Oxygen titration and compliance with targeting oxygen saturation in preterm infants

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COLOFON

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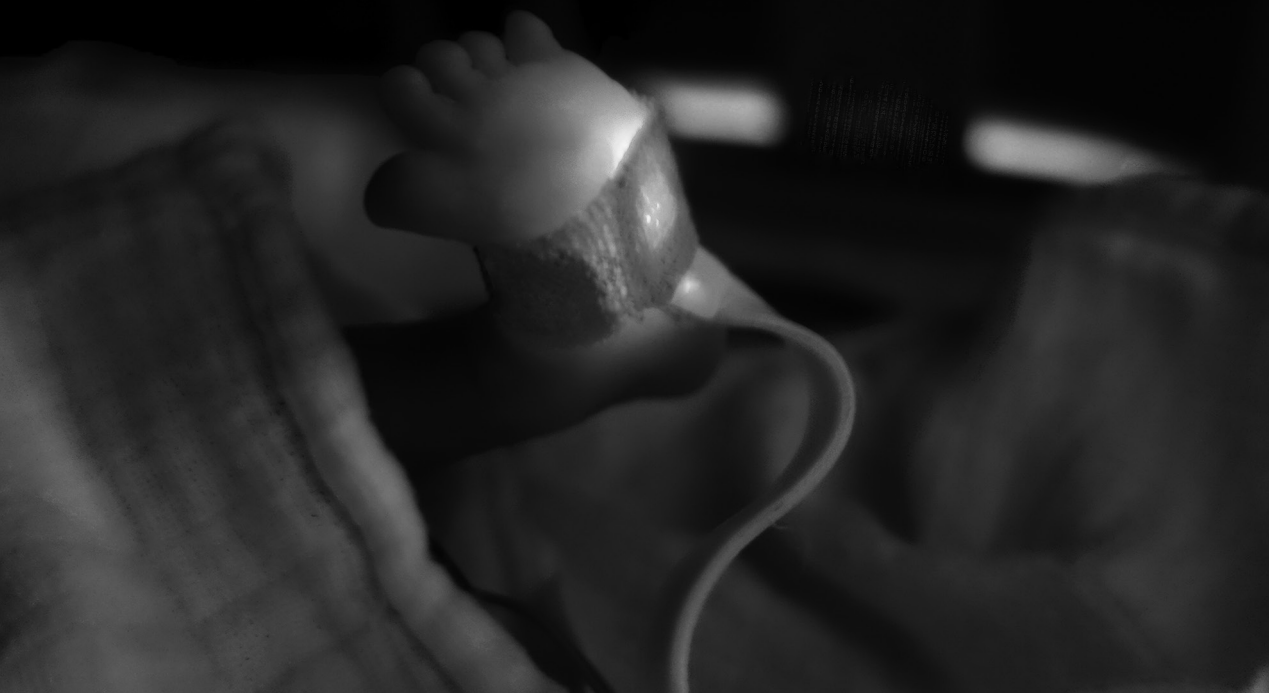
General Introduction



This story is a reflection about a regular day at work for "Nikki", an experienced nurse who has worked at a neonatal intensive care unit (NICU) for more than a decade. It is seven-thirty in the morning, and Nikki has just joined her colleagues for the handover from the night shift. It was apparently a busy night in the NICU – a preterm infant, born at the end of the previous shift had taken the last available space in the unit. The team leader asks Nikki if she can care for two patients today, including the new preterm baby who still requires umbilical lines. The team leader adds, "There are not many experienced nurses around today. But don't worry, the other baby is doing fine; he only had a few desaturation events during the night."

Nikki first takes care of the preterm infant who had had the desaturation events the previous night. The baby is doing well and shows no signs of infection. She checks the CPAP prongs, the ventilator settings, and the alarm settings. Just before she leaves, however, the baby has another apnoea event with desaturation. Nikki turns up the oxygen level to allow the baby to recover. She makes a mental note to have the registrar check on this baby, and – because this infant does not appear to be sick – she decides to first help the registrar with the umbilical line procedure in the new preterm infant. While they perform the procedure, the oxygen saturation alarm sounds for the seemingly stable other baby, indicating that the oxygen saturation is above the target range. "*That alarm can wait a moment,*" Nikki thinks. "*I cannot leave this patient now.*" A few minutes later, a colleague comes in, after preparing medication, and asks Nikki if she needs any help. "Could you please turn off that alarm? It's constantly ringing because the oxygen saturation is too high. I just turned the oxygen up because he was desaturated, so could you turn down the oxygen a bit?" Nikki is relieved when the alarm is silenced, as it was getting on her nerves. However, the silence does not last long, as another alarm indicates that this infant is now experiencing another desaturation event. Thankfully, her colleague comes to the rescue again and increases the oxygen level. She also follows Nikki's advice and adjusts the upper alarm limit to get rid of this "yo-yo" effect. However, the registrar overhears this and is a bit upset regarding this decision. He worries about how the consultant will react when she hears about this. Unfortunately, Nikki has had this kind of discussion more than once. The target values are difficult to track, and the noise created by the alarms cannot be good for the other patients. Nevertheless, the registrar insists upon changing the alarm's settings to their previous settings. Nikki is a bit annoyed by this and replies, "If the neonatal consultant wants to keep this patient's oxygen saturation level within the intended target range, she can come to the unit, sit next to the patient, and titrate the oxygen herself. We are too busy here!"

Thanks to advances in neonatal care in the past few decades, the percentage of extremely preterm infants who survive has increased considerably. Worldwide, approximately 15 million preterm infants (defined as a gestational age below 37 weeks of gestation) are born each year; thus, one in ten pregnant women gives birth to a preterm infant.[1] In the Netherlands, approximately 14,000 preterm infants are born each year, 30% of whom are born before 34 weeks of gestation.[2]

Despite significant improvements in the care of preterm infants, both morbidity and mortality remain high among these infants, and this group has an increased risk of long-term disabilities. At least 50% of all neonatal mortality is due to preterm birth, and preterm infants who survive have an increased risk of developing severe complications, including intracranial haemorrhage and cerebral white matter damage, which can lead to cerebral palsy and other severe motor and/or coordination problems, epilepsy, severe cognitive impairment, and developmental coordination disorder.[3] Long-term complications include an increased risk of asthma and early-onset chronic obstructive pulmonary disease (COPD).[3] Given that nearly half of all severely disabled children were born preterm, this is clearly not a healthy start to life.

Approximately 75 years ago, the introduction of oxygen therapy greatly increased the survival of preterm infants. Today, oxygen is one of the most widely used therapeutic "drugs" in neonatal care.[4-6] Second only to respiratory support, oxygen is the most commonly used intervention in preterm infants with respiratory insufficiency and/or apnoea, and preterm infants often receive supplemental oxygen for prolonged periods. The goal of oxygen therapy is to achieve adequate oxygenation levels using the lowest possible concentration of inspired oxygen.[7] Unfortunately, however, supplemental oxygen therapy has an extremely narrow therapeutic range in preterm infants; as a result, these infants often develop either low blood oxygen levels (hypoxaemia) or high blood oxygen levels (hyperoxaemia), both of which can lead to increased morbidity and mortality.[8] Preterm infants who experience hypoxaemia – defined as oxygen saturation (SpO_2) <80% – have an increased risk of cerebral palsy, patent ductus arteriosus, pulmonary vascular resistance, apnoea, and death. On the other hand, preterm infants who experience hyperoxaemia – defined as SpO_2 >95% – have an increased risk of developing complications that can include retinopathy of prematurity (ROP) and bronchopulmonary dysplasia.[9-15]

Pulse oximeters are commonly used to measure peripheral SpO_2, providing a continuous measure of oxygenation.[16] To prevent hypoxaemia and hyperoxaemia, the nurse routinely titrates the oxygen level manually in order to maintain SpO_2 within a prescribed target range. Strict control of SpO_2 – measured indirectly using pulse oximetry – can reduce both mortality and morbidity in preterm infants.[16] However, it can be extremely difficult to implement SpO_2 policies in daily clinical practice, particularly in a neonatal intensive care setting. Titrating the oxygen level in order to maintain a narrow target range of SpO_2 can be challenging for the

nurse, particularly during and/or following an apnoea event accompanied with bradycardia and/or oxygen desaturation. Several factors can influence the nurse's compliance, which is generally defined as the extent to which the nurse adopts behaviours that are consistent with the prescribed clinical intervention.[17] Several studies have reported poor compliance among nurses with respect to targeting SpO_2 levels and in SpO_2 alarms settings.[18-20] Improving compliance – which would reduce the prevalence of both hypoxaemia and hyperoxaemia – would considerably improve the outcome of preterm infants.

Auditing is an effective way to improve compliance and is widely used and recommended in nursing practice in order to improve quality of care.[21 22] With auditing, the caregiver is prompted to modify their clinical practice when necessary. A clear benefit of clinical auditing is that it can be used to monitor the effectiveness of daily practice and can lead to improvements. The ability of auditing to improve effectiveness can be influenced by the caregivers themselves, particularly when they believe that the audit is relevant to their practice, when the auditing process fits within their daily routine, and when other factors apply, such as the caregiver's willingness to change.[23]

In 2012, our neonatal intensive care unit audited both oxygen titration practices and compliance regarding the targeting of SpO_2. We first measured baseline performance in order to determine how oxygen was handled during oxygen titration in response to hypoxaemic events. Alarmed by the findings, we initiated a quality improvement project. To increase awareness among the staff in the NICU with respect to oxygen use, we created and implemented a guideline regarding oxygen titration. We then performed a second audit in order to evaluate the effectiveness of this new guideline. Based on the results of recent trials to study oxygen targeting, the target range for SpO_2 was narrowed towards the higher end of the target range. We then performed another audit in order to assess how this change affected the nurses' compliance with respect to targeting SpO_2 values. A final audit was performed after we implemented automated oxygen control in order to further improve targeting (Figure 1).

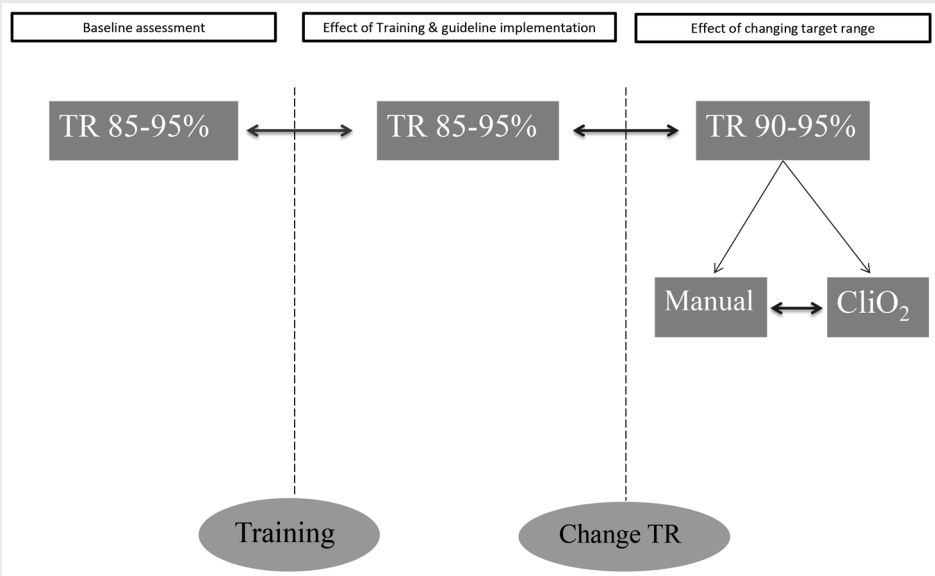


Figure 1. Performed audits

OUTLINE OF THIS THESIS

The general aim of this thesis project was to assess the effect of changing practices with respect to oxygen titration and compliance in preterm infants born before 30 weeks of gestation, admitted to the NICU at Leiden University Medical Centre (LUMC) in Leiden, the Netherlands. All of the preterm infants included in the study required either non-invasive or invasive respiratory support, and all infants received supplemental oxygen.

In **Chapter 2**, we discuss the literature regarding compliance with respect to targeting SpO_2 in very preterm infants within the NICU. Here, we did not limit the search criteria with respect to study design or methodology; this approach led to a variety of different aspects regarding compliance, which required a narrative-style review.

In **Chapter 3**, we report the occurrence and duration of hyperoxaemia following the administration of additional oxygen by manual titration following ABC (apnoea combined with bradycardia and cyanosis) in very preterm infants in our NICU.

Chapter 4 reports the results of an audit to assess the effect of introducing an oxygen titration guideline for SpO_2 distribution and compliance with respect to targeting SpO_2 in very preterm infants, as well as how oxygen was titrated during and following ABC.

In accordance with both European and Dutch guidelines, the SpO_2 target ranges were adjusted. Specifically, the target range for SpO_2 in preterm infants was narrowed from 85-

95% to 90-95%. In **Chapter 5**, we describe the effect of this smaller target range on SpO_2 distribution, compliance regarding the targeting of SpO_2, and how ABC is treated in preterm infants.

In **Chapter 6**, we describe the effect of implementing automated oxygen control in preterm infants with respect to SpO_2 distribution, compliance regarding the targeting of SpO_2, and the way in which oxygen is titrated in response to ABC. In **Chapter 7**, we provide a follow-up on **Chapter 6** by reporting the effect of implementing automated oxygen control on ABC in preterm infants.

In **Chapter 8**, we discuss the main findings of this thesis, and we provide future perspectives. English and Dutch summaries are presented in **Chapter 9**, and the references are provided in **Chapter 10**.

Chapter 2

Compliance in targeting oxygen saturation in preterm infants: a systematic review

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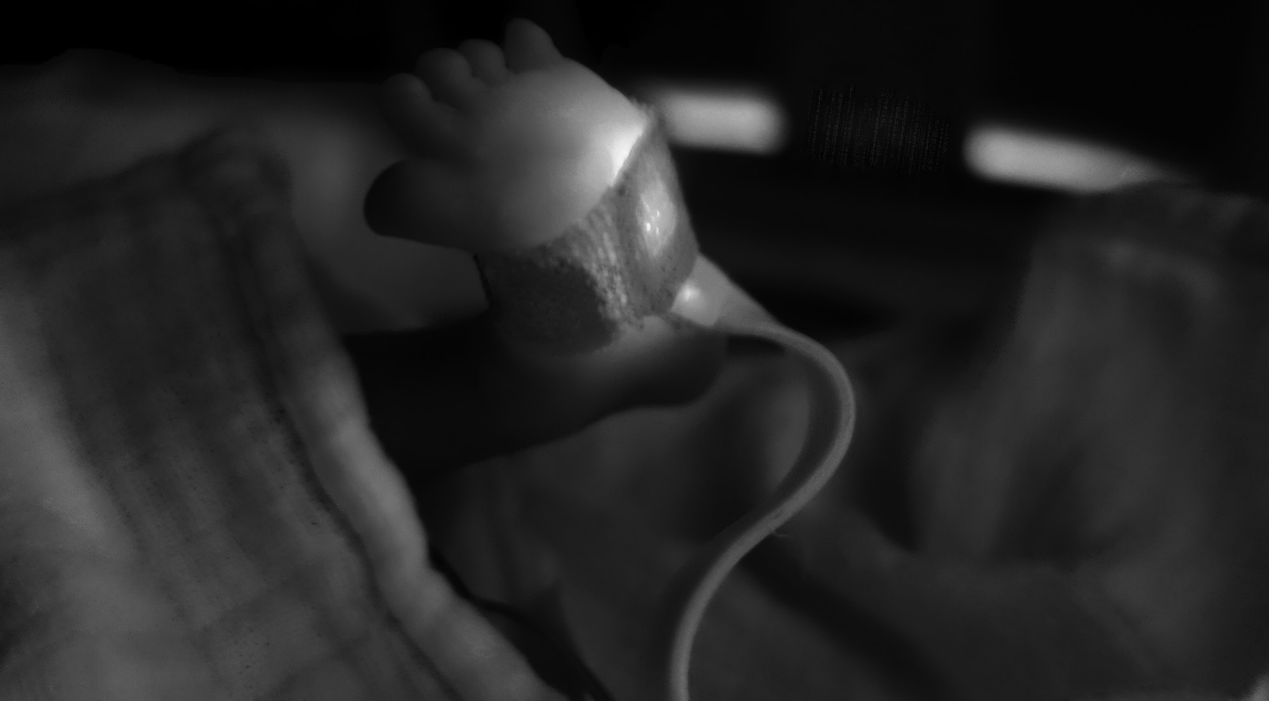
Eur J Pediatr. 2015 Dec;174(12):1561-72



ABSTRACT

During oxygen therapy in preterm infants, targeting oxygen saturation (SpO_2) is important to avoid hypoxaemia and hyperoxaemia but this can be very difficult and challenging to neonatal intensive care unit (NICU) nurses.

We systematically reviewed the qualitative and quantitative studies investigating the compliance in targeting SpO_2 in preterm infants and factors that influence this compliance. We searched PubMed, Embase, Web-of-Science, Cochrane, CINAHL, and ScienceDirect from 2000 to 2015. Sixteen studies were selected, which involved a total of 2935 nurses and 574 infants. The studies varied in methodology, and we have therefore used a narrative account to describe the data. The main finding is that there is a low compliance in targeting SpO_2; the upper alarm limits are inappropriately set, and maintaining the SpO_2 below the upper limit presented particular difficulties. Although there are little data available, the studies indicate that training, titration protocols and decreasing workload could improve awareness and compliance. Automated oxygen regulations have shown to increase the time SpO_2 is within the target range (TR).

Conclusion: The compliance in targeting SpO_2 during oxygen therapy in preterm infants is low, especially in maintaining the SpO_2 below the upper limit.

What is Known

The use of oxygen in preterm infants is vital, but the optimal strategy remains controversial. Targeting SpO_2 during oxygen therapy in preterm infants has shown to reduce mortality and morbidity.

What is New

Review of the literature showed that the compliance in targeting SpO_2 and alarm settings is low.

Creating awareness of risks of oxygen therapy and benefits in targeting, decreasing nurse:patient ratio, and automated oxygen therapy could increase compliance.

INTRODUCTION

Additional oxygen is often administered to preterm infants for hypoxemic episodes during respiratory distress or apnoeas. It is important to prevent hypoxaemia (defined as a decrease in blood saturation of ≤80% for ≥10 seconds) as frequent episodes could lead to an increased risk of morbidities, including retinopathy of prematurity (ROP), impaired growth, longer term cardio respiratory instability, and adverse neurodevelopmental outcome. In extreme cases it can even lead to death.[8 12] Hyperoxaemia (blood saturation of >95% for ≥10 seconds) also needs to be prevented as administering supplemental oxygen can potentially lead to high oxygen levels. High concentration of oxygen is toxic to living cells and is known to be an important pathogenic factor for bronchopulmonary dysplasia (BPD) and ROP [15], and is correlated with cerebral palsy.[9]

Pulse oximetry (PO) is most commonly used for continuous monitoring of oxygen saturation (SpO_2) in a non-invasive manner.[16] To prevent hypoxaemia and hyperoxaemia nurses usually titrate oxygen manually to maintain SpO_2 between the prescribed TR. However, maintaining the SpO_2 within this range can be challenging, and compliance – defined as the nurse's behaviour that follows the clinical guidelines[17] is influenced by several factors.[24] This compliance is important as it can largely influence the effect of a certain SpO_2 target range (TR). The optimal range of SpO_2 for preterm infants remains undefined, but recent trials have shown that aiming for 91-95% decreased mortality but increased incidence of ROP.[25] However, oxygen was titrated manually in these trials, which caused a large overlap in the distribution of SpO_2 between the two groups and may have decreased the observed differences in outcome.

Although comparison of SpO_2 TR has been subject to systemic review,[26] a review in the compliance in oxygen targeting is not available but equally important as the optimal TR. The purpose of this study is to systematically review the available literature in compliance - and the factors influencing this compliance - in targeting SpO_2 in preterm infants.

METHODS

We performed a systematic review, following PRISMA guidelines where possible (Figure 1).[27] The aim of the PRISMA statement is to help authors improve the reporting of systematic reviews and meta-analyses, which made it a particularly useful framework for this report. Eligible studies were identified by searching online databases from January 2000 to January 2015 in PubMed, Embase, Web-of-Science, Cochrane, CINAHL, and ScienceDirect (keywords in Table 1). After selecting the eligible studies, we manually searched the reference lists of the selected studies to identify additional references. The criteria for inclusion limited

the selection to articles published in English or Dutch which referred to preterm infants, (nursing) compliance, SpO_2 monitoring by PO, and targeting SpO_2 during admission at the neonatal intensive care unit (NICU). Both qualitative and quantitative designs were included, but publications that were not primarily research studies, i.e. letters, abstracts, reviews and editorials, were not (Figure 1). Three authors (HvZ, RT, AH) independently graded the selected studies using the QualSyst tool for quantitative and qualitative studies.[28] In case of disagreement, consensus was reached through discussion or consultation of a fourth co-author (AtP). The QualSyst tool for quantitative studies is a validated generic checklist consisting of fourteen items with scores from zero to two and the possibility to score 'not applicable'. Items rated 'not applicable' were excluded from the calculation of the summary score. The maximum total score is 28. The summary score was calculated by summing the total score obtained across the relevant items and dividing that by the total possible score.

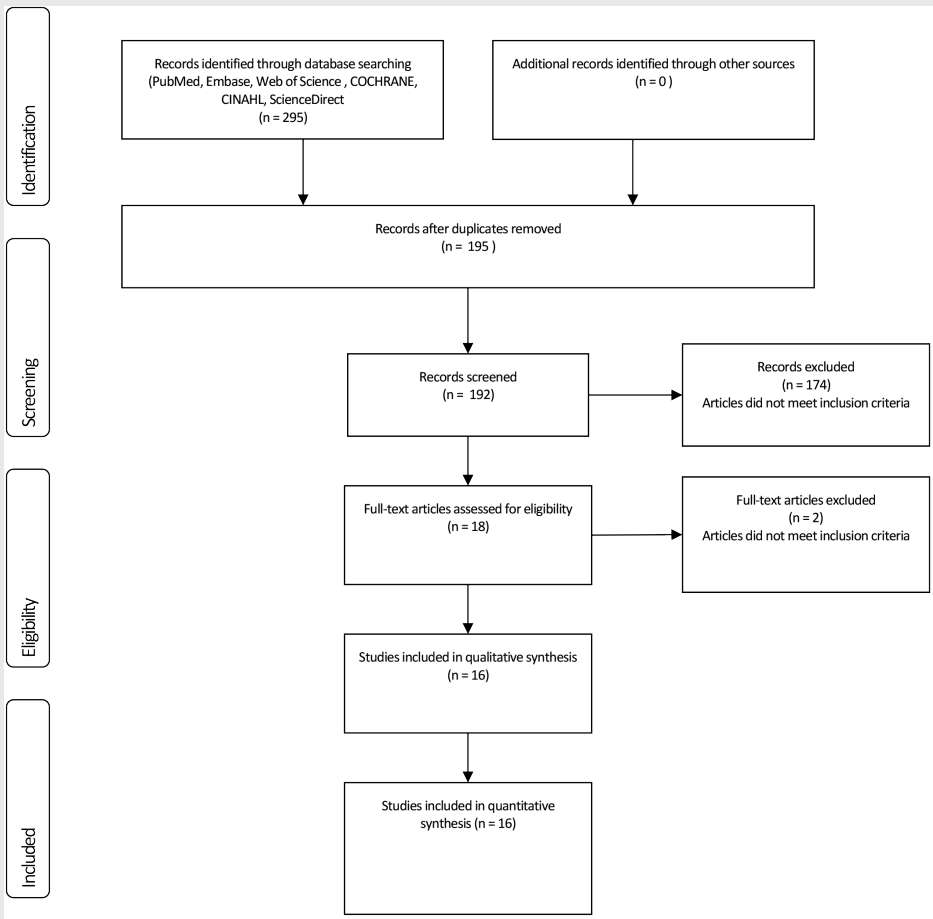


Figure 1. Flow diagram selected studies

Table 1. Keywords in different databases

Database	Keywords (including MeSH) terms
PubMed	Hyperoxia+, Hyperoxia*, hyperoxygenation, Hyperoxias, Hyperoxie, Hyperoxic, Hyperox*, hyperoxemic episode, hyperoxemic episodes,hypoxia, hypox*, hypoxemic episode, hypoxemic episodes, cyanosis cyanoses pulse oximetry, pulse oximeter, pulse oximeters, *Infant+, Premature+, prematurity, prematur*, Pre-mature, pre-maturity, preterm, preterm*, low birth weight infant, low birth weight infants,* **Oxygen Inhalation Therapy+, Hyperbaric Oxygenation+, Oxygen/administration and dosage+,oxygen/therapeutic use+ Oxygen/therapy+, Oxygen/Consumption+, oxygen consumption, oxygen, oxygenation, FiO2, FiO 2, FiO(2),FiO, increas*, fraction* exposure*, increase oxygen, increased oxygen, oxygen supplementation, oxygen therapy, supplemental oxygen,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, Oxygen Inhalation Therapy/ instrumentation+, Respiration, Artificial/instrumentation+ ***complia*, nursing compliance, Adherence, adher*, Guideline Adherence+, Advance Directive Adherence+, Goals+, nursing procedures***
CINAHL	Hyperoxia, hyperoxias, Hyperoxia* hyperoxygenation, hyperoxie, hyperoxic, hyperox* cyanosis, cyanoses, hypoxia*,pulse oximetry, pulse oximeter, pulse oximeters, *prematur*, Prematurity, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant,low birth weight infants,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO, increas*, fraction, fractions, fraction*, exposure***, *exposures, exposure*, increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration,oxygen therapy,* *Automated closed loop control,FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control,* ***compliance, complia*, nursing compliance, Adherence, adher****
Web of Science	Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*, cyanosis, cyanoses pulse oximetry, pulse oximeter, pulse oximeters, hypoxia*, hypoxemic episodes, hyperoxemic episodes, hypoxemic episode, hyperoxemic episode, cyanosis, cyanoses, *premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, elbw infant*, low birth weight infant*,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO, increas*, fraction, fractions, fraction*, exposure, exposures, exposure*,increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, compliance, complia*, nursing compliance, Adherence OR adher*
Embase	Hyperoxia/, pulse oximetry/, exp Hypoxia/, Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*, pulse oximetry, pulse oximeter, pulse oximeters, hypoxia, hypoxemic episodes, hyperoxemic episodes" hypoxemic episode, hyperoxemic episode, cyanosis/, cyanosis, cyanoses, *prematurity/, premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant, low birth weight infants,* **Oxygen*, FiO2, FiO 2,FiO(2),FiO) increas*, fraction,fractions, fraction*, exposure, exposures, exposure*, increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy, exp oxygen therapy/,oxygen saturation/,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control,oxygen delivery device/, exp* ***patient compliance/ compliance, complia*, nursing compliance, Adherence, adher* "nursing procedures"***
Sciencedirect	Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*,pulse oximetry, pulse oximeter, pulse oximeters, hypoxia*, cyanosis, cyanoses*, premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant, low birth weight infants,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO,increas*, fraction, fractions, fraction*, exposure, exposures, exposure*, increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, ***compliance OR complia* OR nursing compliance OR Adherence OR adher****
Cochrane	Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*, pulse oximetry, pulse oximeter, pulse oximeters, hypoxia*, *premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant, low birth weight infants,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO, increas*, fraction, fractions, fraction*, exposure, exposures, exposure*,increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, ***compliance, complia*, nursing compliance, Adherence, adher****

+Keywords that were MeSH terms

The QualSyst tool for qualitative studies is a validated generic checklist consisting of ten items with scores from zero to two, with the maximum total score of 20. A summary score was calculated for each study by summing the total score across the ten items and dividing them by the total possible score of 20.[28] Data from selected studies were extracted using a data extraction form. The following study characteristics were extracted: author, year, design, sample, time points, length of measurement, TR and key results.

