voor premature neonaten. Dit heeft geleid tot twijfels, met name met betrekking tot de interactie tussen de zwangerschapsduur en de zuurstofsaturatiedoelen.

In een observationele studie uitgevoerd in het Erasmus Medisch Centrum werden de uitdagingen bij het bereiken van zuurstofsaturatiedoelen tijdens de reanimatie van zeer premature baby's, geboren vóór 30 weken zwangerschapsduur, gekwantificeerd door te focussen op de eerste 10 minuten na de geboorte. Ondanks richtlijnen van de European Resuscitation Council die SpO2-doelen aanbevelen, blijkt de controle van de SpO2 bij pasgeborenen moeilijk te zijn. De studie onthult significante variaties in SpO2-niveaus tijdens de eerste 10 minuten en benadrukt de moeite om de SpO2 binnen het streefbereik te houden tijdens stabilisatie (hoofdstuk 3).

Metingen tijdens de stabilisatie van zeer premature neonaten onthullen verrassende observaties in vergelijking met referentiecurves voor regionale cerebrale weefselzuurstofsaturatie (crSO2). De initiële crSO2-waarden waren opmerkelijk lager dan de referentiewaarden, wat mogelijk wijst op problemen met cardiale output of zuurstofverdeling bij extreme premature neonaten bij de geboorte. De studie benadrukt de noodzaak om een beter begrip te krijgen van de aanpassing van circulatie en perfusie bij zeer premature neonaten en de impact daarvan op neurologische uitkomsten (hoofdstuk 4).

" Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs" (hoofdstuk 5) onderzoekt de toepassing van volledig

geautomatiseerde FiO2-controle op basis van vooraf bepaalde SpO2-doelen bij de stabilisatie en ventilatie van premature lammeren. De hypothese is dat geautomatiseerde controle van de zuurstoftoediening de SpO2 binnen gespecificeerde saturatiedoelen kan houden tijdens verschillende fysiologische omstandigheden. Resultaten geven aan dat geautomatiseerde FiO2-controle haalbaar is en helpt hyperoxie tijdens stabilisatie te vermijden, wat wijst op het potentieel om reanimatie van premature neonaten te ondersteunen.

Bij het onderzoeken van de impact van zwangerschap op grote hoogte op pasgeborenen, observeert de studie uitgevoerd in Puno, Peru, een verhoogde microvasculaire dichtheid bij neonaten geboren uit moeders die op grote hoogte wonen. Ondanks lagere arteriële zuurstofsaturatie bij Peruaanse baby's wordt een verhoogde vaatdichtheid geïdentificeerd als een potentieel aanpassingsmechanisme aan een sterk hypoxische antenatale omgeving (hoofdstuk 6).

" Noncontact monitoring of respiratory rate in newborn infants using thermal imaging" (hoofdstuk 7) introduceert een "black-box" algoritme voor niet-invasieve monitoring van de ademhalingsfrequentie bij pasgeborenen via thermische beeldvorming. Het algoritme onderscheidt ademhalingssignalen van ruis zonder te vertrouwen op specifieke anatomische kenmerken. Resultaten van studies bij gezonde vrijwilligers en pasgeborenen tonen een goede overeenstemming tussen de geschatte ademhalingsfrequentie door het algoritme en traditionele metingen, wat wijst op het potentieel van infrarood thermografie als een niet-invasief alternatief voor ademhalingsfrequentiebewaking in de neonatologie.

De resultaten van de gepresenteerde studies benadrukken de behoefte aan verbeteringen in zuurstoftherapie voor premature neonaten, waarbij het belang van gepersonaliseerde benaderingen en de integratie van innovatieve technologieën in de dagelijkse klinische zorg wordt benadrukt. Uitdagingen in naleving van protocollen, de toepassing van volledig geautomatiseerde controle en het toekomstige landschap van niet-invasieve monitoringstechnologieën werden onderzocht. Ondanks vooruitgang blijft het bereiken van de ideale zuurstoftherapie een uitdaging, waarbij het evenwicht tussen het omarmen van innovaties en het zorgen voor effectieve implementatie cruciaal is voor verbeterde neonatale zorg.

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Then there is a large group of colleagues at Erasmus Medical Centre that deserve an acknowledgement, especially at the departments of neonatology and medical technology, where I was quickly made to feel at home. Rogier and Florian who had to put up with the mess that could form in our office, and were happy to fuel a shared love of better coffee.

Early on I found a kindred spirit in Willem, focusing on the benefits that software, automation and good quality data acquisition can bring to medical research. Which led to our shared patents. With the addition of Frank it has led to some fun tinker projects to see what was possible when pushing integration. And patents that together with John Vlot actually led to a startup where the three of them try to take some of the ideas and get them into the operating room. The support of Jasper Keijman, back then form the Erasmus MC Technology Transfer Office helped us to navigate research, patent law, financial incentives and collaboration with different companies.

