Outcomes after automated oxygen control for preterm infants

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OUTCOMES after AUTOMATED **OXYGEN CONTROL** for PRETERM **INFANTS**

Hylke Salverda

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Voor mijn broer

What is now proved was once only imagined.
– William Blake

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Preface

Oxygen is crucial for the survival of all organisms. Without it, there would be no life. This much humankind has known since the first scientists discovered oxygen, one may have been as early as 1604. However, it was not until 1790 that oxygen was first mentioned for medical purposes and it would take another 110 years before it was first used in neonatal care.

To get oxygen in our blood to enable the essential metabolic processes in our body, we use our lungs. The lungs of a preterm infant are not fully developed and they are thus not always capable of taking in enough oxygen. This prompts clinicians to give extra oxygen – a key treatment which has helped save many lives. Exactly how much oxygen clinicians can safely give is still unknown and can change within seconds for preterm infants. As with so many things in life, too little or too much can be harmful. A fine balance needs to be kept.

In the first half of the 20th century, neonatal care saw little involvement from physicians. Few medical procedures were done to neonates. It was believed that handling during care led to cyanosis and apnoea and as a result, care was mostly limited to warming, feeding and isolation. Giving extra oxygen to preterm infants was also rare. The first mention of administering oxygen to preterm infants was by Budin in 1900, when he reported a beneficial effect of administering oxygen during cyanotic bouts. In the following years physicians noted that administering oxygen could also reduce irregular, also known as periodic, breathing. As a result, extended periods of oxygen administration were recommended and oxygen use for preterm infants became common practice. Oxygen hoods, funnels and even incubators were designed to administer oxygen, all with the aim of mixing in as little ambient air as possible.

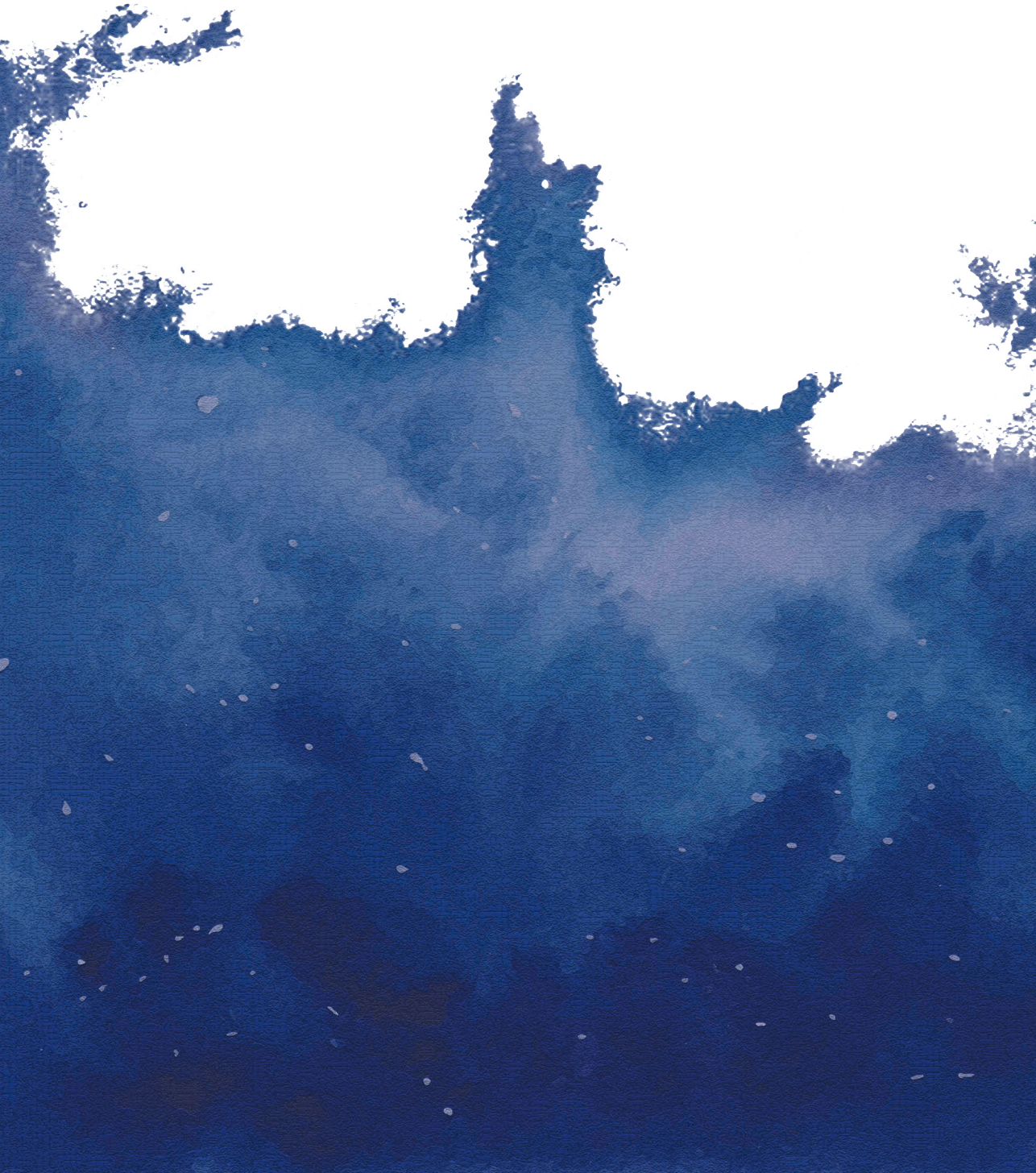
The first sign of the drawbacks of administering such a high fraction of oxygen in the air infants breathed appeared in 1940, when paediatrician Clifford noticed a new eye condition, later called retrolental fibroplasia. This new condition was meticulously studied by ophthalmologist Terry in the following years and another eleven years of research were needed to link this blindness-causing disease to administering oxygen. From then on, physicians began to realize that too much oxygen was harmful, and a more restrictive approach followed in the mid-1950s.

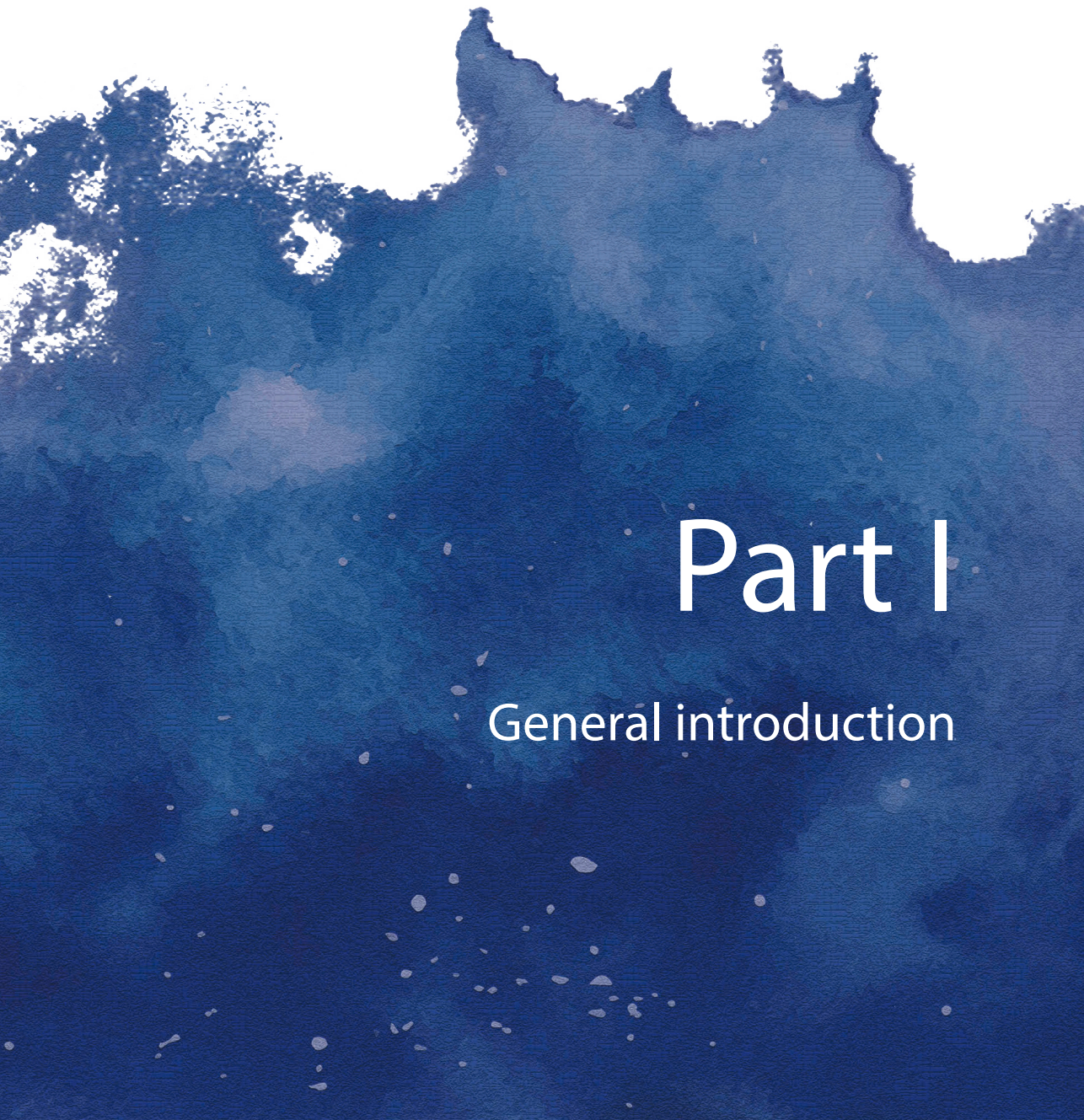
Physicians lowered the oxygen content in supplied breathing air to 40%, and as a result the rate of retinopathy of prematurity - the contemporary name for retrolental fibroplasia - decreased. This change in practice was not based on evidence from research, but on clinical findings from individual paediatricians. Lowering the oxygen content also had a problem: both the rate of hyaline membrane disease, now known as respiratory distress syndrome, and the rate of cerebral palsy went up for preterm infants - keeping the balance between too much and too little was, and still is, difficult.

Although a form of a pulse oximeter - a device to measure the oxygen saturation of the blood – was developed in 1935, titrating oxygen on the basis of the oxygen content in the blood only started in the 1960s, when blood gas monitoring became readily available. It would not be pulse oximetry as used today, as this was only developed by researcher Takuo Aoyagi in 1974. These early pulse oximeters were highly inaccurate when patients moved. This poses a particular problem for preterm infants, who cannot be instructed to lie still. Eventually, in 1995, Masimo developed Signal Extraction Technology, which is more resistant to motion, and this is now the basis for guiding how much oxygen to give preterm infants.

Technology has become more and more sophisticated. In our unit, infants in need of respiratory support can receive breath volumes as low as 2 millilitres. The breath is given at the exact moment the baby attempts to breathe, and the amount of oxygen is automatically adapted to the infants' need by measuring the oxygen saturation of the blood. By continuous automatic adjustment of the oxygen content we give, we are better than ever at keeping the fine balance between too much and too little.

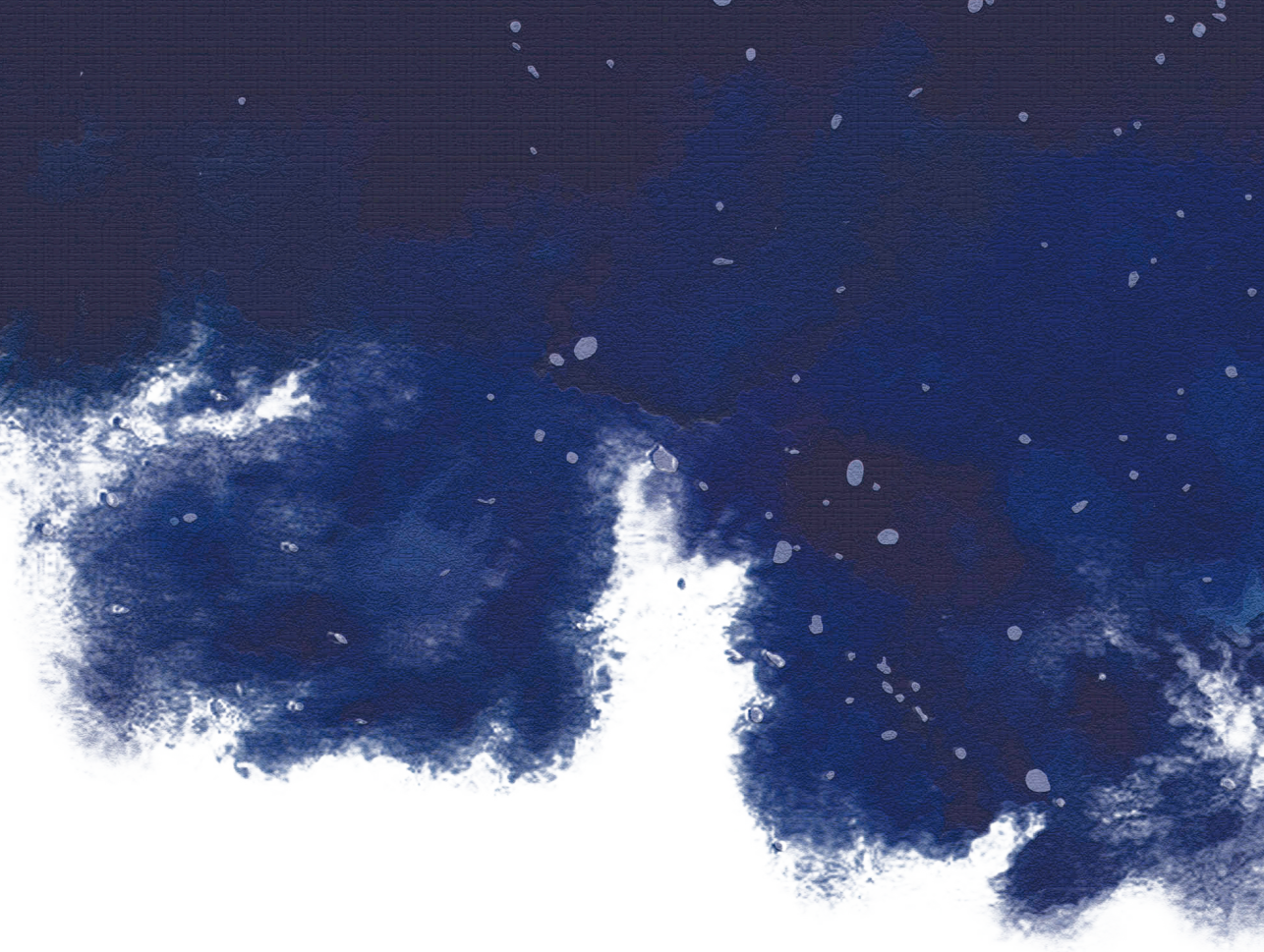
Despite these improvements many infants still suffer from the complications of prematurity every year. With this thesis, I hope to contribute to a better life for these infants by researching how the devices for automated oxygen control work, how well they work to balance the oxygen saturation in the blood and, most importantly, what the health outcomes are of the preterm infants treated with these devices.





Part I

General introduction



Chapter 1

General introduction and outline of this thesis

Supplemental oxygen for preterm infants is paramount against respiratory insufficiency related to preterm birth, but is a double-edged sword. On the one hand, supplemental oxygen helps prevent hypoxia which can lead to morbidity and mortality. But, inappropriate administration of oxygen can lead to hyperoxia, which is related to morbidities such as bronchopulmonary dysplasia, retinopathy of prematurity and neurodevelopmental impairment. Oxygen must therefore be carefully titrated within a safe range, but this is a difficult task. Automated titration of the administered oxygen by a machine – an automated oxygen controller – can help reduce hypoxia and hyperoxia, and improve the time within this safe, or target, range. However, which commercially available automated oxygen controller is most effective is unknown, as is the effect of using an automated oxygen controller on clinical and long-term outcome. This thesis provides an overview of outcomes after using two different automated oxygen controllers employing different titration strategies.

Supplemental oxygen and effects on morbidity

Supplemental oxygen is one of the most common therapies for preterm infants on respiratory support. Oxygen is fundamental for generating intracellular energy and is therefore essential to human life. A deficit of oxygen in the blood, or hypoxaemia, is common in preterm infants due to the immaturity of their lungs and respiratory centre, and can lead to oxygen shortage in the mitochondria which will eventually lead to cell death.[1] Oxygen supplementation is therefore used to avert cell death and subsequent effects of hypoxaemia on the central nervous system, lungs, vasculature and other organs. As development of the respiratory system occurs until after term age,[2] supplemental oxygen for preterm infants is often given for long periods of time. However, as with any drug, too much of it can lead to toxicity.

The higher oxygen tension present in the extra-uterine atmosphere can harm a preterm infants' organs, even without supplemental oxygen. The immaturity of a preterm infants' anti-oxidant system renders them vulnerable to free radicals, also known as reactive oxygen and nitrogen intermediates, formed under the influence of excess oxygen in the blood. These free radicals cause membrane disruption and activate inflammatory pathways through lipid peroxidation.[3] Indeed, infants developing a chronic lung condition called bronchopulmonary dysplasia were found to have elevated lipid peroxidation products.[4] Causal evidence on the effect of hyperoxia is scarce for preterm infants, but plenty of evidence from animal experiments exists. Neonatal mice demonstrated that exposure of the lung to hyperoxia decreased the alveolarization, changed the vasculature of the lung, and increased lung fibrosis.[5] Furthermore, intestinal histology of rat pups was markedly changed in pups continuously exposed to hyperoxia immediately after birth.[6] Finally, hyperoxia has been shown to alter cerebral blood flow in mice, induce neuronal apoptosis and inflammation.[7, 8]

The first morbidity attributed to hyperoxaemia in preterm infants was retinopathy of prematurity (ROP), a neurovascular disease leading to blindness.[9] The aetiology is not fully understood. Initially not enough retinal blood vessels are formed due to insufficient nutrition, insufficient growth factors, sepsis and a fluctuating oxygenation of the blood. The vasculogenesis of the retina is further reduced by iatrogenic hyperoxaemia inhibiting the formation of vascular endothelial growth factor. In this initial phase the retina is particularly susceptible to damage from intermittent hypoxia due to the scarce blood supply. After this phase uncontrolled blood vessel formation occurs under the influence of vascular endothelial growth factor eventually leading to retinal detachment.[10] Given this aetiology, it is not surprising both intermittent

hypoxia, hyperoxia and fluctuation in oxygenation all increase the rate of ROP in preterm infants.[11-13] Oxygen and other improvements in neonatal care throughout the last century have led to increased survival, but have also increased the incidence of retinopathy of prematurity.[14] Globally for the year 2010, it was estimated that ROP led to 20,000 blind infants, and left another 12,300 visually impaired.[15]

Bronchopulmonary dysplasia (BPD), a chronic disease of the lungs, is a major cause of respiratory illness in preterm infants leading to significant morbidity and mortality after discharge from the neonatal intensive care unit (NICU). The aetiology is multifactorial and involves disruption of the later phases of lung development and injury to the lung. Specifically for oxygen toxicity, high concentrations of free radicals are thought to cause chronic inflammation to the lung.[16] This chronic inflammation in turn leads to changes in lung tissue: decreased alveolarization leading to less surface area for gas exchange; vascular remodelling leading to an increase in pulmonary resistance which in turn may lead to pulmonary hypertension;[17] and changed lung elasticity.[18] The incidence of BPD differs depending on the definition applied. When defined as supplemental oxygen requirement at 36 weeks postmenstrual age the overall incidence was estimated at 42% of infants born between 22-28 weeks gestational age, where a higher gestational age at birth reduced the change of having BPD.[19]

Titration of supplemental oxygen

Mindful of the effects of supplemental oxygen on morbidity, its level must be carefully balanced within safe limits. Continuous monitoring using pulse oximetry (SpO_2, the percentage of peripheral oxyhaemoglobin over total haemoglobin) is currently the most appropriate tool to guide the fraction of inspiratory oxygen (FiO_2) delivered to the patient. In contrast to repeated arterial blood sampling, SpO_2 is non-invasive and continuous. The ideal range for SpO_2 in a given subject has been the subject of considerable debate,[20] and remains unsolved to date. The accepted target in preterm infants has recently undergone refinement as a result of a series of randomised controlled trials comparing two SpO_2 target ranges (SpO_2 85-89% vs 91-95%).[21-23] These trials once again highlighted the impact of hypoxaemia and hyperoxaemia on preterm infants, with the lower target range associated with an increase in mortality and necrotizing enterocolitis, and higher target range with ROP.

The need for supplemental oxygen is more common and prolonged in very preterm infants. These infants often present with respiratory instability and fluctuation in oxygenation. Whilst the need to target an SpO_2 range is widely accepted, data from

cohort studies[24-26] and randomised controlled trials[27-29] point to the difficulty of SpO_2 targeting, with most studies reporting SpO_2 values to be within the target range less than half of the time. Although bedside staff frequently adjusts FiO_2 to maintain SpO_2 within the target range prescribed by the clinician, their workload limits time availability and makes continuous tailoring of FiO_2 to the infant's needs difficult. This is further complicated by the neonatal oxygenation physiology being unpredictable and non-linear, with a long time delay between an adjustment in FiO_2 and a stable SpO_2.[30] Even in the presence of a dedicated respiratory therapist to titrate FiO_2, time within target range was only 66%.[31] In premature infants with frequent fluctuations in oxygenation, clinical personnel usually respond to the occurrence of alarms in the pulse oximeter triggered by episodes of hypoxaemia with a manual increase in FiO_2. When these episodes resolve and SpO_2 returns to the desired range, FiO_2 should be reset to the basal level. However, under routine clinical conditions, staff limitations can result in inconsistencies in response and timing. As a consequence, premature infants are often exposed to periods of insufficient oxygenation, unnecessary oxygen exposure and hyperoxaemia.[32] Also, in these infants, the FiO_2 set by the bedside staff often exceeds the level required to maintain an acceptable range of SpO_2. This is done in an attempt to reduce the frequency of the hypoxemic episodes. However, this is not always effective and can increase the exposure to supplemental oxygen and hyperoxaemia.[33]

Considering the effect of target range deviations and the difficulty of targeting SpO_2, feedback-controlled adjustment of FiO_2 by a machine –an automated oxygen controller (AOC)– is a logical improvement on current practice. In essence, SpO_2 readings are continuously fed into a device holding a set of computational instructions (an algorithm), which then gives an output, an updated value for FiO_2. The effectiveness of automated control of inspired oxygen and its effects on the fluctuation of oxygenation during the care of premature infants may result in improved neurodevelopmental outcomes.[34] Randomised trials comparing automated FiO_2 systems with manual titration for short periods demonstrated an increase in the proportion of time spent with SpO_2 within target range varying between 8% and 24%.[35-43] Automated FiO_2 control also decreased the required nursing time in preterm infants with frequent severe desaturations.[36, 37, 44] Several automated oxygen control devices are commercially available and used in NICUs, but it is unknown whether these devices lead to different clinical or long-term outcome. Furthermore, it is unknown which of these controllers is most effective, as no comparisons have been made between the performance of different AOCs.

Aim and outline of this thesis

The general aim of this thesis was to evaluate the effects on outcome after automated oxygen control for preterm infants. This thesis aims to: describe currently available automated oxygen control algorithms and what to expect when they are used (**Part II**); compare effectiveness of automated oxygen control algorithms on oxygenation in the NICU (**Part III**); and investigate clinical and long-term outcome after using automated oxygen controllers (**Part IV**). This thesis comprises of observational studies and a randomised clinical trial.

Part II consists of **Chapter 1** in which an overview of approaches for algorithm design are described, after which the details on six commercially available oxygen control algorithms are set out. Per algorithm an outline follows on how the algorithm works, and what clinical effects were reported. In this narrative review we conclude that although all available controllers seem to improve time within target range and have a beneficial effect on the occurrence of hypoxia and hyperoxia, the most effective strategy is unknown, as available clinical studies were heterogenous.

Part III reports on the effects of automated oxygen control on oxygenation. The NICU of the LUMC was the first to implement automated oxygen titration as standard of care. As of August 2015, all infants requiring respiratory support with supplemental oxygen received automated oxygen titration by the $CLiO_2$ algorithm built into the AVEA ventilator (Vyaire, Yorba Linda, California, USA). In November 2018, all AVEA ventilators were replaced with SLE6000 ventilators (SLE Limited, South Croydon, UK), employing the OxyGenie algorithm for automated oxygen control. This led to a unique setting in which caregivers were competent to handle both ventilators allowing for a comparative, randomised, crossover trial. In **Chapter 2** the results of this randomised crossover trial are presented. The effectiveness of an automated oxygen controller may vary depending on the postnatal age of the infant. The condition of the lungs and frequency of apnoea can change markedly during the course of admission. With the exception of one study, all studies report on achieved target range times while using automated oxygen control in an experimental setting and for a short period of time (maximum 24 hours). In **Chapter 3** the achieved times within certain SpO_2 ranges from birth to 32 weeks of postmenstrual age are compared when either using the $CLiO_2$ or the OxyGenie controller as standard of care. Contemporary patient data management systems for intensive care may be limited to storing vital parameters once per minute, which is not sufficient to register all variation in vital parameters such as SpO_2 and FiO_2. In **Chapter 4** we investigate whether one-per-minute data can be used to perform

retrospective comparisons of descriptive statistics.

In **Part IV** we focus on clinical outcomes after using automated oxygen controllers as standard of care. Over 300 very preterm infants have received $CLiO_2$ automated oxygen titration as standard of care. In **Chapter 5** we compare the neonatal outcomes of these infants with infants born in the years before implementation of automated oxygen control. All preterm infants born under 30 weeks of gestation are invited to the outpatient clinic for standard follow-up at two years. In **Chapter 6** we compare neurodevelopmental outcome of the same infants at a corrected age of two years. We conclude **Part IV** in **Chapter 7** by comparing outcomes of infants treated with the $CLiO_2$ algorithm with infants that received automated oxygen titration by the OxyGenie algorithm.

Finally, in **Part V** of this thesis, the main findings of these studies are discussed and future perspectives are considered. The thesis is concluded with a summary of the studies, provided in English and Dutch.