RESULTS

Sixteen articles met the inclusion criteria for this review (Figure 1), detailing studies that included a total of 574 infants and 2935 nurses. Fourteen of these studies used a quantitative design[18-20 29-39] while the remaining two used qualitative methods.[40 41] Pooling the data for meta-analysis was not possible, as there was no homogeneity in the study designs. We therefore discuss the studies and their results using a narrative format organised under thematic headings and summarised in tables.

Quality assessment

The studies varied in quality, but none were excluded because of low quality scores. One observed weakness was the lack of power analysis in four of the studies[18 19 30 32] and all studies were unclear in the reasoning behind the timing and duration of SpO_2 data collection (Table 2,3).[18-20 29-32 35-41]

Study Designs

The designs of the quantitative studies varied, and were composed of: one efficacy study [33]; two pilot clinical trials[39 42]; three randomised clinical trials[35 36 38]; and eight observational studies, of which six had a prospective design [18-20 29 30 37] and two were retrospective.[31 32] Both qualitative studies employed a descriptive design (Table 4). [40 41]

Target ranges of SpO_2

The lower limit of the TR varied between studies from 80-92%[19 38] and upper limits of TR varied from 92-96% respectively (Table 4).[18-20 30 31 33 37]

Time points and length of measurements

All studies were conducted in the period the infants needed supplemental oxygen, but the starting time points and duration of data collection differed between studies. The starting time point varied between the first day of life[37 40] and 33 days[34] (Table 4). In one study, the postnatal age was not described.[30] The duration of data collection also varied widely, the

shortest covering was only four hours[33] and the longest lasted the entire period between admission and discharge.[18] The data were collected continuously in eight studies[31-39] and intermittently in the remaining studies (Table 4).[18 19 29 30]

Table 2. Quality appraisal of included quantitative studies

Quality assessment quantitative studies															
Studies		2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	
	Question	Study design	Selection	Subject Characteristics	Random Allocation	Blinding Investigator	Blinding Subjects	Outcome	Sample Size	Analytic Methods	Estimate on variance	Confounding	Results	Conclusion	Summary score
Claure, N. *et al.* (2001)	1	1	1	2	1	0	n/a	1	n/a	2	2	1	1	1	14/24 = 0.58
Claure, N. *et al.* (2009)	1	1	1	2	1	0	n/a	1	2	2	2	1	1	1	16/26 = 0.62
Claure, N. *et al.* (2011)	2	2	2	2	1	0	0	2	2	2	2	1	2	2	22/28 =0.79
Clucas, L. *et al.* (2007)	2	2	1	2	0	0	0	2	0	2	2	1	2	2	18/28 = 0.64
Hagadorn, J.I *et al.* 2006)	2	2	1	2	1	0	0	1	0	2	2	1	1	1	16/28 = 0.57
Laptook, A.R. *et al.* (2006)	1	1	1	2	0	0	0	1	2	2	2	1	1	1	15/28 = 0.54
Mills, B.A. *et al.* (2010)	2	2	1	2	1	0	0	1	0	2	2	1	1	2	17/28 = 0.61
Sink, D.W. *et al.* (2011)	2	1	1	1	0	0	n/a	1	n/a	2	0	1	1	1	11/24 = 0.46
Urschitz, M.S. *et al.* (2004)	2	2	2	2	2	0	0	1	2	2	2	1	2	2	22/28 = 0.79
Van der Eijk, A.C. *et al.* (2012)	1	2	2	2	0	0	0	1	0	2	1	1	1	1	14/28 = 0.5
Zapata, J. *et al.* (2014)	2	2	2	2	2	0	0	2	1	2	2	1	2	2	22/28 = 0.79
Lim, K. *et al.* (2014)	2	2	2	2	n/a	n/a	n/a	2	n/a	2	2	2	2	2	20/20=1
Arawiran, J. *et al.* (2014)	2	2	2	2	n/a	n/a	n/a	1	1	2	2	1	2	1	18/22 = 0.82
Hallenberger, A. *et al.* (2014)	2	2	2	2	2	0	0	2	2	2	2	1	1	1	21/28 = 0.75

2 = yes; 1 = partial; 0 = no; n/a = not applicable

Table 3. Quality appraisal of included qualitative studies

Quality assessment qualitative studies											
Studies	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	
	Question objective	Study design	context	Theoretical framework	Sampling strategy	Data Collection	Data Analysis	Verification procedure	Conclusion	Reflexivity	Summary score
Nghiem, T.H. *et al.* (2008)	2	2	2	2	1	2	2	0	1	2	16/20 = 0.8
Armbruster, J. *et al.*. (2010)	1	2	2	2	2	2	0	0	2	2	15/20 = 0.75

2 = yes; 1 = partial; 0 = no

Compliance in target ranges

Twelve studies investigated how often SpO_2 values were in or outside the TR, expressed as the percentage of monitored time.[19 20 29 31-39] In a multi-centre study, Hagadorn *et al.* observed that SpO_2 was below, within or above TR in 16 (0-47)%, 48 (6-75)%, and 36 (5-90)% respectively of the monitored time.[19] Van der Eijk *et al*. reported similar values, finding that SpO_2 was below TR for 16 % of the time and above it for 30%.[32] In contrast, Lim *et al*. only studied infants receiving supplemental oxygen during Continuous Positive Airway Pressure (CPAP) and SpO_2 was below the TR for 9% and above it for 58% of the time.[20]

Education and training

Two studies demonstrated the impact of an educational program in targeting SpO_2. Laptook *et al*., observed that training did not change the time SpO_2 was below (26.9 vs. 26.6%; ns) or above TR (15.4 vs. 14.0%; ns).[29] Interestingly, Arawiran *et al*. even observed that training had an adverse effect, and that the time SpO_2 was within TR decreased after training (44.5 ± 14.4 % vs 40.4 ± 12.8 %) with an increase in time above TR (from 36.9 ± 17.2% vs 41.9 ± 15.6%).[37]

Nurse:patient ratio

Sink *et al*. studied the influence of the nurse:patient ratio on compliance in SpO_2 targeting. They observed that the proportion of time when SpO_2 was below TR decreased from 0.06 to 0.03 and time above TR increased from 0.56 to 0.82 when a third or fourth patient was

added to the nurse's workload.[31] The high percentage of time above TR was probably due to the use of a lower upper limit (92%) in comparison with other studies.[29 32-36] Lim *et al*. also confirmed that more than one infant per nurse was associated with an increase in the time when SpO_2 was above TR (Table 4).[20]

Automated regulation of inspired oxygen

Six recent studies reported that, compared to manual titration, the use of automated regulation of inspired oxygen increased the time SpO_2 spent within TR.[33-36 38 39] In a multicentre crossover study of ventilated preterm infants, Claure *et al.* observed that the time SpO_2 was within TR increased significantly during the automated period compared to the manual period (40% (14) vs 32% (13) (mean (SD);p<0.001). The time periods with SpO_2 >93% or >98% were thus significantly reduced during the automated period.[35] Although most studies observed that the time SpO_2 was above TR decreased[33-36 39] while the time below TR increased,[34-36 39] Hallenberger *et al.* found different results. They observed no change in time above TR (16 (0.0-60) vs 15.9 (1.9-34.8);p=0.108) during automatic control of inspired oxygen and therefore no difference with manual control (Table 4).[38]

Compliance in alarm limits setting

Two studies investigated nursing compliance in setting the appropriate alarm limits for PO in preterm infants.[18 30] The actual SpO_2 values were not reported, but Clucas *et al.* observed the lower and upper alarm limit to be set correctly in 91% and 23% of monitored time respectively.[18] Mills *et al.* compared compliance in alarm settings of SpO_2 according to whether or not infants participated in a trial. When infants were participating in the BOOST II trial the lower and upper alarm limit for SpO_2 was set correctly in 94% (88-100%) and 80% (71-88%) of the monitored time period. However, this decreased to 87% (75-99%) and 29% (17-40%) when infants were not participating in the trial (Table 4).[30]

Nurses' perception and awareness

When Armbruster *et al.* interviewed nurses about compliance, they stated that the following would improve their compliance: further education, prompt response to alarm limits, a favourable patient to staff ratio, root cause analyses at the bedside, and high priority given to control oxygen therapy.[40] Nghiem *et al*. reported that 63% of the nurses were aware of the local SpO_2 guidelines and 57% of them correctly identified the target limits specified by their NICU guidelines (Table 4).[41]

Table 4. Summary of included studies

Author	Year	Design	Study objects	Timing of measurement	Target range	Key results
Armbruster, J. *et al.*	2010	Qualitative study with Individual open-ended interviews	41 nurses	First three days of life while infants were receiving supplemental oxygen	88% - 92%	Saturations of infants in the COT- study (Canadian Oxygen Trial) were in the intended range in 68%-79% of time. Nurses identified education, prompt response to alarm limits, and a favourable patient to staff ratio as important determinants of good compliance
Claure, N. *et al.*	2009	Pilot clinical trial	16 premature infants, GA 24.9 ±1.4 weeks receiving mechanical ventilation and FiO_2 >0.21	Four hour period with FiO_2 adjustment by clinical staff members (manual) and 4-hour period with automated FiO_2 adjustments (automated) PNA 33 days (SD±15)	88% - 95%	**In automated mode:** • % of time within SpO_2 target range was 58% • % of time SpO_2 >95% was 9% • % of time SpO_2 <88% was 33% **In manual mode:** • % of time within SpO_2 target range was 42% • % of time SpO_2 >95% was 31% • % of time SpO_2 <88% was 27%
Claure, N. *et al.*	2001	Efficacy study	14 infants, GA 25 weeks (SD ±1.6) receiving mechanical ventilation and FiO_2 >0.21	two hours in manual FiO_2 mode and two hours in automatic FiO_2 mode in random sequence. PNA 26 days (SD±11)	88-96%	**In automatic FiO_2 mode** • % of time within SpO_2 target range was 74.9 % • the percentage of time saturations were < 88% was 16.5% and • >96% in 9.9% of the time. **In manual FiO_2 mode** • % of time within SpO_2 target range was 66.3% • the percentage of time saturations < 88% was 18.7% and • >96% in 14.9% of time.
Claure, N. *et al.*	2011	Clinical trial	32 premature infants GA 25 (24-27) wks receiving mechanical ventilation and FiO_2 >0.21	24 –hour period with FiO_2 adjustment by clinical staff members (manual) and 24-hour period with automated FiO_2 adjustments (automated) PNA 27 days (range 17-36)	87%-93%	**In automated mode:** • % of time within SpO_2 target range was 40% • % of time SpO_2 >93% was 28% • % of time SpO_2 <87% was 32% **In manual mode:** • % of time within SpO_2 target range was 32% • % of time SpO_2 >93% was 43% • % of time SpO_2 <87% was 23%

Clucas, L. *et al.*	2007	Prospective cohort study	80 infants with receiving supplemental oxygen mean GA of 28,4 weeks (SD ±2.4) 1073 lower and upper alarm limit values	Daily during weekdays, when the infant was on oxygen until discharge PNA five days (IQR 2-34.5)	88% -92%	The lower alarm limit was set correctly in 91.1% of the time, 6.3% was set lower and 2.7% were set higher than intended; Upper alarm limit was set correctly in 23.3% of the time, 0.2% was set lower and 76.5% were set higher than intended.
Hagadorn, J.I. *et al.*	2006	Prospective multi-centre cohort study	84 infants GA 26.3 Median: (29.4 - 27,4) 14 centres from three counties 307 monitor periods of median duration of 67.3 hours	Saturation for 72 hours each week for the first four weeks of life	Center specific Intended TR 92–96% 90–95% 88–95% 88–97% 88–92% 87–94% 92–96% 90–96% 85–98% 88–94% 85–94% 88–92% 83–93%	Overall, infants spent 16% below intended range and 36% above their NICUs intended range
Laptook, A.R. *et al.*	2006	Prospective observational study	Group 1: 23 infants GA 27 weeks (± 2) receiving continuous supplemental oxygen (with or without ventilator) group 2: 49 infants, GA 26 weeks (± 2) receiving continuous supplemental oxygen (with or without ventilator)	24 hours of data twice a month during six months when the author was available PNA group 1: 23 days (±21) PNA group 2: 23 days (±19)	Group 1: target range 90-95%, Group 2: target range: 88-94%	**Group 1:** SpO_2 values were under target range in 26.9% and above the target range in 15.4 % of time **Group 2:** SpO_2 values were under target range in 26.6% and above the target range in 14.0 % of time
Mills, B.A. *et al.*	2010	Prospective cohort study	56 infants mean GA 26.7 wks (SD 2.0) receiving supplemental oxygen 22 infants in BOOST II trial Number of recordings = 454	Daily during weekdays, when the infant was on oxygen until discharge	88% - 92%	**Lower alarm limits:** In BOOST II trial; 94.2% was set correctly; not in BOOST II; 87.3 % was set correctly. **Upper alarm limits:** In BOOST II trial; 79.8% was set correctly; not in BOOST II; 28.8% was set correctly

Nghiem, T.H. *et al.*	2008	Survey	59 NICUs 2805 nurses who submitted surveys	First four weeks of life of preterm infants	68% of included NICUs, had policy specified SpO_2 target limits; not exactly defined	Of 1957 nurses at NICUs with policies; 64% of nurses were aware that policy for SpO_2 was present in their NICU. 715 (37%) nurses correctly identified the SpO_2 limits specified by their NICU policy
Sink, D.W. *et al.*	2011	Retrospective observational study	14 infants GA < 26.6 (SD±1.6) weeks with oximeter data 87 nurses	Every two seconds during routine bedside oximetry monitoring PNA 31.6 weeks (mean range 24.1-40.7 weeks)	85% - 92%	SpO_2 in infants <28 GA were 61% above intended range and 6% under de intended range. Infants of 28-31 weeks gestation were 70% above intended range and 7% under de intended range. Hyperoxaemic time increased from 48% to 71% with assignment of a second patient to the infant's nurse and to 82% with assignment of a third patient to the infant's nurse
Urschitz, M.S. *et al.*	2004	Randomized controlled clinical trial (Validation and efficacy trial)	**Validation trial:** 12 preterm infants GA; Median (IQR)24.5 (24-28) receiving ventilator support and FiO_2 >0.21 **Efficacy trial;** 12 preterm infants GA; median (IQR) 25.5 (24-33) receiving ventilator support and FiO_2 >0.21	one day during five periods of different modes, 90 minutes in each mode • Baseline 1, • Routine Manual control, • Optimal Manual Control, • Closed-loop Control, • Baseline 2 **Validation trial:** PNA 21 days (median range 8-57) **Efficacy trial;** PNA 20.5 days (median range 4-78)	87-96%	**Validation trial:** % of time within SpO_2 target range was: • Baseline 1, 75.3% • Routine Manual control, 79.7% • Optimal Manual Control, 85.8% • Closed-loop Control, 82.1% • Baseline 2, 79.4% No information on hypoxaemic and hyperoxaemic periods **Efficacy trial:** % of time within SpO_2 target range was: • Baseline 1, 82.9% • Routine Manual control, 81.7% • Optimal Manual Control, 91% • Closed-loop Control, 90.5% • Baseline 2, 81,2% **duration of hypoxaemic episodes** • Baseline 1, 20.2s (11.3%) • Routine Manual control, 19s (10.7%) • Optimal Manual Control, 16.4s (9.2%) • Closed-loop Control, 12.4s (7%) • Baseline 2, 19.1s (10.7%)

						duration of hyperoxaemic episodes • Baseline 1, 24.7s (6.7%) • Routine Manual control, 19.3 s (5.2%) • Optimal Manual Control, 16.4s (5%) • Closed-loop Control, 10.1s (2.7%) • Baseline 2, 17.4s (4.7%)
Van der Eijk, A.C. *et al.*	2012	Observational cohort study	12 infants, median GA 26 2/7 weeks (range24 2/7 -28) with a need for supplemental oxygen	Recording started when FiO_2 was >0.21 in the first two weeks op life PNA four days (range 2-12)	88%-94%	SpO_2<88% in 16% of the time and >94% in 30% of the time
Zapata, J. *et al.*	2014	Pilot clinical trial	20 infants, mean GA 27.3±1.7 vs 27.7±1.7 weeks receiving supplemental oxygen by nasal cannula	12 hour study period PNA 5-14 days	85%-93%	**With automixer:** • % of time within SpO_2 target range was 58% • % of time SpO_2 >95% was 26.5% • % of time SpO_2 <85% was 14% **In manual routine care:** • % of time within SpO_2 target range was 33.7% • % of time SpO_2 >95% was 54.8% • % of time SpO_2 <85% was 11.5%
Hallenberger, A. *et al.*	2014	Multicente randomised controlled crossover clinical trial	34 infants median GA (range) 26.4 (23.0–35.3) receiving mechanical ventilation or nasal CPAP and supplemental oxygen	24 hour period with routine manual control (RMC) and 24 hour period with closed loop automated control (CLAC) PNA 29.9 (26.0–35.6) weeks (median (range))	4 centre-specific TR 90–95% 80–92% 83–93% 85–94%	**In closed loop automated control (CLAC):** • % of time within SpO_2 target range was 72.1 (13.6) (mean(SD)) • % of time SpO_2 above TR was 15.9 (1.9–34.8) (median (range)) • % of time SpO_2 below TR was 9.1 (1.9–24.2) (median (range)) **In routine manual control (RMC)** • % of time within SpO_2 target range was 61.0 (15.2) (mean(SD)) • % of time SpO_2 above TR was 16.0 (0.0–60.0) (median (range)) • % of time SpO_2 below TR was 15.0 (0.5–39.6) (median (range))

Arawiran, J. *et al.*	2014	Prospective observational cohort study	71 premature infants GA <31 weeks **Pre-intervention phase:** 41 infants: 25 ± 1.6 weeks (mean ± SD) **Post-intervention phase:** 30 infants: 25 ± 1.9 weeks (mean ± SD)	Study period from first day of life as long as they received supplemental oxygen or were taken off the Masimo monitors or reached 31 weeks postconceptual age, whichever occurred first	85% - 92%	**Pre-intervention phase:** • Proportion of time spent per 12-h shift in which individual babies were (mean(%)±SD(%)) • <70% was 3.4 ± 2.6 • 70–74% was 1.6 ± 1.3 • 75–79% was 4.0 ± 2.9 • 80–84% was 9.6 ± 5.63 • 85–92% was 44.5 ± 14.4 • 93–100% was 36.9 ± 17.2 **Post-intervention phase:** • Proportion of time spent per 12-h shift in which individual babies were (mean(%)±SD(%)) • <70% was 3.3 ± 2.5 • 70–74% was 1.6 ± 1.1 • 75–79% was 3.9 ± 2.3 • 80–84% was 8.9 ± 4.3 • 85–92% was 40.4 ± 12.8 • 93–100% was 41.9 ± 15.6
Lim, K. *et al.*	2014	Multicentre prospective observational cohort study	45 premature infants GA 30 (IQR 27-32 weeks) 2971 hours receiving supplemental oxygen	Age at first recording was at day one (IQR 0-8 days)	88% - 92%	median (IQR) proportion of time in % • % of time within SpO_2 target range was 31 (19-39)% • % of time SpO_2 >93% was 59 (36-74) % • % of time SpO_2 <87% was 9 (4.3-18)% more than one infant per nurse was associated with a greater frequency of significant hyperoxaemia (SpO_2 >98%) when infants were in supplemental oxygen and a trend towards less eupoxaemia

DISCUSSION

The wide variation in study methodologies made it necessary to use narrative reporting when discussing the results of this systematic review. Although the power of some of the studies was limited and the quality varied, all were considered eligible for inclusion. Moreover, they focused on different aspects of compliance in targeting SpO_2. The design, TR of SpO_2, time points and duration of each study differed.

The central finding is that compliance in targeting SpO_2 was low, as were the alarm settings. All studies in compliance in oxygen targeting reported that maintaining the SpO_2 below the upper limit was the most difficult to adhere to.[18-20 30-32 35 37-39 42] The analysis of the large clinical trials comparing lower vs higher SpO_2 TR was based on the intention to treat principle. However, the larger proportion of the SpO_2 was either below or above the intended TR and there was also an overlap between the two TRs.[25 43 44] Although compliance was audited[30], it is possible that this has influenced the outcome of the trials. This underlines the importance in improving compliance in targeting SpO_2, as improved compliance could have influenced the results.

According to the studies

Several factors may play a role in low compliance in targeting SpO_2: lack of awareness of the TR settings, limited knowledge of the effects of hypoxaemia and hyperoxaemia, and an increased nurse:patient ratio.[20 31 40 41 45] Many caregivers were unaware of the appropriate SpO_2 limits.[41] In addition, nurses tend to rely on subjective observations for oxygen titration, such as skin color and chest excursions, as well as on PO and blood gases.[46] So far, studies indicate that the effects of education and training in improving the compliance targeting SpO_2 are disappointing.[37 45]

On the other hand, the use of automated fraction of inspired oxygen (FiO_2) regulation, which eliminates the need for the nurses' compliance, has been shown to improve the time SpO_2 remains within TR.[33-36 39] The increase in time within TR was small, but it is possible that the effect of automated FiO_2 regulation has been underestimated. A Hawthorne effect could have increased the nurses' compliance during the short study period, thus decreasing the difference between the manual and automated periods. The effectiveness of automated regulation on oxygenation variability, and whether this results in an improved outcome, remains to be investigated.[47]

It has been suggested that the absence of a FiO_2 titration protocol leads to saturations which would frequently exceed or fall below the TR.[48] Manual adjustments of FiO_2 can vary widely in frequency and step size, so standardization of these adjustments could decrease large fluctuations in SpO_2.[32] After implementing an oxygen titration protocol for reducing the incidence of severe ROP, Lau *et al.* observed that the period during which SpO_2 was above TR decreased significantly.[48]

Although fewer studies investigated this, compliance with alarm settings appeared to be low as well, especially the upper alarm limit.[18 30] In addition, even when alarm limits are appropriately set, caregivers seem to have a preference for SpO_2 close to the upper alarm limit.[13 44] This was also demonstrated in the large trials comparing TR of SpO_2.[25] It is possible that caregivers are more accustomed to prevent hypoxaemia than hyperoxaemia. It is also possible that infants are more stable in SpO_2 when kept at the higher end of the TR. A regular check of alarm limit settings each shift could increase awareness of this issue.

Educational programs on hyperoxaemia improved knowledge levels,[49 50] but did not lead to better compliance. Earlier research has shown that after education in risks related to hyperoxaemia the nurses' performance was still variable and only 51% of nurses were successful in minimising exposure of their infants to hyperoxaemia.[51] Nurses usually take care of more than one patient and perform multi-tasking[52] and an increased workload decreases their compliance in TR.[20 31] Also, nurses frequently have to deal with alarms, but a large proportion of the alarms are false.[53] The common occurrence of false alarms or "cry wolf" phenomenon could lead to no or delayed response of caregivers.

The decision not to limit inclusion criteria in terms of study design and methodology led to a high level of variety within the chosen studies, necessitating a narrative review. The advantage of this method, however, is that it enabled us to have a complete overview of a range of different aspects related to compliance in targeting SpO_2. However, the review was restricted to recent studies published in English and Dutch; similar studies published in other languages may have been missed. In addition, the selection process was conducted by the first author only and selection bias could have occurred.

In conclusion, the main finding of this literature review is that there is a low compliance in SpO_2 targeting and alarm settings during oxygen therapy in preterm infants, especially in maintaining the SpO_2 below the upper limit and in setting the upper alarm limit. Although there is little data available, it is likely that training, titration protocols, and decrease of the nurses' workload could improve awareness and compliance. Automated oxygen regulations have been shown to increase the time SpO_2 remains within the TR. Improving the compliance in targeting SpO_2 and automated control has the potential to improve the outcome in preterm infants, but this needs further investigation.

Chapter 3

The risk for hyperoxaemia after apnoea, bradycardia and hypoxaemia in preterm infants

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ABSTRACT

Objective: To investigate the occurrence and duration of oxygen saturation (SpO_2) >95%, after the administration of supplemental oxygen for apnoea, bradycardia, cyanosis (ABC), and the relation with the duration of bradycardia and/or SpO_2 <80%.

Methods: All preterm infants born <32 weeks gestation supported with nasal Continuous Positive Airway Pressure (nCPAP) admitted to our centre were eligible for the study. We retrospectively identified all episodes of ABCs. In ABCs where oxygen supply was increased, duration and severity of bradycardia (<80bpm), SpO_2 <80%, SpO_2 >95% and their correlation were investigated.

Results: In 56 infants 257 ABCs occurred where oxygen supply was increased. SpO_2 >95% occurred after 79% (202/ 257) of the ABCs, duration of supplemental oxygen supply was longer in ABCs with SpO_2 >95% than without SpO_2 >95% (median (IQR) 20 (8-80) vs 2 (2-3) minutes;*p* <0.001). The duration of SpO_2 >95% was longer than bradycardia and SpO_2 <80% (median (IQR) 13 (4–30) vs 1 (1-1) vs 2 (1-2) minutes;*p*<0.001). We found no correlation between duration of bradycardia- SpO_2 >95% and SpO_2 <80%- SpO_2 >95%. SpO_2 >95% lasted longer when infants where in ambient air than when oxygen was given before the ABC occurred (median (IQR)14 (5–40) min vs 8 (4–26) min;*p*< 0.01).

Conclusion: In preterm infants supported with nCPAP in the neonatal intensive care unit (NICU), SpO_2 >95% frequently occurred when oxygen was increased for ABCs and lasted longer than the bradycardia and SpO_2 <80%.

What is already known on this topic

1. SpO_2 >95% during oxygen therapy in preterm infants occurs often, increasing the risk for hyperoxaemia.
2. The long-term consequences of frequent ABCs are often attributed to bradycardia and hypoxaemia.
3. Hyperoxaemia has been shown to be an important pathogenic factor in neonatal morbidity as well.

What this study adds

1. SpO_2 >95% occurred often after oxygen therapy for ABC and lasted longer than the bradycardia and/or SpO_2 <80% during ABCs
2. There is more awareness of alarms of bradycardia and SpO_2 <80% than for SpO_2 >95%.

INTRODUCTION

Apnoea of prematurity, defined as a respiratory pause >20 seconds or when this pause is combined with hypoxia, pallor, hypotonia and/or bradycardia,[54] is one of the most common and recurrent problems in preterm infants.[55] The incidence of apnoeas is inversely correlated with gestational age and birth weight. Nearly all infants born <29 weeks gestation exhibit apnoeas compared to only 7% at 34-35 weeks gestation.[55] The treatment of apnoeas in preterm infants can sometimes be challenging. If an infant does not respond to tactile stimulation, interventions such as an increase in fraction of inspired oxygen (FiO_2) and mask ventilation are necessary.

Apnoeas are often combined with bradycardia and cyanosis (ABC) and can result in morbidity, which includes retinopathy of prematurity (ROP), impaired growth, cardio-respiratory instability and impaired neurodevelopmental outcome.[12] The risk for hypoxaemic episodes increases when oxygen saturation (SpO_2) decreases <80% for >10 seconds.[12] However, often supplemental oxygen is given as intervention to resolve ABCs, which alternately could increase the risk of hyperoxaemia (SpO_2 >95% for ≥ 10 seconds).[12] In analogy with hypoxaemia, hyperoxaemia has also been shown to be an important pathogenic factor for neonatal morbidity such as bronchopulmonary dysplasia (BPD), ROP and cerebral palsy.[9 56]

To prevent episodes of SpO_2 <80% and >95%, infants are monitored using pulse oximetry and oxygen therapy is titrated to maintain the SpO_2 within certain ranges.[8 16] However, keeping an infant within narrow target SpO_2 ranges may be challenging to a nurse and poor compliance has been observed.[18 19 30] Increasing the FiO_2 may often be needed, but could also unintendedly lead to a risk of hyperoxaemia.