A large part of this research has been done in collaboration with a number of companies, finding a balance between profiting from their abilities and willingness to develop and repaying that with new ideas, algorithms and results. Ronald, Thomas, Maurizio, Peter and Rainer at Acutronic made one of these collaborations both enjoyable and rewarding. Enabling the development and implementation of the PRICO algorithm . And the same holds for Josef, Peter and John at Sentec, supporting the research at the department of Neonatology, challenging and pushing us, but also always willing to share a good cheese fondue. And special mention for Andreas, bouncing between Sentec, and Acutronic what is now Vyaire a few times, but managing to keep the collaboration with Erasmus as the stable factor, you can also just give in to it and apply for a job at Erasmus.

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I also had the pleasure of joining some experts in the field, visiting Berndt and Gerhard in Graz and Georg in Edmonton. All three of you invited me with open arms, and reinforced our notion what can be achieved by the close collaboration between technical and medical experts. Although it won't be possible to share it with Berndt, I'm looking forward to having another beer with you, or a Lagavulin or indian meal in his memory with you, next time we meet. The news of Berdt's passing still hasn't fully sunken in and I mourn the loss.

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Reinforcement for the more data driven and software side of research at the department came with the addition of Roy and Annelies to the team, thank you and I see you both

as vital parts for the ambitions that the department of neonatology has. The merger of the departments of neonatology and paediatrics has brought existing collaboration with Rogier, Matthijs, Jan Willem and now Eris to a new level and I hope that they can flourish and it will mean that the result is greater than the sum of its parts.

Teaching for Clinical Technology with Peter was a pleasure, and has shown me that there is so much more we can and need to learn. Because there is so much we don't fully understand yet, and nothing makes that clearer than trying to put it into a simulation. It aided in the collaboration with the adult ICU, and Diedrik in particular, with whom we share a PhD candidate in the form of Jantine. Which all will hopefully bring us a step closer to obtaining some of that knowledge. But I would like to express my deepest appreciation to the three of you for the opportunity to try.

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Wouter it is always a pleasure to work with you, your view and attitude when it comes to supervising students is one I fully agree with and strive to life up to. And thank you

Caitlin, even though we did not get as far as we wanted and it did not work out as planned, I did enjoy our collaboration and your enthusiasm for improving the world.

The research on resuscitation has logically led to collaborations with the department of Obstetrics and Gynaecology, with the highlight being a shared PhD candidate with Alex in the form of Chantal, many thanks to both of you. And collaborations that deviated even further from my core topic have given me the chance to work with more wonderful researchers, like the search for circadian rhythm with Bert and Inez, micro circulation with Can, and the effects of altitude on the microcirculation with Norina, Max and Daniel. Not to mention the chance to conduct research at altitude in Peru thanks to Hugo, Claudia, Maria, Saul and Luis.

During the time of this research, I had the chance to supervise over 40 students, as they worked on their master's degree or joined us for smaller projects. It goes too far to mention you all by name, but I am very grateful to have had the chance to aid in your education. And know that you aided in mine. With so many people to be grateful for, I must have forgotten some. If I have forgone to mention you, my apologies. It is in no way a reflection of my lack of appreciation. Just a sign that it's been fruitful and extensive collaborations with many people to be grateful for. Thank you.

All this work would not have been possible without breaks and support in my personal life. At the start Mike and Tim were still nearby, and I miss the short notice, late night, beer fuelled discussions we used to have. Distance makes those impossible but I do look forward to visiting you both again soon, and in the case of Mike to also have the chance to meet you wife and your beautiful daughter.

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That leaves the one person who sadly cannot witness the completion of this thesis, and will not be able to join in its defence. Mom, I miss you and wish with all my heart you could be here. I dedicate this thesis to you.

Curriculum Vitae

Tom Goos was born on August 22, 1982 in Zuidhorn. After a few years in The Hague, he returned to Zuidhorn to obtain his primary school diploma. He obtained his VWO diploma at the H.N. Werkman College in Groningen via the Leon van Gelder Middenschool. After a winter of snowboarding and following the training to become a snowboard instructor at the Wiener Ski und Snowboardlehrer Verband, Tom started the Bachelor of Mechanical Engineering at Delft University of Technology in 2002. The Bachelor was followed by a Master of Science in BioMedical Engineering, with a Specialization in Medical Instruments and Medical Safety. After an internship at the Leiden University Medical Centre, Department of Development, where he designed, prototyped and tested a stabilized introducer sheath for hybrid access vascular procedures, resulting in clinical prototype and patent application, he did his graduation research at the department of Neonatology at Erasmus Medical Center, which he completed in 2013 with the thesis: "Advisory System for Oxygen administration during Resuscitation of preterm infants: The ASOR, a clear view on oxygen saturation", research with a graphical user interface to optimize the administration of oxygen during the resuscitation of premature neonates. During this research, he was already offered the opportunity to follow it up as a PhD candidate at the Erasmus Medical Center, of which this dissertation is the result.

In addition to his work as a researcher at the Neonatology department, Tom has been working at the Medical Technology department since 2022, where he has been responsible as a project manager for the implementation of the new Medical Integral Communication and Information System since 2023.

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