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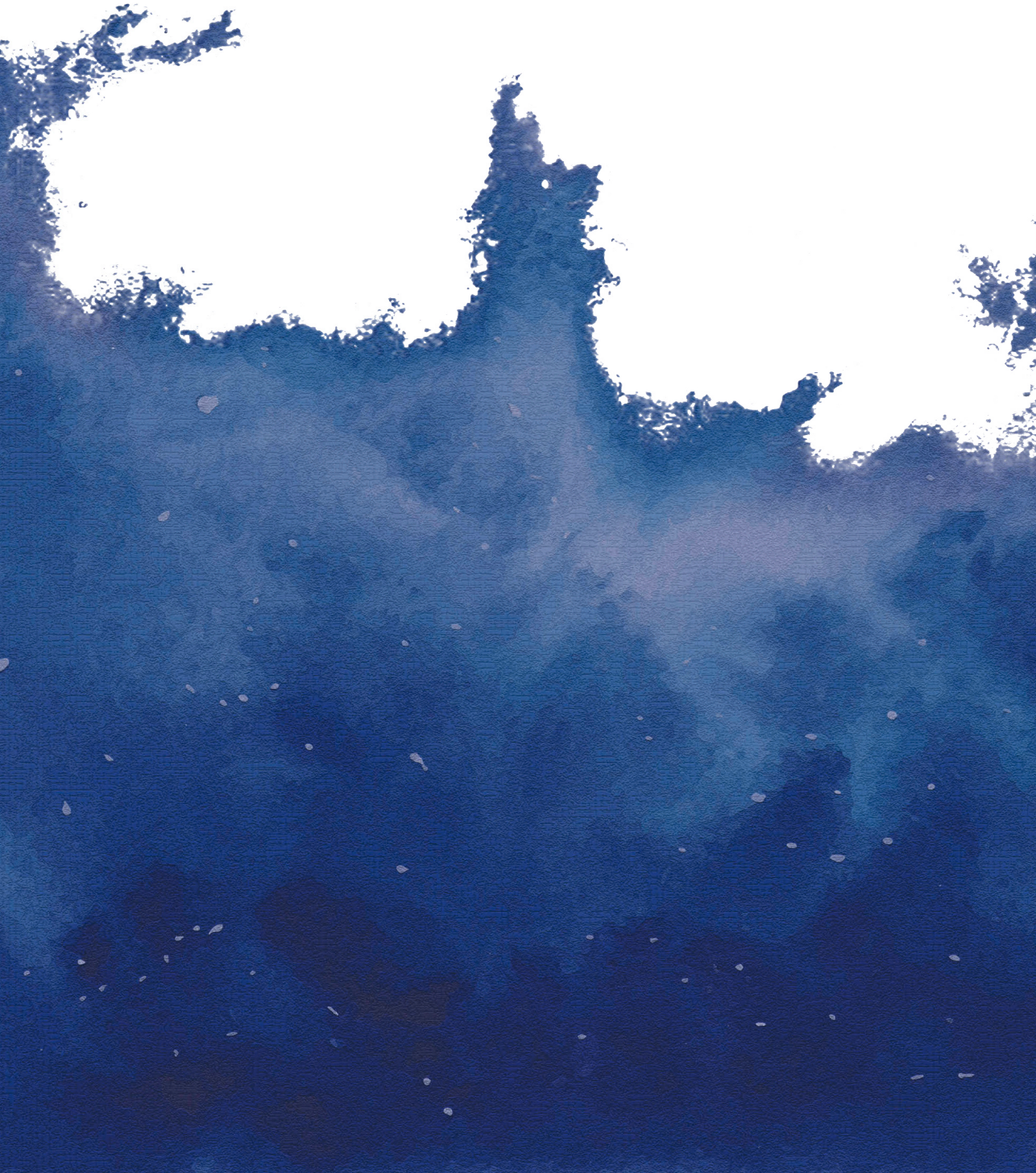
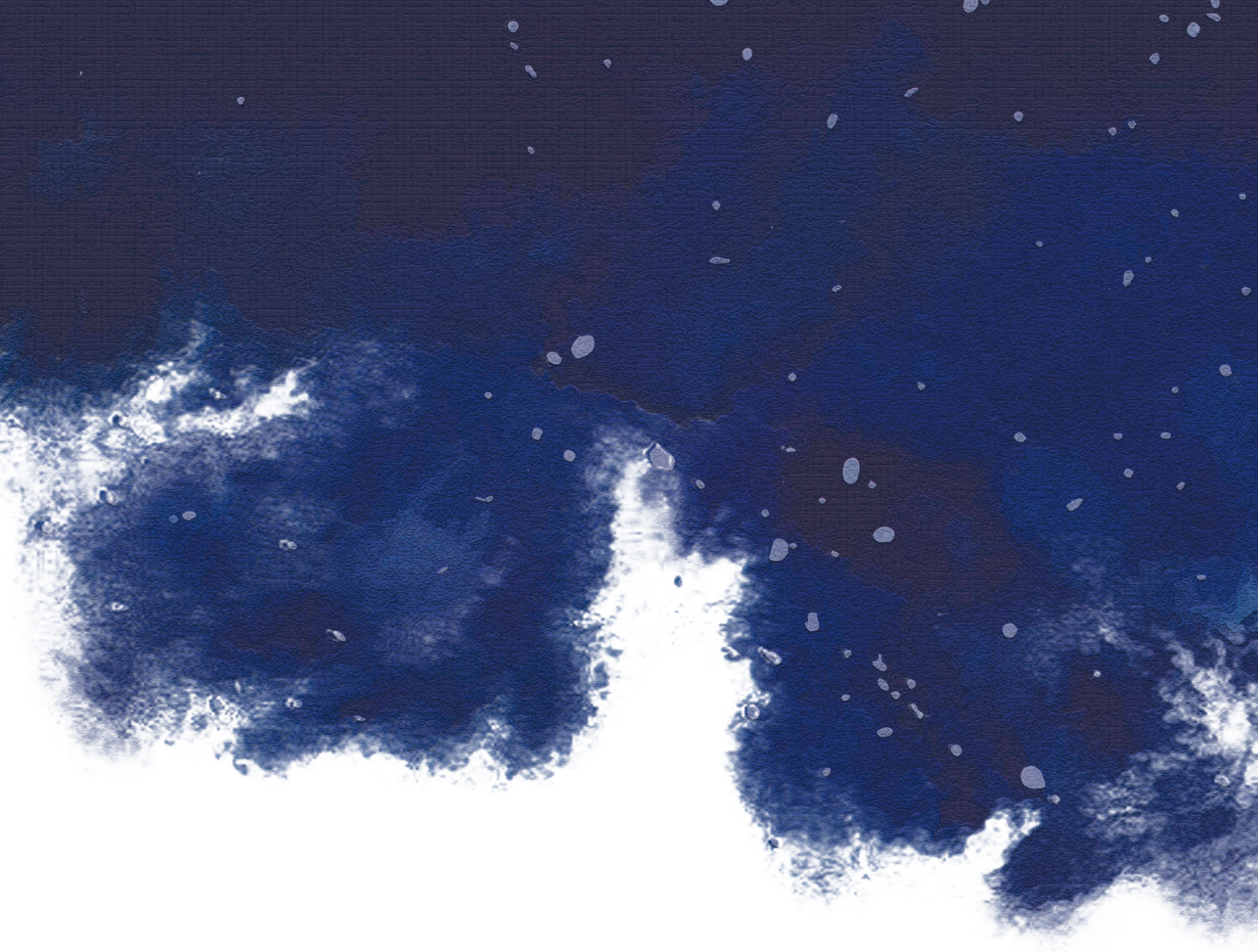


Part II

Currently available automated oxygen control algorithms



What is known about this topic

- All contemporary automated oxygen control algorithms increase time spent within oxygen saturation target range.
- The automated oxygen control algorithms are all different in design and function.

What this study adds

- The basal oxygen requirement, the amount and magnitude of interventions by an automated oxygen controller can possibly be used as an indicator of clinical deterioration.
- Studies involving automated oxygen controllers are heterogenous and cannot be compared.
- A head-to-head comparison of algorithms is required to understand how to best utilise this technology.

Chapter 2

Automated oxygen control in preterm infants, how does it work and what to expect; a narrative review

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Abstract

Background: Automated oxygen control systems are finding their way into contemporary ventilators for preterm infants, each with its own algorithm, strategy and effect.

Objective: To provide guidance to clinicians seeking to comprehend automated oxygen control and possibly introduce this technology in their practice.

Method: A narrative review of the commercially available devices using different algorithms incorporating rule-based, proportional-integral-derivative and adaptive concepts are described and explained. An overview of how they work and, if available, the clinical effect is given.

Results: All algorithms have shown a beneficial effect on the proportion of time that oxygen saturation is within target range, and a decrease in hyperoxia and severe hypoxia. Automated oxygen control may also reduce the workload for bedside staff. There is concern that such devices could mask clinical deterioration, however this has not been reported to date.

Conclusions: So far, trials involving different algorithms are heterogenous in design and no head-to-head comparisons have been made, making it difficult to differentiate which algorithm is most effective and what clinicians can expect from algorithms under certain conditions.

Keywords: Hypoxemia; hyperoxia; closed-loop; algorithm; neonate

Introduction

Preterm infants often receive respiratory support, including supplemental oxygen therapy for a prolonged period of time during their first hospitalisation. Provision of supplemental oxygen must aim to keep oxygen saturation within a normoxic range, thereby minimising occurrence of hypoxia and hyperoxia, both of which are associated with organ injury.[1-6] But titrating oxygen therapy manually within the narrow therapeutic range is a difficult task to perform.[7, 8]

Over the last four decades, a number of algorithms have been developed to facilitate automatic titration of oxygen for preterm infants. All the contemporary algorithms use oxygen saturation as measured by pulse oximetry (SpO_2) as their input, but each has a different design in processing the input and computing an adjustment in the fraction of inspired oxygen (FiO_2). An important prerequisite to successfully applying automated oxygen control (AOC) in clinical practice will be for clinicians to understand how the control algorithms operate and what effect differences in design have.[9-21]

Six oxygen control algorithms are currently embedded in commercially available neonatal ventilators. This narrative review will consider the different approaches to algorithm design, explain how the contemporary algorithms operate and, based on available data, discuss their clinical effects in preterm infants. For this, we performed a search on PubMed, Embase, Web of Science, Cochrane and Emcare for (pre)clinical studies and reviews comparing AOC with manual titration of oxygen in preterm infants receiving respiratory support and oxygen therapy. A cross-check for search completeness was made using the reference list of primary resources, aiming to identify any studies not located in the initial search. Additionally, patent documents and device operating manuals were studied where available.

Algorithm design

Different approaches have been used for designing AOC algorithms. Generally, a combination of three methods is used: rule-based, proportional-integral-derivative (PID) and adaptive. Central to each of these approaches is the derivation of an SpO_2 error, the deviation from the desired value, i.e. the positive or negative difference between the current measured SpO_2 and the middle or upper/lower limit of the target range (TR).

Rule-based

A rule-based algorithm uses a set of rules to decide on an FiO_2 adjustment much like a decision tree. The rules are often derived from expert knowledge (for example: "in case of mild hyperoxia, lower FiO_2 by 0.02"; Figure 1). Incorporating clinical experience makes this type of algorithm quick to develop and intuitive for clinicians. By combining a large set of rules an attempt is made to cover all possible scenarios. However, there is great heterogeneity in response to a change in FiO_2[22, 23], making it virtually impossible to have an exhaustive set of rules for each circumstance.

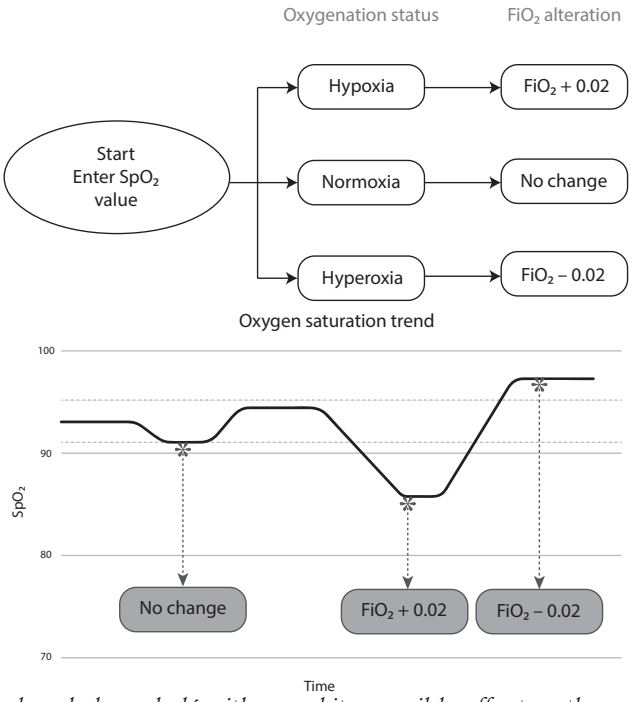

Figure 1: *A simple rule-based algorithm and its possible effect on the oxygen saturation trend.*

Proportional-integral-derivative

Proportional-integral-derivative (PID) control is a longstanding mathematical approach widely used in industry (e.g. automotive cruise-control, thermostats). The proportional term reflects the current error; the integral term reflects the sum of previous errors; and the derivative term accounts for the direction the SpO_2 error is heading (Figure 2). The computation includes a unique coefficient for each of the P, I and D terms, thus balancing their relative influence. The sum of the P, I and D terms – which may be opposite in sign – determines the magnitude of the change in FiO_2.

Although PID control is more abstract and its function more difficult to understand, it makes use of the breadth of available oxygenation information. However, the choice of PID coefficients is vital, as inappropriate coefficients could lead to major fluctuations or oscillations in oxygen saturation and result in oxygen control that is worse than manual titration.[21]

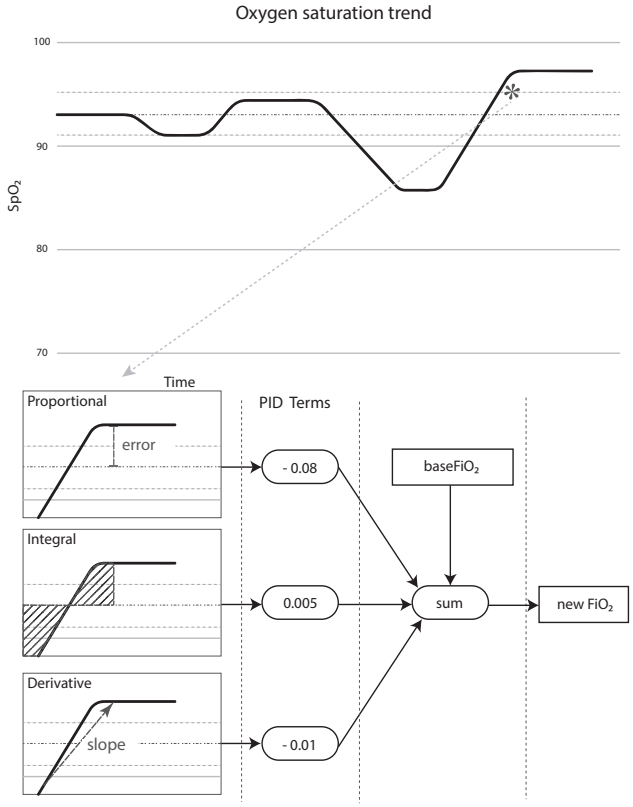

Figure 2: *The three components of the PID algorithm hidden in the oxygen saturation trend.*

Adaptive

Adaptive control is an element of an algorithm whereby the behaviour of the controller changes while it is in use. The aim is to tailor the controller to the oxygenation system of the baby by including patient-specific parameters as input to the algorithm. The most apparent example is to change the magnitude of adjustments in response to a change in the severity of lung disease (estimated by baseline oxygen requirements). The basal oxygen requirement (*baseFiO$_2$*) of a preterm infant almost always changes over time, as will the response of SpO_2 to an FiO_2 adjustment. Adding *baseFiO$_2$* to the algorithm will lead to an adaptation to the degree of lung disease. An example of the behaviour of such an algorithm is given in Figure 3.

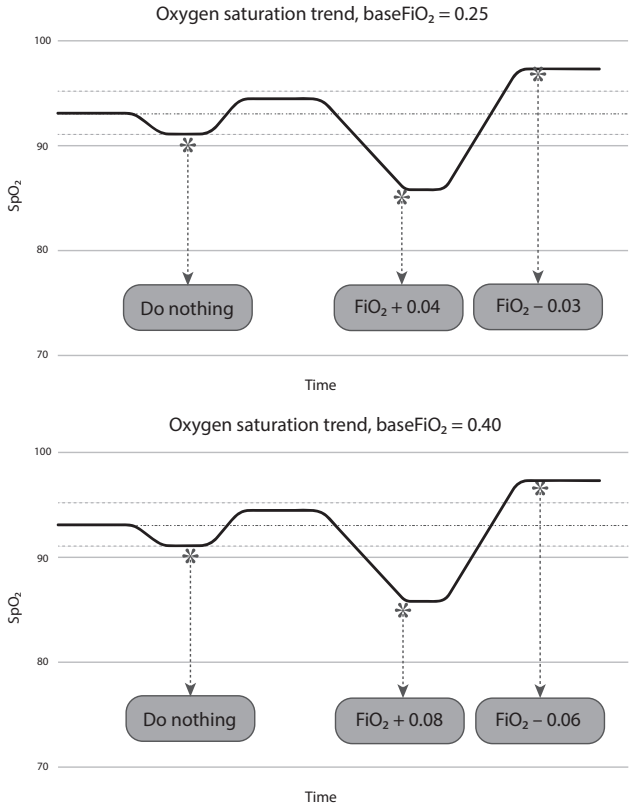

Figure 3: *The possible effect and responses of an adaptive algorithm in two cases with a different baseFiO$_2$*

Commercially available algorithms

Details of six commercially available oxygen control algorithms are set out below, with a precis of the known function of the algorithm followed by a section on clinical effect where data are available.

Closed-Loop Automatic oxygen Control[17]

How it works

The Closed-Loop Automatic oxygen Control (CLAC) is a rule-based algorithm commercially available in the Leoni ventilator (Löwenstein medical, Rheinland-Pfalz, Germany). The algorithm deduces two parameters from the SpO_2 signal once per second: the *state* and *trend* parameters.

The *state* parameter is calculated by taking SpO_2 values of the last three minutes, filtering out values far out-of-range, and forming a so-called 'spread' from the remaining information: a regression line combined with an *adapted standard error*. Using the middle of this spread the algorithm labels the *state* 'substantially above', 'above', 'normal range', 'below', or 'substantially below' target range, in response to which FiO_2 will be adjusted in the range of -0.02 to +0.05 (-0.02, -0.01, +0.01, +0.02 and +0.05).

The *trend* parameter – the slope of SpO_2 trend in the last 60 seconds – can postpone an adjustment, dependent on an increasing, stable or decreasing trend. This to account for when the SpO_2 is outside the TR but normalising.[17, 24, 25] After making an adjustment the algorithm pauses for 180 seconds to allow the baby to reach a new steady oxygenation state. Recently, the alternative to pause for 30 seconds was added.[26] The system can pause for safety (reasons are: *adapted standard error* above a cut-off value; missing or invalid oximetry input; acute hypoxia (SpO_2 < 80%) for more than 4 seconds) during which bedside staff is alerted and can intervene if necessary.

Clinical effect

Three randomised crossover trials reported the use of the CLAC algorithm (Table 1). While infants spent more time within TR during AOC (90.5% vs 81.7%, P = 0.01) during the first study, the short study span probably led to the high proportion of time in TR in both groups. The reduction in manual adjustments (89%) is however striking and could be beneficial in reducing workload for bedside caregivers.[17] In a subsequent multicentre study[27] infants on (non)invasive ventilation were studied

Table 1: Studies on automated oxygen control

Oxygen control algorithm	Author (year)	Study duration	SpO_2 TR	Gestational age in weeks	Age at entry study	n
$CLAC_{slow}$	Urschitz (2004)[17]	3x90 min	87%-96%	25.5 (24-33)	20.5 days (4 - 78)	12
	Hallenberger (2014)[27]	2x24 hrs	90%-95% 80%-92% 83%-93% 85%-94%	26.4 (23.0-35.3)	29.9 weeks (26.0 – 35.6)	34
$CLAC_{fast}$	Schwarz (2019)[26]	3x8 hrs	90%-95% 85%-93% 85%-96%	26.4 (24.0-32.7)	24 days ± 10	19
$CLiO_2$	Claure (2001)[18]	2x2 hrs	88%-96%	25 ±1.6	26 days ± 11	14
	Claure (2009)[28]	2x4 hrs	88%-95%	24.9 ±1.4	33 days ± 15	16
	Claure (2011)[29]	2x24 hrs	87%-93%	25 (24-27)	27 days [17-36]	32
	Waitz (2015)[30]	2x24 hrs	88%-96%	25 (23-28)	34 days [19-75]	15
	Van Kaam (2015) [31]	2x24 hrs	91%-95% (1) 89%-93% (2)	26 (25-28)	18 days [10-29]	80
	Lal (2015)[32]	2x12 hrs	90%-95%	25 (24-27)	16 days [9-27]	27
	Van Zanten (2017)[33]	3-28 days	90%-95%	27+6 (26+3-28+4) 27+3 (26+0-28+2)	n/a	42
PRICO ‡	n/a	n/a	n/a	n/a	n/a	n/a
SPO_2C	Gajdos (2018)[34]	2x24 hrs	88%-96%	25.3 (23-26)	31.5 days [12 – 62]	12
$IntellO_2$	Reynolds (2018)[35]	2x24 hrs	93% (A) 90%-95% (M)	26 (24-27)	29 days [18-53]	30
VDL1.0	Plottier (2017)[36]	3x4 hrs	91%-95% (A) 90%-94% (M)	27.5 [26-30]	8 days [1.8-34]	20

*Mean ±SD or median[IQR] or (range). TR, target range; n/a, not applicable/available; RMC, routine manual control; NCPAP, nasal continuous airway pressure; MV, mechanical ventilation. P-values are two sides unless indicated otherwise. *one sided superiority test; †one sided non-inferiority test. ‡For PRICO no clinical data are available to date.*

Number on mode of support	Control group	Proportion of time spent in TR (%) Control	AOC	p-value
12 *nCPAP*	1) RMC 2) Fully dedicated operator	1) 82 (39-100) 2) 91(41-99)	91 (59 - 99)	0.01
23 *nCPAP* 11 *MV*	RMC	61 ±15	72 ±14	<0.001
18 *nCPAP* 1 *MV*	1) RMC 2) CLAC slow	1) 58 ±11 2) 65 ±11	68 ±11	1) 0.0001 * 2) 0.0005 †
14 *MV*	Fully dedicated operator	66 ±14	75 ±13	<0.05
16 *MV*	RMC	42 ±9	58 ±10	<0.001
32 *MV*	RMC	32 ±13	40 ±14	<0.001
14 *nCPAP/NIPPV* 1 *MV*	RMC	69 ±8.2	76 ±9.2	<0.01
50 *nCPAP* 30 *MV*	RMC	(1) 58 ±16 (2) 54 ±16	(1) 62 ±17 (2) 62 ±17	<0.05 <0.001
27 *MV*	RMC	60 (49-73)	73 (59-83)	0.031
nCPAP or *MV*	RMC	48 (42-56)	62 (49-72)	<0.01
n/a	n/a	n/a	n/a	n/a
10 *nCPAP/NIPPV* 2 *MV*	RMC	69 ± 7.7	78 ± 7.1	0.0012
30 *HFNC*	RMC	49 (40-57)	80 (70-87)	<0.0001
7 *HFNC* 13 *nCPAP*	RMC	56 (48-63)	81 (76-90)	<0.0001

for 2x24 hours, and a similar difference in time in TR was seen (71.2% vs. 61.4%, P < 0.001). Different TRs (range 80-95%) were used between participating centres which make results potentially more generalisable but also harder to interpret, as a different target range will influence controller performance. Finally, the last study showed that the 30-second pause was superior to manual control and non-inferior to the 180-second pause, with similar increases in TR time.[26]

CLAC is not designed to treat acute SpO_2 deterioration; the algorithm will raise an alarm and cease operation if low SpO_2 values occur. Also, suspending action after an adjustment might be undesirable, as an algorithm could also use SpO_2 feedback to try to resolve hypoxia more swiftly and diminish subsequent overshoot.

Closed-loop Inspired Oxygen Control ($CLiO_2$)[18]

How it works

The first algorithm for AOC to be embedded in a neonatal ventilator was $CLiO_2$ available in the AVEA ventilator (Vyaire Medical, Mettawa, United States). This algorithm, a hybrid of rule-based and proportional-derivative control with an adaptive element, runs through a large set of instructions each second.[37]

The algorithm starts with SpO_2 validation, and determination of the status of oxygenation (normoxic, hyperoxic or hypoxic). After a change in oxygenation status for ≥ 3 seconds (to filter out short fluctuations), an initial FiO_2 adjustment is made, proportional to the magnitude of the error. For the $CLiO_2$ algorithm, the SpO_2 error is calculated in relation to the upper and lower limits of the TR in hyperoxia and hypoxia, respectively, rather than the mid-point. The timing and magnitude of further FiO_2 adjustments are then determined in relation to the SpO_2 error (via a proportional term), the SpO_2 trend (via a derivative term) and the *baseFiO*$_2$ (via an adaptive component). The FiO_2 increments will be amplified if SpO_2 is deviating further from the TR limits, and with progressively smaller increments as SpO_2 approaches the TR.

With the $CLiO_2$ algorithm, the adjustments in FiO_2 rarely lead to an FiO_2 below *baseFiO*$_2$; only long-lasting periods of mild hyperoxia will result in an FiO_2 below the base value. *BaseFiO*$_2$ is updated periodically after at least 5 minutes, using the last 300 FiO_2 values that meet specific conditions. The average of these values is limited to ±10% of the current *baseFiO*$_2$ and then again averaged with the current *baseFiO*$_2$.[37]

Clinical effect

$CLiO_2$ is the most researched algorithm in clinical setting.[18, 28-33] All seven studies reported a significant increase in time spent within TR, including a reduction of[28-30, 32, 33] or equal[18, 31] time spent above it (Table 1). Three studies demonstrated a small but significant increase of mild hypoxia.[28, 29, 33] But, in the largest multicentre trial[31] the gain in TR time was mainly attributed to less hypoxia, rather than hyperoxia. There was heterogeneity in sample size, study duration and modes of respiratory support in the studies. The TR upper and lower limits also varied, this being relevant for the calculation of SpO_2 error, thus influencing algorithm function. The $CLiO_2$ algorithm has thus been seen to be superior to manual oxygen titration in a range of situations, including when used for longer periods of time as shown by van Zanten et al.[33] In a recent meta-analysis[38] on AOC, the effect on SpO_2 targeting was somewhat diminished when only including the $CLiO_2$ studies compared to when all studies were included (8.9% vs 12.8% increase in time within TR).

In our experience[33], the $CLiO_2$ algorithm performs well in both stable and unstable preterm infants. However, there appears to be room for improvement, especially regarding the rapidity of FiO_2 reduction in the event of clinical improvement, for example after surfactant therapy. The algorithm needs substantial time to adjust *baseFiO*$_2$ downwards in this circumstance, which poses a problem as most FiO_2 adjustments are limited to be ≥ *baseFiO*$_2$. In addition, in unstable babies with frequent hypoxia the *baseFiO*$_2$ does not reflect the basal oxygen requirement. AOC with the $CLiO_2$ algorithm has been implemented in the NICU in Leiden University Medical Centre since mid-2015. A practical solution for the *baseFiO*$_2$ problem has been to reset the algorithm when needed, which adopts the clinician-set FiO_2 as *baseFiO*$_2$.

IntellO$_2$[35]

How it works

The IntellO$_2$ algorithm is a recent PID algorithm implemented in the Vapotherm Precision Flow device for delivering nasal high flow.[35] Details on the algorithm are limited. It is reported to be a modified version of an earlier algorithm described by Bhutani.[9] As with other algorithms, SpO_2 is measured by a built-in pulse-oximeter. If the SpO_2 is lost for two minutes or is degraded by more than 50% in the last four minutes, the algorithm reverts to the back-up FiO_2 value (the highest of a clinician-set back-up value or the median of the last three FiO_2 values).

Clinical effect

Reynolds et al. reported an increase of 31% more time within TR (80% during automated, 49% during manual; P < 0.0001) in 30 preterm infants (Table 1). This was accompanied by less time in hypoxia and hyperoxia, albeit with more hyperoxic episodes in the automated arm. These so-called overshoot episodes are common[39], and perhaps impossible to prevent.

Predictive Intelligent Control of Oxygenation[19]

How it works

PRICO (Predictive Intelligent Control of Oxygenation) is a rule-based algorithm originally designed for the delivery room. It is now available for NICU use in the Fabian ventilator (Acutronic, Hirzel, Switzerland). The algorithm uses the current SpO_2, its trend, and a prediction of what SpO_2 will become to make step-wise adjustments. Comparable to CLAC, each adjustment is followed by a pause of at least 30 seconds. The set FiO_2 is limited to an *adjustment range* which is specified by the caregiver. If the limits of this range are met, PRICO will alarm and pause until the issue is resolved.

Information on how exactly the algorithm operates is limited. Whilst in TR step-wise adjustments are limited to ±1%, whereas outside the TR adjustments vary from ±1-10%. Large, swift changes are recognised using the SpO_2 trend and are used to fine tune the magnitude of the FiO_2 adjustments. A prediction based on this trend is used to limit possible under/overshoots. Before an adjustment safety checks are performed (reliability of the connection, assessment of the correctness of parameters).[19, 40] There is currently not enough data available to give a complete appraisal of this algorithm.

Clinical effect

So far, for PRICO there is no clinical data available to date, feasibility has only been tested on preterm lambs while using volume guarantee ventilation.[19] The time spent within target range was significantly higher with AOC (93.2% vs 84.0%, P < 0.05). A 30 second lockout could potentially delay appropriate intervention against hypoxia and hyperoxia.

SPO_2C[34]

How it works

The SPO_2C algorithm was developed in Ulm, Germany and is commercially available

in the Sophie ventilator (Stephan GmbH, Gackenbach, Germany). Information on the workings of the algorithm is limited.[34] The control loop iterates every two seconds, conveniently using the SpO_2 measured by an existing bedside monitor. Separate PID controllers update the set FiO_2 and the *baseFiO*$_2$.

The primary controller adjusting set FiO_2 unconventionally uses variable PID coefficients which depend on the range in which SpO_2 falls and the speed and direction of the change. In an attempt to account for the shape of the oxygen-dissociation curve, the proportional term is exponentially weighted. The second PID loop updates the *baseFiO*$_2$ every 5 minutes by comparing recent values for set FiO_2 to the previous *baseFiO*$_2$.

Clinical effect

Although the data was only recently published[34] the algorithm was clinically tested in 2014 in a randomised crossover trial (Table 1). The algorithm proved superior to manual titration in twelve preterm infants on non-invasive respiratory support (manual titration: 68.5% within TR; SPO_2C controller: 77.8%; $p<0.001$).

VDL 1.1[21]

How it works

The VDL 1.1 algorithm, an adaptive PID algorithm, is available as the Oxygenie option on the SLE6000 ventilator (SLE, Croydon, United Kingdom). Like other algorithms it uses the baseline oxygen requirement, known as *reference FiO*$_2$, which is calculated every 30 minutes using the preceding 60 minutes of data. Combining this value and the P, I and D terms the algorithm calculates a new value for the set FiO_2 each second, rounded to 0.5%. Measurements with low signal IQ are labelled as missing, in which case the last set value for FiO_2 is used. The algorithm does not use a lock-out period.

To account for known pathophysiological idiosyncrasies, as well as the limitations of pulse oximeters, each of the PID terms is modified in different ways. The proportional term is adapted to the degree of lung dysfunction by multiplying with 0.5-1, corresponding to a *reference FiO*$_2$ in the range of 21%-40%. Furthermore, the error in the proportional term is attenuated whilst SpO_2 is in TR to minimise adjustments during good control.[21, 36, 41] Finally, to correct for the increasing imprecision of pulse oximetry at SpO_2 values below 80%[42], the negative error is limited to 13%.

During protracted hypoxia, the integrand (sum of past errors) will rapidly increase in

magnitude, pushing FiO_2 up. To prevent inappropriately high oxygen administration, the set FiO_2 is capped to 40% above the *reference FiO_2*. The algorithm adjusts for the non-linearity of the oxygen-dissociation curve by applying an error multiplier to positive errors while the integral term remains positive. This rapidly decreases the integral term towards zero, leading to FiO_2 reduction and hopefully eliminating overshoot. Whilst in 21% oxygen, values of SpO_2 above TR are not considered to represent hyperoxia and the integral term is therefore not altered.