Although the long-term consequences of frequent ABCs are attributed to the occurrence of bradycardia and hypoxaemia,[12] hyperoxaemia following after an ABC could also contribute to a detrimental outcome. Data is scarce on how frequently SpO_2 >95% occurs after ABCs and the duration of these episodes. We aimed to investigate the occurrence and duration of SpO_2 >95% in preterm infants treated with supplemental oxygen after ABCs and the relation between the duration of SpO_2 >95% is related to the duration of bradycardia and SpO_2 <80%.

METHODS

A retrospective study was performed in the neonatal intensive care unit (NICU) of Leiden University Medical Centre (LUMC), the Netherlands, which is a tertiary level perinatal centre with a yearly average of 475 intensive care admissions. Approval was obtained from the medical ethical review board (C12.168).

All infants with a gestational age (GA) at birth <32 weeks admitted to our unit between October 2011 and October 2012 and supported with nasal Continuous Positive Airway Pressure (nCPAP) admitted to the NICU were identified and evaluated. In our NICU, nCPAP is given by mechanical ventilators (AVEA, CareFusion, Houten, The Netherlands) which are connected to a Patient Data Management System (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). Infants without ventilator support were excluded from the study as well as infants requiring nasal flow cannula or endotracheal mechanical ventilation. In addition, infants with major congenital heart disease were excluded; different SpO_2 and separate guidelines on oxygen supply are targeted in this group. Clinical parameters of each infant were stored every minute and collected in PDMS.

In all infants, ABCs (apnoeas >20 seconds, associated with bradycardia (<80 beats per minute (bpm)) and oxygen desaturation <80%, where supplemental oxygen was given were identified and analysed in detail. ABCs were retrieved from the charts in two ways. Firstly, apnoea were manually registered in the respiratory chart in PDMS. As this was not always registered at the exact time point the apnoea occurred, the moment of bradycardia combined with SpO_2 <80% was retrieved which was the closest to the registered apnoea. Secondly, when apnoeas were not registered, they could be derived from the respiratory rate; an apnoea was documented in case of a respiratory rate in PDMS of zero, combined with bradycardia and SpO_2 <80%.

Data collection was started at the occurrence of an ABC and was continued until the supplemental oxygen was back at the baseline oxygen level before the ABC occurred (Figure 1). As data is sampled every minute, every ABC where supplemental oxygen was titrated was evaluated by documenting the following characteristics: lowest stored minute value (depth) and count in low minute values (duration) of HR <80 bpm, lowest stored minute value (depth) and the count in low minute values (duration) of SpO_2 <80%, baseline oxygen concentration and additional oxygen given, the count in minute values with additional oxygen, occurrence and count in minute values with SpO_2 >95%. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%. the duration of supplemental oxygen given (measured from the start of supplemental oxygen after the ABC until oxygen was titrated to the baseline oxygen), incidence and duration of SpO_2 >95%. ABC characteristics were analysed comparing exposure to SpO_2 >95% versus no SpO_2 >95% during apnoeic episodes. Of those with SpO_2 >95%, baseline oxygen characteristics where compared (exposure to ambient air versus supplemental oxygen).

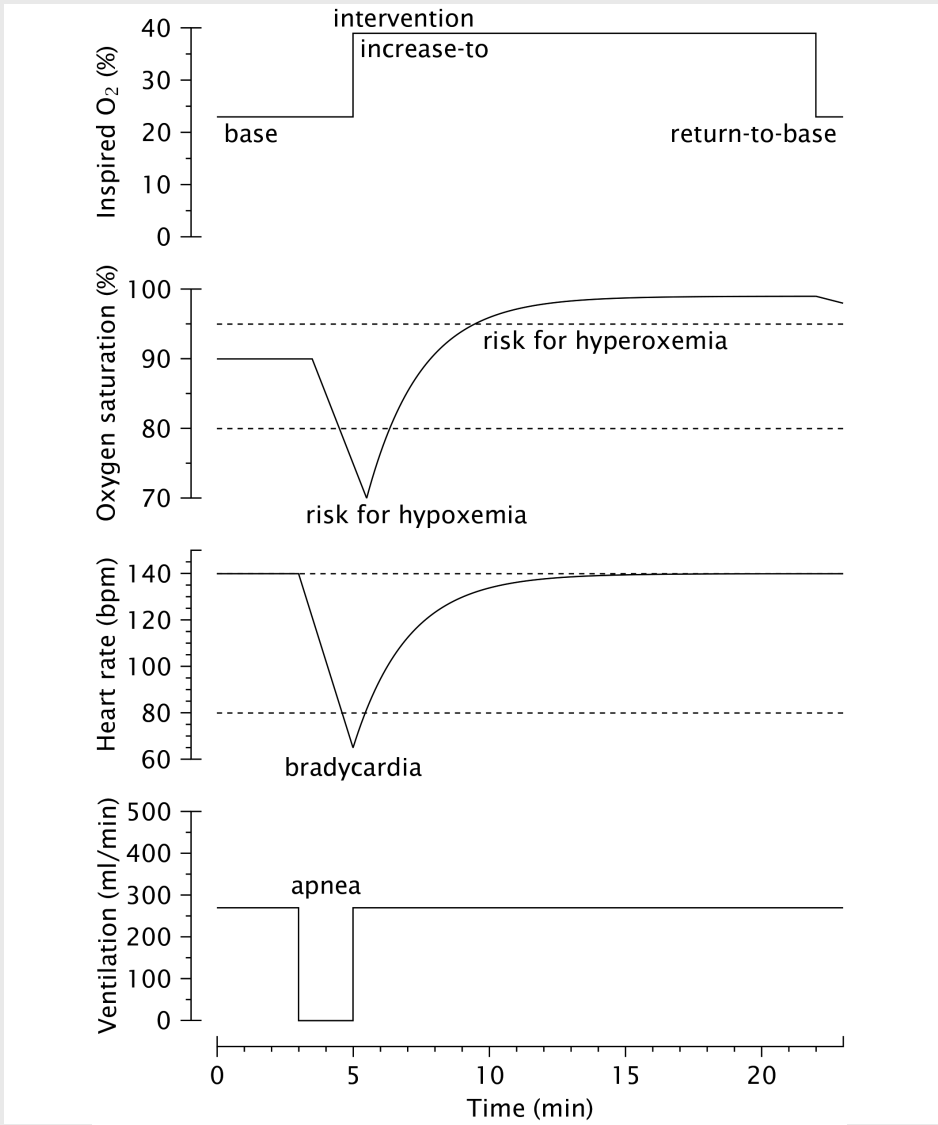

Figure 1. Graphic representation of measuring SpO_2 >95% after an ABC

Statistical analyses

Quantitative data are expressed as median and interquartile range (IQR), or number (percentage) when appropriate. Independent samples Mann-Whitney U tests were used for comparisons between SpO_2 >95% or not, and occurrence of hyperoxaemia in baseline oxygen requirements (ambient air or supplemental oxygen). The correlations between duration of

bradycardia, hypoxaemia and hyperoxaemia were investigated using Pearson's correlation coefficient for normal distributions or Spearman's rank when normal distribution could not be assumed. *p*-values less than 0.05 were considered as statistically significant. Statistical analysis was performed by IBM SPSS Statistics version 20 (IBM Software, NY, USA, 2012).

RESULTS

From October 2011 until October 2012, 194 infants <32 weeks gestation were admitted to our NICU and received nCPAP during their admission. One infant was diagnosed with a congenital heart disease and was excluded. The medical charts of the 193 eligible infants were reviewed for ABCs where supplemental oxygen was given. Patients characteristics are shown in Table 1. In 56/193 infants, 257 ABCs occurred where oxygen was increased, which were 11% of all ABCs that occurred. The median (IQR) depth of bradycardia was 70 (63-76) bpm with a duration of 1(1-1) minute. The median (IQR) depth of saturation was 68 (61-73)% with a duration of 2 (1-2) minutes. The median (IQR) baseline fraction of inspired oxygen (FiO_2) before ABC occurred was 0.23 (0.21-0.28) and increased to 0.39 (0.30-0.67) after the ABC (absolute increase of 16%). The duration of titrating down the oxygen to the baseline concentration was 14 (4-52) minutes (Table 2).

Table 1. General characteristics of infants who received supplemental oxygen for ABC.

Patients' characteristics	N=56
Gestational age, weeks (median (IQR)	28+1 (26+1-29+3)
Birth Weight, grams (median (IQR)	908 (800-1167)
Males, n (%)	29 (52)
Apgar 5 minutes, median (range)	8 (5-10)
Singletons, n (%)	22 (41)
Caesarean Delivery, n (%)	27 (50)
Mortality, n (%)	4 (7)
$BPD_{moderate\text{-}severe}$ at 36 weeks GA, %*	7
ROP ≥ stage 3,%**	7
NEC ≥ stage 2a, %***	5
IVH grade ≥ 2, %****	18

*Moderate/severe bronchopulmonary dysplasia (BPD), defined as oxygen dependence at 36 weeks post menstrual age[57]
** Moderate/severe retinopathy of prematurity (ROP), defined as ≥ grade 3 and/or the presence of plus disease[58]
***Necrotising enterocolitis (NEC), defined as grade ≥2a[59]
****Moderate/severe intraventricular haemorrhage (IVH), defined as grade ≥II[60].

Table 2. ABC characteristics.

ABC characteristics	N=257
Lowest minute value during bradycardia, bpm (depth)	70 (63-76)
Count minute values with bradycardia, min (duration)	1 (1-1)
Lowest minute value during SpO_2 <80%, % (depth)	68 (61-73)
Count minute values SpO_2 <80%, min (duration)	2 (1-2)
Baseline FiO_2,	0.23 (0.21-0.28)
Max increase FiO_2	0.39 (0.30-0.67)
Duration of titration to baseline oxygen concentration, min	14 (4-52)
Count minute value with SpO_2 >95%, min	13 (4-30)

Data are expressed as median (IQR)

SpO_2 >95% occurred in 79% (202/257) of the ABCs where oxygen was increased and lasted a median (IQR) time of 13 (4-30) minutes. When comparing ABCs with and without the occurrence of SpO_2 >95%, no differences were observed in the depth of bradycardia, duration of bradycardia, depth of hypoxaemia, duration of hypoxaemia, baseline oxygen concentration and maximum increase of oxygen concentration (Table 3). After supplemental oxygen was given, the time needed to return to baseline level was longer in ABCs with SpO_2 >95% (20 (8-80) vs 2 (2-3) minutes;p<0.001) (Table 3). There was no correlation between the duration of SpO_2 >95% and SpO_2 <80% (r = -0.05; ns) or bradycardia (r = -0.05; ns).

Table 3. Comparison of ABCs followed by exposure to SpO_2 >95% vs no exposure to SpO_2 >95%.

ABC characteristics and oxygen support N=257	exposure to SpO_2 >95% N= 202	no exposure to SpO_2 >95% N= 55	*p*-value*
Lowest minute value during bradycardia, bpm (depth)	70 (63-76)	70 (63-77)	ns
Count minute values with bradycardia, min (duration)	1 (1-1)	1 (1-1)	ns
Lowest minute value during SpO_2 <80%, % (depth)	68 (61-73)	69 (62-73)	ns
Count minute values SpO_2 <80%, min (duration)	2 (1-2)	2 (1-2)	ns
Baseline FiO_2,	0.23 (0.21-0.28)	0.23 (0.21-0.33)	ns
Max increase FiO_2,	0.37 (0.30-0.65)	0.45 (0.34-0.68)	ns
Count minute values of FiO_2 titration to baseline oxygen concentration, min	20 (8-80)	2 (2-3)	< 0.001
count minute value with SpO_2 >95%, min	13 (4 -30)	-	

Data are expressed as median (IQR). * Independent samples Mann-Whitney U test

In 52% (105/202) of ABCs with SpO_2 >95%, ambient air was given as baseline and in 48% (97/202) supplemental oxygen was given as baseline before the ABC occurred. No differences were observed in depth and duration of bradycardia (Table 4). The depth was less severe and duration of SpO_2 <80% lasted shorter in ABCs where ambient air was the baseline concentration than in ABCs where supplemental oxygen was given (median (IQR) SpO_2 69 (64-75) vs 67 (58-73)%;*p*=0.05 and median (IQR) time 2 (1-2) vs 2 (1-3) min;*p*=0.001). Although there were no differences in the median (IQR) time needed to return to baseline level (22 (8-101) vs 19 (8-63) min; ns), the median (IQR) duration of SpO_2 >95% lasted significantly longer when ambient air had been given compared to when supplemental oxygen was given as baseline concentration (14 (5-40) min vs 8 (4-26) min;*p*< 0.05) (Table 4). There was a correlation between the baseline oxygen concentration before ABC and the duration of SpO_2 >95% after ABC (*r* =0.2;*p*<0.01)

Table 4. Comparison of ABCs with exposure to SpO_2 >95%: ambient air vs supplemental oxygen at baseline

ABC characteristics and oxygen support N= 202	ambient air N= 105	oxygen N= 97	*p*-value*
Lowest minute value during bradycardia, bpm (depth)	72 (63-77)	70 (62-75)	ns
Count minute values with bradycardia, min (duration)	1 (1-1)	1 (1-1)	ns
Lowest minute value during SpO_2 <80%, % (depth)	69 (64-75)	67 (58-73)	0.05
Count minute values SpO_2 <80%, min (duration)	2 (1-2)	2 (1-3)	0.001
Baseline FiO_2,	0.21 (0.21-0.21)	0.28 (0.25-0.34)	< 0.001
Max increase FiO_2,	0.32 (0.27-0.45)	0.44 (0.35-0.77)	< 0.001
Count minute values of FiO_2 titration to baseline oxygen concentration, min	22 (8-101)	19 (8-63)	ns
count minute value with SpO_2 >95%, min	14 (5-40)	8 (4-26)	< 0.05

Data are expressed as median (IQR). * Independent samples Mann Whitney U test

DISCUSSION

In this retrospective study in preterm infants on nCPAP, we observed that when supplemental oxygen was given to treat ABCs, SpO_2 >95% frequently occurred and lasted significantly longer than the bradycardia or SpO_2 <80%. The ABCs were often short in duration and did not correlate to the duration of SpO_2 >95%. However, SpO_2 >95% lasted longer when patients were in ambient air before the ABC occurred. Also, when SpO_2 >95% occurred, we recorded a significantly longer time needed to titrate oxygen back to the baseline concentration than after ABCs where SpO_2 >95% did not occur. Our results suggest that caregivers showed a prompt response to an ABC because of the shorter duration of bradycardia and SpO_2 <80% but when supplemental oxygen is given, it is not carefully titrated down, once the SpO_2 <80% is over. Caregivers should be more aware of the hazards of ABCs, but also in particularly of the risk of hyperoxaemia that could occur afterwards, when supplemental oxygen is given.

The high incidence of SpO_2 >95% during oxygen therapy and the caregiver's compliance in our unit is comparable to what has been reported in previous studies.[29 32 61] However, this is the first study describing the occurrence and duration of SpO_2 >95% after oxygen has been increased when ABCs occur. The compliance of nurses could be affected by the nurse:patient ratio, which is in our unit on average 1:2. Sink *et al*. showed that duration

of SpO_2 above TR increased when nurse:patient ratio increased from 1:1 to 1:3.[61] Also, an incorrect setting of the alarm limits could explain the high incidence and duration of SpO_2 >95% in this study. Previous studies have reported a low compliance of alarm limits' settings for pulse oximetry.[18 19 30] The nursing compliance with alarm limits for pulse oximetry in preterm infants was related to the level of supplemental oxygen needed. In infants requiring high levels of supplemental oxygen, the upper alarm limit was set correctly in 35.7%, compared with 23.6% in the moderate group and 6.2% in the low oxygen group.[18] Similarly, we observed that the duration of SpO_2 >95% was significantly longer when infants were in ambient air before the ABC occurred where possible alarm limits were not adjusted when supplemental oxygen was started (from 85-100% to 85-95%).

The long-term consequences of ABCs for preterm infants have been well established.[12] Most caregivers are aware that frequent bradycardia and hypoxaemic events can result in morbidity, which includes ROP, impaired growth, persistent cardio-respiratory instability and impaired neurodevelopmental outcome.[12] Hyperoxaemia on the contrary, has also been shown to be an important contributing factor in these morbidities.[9 56] In this study we observed that the highest risk of hyperoxaemia occurs often immediately after an ABC and lasts even longer than the ABC itself. However, it is not possible to distinguish the effect of SpO_2 >95% from the effect of bradycardia of hypoxaemia on long-term outcome. The risk of iatrogenic hyperoxaemia, that often follows after an ABC, could also play an important role in the long-term consequences of ABCs.
It is possible that due to the lack of proper guidelines for titrating oxygen, SpO_2 is frequently above TR when it is controlled manually by the nursing staff.[48] Caregivers easily administer large amounts of oxygen in order to prevent hypoxaemia and adjustments vary widely in frequency and steps.[32] Standardisation of FiO_2 adjustments could reduce fluctuations of saturations and periods of hypoxaemia and hyperoxaemia.[48] In addition, several studies have shown oxygen saturations were less variable and more often maintained within TR when oxygen therapy was automatically adjusted instead of manually.[33 36 62 63] Also education and training have shown to be effective in improving the maintenance of the intended range of SpO_2.[50] In contrast, other studies reported that knowledge about the risk of hyperoxaemia did not reduce the time preterm infants had oxygen saturations above TR.[49 51]

The results of this study are limited by the small sample size; only infants admitted to the NICU could be included in the study. Also, it is possible that the reported occurrence of SpO_2 >95% due to oxygen therapy for ABCs does not reflect the occurrence in our total cohort of preterm infants. However, we do not expect that this will influence the occurrence considerably as in the step down unit, larger and more stable preterm infants are admitted and therefore less likely to have significant ABCs.

CONCLUSION

In preterm infants treated with nCPAP, SpO_2 >95% occurred often after oxygen therapy for ABCs and the duration of these hyperoxaemic periods was longer than the duration of bradycardia and SpO_2 <80%. The duration of SpO_2 >95% was much longer in infants breathing ambient air compared to infants with supplemental oxygen before ABC occurred. This considerably increases the risk of iatrogenic hyperoxaemia after ABC and it is possible that this might contribute to the long-term consequences of apnoeas. NICU caregivers should be more aware of the occurrence of the risk of hyperoxaemia after ABCs when supplemental oxygen is given. More vigilance is needed for alarm settings and oxygen titration to get back to baseline oxygen condition as soon as possible.

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Chapter 4

Improving manual oxygen titration in preterm infants by training and guideline implementation

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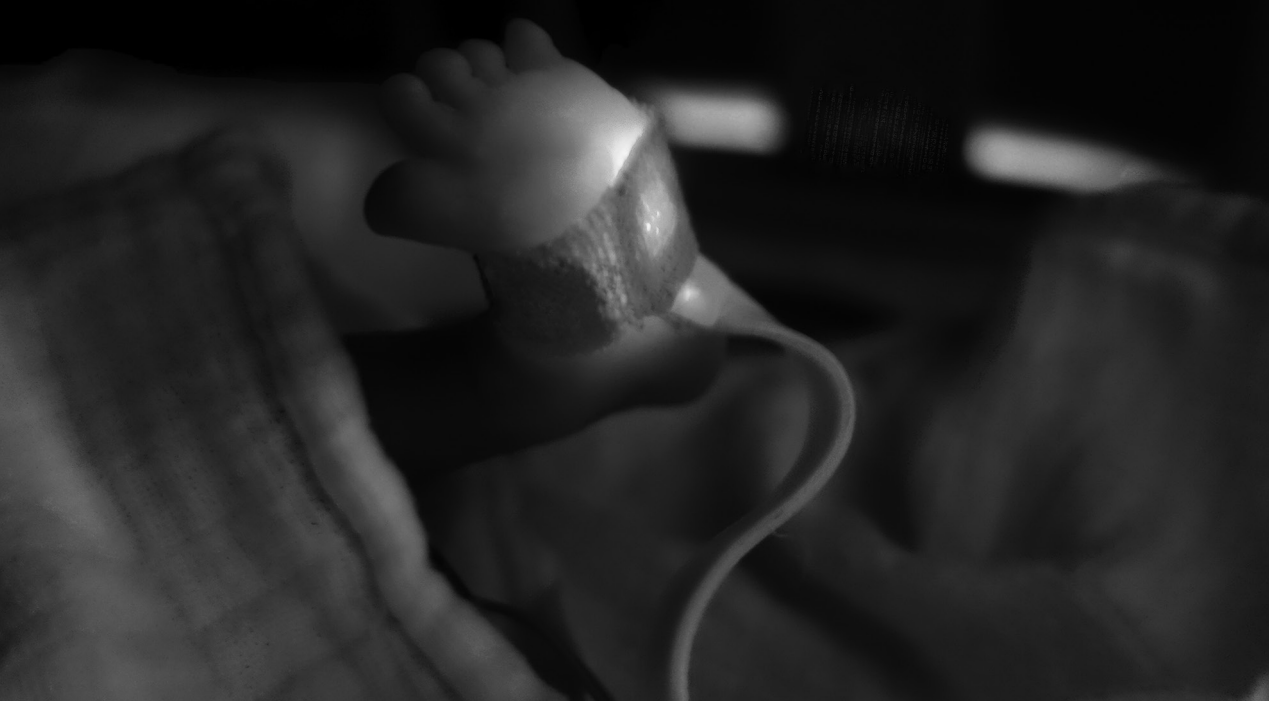

ABSTRACT

Two cohorts of preterm infants <30 weeks of gestation needing respiratory support and oxygen therapy were compared, to study oxygen saturation (SpO_2) targeting before and after training and guideline implementation of manual oxygen titration. The percentage of time spent with SpO_2 within target range (85-95%) was calculated (%SpO_2-wtr). SpO_2 was collected every minute when fraction of inspired oxygen (FiO_2) >0.21. ABCs where oxygen therapy was given were identified and analysed.

After training and guideline implementation the %SpO_2-wtr increased (median (IQR) 48.0(19.6-63.9)% vs 61.9(48.5–72.3)%;*p*<0.005), with a decrease in the %SpO_2 >95% (44.0(27.8–66.2)% vs 30.8(22.6–44.5)%;p< 0.05). There was no effect on the %SpO_2 <85% (5.9(2.8 – 7.9)% vs 6.2(2.5 - 8)%;ns) and %SpO_2 <80% (1.9(1.0 – 3.0)% vs 1.7(0.8 – 2.6)%; ns). In total 186 ABCs with oxygen therapy before and 168 ABCs after training and guideline implementation occurred. The duration of SpO_2 <80% reduced (2(1-2) vs 1(1-2) minutes;*p*<0.05), the occurrence of SpO_2 >95% did not decrease (73% vs 64%;ns), but lasted shorter (2(0-7) vs 1(1-3) minutes;*p*<0.004).

Conclusion: Training and guideline implementation in manual oxygen titration improved SpO_2 targeting in preterm infants with more time spent within target range and less frequent hyperoxaemia. The durations of hypoxaemia and hyperoxaemia during ABCs were shorter.

What is known

Targeting SpO_2 in preterm infants can be challenging and the compliance is low when oxygen is titrated manually.

Hyperoxaemia occurs often after oxygen therapy for oxygen desaturation during apnoeas.

What is new

Training and implementing guidelines improved targeting SpO_2 and reduced hyperoxaemia.

Training and implementing guidelines improved manual oxygen titration during apnoea, combined with bradycardia and cyanosis (ABC).

INTRODUCTION

Oxygen is the most commonly used therapy in neonatal intensive care units (NICUs).[6] To assure adequate delivery of oxygen to the tissue without creating oxygen toxicity, [64] infants admitted to the NICU are continuously monitored using pulse oximetry. Oxygen is titrated manually to maintain the pulse oxygen saturation (SpO_2) within target ranges (TR), but this can be challenging. Several studies reported low compliance in targeting SpO_2 and described a tendency of caregivers to accept higher SpO_2.[18 20 24 30 31 40 41] It has been suggested that caregivers are more focused to prevent hypoxaemia than hyperoxaemia.[10 32] However, improving the knowledge of caregivers in the hazards of hyperoxaemia could lead to more vigilance against alarm settings and oxygen titration and thus decrease the time outside TR in preterm infants considerably.[10]

Oxygen is most frequently manually titrated when an apnoea occurs, apnoea is defined as a respiratory pause >20 seconds and/or shorter accompanied by bradycardia or cyanosis, hypotonia and pallor (usually termed ABC: apnoea, bradycardia, cyanosis).[65] We recently demonstrated that manual titration of oxygen therapy in preterm infants during ABC unintendedly led to the occurrence of hyperoxaemia (SpO_2 >95%).[24] To improve compliance, especially during ABCs, all neonatal caregivers in our NICU received additional training about the risk of hypoxaemia and hyperoxaemia, and a guideline for manual oxygen titration was introduced.

Efforts have been taken to increase the nurses' compliance in SpO_2 targeting by creating awareness by training and implementing guidelines, with variable success.[29 37 48-50 66] We aimed to investigate the effect of training combined with an oxygen titration guideline on the proportion of time SpO_2 was within TR (%SpO_2-wtr) and the occurrence and duration of hypoxaemia and hyperoxaemia during and after ABCs.

METHODS

A prospective observational study was performed at the NICU of the Leiden University Medical Centre (LUMC), which is a tertiary level perinatal centre in the Netherlands with an average of 650 intensive care admissions per year. This study was an audit and part of a quality improvement project and did not need to comply with the Dutch law on Medical Research in Humans; the Research Ethics Committee issued a statement of no objection. All infants born <30 weeks of gestation admitted to the NICU in LUMC between March 2013 and December 2013 (before training and guideline implementation) and between

February 2014 and November 2014 (after training and guideline implementation) were retrospectively compared.

To increase awareness in SpO_2 targeting and oxygen titration, all caregivers were trained in a months' period (January 2014). Before the afternoon shift started, nurses were asked to attend a lesson that lasted 30-45 minutes. Each session was attended by 6-8 nurses. An attendance list was updated to make sure every nurse attended the lesson. The medical staff was trained separately during a grand round session. The training was given by the nurse (first author) or neonatal consultant (last author) responsible for the quality improvement project. During this training the results of our previous study were discussed, which demonstrated frequent occurrence of hyperoxaemia after ABCs when oxygen therapy was given.[24] Caregivers were also educated in the risks of exposure of preterm infants to frequent hypoxaemia and hyperoxaemia. To pursue an uniform approach to oxygen titration, a guideline for oxygen titration was introduced and discussed (Figure 1). After the training, the nurse and consultant responsible for the project were available during daytime and frequently actively approached the staff whether there were questions or issues related to the oxygen titration and/or the guideline. Also, the medical staff was asked to standardly check the SpO_2 distribution during the daily rounds.

The guideline was specially developed for a randomised trial comparing manual versus automated oxygen titration.[67] During the trial the nurses used the guideline during the manual periods. The guideline was then discussed by members of the project and the nurses that received special training in ventilation. Based on their feedback, small amendments were made to make it more practicable for the nurses.

All preterm infants receiving respiratory support (endotracheal and non-invasive ventilation) in the NICU were included in the study. Infants with major congenital heart disease with different SpO_2 target ranges were excluded. All infants received routinely a loading dose of 10 mg/kg caffeine base directly after birth followed by 5 mg/kg/day. Dopram (2 mg/kg/hr) was given in case of refractory apnoeas. Respiratory support was given by a mechanical ventilator (AVEA, Carefusion, Houten, The Netherlands), which was connected to the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). SpO_2 was measured using Masimo SET Radical pulse oximeter (software version 46.02) (Masimo Radical, Masimo Corporation, Irvine CA, USA), integrated in the bedside monitor (Philips Healthcare Nederland, Eindhoven, The Netherlands). The pulse oximeter probe was placed around the hand or foot of the infant. (right hand in case of a patent ductus arteriosus). Basic characteristics were collected from the patient files in PDMS. All clinical parameters were collected every minute from PDMS. In both periods, the SpO_2 TR was 85-95% when

FiO_2 >0.21 and the alarm limits were set at 84% and 96%.Before the start of each shift, the TR and alarm setting were checked by the nurse.
%SpO_2-wtr, SpO_2 < 85% and SpO_2 > 95%, when FiO_2 >0.21 was calculated for each patient during the time period infants received respiratory supported. Additionally, all ABC events were documented and evaluated in all preterm infants on non-invasive ventilation (nasal CPAP and non-invasive intermittent mandatory ventilation). An ABC was defined as apnoea (>20 seconds or shorter), accompanied with bradycardia (<80 beats per minutes (bpm)) and cyanosis (SpO_2 <80%). As data is sampled every minute, every ABC where supplemental oxygen was titrated was evaluated by documenting the following characteristics: lowest stored minute value (depth) and count in low minute values (duration) of HR <80 bpm, lowest stored minute value (depth) and the count in low minute values (duration) of SpO_2 <80%, baseline oxygen concentration and additional oxygen supplied, the count in minute values with additional oxygen, occurrence and count in minute values with SpO_2 >95%. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%.
All ABCs were manually identified in PDMS and analysed starting at the occurrence of an ABC and was continued until the supplemental oxygen administered was returned to the baseline oxygen level before the ABC occurred.

Statistical analyses
Quantitative data are presented as median (IQR), mean (SD) or number (percentage) where appropriate. Time with SpO_2 within various ranges for FiO_2 >0.21 were collated for each infant individually before and after training and aggregated as proportions of the recorded time (median and IQR). Statistical analysis comprised non-parametric Kruskal-Wallis rank sum test. The Mann Whitney U test was used for non-parametric comparisons for continuous variables to compare the patient characteristics and the ABC characteristics. P-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Software, NY, USA, 2012) and R 3.2.0 (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

We considered an increase of 10% SpO_2-wtr clinically relevant. In previous studies the standard deviation of the mean %SpO_2-wtr was 16.[67] To detect a change of 10% SpO_2-wtr in each period by a Kruskal-Wallis test with a 80% power and a significance level of 0.05 (two-tailed test), at least 44 patients in each group were required. This number was calculated by running a simulation taking samples from two normal distributions with means 0 and 10 and a standard deviation of 16 to model the clinically relevant increase in %SpO2-wtr.

RESULTS

Patient characteristics

During the two study periods of 10 months, a total number of 136 infants born <30 weeks of gestation were admitted to our NICU. Of these infants, 79 infants were admitted and treated before education on oxygen titration and the implementation of a guideline, 57 infants after were admitted after these changes. The median interquartile range (IQR) of gestational age was (28+2 (27+3 - 29) vs 28+3 (26+4 -29) weeks; ns) and birth weight (1090 (857-1277) vs 1000 (855-1206); ns) were not different (Table 1).

Table 1. Patient characteristics

	Before Training N= 79	After Training N= 57	*p*-value
Gestational age at birth (weeks), Median (IQR)	28+2 (27+3 - 29)	28+3 (26 +4 – 29)	0.36 [a]
Birth weight (grams) median (IQR)	1090 (857-1277)	1000 (855 – 1206)	0.56 [a]
Male sex, no (%)	46 (58)	32 (56)	0.96 [b]
Caesarean delivery, no (%)	39 (49)	31 (54)	0.56 [b]
Singletons, no (%)	51 (65)	39 (68)	0.26 [b]
Apgar at 5 min. median, (IQR)	7 (7-8)	7 (6-9)	0.66 [a]
Days on respiratory support, median (IQR)	9 (3-14)	8 (4-24)	0.89 [a]
Length of stay on NICU, median (IQR)	15 (8-25)	19 (8-35)	0.32 [a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test

Effect of training and guideline on the %SpO_2-wtr

There was a small but significant decrease in median SpO_2, where IQR remained similar (before vs after training: 94% (91-96)% vs 93% (91-96)%;*p*=0.02). After training and guideline implementation the %SpO_2-wtr significantly increased (before vs after training: 48.0 (19.6 - 63.9)% vs 61.9 (48.5 – 72.3)%; p <0.005), with a simultaneous decrease in SpO_2 >95% (44.0 (27.8 – 66.2)% vs 30.8 (22.6 – 44.5)%; p <0.05) and a non-significant decrease in SpO_2 >98% (9.4 (4.2 – 26.8)% vs 6.1 (2.3 - 12.1)%; ns). %SpO_2 <85% remained similar (5.9 (2.8 - 7.9)% vs 6.2 (2.5 – 8.0)%; ns) as well as SpO_2 <80% (1.9 (1.0 – 3.0)% vs 1.7 (0.8 – 2.6)%; ns) (Table 2, Figure 2).

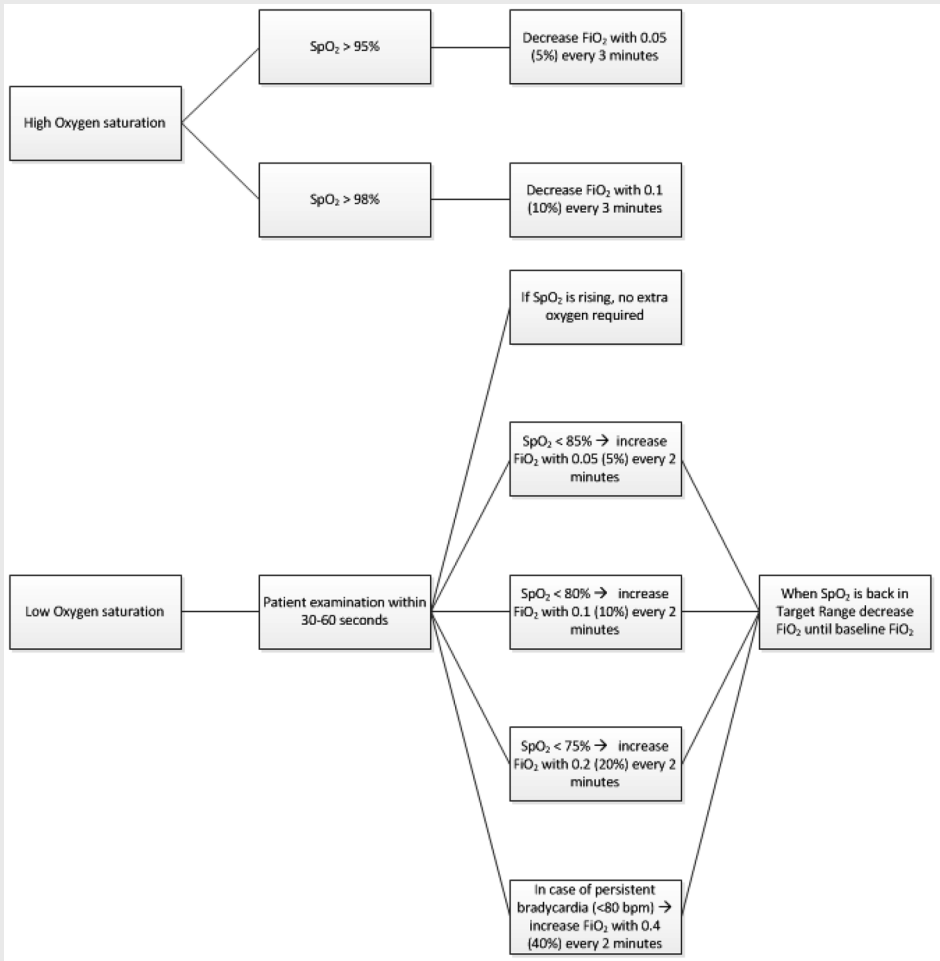

Figure 1. FiO_2 titration guideline

Table 2. Median (IQR) in different saturation ranges

	Before Training	After Training	*p*-value*
%SpO_2 <80%	1.9 (1.0 - 3.0)	1.7 (0.8 - 2.6)	ns
%SpO_2 <85%	5.9 (2.8 - 7.9)	6.2 (2.5 - 8.0)	ns
%SpO_2 - WTR 85-95%	48.0 (19.6 - 63.9)	61.9 (48.5 - 72.3)	< 0.005
%SpO_2 >95%	44.0 (27.8 - 66.2)	30.8 (22.6 - 44.5)	< 0.05
%SpO_2 >98%	9.4 (4.2 - 26.8)	6.1 (2.3 to 12.1)	< 0.06

* Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test.

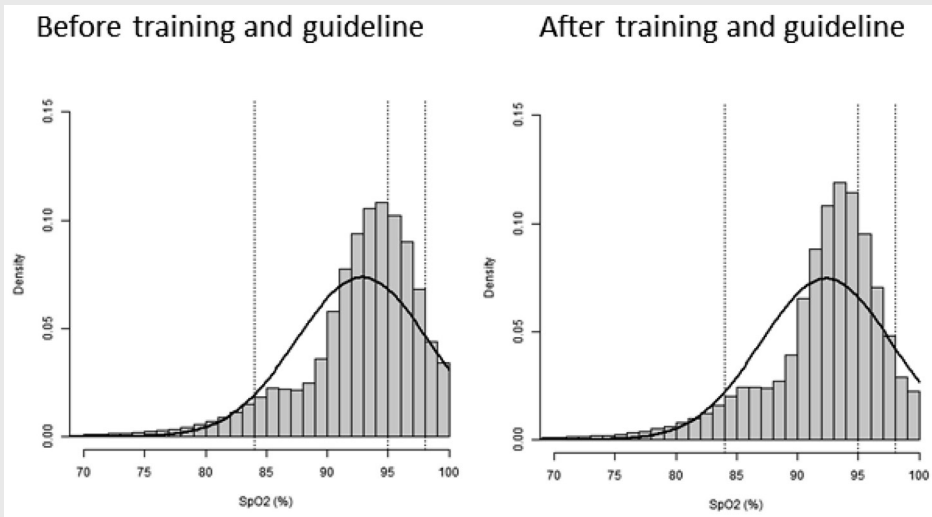

Figure 2. Time with SpO_2 within various ranges collated over all infants and aggregated as total proportion of recorded time

Effect of training and guideline on the occurrence of ABCs

Before training and guideline implementation, 79 infants received non-invasive respiratory support, of which 29/79 (37%) infants had a total of 186 ABCs that required extra FiO_2. After training and guideline implementation, 57 infants received non-invasive respiratory support and 28/57 (49%) infants had a total of 168 ABCs (Table 3). After training and guideline implementation the depth and duration of bradycardia did not change. Although no difference was observed in the depth of SpO_2 <80% during an ABC, the duration of SpO_2 <80% decreased significantly (2 (1-2) minutes vs 1 (1-2) minutes;*p* <0.05) (Table 4). Although the baseline and the maximum increase in FiO_2 during the ABC did not change, the duration of titrating oxygen back to the baseline concentration had a smaller range (3 (2-16) minutes to 3 (2-7) minutes;*p*< 0.05). There was no significant change in the occurrence of hyperoxaemia

after ABCs (73% (135/186) vs 64% (108/168); ns), but the duration significantly decreased from 2 (0-7) minutes to 1(1-3) minutes;p<0.01) (Table 4).

Table 3. Patient characteristics with ABCs.

	Before Training N= 29	After Training N= 28	*p*-value
Gestational age at birth (weeks), Median (IQR)	27+6 (26+5 - 29)	27+2 (26 – 28 +2)	0.19[a]
Birthweight (grams). Median (IQR)	1016 (812-1199)	965 (692 – 1199)	0.51 [a]
Male sex, no (%)	22 (76)	16 (57)	0.14[b]
Caesarean delivery, no (%)	13 (45)	15 (53)	0.51[b]
Singletons, no (%)	22 (76)	22 (79)	0.57 [b]
Apgar at 5 min, Median (IQR)	8 (7-8)	7 (6-9)	0.25[a]
Days with respiratory support, no. Median (IQR)	14 (8-32)	19 (9 -31)	0.5 [a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test

Table 4. ABC characteristics with FiO_2-therapy

	Before Training (ABC= 186)	After Training (ABC = 168)	*p*-value
ABC with SpO_2 > 95%	73%	64%	ns[b]
Number of ABC, n. Median (IQR)	4 (1-9)	4 (2-8)	0.64[a]
Lowest minute value during bradycardia, bpm (dept) Median (IQR)	70 (60-75)	69 (61-75)	ns[a]
Count minute values with bradycardia, min (duration) Median (IQR)	1 (1-1)	1 (1-1)	ns[a]
Lowest minute value during SpO_2 <80%, % (dept)	70 (62-76)	72 (61-77)	ns[a]
Count minute values SpO_2 <80%, min (duration) Median (IQR)	2 (1-2)	1 (1-2)	0.03[a]
Baseline FiO_2	0.25 (0.21-0.31)	0.25 (0.21-0.30)	ns[a]
Max increase FiO_2	0.44 (0.39-0.52)	0.43 (0.37-0.51)	ns[a]
Count minute values of FiO_2 titration to baseline oxygen concentration, min Median (IQR)	3 (2-16)	3 (2-7)	0.010[a]
count minute value with SpO_2 >95%, min Median (IQR)	2 (0-7)	1 (1-3)	0.004[a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test

DISCUSSION

In this study extra training and implementation of a guideline for oxygen titration showed to improve the compliance of caregivers in our NICU in oxygen targeting and a more prompt handling of ABCs. Preterm infants receiving oxygen spent significantly more time within the SpO_2 TR of 85-95%, with a significant decrease in time of SpO_2 levels above 95%. The occurrence of hypoxaemia and hyperoxaemia during ABCs did not decrease, but both episodes lasted significantly shorter. This initiative in quality improvement had a positive effect and if the observed reduction in the risk for hypoxaemia and hyperoxaemia could be maintained through repetitive training, it would be likely to improve the outcome of preterm infants.

Previous studies have reported a quality improvement in oxygen titration and targeting SpO_2, using an approach comparable to ours.[48 50 68] The problems were initially assessed, followed by embedding education and implementation of a protocol, after which effectiveness was evaluated. In line with our findings, Ford *et al*. reported a significant improvement in time spent within the TR (90%-95%) and a reduction of SpO_2 above TR.[50] Lau *et al*. did not report the time spent within TR (85%-92%), but observed a significant reduction in SpO_2 ≥93%.[48] Also, in the study of Chow *et al.* the time spent within TR was not reported. They observed a decrease in severe retinopathy of prematurity (ROP) after introduction of an educational program combined with a titration protocol.[48 50 68] As the findings were similar in most performed studies, including ours, it is plausible that this approach (training and guideline implementation) can be successful in nearly all neonatal units.

It is unclear which part of the quality improvement has contributed most to the effect on the compliance of caregivers in oxygen titration and targeting SpO_2. Previous studies reporting the effect of guideline or education only were less successful compared to our study.[37 69 70] Clarke *et al*. reported no improved time within TR using an a titration guideline. Arawiran *et al.* observed no improved adherence to TR (85 - 92%) after an education intervention with oral and online presentations, discussions of adverse effects of excessive oxygen, and displaying SpO_2 distributions.[37] Also, Deuber *et al*. studied the effect of training with the aim to reduce hyperoxaemia and to increase caregivers knowledge. The time spent within TR (88% - 92%) was not reported, the time above TR was increased after training.[49] However, there are many variables that could have influenced the effect of training. Differences in content, approach and duration of the training, but also the general workload and nurse:patient ratio could have influenced the results.[40] As part of our education we discussed the results of our previous study, showing that SpO_2 >95% occurred in 79% of the ABCs where oxygen was increased.[24] During the training we observed that caregivers felt personally addressed, resulting in behavioral change by better titration of oxygen during apnoeas.

It is clear that guidelines were not followed exactly, and compliance with the exact timing and step size was not measured. Nevertheless, when presented as part of the training the guidelines provided a realistic framework on how to avoid hyperoxaemia, without increasing hypoxaemia. When the guideline was introduced and implemented in our unit we took into account the factors that are important for adopting a guideline. Factors related to organization (i.e. support from physicians), to nurses (i.e. awareness of, and attitudes towards guidelines), anticipated consequences (i.e. benefit to the patient and to nurses' work) and factors related to the patient group (i.e. topic of the guideline) were identified as important factors for adopting a guideline.[71] To get all caregivers involved, the guideline was openly discussed during the training sessions.

Recently, we reported on how nurses responded to an ABC and handled the oxygen titration.[24] In a retrospective study in preterm infants on nCPAP, we observed that when supplemental oxygen was given to treat ABCs, iatrogenic hyperoxaemia occurred and lasted significantly longer than the bradycardia or hypoxaemia that initially prompted the supplemental oxygen administration. Although the duration of hypoxaemia was comparable, the duration of hyperoxaemia was significantly longer (14 (4-52) minutes) in our previous study compared to our current observations in the cohort before the intervention. A possible explanation could be the use of the "increase FiO_2" key on the AVEA-ventilator. When this key is activated, the ventilator increases the oxygen concentration delivered to the infant for two minutes, after which the ventilator will return to prior settings. Nevertheless, training and guideline implementation significantly reduced the duration of hypoxaemia and hyperoxaemia even further. Apparently nurses were more prompt in their handling when an ABC occurred, but also titrated more carefully. Poets *et al*. found an increased risk of adverse outcomes in preterm infants who experienced intermittent hypoxaemia, lasting for approximately one minute or more.[14] This emphasizes the need for awareness and accurate handling of ABCs by the nurses.

In recent years, there is an increasing interest in automatic titration of oxygen in preterm infants. Closed-loop devices designed for monitoring and controlling the oxygenation in (ventilated) preterm infants are clinically used in research related context.[35 36 38 39] These studies have shown that using automated oxygen control significantly increased time of $\%SpO_2$-wtr of approximately 8-24%, however, the time outside TR varied between studies. Most studies, but not all, reduced hyperoxaemia, and some also reduced hypoxaemia.[35 36 38 39] Our study within manual control showed comparable results with automatic devices concerning the increased time $\%SpO_2$-wtr and decreased time $\%SpO_2$ above TR. To make sure that this effect remains, repetitive training should be implemented in our unit.

Recent randomised controlled trials demonstrated a lower mortality in preterm infants when SpO_2 was targeted 91-95% as compared to 85-89%.[15 43 44 72 73] In the time period of this observational study, our local guidelines recommended 85-95%, but were changed to 90-95% after the study. It is possible that this change could lead to different results when measuring the effect of training and guideline implementation. Jones et al. recently demonstrated that preterm infants with bronchopulmonary dysplasia (BPD) were much more stable and less difficult to target when higher SpO_2 targets were used.[74]

A limitation of this study is its retrospective character. The training and oxygen titration guidelines were initiated for quality improvement in our unit and for this reason the effect was audited by comparing the situation before and after the interventions instead of a randomised trial. The dip in the frequencies of SpO_2 87-90% is associated with the generation of Masimo oximeters available in our unit at the time of this study, using an internal calibration algorithm that reduces the frequency of saturations of 87–90% and increases the frequency of higher values.[75] However, this would not have influenced the effect of training and guideline implementation as both groups were measured with the same oximeters.

Furthermore, we did not adjust for the contribution of the amount of ABCs of each patient, but we considered every ABC as an independent event as all ABCs are handled the same for each infant. An important factor that could have influenced the results is the workload of caregivers. However, the nurse:patient ratio, the number of patients, severity of illness and NICU admissions days were not different between the periods, which makes it unlikely that the workload differed between periods. In addition, based on findings in recent large trials in SpO_2, in our unit the TR was narrowed towards the higher end (90-95%). It is possible that different results will be reached as it will be more difficult to comply with a smaller TR.

CONCLUSION

Based on the observations of this study, training of caregivers combined with an oxygen titration guideline, improved the compliance to stay within SpO_2 TR in preterm infants. Additionally the amount of hyperoxaemia reduced, without an increase of hypoxaemia. Thereby, oxygen was better titrated and reduced the duration of hyperoxaemia after ABCs.

Chapter 5

The effect of a smaller target range on the compliance in targeting and distribution of oxygen saturation in preterm infants

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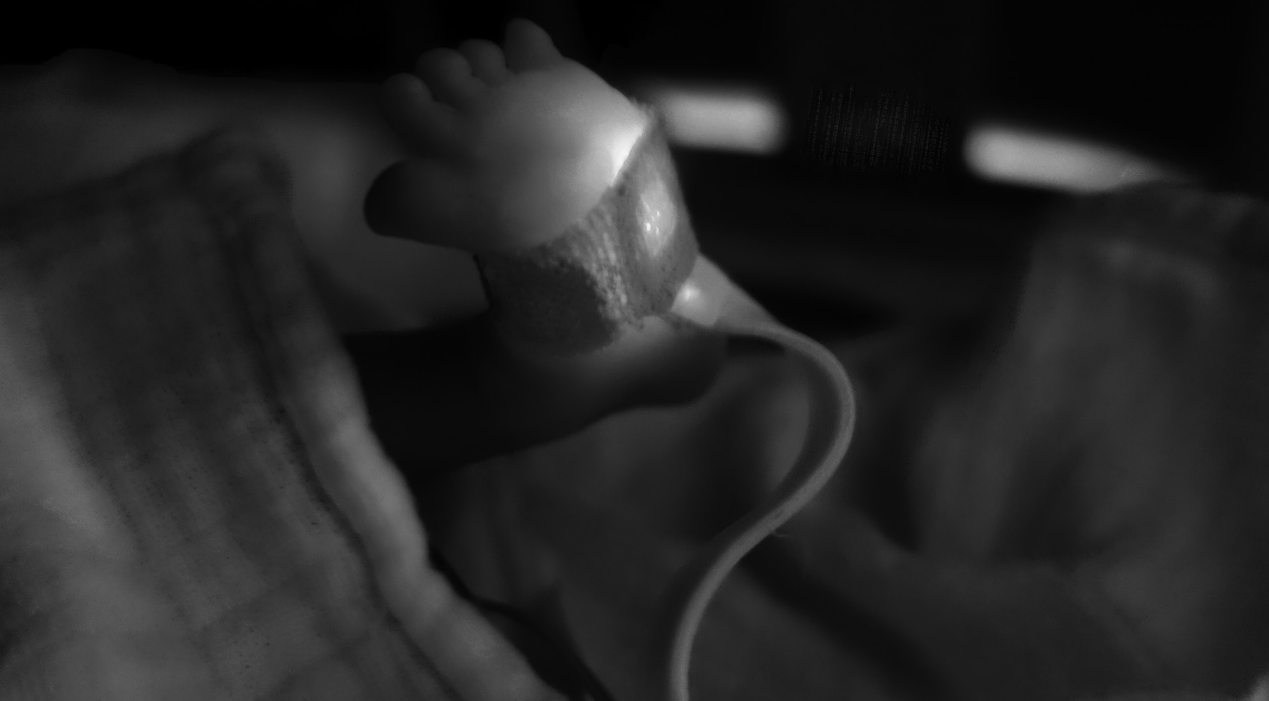
Submitted



ABSTRACT

Background: Following recent recommendations, the oxygen saturation (SpO_2) target range (TR) for preterm infants in our nursery was narrowed towards the higher end from 85-95% to 90-95%.

We determined the effect of narrowing the SpO_2 TR on the compliance in TR and distribution of SpO_2 in preterm infants.

Methods: Infants <30 weeks of gestation receiving oxygen were retrospectively compared, before and after changing the TR from 85-95% to 90-95%, during their admission on the neonatal intensive care unit (NICU). For each infant distribution of SpO_2 was noted by collecting SpO_2 samples every minute, and the percentage of time spent with SpO_2 within and outside TR was calculated. During both periods oxygen was manually adjusted. Hypoxaemic events (SpO_2<80%) where oxygen was titrated were identified and analysed.

Results: Data were analysed for 104 infants (57 before and 47 after the range was narrowed). The narrower range was associated with an increase in the median SpO_2 (93 (91–96)% vs 94 (92-97)%;*p*< 0.01), but did not lead to an increase in median (IQR) time SpO_2 within 90-95% (49.2 (39.6-59.7)% vs 46.9 (27.1-57.9)%;ns). The distribution of SpO_2 shifted to the right with a significant decrease in SpO_2 <90%, but not <80%, and a trend towards a higher occurrence of SpO_2 >95%. There was no difference in the frequency, depth and duration of hypoxaemic events and the titration of oxygen.

Conclusion: Narrowing the TR from 85-95% to 90-95% in preterm infants caused a shift of the SpO_2 distribution to the right with less occurrence of a low SpO_2, no change in time spent between 90-95%, but a trend towards more time with SpO_2 >95%.

What is already known

1. Titrating oxygen manually to maintain SpO_2 within intended target range can be challenging.
2. A higher SpO_2 target range (91-95%) leads to a lower mortality, but also more retinopathy of prematurity (ROP) when compared to a lower SpO_2 target range (85-89%).

What this study adds

1. Implementing a narrower TR from 85-95% to 90-95% did not lead to a change in duration of a SpO_2 level between 90-95%.
2. The distribution of SpO_2 shifted towards the right, with less lower SpO_2, but no decrease in hypoxaemia (SpO_2 <80%), and a trend towards hyperoxaemia (SpO_2 >95%).

INTRODUCTION

Oxygen therapy in preterm infants is routinely monitored by pulse oximetry during their admission in a neonatal intensive care unit (NICU). In order to prevent the risk of hypoxaemia and hyperoxaemia, neonatal caregivers in most units titrate fraction of inspired oxygen (FiO_2) manually in order to stay within the set oxygen saturation (SpO_2) target range (TR). Recent randomised trials in evaluating lower SpO_2 TR (85%-89%) versus higher SpO_2 TR (91%-95%) in preterm infants[25 43 44] have shown that using a higher SpO_2 TR led to a reduced mortality but increased the rate of retinopathy of prematurity (ROP) when compared to a lower SpO_2 TR.[25 44] Although the groups in the studies[25 43 44] had a substantial overlap in SpO_2 levels and the optimal TR remains undefined, European and Dutch guidelines now recommend a SpO_2 TR of 90–95% for preterm infants.[76]

Maintaining SpO_2 within TR during oxygen therapy requires compliance with alarm limit settings, prompt responses and careful oxygen titration of caregivers which can be a difficult task to perform.[18-20] Hyperoxaemia can easily occur, especially when supplemental oxygen is given after hypoxaemic events.[24] The workload of caregivers, education and awareness about the hazards of hypoxaemia and hyperoxaemia, and appropriate alarm settings, can also influence the caregivers compliance in SpO_2 targeting.[18 31 40]

We recently reported that the compliance in SpO_2 targeting significantly improved after creating more awareness by training and implementation of a guideline for manual oxygen titration.[77] However, following the recommendation of European and Dutch guidelines our TR for SpO_2 was recently changed from 85-95% to 90-95%. This could lead to more intrinsic stability in infants[74] but we also recognised that complying with this smaller range could be challenging for the NICU-nurses.[18 30 74] We audited the effect of narrowing TR towards the higher end on the distribution of SpO_2 and compliance in SpO_2 targeting during oxygen therapy.

METHODS

A prospective designed, retrospective pre-post implementation study was performed in the NICU of the Leiden University Medical Centre (LUMC), which is a tertiary level perinatal centre with an average of 550 intensive care admissions per year. In the Netherlands, no ethical approval is required for anonymised studies with medical charts and patient data that were collected and noted for standard care. The LUMC Medical Ethics Committee provided a statement of no objection for obtaining and publishing the anonymised data. All

preterm infants born <30 weeks of gestation (GA) admitted to the NICU in LUMC between February 2014 and October 2014 (SpO_2 TR 85-95%) and November 2014 and March 2015 (SpO_2 TR 90-95%) receiving respiratory support (endotracheal and non-invasive ventilation) in the NICU. For respiratory support the AVEA ventilator (CareFusion, Yorba Linda California) was used. Data were collected until infants were transferred from the NICU. Preterm infants with major congenital heart disease were excluded. All preterm infants received, as part of standard care, a loading dose of 10 mg/kg caffeine base followed by 5 mg/kg/day. Doxapram hydrochloride (2 mg/kg/hr) was added in case of refractory apnoeas.

The characteristics of each infant as well as clinical parameters and ventilator settings (including FiO_2 and SpO_2) were sampled every minute and routinely collected in the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). During both periods the heart rate and SpO_2 were collected using a Masimo pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA) integrated in a Philips bedside Intellivue monitor (Philips Healthcare Nederland, Eindhoven, The Netherlands) with an averaging time set at eight seconds. The pulse oximeter probe was placed around the hand or foot of the infant (right hand in case of a patent ductus arteriosus). During both periods caregivers titrated the supplemental oxygen manually following local guidelines (Figure 1). During both periods the alarm was activated when SpO_2 was below or above the set TR. Before the start of each shift the TR and alarm settings were checked by the nurse.