Lastly, the handling of the derivative term is modified during hyperoxia. A negative SpO_2 slope is nullified if all last five SpO_2 values are above the TR midpoint. This means that during hyperoxia a negative slope will not drive up the FiO_2.[21, 36, 41]

Clinical effect

A forerunner algorithm, VDL 1.0 was first tested and refined in a (validated) computer model for the respiratory system of a preterm infant using paired values for ventilation-perfusion (V/Q) ratio and shunt (Q_s/Q_t) (based on 3788 hours of clinical data).[22] Consequently a study[36] involving 20 preterm infants on non-invasive respiratory support and supplemental oxygen was done, in which a 4-hour period of AOC was compared with manual control during flanking 4-hour periods (Table 1). Time spent within TR increased during AOC, whereas hypoxia with SpO_2 <80% and hyperoxia with SpO_2 >98% greatly reduced (0.7% (0.1%-1.3%) vs 0% (0%-0.17%); p=0.0006 and 0.46% (0.22%-1.4%) vs 0% (0%-0.12%); p=0.0010, respectively).[36]

Discussion

Although all contemporary oxygen controlling algorithms appear to increase time spent within TR, the most effective strategy is currently unknown. Comparing these algorithms in the available studies is hindered by variation in TR, pulse oximeter settings, ventilator mechanics, patient populations, modes of respiratory support and aims between studies. A direct head-to-head comparison of algorithms could be performed in infants using a cross-over design, but changes in respiratory condition would likely preclude testing of more than two algorithms at a time. Ultimately the most meaningful and informative comparison of all algorithms may therefore be achieved by bench-top testing of the algorithms embedded in their different ventilators using *in silico* patient simulations.

Titration of FiO_2 is challenging for caregivers, especially during hypoxic and bradycardic events related to apnoea of prematurity.[39] In addition to better TR adherence, Claure et al. demonstrated that AOC leads to a significant reduction in

workload when most adjustments are performed automatically, leaving more time for other patient-related care.[29]

There might be a trade-off in the rapidity of response of AOC systems. An algorithm making swift changes will result in quick resolution of hyperoxic overshoot, a commonly observed problem during recovery from hypoxia both with manual and automated control.[39] However such an algorithm will tend to produce a lower mean SpO_2 on the steeper part of the oxygen-dissociation curve, potentially leading to more instability in SpO_2.[43] Smaller alterations would then have a bigger impact on SpO_2 resulting in a less stable oxygen saturation. Conversely, an algorithm making slow changes could prolong both hypoxic and hyperoxic episodes unnecessarily.

A proxy for PaO_2, oxygen saturation via pulse oximetry (i.e. SpO_2), is used for continuous non-invasive monitoring of oxygenation, but is limited in accuracy.[42, 44, 45] Unfortunately for now no adequate alternatives to pulse oximetry exist. The FiO_2-SpO_2 relationship shows substantial intra-subject variability in the change in SpO_2 following an adjustment in FiO_2.[22] Many factors will influence the SpO_2 response, including for example, the changes in the oxygen-dissociation relationship during transition from foetal to adult haemoglobin. This shift will be quite pronounced in preterm infants who receive transfusions of adult blood.

A potential reason to apply lock-out periods or filtering out SpO_2 values far out of range could be to prevent inappropriate FiO_2 adjustments based on short-term fluctuations, not reflecting the actual oxygenation state. Rather than using these techniques and risking unnecessary delay, focus should lie on preventing erroneous values by developing new or improved methods of measuring oxygenation. Algorithms could benefit from multiple input parameters to better assess oxygenation and overall condition of the premature infant, as pulse oximeters become more inaccurate in critically ill patients.[42] Essential for this will be easy linking of bedside devices (e.g. patient monitors, ventilators, electronic patient records) from different manufacturers, an area in which improvements should be made.

Modern techniques could be used to further improve AOC for preterm infants.[46] For example, a prediction model involving artificial intelligence strategies such as deep learning could result in earlier mitigation or even prevention of hypoxia and hyperoxia. Another example is an algorithm evaluating its own performance. By continuous assessment of the effect of adjustments in FiO_2 during operation, even better adaptivity could be achieved. Additionally, the risk for retinopathy of prematurity may be decreased if the algorithm would take gestation at birth and postnatal age into account and thus determine a vulnerability score for retinopathy and an appropriate

strategy for oxygen titration. It is possible that some of these improvements have already been included in contemporary algorithms, but unfortunately details on the exact operation of most algorithms are lacking in literature. It should be noted that extra input also gives a potential source of error.

Although AOC is more effective in keeping SpO_2 in TR when compared to manual control, the effect on clinical outcome is currently unknown. Studies are needed using a large sample size where continuous AOC is used for a longer period during NICU admission. Currently the FiO_2-C study is aiming to provide such information by recruiting infants < 28 weeks of gestation, with all available control algorithms allowed to be used.[47]. All studies of AOC to date report an increase in time spent in TR, with less hyperoxia and severe hypoxia, both in frequency and duration. Also, there is an abundant evidence underlining the deleterious effect of hypoxia and hyperoxia[3-5, 48-51]. It is therefore reasonable to expect that these devices will change outcomes. Recent trials comparing a low versus a high oxygen saturation target once again emphasised the importance of which oxygen saturation to target.[52]

The masking of clinical deterioration is an often-mentioned concern of AOC, which could lead to later detection than when nurses handle oxygen manually. However, this concern can be countered by alarming clinicians when the baseline oxygen requirement is increased above a certain threshold. Since the study by van Zanten et al.[33], implementation of the $CLiO_2$-algorithm as part of standard care in the NICU of Leiden has been successful. Three years after implementation caregivers are experienced in using and interpreting the handling of the controller. *BaseFiO_2* and the amount and magnitude of interventions performed by AOC are assessed regularly, now providing us with a novel indicator of clinical deterioration. Therefore, to utilise the full potential and to safely apply AOC, adequate training should be a prerequisite.

Conclusion

In summary, the field of automated oxygen control is evolving and the technology unquestionably holds promise. Automated oxygen control increases time spent within SpO_2 target range, decreases hyperoxia and severe hypoxia and is likely to reduce workload. Several solutions are commercially available, each of which has its own strategy. However, there are many unknown factors in the response of premature infants to each algorithm. Studies using the algorithms are heterogeneous and meaningful comparative data are lacking. Evidence is needed on how different controllers perform under certain circumstances, so clinicians know what to expect. A head-to-head comparison of algorithms is required under uniform conditions so that clinicians can fully understand how to apply this technology as part of the vital respiratory care provided to preterm infants.

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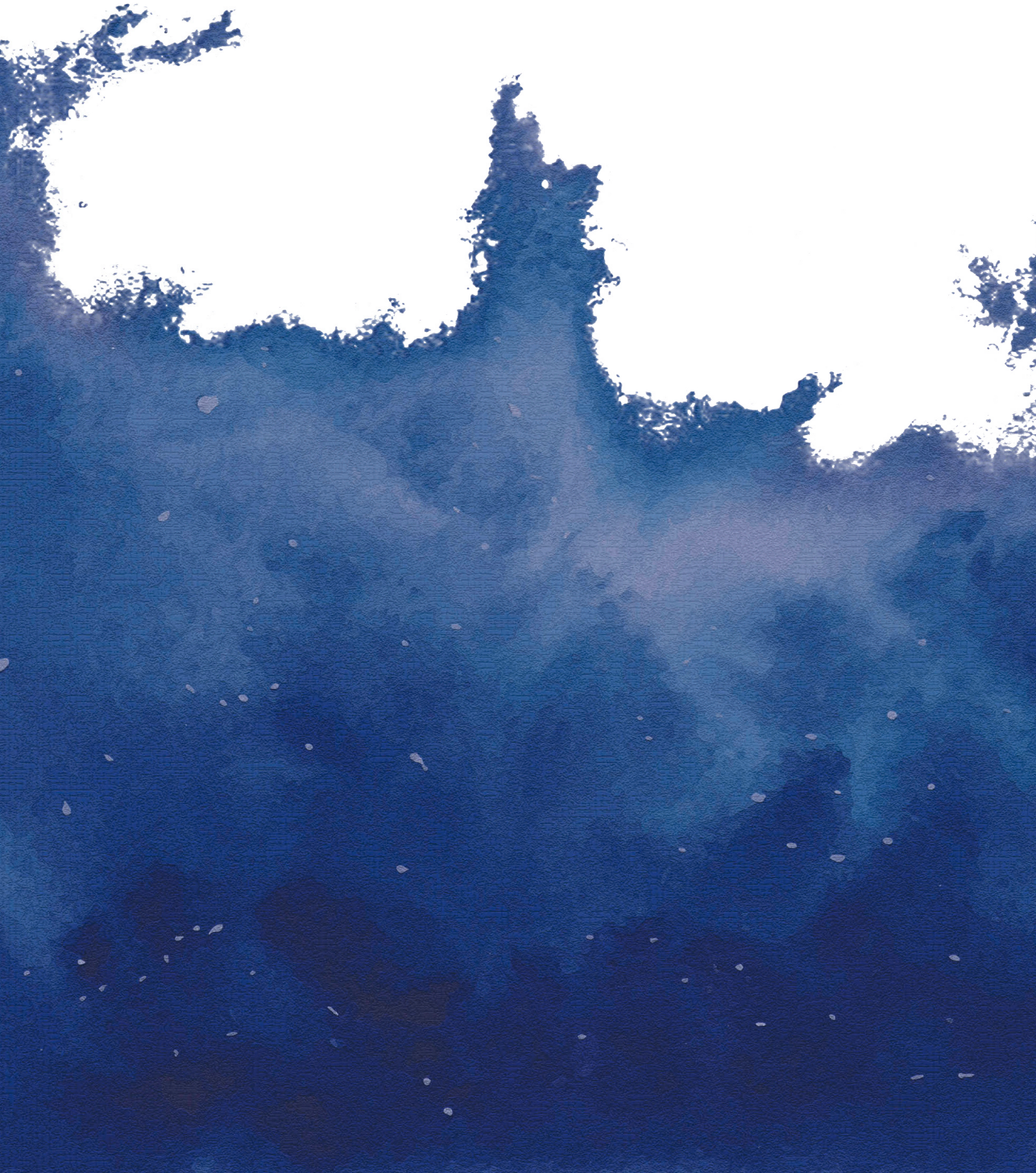

Part III

Effectivity of automated oxygen control algorithms on oxygenation of preterm infants in the NICU

What is known about this topic

- Automated oxygen controllers, including the ones utilised in this study, increase time spent within the oxygen saturation target range compared with manual control.
- Hypoxaemia and hyperoxaemia have been linked to morbidity and mortality in preterm infants.

What this study adds

- The OxyGenie controller was more effective in keeping the oxygen saturation within SpO_2 target range than the $CLiO_2$ controller.
- With OxyGenie less time was spent above target range, fewer hypoxaemic and hyperoxaemic episodes occurred, albeit with a small increase in time below target range.
- Algorithm design influences how effective SpO_2 targeting will be.

Chapter 3

Comparison of two devices for automated oxygen control in preterm infants – a randomised cross-over trial

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Abstract

Objective To compare the effect of two different automated oxygen control devices on target range (TR) time and occurrence of hypoxaemic and hyperoxaemic episodes.

Design Randomised cross-over study.

Setting Tertiary level neonatal unit in the Netherlands

Patients Preterm infants (n=15) born between 24+0-29+6 days of gestation, receiving invasive or non-invasive respiratory support with oxygen saturation (SpO_2) TR of 91% - 95% . Median gestational age 26 weeks and 4 days (IQR 25 weeks 3 days-27 weeks 6 days) and post-natal age 19 (IQR 17-24) days.

Interventions Inspired oxygen concentration was titrated by the OxyGenie controller (SLE6000 ventilator) and the $CLiO_2$ controller (AVEA ventilator) for 24 hours each, in a random sequence, with the respiratory support mode kept constant.

Main outcome measures Time spent within set SpO_2 TR (91%-95% with supplemental oxygen, or 91%-100% without supplemental oxygen)

Results Time spent within the SpO_2 TR was higher during OxyGenie control (80.2 (72.6–82.4)% vs 68.5 (56.7–79.3)%, $p<0.005$). Less time was spent above TR while in supplemental oxygen (6.3 (5.1-9.9)% vs 15.9 (11.5-30.7)%, $p<0.005$) but more time spent below TR during OxyGenie control (14.7 (11.8-17.2%) vs 9.3(8.2-12.6)%, $p<0.05$). There was no significant difference in time with $SpO_2<80\%$ (0.5 (0.1-1.0)% vs 0.2 (0.1-0.4)%, $p=0.061$). Long-lasting SpO_2 deviations occurred less frequently during OxyGenie control.

Conclusions The OxyGenie control algorithm was more effective in keeping the oxygen saturation within target range and preventing hyperoxaemia, and equally effective in preventing hypoxaemia ($SpO_2<80\%$), albeit at the cost of a small increase in mild hypoxaemia.

Keywords: Hypoxemia; hyperoxia; closed-loop; algorithm; neonate

Introduction

Oxygen therapy for preterm infants with respiratory insufficiency aims to prevent or moderate the effects of hypoxaemia on the central nervous system, lungs, and other organs. Conversely, the immaturity of the premature infant's lungs, eyes and antioxidant system renders them vulnerable to exposure to supplemental oxygen, and hyperoxaemia has been linked to the development of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP).[1, 2]

Mindful of these morbidities, the inhaled fraction of oxygen (FiO_2) is titrated manually, based on oxygen saturation (SpO_2) readings derived from transcutaneous oximetry. Current guidelines recommend a lower limit for the SpO_2 target range (TR) of at least 90% for the preterm infant,[3] based on the recent NeOProM meta-analysis of individual patient data from large randomised controlled trials.[4] These trials highlighted the potential impact of hypoxaemia and hyperoxaemia on preterm infants, with the lower TR (85-89%) associated with an increased risk of mortality and necrotising enterocolitis (NEC), and the higher TR (91-95%) with an increased rate of ROP.

Whilst the need to target an SpO_2 range is widely accepted, data from cohort studies and randomised controlled trials point to the difficulty of SpO_2 targeting by manual oxygen titration,[5-10] with most studies reporting SpO_2 values to be within the TR less than 50% of the time. Although bedside staff adjust the fraction of inspired oxygen (FiO_2) relatively frequently to maintain SpO_2 within TR, their workload limits time availability and makes it difficult to tailor FiO_2 continuously to the infant's need. This is compounded by the neonatal oxygenation physiology being unstable and non-linear with significant time delay between FiO_2 adjustment and when SpO_2 reaches a new stable level.[11]

Given both the importance and difficulty of SpO_2 targeting, automated oxygen control (AOC) is a logical improvement on current practice. In essence, the concept is of an SpO_2 input to a device holding a set of computational instructions (an algorithm), which then gives an output, an updated value for FiO_2. Studies comparing automated oxygen titration systems with manual titration, conducted over short periods (2-24 hours per epoch), have demonstrated an absolute increase in the proportion of time spent with SpO_2 within TR varying between 8% and 31%.[12-23] A single study conducted in our institution has examined the effect of implementation of AOC as standard of care, finding a 14% increase in TR time in the post-implementation cohort, mostly related to a decrease in time above TR.[24]

Although several devices offering AOC are now commercially available and used in Neonatal Intensive Care Units (NICUs), comparisons between them are lacking. The NICU of the Leiden University Medical Center (LUMC) implemented AOC with the $CLiO_2$ algorithm (Vyaire, Yorba Linda, California, USA) with the AVEA ventilator as routine care in August 2015. We recently replaced the AVEA ventilators with SLE6000 ventilators (SLE Limited, South Croydon, UK), which have the VDL 1.1 algorithm for automated oxygen control embedded as the "OxyGenie" option.[17, 25] This provided the unique setting where caregivers were competent to work with both ventilators, thus making feasible a safe comparison between the two oxygen controllers.

Based on described differences in the function of algorithms developed for AOC it is likely that they will exhibit differences in performance.[17, 25] We recently observed that $CLiO_2$ algorithm was effective mostly in decreasing time above TR,[24] whereas the first clinical study using OxyGenie reported a decrease in both time under and above TR and a virtual elimination of longer episodes outside the TR.[23] We therefore hypothesized that the OxyGenie may be more effective than $CLiO_2$ in maintaining SpO_2 within the desired TR in preterm infants receiving respiratory support.

Methods

Study setting

We performed a randomised cross-over trial in the NICU of the LUMC, a tertiary level neonatal unit with 25 NICU beds and 850 intensive care admissions per year. The Dutch Central Committee on Research Involving Human Subjects approved the study. Written informed parental consent was acquired prior to participation of each infant in the study.

Study population

Preterm infants born between 24 weeks up to and including 29 weeks of gestation who were receiving invasive mechanical ventilation or non-invasive respiratory support were assessed for eligibility. Initially, infants were considered eligible if they required supplemental oxygen with an $FiO_2 \geq 0.25$ at the time of enrolment and for at least 18 hours of the preceding 24 hours, but as the study progressed an alternative FiO_2 eligibility criterion was added (FiO_2 coefficient of variation ≥ 0.1 in the preceding 24 hours) to improve recruitment rate. Infants were excluded in case of major congenital anomalies or acute instability.

Automated oxygen control algorithms

The $CLiO_2$ algorithm embedded in the AVEA ventilator is a hybrid rule-based adaptive controller. It makes initial FiO_2 adjustments that are proportional to the difference between the measured SpO_2 and the limits of the SpO_2 TR. Subsequent adjustments also take into account this difference, as well as the SpO_2 trend and basal oxygen requirement, the *baseFiO_2*. The *baseFiO_2* is periodically updated by interrogation of 5 minutes of recent SpO_2 and FiO_2 data where specific conditions are met, averaged along with the current *baseFiO_2* value.[26]

The OxyGenie algorithm embedded in the SLE6000 ventilator is an adaptive proportional-integral-derivative (PID) controller. The P, I and D terms each have separate coefficients, and in each case are adjusted from raw values to better suit the physiology of a neonate and account for the limitations of pulse oximetry. The basal FiO_2, referred to as *Reference FiO_2*, is calculated every 30 minutes using 60 minutes of preceding FiO_2 and SpO_2 values.

Study procedures

A crossover design was used to study each infant on the same respiratory support mode. Infants received two consecutive study periods of 24 hours each, one with oxygen therapy under the control of the CLiO2 algorithm and the other with the OxyGenie algorithm, in random sequence. Web-based randomisation by Castor EDC (Castor, Amsterdam, The Netherlands) was used, stratified by mode of respiratory support (invasive or non-invasive) using variable (4, 6) block sizes. After the first study period the alternative ventilator was substituted, and a wash-out period of 1 hour was applied before data recording re-started to prevent a carry-over bias. The study was completed when automated oxygen control with each device had been applied for 24 hours, with standard respiratory management thereafter resuming. The SpO_2 TR for both study periods was 91%-95%.

No other extra interventions were given. Infants did receive all standard treatments, and ventilation settings were at the discretion of the caregiver.

Data collection and analysis

Baseline characteristics were noted for each infant, including details on respiratory support and clinical state. The primary outcome was the proportion of time spent within the SpO_2 TR (91%-95% with supplemental oxygen, or 91%-100% without supplemental oxygen). SpO_2 and intended FiO_2 values were recorded each second

from the data port or display of the ventilator under investigation. Secondary outcomes included: proportion of time in various degrees of hypoxaemia (SpO_2 <80%, SpO_2 80%-84%, SpO_2 85-90%, SpO_2 ≤90%) and hyperoxaemia (SpO_2 >95%, SpO_2 96%-98%, and SpO_2 >98% while receiving supplemental oxygen); SpO_2 and FiO_2 coefficient of variation; frequency of 30 and 60 second episodes in hypoxaemia and hyperoxaemia; bradycardic episodes (heart rate <100 beats per minute for ≥10 consecutive seconds); frequency of FiO_2 adjustments, both manual and automatic; and average oxygen exposure.

Continuous data is represented as median (IQR) or mean ±SD as appropriate, with standard tests for normality. Time within particular SpO_2 ranges was collated for each infant individually and expressed as proportion of usable recorded time. Differences in time in target range and other outcomes were assessed with the Wilcoxon matched-pairs test. The intention-to-treat principle was applied. Statistical analyses were performed by an analysist blinded to allocation using R 3.4.4 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Sample size calculation was based around data from previous studies of the two automated control algorithms. In a study using the $CLiO_2$ in Leiden in preterm infants the proportion of time in the SpO_2 TR was 60.4% (±15.6%). [24] In the first clinical study of the OxyGenie algorithm TR time was 78% (±15%). We considered a difference of 5% TR time a clinically relevant difference. For a two-sided paired statistical test, 44 infants would be needed assuming a standard deviation of 10% for a power of 90% and an alpha of 0.05. Because a non-parametric test would be used in the analysis we made a 15% addition to the sample size, as described by Lehmann,[27] requiring a total of 50 participants.

Early termination

Just prior to study commencement, the SLE6000 ventilator was deployed as the standard device for neonatal respiratory support at LUMC. The AVEA ventilators were thereafter only used when an infant was included in the study. Based on historical data, we anticipated to complete recruitment in a year, which was also considered the maximum time competence of medical staff in working with both ventilators could be guaranteed. However, the recruitment rate was slower than expected and to ensure patient safety and an unbiased comparison of both oxygen control with the two ventilators the trial was terminated after a 12 month recruiting period.

Results

The study ran from February 2019 to February 2020, during which consent was sought from 27 parent couples of which 15 agreed to participate (Figure 1). All participating infants (n=15, baseline characteristics Table 1) completed the crossover comparison. In one infant the second study period (OxyGenie control) was halted after 18 hours to allow treating clinicians to switch from CPAP to nasal high flow in response to nasal pressure areas. All study periods were included in the analysis. The total duration of recordings was 23 hours and 19 minutes (22:52-23:30) during OxyGenie control and 23 hours and 51 minutes (23:49-23:56) with the $CLiO_2$™ controller. A total of 2.9% (2.1%-5.0%) and 0.3% (0.2%-0.6%) of the time the SpO_2 signal was missing, respectively.

Figure 1: Consort flow diagram

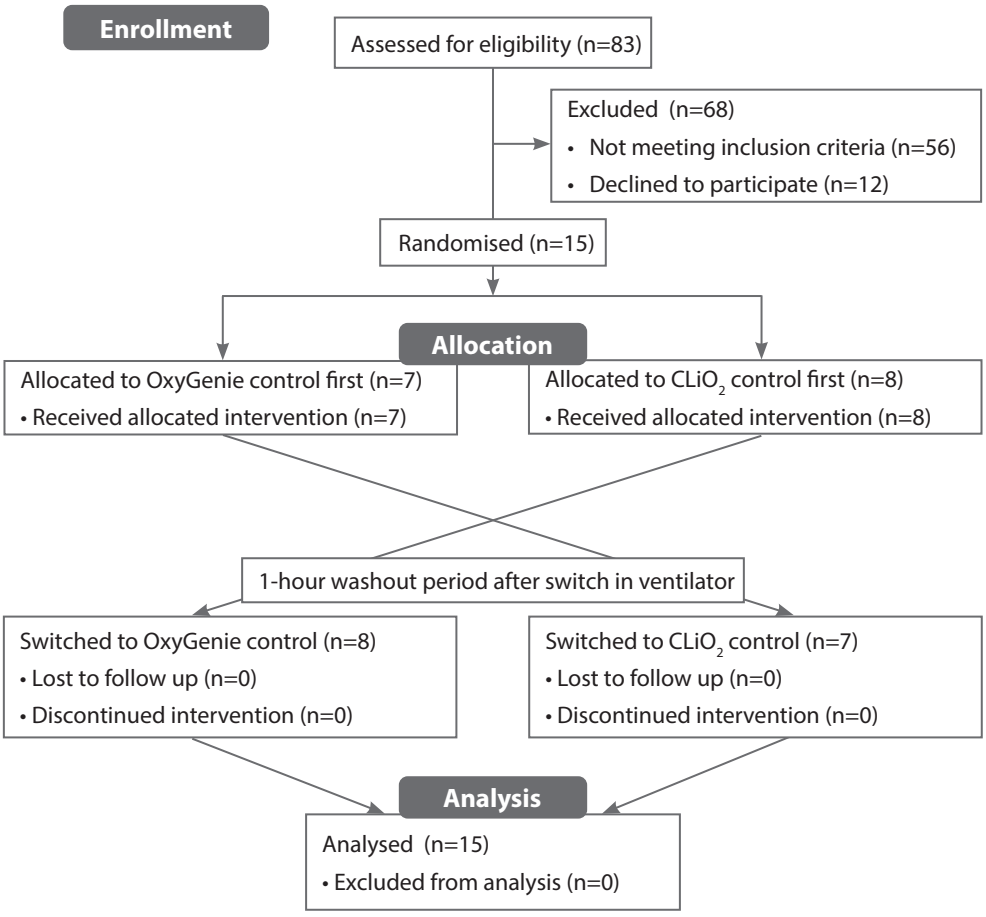

Table 1. Baseline characteristics

Characteristic n = 15	Definition	Statistics	Results
Gestational age	weeks.days	median (IQR)	26.4 (25.3 – 27.6)
Birth weight	grams	median (IQR)	945 (740 – 1120)
Postnatal age	days	median (IQR)	19 (17-24)
Gender	female/male	n	4/11
Ventilation mode	IMV/CPAP	n	2/13
Average FiO_2 24 hours pre-study	fraction	median (IQR)	0.26 (0.24 - 0.29)
Weight at study entry	grams	median (IQR)	1197 (1021 – 1300)
Allocation study entry	Oxygenie /$CLiO_2$	n	7/8

IMV, invasive mechanical ventilation, FiO_2, fraction of inspirated oxygen; SpO_2, peripheral oxygen saturation

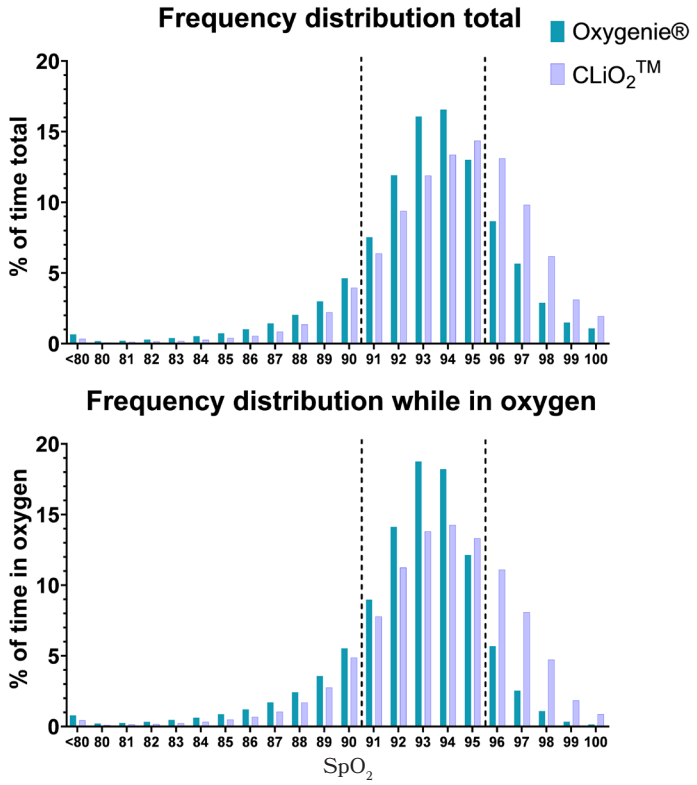

Figure 2: *SpO_2 histograms. Pooled time spent per SpO_2 value as proportion of total usable time, while receiving supplemental oxygen and ambient air (total), or while only receiving supplemental oxygen. Dashed lines represent the limits of the target range.*

Histograms of pooled SpO_2 data from the two automated control periods are shown in Figure 2, demonstrating a narrower SpO_2 distribution and a lower median SpO_2 during OxyGenie control resulting in a higher proportion of time within the SpO_2 TR. On per patient analysis, for the study primary outcome there was a 11.7% increase in time within the SpO_2 TR during oxygen control with the OxyGenie algorithm when compared to the $CLiO_2$ device (Table 2). Twelve infants spent more time in TR with OxyGenie control, and three with $CLiO_2$ control (Figure 3). During the OxyGenie period, less time was spent above the TR while in supplemental oxygen, but more time spent below TR. SpO_2 values <80% were very infrequent throughout the study, and the time with SpO_2 <80% did not differ between control devices. The coefficient of variation for SpO_2 was similar for both devices (3.3% (2.6% - 4.0%) vs 3.2% (3.0% – 3.4%), p = 0.82).

Table 2. Proportions of time within SpO_2 ranges

	Oxygenie	**$CLiO_2$**	**p Value***
Time SpO_2 in target range†	80.2 (72.6 – 82.4) %	68.5 (56.7 – 79.3) %	0.005
Time SpO_2 < target range	14.7 (11.8 – 17.2) %	9.3 (8.2 – 12.6) %	0.020
Time SpO_2 > target range‡	6.3 (5.1 – 9.9) %	15.9 (11.5 – 30.7) %	0.001
SpO_2 85% - 90%	12.6 (10.9 – 13.1) %	8.5 (7.6 – 11.0) %	0.020
SpO_2 80% - 84%	1.2 (0.7 – 3.0) %	0.8 (0.5 – 0.9) %	0.003
SpO_2 < 80%	0.5 (0.1 – 1.0) %	0.2 (0.1 – 0.4) %	0.061
SpO_2 96% - 98% & FiO_2 >= 0.22	6.1 (5.0 – 9.5) %	15.5 (10.9 – 27.4) %	0.001
SpO_2 > 98% & FiO_2 >= 0.22	0.2 (0.1 – 0.4) %	1.4 (0.4 – 3.7) %	0.001

*Data in median (IQR). * Wilcoxon matched pairs test. † 91% <= SpO_2 <= 95% or SpO_2 >= 96% while FiO_2 = 0.21. ‡ SpO_2 >= 96% while FiO_2 >= 0.22*

There was a decrease in frequency of both hypoxaemic and hyperoxaemic episodes during OxyGenie control (Table 3). Bradycardic episodes (<100 bpm for ≥10 seconds) were rare in both epochs and were not different (0.3 (0.1 - 0.6) vs 0.2 (0.0 – 0.5) per hour, p = 0.22).