We were interested in the extent to which nurses were able to comply with the narrower TR, and compared the percentage of time spent with SpO_2 between 90-95% when FiO_2 >0.21. Additionally the percentage of time spent with SpO_2 85-95%, >95%, >98%, <90%, <85% and <80% were calculated. To evaluate whether the SpO_2 distribution changed when no oxygen therapy was given to the infant, the percentage of time that SpO_2 was <90%, <85% and <80% when infants were breathing room air was also calculated.

In addition, all hypoxaemic events during non-invasive ventilation were identified in PDMS and analysed starting at the occurrence of SpO_2 <80% accompanied with bradycardia (<80 beats per minutes (bpm)), until the administered oxygen returned to the baseline oxygen level before the hypoxaemic event occurred. As data is sampled every minute, every hypoxaemic event where supplemental oxygen was titrated were evaluated by documenting the following characteristics: lowest stored minute value (depth) and count in low minute values (duration) of HR <80 bpm, lowest stored minute value (depth) and the count in low minute values (duration) of SpO_2 <80%, ΔFiO_2 (maximum additional FiO_2 minus baseline FiO_2), the count in minute values with additional oxygen, occurrence and count in minute values with SpO_2 >95%. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%.

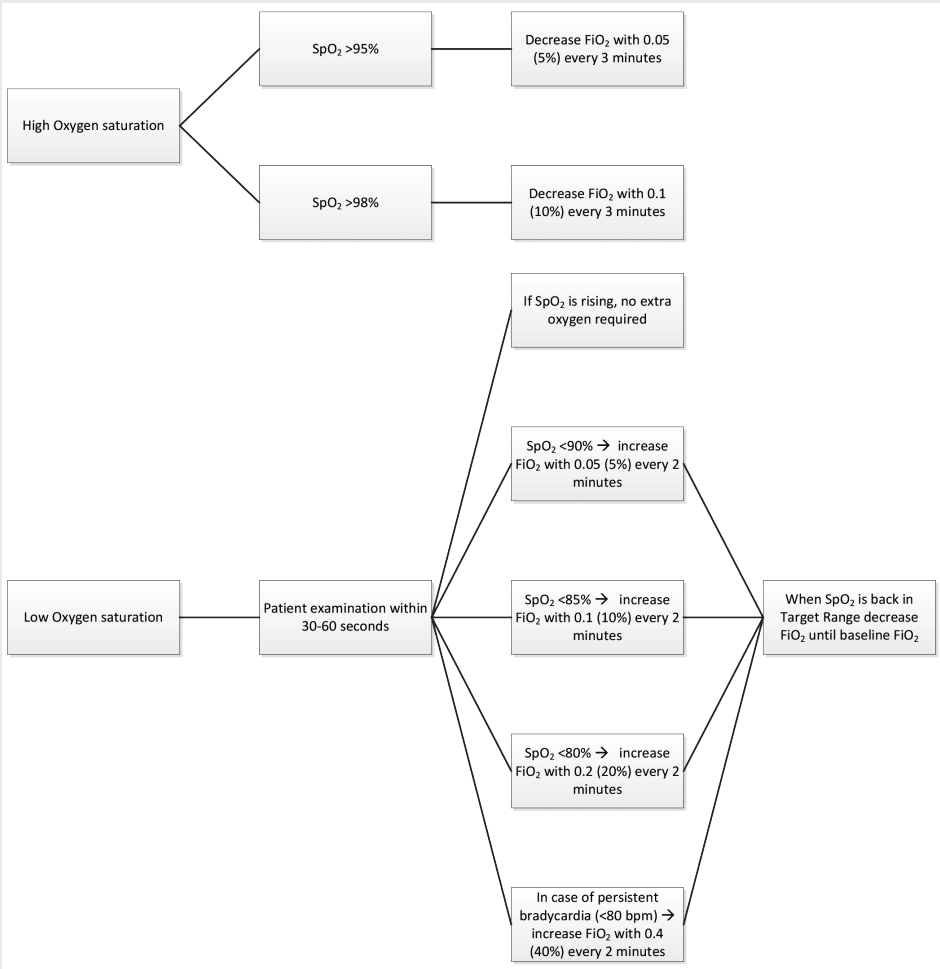


Figure 1. Oxygen Titration guideline

Statistical analyses

For this study a convenience sample was used. For the first period, infants were included that were born one month after the implementation of staff training and an oxygen titration guideline was implemented until TR was changed. For the second period, infants were included after implementing the new TR, until the time point automated oxygen control was implemented in our unit. Quantitative data are presented as median (IQR), mean ± SD or number (percentage) where appropriate. The total time with SpO_2 levels within various ranges for FiO_2 >0.21 was collected for each infant individually before and after implementation of a narrowed TR and was aggregated as a percentage of recorded time (median (IQR)). The

Mann-Whitney-U test for non-parametric comparisons for continuous variables is used, to compare the patient characteristics and the hypoxaemic event characteristics. The Kruskal-Wallis rank sum test was used to compare proportions of recorded time with SpO_2 within various ranges for each patient individually. A Chi-square test was used to analyse discrete variables. If one of the cells had an expected count of less than five the Fisher's exact test was used. P-values < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Software, NY, USA, 2012) and R 3.2.0 (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

During the study period of 13 months, a total number of 104 infants born <30 weeks of gestation were admitted to our NICU. Of these infants, 57 were born before changing the SpO_2 TR, and 47 infants after this change. No infants were excluded for congenital abnormalities. There were no differences in median (IQR) GA (28+3 (26+4 – 29) vs 27+5 (26+1 – 29) weeks; ns) and birth weight (1000 (855 – 1206) vs 900 (740 – 1153) grams; ns) or other characteristics (Table 1).

Table 1. Patient characteristics

	SpO2 TR 85-95% N= 57	SpO2 TR 90-95% N= 47	*p*-value
Gestational age (wk)	28+3 (26 +4 – 29)	27+5 (26+1 – 29)	0.25[a]
Birth weight (g)	1000 (855 – 1206)	900 (740 – 1153)	0.17[a]
Male, no (%)	32 (56)	26 (55)	0.93[b]
Caesarean delivery, no (%)	31 (54)	25 (53)	0.90[b]
Singletons, no (%)	39 (68)	26 (55)	0.17[b]
Apgar 5 min.	7 (6-9)	7 (7-9)	0.49[a]

[a] Independent samples Mann-Whitney U test
[b] Chi square test

Effect on compliance and SpO_2 distribution

During the TR 85-95% period 630.244 data points were collected and during the TR 90-95% period 402.993 data points of SpO_2 measurements were collected when oxygen therapy was given. The median (IQR) number of data points per infant were not significantly different (2359 (377 - 14129) vs 3082 (1352 – 15024) data points; ns).

After changing the TR, there was a slight, but significant increase in median (IQR) SpO_2 (93 (91 – 96)% vs 94 (92 - 97)%);p<0.02) (Figure 2), while the FiO_2 slightly decreased (0.28 (0.25-0.32) vs 0.26 (0.24-0.30);p<0.01). Narrowing TR did not lead to an increase in median (IQR) length of time SpO_2 was within 90-95% (49.2 (39.6-59.7)% vs (46.9 (27.1-57.9)%; ns) (Table 2, Figure 2). The time SpO_2 was >95% and >98% increased, but did not reach statistical significance (Table 2, Figure 2). Changing the TR led to a significant decrease in both SpO_2 <90% (15.7 (7 - 21)% vs 10.7 (8.4 - 13.7)%;p<0.05) and for SpO_2 <85% (6.2 (2.5 - 8.0)% vs 3.5 (2.6 - 5.3)%;p<0.05), but SpO_2 <80% was similar (Table 2, Figure 2).

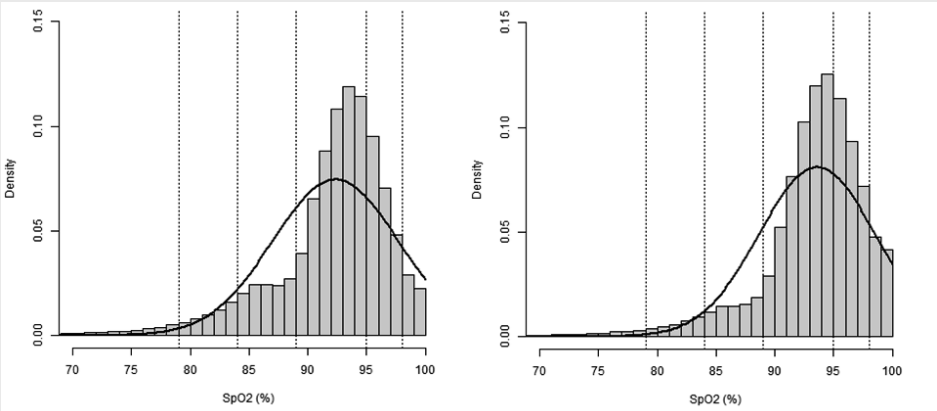


Figure 2. Time with SpO_2 within various ranges collated over all infants and aggregated as total proportion of recorded time

Table 2. Median (IQR) in different saturation ranges

	TR 85-95%	TR 90-95%	*p*-value*
SpO_2 <80%	1.7 (0.8-2.6)	1.5 (0.8 - 2.1)	ns
SpO_2 <85%,	6.2 (2.5 - 8.0)	3.5 (2.6 - 5.3)	<0.05
SpO_2 <90%	15.7 (7 - 21)	10.7 (8.4 - 13.7)	<0.05
SpO_2 85-95%,	61.9 (48.5 – 72.2)	56.5 (32.6 – 64.7)	ns
SpO_2 90-95%,	49.2 (39.6 - 59.7)	46.9 (27.1 - 57.9)	ns
SpO_2 >95	30.8 (22.6 - 44.5)	39.0 (28.8 - 59.2)	ns
SpO_2 >98%,	6.1 (2.3 - 12.1)	8.9 (3.3 - 17.9)	ns

*Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test.

During the TR 85-95% period 471.642 data points were collected and in the TR 90-95% period 424.700 data points of SpO_2 measurements were collected when infants were breathing room air. The median (IQR) number of data points per infant, was not significantly different (5722 (3112 - 10395) vs. 8102 (3635 – 13363) data points; ns). Changing the TR did not lead to significant changes in SpO_2 distribution and SpO_2 <90% was similar when infants were breathing room air (Table 3).

Table 3. Median (IQR) in different saturation ranges when breathing room air

	TR 85-95%	TR 90-95%	*p*-value*
SpO_2 <80%	0.3 (0.1-0.9)	0.3 (0.1 – 0.9)	ns
SpO_2 <85%,	1.1 (0.5 – 2.9)	1.2 (0.7 – 2.7)	ns
SpO_2 <90%	3.6 (1.6 – 11.7)	4.5 (2.1 – 7.9)	ns
SpO_2 90-95%,	29.8 (14.7 – 49.8)	36.5(20.7 – 46.1)	ns
SpO_2 >95%	60.1 (39.5 – 83.2)	58.2 (41.1 – 76.6)	ns
SpO_2 >98%,	14.9 (5.8 – 42.8)	13.9 (6.2 – 27.3)	ns

*Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test.

Effect on hypoxaemic events and how oxygen was titrated

During non-invasive respiratory support 168 hypoxaemic events with supplemental oxygen occurred in 28/57 (49%) infants before TR was changed and 204 events in 32/47 (68%) infants after the TR was changed (ns). There was no difference between the lowest minute value and the count in minute values with bradycardia and SpO_2 <80% (Table 4). There was a trend towards more often hyperoxaemia after the TR was changed (63% (106/168) vs 73% (148/204);*p*=0.051) (Table 4), while there was no difference in ΔFiO_2, duration of titrating oxygen down to the baseline and count in minute values with hyperoxaemia (Table 4).

Table 4. ABC characteristics with oxygen therapy

	TR 85-95% (ABC= 168)	TR 90-95% (ABC = 204)	*p*-value*
ABC with SpO2 >95%	64%	73%	ns
Lowest minute value during bradycardia, bpm (depth)	69 (61-75)	70 (62-75)	ns
Count minute values with bradycardia, min (duration)	1 (1-1)	1 (1-1)	ns
Lowest minute value during SpO_2 <80, % (depth)	72 (61-77)	73 (63-77)	ns
Count minute values SpO_2 <80%, min (duration)	1 (1-2)	1 (1-2)	0.004
ΔFiO_2 (Maximum increase – baseline FiO_2)	0.19 (0.6-0.21)	0.19 (0.7-0.21)	ns
Count minute values of FiO_2 titration to baseline oxygen concentration, min	3 (2-7)	2 (2-6)	ns
count minute value with SpO_2 >95%, min	1 (1-3)	1 (0-2)	ns

DISCUSSION

Our study demonstrated the effect of narrowing the SpO_2 TR of 85-95% to 90-95% on SpO_2 distribution of preterm infants when supplemental oxygen is supplied. We observed a small increase in median SpO_2 and a shift of the distribution to the right with the new TR. This led to a decrease in SpO_2 between 80% and 89%, the occurrence in hypoxaemia (<80%) did not change. Changing the TR did not lead to a change in the time SpO_2 spent between 90-95%, but there was a trend towards more hyperoxaemia. A similar effect was observed around hypoxaemic events. There was no change in occurrence and duration of hypoxaemic events and how oxygen titration was performed, but the occurrence of hyperoxaemia increased, although this raise was not significant.

These results reflect the effort taken by the nurses to comply with the new TR, but it was difficult for them to titrate oxygen in order to stay within the narrow TR. Nevertheless, as we managed to decrease the exposure to SpO_2 <90%, narrowing the TR in our unit could lead to similar beneficial effects as were shown in recent trials. [25 43 44]

To our knowledge this is the first report on the effect when the TR is significantly narrowed to only the upper part of the original TR when oxygen is manually titrated. Laptook *et al*. reported the effect of changing the SpO_2 TR, but the change in range was much smaller (from 90-95% to 88-94%) when compared to ours.[29] It is difficult to compare our results with their findings, but they also reported no change in the time SpO_2 spent within the TR. They also observed no difference in the mean percentage of time spent within the TR, but this might be attributed to the small change in TR.[29] Mills *et al*. reported a lower compliance when a narrow SpO_2 TR was used, except when preterm infants participated in a trial comparing TR.[30]

Changing the TR did not lead to a change in SpO_2 distribution when infants were breathing room air and there was no decrease in lower SpO_2. This finding, together with the observation that the time SpO_2 was 90-95% did not change when oxygen was given, could indicate that the nurses in our unit already had the tendency to keep SpO_2 in the higher end of the intended TR when 85-95% was used. This is in line with the observation in previous studies that nurses were less compliant in the upper alarm limits.[18 19 74 78] Indeed, the clinical trials comparing lower vs higher SpO_2 TR also reported that the median levels of oxygen saturations were higher than intended TR in both treatment groups.[25 43 44] It is likely that caregivers favour SpO_2 closer to the higher end of TR because infants are intrinsically more stable in the higher SpO_2 region.

We observed a decrease in time SpO_2 spent <90% when oxygen was given, which is comparable to the findings of recent trials comparing low (85-89%) vs high TR (91-95%). These trials showed that a TR above 90% led to a decrease in mortality.[25 43 44] A low SpO_2 TR has been associated with an increased rate of hypoxaemic events.[29 79] However, we did not observe a change in hypoxaemia, or hypoxaemic events and how these were handled, after we increased the lower limit of the TR. This lack of effect is probably also a consequence of how nurses titrated oxygen before the TR was changed. Changing the TR towards the higher end led to a non-significant increase in hyperoxaemia and more often hyperoxaemia when oxygen was titrated after an hypoxaemic event. This has also been observed in previous studies, as also in the trials comparing lower and higher TRs,[25 43 44] which could then potentially lead to an increase in retinopathy of prematurity (ROP).

Titrating oxygen, using a smaller TR in instable premature infants with fluctuating SpO_2 requires constant nursing intervention.[24] It has been reported that a narrower TR leads to an inevitable increase of SpO_2 alarms.[80] These alarms contribute to all other alarms on a NICU where a high number of alarms are false, or without any clinical relevance.[81] Excessive exposure to alarms can effect alarm response from caregivers and lead to alarm fatigue, which is potentially harmful to patients.[82 83] Although we have not measured the number of alarms in our study, but this can affect the compliance in TR negatively.

While maintaining SpO_2 within a narrow TR is a difficult task to perform when oxygen needs to be titrated manually, automated oxygen regulation could be more effective and lead to the desired compliance in keeping SpO_2 within the narrow range.[33 35 36 38 39] However, when Wilinska *et al*. used automated oxygen control and compared the TR 87-93% with a more narrow TR (90-93%), results similar as in our study were observed. The narrow range of 90-93%, resulted in less time with lower SpO_2 (80-86%), but more time with higher SpO_2 (94-98%). In addition, there were also no differences in the amount and duration of hypoxaemic events.[84]

This study is a report of a quality improvement project, and inherently the retrospective character is a limitation. Although the groups compared were not different in basic characteristics and also there were no further policy changes occurred during the study period, conditions we did not recorded or measure could have led to bias. Also, the Masimo oximeter algorithm could not be updated in the Philips monitors we used in our unit, which is reflected by the well described dip[75] in the frequencies of SpO2 87-90%. However, the same oximeters and monitors were used in both groups and thus did not influence the observed distributions when comparing the groups. Furthermore, we did not adjust for the contribution of the number of hypoxaemic events of each patient, but we considered

every hypoxaemic event as an independent event because all events are handled the same for each infant. Due to the retrospective character, we could only use a one-minute time interval for sampling parameters, which is less frequent than reported in other studies.[14 85] It is possible that in both groups we missed hypoxaemic events that were resolved within one minute. These limitations indicate that the results have to be interpreted with caution, this study was not designed to compare morbidity and mortality but as an audit in SpO_2 targeting.

In conclusion, narrowing the TR from 85-95% to 90-95% in preterm infants did not lead to a change in the time SpO_2 spent within 90-95%. There was however a shift of the SpO_2 distribution to the right with a decrease in SpO_2 less than 90%, no change in hypoxaemia, but a trend in hyperoxaemia. This beneficial effect could be further improved by increasing the compliance to a narrow TR.

Chapter 6

The effect of implementing an automated oxygen control on oxygen saturation in preterm infants

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ABSTRACT

Objective: To evaluate the effect of implementing automated oxygen control as routine care in maintaining oxygen saturation (SpO_2) within target range (TR) in preterm infants.

Methods: Infants <30 weeks gestation in LUMC before and after the implementation of automated oxygen control were compared. The percentage (%) of time spent with SpO_2 within and outside TR (90-95%) was calculated. SpO_2 values were collected every minute and included for analysis when infants received supplemental oxygen.

Results: In a period of 9 months, 42 preterm infants (21 manual, 21 automated) were studied. In the automated period the median (IQR) time spent with SpO_2 within TR increased (manual vs automated: 48.4 (41.5 - 56.4)% vs 61.9 (48.5 – 72.3)%; p< 0.01) and time SpO_2 >95% decreased (41.9 (30.6 - 49.4)% vs 19.3 (11.5 - 24.5)%; p< 0.001). The time SpO_2 <90% increased (8.6 (7.2 - 11.7)% vs 15.1 (14.0 - 21.1)%; p <0.0001), while SpO_2 <80% was similar (1.1 (0.4 - 1.7)% vs 0.9 (0.5 - 2.1)%; ns).

Conclusion: During oxygen therapy, preterm infants spent more time within the SpO_2 TR after implementation of automated oxygen control, with a significant reduction in hyperoxaemia, but not hypoxaemia

What is already known on this topic

1. The frequency and duration of hypoxaemia and hyperoxaemia in preterm infants influence survival and long term outcome.
2. Titrating oxygen manually to maintain oxygen saturation within a narrow target range can be challenging.
3. Randomized trials have shown that automated oxygen control is effective, but this has only been measured for short periods.

What this study adds

1. After implementation of automated oxygen control for daily care, preterm infants spent more time with their oxygen saturation within the target range.
2. After implementation, hyperoxaemia significantly decreased during oxygen therapy, but there was no effect on hypoxaemia.

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INTRODUCTION

To prevent hypoxaemia and hyperoxaemia in preterm infants, nurses manually titrate the fraction of inspired oxygen (FiO_2) in order to maintain peripheral oxygen saturation (SpO_2) within a set target range (TR). Studies have shown that compliance with SpO_2 targets is low and there is a tendency for nurses to accept higher SpO_2.[18 30 31 40 41] Manual titration of oxygen is challenging, especially during hypoxaemic and bradycardic events related to apnoea of prematurity.[10 24] We recently demonstrated that manual titration of oxygen therapy in preterm infants during these hypoxaemic and bradycardic events, led to unintended hyperoxaemia (SpO_2 >95%).[24] Both hypoxaemia and hyperoxaemia are associated with morbidity (impaired growth, bronchopulmonary dysplasia, retinopathy of prematurity, cerebral injury) and mortality. Reducing periods of hypoxaemia and hyperoxaemia may improve survival and neurodevelopmental outcome.[9-15]

Compliance in SpO_2 targeting can be improved by training and implementation of guidelines.[37 48-50] Additionally, FiO_2 can be titrated automatically.[86 87] Randomised trials comparing automated FiO_2 systems with manual titration for short periods, demonstrated an increase in the percentage of time spent with SpO_2 within TR varying between 8-24%.[35 36 38 39] Automated FiO_2 control also decreased the required nursing time in preterm infants with frequent severe desaturations.[35 88 89] However, the use of automated FiO_2 control for longer periods has not been investigated.

In the neonatal intensive care unit (NICU) in Leiden University Medical Centre (LUMC) an automated FiO_2 control system (Closed Loop of inspired Oxygen, Avea-$CLiO_2$, CareFusion, Yorba Linda, California) was implemented and routinely used since August 2015 in order to improve targeting SpO_2. We performed an observational study in preterm infants to evaluate automated FiO_2 control when it was used as standard care and thus for a longer period. The aim was to compare the effectiveness of the automated FiO_2 system versus manual titration of FiO_2 in maintaining the SpO_2 within the intended TR.

METHODS

A prospective observational study was performed in the NICU of the LUMC, which is a tertiary level perinatal centre in the Netherlands with an average of 650 intensive care admissions per year. In the Netherlands, no ethical approval is required for anonymised studies with medical charts and patient data that were collected and noted for standard care. The LUMC Medical Ethics Committee provided a statement of no objection for obtaining and publishing the anonymised data. All preterm infants born <30 weeks of gestation (GA) admitted to the NICU before and after the implementation of the automated FiO_2 control in August 2015

(May 2015 - January 2016) receiving respiratory support (endotracheal and non-invasive ventilation) using the AVEA ventilator (CareFusion, Yorba Linda California) were included. Preterm infants with major congenital heart disease were excluded.

The characteristics, of each infant as well as clinical parameters and ventilator settings (including FiO_2 and SpO_2) were sampled every minute and routinely collected in the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). During both periods the heart rate and SpO_2 was collected using a neonatal pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA) with an averaging time set at 8 seconds. Data were included until the infants reached a GA of 32 weeks. After 32 weeks most infants are transferred out of the intensive care area in our unit or to a regional hospital, where no automated FiO_2 control is available.

During the manual and the automated FiO_2 control periods, SpO_2 was measured using a neonatal pulse oximeter integrated into the AVEA ventilator. During the manual period the nurses manually titrated the supplemental oxygen following local guidelines. During the automated period, an automated FiO_2 control device integrated in the ventilator was used ($CLiO_2$), in addition to manual adjustments. The $CLiO_2$ function is a Closed-Loop controller, designed to regulate FiO_2 levels for preterm infants receiving support and oxygen from a mechanical ventilator. The FiO_2 is automatically adjusted to maintain the SpO_2 within the TR set by the clinician.[34] The $CLiO_2$ was turned off during episodes where SpO_2 remained 100% for more than 30 minutes when FiO_2 was 0.21 as recurrent alarms would occur. In case extra oxygen was needed again, the $CLiO_2$ was switched on, and data analysis continued. The episodes without supplemental oxygen were not included in the analysis. In this study, for both manual and automated FiO_2 control periods, the SpO_2 TR was 90% to 95% during oxygen therapy. The alarm was activated if SpO_2 was below 90% or above 95%.

Before the start of each shift the set TR of the $CliO_2$ and alarm settings were checked by the nurse. Also backup-FiO_2 was checked before the start of each shift or when a procedure was performed (e.g. surfactant administration) and was adjusted if necessary. High FiO_2 alarm was set at 70% with a delay of 60 seconds. All preterm infants received, as part of standard care, a loading dose of 10mg/kg caffeine base followed by 5 mg/kg/day. Dopram (2 mg/kg/hr) was added in case of refractory apnoeas.

The primary outcome was the percentage of time spent with SpO_2 within the intended TR (90-95%) when FiO_2 was >0.21. Also the percentage of time spent with SpO_2 >95%, >98%, <90%, <85% and <80% were calculated. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%.

Statistical analyses

Quantitative data are presented as median (IQR), mean ± SD or number (percentage) where appropriate. Time with SpO_2 within various ranges for FiO_2 >0.21 were collated for each infant, and aggregated as percentages of the recorded time (median and IQR). A Kruskal-Wallis rank sum test was used to compare the percentage of time that SpO_2 was within TR (SpO_2-wtr) of 90-95% between the manual period and the automated period. A Chi-square test was used to analyse discrete variables. If one of the cells had an expected count of less than five the Fisher's exact test was used. Statistical analyses were performed by IBM SPSS Statistics version 23 and R 3.2.0 (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

An increase of 10% in time that SpO_2 was within the intended TR when using the automated FiO_2 control was considered clinically relevant. Based on a previous study, we estimated a standard deviation of 10%.[67] Therefore, 21 patients in each arm were required to detect a change of 10% SpO_2-wtr between the periods with an 80% power and a significance level of 0.05.

RESULTS

In a nine months period 42 infants with a GA <30 weeks were admitted and supported using the AVEA-ventilator, of which 21 infants <30 weeks in four months before the implementation of the automated FiO_2 control and 21 infants in five months after implementation (characteristics Table 1). In one patient the $CLiO_2$ was turned off for three days and during that period SpO_2 data points were excluded from the analysis. In total, 234.541 data points (minute values) during the manual period and 392.211 data points (minute values) during the automated period were collected when FiO_2 >0.21. The median (IQR) number of data points per infant were not significantly different (manual vs. automated period: 4805 (1238 -16980) vs 16527 (1324 – 33625) data points; ns). The total number of days preterm infants were on respiratory support (with or without extra oxygen) were not different 16 (10-22) vs 14 (3-28) days; ns).

After implementation of the automated FiO_2 control, there was a slight, but significant decrease in median (IQR) SpO_2 (manual vs automated: 94 (92 - 96)% vs 93 (91 - 95)%;p<0.001) (Figure 1), while the FiO_2 used increased (0.25 (0.24-0.29) vs 0.27 (0.25-0.32);p< 0.009) (Figure 2).

Table 1. Patient characteristics, manual vs automated oxygen titration period.

Patients characteristics N=42	Manual N=21	Automated N=21	p Value
Gestational age in weeks, median (IQR)	27+6 (26+3 – 28+4)	27+3 (26 – 28+2)	0.2[a]
Birth weight in grams, median (IQR)	966 (843-1235)	940 (825-1242)	0.6[a]
Males, n (%)	10 (48)	12 (57)	0.5[b]
Apgar score 5 min, median (IQR)	7 (6-9)	8 (6-9)	0.9[a]
Caesarean delivery, n (%)	10 (47.6)	7 (33.3)	0.3[b]
Singletons, n (%)	15 (71.4)	10 (47.6)	0.1[b]
Invasive ventilated days, median (IQR)	1 (0-8)	2 (0-7)	0.8[a]
Use of dopram, n(%)	7 (33)	6 (28)	0.7[b]
Mortality, n (%)	0 (0)	3 (14)	0.2[c]

[a] Statistical analysis comprised nonparametric Mann Whitney U test; [b] Statistical analysis comprised Chi square test; [c] Statistical analysis comprised Fisher's Exact Test.