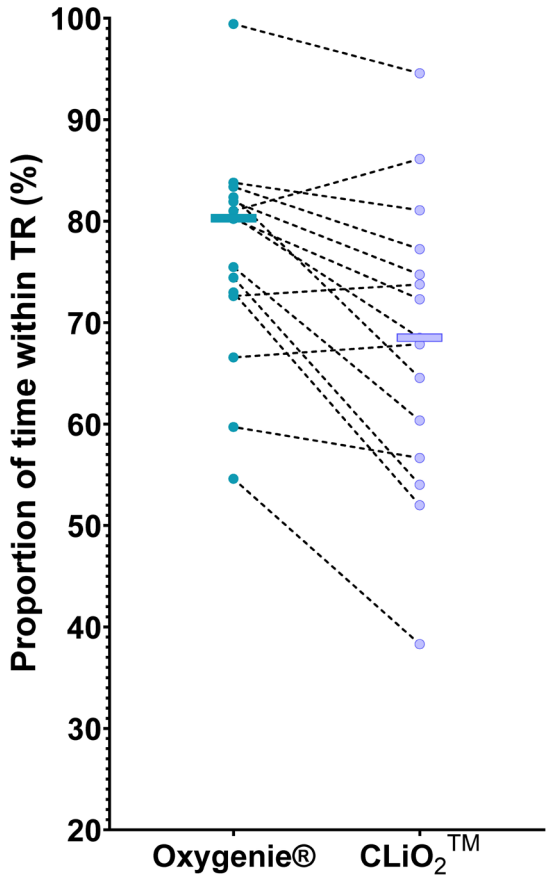

Figure 3: *Comparison of OxyGenie control with $CLiO_2$ control. Individual paired values of proportion of time within target range while on OxyGenie control and while on $CLiO_2$ control. Horizontal bar=median. Within target range=91%-95% with supplemental oxygen, or 91%-100% without supplemental oxygen. TR=Target range.*

Table 3. Hypoxaemic and hyperoxaemic episodes

	30 second episodes / 6 hours			60 second episodes / 6 hours		
SpO_2	Oxygenie	$CLiO_2$	p value*	Oxygenie	$CLiO_2$	p value*
<85%	0.5 (0.2 - 1.1)	0.8 (0.5 - 1.7)	0.022	0 (0 - 0.24)	0.2 (0 - 0.8)	0.027
<80%	0 (0 - 0)	0.2 (0 - 0.5)	0.011	0 (0 - 0)	0 (0 - 0)	0.257
>95%†	4.4 (2.6 - 10.7)	37.3 (15.8 - 54.3)	0.009	0.8 (0.4 - 2.6)	14.6 (5.5 - 22.8)	0.008
>98%†	0.2 (0 - 0.8)	6.3 (1.7 - 13.6)	0.004	0 (0 - 0.2)	1.7(0.5 - 5.3)	0.002

*Data in median (IQR). * Wilcoxon matched pairs test. † While FiO_2 >= 0.22*

OxyGenie adjusted FiO_2 about 10 times more frequently than the $CLiO_2$ device (1155 (1044 – 1255) vs 194 (178 – 205) adjustments/hour, p = 0.001). The average delivered FiO_2 was similar during both study periods (0.27 +-0.05 vs 0.26 +- 0.08, p = 0.56). FiO_2 was more variable when titrated by the OxyGenie algorithm (coefficient of variation 19.5% (15.2% - 25.0%) vs 13.3% (12.8% - 19.0%), p = 0.015). During OxyGenie control, manual overrides of the AOC were made only in one individual subject (4 adjustments) versus nine individuals (16 adjustments) with manual overrides during the period of $CLiO_2$ oxygen control.

Discussion

In this randomised controlled crossover study, automated titration of inspired oxygen concentration using the OxyGenie controller significantly increased the time spent within the SpO_2 TR when compared to the $CLiO_2$ controller. The difference in controller function was reflected in the SpO_2 histogram, with a more balanced distribution of SpO_2 values within and around the TR during OxyGenie control. This resulted in significantly less time spent above the TR, and fewer hyperoxaemic episodes, albeit at the cost of a small increase in time spent with SpO_2 values below TR. The greater time with SpO_2 in the range 80-90% with OxyGenie compared with $CLiO_2$ control was not accompanied by an increase in the frequency of hypoxic episodes, which were, indeed, significantly fewer during OxyGenie control. These results suggest that algorithm design, and in particular algorithm responsiveness, plays an important role in how successful SpO_2 targeting will be with a given oxygen control device.

This is the first study to compare two different ventilators incorporating AOC algorithms head-to-head. Although earlier studies have individually compared the algorithms in question to manual oxygen titration,[15-20, 23, 24] heterogeneity between the studies has precluded drawing inferences about their function relative to each other. Our findings in relation to proportion of time within TR were similar to previous studies, implying that the SpO_2 targeting results achieved by controllers in our study were representative of their overall performance. Compared with the TR time of 80% in this study, other studies of OxyGenie control have demonstrated TR times of 81% [23] and 88%.[28] For $CLiO_2$ (69% TR time in this study), other studies have shown TR time of 40%[15], 58%[16], 62%[18], 76%[19], 73%[20] and 62%[24])

The study was terminated before reaching the predetermined sample size of 50 infants. The deployment of the SLE6000 ventilator at LUMC had an impact on numbers of eligible infants by virtue of 1) the option of nasal high flow (not available

with the AVEA ventilator) being taken up at an early juncture in many preterm infants, precluding involvement in the study, and 2) fewer infants spending >18 of the preceding 24 hours with an $FiO_2 \geq 0.25$, in part attributable to the progressive approach to weaning FiO_2 inherent in OxyGenie control. As a result, the recruitment rate was lower than expected. To prevent a loss of competence in handling the AVEA ventilator, potentially introducing a bias into the study, we decided to terminate the study prematurely. Truncated clinical studies can lead to over-exaggerated observed effects.[29, 30] For our study, this would mean that the observed benefit for the OxyGenie controller in comparison to $CLiO_2$ controller may over-estimate the true benefit. However, if we had planned for an interim analysis to decide for stopping the trial after 15 patients, we would have surpassed both the Pocock and O'Brien-Fleming boundary criteria for clearly showing evidence of benefit for the OxyGenie controller. For a single interim analysis Pocock recommends a p-threshold of 0.0294[31] and O'Brien-Fleming recommends a more conservative 0.0054 p-threshold[32] to control for type I error due to repeated testing. The apparent benefit of OxyGenie is also demonstrated by a 11.7% improvement which is more than twice the clinically relevant difference of 5% for which the current study was powered.

There was an imbalance between the two oxygen control devices in the proportion of missing values. Both algorithms use a built-in Masimo pulse oximeter with similar algorithms making it unlikely that the actual reliability of pulse oximeter measurement was different between ventilators. But, to ensure a prompt response to TR deviations, OxyGenie uses a 2-4 second averaging time whereas $CLiO_2$ uses an 8 second averaging time. This could lead to more missing signal, as shorter averaging times are inherently more susceptible to disturbances. Furthermore, although the same SET technology is used, manufacturers are free to choose the signal quality threshold below which SpO_2 is reported as missing. It seems likely that the handling of the SpO_2 signal within the SLE6000 is more conservative in this respect. Because the proportion of missing signal was still relatively low in both oxygen control periods, its effect on the outcomes of this study is likely to have been modest.

This study compared two ventilators rather than purely the AOC algorithms. It is possible that ventilator mechanics also played a role in the effectiveness of oxygen control, as well as other aspects of ventilator function including the circuit flow characteristics.[33] However, this was a pragmatic choice as license agreements precluded us from implementing two algorithms in one ventilator.

Contrary to our hypothesis, the benefit of an increase in SpO_2 TR time with OxyGenie control was gained with a lesser occurrence of hyperoxaemia, at the cost of a minor

increase in time spent with SpO_2 80%-90%. Although at first glance it appears there is a trade-off between hyperoxaemia and hypoxaemia, the reduction in hypoxaemic episodes with OxyGenie control suggests that hypoxaemia is resolved more quickly. This is in line with the clinical observation of caregivers, who reported that OxyGenie responded more rapidly to SpO_2 deviations into hypoxaemia than $CLiO_2$. Compared to other studies, time with SpO_2 <80% was modest with both controllers. For the OxyGenie controller it was 0.5% in our study vs 0% [23] previously; for the $CLiO_2$ controller it was 0.2% whereas other studies reported 9.8% [15], 1.2% and 0.8% [18], 3.1% [19], 1.3% [20] and 0.9% [24].

The increase in time spent under TR could be due to a lower median SpO_2 during OxyGenie control (93% vs 94%) on the steeper part of the oxygen-dissociation curve. The higher median SpO_2 during $CLiO_2$ control could be because, according to the patent, an SpO_2 of 94% is targeted while in TR and the FiO_2 is rarely titrated below the *Base*FiO_2.[26]

Even though the benefit of AOC on SpO_2 TR time is well-established, the effect on clinical outcome is still unknown. The effect of SpO_2 targeting within different ranges on clinical outcome was demonstrated by the NeOPRoM trials,[4] and a range of studies have evidenced the harmful effects of hypoxaemia and hyperoxaemia (and episodes thereof),[34-39] both of which are affected by AOC. We would maintain that when searching for clinical effect of AOC it is important to use an algorithm that most successfully avoids and mitigates SpO_2 deviations, because the effect on clinical outcomes may be modest and in some cases may be difficult to detect given their relatively low incidence.

Finally, low compliance in TR adherence such as reported in the NeOPRoM trials[4] could be improved upon by using AOC. For the best differentiation between treatment groups it is important to have a controller that best targets the predefined ranges.

Conclusion

In this study the OxyGenie controller was more effective in keeping the oxygen saturation within target range and preventing hyperoxaemia, and just as effective in preventing hypoxaemia (SpO_2<80%), albeit at the cost of a small increase with SpO_2 80%-90%.

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What is known about this topic

- Automated oxygen control has been proven to increase time spent within SpO_2 target range when compared with manual titration in cross-over studies lasting a maximum of 24 hours.
- Algorithm choice may influence how successful titration will be, but comparisons of algorithms head-to-head are scarce.
- A preterm infant's response to an adjustment in FiO_2 may change during the course of the admission as respiratory distress syndrome progresses.

What this study adds

- Automated oxygen titration by the OxyGenie algorithm was associated with better oxygen saturation targeting during the entire admission while given oxygen when compared to titration by the $CLiO_2$ algorithm.
- This was accompanied by less time spent in hypoxia and hyperoxia for preterm infants supported by the OxyGenie algorithm.
- Including episodes where no supplemental oxygen is administered reduces the effect size.

How this study might affect research, practice or policy

- Choice of automated oxygen controller is associated with how successful oxygenation targeting will be during the entire admission.
- When researching a long period of oxygen titration focus should lie on phases of respiratory instability and/or when supplemental oxygen is administered.

Chapter 4

Comparison of two automated oxygen controllers in oxygen targeting in preterm infants during admission – an observational study

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Abstract

Objective To compare the effect of two different automated oxygen control devices in preterm infants on time spent in different oxygen saturation (SpO2) ranges during their entire stay in the NICU.

Design Retrospective cohort study of prospectively collected data.

Setting Tertiary level neonatal unit in the Netherlands.

Patients Preterm infants (OxyGenie 75 infants, CLiO2 111 infants) born at 24-29 weeks gestation receiving at least 72 hours of respiratory support between October 2015 and November 2020.

Interventions Inspired oxygen concentration was titrated by the OxyGenie controller (SLE6000 ventilator) between February 2019 and November 2020 and the CLiO2 controller (AVEA ventilator) between October 2015 and December 2018 as standard of care.

Main outcome measures Time spent within SpO2 target range (TR, 91-95% for either epoch) and other SpO2 ranges.

Results Time spent within the SpO2 TR when receiving supplemental oxygen was higher during OxyGenie control (median 71.5 [IQR 64.6–77.0]% vs 51.3 [47.3–58.5]%, $p<0.001$). Infants under OxyGenie control spent less time in hypoxic and hyperoxic ranges (SpO2<80%: 0.7 [0.4–1.4]% vs 1.2 [0.7–2.3]%, $p<0.001$; SpO2 >98%: 1.0 [0.5-2.4]% vs 4.0 [2.0-7.9]%, $p<0.001$). Both groups received a similar FiO2 (29.5 [28.0 – 33.2]% vs 29.6 [27.7-32.1]%, p=non significant)

Conclusions Oxygen saturation targeting was better in the OxyGenie epoch in preterm infants, with less time in hypoxic and hyperoxic SpO2 ranges during their stay in NICU.

Keywords: Hypoxemia; hyperoxia; closed-loop; algorithm; neonate

Introduction

Caregivers in the Neonatal Intensive Care Unit (NICU) must continuously maintain a fragile balance between administering too much and too little supplemental oxygen to preterm infants to prevent neonatal morbidity and mortality. Several neonatal morbidities have been linked to a disturbance in this balance, with intermittent hypoxia being associated with retinopathy of prematurity,[1] neurodevelopmental impairment and death,[2] and hyperoxia long known to be causative of retinopathy of prematurity.[3]

Maintaining the balance involves titration of the inspired fraction of oxygen (FiO_2). When done manually this often leads to an achieved time within the oxygen saturation (SpO_2) target range of 50% or less.[4] Automated targeting of SpO_2 by a device titrating FiO_2 can increase the time that preterm infants spend within the target range.[5, 6] In general, automated oxygen titration entails a computer program that automatically adjusts the FiO_2 based on the measured SpO_2. The magnitude of the FiO_2 adjustment is usually determined by several factors, such as the currently administered FiO_2 and the difference between the measured SpO_2 and the intended SpO_2. Several of these devices are available commercially.[7-13] The function of all of these devices has been examined in cross-over studies lasting 24 hours or less per arm, and has proved superior to manual titration, but head-to-head comparisons of devices are scarce.[12, 14]

Algorithm choice may influence how successful titration will be.[15] We recently demonstrated the OxyGenie controller (SLE Limited, South Croydon, UK) to be more effective in maintaining SpO_2 within target range than the $CLiO_2$ controller (Vyaire, Yorba Linda, California, USA) in a randomised 48 hour crossover study.[14] In this trial, infants were studied at a median postnatal age of 19 days at which time the lung disease and response to changes in FiO_2 may not be representative of each phase of admission.

To date no studies have compared automated oxygen controllers head-to-head over long periods of time. In our centre, we are in the unique position of having used two different automated oxygen controllers as standard of care for a total of 6 years, making a comparison between these two controllers feasible. We used the AVEA ventilators with the $CLiO_2$ automated oxygen control (AOC) algorithm integrated for over three years (since August 2015), after which the ventilators were replaced for SLE6000 ventilators with OxyGenie AOC algorithm in November 2018. In this study we compared the effectiveness of these controllers in very preterm infants receiving AOC as standard of care by either the $CLiO_2$ or the OxyGenie controller

during their entire admission. Considering the results from our cross-over study[14], we hypothesized that OxyGenie is more effective in maintaining SpO_2 within the target range during respiratory support of preterm infants.

Methods

Study setting

We retrospectively retrieved prospectively collected data of all patients born at 24-29 weeks gestation, admitted to the NICU of the LUMC between October 2015 and November 2020. Our centre is a tertiary-level perinatal centre in Leiden, the Netherlands, and we have an average of 100 infants born under 30 weeks of gestation per annum. In the Netherlands, no ethical approval is required for anonymised studies with patient data collected for standard care. The Medical Ethical Review Committee of Leiden Den Haag Delft provided a statement of no objection for obtaining and publishing the anonymised data.

Infants were excluded if they: were admitted >24 hours after birth, had major congenital abnormalities, or received less than 72 hours of respiratory support. A minimum of 72 hours was chosen to exclude unrepresentative extreme scores from infants transferred within days after birth with little respiratory support, or infants who died shortly after birth. In both situations the impact of automated oxygen titration would likely be negligible. The AVEA cohort consisted of infants admitted between October 18th 2015 (three months after implementation of $CLiO_2$ into standard care) to December 1st 2018, the SLE cohort consisted of infants born between February 1st 2019 and November 1st 2020, allowing for a wash-out period of two months.

Respiratory support

Both the OxyGenie and the $CLiO_2$ algorithm change the FiO_2 automatically according to the measured SpO_2, where generally larger deviations from the SpO_2 target range lead to larger changes in FiO_2. Both are adaptive in the sense that when a patients' average supplemental oxygen requirement is higher, adjustments in FiO_2 will also be larger. One difference lies in the exact way the adjustment in FiO_2 is calculated: both OxyGenie and $CLiO_2$ base the magnitude of adjustment on how far out of the target range the current SpO_2 is, and the trajectory of recent values, but OxyGenie also takes past values into account (by addition of an integral term, the sum of past differences between desired and measured SpO_2). More detail on the function of these algorithms can be found elsewhere.[15]

Modes of respiratory support used during both epochs were invasive mechanical ventilation (volume targeted, high frequency oscillation (HFO)), continuous positive airway pressure or non-invasive positive pressure ventilation, high flow nasal cannula (HFNC), and low flow. The SLE6000 supports all these modes, whereas during the AVEA epoch HFNC was administered via the Optiflow system (Fisher & Paykel Healthcare, Auckland, New Zealand) and HFO via a Sensormedics 3100 A ventilator (Vyaire, Yorba Linda, California, USA). Both the AVEA and the SLE6000 ventilator have Masimo SET technology on board to measure SpO_2, but with different fixed settings for averaging time during AOC (SLE6000: 2-4 seconds, AVEA: 8 seconds). Automated oxygen control was not available during HFNC or HFO support during the AVEA period, and these periods were excluded in the primary analysis for both epochs.

The SpO_2 target range during $CLiO_2$ control was 90%-95%, which needed to be changed to 91%-95% on introduction of the SLE6000 as this is a pre-set target range. For the purpose of the primary analysis the target range was considered to be 91%-95%. Local protocol is to disable automated oxygen control when infants received no supplemental oxygen while saturating >98% for more than 30 minutes or a few days prior to transfer to a different hospital. Our local protocol is to set SpO_2 alarm limits to 88%-98%.

Data collection and analysis

Patient characteristics and vital parameters up to a postmenstrual age of 30 weeks were sourced from our patient data management system (PDMS Metavision; IMDsoft, Tel Aviv, Israel). The instantaneous SpO_2 and FiO_2 were stored once per minute, we recently demonstrated that there were no significant differences when using one-per-minute vs. one-per-second data for descriptive statistics such as time within target range.[16] Small for gestational age was defined as a birth weight under p10 in the Hoftiezer curves.[17]

There is an incongruency in the incoming FiO_2 values between the SLE6000 and AVEA. In case of the SLE6000, data forwarded to our patient data management system consists of measured FiO_2 by the SLE6000's oxygen cell. For this cell the accuracy is 3%.[18] In some cases this leads to situations where the ventilator is providing no supplemental oxygen, or 21% of oxygen, while the recorded FiO_2 is 23%. Contrary to the SLE6000, AVEA's recorded values for FiO_2 are based on the intended, or set, FiO_2 rather than the measured FiO_2. Therefore we chose to define room air, or no supplemental oxygen, as any FiO_2 value of 23% or lower.

For the primary analysis, recording periods where no supplemental oxygen was administered were removed. Infants receiving less than 72 h of supplemental oxygen were excluded from the primary analysis. We then calculated the proportion of time within SpO_2 target range (SpO_2 91%-95%), proportions of time in various degrees of hypoxia (SpO_2 <80%, SpO_2 80%-84%, SpO_2 85-90%, SpO_2 ≤90%) or hyperoxia (SpO_2 >95%, SpO_2 96%-98%, and SpO_2 >98, and average FiO_2. These outcomes were calculated overall and per day. Finally, we calculated the proportion of time within target range per week of postmenstrual age. For the secondary analysis we calculated the overall outcomes using all periods of respiratory support (i.e. also room air) from infants receiving at least 72 hours of respiratory support.

Continuous data is represented as median (IQR) or mean ±SD as appropriate, with standard tests for normality. Differences in time in target range and other outcomes were assessed with the Kruskal-Wallis test. Statistical analyses were performed using MATLAB (Matlab R2020b; The MathWorks Inc., Natick, Massachusetts, USA).

Results

Patient characteristics

In the study period 449 preterm infants born at 24-29 weeks of gestation were admitted to the LUMC NICU within 24 hours after birth, 154 in the OxyGenie epoch and 295 in the $CLiO_2$ epoch. Of these, 146 infants remained in the OxyGenie epoch and 269 infants in the $CLiO_2$ epoch after exclusion of infants receiving less than 72 hours of respiratory support. The primary analysis, including only infants receiving at least 72 h supplemental oxygen, involved 75 infants in the OxyGenie epoch and 111 infants in the $CLiO_2$ epoch. There were no significant differences in any of the baseline characteristics for the primary outcome population (Table 1). The median recording length of vital parameters was 336 hours [IQR 186 – 598] in the OxyGenie epoch and 398 [IQR 165 – 693] in the $CLiO_2$ epoch (p = not significant (ns)).

Table 1. Baseline characteristics of recordings >72 hours while supplemental oxygen administered

Patient characteristics **n = 186**	**Oxygenie** **n=75**	**$CLiO_2$** **n=111**	**p value***
Gestational age in weeks ^{days}, median [IQR]	27^0 [25^3 – 27^5)	26^6 [25^4 – 28^0]	n.s.
Birth weight in grams, mean (SD)	934 (239)	901 (215)	n.s.
Small for gestational age, n (%)	8 (10.7)	8 (7.2)	n.s.
Males, n (%)	42 (56.0)	52 (46.8)	n.s.
Antenatal corticosteroids, n (%)	66 (88.0)	94 (84.7)	n.s.
Caesarean delivery, n (%)	36 (48.0)	63 (56.8)	n.s.
Multiple pregnancy, n (%)	26 (34.7)	42 (37.8)	n.s.
Recording length in hours, median [IQR]	336 [186 – 598]	398 [165 – 693]	n.s.

*FiO_2, fraction of inspired oxygen; CPAP, continuous positive airway pressure; *Mann-Whitney U test, independent T-test or chi-square test as appropriate*

Baseline characteristics for the secondary analysis population also did not differ between epochs (Table 2). Median recording length of vital parameters was 490 hours [IQR 350 – 747] in the OxyGenie epoch and 520 [IQR 321 – 751] in the $CLiO_2$ epoch (p = ns).

Table 2. Baseline characteristics of all recordings >72 hours, including room air episodes

Patient characteristics **N = 415**	**Oxygenie** **N=146**	**$CLiO_2$** **N=269**	**p value***
Gestational age in weeks ^{days}, median [IQR]	28^0 [26^6 – 29^0]	28^1 [26^6 – 28^6]	n.s.
Birth weight in grams, mean (SD)	1038 (270)	1050 (250)	n.s.
Small for gestational age, n (%)	16 (11.0)	21 (7.8)	n.s.
Males, n (%)	137 (50.9)	80 (54.8)	n.s.
Antenatal corticosteroids, n (%)	133 (91.1)	236 (87.7)	n.s.
Caesarean delivery, n (%)	74 (50.7)	148 (55.0)	n.s.
Multiple pregnancy, n (%)	55 (37.7)	93 (34.6)	n.s.
Recording length in hours, median [IQR]	490 [350 – 747]	520 [321 – 751]	n.s.

*FiO_2, fraction of inspired oxygen; CPAP, continuous positive airway pressure; *Mann-Whitney U test, independent T-test or chi-square test as appropriate*

Time within SpO_2 ranges

In the primary analysis where episodes of room air were excluded, infants in the OxyGenie epoch spent 71.5 [64.6 – 77.0] % of the time within target range of 91%-95% versus 51.3 [47.3 – 58.5] % in the $CLiO_2$ epoch ($p < 0.001$, Table 3). This was mainly attributable to less time above the target range in the OxyGenie epoch (OxyGenie 11.5 [8.7 – 15.8] %, $CLiO_2$ 23.9 [16.3 – 32.1] %, $p < 0.001$), and to a lesser extent to a reduction in time under the target range (OxyGenie 16.1 [12.6 – 19.2], $CLiO_2$ 22.0 [18.2 – 26.0], $p < 0.001$). Oxygen saturations under 80% were measured 0.7 [0.4 – 1.4] % of the time with OxyGenie and 1.2 [0.7 – 2.3] % of the time with $CLiO_2$ ($p < 0.001$); oxygen saturations above 98% were measured 1.0 [0.5 – 2.4] % of the time with OxyGenie and 4.0 [2.0 – 7.9] % of the time with $CLiO_2$ ($p < 0.001$). The average FiO_2 was not significantly different.

Table 3. Recordings >72 hours while supplemental oxygen administered, excluding episodes in room air

Outcome		Oxygenie N=75	$CLiO_2$ N=111	p value*
Time SpO_2 in target range†	%	71.5 [64.6 – 77.0]	51.3 [47.3 – 58.5]	<0.001
Time SpO_2 < target range	%	16.1 [12.6 – 19.2]	22.0 [18.2 – 26.0]	<0.001
Time SpO_2 > target range	%	11.5 [8.7 – 15.8]	23.9 [16.3 – 32.1]	<0.001
SpO_2 85% - 89%	%	8.3 [6.5 – 9.9]	11.6 [9.5 – 14.1]	<0.001
SpO_2 80% - 84%	%	1.7 [1.0 – 2.3]	2.9 [1.8 – 3.8]	<0.001
SpO_2 < 80%	%	0.7 [0.4 – 1.4]	1.2 [0.7 – 2.3]	<0.001
SpO_2 96% - 98%	%	10.5 [7.7 – 13.7]	19.3 [14.3 – 24.1]	<0.001
SpO_2 > 98%	%	1.0 [0.5 – 2.4]	4.0 [2.0 – 7.9]	<0.001
Average FiO_2§	%	29.5 [28.0 – 33.2]	29.6 [27.7 – 32.1]	n.s.

*Data in median [IQR]; * Kruskal-Wallis test; † 91% <= SpO_2 <= 95%; § Average FiO_2 is based on measured FiO_2 for OxyGenie and on intended/set FiO_2 for $CLiO_2$*

In figure 1A, 1C and 1D the average proportion of time within the SpO_2 different ranges (SpO_2 91-95%, SpO_2 <80%, SpO_2 >98% respectively) can be viewed per day since birth, which shows a decline in proportion with increasing age. When set against the postmenstrual age this decline is less apparent in the OxyGenie group (Figure 1B). The average FiO_2 excluding room air (Figure 2) has a similar course for both epochs, although around the age of 30 days and 50 days there are fewer infants contributing to the data leading to a higher standard deviation and differences between controllers.

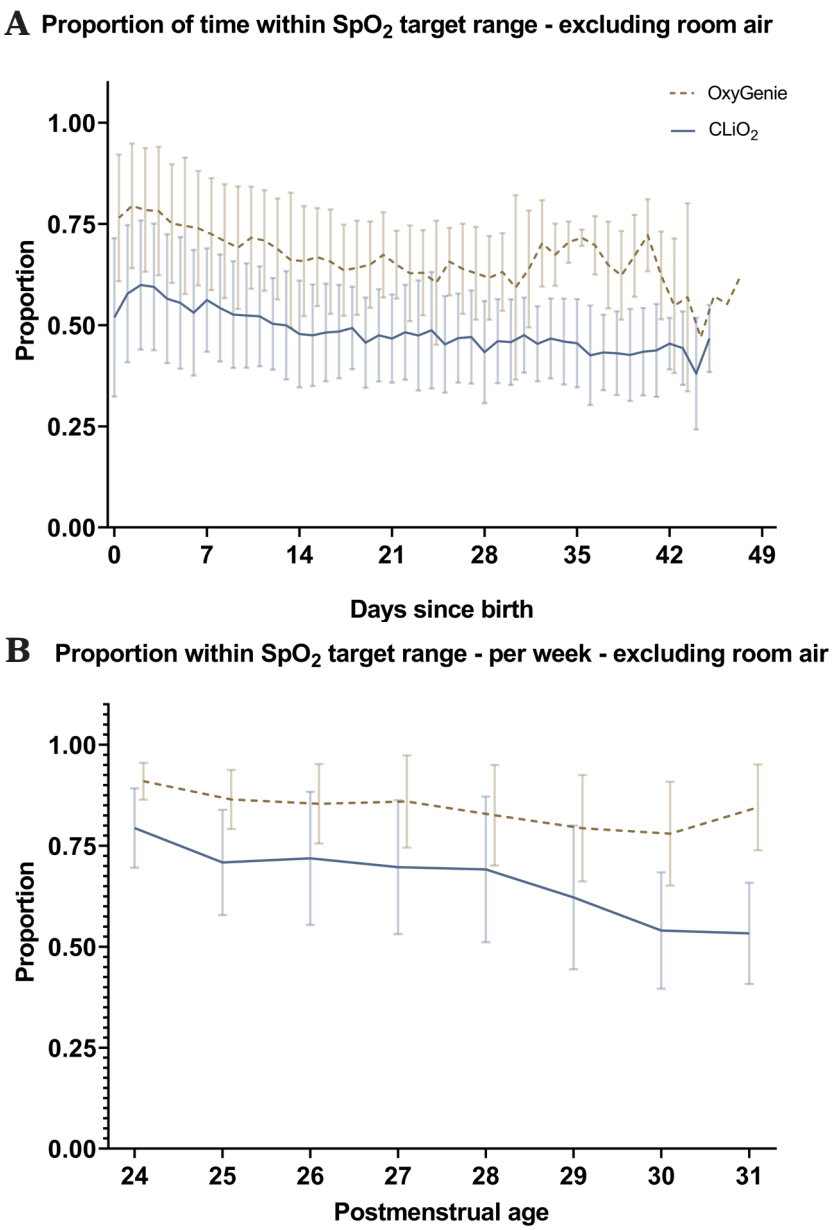

Figure 1A-B. *Proportion of time spent within different SpO_2 ranges excluding periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$. (A): Proportion of time within the 91%-95% range plotted against postnatal age. (B): Proportion of time within the 91%-95% range plotted against postmenstrual age. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$.*

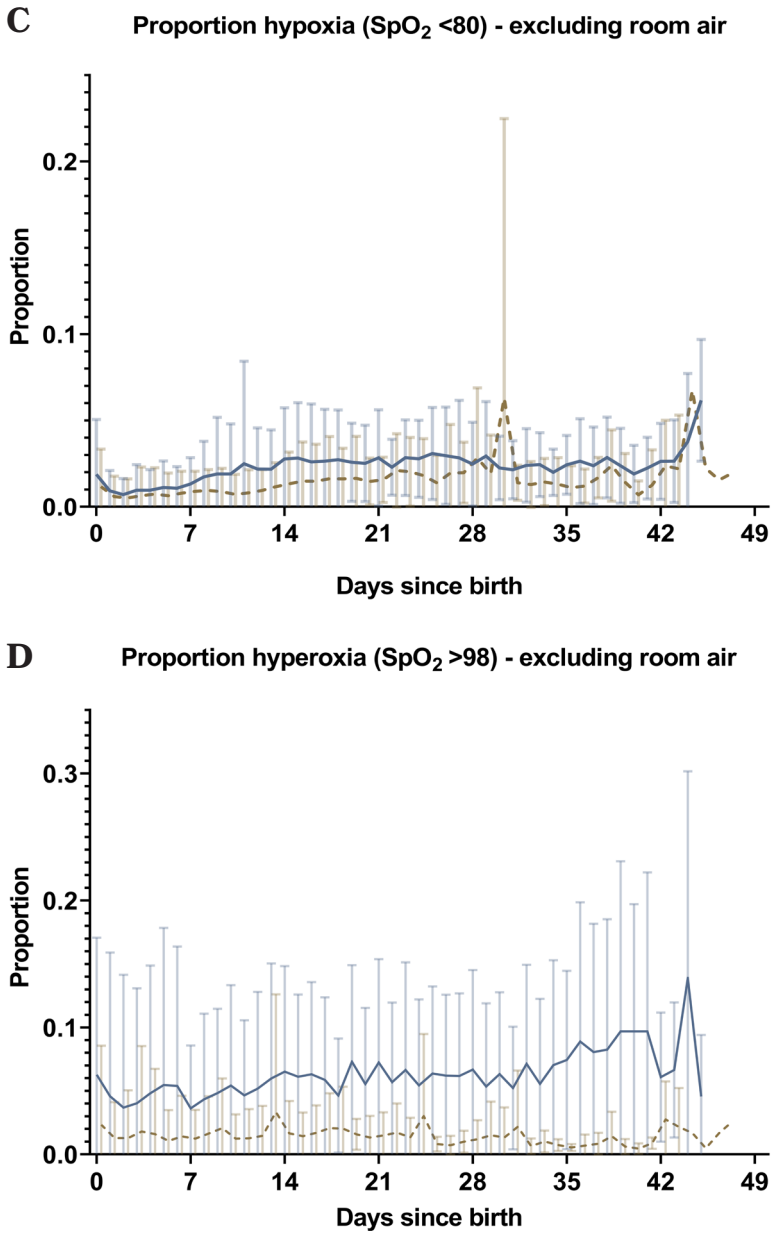

Figure 1C-D. *Proportion of time spent within different SpO_2 ranges excluding periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$. (C): Proportion of time in hypoxia (SpO_2 <80%) against postnatal age. (D): Proportion of time in hyperoxia (SpO_2 >98%) against postnatal age. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$.*

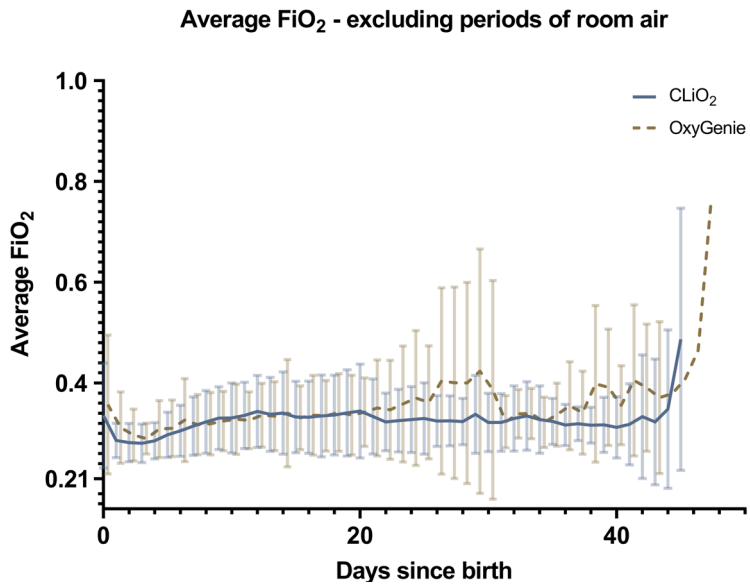

Figure 2. *Average FiO_2 excluding values FiO_2<0.24 plotted against postnatal age.*

In the secondary analysis infants on OxyGenie spent 92.5 [91.8 – 97.2] % of the time within target range versus 90.2 [75.2 – 96.0] % of the time for infants on $CLiO_2$ (p = 0.005, Table 4, Figure 3A per day, Figure 3B per week postmenstrual age). Contrary to the primary analysis, the differences were mainly attributed to a reduction in time under the target range, which was 5.0 [2.2 – 5.9] % in OxyGenie and 6.8 [3.3 – 13.6] % in $CLiO_2$ (p = 0.003). Time above target range was similar (OxyGenie 2.0 [0.7 – 5.9], $CLiO_2$ 2.5 [0.4 – 10.9, p = ns). Major SpO_2 deviations were less common in OxyGenie (SpO_2 <80%: OxyGenie 0.2 [0.1 – 0.5] %, $CLiO_2$ 0.3 [0.2 – 0.8] %, p <0.001, Figure 3C; SpO_2 >98%: OxyGenie 0.2 [0.1 – 0.6] %, $CLiO_2$ 0.4 [0.1 – 1.7] %, p <0.001, Figure 3D). The recorded average FiO_2 was lower in the $CLiO_2$ group (OxyGenie 23.0 [21.8 – 25.8] %, $CLiO_2$ 21.8 [21.1 – 24.8] %, p < 0.001).

Table 4. Recordings >72 hours, including episodes in room air

Outcome		Oxygenie n=146	$CLiO_2$ n=269	p value*
Time SpO_2 within target range†	%	92.5 [81.8 – 97.2]	90.2 [75.2 – 96.0]	0.005
Time SpO_2 below target range	%	5.0 [2.2 – 10.6]	6.8 [3.3 – 13.6]	0.003
Time SpO_2 above target range‡	%	2.0 [0.7 – 5.9]	2.5 [0.4 – 10.9]	n.s.
SpO_2 85% - 89%	%	2.7 [1.1 – 5.3]	3.7 [1.6 – 7.6]	0.002
SpO_2 80% - 84%	%	0.4 [0.2 – 1.2]	0.8 [0.3 – 1.7]	<0.001
SpO_2 < 80%	%	0.2 [0.1 – 0.5]	0.3 [0.2 – 0.8]	<0.001
SpO_2 96% - 98% while FiO_2 >= 0.24	%	1.7 [0.6 – 5.2]	1.9 [0.3 – 9.0]	n.s.
SpO_2 > 98% while FiO_2 >= 0.24	%	0.2 [0.1 – 0.6]	0.4 [0.1 – 1.7]	<0.001
Average FiO_2§	%	23.0 [21.8 – 25.8]	21.8 [21.1 – 24.8]	<0.001

*Data in median (IQR). * Kruskal-Wallis test. † 91% <= SpO_2 <= 95% or SpO_2 >= 96% while FiO_2 <= 0.23. ‡ SpO_2 >= 96% while FiO_2 >= 0.24 § Average FiO_2 is based on measured FiO_2 for OxyGenie and on intended/set FiO_2 for $CLiO_2$*

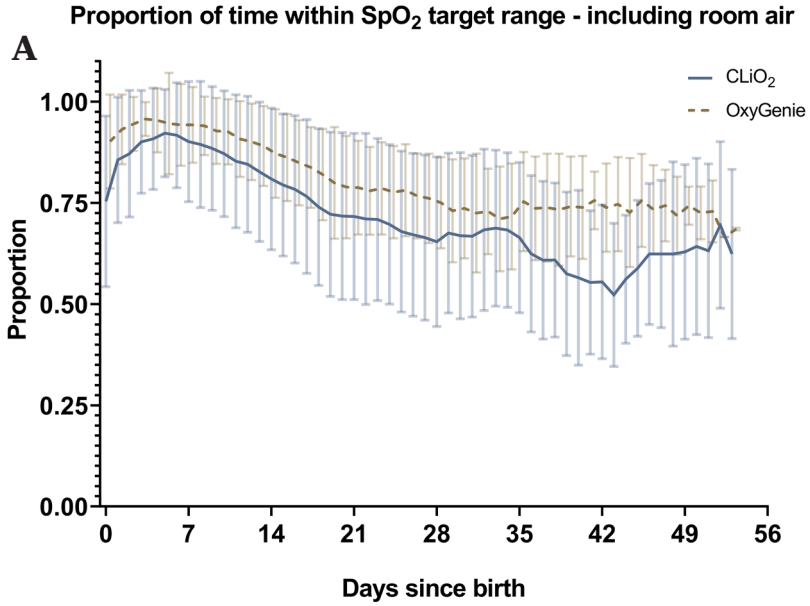

Figure 3A. *Proportion of time spent within different SpO_2 ranges including periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$*

(A): Proportion of time within the 91%-95% range plotted against postnatal age.

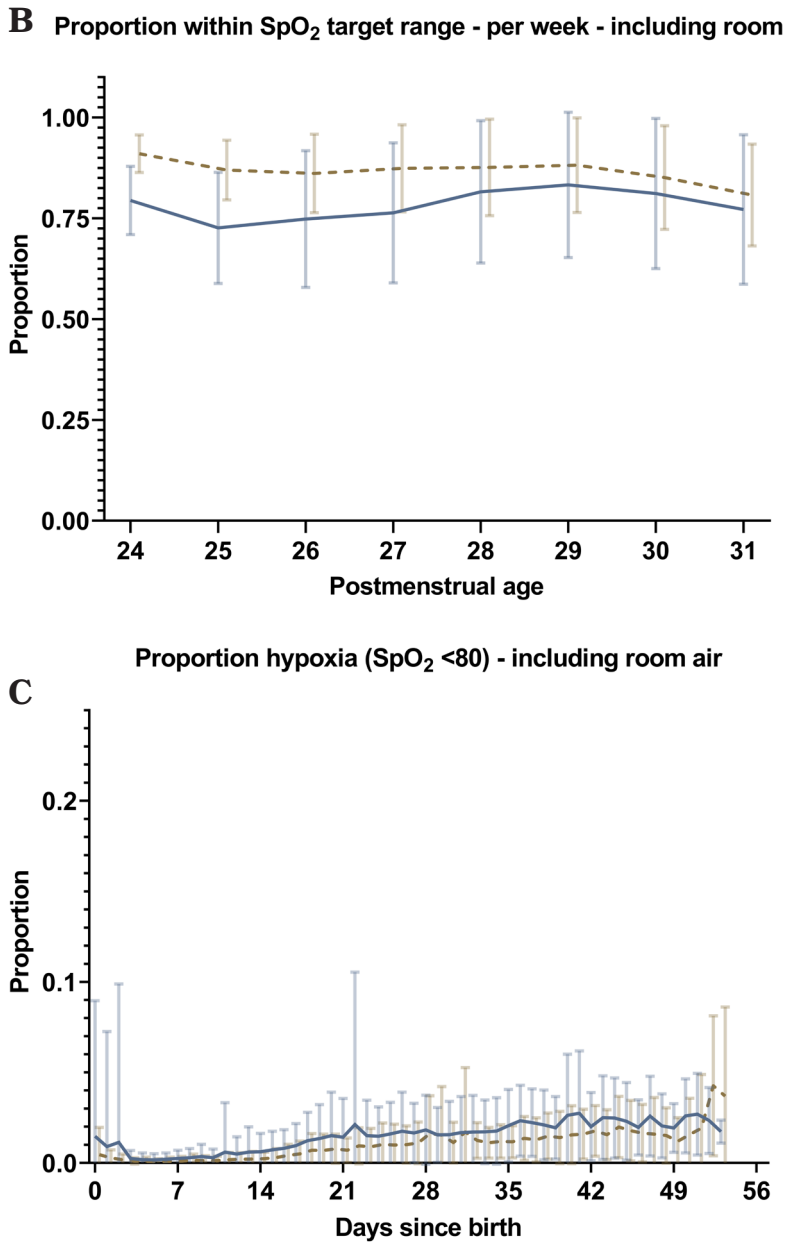

Figure 3B-C. *Proportion of time spent within different SpO2 ranges including periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: CLiO$_2$*

(B): Proportion of time within the 91%-95% range plotted against postmenstrual age. (C): Proportion of time in hypoxia (SpO$_2$ <80%) against postnatal age.

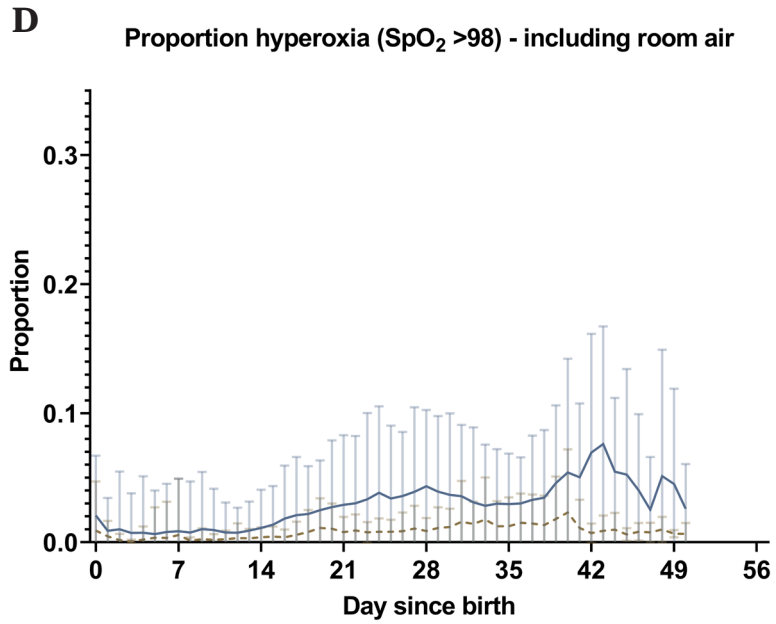

Figure 3D. *Proportion of time spent within different SpO2 ranges including periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$*

(D): Proportion of time in hyperoxia (SpO_2 >98%) against postnatal age.

Discussion

In this study preterm infants receiving OxyGenie automated oxygen control during their stay in the NICU spent significantly more time within the target range than infants receiving $CLiO_2$ automated oxygen control. This improvement was driven by less time spent in all hypoxic and hyperoxic ranges during supplemental oxygen therapy, and this improvement remained during all postnatal and postmenstrual ages. No differences were found in average inspired oxygen when supplemental oxygen is administered. The effect size reduced when episodes without supplemental oxygen were also included, but the superiority of OxyGenie was nevertheless still present. These results suggest that the conclusion from our randomised cross-over study[14] – the choice of oxygen control device determines how successful SpO_2 targeting will be – holds true for the entire stay in the NICU.

This is the first study to describe the proportions of time within certain oxygen saturation ranges during different phases of a preterm infants' stay in the NICU. In only one study automated oxygen control during the entire stay was researched.

In this study, where $CLiO_2$ was compared with manual titration, results for hypoxia were similar to our $CLiO_2$ study group, but hyperoxia was slightly lower and time within target range higher. Contrary to the randomised cross-over study[14] comparing OxyGenie with $CLiO_2$ for 24-hours periods, OxyGenie control was associated with less time under target range. This may be due to the differences in analysis (in the crossover study periods without supplemental oxygen were included, and intended FiO_2 rather than measured FiO_2 was collected for both devices).

Our choice in definition of room air may have influenced the results. Unfortunately, it was not possible to retrieve the intended FiO_2 for the OxyGenie group, as this is not routinely collected, and measured FiO_2 was not routinely collected for the $CLiO_2$ group. To increase the validity of the comparison between AVEA and SLE6000, we excluded periods where the inspired oxygen concentration was 23% or lower, reducing the penalty the SLE6000 would inherently receive for measuring more than 21% of inspired oxygen while no supplemental oxygen is given. As such, only less stable episodes with higher risk of hyperoxaemia are studied.

Unique in this study is that we investigated the relation between postnatal age and time spent within certain oxygen saturation ranges. As demonstrated in our secondary analysis, comparing achieved target range time can be heavily influenced by the relatively stable respiratory period that usually occurs after a postmenstrual age of 30 weeks. Compared with our primary analysis, one can ascertain all results are diluted by this stable period of near-100% time within target range. Better oxygenation results will not be achieved in phases where infants receive no supplemental oxygen because they are adequately saturated. Indeed, the benefit of an AOC will be modest as then its only role is to respond to intermittent hypoxia, triggered by apnoea or other destabilising events. The focus for research concerning the entire admission should lie on phases where the infant exhibits less respiratory stability and receives supplemental oxygen.

Decisions made during the analysis may have influenced the results, but were important to maintain generalisability. Periods in the AVEA epoch where HFO or HFNC was the mode of respiratory support were excluded in the oxygen-only analysis, as there was no automated oxygen control available during these times. Furthermore, we excluded infants requiring less than 72 hours of respiratory support because their data could skew the results while their outcome was based on relatively little information and not representative for the average very preterm infant: they were either too stable and saturated fully immediately or they died soon after birth, which is highly unlikely to be related to choice of oxygen control device.

The difference in algorithm design and responsiveness could explain our results. Exact and clear information on the workings of the $CLiO_2$ algorithm is limited, but one can infer from the patent document that only in few cases FiO_2 is titrated below the *BaseFiO2* – a derivative of the average oxygen requirement. This could mean $CLiO_2$ is slower to reduce the administered oxygen, possibly leading to more hyperoxia. Moreover, a longer averaging time employed by $CLiO_2$ leads to a delay in pickup of deviations, which is further amplified by a timeout applied to prevent responding to erroneous SpO_2 values.[19] These choices in algorithm design can lead to tardier algorithm responsiveness, and may therefore lead to less time within the oxygen saturation target range.

Combined with the results of our cross-over study, the results show that choice of oxygen control device influences achieved time within oxygen saturation ranges in the preterm infant. Although choice of AOC may not be of great impact on achieved target range time over the entire course of admission, it could very well be that most morbidity finds its genesis in the periods of respiratory instability, during which a prominent difference is noted between the two AOC algorithms. A higher incidence of retinopathy of prematurity has been found to be associated with intermittent hypoxia[1] as well as hyperoxia, both of which occur more often in periods of respiratory instability. Indeed, in a matched cohort study we reported a lower incidence of retinopathy of prematurity for infants under OxyGenie automated oxygen control.[20] Although causality cannot be inferred from these results, all results of our recent studies are pointing in the same direction.

Conclusion

In this cohort study of oxygen saturation data collected from entire NICU admissions, the epoch in which OxyGenie was used was associated with significantly better oxygen saturation targeting when compared to the period in which $CLiO_2$ was used. This was accompanied by less time spent in hypoxia and hyperoxia for infants supported by OxyGenie automated oxygen control.

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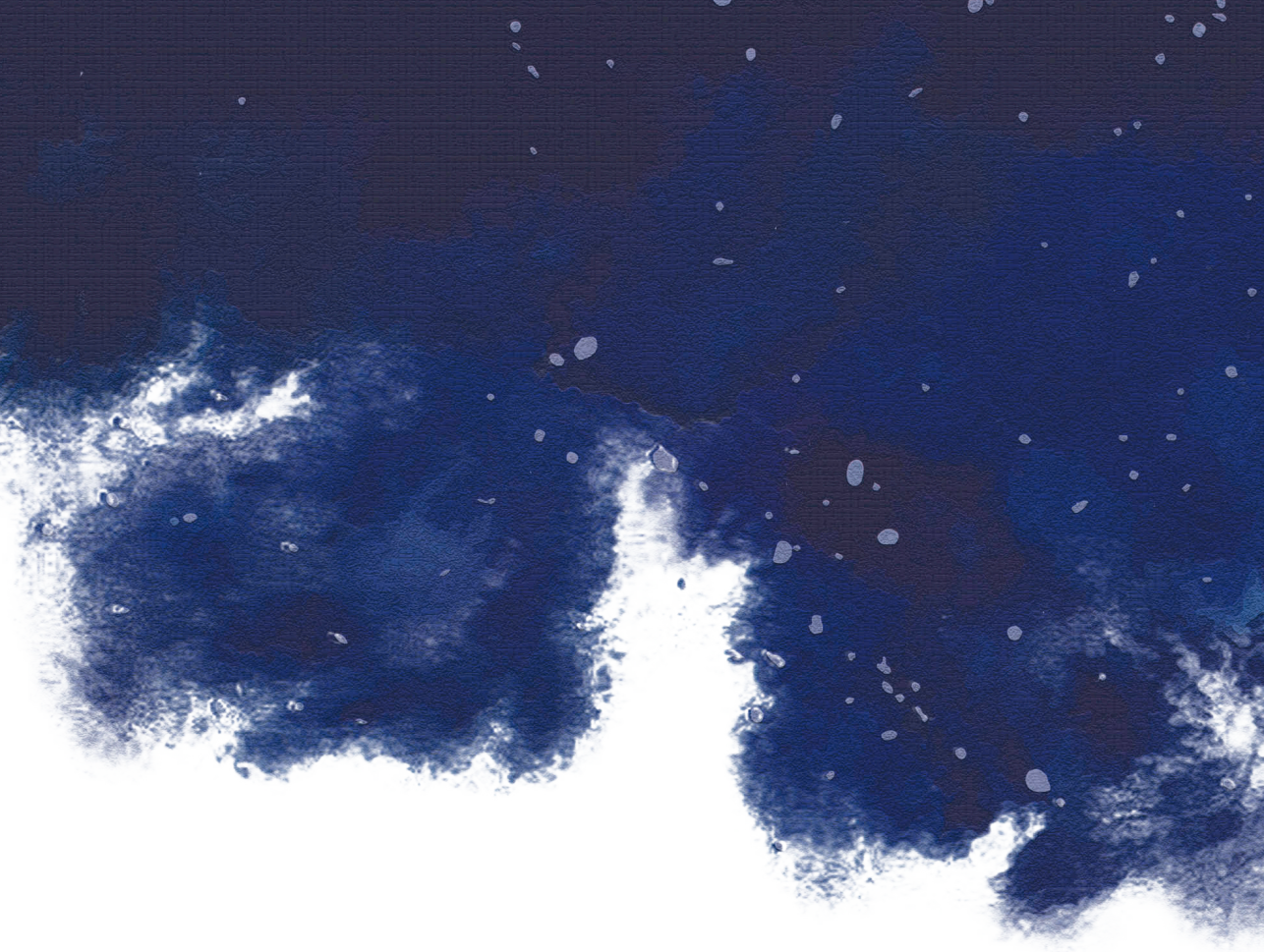

Chapter 5

Comparing descriptive statistics for retrospective studies from one-per-minute and one-per-second data

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Abstract

Background Large amounts of data are collected in neonatal intensive care units which could be used for research. It is unclear whether this data, usually sampled at a lower frequency, is sufficient for retrospective studies. We investigated what to expect when using one-per-minute data for descriptive statistics.

Methods One-per-second inspiratory oxygen and saturation was processed to one-per-minute data and compared on average, standard deviation, target range time, hypoxia, days of supplemental oxygen, and missing signal.

Results Outcomes calculated from data recordings (one-per-minute=92, one-per-second=92) showed very little to no difference. Sub analyses of recordings under 100 and 200 hours showed no difference.

Conclusion In our study descriptive statistics of one-per-minute data were comparable to one-per-second and could be used for retrospective analyses. Comparable routinely collected once per minute data could be used to develop algorithms or find associations retrospectively.

Keywords: neonatology, technology, data, methodology, retrospective.

Introduction

The wealth of routinely collected data in Neonatal Intensive Care Units (NICUs) has great potential. Morbidities such as bronchopulmonary dysplasia, retinopathy of prematurity and sepsis can possibly be predicted when coupling analyses of routinely measured vital signs or derivatives with outcomes. One example is the HeRO symphony system predicting sepsis from variability of heart rate.[1] In real time, algorithms can summarize relevant data, detect anomalies and notify bedside staff of risk factors for certain diseases. Routinely collected data could be used to develop algorithms or find associations retrospectively.

However, it is unclear at what frequency data should be sampled. In our NICU, data is often sampled at least once per second (one-per-second data, f.e. 1 heart rate value per second) for prospective studies, but routinely collected vital parameters are only sampled once per minute (one-per-minute data). This keeps up performance of the clinical patient data management system, and prevents high costs associated with storage of data. Other NICUs may have similar infrastructure in place with data already collected and available. Although the data could be collected at a higher frequency, it is unclear whether lower frequency data is already enough.

We hypothesized that lower frequency data could in some cases be sufficient to run retrospective studies. In this short report we investigated what to expect when using one-per-minute data abstracted from one-per-second data and investigated under what conditions one-per-minute data could be used.

Materials and methods

Routinely collected data from a previous study was used, the ethical review committee of Leiden Den Haag Delft provided a statement of no objection for obtaining and publishing the anonymized data (G19.075).[2] Data recordings were included from infants born under 30 weeks of gestation in our tertiary-level perinatal center between November 1st 2018 and March 15th 2020. Recordings were excluded if they contained no data on peripherally measured oxygen saturation (SpO_2).

Data collection and outcome measures

Parameters collected were 2-4s averaged SpO_2 measured by a weight-appropriate pulse-oximeter probe (LNCS Neo Masimo SET; Masimo Irvine, California, USA), and measured inspiratory fraction of oxygen (FiO_2). These data were sent from a

SLE6000 respirator (SLE Limited, South Croydon, UK) with OxyGenie automated oxygen titration to a MP70 bedside monitor (Philips, Eindhoven, the Netherlands) or, if no respiratory support was given, SpO_2 was measured by a Masimo module on the Philips monitor.

From the bedside monitor data is sent to two databases: a Philips Datawarehouse Connect feed to a database in which numerical data is stored once per second for 1 year; and a once per minute feed (HL7 data transfer protocol) which sends the exact value at the set interval time, which may be between 5-60 seconds (in our situation 1-per-minute). The HL7 message is picked up by our patient data management system (PDMS Metavision; IMDsoft, Tel Aviv, Israel). These data are stored for at least 15 years. No filtering, anti-aliasing, averaging or other processing is done on data prior to entry in the database.

To prevent synchronization issues caused by systems running on different timeclocks we chose to process the one-per-second data into one-per-minute data: one value per minute was extracted from one-per-second data by taking the value at the change of the minute (i.e. at 0 seconds). For both the one-per-second and one-per-minute data for SpO_2 we calculated the average, standard deviation, proportion of time within target range or hypoxia (<80). Within target range was defined as SpO_2 between 91%-95% irrespective of FiO_2, or 96%-100% when room air was being inspired. For the FiO_2 average and oxygen days were calculated. An oxygen day was defined as at least half of the data FiO_2 values of that day above 21%. Please note that this may not represent the true oxygen exposure, as the oxygen sensor can have a deviation of 1%. Finally, the number of data points and the difference between the first and last timepoint in each dataset were noted.

Data are presented as mean (SD) and median [IQR] with standard tests for normality. Data processing and analyses were done by custom written software in MATLAB (Matlab R2020b; The MathWorks Inc., Natick, Massachusetts, USA). No statistical hypothesis testing was done as we were not testing for a differences between treatments, but examining for comparability.

Results

There was data available from 92 patients, with a median of 1151774 [577843 - 2586608] one-per-second data points per patient. An excerpt from a data recording is shown in Figure 1. When processed to one-per-minute data, there were 19462 [9129 – 43162] data points left. The time difference between the first and last entry in the

data recording was 375 hours, 24 minutes and 46 seconds [157:59:33 – 762:23:11] for the one-per-second data, and 367 hours, 58 minutes and 30 seconds [155:11:45 - 757:12:00] for the one-per-minute data.