The time spent with SpO_2 within TR increased during the automated period (48.4 (41.5 - 56.4)% vs 61.9 (48.5 – 72.3)%;p<0.01) (distribution is given in Figure 1). The time spent with SpO_2 >95% significantly decreased during the automated period (41.9 (30.6 - 49.4)% vs 19.3 (11.5- 24.5)%;p<0.001) as did SpO_2 >98% 10.1 (3.7 - 14.4)% vs 2.1(0.7 - 3.1)%;p<0.0005) (Table 2). The time spent with SpO_2 <90% significantly increased during the automated period (8.6 (7.2 - 11.7)% vs 15.1 (14.0 - 21.1)%;p<0.0001), which was mostly influenced by an increase in time SpO_2 was between 85% and 89% (Table 2). There was no significant difference in time spent with SpO_2 <85% (2.7 (1.4 - 4.0)% vs 3.2 (1.8 - 5.1)%; ns), or % time with SpO_2 <80% (1.1 (0.4 – 1.7)% vs 0.9 (0.5 - 2.1)%; ns).

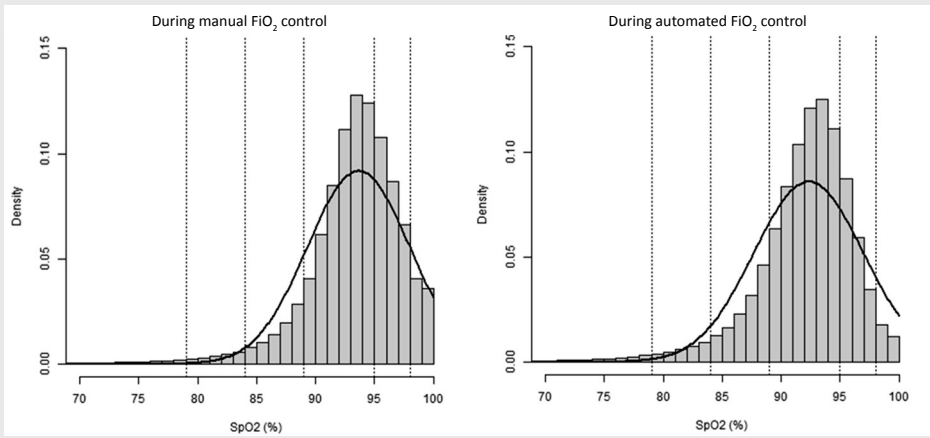

Figure 1. Time with SpO_2 within various ranges collated over all infants and aggregated as total proportion of recorded time

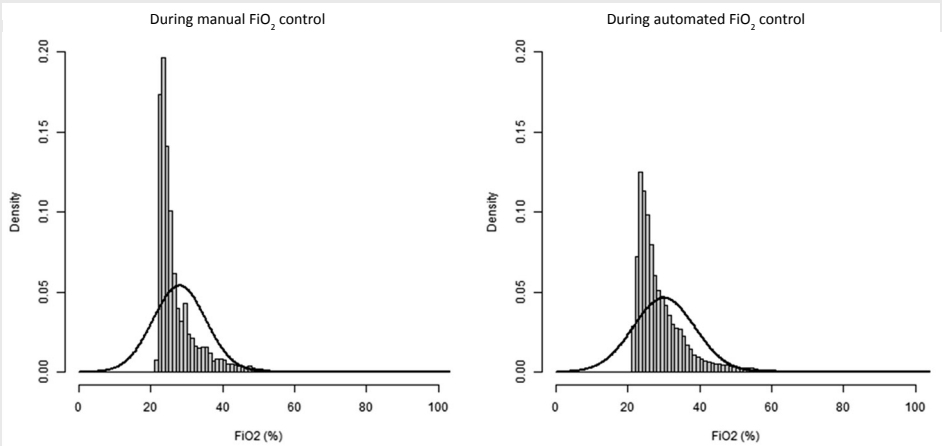

Figure 2. Time with FiO_2 within various ranges were collated over all infants and aggregated as total proportion of recorded time.

Table 2. Median (IQR) time with SpO_2 values within and outside TR with FiO_2>0.21

	Percentage of time, % Manual	Automated	p-value*
SpO_2 <80%	1.1 (0.4 - 1.7)	0.9 (0.5 - 2.1)	ns
SpO_2< 85%	2.7 (1.4 - 4.0)	3.2 (1.8 - 5.1)	ns
SpO_2 < 90%	8.6 (7.2 - 11.7)	15.1 (14.0 - 21.1)	< 0.0001
90% ≤ SpO_2 ≤ 95%	48.4 (41.5 - 56.4)	62.0 (56.4 - 68.6)	< 0.01
SpO_2 >95%	41.9 (30.6 - 49.4)	19.3 (11.5 - 24.5)	< 0.001
SpO_2 >98%	10.1 (3.7 - 14.4)	2.1 (0.7 - 3.1)	< 0.0005

*Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test. SpO_2, pulse oxygen saturation; FiO_2, fraction of inspired oxygen.

DISCUSSION

We observed that preterm infants spent significantly more time with SpO_2 within their intended TR and less time with SpO_2 above their intended TR, while FiO2 used was higher after implementing automated FiO_2 control for routine care. Although the infants spent more time with SpO_2 between 80% and 90% during automated control, no significant effect on the time spent with hypoxaemia (SpO_2 <80%) was observed. It is likely that automatic FiO_2 control had little effect on the infants' intrinsic stability, but rather that correction of fluctuations in SpO_2 were faster than during manual oxygen titration and with less overshoot.

Furthermore, the use of an automated device precludes the tendency of nurses to maintain the SpO_2 in the higher end of TR, which could lead to more hyperoxaemia.[18 30 31 40 41] The effect of an increased time that SpO_2 was between 80% and 90% is unclear, while the reduction in hyperoxaemia may reduce the risk of major morbidities.[9-15 24 34] Routine use of automated oxygen control has the potential to improve outcome in preterm infants.

Randomised and non-randomised studies have compared short periods using automated FiO_2 with manual titration.[11 34-36 38 39 67 90] This is the first study reporting the impact when an automated FiO_2 was implemented in routine care for longer periods. Although the previous studies showed that automated FiO_2 control improved time spent with SpO_2 within the intended TR, the short study periods may have increased the risk for a Hawthorne effect.[11 34-36 38 39 67 90] We compared automated FiO_2 with manual titration for a much longer period and observed a bigger increase in time SpO_2 was within the TR than has been observed in other studies. This is important as it supports that in routine use, the potential for improvement of automated FiO_2 is higher. This was not a randomised trial but our results reflect the effect of the automated FiO_2 control when there was less risk of influencing the attentiveness of caregivers by participating in a study. It is likely that the results of this study can be extrapolated to other level III NICU centers.

Whether there was a decrease in time SpO_2 was above or below TR or both, varied between previous reported studies.[11 34-36 38 39 67 90] We observed a decrease in time with SpO_2 above TR which was comparable with previous studies.[11 34-36 39 90] While some studies of automated control observed a decrease in time spent with SpO_2 below TR,[36 38 67 90] we observed an increase. This has also been reported by others.[34 35] Explaining this conflicting finding is complicated by differences in methodology used (devices, study period, TR).[36 38 67] We observed the largest increase in time spent just below TR (85%-90%) with no increase in hypoxaemia (< 80%), consistent with others.[34 35] The $CliO_2$ algorithm has been designed to prevent hyperoxaemia when overshoot occurs when the oxygen is increased. It is also known that nurses tend to give more liberal oxygen during desaturation resulting in a shorter duration with SpO_2 below TR, but longer duration with time above TR. Indeed, in a previous study we reported that there is more awareness for alarms for SpO_2 below TR than above.[24] Comparable to most previous studies, we could not detect a decrease in the total time with hypoxaemia when automated FiO_2 was implemented. This likely reflects the aversion of caregivers to very low SpO_2 values.[11 34 35 39] Apparently the occurrence and depth of hypoxaemia is not prevented, but infants profit from a faster response provided by an automated FiO_2 device when a hypoxaemic event occurs. Likewise, the gradual but constant downward titration of oxygen of the automated FiO_2 control explains of the decrease in hyperoxaemia. It is possible that other devices for auto FiO_2 control give different results as the algorithms can differ.[91]

In considering the results of our study and others, it is clear that the SpO_2 distribution achieved using manual control differs from that achieved using automated control, even when the intended TR is the same.[84] Others have also shown the effect of shifting automated control ranges.[84] For that reason selecting the best TR for use with automated control should consider the likely SpO_2 exposure and not just an adoption of the optimum standard of practice for manual control.

This study was performed as an audit after implementation of automated FiO_2 control as standard care in our unit. The results reflect the real situation as data were collected for the duration infants were admitted, while nurses taking care of them, with varying workload. Although the characteristics of the groups were similar, this was not a randomised study and it is possible that there were differences between the group of infants admitted during the observed periods. We compared SpO_2 values that were routinely sampled every minute and although the value is an average of 8 seconds, it is possible we missed SpO_2 fluctuations in between the samples taken.[92] However, our findings and distribution of SpO_2 in the compared groups are similar when higher sample rates were used[43 44] and it is likely that this is an accurate reflection of the SpO_2 of the infants admitted.

Reducing the occurrence and duration of hypoxaemia and hyperoxaemia is known to reduce the related morbidity and mortality. Currently randomised trials are planned to determine the effect of automated FiO_2 on clinical outcome in preterm infants.[93] In anticipation of these upcoming trials, we implemented the automated FiO_2 as standard care for all infants receiving respiratory support in the NICU as part of a quality improvement in our unit. Although difficult to measure, during evaluations nurses reported that after implementation of the automated FiO_2 control their workload was less and they would be very reluctant to go back to the manual titration. Studies have reported that automated FiO_2 control decreased the required nursing time in preterm infants with frequent severe desaturations.[35 88 89] However, thresholds should be set very carefully in order not to mask deterioration of a patient and nurses need to stay attentive as well as the automated FiO_2 control should give a warning if the FiO_2 baseline rises above a predefined level.

In conclusion, implementation of automated FiO_2 control led to an increased compliance of maintaining SpO_2 within the intended TR during oxygen therapy, with a decrease in the time in which SpO_2>95% and SpO_2>98%. Although the observed effects of the automated FiO_2 control have the potential to improve outcome, this study was not designed to demonstrate this. Randomised studies are needed to confirm the beneficial effects of the automated FiO_2 control on the outcome of preterm infants.

Chapter 7

The effect of implementing an automated oxygen control on hypoxaemic events in preterm infants

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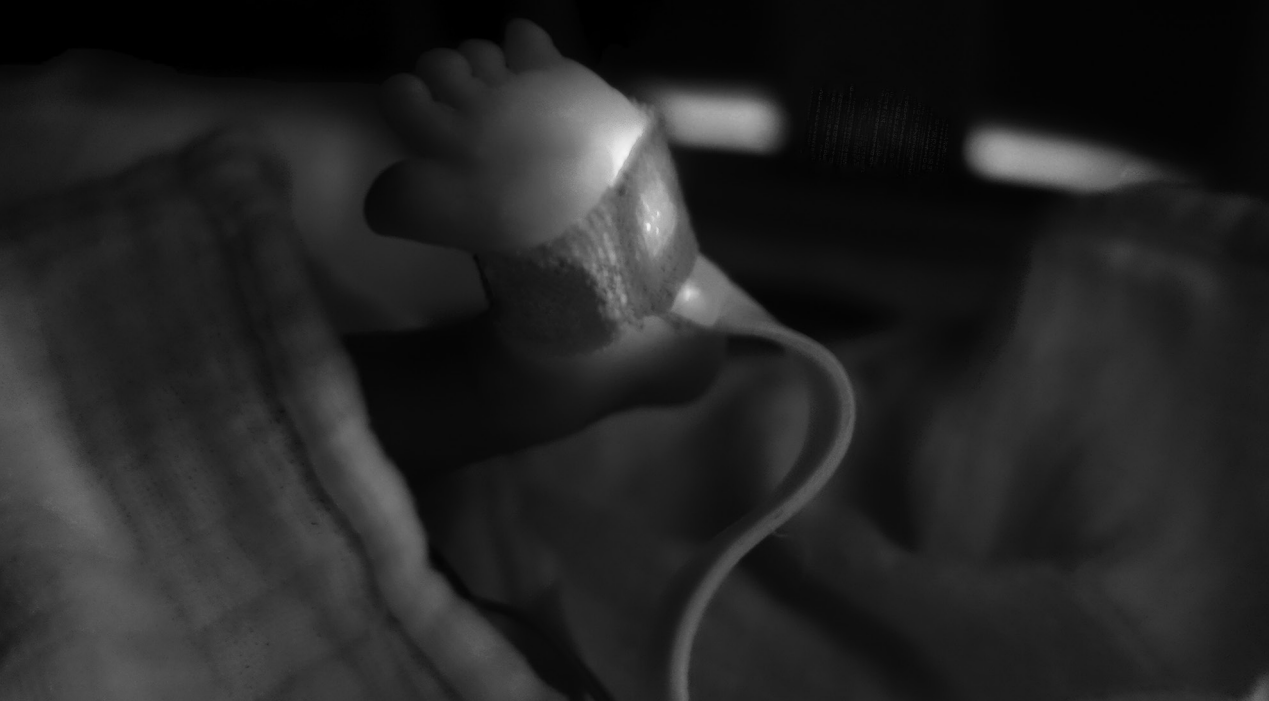
Manuscript in preparation



ABSTRACT

Objective: To study the effect of automated versus manual titration on apnoea, bradycardia, cyanosis (ABC) and oxygen therapy in preterm infants.

Methods: Preterm infants born <30 weeks of gestation and admitted to the neonatal unit of the Leiden university medical centre (LUMC) between May and December 2015 before and after implementation of the automated fraction of inspired oxygen (FiO_2) system were retrospectively compared. Oxygen saturation (SpO_2), heart rate and respiratory rate were collected every minute and included for analysis when infants received supplemental oxygen. The count of minute values is used to express duration and the lowest minute value is used to express depth of SpO_2 and heart rate. ABCs where oxygen therapy was given were identified and analysed.

Results: 12/21 (57%) infants admitted during the manual period vs 12/21 (57%) infants during the automated period had ABCs (61 vs 252;p=0.004) during non-invasive respiratory support and where supplemental oxygen was given. In the automated period the duration of hypoxaemia (SpO_2<80%) during ABC was reduced (2(1-3) min vs 1(1-2) min;p<0.05), but not the depth (68(50-73)% vs (68(56-75)%;ns). Hyperoxaemia (SpO_2 >95%) occurred less often (83.6% vs 67.3%;p<0.05) and lasted shorter (5(3-11)min vs 2(1-4)min;p<0.001).

Conclusion: Implementing automated oxygen control for preterm infants led to a shorter duration of hypoxaemia and hyperoxaemia during and after ABCs. Nurses should stay alert for hypoxaemic events related to apnoeas.

INTRODUCTION

Manual titration of oxygen in order to maintain the oxygen saturation (SpO_2) within the target range (TR) has been shown to be quite challenging, especially during apnoea, combined with bradycardia and cyanosis (ABC).[10 24] We recently demonstrated that manual titration of oxygen therapy in preterm infants during ABCs, unintendedly led to occurrence of hyperoxaemia (SpO_2 >95%).[24] Both hypoxaemia and hyperoxaemia have been associated with prematurity related short and long term consequences (impaired growth, bronchopulmonary dysplasia, retinopathy of prematurity, cerebral injury) and mortality. Reducing the periods of hypoxaemia and hyperoxaemia has the potential to improve survival and neurodevelopmental outcome.[9-13 15 34]

Randomised trials comparing automated fraction of inspired oxygen (FiO_2) systems with manual titration for short periods, demonstrated an increase in the proportion of time spent with SpO_2 within TR and a decrease in hyperoxaemia.[35 36 38 39] However, how hypoxaemic events (ABC) are handled when automated oxygen control is used has not been investigated. In the neonatal intensive care unit in Leiden University Medical Centre (LUMC) an automated oxygen control (Closed loop of inspired Oxygen, $CliO_2$, Avea, Carefusion, Yorba Linda, California) was implemented and routinely used since August 2015 in order to improve the SpO_2 targeting during oxygen therapy. We performed a prospective study in preterm infants to evaluate the automated FiO_2 control when it was used as standard care and for a longer period. The aim was to compare the effect on ABC and oxygen therapy when oxygen was titrated automatically or manually.

METHODS

A prospective pre-post implementation study was performed in the neonatal intensive care unit (NICU) of the LUMC, which is a tertiary level perinatal centre in the Netherlands with an average of 650 intensive care admissions per year. In the Netherlands, no ethical approval is required for anonymised studies with medical charts and patient data that were collected and noted for standard care. The LUMC Medical Ethics Committee provided a statement of no objection for obtaining and publishing the anonymised data. All preterm infants born <30 weeks of gestation (GA) admitted to the NICU before and after the implementation of the automated FiO_2 device in August 2015 (May 2015 - January 2016) receiving (non-) invasive respiratory support using the AVEA ventilator (Carefusion, Houten, The Netherlands) were included. Preterm infants with major congenital heart disease were excluded, since different oxygen saturations and guidelines are followed for this group.

Patient basic characteristics, as well as clinical parameters of each infant and ventilator settings (including FiO_2 and SpO_2) were standardly collected and stored every minute in the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). The data of clinical parameters and ventilator settings of each infant were analysed until the infants reached a GA of 32 weeks. After 32 weeks most infants are transferred to the post IC in our unit or regional hospital, where no automated FiO_2 system was available.

During the manual and the automated oxygen control period, SpO_2 was measured using a neonatal pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA) integrated into the ventilator. During the manual FiO_2 control period the nurses titrated the supplemental oxygen following local guidelines manually. During the automated oxygen control period, an automated oxygen control system integrated in the ventilator was used ($CliO_2$; Avea, Carefusion, Yorba Linda, California). The $CliO_2$ function is a closed-loop controller designed to regulate FiO_2 levels for preterm infants receiving support and oxygen from a mechanical ventilator. The FiO_2 will be automatically adjusted to maintain the SpO_2 within the TR set by the clinician.[33] In this study, the SpO_2 TR was set from 90% to 95%. The alarm was activated if SpO_2 was below 90% or above 95%. During the manual control period the intended TR and alarms were the same. All preterm infants received, as part of standard care, a loading dose of 10mg/kg caffeine base followed by 5 mg/kg/day. Dopram (2 mg/kg/hr) was added in case of refractory apnoeas.

ABCs during non-invasive ventilation were manually identified in PDMS and analysed starting at the occurrence of an ABC until the oxygen supplied returned to the baseline before the ABC occurred. ABC was defined as apnoea (respiratory pause >20 seconds (or shorter when this pause is combined with hypoxaemia and/or bradycardia), accompanied with bradycardia (<80 beats per minutes (bpm)) and cyanosis (SpO_2 < 80%). As data is sampled every minute, every ABC where supplemental oxygen was titrated was evaluated by documenting the following characteristics: lowest stored minute value (depth) and count in low minute values (duration) of HR <80 bpm, lowest stored minute value (depth) and the count in low minute values (duration) of SpO_2 <80%, baseline FiO_2 and additional oxygen given, the count in minute values with additional oxygen, occurrence and count in minute values with SpO_2 >95%. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%.

Statistical analyses

Quantitative data are presented as median (IQR), mean ± SD or number (percentage) where appropriate. The Mann-Whitney-U test was used to compare the frequency, duration, and depth of each ABC in each group. A Chi-square test was used to analyse discrete variables. If one of the cells had an expected count of less than five, the Fisher's exact test was used. Statistical analyses were performed by IBM SPSS Statistics version 23.

RESULTS

During non-invasive respiratory support 61 hypoxaemic events followed by supplemental oxygen occurred in 12/21 (57%) infants in the manual period and 252 events in 12/21 (58%) infants in the automated period. Infants in the manual period had a higher gestational age when compared to the automated period, but this was not significantly different (28+3 (26+2 – 28+6) weeks vs 26+4 (26+0-28+0)weeks;*p* =0.09) Further patient characteristics were not different between the two periods (Table 1). The amount of ABCs per day during respiratory support and supplemental oxygen was higher during the automated period, but this was not significantly different (Table 2). During ABCs, the depth and duration of bradycardia were not different between the two periods. Also no differences were observed in the depth of hypoxaemia (68 (50-73)% vs 68 (56-75)%; ns). However, the duration was shorter in the automated period (2 (1-3) vs 1 (1-2) minute values;*p*<0.05). The occurrence of hyperoxaemia after an ABC significantly reduced (83.6% vs 67.3%;*p*<0.05) and lasted shorter (5 (3-11) vs 2 (1-4) minute values;*p*<0.001) (Table 1). There were no differences in the duration of titrating FiO_2 back to baseline FiO_2, but the amount of supplemental FiO_2 given during an ABC was non-significantly higher after implementation of the automated oxygen control. The baseline FiO_2 before an ABC was slightly higher in the automated period (0.24 (0.21-0.27) vs 0.27 (0.25-0.31);*p*<0.001)(Table 2).

Table 1. Patient characteristics with ABCs

	Manual period N= 12	Automated period N= 12	*p*-value
Gestational age at birth (weeks), Median (IQR)	28+3 (26+2–28+6)	26+4 (26 –28)	0.09[a]
Birthweight (grams). Median (IQR)	901 (806-1299)	855 (708–948)	0.2 [a]
Male sex, no (%)	6 (50)	8 (77)	0.4[b]
Caesarean delivery, no (%)	6 (50)	3 (25)	0.4[c]
Singletons, no (%)	8 (66)	3 (25)	0.09[b]
Apgar at 5 min, Median (IQR)	7 (6-9)	8 (6-9)	0.25[a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test
[c] Fisher's exact

Table 2. Comparison of ABCs: manual vs automated

ABC characteristics	Manual N= 61	Automated N=252	p Value 0.004[a]
Number of ABC/24h, n,	0.18 (0-0.74)	0.31 (0-2.26)	*ns*[b]
Lowest minute value during bradycardia, bpm (depth)	67 (61-72)	69 (60-74)	*ns*[a]
Count minute values with bradycardia, min (duration) Median (IQR)	1 (1-1)	1 (1-1)	*ns*[a]
Lowest minute value during SpO_2 <80%, % (depth)	68 (50-73)	68 (56-75)	*ns*[a]
Count minute values SpO_2 <80%, min (duration)	2 (1-3)	1 (1-2)	< 0.03[a]
Baseline FiO_2,	0.24 (0.21-0.27)	0.27 (0.25-0.31)	<0.001[a]
Maximum increase FiO_2,	0.20 (0.19-0.46.5)	0.30 (0.18-0.50)	*ns*[a]
Count minute values of FiO_2 titration to baseline oxygen concentration, min	3 (2-6)	3 (2-4)	*ns*[a]
Hyperoxaemia, n(%)	51 (83.6)	171 (67)	< 0.03[b]
Count minute value with SpO_2 >95%, min	5 (3-11)	2 (1-4)	<0.001[a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test
ABC, apnoea, bradycardia, cyanosis; SpO_2, pulse oxygen saturation; FiO_2, fraction of inspired oxygen.

DISCUSSION

This study demonstrated the impact of routine use of an automated oxygen control during respiratory support and oxygen therapy of preterm infants admitted in a neonatal intensive care unit. During ABCs, we observed that the automated oxygen control had no effect on the depth of SpO_2 and heartrate, but the duration of hypoxaemia was reduced with 50%. Although the duration of supplemental oxygen titration did not change and the maximum FiO_2 given after an ABC was higher, the occurrence and duration of SpO_2 >95% decreased. This discrepancy is likely the result of a faster and more diligent titration when this is regulated automatically. It is possible that responding automatically to a hypoxaemic event with a higher FiO_2 than would have been given manually led to a shorter duration of hypoxaemia. Likewise, the more frequent correction of FiO_2 when SpO_2 was measured above TR probably led to the reduction in hyperoxaemia.

An unexpected finding was the increase in ABCs with oxygen therapy during the automatic period. This is in contrast with the findings of a previous study comparing manual and automated oxygen titration, where a reduction in hypoxaemic episodes was observed,[85] however, it is difficult to compare our results with their findings. The TR was wider (88-96%

vs 90-95%), and hypoxaemic events were defined as SpO_2 <88% instead of <80%, and not combined with bradycardia <80 bpm as in our study.[85] Our study was not randomized and an unbalance between the groups could not be avoided. Indeed, the infants in the automatic period were younger and could have been more unstable. Similarly, the observation that the infants in the automatic period spent more time in the 80-89% could be a reflection of this instability instead that this was an effect of the automatic control. Likewise, infants in the manual period could have been more stable as they spent more time in higher SpO_2 values and desaturations are less likely to occur.[74] In contrast, when the more frequent desaturation in the 80-89% region would have been an effect of the automated titration, using a higher and more narrow TR could improve this. However, we could not confirm this in a recent randomized trial.

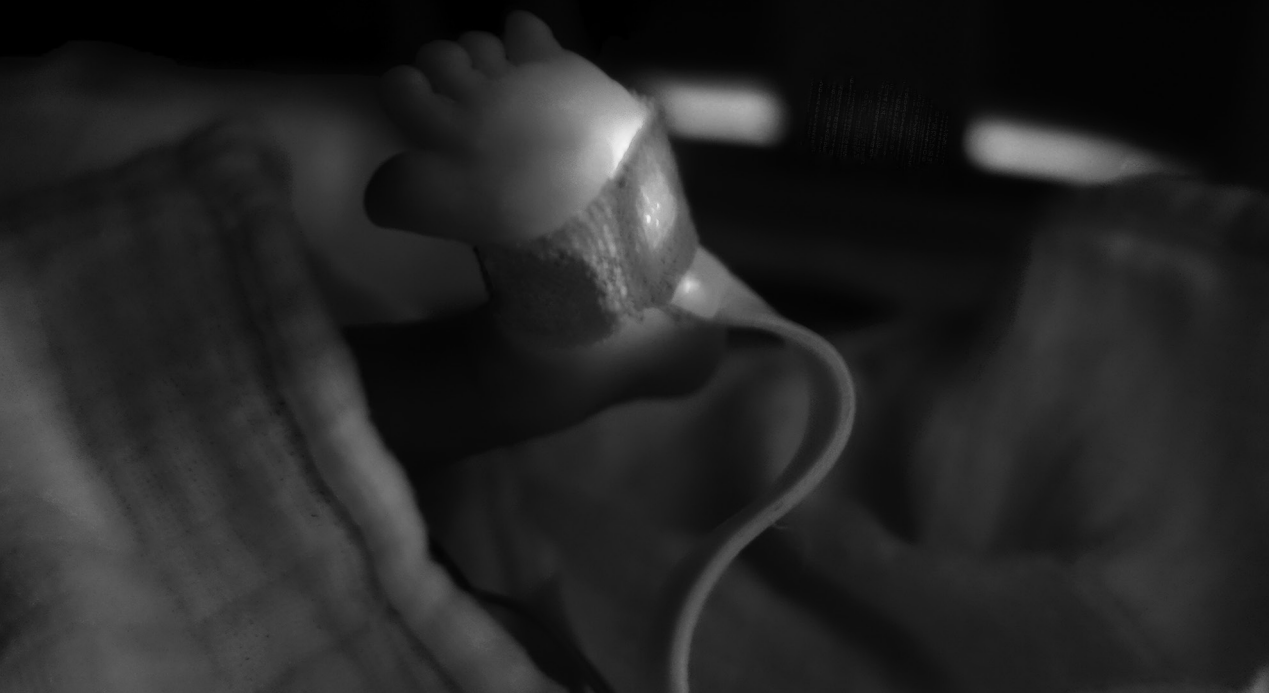
The difference in the amount of ABCs could also be explained by the fact that nurses performed other routines before increasing the fraction of inspired oxygen during manual control, resulting in less intervention with oxygen. Nurses often already responded to ABC before our criteria of noting an ABC were met. This could be repositioning CPAP prongs/ mask, tactile stimulation, and/or suctioning whereas automatic oxygen controllers can only rely on one intervention to a single input parameter (SpO_2): increasing the oxygen. It is obvious that solely increasing the oxygen is not adequate enough when an apnoea occurs and more interventions such as tactile stimulation are needed. Therefore, automatic oxygen control does not decrease the need for manual intervention when an apnoea occurs and the nurses should stay attentive to these events.