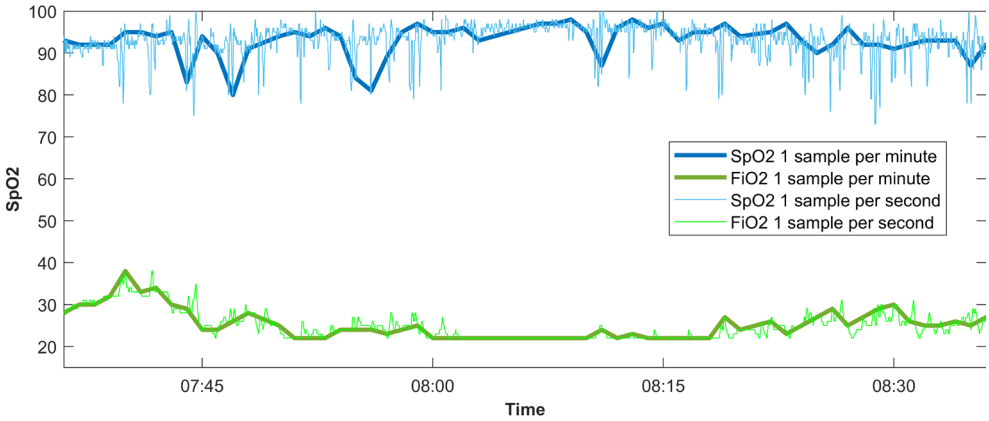

Figure 1. *An example of a data recording displaying the effect of taking one sample every sixty seconds from a 1-per-second data recording. SpO_2, oxygen saturation measured by pulse-oximetry; FiO_2, fraction of inspired oxygen.*

In the one-per-second data, the mean SpO_2 was 94.96 (1.88) vs. 94.96 (1.87) in the one-per-minute data (Table 1) and the standard deviation of SpO_2 was 3.14 (0.92) vs. 3.15 (0.91) respectively. SpO_2 was found to be within the target range in 70.96 [57.16 - 91.50] % of the time in the one-per-second data, and in 71.06 [57.00 - 91.53] % of the time in one-per-minute data. Hypoxic values under 80% were found in 0.36 [0.09 - 0.85] % of SpO_2 values in the one-per-second dataset vs. 0.35 [0.10 - 0.85] % of SpO_2 values for the one-per-minute dataset. Missing values were also similar (2.06 [1.59 - 2.91] % vs. 2.06 [1.52 - 2.87] %). Bland-Altman plots can be found in the supplemental figures S1-S6 at the end of this chapter.

Table 1. Analysis of recordings

n=92		one-per-second	one-per-minute
Average SpO_2	mean (SD)	94.96 (1.88)	94.96 (1.87)
Standard deviation SpO_2	mean (SD)	3.14 (0.92)	3.15 (0.91)
Percentage SpO_2 in target range†	median [IQR]	70.96 [57.16 - 91.50]	71.06 [57.00 - 91.53]
Percentage SpO_2 <80%	median [IQR]	0.36 [0.09 - 0.85]	0.35 [0.10 - 0.85]
Average FiO_2	median [IQR]	22.65 [21.67 - 24.56]	22.70 [21.69 - 24.59]
Days of supplemental oxygen	median [IQR]	0 [0-2]	0 [0-2]
Percentage missing SpO_2	median [IQR]	2.06 [1.59 - 2.91]	2.06 [1.52 - 2.87]
Number of data points	median [IQR]	1151774 [577843 - 2586608]	19462 [9129 - 43162]
Duration hours:min:sec	median [IQR]	375:24:46 [157:59:33 - 762:23:11]	367:58:30 [155:11:45 - 757:12:00]

FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation. † 91% <= SpO_2 <= 95% or SpO_2 >= 96% while FiO_2 = 0.21

The per-patient average inspired FiO_2 was 22.65 [21.67 - 24.56] vs. 22.70 [21.69 - 24.59], and there was no difference in oxygen days (0 [0 – 2] in both datasets).

Sub analyses of groups with only less than 100 hours (table 2), 200 hours and half of the total dataset showed similar results with little difference between one-per-second and one-per-minute data.

Table 2. Sub analysis of shorter recordings

Recordings <100 hours (n=11)		**one-per-second**	**one-per-minute**
Average SpO_2	mean (SD)	96.74 (1.74)	96.74 (1.67)
Standard deviation SpO_2	mean (SD)	3.07 (1.04)	3.17 (1.08)
Percentage SpO_2 in target range†	median [IQR]	93.58 [52.76 - 98.80]	93.87 [55.43 - 98.85]
Percentage SpO_2 <80%	median [IQR]	0.60 [0.08 - 0.81]	0.75 [0.14 - 0.96]
Average FiO_2	median [IQR]	21.05 [21.00 - 22.03]	21.05 [21.00 - 22.13]
Days of supplemental oxygen	median [IQR]	0 [0-2]	0 [0-2]
Percentage missing SpO_2	median [IQR]	2.85 [1.43 - 5.16]	3.04 [1.41 - 5.14]
Number of data points	median [IQR]	161742 [82864 - 188130]	2699 [1381 - 3364]
Duration hours:min:sec	median [IQR]	51:18:47 [32:40:20 - 51:17:00]	51:17:00 [24:13:00 - 62:04:00]
Recordings <200 hours (n=28)		**one-per-second**	**one-per-minute**
Average SpO_2	mean (SD)	95.43 (2.06)	95.43 (2.04)
Standard deviation SpO_2	mean (SD)	3.00 (1.01)	3.03 (1.04)
Percentage SpO_2 in target range†	median [IQR]	90.21 [60.06 - 96.47]	90.49 [59.62 - 94.69]
Percentage SpO_2 <80%	median [IQR]	0.32 [0.07 - 0.92]	0.30 [0.07 - 1.01]
Average FiO_2	median [IQR]	21.99 [21.01 - 25.40]	21.95 [21.01 - 25.44]
Days of supplemental oxygen	median [IQR]	0 [0-3]	0 [0-3]
Percentage missing SpO_2	median [IQR]	2.58 [1.65 - 3.45]	2.58 [1.48 - 3.28]
Number of data points	median [IQR]	507425 [175763 - 542365]	8458 [3027 - 9041]
Duration hours:min:sec	median [IQR]	149:49:41 [55:26:45 - 154:20:26]	149:48:30 [55:25:45 - 154:20:00]

FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation. † 91% <= SpO_2 <= 95% or SpO_2 >= 96% while FiO_2 = 0.21

Discussion

In this study we found little to no difference when comparing descriptive statistics of one-per-minute data and one-per-second data from the same source. This included clinically relevant outcomes as proportion of time within oxygen saturation target range, hypoxia and days of supplemental oxygen. Sub analyses of recording under 100 or 200 hours showed no difference. The results suggest that routinely collected data recordings of comparable length or longer could be used for retrospective studies.

Although using routinely collected vital parameters for big data analysis and machine learning is increasingly popular, to our knowledge there is no literature available describing the minimum data sampling frequency for our purpose. From the field of data signal processing the Nyquist-Shannon sampling theorem[3] provides us with a guideline for a sufficient sample-rate, but this is aimed at reproducing the original signal, and not the summarizing statistic we often require for our retrospective studies.

One could argue that taking a sample every minute from continuous vital signs monitoring is somewhat analogous to research in general. It is uneconomical to study an entire population, thus we take a representative sample. When the change of being sampled is related to the outcome there is a chance of biased results. Although our sample is not at random, the value is always extracted in the first second of the minute. It is unlikely that a vital parameter like heart rate is systematically lower in the first second of the minute or in other words related to the outcome. There may be a detectable circadian trend in the average heart rate, but the instantaneous heart rate should not be related to a certain second within a minute.

Limitations of our study are that 1-per-minute data cannot be used to calculate the length of vital sign episodes, for example the duration of a hypoxic episode, or other more elaborate outcomes from complex signal processing techniques. We have only investigated descriptive statistics of SpO_2 and FiO_2 and most of the data recordings had a minimum duration of 100 hours. It should also be noted that intra-recording differences were present but these are averaged out over the entire set. Finally, to prevent synchronization issues we did not compare our PDMS data directly with our higher frequency data, but down-sampled the latter. However, because in neither case filtering, anti-aliasing or other processing was done they are comparable.

Conclusion

In our study descriptive statistics of lower frequency data were comparable to high frequency data and could be used for retrospective analyses. Comparable routinely collected once per minute data could be used to develop algorithms or find associations retrospectively.

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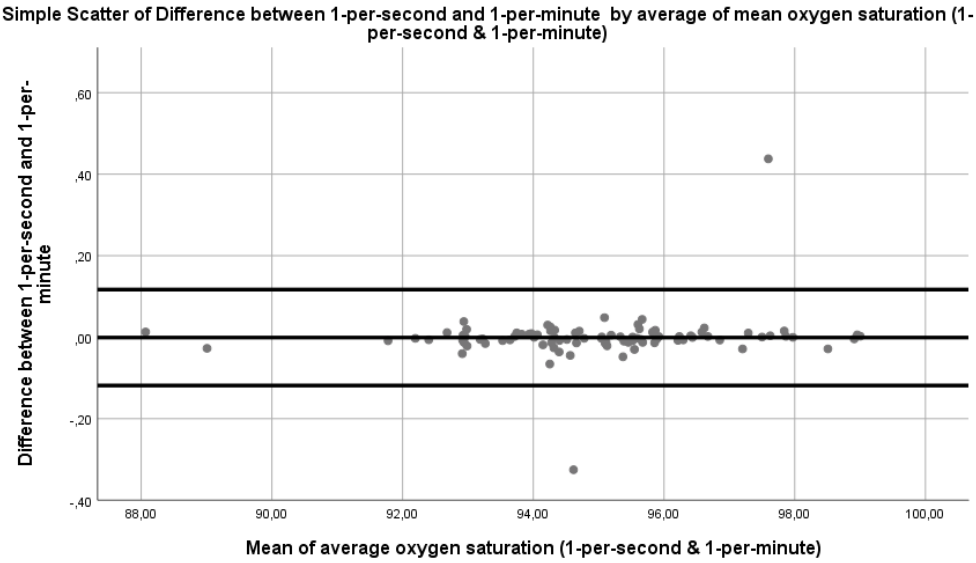
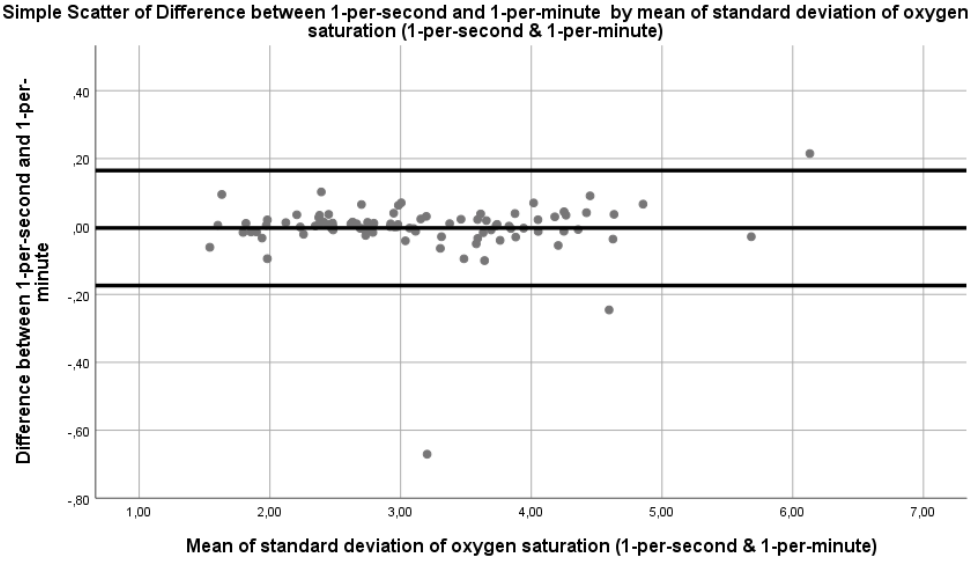
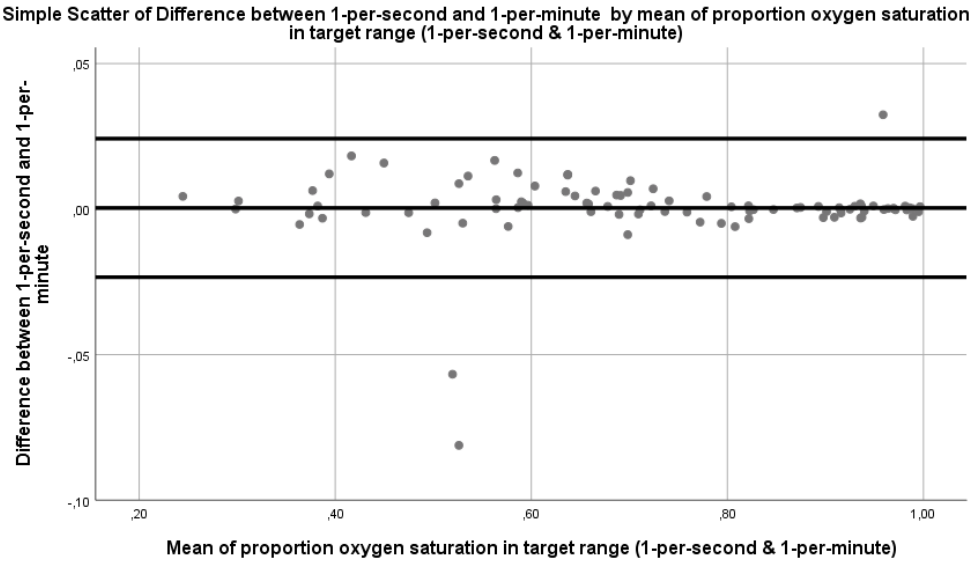
Supplemental material



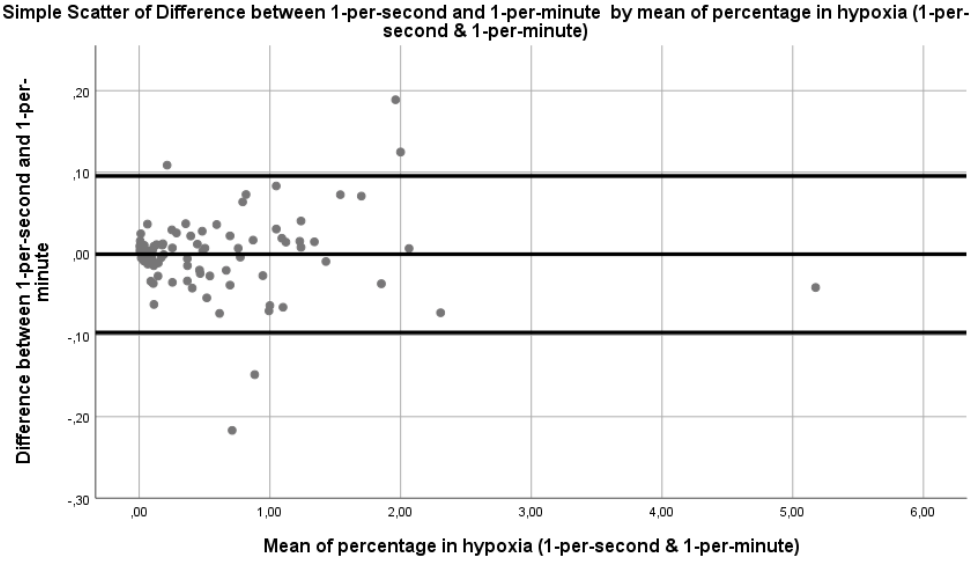
Supplementary Figure 1. *Bland-Altman plot of average oxygen saturation 1-per-second data & 1-per-minute data*



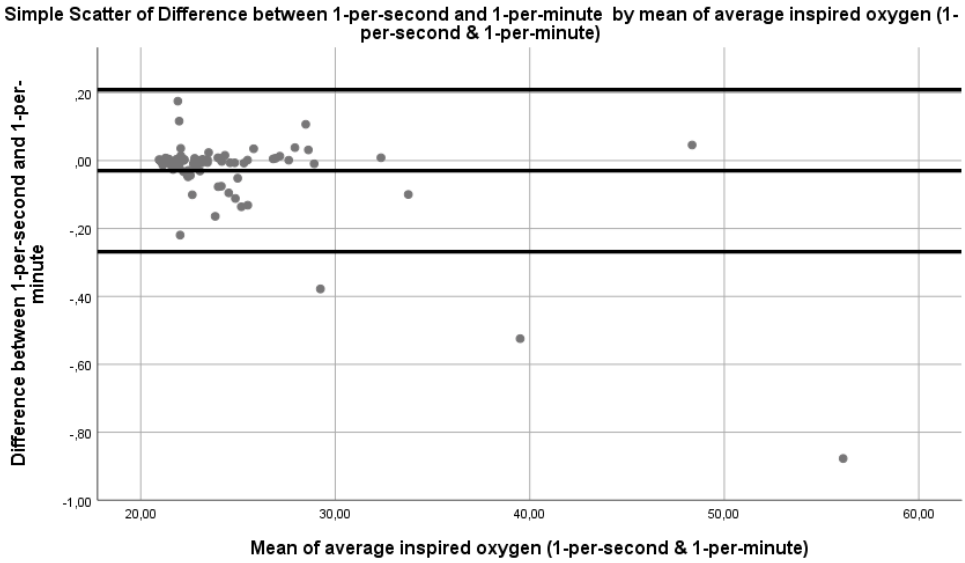
Supplementary Figure 2. *Bland-Altman plot of standard deviation oxygen saturation 1-per-second data & 1-per-minute data*



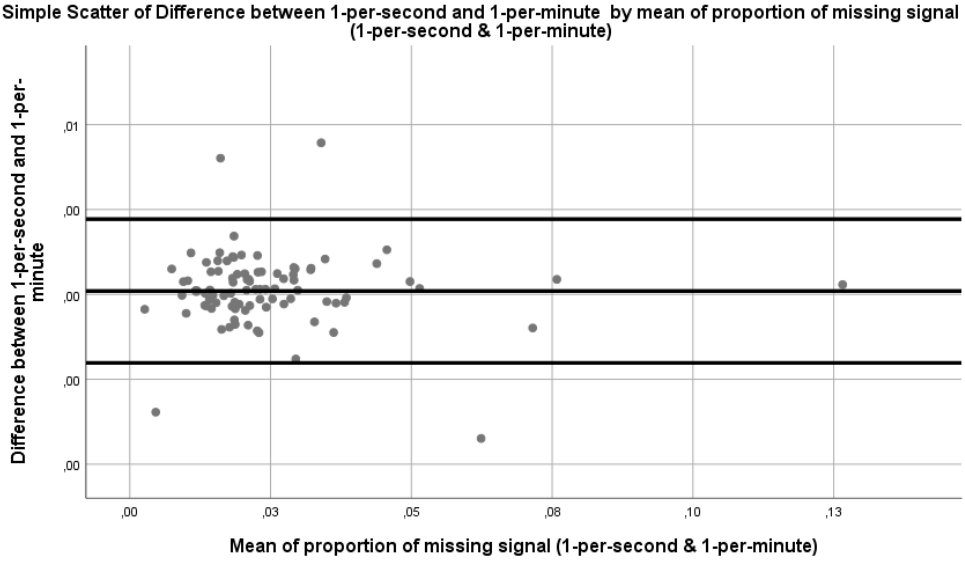
Supplementary Figure 3. *Bland-Altman plot of oxygen saturation in target range 1-per-second data & 1-per-minute data*



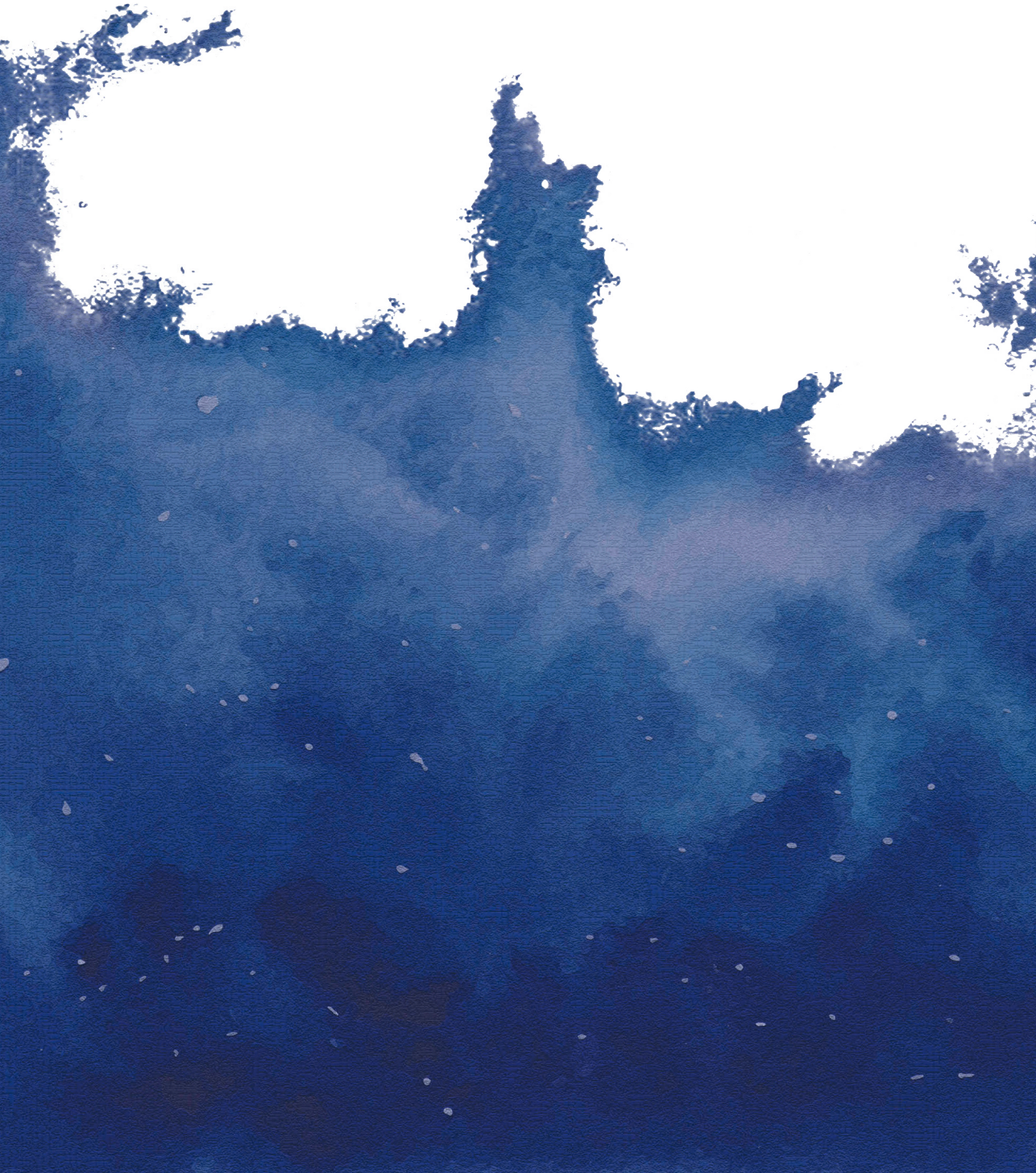
Supplementary Figure 4. *Bland-Altman plot of hypoxia 1-per-second data & 1-per-minute data*



Supplementary Figure 5. *Bland-Altman plot of average inspired oxygen 1-per-second data & 1-per-minute data*

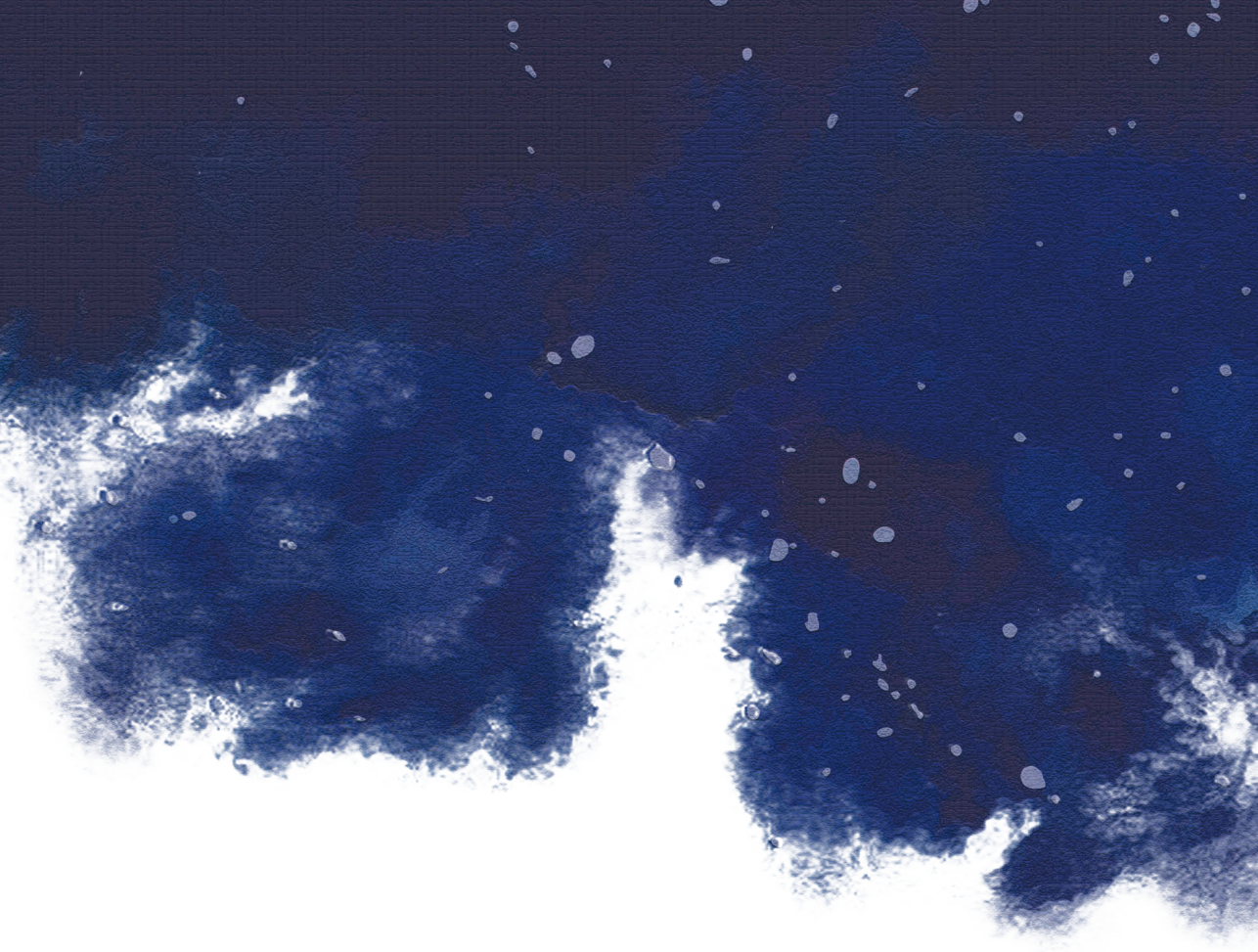


Supplementary Figure 6. *Bland-Altman plot of missing signal 1-per-second data & 1-per-minute data*



Part IV

Clinical and long-term outcome after using automated oxygen controllers for preterm infants during NICU stay



What is known

- Prolonged and intermittent oxygen saturation deviations are associated with mortality and prematurity-related morbidities.
- Automated oxygen controllers can increase the time spent within oxygen saturation target range.

What is new

- Implementation of automated oxygen control as standard of care did not lead to a change in mortality or morbidity during admission.
- In the period after implementation of automated oxygen control there was a shift toward more non-invasive ventilation.

Chapter 6

The effect of automated oxygen control on clinical outcomes in preterm infants: a pre- and post-implementation cohort study

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Abstract

Several studies demonstrated an increase in time spent within target range when automated oxygen control (AOC) is used. However, the effect on clinical outcome remains unclear. We compared clinical outcomes of preterm infants born before and after implementation of AOC as standard of care. In a retrospective pre-post implementation cohort study of outcomes for infants of 24-29 weeks gestational age receiving respiratory support before (2012-2015) and after (2015-2018) implementation of AOC as standard of care were compared. Outcomes of interest were mortality and complications of prematurity, number of ventilation days and length of stay in the Neonatal Intensive Care Unit (NICU). A total of 588 infants were included (293 pre- vs 295 in the post-implementation cohort), with similar gestational age (27.8 weeks pre- vs 27.6 weeks post-implementation), birth weight (1033 grams vs 1035 grams) and other baseline characteristics. Mortality and rate of prematurity complications were not different between the groups. Length of stay in NICU was not different, but duration of invasive ventilation was shorter in infants who received AOC (6.4 ±10.1 vs 4.7 ±8.3, p=0.029).

Conclusion: In this pre-post comparison, the implementation of AOC did not lead to a change in mortality or morbidity during admission.

Keywords: Hypoxemia; hyperoxia; closed-loop; algorithm; neonate; respiratory

Introduction

Preterm infants born under 30 weeks of gestation spend a long period in the neonatal intensive care unit (NICU), where they experience considerable morbidities during and after their admittance.[1] Often they receive respiratory support which includes supplemental oxygen, administered with the aim of keeping oxygen saturation (SpO_2) within a prescribed target range (TR) and preventing hypoxia and hyperoxia. Both frequent and prolonged SpO_2 deviations have been associated with mortality and prematurity-related morbidities, including retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and neuro-developmental impairment.[2-5]

Titrating the fraction of inspired oxygen (FiO_2) to keep SpO_2 within the TR has proved challenging. Several studies have reported on the difficulty of SpO_2 targeting when FiO_2 is titrated manually, reflected in a proportion of SpO_2 TR time of around 50% or less. Lack of knowledge and a high workload for the caregivers were described as important factors for low compliance.[6-10] Continuous oxygen titration by an automated oxygen control (AOC) device aims to circumvent these problems and improve SpO_2 targeting whilst reducing the bedside workload. During AOC, signals from a pulse oximeter are continuously input to a computer algorithm which determines what adjustments to FiO_2 are necessary based on the oxygenation feedback.[11] The changes to FiO_2 are actuated automatically within a ventilator or other respiratory support device. Studies investigating the effect of AOC on oxygen saturation over 24 hour periods have demonstrated a beneficial effect, with infants spending more time within TR, accompanied by a decrease of severe hypoxia and hyperoxia.[12-19]

AOC was implemented as standard care in the Neonatal Intensive Care Unit (NICU) of the Leiden University Medical Center (LUMC) in August 2015. We recently reported the effect of this implementation on oxygen saturation in preterm infants during admission.[20] Infants spent more time within TR and less time with SpO_2 >95%, but there was a lesser effect on duration of SpO_2 <80%. Thus far, none of the studies comparing manual oxygen control with AOC have reported the effect on clinical outcomes. We therefore aimed to assess the effect of implementation of AOC as standard care on outcomes in preterm infants during their hospital admission.

Materials and methods

Study design

A retrospective observational study was performed in the NICU of the Leiden University Medical Center (LUMC). This is a tertiary-level perinatal centre with an average of 100 intensive care admissions per year of infants born before 30 weeks of gestation. The ethical board of the LUMC provided a statement of no objection for obtaining and publishing the anonymised data.

Infants born from 24+0 until 29+6 weeks of gestation and admitted to the NICU between May 1st 2012 and December 31st 2018 were included in the study. Infants were excluded from the analysis if admitted >24 hours after birth, had major congenital abnormalities, or required no invasive or non-invasive respiratory support during their admission.

The pre-implementation cohort consisted of infants admitted between May 1st 2012 and June 17th 2015 who received manual FiO_2 titration from bedside staff according to local guidelines. The post-implementation cohort was composed of infants admitted from October 18th 2015 to December 2018, allowing for a washout period of 4 months.

Data collection

All data were retrieved from our patient data management system (Metavision; IMDsoft, Tel Aviv, Israel). The following outcomes were noted: mortality, ROP, BPD, NEC, culture proven sepsis, intraventricular haemorrhage (IVH), PVL, and length of NICU stay. The duration of respiratory therapy and supplemental oxygen (measured fraction of inspiratory oxygen above 0.21) was calculated from our patient data management system which routinely samples clinical parameters and ventilator settings once per minute. Mortality until one month after corrected term age was noted. The ophthalmologists in our hospital implemented the Early Treatment of Retinopathy of Prematurity study (ETROP) classification for findings of retinal examination in 2013 and ROP was defined according to this classification.[21, 22] When retinal findings were described otherwise, researcher *NJO* classified according to the ETROP criteria retrospectively, assisted by an ophthalmologist where necessary. An assessment for BPD was made at 36 weeks postmenstrual age, using where necessary discharge papers from regional hospitals and classified as mild, moderate, or severe according to criteria from the 2000-NICHD consensus. [23] NEC was defined

according to the modified Bell staging criteria.[24] IVH was classified according to Papile's adapted classification [25, 26], PVL according to the de Vries' classification. [27]

Oxygen titration

Following the recent European guidelines [28], the SpO_2 TR in our NICU changed from 85%-95% to 90-95% in November 2014. The ventilator used for respiratory support was the AVEA ventilator (Vyaire, Yorba Linda CA, United States) during the majority of the study period. In August 2015 the $CLiO_2$ ™ algorithm (Closed Loop of inspired Oxygen) [14] was implemented in the AVEA ventilator. This is a hybrid rule-based adaptive algorithm designed for AOC in preterm infants. In November 2018 the SLE6000 (SLE, London, United Kingdom) was introduced as standard of care ventilator. The SLE6000 has the VDL1.1 algorithm [29] built-in as the Oxygenie® option, a PID algorithm with several enhancements. Both algorithms are described in more detail elsewhere. [30]

Data analysis

Data are presented as mean (SD), median (range) or number (percentage) as appropriate, with standard tests for normality. Statistical comparison was performed using an independent t-test, a Mann-Whitney U test, a chi-square or Fisher's exact respectively. Statistical analyses were performed by IBM SPSS Statistics for Mac, version 25 (IBM, Armonk, New York, USA). Two-tailed P-values of <0.05 were considered statistically significant.

Results

Patient characteristics

During the study period 588 infants within the gestation range 24-29 weeks were admitted to the LUMC NICU, of which 8 were excluded from analysis (admitted >24 h, n=6; major congenital anomaly, n=2). In the pre-implementation cohort 293 infants were included and compared with 295 infants in the post-implementation cohort. There were no significant differences in baseline characteristics between the groups (table 1), so we can assume that treatment assignment cannot be retrospectively related to patient characteristics. The LUMC is a national referral centre for foetal therapy, which is reflected by a high number of multiple pregnancies in both groups.

Table 1. Patient characteristics

Patient characteristics **N = 588**	**Pre-AOC** **N = 293**	**Post-AOC** **N = 295**	**p value***
Gestational age in weeks, mean (SD)	27.8 (1.5)	27.6 (1.6)	0.12
Birth weight in grams, mean (SD)	1038 (292)	1035 (260)	0.88
Small for gestational age, n (%)	32 (10.9)	21 (7.2)	0.15
Males, n (%)	165 (56.3)	155 (52.5)	0.36
Antenatal corticosteroids, n (%)	250 (86.2)	255 (87.3)	0.69
Caesarean delivery, n (%)	145 (49.5)	157 (53.2)	0.37
Multiple pregnancy, n (%)	115 (39.2)	99 (33.5)	0.45
of which monochorionic twins, n (%)	71 (61.7)	64 (64.6)	
Perinatal asphyxia, n (%)	4 (1.4)	8 (2.7)	0.25
Apgar score at 5 minutes, median (range)	8 (2-10)	8 (1-10)	0.87

**Statistical analysis with independent T-test, chi-square, or nonparametric Mann-Whitney U test as appropriate*

Clinical outcomes

Mortality up until one month beyond full term corrected age was similar between groups (pre vs. post implementation: 30 (10.2%) vs 32 (10.8%); p=0.81; table 2). There were no differences in morbidities between the groups, except that the incidence of culture proven sepsis in the post-implementation group was higher (96 (32.8%) vs 121 (41.0%); p = 0.038). The length of stay in the NICU was not different between groups (32.9 ±15.4 vs 35.4 ±27.0; p = 0.27).

Table 2. Clinical outcomes

	Pre-AOC	Post-AOC	P value*
Died, n (%)	30 (10.2)	32 (10.8)	0.81
Culture proven sepsis, n (%)	96 (32.8)	121 (41.0)	0.038
Necrotising enterocolitis (> stage 2A), n (%)	25 (8.5)	27 (9.2)	0.79
Retinopathy of prematurity			
none, (%)	225 (90.0)	226 (90.0)	
ETROP 1, n (%)	16 (6.4)	22 (8.8)	0.14
ETROP 2, n (%)	9 (3.6)	3 (1.2)	
Received laser coagulation, n (%)	13 (5.2)	14 (5.6)	0.84
Intraventricular haemorrhage (≥ stage 2), n (%)	55 (18.8)	50 (16.9)	0.56
Periventricular leukomalacia (≥ stage 2), n (%)	4 (1.4)	6 (2.0)	0.75
Days in NICU, mean (SD)	32.1 (25.6)	35.1 (27.2)	0.18
Bronchopulmonary dysplasia			
severe, n (%)	36 (14.0)	48 (18.6)	0.10
moderate, n (%)	12 (4.7)	4 (1.6)	
mild, n (%)	45 (17.4)	38 (14.7)	

*Necrotising enterocolitis according to modified Bell staging criteria; ETROP, early treatment of retinopathy of prematurity; Intraventricular haemorrhage according to Papile's classification; Days on NICU until transfer to peripheral hospital or discharge; Bronchopulmonary dysplasia classification according to Dutch paediatric guidelines. *Statistical analysis with independent T-test, chi-square, Fisher's exact, or nonparametric Mann-Whitney U test as appropriate*

Respiratory therapy

Use of a minimally invasive technique for surfactant administration was more prevalent in the post-implementation cohort (table 3). In the post-implementation cohort, the duration of non-invasive mechanical support was longer (CPAP: 10.8 ±11.7 vs 13.9 ±15.2; HFNC: 2.3 ±5.4 vs 5.8 ±8.1), whereas the duration of invasive mechanical ventilation was shorter (6.4 ±10.1 vs 4.7 ±8.3). More supplemental oxygen was given in the post-implementation cohort (8.0 ±13.5 vs 11.3 ±16.9). Otherwise both groups received similar respiratory therapy, including a similar average inspired oxygen while on respiratory support (first week: 25.2% ±10.2% vs 24.8% ±8.8%; entire stay: 25.7% ±9.8 vs 25.7% ±9.1).

Table 3. Respiratory therapies

	Pre-AOC	Post-AOC	P value*
High frequency oscillation, n (%)	56 (19.1)	51 (17.3)	0.57
Inhaled nitric oxide, n (%)	31 (10.6)	32 (10.5)	0.92
Dexamethasone, n (%)	27 (9.2)	29 (9.8)	0.80
Surfactant, n (%)	164 (56.0)	147 (49.8)	0.14
via intubation, n (%)	131 (44.7)	76 (25.8)	< 0.001
via minimally invasive technique, n (%)	33 (11.3)	71 (24.1)	
Invasive ventilation days, mean (SD)	6.4 (10.1)	4.7 (8.3)	0.029
CPAP days, mean (SD)	10.8 (11.7)	13.9 (15.2)	0.006
HFNC days, mean (SD)	2.3 (5.4)	5.8 (8.1)	< 0.001
Low flow days, mean (SD)	1.5 (3.4)	1.5 (3.2)	0.86
Supplemental oxygen days, mean (SD)	8.0 (13.5)	11.3 (16.9)	0.008
Average inspired oxygen			
during first week, mean (SD)	25.2 (10.2)	24.8 (8.8)	0.58
during entire admittance, mean (SD)	25.7 (9.8)	25.7 (9.1)	0.93

*CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; Average inspired oxygen (expressed as %) while on respiratory support. *Statistical analysis with independent T-test or chi-square test as appropriate*

Discussion

In this retrospective study, we compared two large cohorts of preterm infants admitted to the NICU before and after implementation of AOC. Implementation led to no change in mortality and morbidities in preterm infants admitted to the NICU, despite a shift towards more non-invasive ventilation. The rates of mortality and morbidities were not very different from previous studies reporting short term outcome in infants < 30 weeks of gestation. [1, 31] Although we recently demonstrated that infants spent more time within TR after implementation of AOC, this does not seem to have had a clinically relevant impact in a large cohort.

This is the first study reporting on the effect of AOC on clinical outcome in preterm infants when this is implemented as standard of care. Several observational studies and clinical trials have demonstrated a beneficial effect of AOC on time spent within TR.[12-19] Although all authors speculated that this could affect clinical and neurodevelopmental outcome, these studies were not designed to demonstrate a difference in clinical outcome. To the best of our knowledge there are no completed studies directly relating the achieved time within TR to clinical outcome. However, post-hoc analysis of the SUPPORT trial[7] demonstrated an increase in mortality for infants with a lower median SpO_2. This could suggest that when 91%-95% is considered the appropriate TR, more time under this range could lead to a lower median SpO_2 and associated increase in mortality. Post-hoc analysis from the BOOST-II UK trial[32] also demonstrated that a lower achieved oxygen distribution was associated with an increase in NEC and mortality.

Using AOC in clinical practice could lead to a leftward shift of the SpO_2 distribution. Bedside staff would seem to prefer to target higher SpO_2 values within a prescribed range,[33] whereas AOC devices for the most part target the middle SpO2 value of the TR, potentially leading to a lower median SpO_2. A further consideration raised in regard to AOC implementation is that clinical deterioration may be masked, with possible adverse effects.[34] However none of the AOC trials have reported this and our current findings showed no sign of this possible detrimental effect, with rates of mortality and morbidity similar between cohorts and in relation to previous studies.[1, 31] Indeed, it can be argued that continual assessment and display of the basal oxygen requirement as well as the number and magnitude of interventions by the AOC device could be used as an additional objective indicator of clinical deterioration. A large randomised controlled trial, the FiO_2-C study [35], comparing AOC using any of the commercially available algorithms with manual titration, is currently being undertaken and will provide more data on the effect of AOC on clinical outcome.

The lack of effect of AOC on clinical outcome could be attributed to several causes. Some of the outcomes being assessed are relatively uncommon, and although we compared two large cohorts, effect sizes in outcome differences are likely to be small given the power in the study. Secondly, in our earlier study[16] the increased time in TR while using AOC was mainly attributable to a substantial decrease in SpO_2 values above TR, whereas the time with SpO_2 <80% was similar to manual titration. It could be that outcome is more largely influenced by the frequency and duration of hypoxia and hypoxic events,[36] and by time above TR to a lesser extent. Finally, several changes to standard of care have been made during the study span which could have simultaneously influenced the outcome in either direction. For example, in November 2014 the lower limit of the TR was changed from 85% to 90% (likely narrowing the SpO_2 distribution and shifting it to the right), and minimally invasive surfactant therapy was introduced. There may have been other factors we did not measure. A limitation of this study could be these unmeasured factors as they are not adjusted for.

It is conceivable and plausible that the introduction of AOC has contributed to a shift toward more non-invasive ventilation in our NICU. It may have contributed in two ways, firstly by rendering more stability to oxygenation and secondly by reducing the baseline oxygen requirement, as a direct consequence of continuous titration of FiO_2 to target the midpoint of the SpO_2 range. Although the retrospective nature of this study precludes the drawing of a definitive conclusion, the shift towards more non-invasive ventilation could prove promising. Prolonged mechanical ventilation is a risk factor for complications and has been directly associated with poor neurodevelopmental outcome. [37]. In planned further studies, follow-up outcomes at 2 years will be compared between these cohorts.

Beyond its retrospective nature, another limitation of our study is that the actual time infants received AOC was not recorded. Local policy is to disable AOC once SpO_2 values >98% are recorded continuously for 30 minutes without supplemental oxygen, and thus it is possible that some infants only received AOC during a short period, diminishing any treatment effect. However, as we took the entire sample of patients admitted during the period of 2012-2018, the results are likely to be generalisable for NICUs in similar settings.

Conclusion

The implementation of AOC in a tertiary NICU had no significant effect on clinical outcomes at hospital discharge in this retrospective study of preterm infants, but was associated with a shift toward more non-invasive ventilation.

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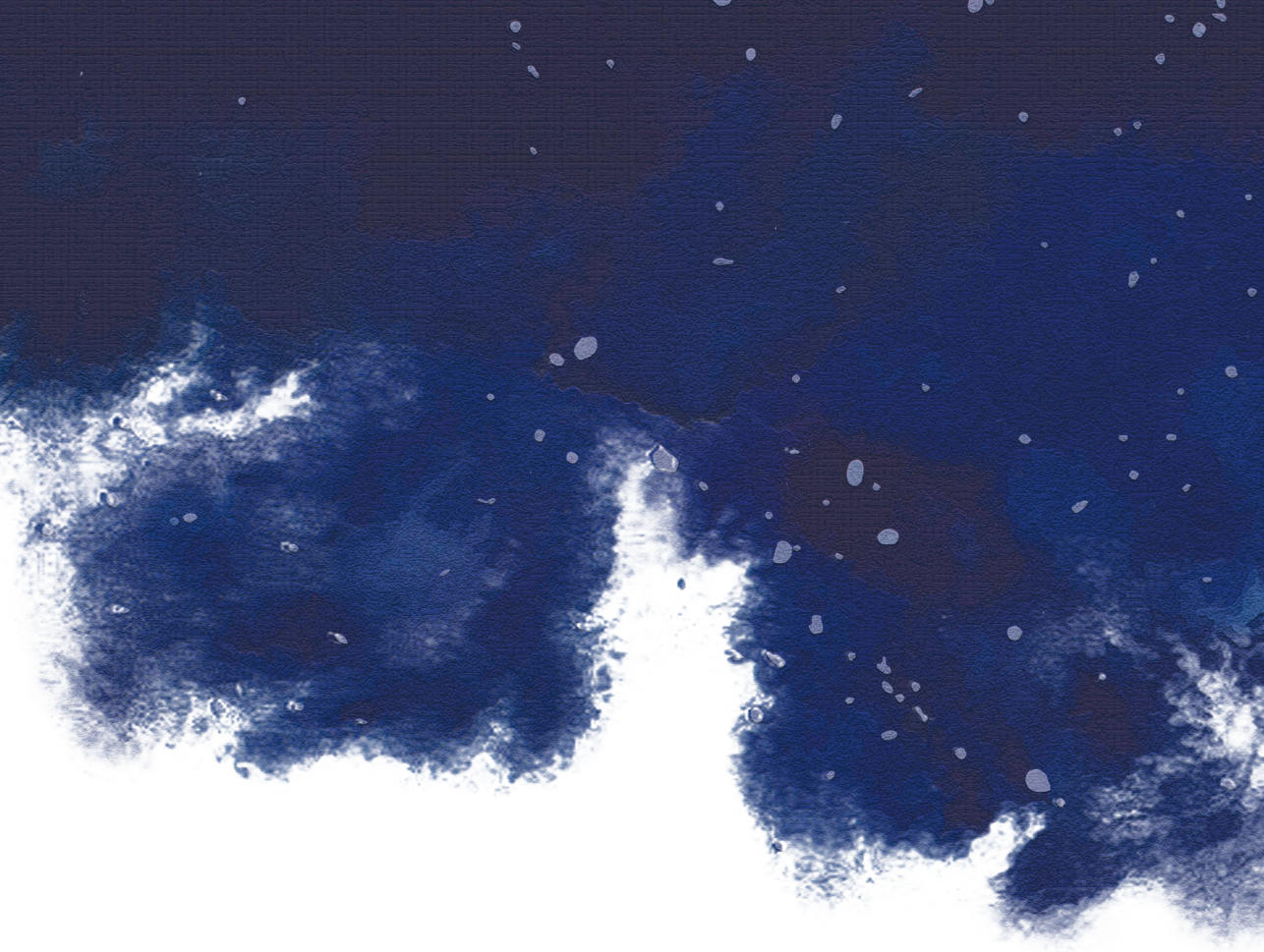

Chapter 7

Automated oxygen control for very preterm infants and neurodevelopmental outcome at two years – a retrospective cohort study

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Abstract

Faster resolution of hypoxaemic or hyperoxaemic events in preterm infants may reduce long-term neurodevelopmental impairment. Automatic titration of inspiratory oxygen increases time within the oxygen saturation target range and may provide a more prompt response to hypoxic and hyperoxic events. We assessed routinely performed follow-up at two years of age after implementation of automated oxygen control (AOC) as standard care and compared this with a historical cohort. Neurodevelopmental outcomes at two years of age were compared for infants born at 24-29 weeks gestational age before (2012-2015) and after (2015-2018) implementation of AOC as standard of care. Primary outcome was a composite outcome of either mortality or severe neurodevelopmental impairment (NDI), other outcomes assessed were mild-moderate NDI, Bayley-III composite scores, cerebral palsy GMFCS and CBCL problem behaviour scores. 289 infants were eligible in the pre-AOC epoch and 292 in the post-AOC epoch. Baseline characteristics were not significantly different. 51 infants were lost to follow-up (pre-AOC 6.9% (20/289), post-implementation 10.6% (31/292)). The composite outcome of mortality or severe NDI was observed in 17.9% pre-AOC (41/229) vs. 24.0% (47/196) post-AOC (p=0.12). No significant differences were found for the secondary outcomes such as mild-moderate NDI, Bayley-III composite scores, cerebral palsy GMFCS and problem behaviour scores, with the exception of parent-reported readmissions until moment of follow-up which was less frequent post-AOC than pre-AOC.

Conclusion In this cohort study, implementation of automated oxygen control in our NICU as standard of care for preterm infants led to no statistically significant difference in neurodevelopmental outcome at two years of age.

Keywords: Hypoxemia; hyperoxia; closed-loop; algorithm; neonate; respiratory; follow-up

Introduction

Maintaining appropriate oxygenation in preterm infants admitted to the Neonatal Intensive Care Unit (NICU) has proved challenging but of importance to outcome. Neonatal morbidity and mortality are linked to hypoxemia, hyperoxaemia and choice of SpO_2 target range.[1-3] Post-hoc analysis of the Canadian Oxygen Trial data associated adverse neurodevelopmental outcome with hypoxia, in particular hypoxic episodes lasting more than 1 minute.[4] Hunt et al. reported similar evidence in their report of home-monitored preterm and term infants: having five or more apneic/bradycardic events was associated with a 5.6 point lower mental development index.[5] Neither study showed a significant difference for episodes under 1 minute. These results could indicate that faster resolution of hypoxaemic or hyperoxaemic events may reduce long-term neurodevelopmental impairment (NDI).

Automatic titration of inspired oxygen (FiO_2) can provide a more prompt response to these events than when titration is done manually by bedside staff. With the aim of keeping SpO_2 in a specified target range, an automated oxygen controller (AOC) built into the respirator continually evaluates on the measured SpO_2 and makes changes in FiO_2 where necessary. Beside potential benefits to workload, it has been demonstrated that several commercially available controllers increase the time preterm infants spent within the target range while used for 2-24 hour periods, and prolonged episodes of hypoxemia and hyperoxaemia are reduced.[6-13] This was also reflected in a study[14] done in our centre while using an AOC as standard of care. However, to date evidence on clinically relevant neonatal outcome is scarce,[15] and lacking altogether beyond the neonatal period.

In August 2015 AOC was implemented as standard of care in the Neonatal Intensive Care Unit (NICU) of the Leiden University Medical Center (LUMC). Recently we reported the effect of this implementation on clinical outcome of preterm infants during admission.[15] Implementation did not lead to a change in mortality or rate of retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), or bronchopulmonary dysplasia (BPD), but there was less invasive ventilation in the post-implementation cohort. Thus far, none of the studies comparing manual oxygen control with AOC have reported the effect on long-term neurodevelopmental outcome. We therefore aimed to compare the neurodevelopmental outcome of preterm infants born before and after the implementation of AOC as standard care with routinely performed two year follow-up assessment.

Materials and methods

Study design

A retrospective study was conducted in the NICU of the LUMC, a tertiary-level perinatal centre with annually around 100 intensive care admissions of infants born before 30 weeks of gestation. A statement of no objection (G19.075) for obtaining and publishing the anonymised data was provided by the ethical board of the LUMC.

Infants admitted to the NICU between May 1, 2012 and December 31, 2018 and born between 24 and 29 weeks and 6 days of gestation were included in the analysis. Infants were excluded from the study if they were admitted > 24 h after birth, required no invasive or non-invasive respiratory support during their admission or had major congenital abnormalities.

The pre-implementation cohort included patients admitted between May 1st 2012 and June 17th 2015 that received FiO_2 manually titrated by bedside staff according to local guidelines. The post-implementation cohort consisted of infants admitted from October 18th 2015 to December 2018, taking into consideration a washout period of 4 months.

Data collection

All data were obtained from our patient data management systems (Metavision; IMDsoft, Tel Aviv, Israel and HiX; ChipSoft, Amsterdam, The Netherlands). Infants were invited for follow-up at 24 months corrected age for assessment by a neonatologist, paediatric physiotherapist and paediatric psychologist. Respectively they were responsible for the general and neurological examination, the assessment of motor function and assessment of cognitive functioning. Primary outcome was a composite outcome of mortality or severe neurodevelopmental impairment (NDI). Secondary outcomes were as follows: mild to moderate NDI, early mortality (mortality until one month after corrected term age), late mortality (mortality between one month after corrected term age and 2-year follow-up), motor and cognitive development scores, visual impairment, hearing loss, cerebral palsy, behavioural functioning and number of readmissions. Severe NDI was defined as at least one of the following: cerebral palsy (Gross Motor Function Classification System (GMFCS)16 ≥ level 3), Bayley-III-NL cognitive or motor scores less than two standard deviations under the mean, severe bilateral visual impairment or blindness and/or bilateral sensorineural hearing loss or deafness needing hearing aids or cochlear implants.

Mild to moderate NDI was defined as cerebral palsy GMFCS level 1 or 2, Bayley-III-NL cognitive or motor scores below one standard deviation under the mean, mild visual and/or hearing impairment. Motor and cognitive development were assessed using the Bayley Scales of Infant and Toddler Development Third Edition, Dutch version (Bayley-III-NL).[17, 18] As the minimum cognitive composite score using the Bayley III is 55, children failing to achieve this were nominally assigned a score of 54. Bayley III floor motor composite score is 46 hence children failing to achieve this were nominally assigned a score of 45.[19] Visual impairment was classified as mild (needing treatment by an ophthalmologist or orthoptist), impaired vision with the ability to see or blind. Hearing loss was defined as mild, neurosensory hearing loss or deaf. Behavioural outcome was assessed using the Child Behavioural Checklist (CBCL 1.5–5 years) completed by parents.[20] A classification of level 3 or higher on the GFMCS was considered severe.[16] When data could not be collected from the patient data management systems, The Dutch Perinatal and Neonatal register (Landelijke Neonatale Registratie) or other follow-up centres (university hospitals, revalidation centres) were consulted to complement the data.

Oxygen titration

During almost the entire study period the AVEA ventilator (Vyaire, Yorba Linda CA, United States) was used for respiratory support, after August 2015 this involved AOC by the CLiO$_2$ (Closed Loop of inspired Oxygen) controller.[8] As of November 2018 newly born preterm infants were supported by the SLE6000 ventilator (SLE, London, United Kingdom) with the OxyGenie option for AOC.[21] Following recent European guidelines,[22] in November 2014 we changed the SpO$_2$ target range in our NICU from 85–95% to 90–95%.

Data analysis

Data are reported as mean (SD), median (range), or number (percentage) as appropriate, with standard tests for normality. Statistical comparison was executed using an independent t-test, a Mann-Whitney U test, and a chi-square or Fisher's exact test as appropriate. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM, Armonk, New York, USA). Two-sided p-values of < 0.05 were considered statistically significant.

Results

Patient characteristics and neonatal period

In the period of 2012 – 2018, 588 infants were born in the LUMC or transferred to the NICU within 24 hours after birth, 293 infants in the pre-implementation period (pre-AOC) versus 295 infants in the post-implementation cohort (post-AOC). There were no differences in baseline characteristics (Table 1). In the neonatal period there were similar rates of IVH, PVL and laser coagulation for ROP. More details on the neonatal period can be found in our previous study.[15] 3 children were excluded from analysis due to major congenital abnormalities affecting neurodevelopment (2 pre-AOC, 1 post-AOC) and 4 were excluded because they moved to a different country (2 pre-AOC, 2 post-AOC) leaving 289 infants in the pre-AOC group and 292 infants in the post-AOC group. We were unable to obtain any follow-up data for 51 infants (pre-AOC 6.9% (20/289), post-implementation 10.6% (31/292), baseline characteristics Supplemental Table 1-2).

Table 1. Patient characteristics and neonatal outcome

Patient characteristics	**Pre-AOC n = 289**	**Post-AOC n = 292**	**p value***
Gestational age in weeks^{days}, median [IQR]	28^{2} [26^{6} – 29^{0}]	28^{0} [26^{3} – 28^{6}]	0.09
Birth weight in grams, mean (SD)	1037 (291)	1037 (261)	1.00
Males, n (%)	162 (56.1)	155 (53.1)	0.47
Antenatal corticosteroids, n (%)	246 (86.0)	253 (87.5)	0.59
Caesarean delivery, n (%)	143 (49.5)	154 (52.7)	0.43
Multiple pregnancy, n (%)	115 (39.8)	97 (33.1)	0.10
of which monochorionic twins, n (%)	71 (61.7)	62 (63.9)	0.36
Perinatal asphyxia, n (%)	4 (1.4)	8 (2.7)	0.25
Apgar score at 5 minutes, median (range)	8 (2-10)	8 (1-10)	0.90
Intraventricular haemorrhage (≥ stage 2), n (%)	55 (19.0)	49 (16.8)	0.48
Periventricular leukomalacia (≥ stage 2), n (%)	4 (1.4)	6 (2.1)	0.53
Received laser coagulation for ROP, n (%)	13 (5.3)	14 (5.6)	0.85
Bronchopulmonary dysplasia			
severe, n (%)	36 (14.2)	48 (18.8)	
moderate, n (%)	12 (4.7)	4 (1.6)	0.10
mild, n (%)	44 (17.3)	37 (14.5)	

*AOC, Automated Oxygen Control; ROP, Retinopathy of prematurity; *Statistical analysis with independent T-test, chi-square, nonparametric Mann-Whitney U test*

Outcomes at two year follow-up

The composite primary outcome of mortality or severe NDI occurred in 17.9% (41/229; Table 2) before implementation of AOC versus 24.0% (47/196) after implementation (p=0.12). The majority was related to neonatal death (10.2% (30/289) vs. 10.8% (32/292) p=0.82). After the neonatal period 0.4% (1/259) vs. 0.8% (2/259; p=0.56) children died. Severe NDI was observed in 5.1% (10/198) before vs. 8.0% (13/162) after the implementation of AOC (p=0.25). Mild to moderate NDI was detected in 38.5% (82/213) infants pre-AOC vs. 43.8% (78/178) after implementation (p=0.29).