We did not adjust for the contribution of the amount of ABCs of each patient, but we considered every ABC as an independent event because all ABCs are handled the same for each infant. However, we could only use a 1-minute time interval for sampling parameters, which is less frequent than reported in other studies.[14 85] It is possible that in both groups we missed hypoxaemic or hyperoxamic events that were resolved within one minute. These limitations indicate that the results have to be interpreted with caution.

In conclusion, after implementing automated oxygen control, during ABC in preterm infants the occurrence hypoxaemia did not decrease but lasted shorter. The duration of oxygen titration was not shorter, but less hyperoxaemia occurred. When oxygen is titrated automatically, nurses should stay alert for hypoxaemic events related to apnoeas.

Chapter 8

General Discussion



The neonatal staff at LUMC observed that although a TR for oxygen saturation (SpO_2) was set for preterm infants admitted to the NICU, the actual SpO_2 often fell outside this range, frequently leading to hypoxaemia and/or hyperoxaemia. This was particularly prevalent when oxygen desaturation occurred during apnoea, when additional oxygen was administered as part of the intervention. To verify this observation, we performed an audit to evaluate targeting SpO_2 and to determine how oxygen was titrated. In this first audit, we investigated the occurrence and duration of hyperoxaemia (defined as SpO_2 >95%) after additional oxygen was administered to treat for ABC (apnoea with bradycardia and cyanosis). This audit led to the conclusion that performance with respect to oxygen titration should be improved, which would significantly improve outcome in these infants. In the subsequent three years, we implemented a series of policy changes in order to improve compliance with respect to targeting SpO_2 and to reduce the occurrence and duration of hypoxaemia and hyperoxaemia in these infants. The effect of each of these policy changes was assessed by performing subsequent audits. It is important to note that these audits were designed to test how often a nurse was able to maintain SpO_2 within TR during and following ABCs, as well as the effect on SpO_2 distribution during oxygen therapy.

For these audits, we performed observational pre/post cohort studies. To define the outcome, we used the parameters that were used for standard care, which included the vital signs and treatment parameters that were stored in our patient data management system at one-minute intervals. This approach enabled the caregivers to compare the results during daily rounds.

In the first audit, we were interested in determining how ABC is treated when oxygen therapy was given. We found that nurses were often unable to achieve the target oxygenation range when oxygen was given during an ABC event. We found that when a nurse performed oxygen titration during ABC, post-ABC hyperoxaemia developed in 79% of cases, and the duration of hyperoxaemia was significantly longer than the duration of both bradycardia and hypoxaemia. The duration of oxygen supplementation was also significantly longer in cases in which the ABC included hyperoxaemia compared to cases in which no hyperoxaemia occurred. Strikingly, we found that hyperoxaemia lasted longer when the patient was in ambient air before the ABC occurred; this was likely the consequence of not adjusting the alarm limits for SpO_2 when oxygen therapy was initiated. Our medical and nursing staff were understandably alarmed by these findings, and it was obvious that quality improvement was needed.

Although the results of our first audit were alarming, poor compliance with respect to targeting SpO_2 is not unique to the NICU. Several studies reported low compliance with respect to targeting SpO_2 in terms of both TR[19 20 29 31 37] and alarm settings.[18 30] Moreover, many factors can influence this compliance, including knowledge regarding the adverse effects of hypoxaemia and hyperoxaemia, the nurse-patient ratio, and the availability of a suitable guideline regarding oxygen titration practices.[29 30 37 48-50 68]

In the years following this initial audit, policy changes were implemented with respect to oxygen titration and targeting SpO_2. After each change in the policy, a new audit was performed, and the results obtained in the post-change audit were compared to the results obtained before the change. For training the staff, in addition to explaining the results of the audit we also educated the staff with respect to the risk associated with hypoxaemia and hyperoxaemia. To guide the nurses in terms of oxygen titration, we also introduced a specific guideline. When we presented the results of the first audit, we found that the nurses were highly motivated to improve the way in which they titrate oxygen. After we evaluated the effect of training, we found that we needed to comply with the new international recommendation; therefore, we narrowed the SpO_2 TR by increasing the lower value. This change could have decreased compliance with respect to targeting SpO_2, thereby changing SpO_2 distribution and influencing the effect of the training and guidelines. We performed an audit to evaluate this change. Compliance with a narrow TR can be extremely challenging, particularly in a busy neonatal care unit. We therefore determined whether compliance could be improved by introducing automated oxygen control, after which we performed a final audit.

First, we discuss compliance with respect to targeting SpO_2 and the effect on SpO_2 distribution. We then discuss how ABC was handled, including how oxygen was titrated. Because the strengths and weaknesses associated with these studies are quite similar among the studies, these are discussed at the end of the chapter.

Compliance with respect to targeting SpO_2 and SpO_2 distribution

Several studies have described efforts designed to increase nurses' compliance with respect to targeting SpO_2. These efforts included training and/or the implementation of guidelines, and they had various degrees of success.[29 37 48-50 66] Here, we opted for both approaches (i.e. training and the implementation of guidelines); we therefore developed a training programme designed to teach all caregivers in our NICU regarding the risks associated with hypoxaemia and hyperoxaemia, and we implemented an oxygen titration guideline. There was a change in pulse oximeter use in the unit (Masimo instead of Nellcor) and to compare two cohorts using similar algorithm for pulse oximetry, a new cohort before training was needed. This was a cohort that was admitted 10 months after the implementation of the new pulse oximeters in our unit.

Both the training and implementation of a guideline led to a small but significant decrease in median SpO_2, but did not affect the interquartile range. However, compliance with respect to targeting SpO_2 improved, which was reflected in the SpO_2 distribution. Specifically, the amount of time in which SpO_2 was within TR increased from 46% to 62%. This improvement was primarily reflected in a reduction in the prevalence of hyperoxaemia; however, the amount of time below TR was unchanged, and the prevalence of hypoxaemia did not decrease.

It is likely that the combination of the teaching programme and oxygen titration guideline made the nurses more aware of the hazards associated with hyperoxaemia, which ultimately led to more careful and timely titration of oxygen levels. The lack of an effect with respect to hypoxaemia could be explained by the fact that our nurses already respond to hypoxaemia as promptly as possible, meaning that there was little room for improving recovery time. It is difficult to determine which – if any – component in the policy changes (i.e. training and/or guideline) played the largest role in this improvement; it is also possible that the positive effect was the result of the combined approach. Indeed, previous studies reported less improvement when either training or a guideline was implemented.[37 40 49 70] We recognise that the guideline regarding oxygen titration was likely not followed precisely, and we did not measure compliance with respect to the precise timing and steps taken. Nevertheless, we believe we were successful in terms of giving our nurses guidance with respect to oxygen titration. This initiative had a clear positive effect, and if the observed reduction in hyperoxaemia can be maintained through repetitive training, outcome among preterm infants will likely improve. In addition to performing repeat training sessions, both oxygen titration and SpO_2 distribution are now evaluated daily during rounds.

Recent randomised trials comparing a lower SpO_2 TR (85%-89%) with a higher TR (91%-95%) in preterm infants[25 43 44] revealed that using the higher TR led to reduced mortality, but increased the prevalence of retinopathy of prematurity (ROP) compared to using the lower TR.[25 44] These results led to the development of new European and Dutch guidelines, and we therefore changed the TR for SpO_2 in our NICU from 85-95% to 90-95%. Although this new TR was implemented in order to prevent low SpO_2, we also expected that nurses would be less able to comply with the narrower TR. Therefore, the effect of narrowing the TR towards the higher end was evaluated with respect to SpO_2 distribution and compliance in terms of targeting SpO_2 during oxygen therapy. We observed that the new, narrower TR resulted in a small increase in median SpO_2 and a rightward shift in the distribution. This led to a decrease in the prevalence of SpO_2 at values ranging from 80% to 89%, but had no effect on hypoxaemia (i.e. SpO_2 <80%). Changing TR did not affect the duration at which SpO_2 was 90-95%, although it did cause a trend toward an increasing occurrence of hyperoxaemia. These results indicate that the nurses attempted to comply with the new TR, but found it difficult to titrate oxygen sufficiently to stay within the narrow TR.

The change in median SpO_2 values after TR was narrowed was relatively small. This finding – together with the observation that the time during which SpO_2 was 90-95% did not change – suggests that the nurses in our NICU already tended to maintain SpO_2 at the higher end of the intended TR when the wider range (i.e. 85-95%) was used. This is consistent with previous reports that nurses are generally less compliant with respect to alarm settings for the upper SpO_2 limits.[18 19 74 78] Indeed, clinical trials comparing lower vs. higher TR also reported that the median SpO_2 levels exceeded the intended TR in both treatment groups.[25]

[43 44] It is therefore likely that caregivers favour an SpO_2 value that is closer to the higher end of TR, as infants are intrinsically more stable when maintained at higher SpO_2 levels. Nevertheless, given that we were able to reduce the prevalence of SpO_2 values below 90%, narrowing TR in our unit may have beneficial effects similar to those reported in recent trials.[25 43 44] However, caution must be exercised, as the lower prevalence of SpO_2 values <90% coincided with a trend towards an increased prevalence of hyperoxaemia.

Titrating oxygen manually in order to stay within a narrow TR can be challenging; in contrast, using automatic oxygen titration can provide superior results.[86 87] Randomised trials that compared automated oxygen control systems with manual titration for short periods revealed that the amount of time that SpO_2 was within TR increased by 8-24%.[35 36 38 39] The use of an automated oxygen control system can also reduce the amount of time the nursing staff must spend with preterm infants who frequently experience desaturation.[35 88 89]

In our NICU, we introduced an AVEA-CLiO$_2$ automated closed-loop oxygen control system (CareFusion, Yorba Linda, CA), and we routinely use this system to improve targeting SpO_2. We therefore performed a new audit in order to compare automated oxygen control with manual titration of oxygen in terms of maintaining SpO_2 within the intended TR. Also in this audit a new cohort for measurements before implementation was needed. The Masimo pulse oximeter in the Philips monitor used the unrevised algorithm, while the Masimo pulse oximeter for the automated oxygen control used the revised algorithm. To use similar algorithms in both groups the Masimo pulse oximeter integrated in the ventilator was used for measuring SpO_2, while the automated oxygen control was turned off in the cohort before implementation.

We found that the introduction of automated oxygen control significantly increased the amount of time spent in which SpO_2 was within TR; in addition, the prevalence of hyperoxaemia decreased significantly. On the other hand, the amount of time in which SpO_2 was <90% increased, although we found no change in the total duration of hypoxaemia. Apparently, using automated oxygen control has no effect on the occurrence or depth of hypoxaemia; however, using an automated oxygen control system provides a more rapid response when SpO_2 is below TR. The response to very low SpO_2 values is similar between the automated oxygen control system and manual titration by a nurse. It is known that nurses have an aversion to very low SpO_2 values.[11 34 35 39] Thus, the gradual but incessant titration of oxygen by the automated oxygen control explains the decrease in hyperoxaemia under these conditions.

There is one item that could have influenced the response to the nurses during the pre/post period of the automated oxygen control. During this period the Masimo oximeter was connected to the AVEA ventilator and SpO_2 values were depicted on the AVEA ventilator and not on the Philips bedside monitor. This indicated that this values where only visible at the bedside of the patient. Adding the pulse oximeter measurements to the AVEA automatically

lead to more acoustic alarms. The acoustic alarms in this ventilator are differentiated on the severity of alarms. However the high priority alarm of having a SpO_2 value below of above the set SpO_2 TR, could not be differentiated from an alarm indicating circuit disconnected or high peak pressure. The alarms needed immediately response from nurses and could only be turned off on the AVEA. It is possible that this also has contributed to good compliance as nurses were more often near the patient for evaluating the alarms.

Apnoea, bradycardia, and cyanosis (ABC)

The incidence of apnoea of prematurity (AOP) is inversely correlated with both gestational age and birth weight; thus, nearly all infants born at <29 weeks gestation and/or weighing <1000 grams at birth develop AOP.[55] Because the respiratory system is not fully developed in preterm infants, AOP is often difficult to treat. Moreover, because apnoea is often combined with bradycardia and cyanosis (leading to the condition known as ABC), preterm infants often receive supplemental oxygen for prolonged periods of time. Given the unpredictability and relative frequency of most forms of ABC, maintaining SpO_2 within the TR is often difficult and time-consuming.[33] Importantly, when a preterm infant experiences intermittent periods of hypoxaemia lasting approximately 1 minute or more, the infant develops an increased risk of adverse outcome.[14] Our baseline assessment in 2012 provided us with key insight regarding how ABC was handled and how oxygen was titrated following ABC. The findings underscored the need for increased awareness and more accurate handling of ABC in our NICU. The effect of our policy changes on both ABC outcome and oxygen titration was audited as part of the quality improvement project, using the minute values that were used for standard care. Although we recognise that this is only a crude measurement, the count in minute values reflect the duration of hypoxaemia, bradycardia, and hyperoxaemia, and the lowest measured values reflect the depth of hypoxaemia and bradycardia.

To improve the way in which ABC is handled in our NICU, we provided training and implemented an oxygen titration guideline. We observed that this approach resulted in a faster response by the nurses to hypoxaemia and improved titration of oxygen after ABC. Moreover, although the occurrence of hypoxaemia and hyperoxaemia did not decrease, the duration of both hypoxaemia and hyperoxaemia decreased significantly. When we included the initial first baseline measured in our analysis, we observed that although training decreased the median duration of hyperoxaemia by 50% (from 2 minutes values to 1 minute value), the largest decrease in hyperoxaemia duration (from 7 minutes values to 2 minutes values) occurred before training was given and before the guideline was implemented. Consistent with this finding, the duration of oxygen supplementation after ABC was greatly decreased (from 14 minute values to 3 minute values) even before training. One possible explanation for this finding is that the results of the first audit were already communicated to the nursing staff before the training session and guidelines were implemented. Indeed,

the team members who were responsible for quality improvement were also working daily in our NICU.

The following two items were not difficult to correct once the nurses become aware of them: *i*) setting the alarm, and *ii*) the use of the "increase FiO_2" button on the AVEA ventilator. The "increase FiO_2" button on the AVEA ventilator provides a controlled way to temporarily increase the oxygen being delivered. When this button is pressed, the ventilator increases the fraction of inspired oxygen (FiO_2) by 20% (relative increase) for two minutes, after which FiO_2 returns to the previous setting. In addition, we emphasised the proper use of alarm settings, particularly when the infant was breathing ambient air (SpO_2 alarm set to 100%) but received additional oxygen following ABC (the alarm should be set to 96%). Although these items were stressed both during the training sessions and in the guidelines, it is likely that the early communication of our findings already improved compliance among our nurses and they had already started using the "increase FiO_2" button more often and were more vigilant in adjusting the alarm settings. Nevertheless, the duration of hypoxaemia decreased only after training and guideline implementation, and the duration of hyperxaemia decreased further. Thus, it is likely that training and guideline implementation were successful in terms of creating additional awareness regarding the consequences of ABC and the need to titrate oxygen more diligently. When we consider the total effect of training and implementing the new guidelines, it becomes apparent that our nurses were strongly motivated to improve their responsiveness and intervention.

After we narrowed the TR from 85-95% to 90-95%, we also evaluated how ABC events were handled. Lower SpO_2 is associated with an increased prevalence of hypoxaemia.[79] However, this relationship could not be confirmed in our study, as we observed no decrease in the occurrence or duration of ABC events in cases in which oxygen was given when TR was set to avoid hypoxaemia. It is possible that a beneficial effect occurred in ABC cases in which additional oxygen was not needed; however, we did not measure this. The narrower (higher) TR led to a trend toward an increased prevalence of hyperoxaemia, which is consistent with our observation with respect to SpO_2 distribution. It is possible that the lack of effect was influenced by the higher tendency of nurses to maintain SpO_2 at the upper end of TR when the 85-95% range was used compared to the 90-95% range.

In addition, we examined the effect of using automated oxygen control on ABC outcome. Implementing automated oxygen control had no effect on the depth or duration of bradycardia, but it significantly shortened the duration of hypoxaemia. The need for oxygen prior to ABC was higher with automated oxygen control than with manual control, whereas the prevalence of ABC with hyperoxaemia decreased with the use of automated oxygen control. Furthermore, with automated oxygen control, the duration of hyperoxaemia was significantly shorter compared to manual control. Although the median number of ABC events per day did not change after automated oxygen control was implemented, the total

number of ABC events was higher with automated oxygen control compared to manual control. This unexpected finding may be explained by the fact that nurses intervene more frequently when performing manual control, and this increased diligence could have prevented and/or inhibited apnoea events, leading to less need for additional oxygen. Specifically, the nurse can reposition the CPAP prongs/mask, provide tactile stimulation, and/or perform suctioning; in contrast, an automatic oxygen controller can perform only one intervention (increasing the oxygen level) in response to only one input parameter (SpO_2). However, after this study we also evaluated ABC cases in which no additional oxygen was given, but we observed no differences between automated oxygen control and manual control. Nevertheless, it remains possible that some ABC events were prevented by the nurses' intervention.

The observed increase in the prevalence of ABC events in our study is in contrast with the findings of a previous study by Waitz *et al*. comparing manual and automated oxygen titration, which found a reduction in hypoxaemic episodes in the automated oxygen control group.[85] However, it is difficult to directly compare our results with the findings of Waitz *et al*. First, the TR used by Waitz *et al*. (88-96%) was wider than our TR (90-95%). Moreover, Waitz *et al*. defined hypoxaemia as SpO_2 <88%, whereas our definition was <80%. Finally, in contrast with our study, Waitz *et al*. did not combine hypoxaemia with bradycardia (defined as heart rate <80 bpm).

Strengths and limitations of the studies

The studies described in this thesis were performed in the form of audits after the introduction of various policy changes in our NICU. This study design was pragmatic and did not increase the workload of the medical or nursing staff. The benefit of defining outcome using the data collected from standard care is that the results can easily be translated when evaluating the patient during daily rounds. Moreover, the results reflect the actual clinical situation, as the data were collected for the entire time during which the infants required respiratory support in the NICU, in a setting in which the infants received care from the nursing staff and in which workload varied. Moreover, the data were collected for a relatively long period during routine care, thereby decreasing the risk of a Hawthorne (i.e. observer) effect.

The observed improvement in quality was achieved only because the nursing and medical staff embraced the policy changes and were motived to improve their outcome with respect to targeting SpO_2. We therefore ensured that the entire staff was updated regarding the results of each audit. Group meetings were held regularly, allowing the nursing staff to discuss any problems and/or concerns regarding the policy changes, and these meetings were generally well attended. In addition, it was important that the team members responsible for quality improvement were available for troubleshooting on a daily basis. Another strength of this thesis project lies in the fact that the nurse responsible for quality

improvement was also a working member of the NICU staff and was therefore familiar with all of the practical issues associated with targeting SpO_2 and handling ABC events.

Although this thesis project was comprised of prospective observational cohort studies, we used parameters that were collected during standard care in order to assess outcome. Therefore, the studies have the same limitations intrinsic to a retrospective study. We used data that were sampled at 1-minute intervals and stored in our Patient Data Management System (PDMS). In contrast with other studies,[14 85] we were unable to collect data more frequently. However, although our approach provided a slightly more crude reflection of the time course of SpO_2, the results are still comparable, as the studies used the same methodology. In addition, because the data were collected using standard methods, our medical and nursing staff were familiar with the values and could draw from these data when evaluating patients during daily rounds.

After the first audit, we changed the brand of pulse oximeters in our NICU from a Nellcor oximeter to a Masimo SET pulse oximeter. Then we became aware that the Masimo algorithm integrated into the Philips bedside monitor (Intellivue MP70, Tilburg, The Netherlands), still used the unrevised version, which is reflected by the well described dip in the frequencies of SpO_2 87-90%, and higher frequencies of saturation between 91-96%.[75 94] In contrast, the Masimo integrated to the AVEA ventilator used a revised algorithm. It is therefore possible that this change in pulse oximeter could have influenced the effect of the policy changes. However, to ensure that our analyses of the data were not biased by the use of different pulse oximeters or algorithms, we re-analysed data collected from new cohorts in which the same pulse oximeter was used, and we obtained similar results.

Lastly, we did not adjust our analysis for the number of ABC events in each patient; rather, we considered each ABC to be an independent event, as all events are handled the same. Due to the retrospective nature of the analysis, it is possible that we may have missed any ABC events that were resolved within one minute. Given these limitations, the results presented in this thesis should be interpreted with caution. Moreover, this study was not designed to compare morbidity and mortality before and after policy changes; rather, it was designed to evaluate SpO_2 distribution and compliance with respect to targeting SpO_2.

Overall effect of the project

Compliance and SpO_2 distribution

Although each policy change had relatively little effect on hypoxaemia, we observed a small but steady decrease in hypoxaemia after each change, leading to 50% reduction over three years' time (from 1.9% to 0.9%;Table 1). The effect of quality improvement on hyperoxaemia was considerably larger – hyperoxaemia decreased from 44% to 19%. It is difficult to determine which quality improvement component contributed most to this improvement, as the change in the SpO_2 TR could have obscured the effects of training and/or guideline implementation.

Table 1. Percentage of time in different SpO_2 ranges measured at each audit

	Before training & guideline implementation (baseline)	After training & guideline implementation	After changing SpO_2 TR from 85-95% to 90-95%	Before autoFiO_2	During autoFiO_2
SpO_2 <80%	1.9 (1.0 - 3.0)	1.7 (0.8-2.6)	1.5 (0.8 - 2.1)	1.1 (0.4 - 1.7)	0.9 (0.5 - 2.1)
SpO_2 <85%	5.9 (2.8 - 7.9)	6.2 (2.5 - 8.0)	3.5 (2.6 - 5.3)	2.7 (1.4 - 4.0)	3.2 (1.8 - 5.1)
SpO_2 <90%		15.7 (7 - 21)	10.7 (8.4 - 13.7)	8.6 (7.2 - 11.7)	15.1 (14.0 - 21.1)
SpO_2 85-95%	48.0 (19.6 - 63.9)	61.9 (48.5 - 72.3)	56.5 (32.6 - 64.7)		
SpO_2 90-95%		49.2 (39.6 - 59.7)	46.9 (27.1 - 57.9)	48.4 (41.5 - 56.4)	62.0 (56.4 - 68.6)
SpO_2 >95%	44.0 (27.8 - 66.2)	30.8 (22.6 - 44.5)	39.0 (28.8 - 59.2)	41.9 (30.6 - 49.4)	19.3 (11.5 - 24.5)
SpO_2 >98%	9.4 (4.2 - 26.8)	6.1 (2.3 - 12.1)	8.9 (3.3 - 17.9)	10.1 (3.7 - 14.4)	2.1 (0.7 - 3.1)

Notes: values are presented as the Median (IQR).

Both training and the introduction of automated oxygen control led to increased compliance with respect to targeting SpO_2. Narrowing the SpO_2 TR toward the higher end led to fewer low SpO_2 values but did not decrease hypoxaemia; rather, we observed was a trend toward hyperoxaemia, indicating that the nurses found it difficult to comply with the more narrow TR. The quality improvement steps taken during this thesis project received considerable attention from the nurses and doctors, and it was clear that during the three years the staff became much more aware of the need to effectively target SpO_2 and to avoid both low and high SpO_2 levels during oxygen therapy. Although the introduction of automated oxygen control had relatively little effect on the ability to avoid low SpO_2 levels, it played a large role in decreasing hyperoxaemia.

Handling ABC events and oxygen titration

The quality improvement project in this thesis increased awareness of the need to promptly handle ABC events and titrate oxygen diligently. However, the beneficial effects of the policy changes with respect to *how* ABC events are handled and *how* oxygen is titrated are less clear. When we look at the effect over the three-year project (Table 2), it becomes clear that most of the reduction in hyperoxaemia occurred before the policy changes were implemented. This can likely be explained by the fact that the first audit results were communicated to the nurses even before training and before the guideline was developed.

After training and implementing the oxygen titration guideline, duration of both hypoxaemia and hyperoxaemia after ABC reduced further. We also observed an effect when the target SpO_2 range was narrowed from 85-95% to 90-95%. The effect of training apparently did not last, however, as the duration of both hypoxaemia and hyperoxaemia increased before the introduction of automated oxygen control, which again reduced the duration of both hypoxaemia and hyperoxaemia.

Table 2. Clinical features of the ABC events measured at each audit

	Baseline assessment[a]	Before training & guideline implementation	After training & guideline implementation	After changing SpO_2 TR from 85-95% to 90-95%	Before AutoFiO_2	During AutoFiO_2
Number of independent ABC event, N	257[a]	186[b]	168[b]	204[b]	61[c]	254[c]
ABC with SpO_2 >95%	79%	73%	64%	73%	84%	67%
Depth of bradycardia, bpm	70 (63-76)	70 (60-75)	69 (61-75)	70 (62-75)	67 (61-72)	69 (60-74)
Duration of bradycardia, min	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)
Depth of SpO_2 <80%, min	68 (61-73)	70 (62-76)	72 (61-77)	73 (63-77)	68 (50-73)	68 (56-75)
Duration SpO_2 <80%, min	2 (1-2)	2 (1-2)	1 (1-2)	1 (1-2)	2 (1-3)	1 (1-2)
Baseline FiO_2,	0.23 (0.21-0.28)	0.25 (0.21-0.31)	0.25 (0.21-0.30)	0.22 (0.21-0.25)	0.24 (0.21-0.27)	0.27 (0.25-0.31)
Max increase FiO_2	0.39 (0.30-0.67)	0.44 (0.39-0.52)	0.43 (0.37-0.51)	0.41 (0.31-0.45)	0.20 (0.19-0.47)	0.30 (0.18-0.50)
Duration of titration to baseline oxygen concentration, min	14 (4–52)	3 (2-16)	3 (2-7)	2 (2-6)	3 (2-6)	3 (2-4)
Duration SpO_2 >95%, min	7 (1-25)	2 (0-7)	1 (1-3)	1 (0-2)	5 (3-11)	2 (1-4)

Notes: Values are presented as percentages and median (IQR).
[a] Nellcor oximeter
[b] Masimo oximeter with the unrevised algorithm
[c] Masimo oximeter with the revised algorithm

GENERAL CONCLUSIONS

The stepwise quality improvement project implemented in this thesis project improved compliance with respect to both targeting SpO_2 and improving oxygen titration. This led to improved SpO_2 distribution and decreases in both hypoxaemia and hyperoxaemia, as well as slight improvements in the handling of ABC events and oxygen titration following ABC. The introduction of training sessions, guidelines, and automated oxygen control increased awareness regarding the consequences of hypoxaemia and hyperoxaemia and led to increased efforts to prevent these complications. The beneficial effects culminating from three years of quality improvement will likely continue to improve outcome among preterm infants admitted to our NICU.

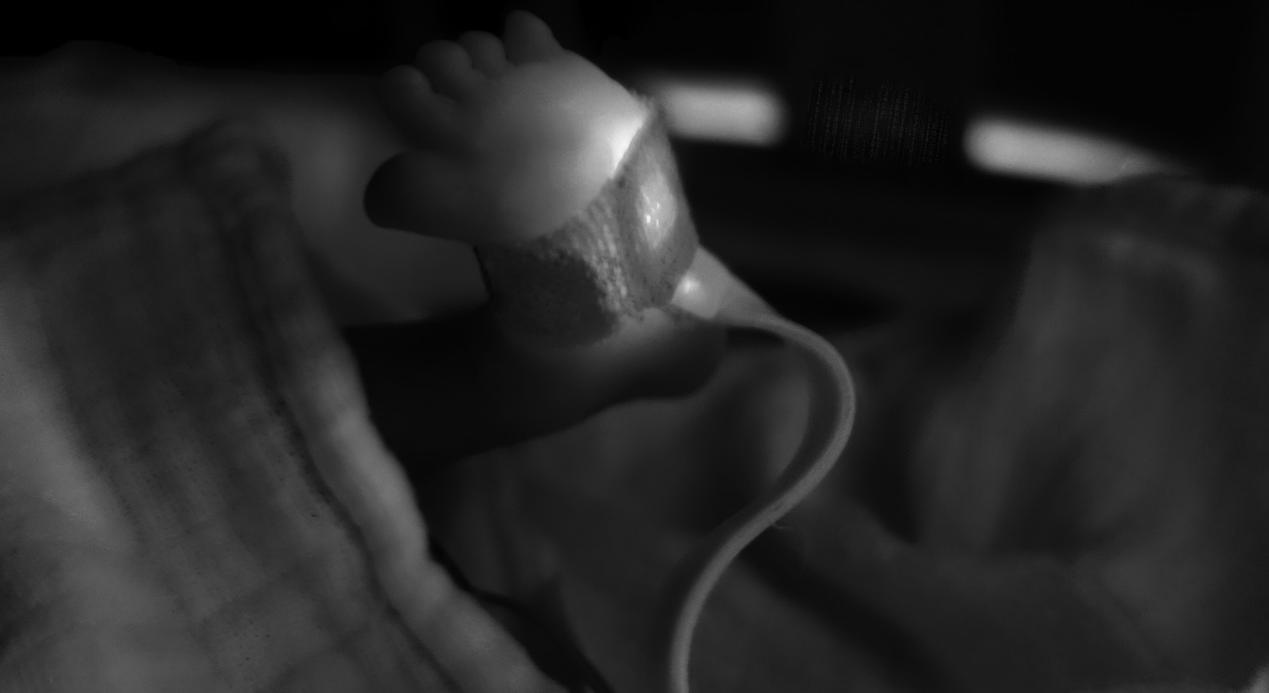
FUTURE PERSPECTIVES

Although we made clear progress with respect to targeting SpO_2 by reducing both hypoxaemia and hyperoxaemia, further studies are needed in order to determine whether these beneficial effects improve the long-term outcome of preterm infants in our NICU. Given that the beneficial effects of training tend to fade with time, the use of repetitive training should be integrated into daily care and should be adjusted as needed. Automated oxygen control systems are used increasingly in neonatal intensive care units, and trials are currently being performed to test its effect on long-term outcome. Although the use of automated oxygen control reduces hyperoxaemia, it appears to have little effect on hypoxaemia, although it is possible that changes in the system's algorithm could improve further. Several automated oxygen control devices are now available, and studies are needed in order to compare their effectiveness. Regardless, increasing oxygen using an automated system has no effect in cases of apnoea-induced oxygen desaturation. Future developments in technology should focus on the early detection and/or prevention of apnoea, as well as an integrated automated response in both oxygen levels and non-invasive ventilation. Additional studies are also needed in order to determine the ideal SpO_2 TR when using automated oxygen control. With respect to policy changes, collecting data at a higher rate (for example, at 1-second intervals instead of 1-minute intervals) may provide a more precise measure of the beneficial effect of specific interventions. This approach will also provide important information regarding fluctuations in SpO_2 in preterm infants and may even serve to indicate that an ABC is imminent, thereby decreasing the incidence of hypoxaemia and bradycardia.

Chapter 9

Summary

Samenvatting



SUMMARY

When providing oxygen therapy to a preterm infant, targeting SpO_2 is essential for avoiding hypoxaemia and/or hyperoxaemia. However, this can be both difficult and challenging for nurses working in a neonatal intensive care unit. The general aim of this thesis project was to assess the effect of changes in clinical practice regarding oxygen titration and compliance with respect to targeting SpO_2 in preterm infants admitted to our NICU.

In **Chapter 2**, we performed a systematic review of published literature regarding compliance in terms of targeting SpO_2 in preterm infants and the factors that influence this compliance. A total of 16 studies, comprising 2935 nurses and 574 infants was included in this review. This chapter provides a narrative perspective of how nurses are able to maintain SpO_2 within target levels using either manual or automated control. The main finding was that poor compliance was observed regarding SpO_2 target ranges, particularly with respect to maintaining SpO_2 below the upper limit. Our analysis revealed that several factors play a role in reducing compliance, including *i*) lack of awareness regarding alarm settings, *ii*) reduced knowledge regarding the risk factors associated with hypoxaemia and hyperoxaemia, and iii*i*) a low nurse:patient ratio. The use of an automatic FiO_2 control led an increased time within the SpO_2 TR. Based on our analysis, we concluded that compliance was generally low in terms of targeting SpO_2 during oxygen therapy in preterm infants. Training, combined with an oxygen titration guideline, a favourable nurse:patient ratio, and the use of automated FiO_2 control could increase this compliance.

In **Chapter 3**, we report the occurrence and duration of hyperoxaemia (defined as SpO_2 >95%) after oxygen administration for treating apnoea, bradycardia, and cyanosis (ABC), and we reported the duration of hypoxaemia (defined as SpO_2 <80%) and/or bradycardia in preterm infants below 30 weeks of gestation in our NICU who were supported with nasal continuous positive airway pressure (nCPAP). We observed that hyperoxaemia occurred after 79% (202 out of 257) ABC events, and the duration of additional oxygen was longer in ABC events with hyperoxaemia than in ABC events without hyperoxaemia. Moreover, hyperoxaemia lasted longer when the infant was on ambient air prior to the onset of ABC compared to when oxygen was administered. We therefore conclude that in preterm infants supported with nCPAP in our NICU, hyperoxaemia was prevalent when oxygen was increased for treating ABC and had longer duration than bradycardia and hypoxaemia.

In **Chapter 4**, we present our study in which we evaluated the effects of training and the implementation of an oxygen titration guideline. Specifically, we compared the results obtained before and after training and guideline implementation. We found that after

training and guideline implementation, the percentage of time that SpO_2 was within TR had increased significantly, and the percentage of time that SpO_2 was above 95% decreased significantly; we found no effect on the percentage of time that SpO_2 was below 85%. In total, 186 and 168 ABC events occurred before and after training/guideline implementation, respectively. The duration of both hypoxaemia and hyperoxaemia was reduced following training and guideline implementation, although the prevalence of hyperoxaemia did not change. We therefore conclude that training and implementing guidelines with respect to manual oxygen titration improved targeting SpO_2 in preterm infants, with more time spent within TR and shorter periods of hyperoxaemia and hypoxaemia during ABC.

Chapter 5 describes the results of our audit in which we evaluated whether narrowing the SpO_2 TR from 85-95% to 90-95% had an effect on SpO_2 distribution or compliance regarding targeting SpO_2 and ABC in preterm infants receiving oxygen. During both periods oxygen was manually adjusted.

We observed that narrowing TR led to a significant increase in median SpO_2, but had no effect on the amount of time during which SpO_2 was within 90-95%. The SpO_2 distribution shifted rightward with a trend towards higher occurrence of hyperoxaemia. There was less SpO_2 below 90%, but without hypoxaemia. Moreover, we observed no change in the frequency, depth, or duration of ABC events, regardless of the manner in which oxygen was titrated. Based on our results, we conclude that narrowing TR from 85-95% to 90-95% in preterm infants *i*) caused a rightward shift in the SpO_2 distribution, *ii*) decreased the amount of time that SpO_2 <90%, *iii*) had no effect on the amount of time in which SpO_2 is 90-95%, and *iv*) caused an increase in hyperoxaemia. These results suggest that although the nurses attempted to comply with the new TR, they found it difficult to titrate oxygen adequately in order to stay within the new, more narrow TR. The findings also indicate that the nurses in our unit already tended to maintain SpO_2 at the upper end of the intended TR when the 85-95% range was used. Nevertheless, given that changing the range led to a decrease in the infant's exposure to SpO_2 levels <90%, narrowing TR in our unit will likely have beneficial effects, as shown recently. [25 43 44]

The objective of the study described in **Chapter 6** was to evaluate the effect of implementing automated oxygen control on maintaining SpO_2 within the 90-95% TR in preterm infants. Specifically, we compared preterm infants before the implementation of automated oxygen control with preterm infants born after automated oxygen control was introduced. Our analysis revealed that after automated oxygen control was introduced to our NICU, preterm infants receiving oxygen therapy were within TR for SpO_2 a higher percentage of time, which resulted in a significant reduction in the prevalence of hyperoxaemia; in contrast, the introduction of automated oxygen control had no effect on the prevalence of hypoxaemia.

In **Chapter 7**, we provided a follow-up on Chapter 6 by reporting the effect of implementing automated oxygen control on ABC in preterm infants and studied the effect of manual titration versus automated titration on apnoea, bradycardia, cyanosis (ABC) and oxygen therapy in preterm infants. Implementing automated oxygen control for preterm infants led to a shorter duration of hypoxaemia and hyperoxaemia during and after ABCs. Nurses should stay alert for hypoxaemic events related to apnoeas.

Finally, in **Chapter 8** we discuss the results of our studies, provide general conclusions, and discuss future perspectives. The quality improvement project introduced in this thesis resulted in improved SpO_2 distribution, decreased hypoxaemia, and decreased hyperoxaemia in preterm infants admitted to our NICU. We also observed slight improvements in the way in which our nurses handled ABC events and titrated oxygen following an ABC event. Together, the training sessions, guideline implementation, and introduction of automated oxygen control increased our nursing staff's awareness of the consequences associated with frequent hypoxaemia and hyperoxaemia, and as a result, our staff now take a more active approach to minimise the occurrence of these conditions. The beneficial effect of this 3-year quality improvement project will likely improve the long-term outcome of preterm infants admitted to our unit.

SAMENVATTING

Premature pasgeborenen krijgen vaak voor een lange periode extra zuurstof toegediend. Het is noodzakelijk om deze zuurstof zorgvuldig te titreren, een te lage zuurstofsaturatie (hypoxie) maar ook een te hoge zuurstofsaturatie (hyperoxie) is schadelijk en dient te worden voorkomen. Deze zuurstoftitratie en ook het nastreven van de zuurstofsaturatiegrenzen kan voor verpleegkundigen die werken op een neonatale intensive care unit (NICU), heel uitdagend zijn. Op de NICU in Leiden zijn er ten behoeve van kwaliteitsverbetering op het gebied van zuurstoftitratie en hanteren van zuurstofsaturatiegrenzen bij premature pasgeborenen een aantal veranderingen in de praktijk doorgevoerd. De doelstelling van dit proefschrift was om het effect van deze veranderingen te evalueren.

In **Hoofdstuk 2** wordt een overzicht gegeven van de literatuur met betrekking tot het nastreven van zuurstofsaturatiegrenzen bij premature pasgeborenen door verpleegkundigen op de NICU. Tevens worden factoren beschreven die deze naleving beïnvloeden. In dit overzicht werden 16 studies geïncludeerd, in totaal omvatte het 2935 verpleegkundigen en 574 premature pasgeborenen. Dit hoofdstuk geeft verhalend verslag van de studies die onderzochten hoe verpleegkundigen in staat zijn om, door middel van zuurstoftitratie, de zuurstofsaturatie binnen de afgesproken grenzen te houden. Naast handmatige zuurstoftitratie is er ook gekeken naar automatische zuurstoftitratie. De voornaamste bevinding was dat de zuurstofsaturatiegrenzen tijdens het geven van zuurstof aan premature pasgeborenen slecht werden nageleefd, zeker als het gaat om de zuurstofsaturatie onder de bovengrens te houden. Hierbij spelen verschillende factoren een rol: *i*) verminderde alertheid met betrekking tot de ingestelde alarmgrenzen, *ii*) onvoldoende kennis over de risicofactoren die samenhangen met hypoxie en hyperoxie en *iii*) de verpleegkundige:patient verhouding. Het gebruik van een automatische zuurstoftitratie leidde tot een toename van de tijd dat de zuurstofsaturatie binnen de gestelde grenzen was. We concludeerden dat de zuurstofsaturatiegrenzen over het algemeen niet goed worden nageleefd. Deze naleving zou kunnen verbeteren door middel van training, gecombineerd met een zuurstoftitratie richtlijn en verlaging van de werkdruk van verpleegkundigen en het gebruik van een automatische zuurstoftitratie.

In **Hoofdstuk 3** beschrijven we een nulmeting die is uitgevoerd op de NICU van het LUMC. We onderzochten hoe zuurstof getitreerd werd na een apneu, gepaard gaande met bradycardie en cyanose (ABC) bij pasgeborenen met een zwangerschapsduur onder de 30 weken die non-invasief respiratoir werden ondersteund. We beschreven het optreden en de duur van hyperoxie (gedefinieerd als een zuurstofsaturatie boven de 95%) en hypoxie (gedefinieerd als een zuurstofsaturatie onder de 80%). We observeerden dat hyperoxie na

ABC's in 79% van de ABC's optrad. De ontstane hyperoxie na zuurstoftitratie duurde langer dan de bradycardie en de hypoxie bij de apneu. Bij ABC's waarbij hyperoxie optrad, werd langer zuurstof gegeven dan bij ABC's waarbij geen hyperoxie optrad. Bovendien merkten wij op dat wanneer premature pasgeborenen geen extra zuurstof ontvingen voordat de ABC optrad, de hyperoxie langer duurde dan wanneer zij vooraf al zuurstofbehoefte hadden. We concludeerden hyperoxie veelal voorkwam na het geven van zuurstof voor de behandeling van ABC's en dat deze langer duurde dan de bradycardie en hypoxie.

In **Hoofdstuk 4** beschrijven we onze studie waarin we de effecten van het geven van training over de gevaren van hypoxie en hyperoxie, en het implementeren van een zuurstoftitratie richtlijn hebben geëvalueerd. We vergeleken een cohort voor en na de training en implementatie om het effect te meten. Na het geven van training en het implementeren van een zuurstoftitratie richtlijn zagen we een toename in de tijd dat de zuurstofsaturatie binnen de gestelde grenzen (85-95%) was. De tijd dat de zuurstofsaturatie boven de gestelde bovengrens was, was aanzienlijk gedaald; we vonden daarentegen geen effect op de tijd dat de zuurstofsaturatie onder de ondergrens bevond. Tijdens ABC's voor en na de training en richtlijn implementatie, zagen we de duur van hypoxie en hyperoxie afnemen, hoewel het voorkomen van hyperoxie na ABC's niet was afgenomen. We concludeerden dat de handmatige zuurstoftitratie was verbeterd en dat training gecombineerd met de implementatie van een zuurstoftitratie richtlijn bijdraagt aan een betere naleving van de zuurstofsaturatiegrenzen. Bij ABC's trad hierdoor minder hypoxie en hyperoxie op.

Hoofdstuk 5 beschrijft het effect van het versmallen van de saturatiegrenzen van 85-95% naar de hoogste helft (90-95%) op het nastreven van deze grenzen tijdens zuurstof therapie aan premature pasgeborenen, zowel in het algemeen als na ABC's. Tijdens de voor- en nameting werd zuurstof handmatig getitreerd. Het versmallen van de saturatiegrenzen had geen effect op de tijd dat de zuurstofsaturatie binnen de grens van 90-95% was. Door een rechtsverschuiving in de SpO_2 distributie observeerden we een trend naar het optreden van hyperoxie. De zuurstofsaturatie was minder vaak onder de 90%, maar zonder een afname in hypoxie (<80%). Hoewel er een toename was van ABC's waarna hyperoxie optrad, bleek dit niet significant. Daarnaast observeerden we geen verandering in de diepte en duur van ABC's. We concludeerden dat het versmallen van de zuurstofsaturatiegrens naar de hogere helft geen verandering gaf in de tijd de zuurstofsaturatie binnen de nieuwe grens doorbracht, maar wel een trend naar meer hyperoxie. Ondanks een afname in lage saturaties, (< 90%) nam de hypoxie niet af. We speculeren dat de verpleegkundigen in onze NICU de zuurstofsaturaties al in het bovenste deel van de grens hielden toen de oorspronkelijke zuurstofsaturatiegrens werd gehanteerd, waarschijnlijk omdat de premature pasgeborenen dan stabieler zouden zijn.

Het doel van de in **Hoofdstuk 6 en 7** beschreven studies was om het effect van automatische zuurstoftitratie te evalueren op het behoud van de zuurstofsaturatie binnen de afgesproken grens van 90-95%. Een periode vooraf, waarbij de zuurstof handmatig werd getitreerd, werd vergeleken met een periode nadat de automatische zuurstoftitratie werd geïmplementeerd in onze NICU. Pasgeborenen met een zwangerschapsduur onder de 30 weken die respiratoir werden ondersteund en zuurstofbehoefte hadden, werden geïncludeerd. We observeerden dat bij de automatische zuurstoftitratie de zuurstofsaturatie significant vaker binnen de saturatiegrens van 90-95% was. Hoewel de zuurstofbehoefte iets hoger was tijdens de automatische zuurstoftitratie, observeerden we tevens een significante daling van hyperoxie (>95%). Zuurstofsaturaties tussen de 85-89% kwamen vaker voor, maar de automatische zuurstoftitratie had geen effect op het voorkomen van hypoxie (<80%). Het percentage ABC's waarbij hyperoxie optrad daalde significant en de duur van hypoxie en hyperoxie tijdens en na ABC's was ook korter. We concludeerden dat de implementatie van automatische zuurstoftitratie leidde tot een toename in het behouden van zuurstofsaturatie binnen de gestelde grenzen tijdens het geven van zuurstof aan premature pasgeborenen, met daarbij een daling van hyperoxie. Deze studie niet was opgezet om effect op lange termijn aan te tonen, maar het lijkt dat automatische zuurstoftitratie de potentie heeft om de uitkomsten van deze patiëntengroep te verbeteren.

Tenslotte bespreken we in **Hoofdstuk 8** de resultaten van onze studies, geven we algemene conclusies en doen we suggesties voor toekomstig onderzoek. De studies beschreven in dit proefschrift hebben geleid tot een betere zuurstoftitratie, minder hypoxie en minder hyperoxie bij premature pasgeborenen opgenomen op de NICU. Hoewel we ook verbeteringen observeerden in de manier waarop verpleegkundigen zuurstof titreerden bij ABC's, was dit effect minder evident. De trainingen, de implementatie van de zuurstoftitratie richtlijn en de invoering van automatische zuurstoftitratie hebben zeker geleid tot meer bewustwording in de gevolgen van hypoxie en hyperoxie, en tot een meer actieve benadering om het optreden hiervan te beperken. Het positieve effect dat we hebben bereikt kan een belangrijke bijdrage leveren aan het verbeteren van de lange termijn uitkomsten van de premature pasgeborenen opgenomen op onze afdeling neonatologie.

Chapter 10

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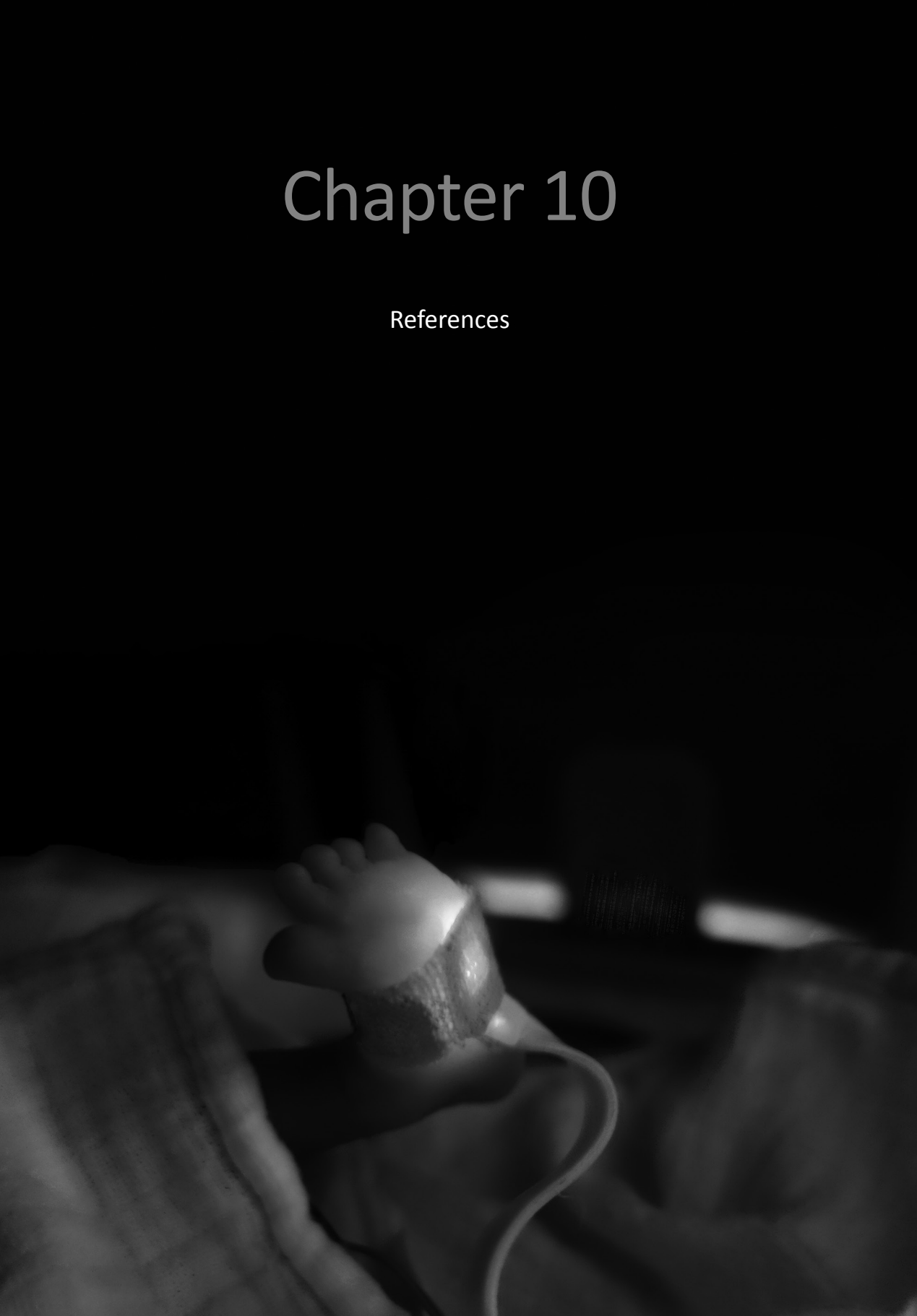

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Appendices

List of abbreviations

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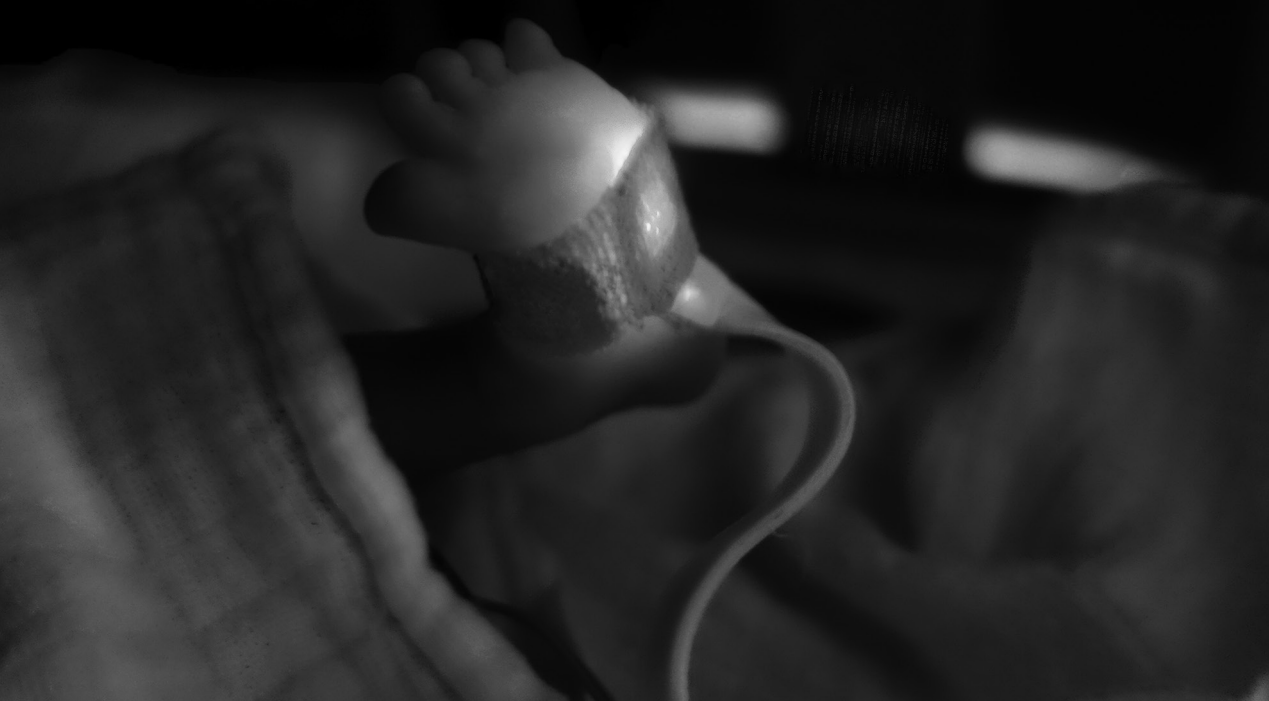
Dankwoord



LIST OF ABBREVIATIONS

ΔFiO_2	Maximum additional FiO_2 - baseline FiO_2
$\%SpO_2$-wtr	Percentage of time in percentage SpO_2 was within the target range
ABC	Apnoea, bradycardia, cyanosis
BPD	Bronchopulmonary dysplasia
nCPAP	Continuous Positive Airway Pressure
FiO_2	Fraction of inspired oxygen
GA	Gestational age
HR	Heart rate
LUMC	Leiden University Medical Centre
NICU	Neonatal intensive care unit
PDMS	Patient data management system
PO	Pulse Oximetry
SpO_2	Pulse oxygen saturation
TR	Target Range

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LIST OF PUBLICATIONS

van Zanten HA, Pauws SC, Stenson BJ, Walther FJ, Lopriore E, Te Pas AB
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Journal of Neonatal Nursing. 2007 Oct; 5(13):186-190.

CURRICULUM VITAE

Henriëtte van Zanten was born in Oudenhoorn, on 8 April 1969. In 1985 she passed her secondary school exams (MAVO) at the Christelijk Scholengemeenschap “De Brug” in Lelystad. She was trained as a nursing assistant in 1988 in Hilversum, whereafter she successfully completed the in-service nursing training at the Zeister Ziekenhuis in Zeist in 1992. She was trained as an intensive care nurse/coronary-care nurse at ‘t Lange Land Ziekenhuis in Zoetermeer from 1996 to 1997, and as a neonatal intensive care nurse at the Leiden University Medical Centre in Leiden from 1998 to 1999. In 2010 she decided to continue her studies and after passing her VWO Mathematics-C exam at the James Boswell Instituut in Utrecht, she started the premaster Clinical Health Sciences at Utrecht University. Henriëtte obtained a Master’s degree in Clinical Health Sciences by completing the programme in Nursing Science in 2013.

From 1992 to 2005 she held various positions as a nurse in general hospitals in Zeist, Leiderdorp, Den Haag, Zoetermeer, and at the Leiden University Medical Centre. In 2005 she started as a neonatal nursing expert to improve quality of patient safety and patient care in the NICU.

She started her PhD training in November 2013 under supervision of Professor F.J. Walther and Dr A.B. te Pas. This thesis represents the research performed during this period. During this period she also worked as a neonatal nurse.

Henriëtte lives with Rendel Munneke. Together they have two children; Joep (2006) and Renske (2007).

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