Table 2. Outcomes at two years follow-up

	Pre-AOC	Post-AOC	p value*
Adverse outcome (severe NDI or death)	41 (17.9)	47 (24.0)	0.12
Severe NDI, n (%)	10 (5.1)	13 (8.0)	0.25
Early death, n (%)	30 (10.2)	32 (10.8)	0.82
Late death, n (%)	1 (0.4)	2 (0.8)	1.00
Mild-moderate NDI, n (%)	82 (38.5)	78 (43.8)	0.29
BSID III Composite motor score, median [IQR]	97 [89 – 107]	98 [89 – 109]	0.18
Score 70-85, n (%)	25 (12.6)	25 (12.8)	0.94
Score <70, n (%)	5 (2.5)	11 (5.6)	0.12
BSID III Composite cognitive score, median [IQR]	96 [87 – 101]	96 [91 – 105]	0.23
Score 70-85, n (%)	31 (13.4)	26 (12.7)	0.85
Score <70, n (%)	7 (3.0)	7 (3.4)	0.81
CBCL externalising T score, mean (SD)	51 (10)	50 (10)	0.69
CBCL internalising T score, median [IQR]	47 [41 – 55]	47 [41 – 55]	0.59
Visual impairment, n (%)			
None	213 (90.6)	166 (86.0)	0.25
Mild impairment	19 (8.1)	25 (13.0)	
Limited vision	3 (1.3)	2 (1.0)	
Blind	0 (0)	0 (0)	
Hearing loss, n (%)			
None	229 (98.3)	185 (96.4)	0.23
Mild hearing loss	2 (0.9)	3 (1.6)	
Abnormal, neurosensory hearing loss	0 (0)	3 (1.6)	
Deaf	2 (0.9)	1 (0.5)	

Table 2 continues on next page

Table 2 continued. Outcomes at two years follow-up

	Pre-AOC	Post-AOC	p value*
Cerebral palsy GMFCS, n (%)			
None	200 (84.7)	190 (88.0)	0.73
Level 1	30 (12.7)	21 (9.7)	
Level 2	4 (1.7)	4 (1.9)	
Level 3	2 (0.8)	1 (0.5)	
Level 4	0 (0)	0 (0)	
Level 5	0 (0)	0 (0)	
Readmissions until follow-up, n (%)			
none	130 (57.0)	149 (69.3)	0.01
1-3	83 (36.4)	50 (23.3)	
>3	15 (6.6)	17 (7.4)	

*AOC, Automated Oxygen Control; NDI, neurodevelopmental impairment; BSID, Bayley Scales of Infant and Toddler Development; CBCL, Child Behaviour Checklist; GMFCS, Gross Motor Function Classification System. *Statistical analysis with independent T-test, chi-square, Fishers' exact, or nonparametric Mann-Whitney U test as appropriate*

The median Bayley-III composite motor score was 97 [89 – 107] pre-AOC and 98 [89 – 109] post-AOC (p=0.18). The composite cognitive score was 96 [87 – 101] vs. 96 [91 – 105] (p=0.23). No significant differences were found in rates of scores between 1-2 SD under the mean (score 70-85) and below -2 SD under the mean (score <70), for motor nor cognitive. Motor scores respectively for pre- vs. post-implementation cohorts: 12.6% (25/199) of the children had scores between 1-2 SD under the mean and 2.5% (5/199) below -2 SD vs. 12.8% (25/195, p=0.94) and 5.6% (11/195, p=0.12) after implementation. Cognitive scores in the pre-implementation group were found in 13.9% (31/232) between 1-2 SD under the mean and under 2 SD under the mean in 3.0% (7/232) vs. 12.7% (26/204, p=0.85) and 3.4% (7/204, p=0.81) respectively. We found no significant differences between groups in externalising (51±10 vs. 50±10 , p=0.69) or internalising (47 [41 – 55] vs. 47 [41 – 55], p=0.59) problem behaviour scores.

Neurological examination, cerebral palsy GMFCS scores, visual impairment and hearing loss yielded no significant differences. However, parents did report significantly fewer readmissions until the moment of follow-up in the post-AOC group (p=0.002).

Discussion

This is the first study to report data on long-term neurodevelopmental follow-up at two years corrected age in very preterm infants treated with automated oxygen titration as standard of care compared with manual oxygen titration as standard of care. Implementation of automated oxygen titration did not lead to a change in mortality or neurodevelopmental outcome at 2 years. Although earlier studies[6-14] demonstrate an increase in time within target range when using automated oxygen titration, we were not able to demonstrate an effect on neurodevelopmental outcome in this large cohort.

To date, there is little data on clinically relevant outcome of infants receiving automated oxygen titration. There is no data available on neurodevelopmental outcome after usage of AOC, and data on follow-up of preterm infants from non-AOC studies are difficult to compare with, because they involved non-standard interventions,[23, 24] infants born almost 15 years ago,[25, 26] or had a study population that had markedly different characteristics[27, 28]. The outcomes of both groups in our study are similar to the outcome of a previous cohort study from our centre.[26]

The reason for fewer readmissions after implementation of automated oxygen titration is not apparent from our data. Rates of BPD, ROP and other morbidity potentially requiring re-hospitalisation are similar, although we did find fewer ventilation days in our previous study for the post-AOC cohort.[29]

A failure to demonstrate an impact on neurodevelopmental outcome after implementing automated titration can have several causes. In the previous study on achieved target range time in our NICU, we demonstrated that although infants spent more time within target range overall, this was mainly attributed to a reduction in time above the target range. In fact, using the $CLiO_2$ controller led to a 6% increase of time spent under the SpO_2 target range (90-95%). This increase was mainly just below (85-90%) target range while still having a similar proportion of hypoxaemia (<80%). If indeed more time spent under the target range is where neurodevelopmental improvement can be gained, the lack of improvement in this area could explain the lack of impact on neurodevelopmental outcome. Furthermore, as reported before it could be that outcome is more largely influenced by the frequency and duration of hypoxia and hypoxic events,[30] which were not investigated in our previous study nor in most other automated oxygen controller studies. Also, preterm infants can experience many potentially harmful stimuli and events before being tested at two years of corrected age, in particular during the neonatal phase. Oxygenation deviations during

respiratory support may play only a minor role in the eventual neurodevelopmental outcome, meaning only very large randomised studies are able to demonstrate a statistically significant difference. Thirdly, neonatal care is a rapidly developing field with frequent changes to standard of care. Some of these unmeasured factors may influence the results in either direction. Finally, some of the adverse outcomes are relatively rare. If the effect of automated oxygen control is modest, a large clinical trial would be needed to observe an effect. Currently, the FiO2-C trial randomises between automated oxygen control or manual titration during the entire NICU stay, and will investigate the effect on clinical and neurodevelopmental outcome at 24 months of corrected age.[29] The study is projected to run until December 2022.

A change in target range may influence the time spent in (mild) hypoxia. In our case one would expect that 76% (223/293) of infants in the pre-implementation group born before November 2014 spent more time in the 85% - 90% range, as the lower limit was changed from 85% to 90%. The achieved proportion of time in the 85% - 90% range based on 1 minute-values of the pre- and post-implementation data show no difference while infants received oxygen (pre-AOC 10.9 [8.6 – 13.5]%, post-AOC 10.4 [7.7 – 12.7]%, p=0.09), and a 1.8% difference when considering the entire period of respiratory support (pre-AOC 5.5 [1.7 – 9.8]%, post-AOC 3.7 [1.6 – 7.6]%, p=0.002; unpublished data). Van Zanten et al. reported before that the change of lower limit led to a reduction in achieved time within the 80%-90% range in our unit, but time spent in hypoxia (SpO_2 < 80%) was not different[31.]

One of the inherent limitations of a retrospective design is the rate of missing data (loss to follow-up in this study: pre-AOC 6.9%, post-AOC 10.6%), which is unfortunately frequently high in follow-up research. The majority of missing children were transferred to another university NICU in the neonatal phase and had subsequent follow-up there, therefore we expect them to be missing at random and not related to neurodevelopmental outcome. However, children lost to follow-up may be under treatment in a special care facility and therefore not missing at random. Parents may be less inclined to present their child for follow-up when they already receive regular tests in such a facility. To limit biased results due to missing such children, we requested data for all children tested elsewhere. A strength of the study is that we have a relatively large cohort in which we had few exclusion criteria, meaning the results are generalisable to other NICUs in a similar setting. Furthermore children are tested by trained professionals as part of a standardized national follow-up programme, improving the repeatability and reliability of the assessment of neurodevelopmental outcome. Finally, most data was collected prospectively during standard follow-up, minimising recall bias.

Besides fewer parent-reported readmissions, no change in outcome occurred after implementation of automated oxygen control. It is reassuring that outcomes did not deteriorate, and that outcome of our follow-up is similar to earlier reported data. Our results show no signs children are affected negatively by using an automated oxygen controller, whereas there are benefits for staff workload.

Conclusion

In this cohort study, implementation of automated oxygen control in our NICU as standard of care for preterm infants led to no significant difference in neurodevelopmental outcome at two years of age.

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Supplemental material

Supplementary table 1: Pre-implementation Automated Oxygen Control loss to follow-up characteristics

Patient characteristics ***Pre-AOC***	**Data available n = 269**	**Loss to follow-up n = 20**	**p value***
Gestational age in weeks^{days}, median [IQR]	28^{2} [26^{5} – 29^{0}]	28^{3} [27^{6} – 29^{1}]	0.09
Birth weight in grams, mean (SD)	1033 (284)	1080 (378)	0.49
Males, n (%)	151 (56.1)	11 (55.0)	0.92
Antenatal corticosteroids, n (%)	227 (85.3)	19 (95.0)	0.23
Caesarean delivery, n (%)	128 (47.6)	15 (75.0)	0.02
Multiple pregnancy, n (%)	104 (38.7)	11 (55.0)	0.15
of which monochorionic twins, n (%)	64 (61.5)	7 (63.6)	0.29
Perinatal asphyxia, n (%)	4 (1.5)	0 (0.0)	1.00
Apgar score at 5 minutes, median (range)	8 (2-10)	8.5 (6-10)	0.03
Intraventricular haemorrhage (≥ stage 2), n (%)	54 (20.1)	1 (5.0)	0.14
Periventricular leukomalacia (≥ stage 2), n (%)	3(1.1)	1 (5.0)	0.25
Received laser coagulation for ROP, n (%)	12 (5.2)	1 (5.9)	1.00
Bronchopulmonary dysplasia			
severe, n (%)	34 (14.4)	2 (11.1)	
moderate, n (%)	12 (5.1)	0 (0.0)	0.29
mild, n (%)	43 (18.2)	1 (5.6)	

*AOC, Automated Oxygen Control; ROP, Retinopathy of prematurity; *Statistical analysis with independent T-test, chi-square, Fisher's exact, or nonparametric Mann-Whitney U test as appropriate*

Supplementary table 2: Post-implementation Automated Oxygen Control loss to follow-up characteristics

Patient characteristics ***Post-AOC***	**Data available n = 261**	**Loss to follow-up n = 31**	**p value***
Gestational age in weeks^{days}, median [IQR]	28^{0} [26^{1} – 28^{5}]	28^{6} [27^{5} – 29^{4}]	0.001
Birth weight in grams, mean (SD)	1020 (263)	1175 (193)	0.002
Males, n (%)	136 (52.1)	19 (61.3)	0.33
Antenatal corticosteroids, n (%)	225 (87.2)	28 (90.3)	0.62
Caesarean delivery, n (%)	140 (53.6)	14 (45.2)	0.37
Multiple pregnancy, n (%)	83 (31.8)	14 (45.2)	0.14
of which monochorionic twins, n (%)	50 (60.2)	12 (85.7)	0.08
Perinatal asphyxia, n (%)	8 (2.7)	0 (0.0)	1.00
Apgar score at 5 minutes, median (range)	8 (1-10)	8 (2-10)	0.36
Intraventricular haemorrhage (≥ stage 2), n (%)	45 (17.2)	4 (12.9)	0.54
Periventricular leukomalacia (≥ stage 2), n (%)	6 (2.3)	0 (0.0)	1.00
Received laser coagulation for ROP, n (%)	13 (6.0)	1 (3.3)	1.00
Bronchopulmonary dysplasia			
severe, n (%)	47 (20.9)	1 (3.3)	
moderate, n (%)	4 (1.8)	0 (0.0)	0.051
mild, n (%)	34 (15.1)	3 (10.0)	

*AOC, Automated Oxygen Control; ROP, Retinopathy of prematurity; *Statistical analysis with independent T-test, chi-square, Fisher's exact or nonparametric Mann-Whitney U test as appropriate*

What is already known on this topic

- Automated oxygen controllers, including the ones utilised in this study, increase time spent within the oxygen saturation target range compared with manual control.
- Hypoxaemia and hyperoxaemia have been linked to morbidity and mortality in preterm infants.

What this study adds

- The period in which the OxyGenie controller was used was associated with less laser treatment for ROP and a shorter stay in the NICU.
- The period in which the OxyGenie controller was used was associated with less invasive ventilation and continuous positive airway pressure days

How this study might affect research, practice or policy

- The currently used definition for BPD may not be suitable when automated oxygen control is used
- Choice of automated oxygen controller may be associated with clinical outcome, a large randomised trial is warranted.

Chapter 8

Clinical outcomes of preterm infants while using automated controllers during standard care: comparison of cohorts with different automated titration strategies

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Abstract

Objective To compare short-term clinical outcome after using two different automated oxygen controllers (OxyGenie and $CLiO_2$)

Design Propensity score matched retrospective observational study

Setting Tertiary level neonatal unit in the Netherlands

Patients Preterm infants (OxyGenie n=121, $CLiO_2$ n=121) born between 24+0-29+6 weeks of gestation. Median [IQR] gestational age in the OxyGenie cohort was 28+3 [26+3.5–29+0] versus 27+5 [26+5–28+3] in the $CLiO_2$ cohort, respectively 42% and 46% of infants were male and mean (SD) birth weight was 1034 (266) grams vs 1022 (242) grams.

Interventions Inspired oxygen was titrated by OxyGenie (SLE6000) or $CLiO_2$ (AVEA) during respiratory support.

Main outcome measures Mortality, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotising enterocolitis.

Results Fewer infants in the OxyGenie group received laser coagulation for ROP (1 infant vs 10; risk ratio 0.1 (95%-CI 0.0 – 0.7); p=0.008), and infants stayed shorter in the NICU (28 [15-42] vs 40 [25-61] days; median difference 13.5 days (95%-CI 8.5 – 19.5); p<0.001). Infants in the OxyGenie group had fewer days on continuous positive airway pressure (8.4 [4.8-19.8] days vs. 16.7 [6.3-31.1]; p<0.001) and significantly shorter number of days on invasive ventilation (0 [0-4.2] days vs. 2.1 [0-8.4]; p=0.012). There were no statistically significant differences in all other morbidities.

Conclusions In this propensity score matched retrospective study, the OxyGenie epoch was associated with less morbidity when compared to the $CLiO_2$ epoch. There were significantly fewer infants that received treatment for ROP, received less intensive respiratory support and, although there were more supplemental oxygen days, the duration of stay in the NICU was shorter. A larger study will have to replicate these findings.

Keywords Hypoxemia; hyperoxia; closed-loop; algorithm; neonate; respiratory

Introduction

Very preterm infants undergo a long undertaking from birth to discharge from the hospital out of which few arise unscathed. Four in ten of these infants experience a serious adverse outcome such as in-hospital mortality, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) requiring treatment or severe neurologic injury.[1] As demonstrated by a post-hoc analysis of the data from NeOProM meta-analysis, these outcomes are likely to be at least partly affected by the degree of success in targeting a specific oxygen saturation range (SpO_2 TR).[2, 3]

Targeting the SpO_2 TR is done by carefully titrating the administered supplemental oxygen during respiratory support, either manually by bedside staff or by an automated oxygen controller (AOC). There are currently multiple systems commercially available for automated titration of the supplied oxygen.[4-9] All current evidence points towards more overall success for AOCs on achieved time within the SpO_2 TR.

However, the available controllers employ different algorithms[10] and it is unclear which of these algorithms lead to better long and short-term outcome. The one algorithm X may on average keep oxygen saturation higher and have fewer desaturations at the cost of more hyperoxaemia; whereas the other algorithm Y may adhere better to the defined oxygen saturation limits at the cost of more short but frequent desaturations. Both the increase in hyperoxaemia with algorithm X could increase the risk for ROP, and the higher incidence of intermittent hypoxaemia with algorithm Y could yield similar effects.[11, 12] Furthermore, the amplitude of SpO_2 fluctuations and the duration of the episodes will most likely also be a factor of influence. Both factors can be influenced by choice of algorithm, for example by algorithm design, pulse-oximeter settings and choice of SpO_2 TR. A similar conundrum may exist for BPD, neurodevelopmental and other long-term outcomes.[12, 13] Studies comparing these clinical outcomes for different AOCs are lacking.

Two controllers employing distinctly different algorithms, the $CLiO_2$ algorithm implemented in the AVEA ventilator (Vyaire, Yorba Linda, California, USA) and the OxyGenie algorithm (VDL 1.1) embedded in the SLE6000 ventilator (SLE Limited, South Croydon, UK) were used in the neonatal unit of Leiden University Medical Center (LUMC). Both algorithms have been described in detail in a recent publication.[10] We recently demonstrated that the OxyGenie algorithm was more effective in keeping SpO_2 within the SpO_2 TR, preventing hyperoxaemia, and just as effective in preventing hypoxaemia. While using the $CLiO_2$ algorithm there was less time spent in the SpO_2 range of 80%-90%, possibly due to the lower median

SpO_2 during OxyGenie control (93% vs 94%) on the steeper part of the oxygen-haemoglobin dissociation curve. We hypothesized that these differences in achieved performance may affect short-term clinical outcome. Both systems have been used as standard of care for over a year in our unit, which prompted us to describe short-term clinical outcomes of preterm infants in a matched cohort study.

Methods

Study design

We performed a propensity score-matched observational study with electronic patient record data from the LUMC, a tertiary hospital with 25 Neonatal Intensive Care Unit (NICU) beds and around 100 admissions per annum of infants born under 30 weeks of gestation. The medical ethical research committee of Leiden Den Haag Delft provided a statement of no objection for obtaining and publishing the anonymised data. Protocol was filed under reference number G19.075.

To ensure equal distribution of patient characteristics that can confound with outcome we matched infants that received respiratory support from the SLE6000 ventilator, born in-hospital between November 1st 2018 and March 15th 2020 (OxyGenie cohort), to infants from a cohort supported by the AVEA ventilator born between 18th of October 2015 and the 31st of April 2018 ($CLiO_2$ cohort). We matched on sex, birthweight, and gestational age using propensity score matching with a match tolerance of 0.1. All infants were born at a gestational age 24+0 until 29+6 weeks. Infants with major congenital malformations were excluded.

Automated oxygen controllers

In August 2015 automated oxygen titration by the $CLiO_2$ algorithm was introduced as standard of care. The $CLiO_2$ algorithm was set to target an SpO_2 TR of 90%-95%. In November 2018 the AVEA ventilators were replaced with SLE6000 ventilators with the OxyGenie option for automated oxygen control. The OxyGenie uses a narrower SpO_2 TR of 91%-95%. The $CLiO_2$ algorithm is of a rule-based design. To determine a fraction of inspiratory oxygen (FiO_2) adjustment $CLiO_2$ incorporates the difference between the SpO_2 TR and the measured SpO_2, the severity of lung disease and the SpO_2 trend. The OxyGenie algorithm is an adaptive proportional-integral-derivative (PID) controller – also employed in automotive cruise-control and rockets – with several enhancements to account for the physiology of a neonate and account for the limitations of pulse oximetry.

Data collection and outcome measures

Patient records are kept digitally in our patient data management system (Metavision; IMDsoft, Tel Aviv, Israel). The following outcomes were noted from either these records or from the discharge papers from the regional hospital where the infant resided before being discharged home: mortality until one month after corrected term age, ROP, BPD, necrotising enterocolitis (NEC), culture proven sepsis, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), and length of NICU stay. The duration of respiratory therapy and supplemental oxygen (measured FiO_2 above 0.21) and the mean of inspiratory oxygen during the first week and entire admission were calculated from our patient data management system which routinely samples clinical parameters and ventilator settings once per minute. High flow nasal cannula (HFNC) was available in SLE6000, not in AVEA. The device we used for HFNC during the $CLiO_2$ period did not allow for automatic data storage or for automated oxygen titration. Therefore to minimise biased results, the duration of supplemental oxygen therapy was analysed both with and without periods of HFNC. The ophthalmologists in our hospital implemented the Early Treatment of Retinopathy of Prematurity study (ETROP) classification for findings of retinal examination in 2013 and ROP was defined according to this classification.[14, 15] Laser coagulation for treatment of severe ROP is first choice, anti-VEGF injections are not standard of care. When retinal findings were described otherwise, researcher *HHS* classified according to the ETROP criteria retrospectively, assisted by an ophthalmologist where necessary. An assessment for BPD was made at 36 weeks postmenstrual age classified as either none, mild, moderate-severe according to adapted criteria from the 2000-NICHD consensus. [16] We chose to combine the moderate and severe classifications as discharge papers from regional hospitals sometimes did not indicate which respiratory therapy was applied at what time. NEC was defined according to the modified Bell staging criteria[17], IVH was classified according to Papile's adapted classification [18, 19], PVL according to the de Vries' classification. [20]

Analysis

Data are presented as mean (SD), median [IQR] or (range), or number (percentage) as appropriate. Standard tests for normality (visual assessment, Kolmogorov-Smirnov, Shapiro-Wilk) were done. Statistical comparison was performed using a related-samples Wilcoxon signed rank test with Hodges-Lehman median difference confidence interval or related-samples McNemar test as appropriate. Outcomes with more than 2 categories were analysed using a Bhapkar test.[21] Risk ratios and confidence intervals were calculated according to the method described by Algresti

and Min[22] to retain the matching of the data. Statistical analyses were performed by IBM SPSS Statistics for Mac, version 25 (IBM, Armonk, New York, USA) and R 4.1.0 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Two-tailed P-values of <0.05 were considered statistically significant.

Results

158 infants were born between November 2018 - March 2020 of which 121 were eligible for inclusion in the OxyGenie cohort. These were then matched with infants born in the period October 2015 - April 2018 to form the control, or $CLiO_2$, cohort (n=121) (table 1). In the OxyGenie cohort 51 infants were male (42%), there was a median gestational age at birth of 28 weeks and 3 days [26 weeks and 3.5 days – 29 weeks] and a birth weight of 1034 (266) grams. In the $CLiO_2$ cohort there were 55 males (46%), there was a median gestational age of 27 weeks and 5 days [26 weeks and 5 days – 28 weeks and 3 days] and a birth weight of 1022 (242) grams. As our centre is a referral centre for foetal treatment we have a relatively large number of multiple pregnancy (45 in the OxyGenie cohort vs. 41 in the $CLiO_2$ cohort). There were no statistically significant differences between groups in beforementioned patient characteristics.

Table 1. Patient characteristics

Patient characteristics n = 242	**OxyGenie n = 121**	**$CLiO_2$ n = 121**	**p value***
Gestational age in weeks^{days}, median [IQR]	28^{3} [$26^{3.5}$ – 29]	27^{5} [26^{5} – 28^{3}]	0.09
Birth weight in grams, mean (SD)	1034 (266)	1022 (242)	0.60
Small for gestational age, n (%)	12 (10.1)	8 (6.6)	0.30
Males, n (%)	51 (42.1)	55 (45.5)	0.60
Antenatal corticosteroids, n (%)	107 (92.2)	106 (89.1)	0.50
Caesarean delivery, n (%)	64 (52.9)	66 (54.5)	0.90
Multiple pregnancy, n (%)	45 (37.2)	41 (33.9)	0.70
of which monochorionic twins, n (%)	22 (48.9)	26 (63.4)	
Perinatal asphyxia, n (%)	5 (4.1)	1 (0.8)	0.22
Apgar score at 5 minutes, median (range)	8 (0-10)	8 (2-10)	0.79

**Statistical analysis with related-samples Wilcoxon signed rank test or related-samples McNemar test as appropriate.*

Respiratory therapies

The OxyGenie cohort had significantly more time during which they received supplemental oxygen (table 2; 17.3 [6.0 – 31.1] days vs. 7.0 [1.1 – 26.1]; p = 0.045). High flow was not available in the AVEA ventilator, when excluding periods where infants where supported using high flow from the analysis there was a non-statistically significant difference (8.5 [2.8 - 22.6) days OxyGenie group vs. 7.0 [1.1 – 26.1] $CLiO_2$ group, p = 0.52). The mean inspired oxygen in the first week of life was similar in both groups (22.8 [21.8 – 25.0] % OxyGenie vs. 22.6 [21.4 – 24.8] %; p = 0.33), as was mean inspired oxygen during the entire stay (22.9 [21.8 – 25.3] % vs. 23.4 [21.6 – 27.0] %; p = 0.21). Infants in the OxyGenie cohort had fewer days of continuous positive airway pressure (CPAP; 8.4 [4.8 – 19.8] days vs. 16.7 [6.3 – 31.1] days; p < 0.001) and fewer days of invasive ventilation (0 [0 – 4.2] vs 2.1 [0 – 8.4]; p = 0.012) while the duration of nasal high flow was similar. There were no significant differences in number of infants who received inhaled nitric oxide, dexamethasone or surfactant.

Table 2. Respiratory therapies

	OxyGenie	**$CLiO_2$**	**p value***
Invasive ventilation days, median [IQR]	0 [0 – 4.2]	2.1 [0 – 8.4]	0.012
CPAP days, median [IQR]	8.4 [4.8 – 19.8]	16.7 [6.3 – 31.1]	<0.001
HFNC days, median [IQR]	10.0 [4.2 – 17.2]	8.2 [2.7 – 14.6]	0.20
Supplemental oxygen days, median [IQR]	17.3 [6.0 – 31.1]	7.0 [1.1 – 26.1]	0.045
excluding nasal high flow, median [IQR]	8.5 [2.8 – 22.6]	7.0 [1.1 – 26.1]	0.52
Mean inspired oxygen			
during first week, median [IQR]	22.8 [21.8 – 25.0]	22.6 [21.4 – 24.8]	0.33
entire admittance, median [IQR]	22.9 [21.8 – 25.3]	23.4 [21.6 – 27.0]	0.21
High frequency oscillation, n (%)	23 (19.0)	26 (21.5)	0.76
Inhaled nitric oxide, n (%)	13 (10.7)	15 (12.4)	0.85
Dexamethasone, n (%)	15 (12.4)	15 (12.4)	1.00
Surfactant, n (%)	67 (55.7)	69 (57.0)	0.89
via intubation, n (%)	28 (41.8)	38 (55.1)	0.32
via minimally invasive technique, n (%)	39 (58.2)	31 (44.9)	

*CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; Average inspired oxygen while on respiratory support. *Statistical analysis with related-samples Wilcoxon signed rank, Bhapkar or related-samples McNemar test as appropriate.*

Clinical outcomes

Fewer infants received laser coagulation for ROP in the OxyGenie cohort (table 3; 1 vs 10; Relative risk ratio (RR) 0.1, 95%-CI 0.0 to 0.7; p = 0.008), no infants were treated with anti-VEGF injections. There were no statistically significant differences in mortality (RR 2.3, 95%-CI 0.6 to 9.0), culture proven sepsis, BPD (RR 1.0 95%-CI 0.7 to 1.3), NEC (>stage 2A, RR 1.1 95%-CI 0.5 to 2.6), IVH (≥ stage 2, RR 1.5 95%-CI 0.8 – 2.7) and PVL (≥ stage 2, RR 0.3 95%-CI 0.0 – 2.2). Infants had a significantly shorter duration of stay in the NICU in the OxyGenie cohort (28 [15-42] vs. 40 [25-61] days; median difference 13.5 days (95%-CI 8.5 – 19.5); p < 0.001).

Table 3. Clinical outcomes

	OxyGenie	**CLiO$_2$**		**p value***
Died, n (%)	7 (5.8)	3 (2.5)	RR 2.3 (0.6 – 9.0)	0.34
Culture proven sepsis, n (%)	45 (37.2)	56 (46.3)	RR 1.2 (0.9 – 1.7)	0.18
Necrotising enterocolitis (> stage 2A), n (%)	9 (7.4)	8 (6.6)	RR 1.1 (0.5 – 2.6)	1.00
Retinopathy of prematurity				
ETROP 1, n (%)	5 (4.5)	13 (11.2)	RR 0.4 (0.2 – 1.1)	0.09
ETROP 2, n (%)	4 (3.6)	1 (0.9)	RR 4.0 (0.4 – 35.8)	
Received laser coagulation, n (%)	1 (0.9)	10 (8.6)	RR 0.1 (0.0 – 0.7)	0.008
Intraventricular haemorrhage (≥ stage 2), n (%)	27 (22.5)	18 (14.9)	RR 1.5 (0.8 – 2.7)	0.21
Periventricular leukomalacia (≥ stage 2), n (%)	1 (0.8)	4 (3.3)	RR 0.3 (0.0 – 2.2)	0.38
Days in NICU, median [IQR]	28 [15 – 42]	40 [25 – 61]	MD 13.5 (8.5 – 19.5)	<0.001
Bronchopulmonary dysplasia	52 (46.0)	58 (48.7)	RR 1.0 (0.7 – 1.3)	0.89
moderate/severe, n (%)	18 (34.6)	31 (53.4)	RR 0.7 (0.4 – 1.1)	0.18
mild, n (%)	34 (65.4)	27 (46.6)	RR 1.3 (0.8 – 1.9)	

*RR, relative risk; MD, median difference; ETROP, early treatment of retinopathy of prematurity; Necrotising enterocolitis according to modified Bell staging criteria; Intraventricular haemorrhage according to Papile's classification; Days on NICU until transfer to peripheral hospital or discharge; Bronchopulmonary dysplasia classification according to Dutch paediatric guidelines. *Statistical analysis with related-samples Wilcoxon signed rank, Bhapkar test or related-samples McNemar test as appropriate.*

Discussion

In this observational study infants in the OxyGenie group had less morbidity. Fewer infants needed laser coagulation for retinopathy of prematurity in the OxyGenie cohort when compared to the $CLiO_2$ cohort. On average, administered supplemental oxygen was of a modest proportion in both groups and with the exception of a shorter duration of continuous positive airway pressure and invasive mechanical ventilation, the durations on other modes of respiratory support were not significantly different. Infants in the OxyGenie cohort had a significantly shorter duration of stay in the NICU. Other short-term clinical outcomes were not significantly different between groups.

In a prior study we reported on the effect of AOC on clinical outcome during standard of care for preterm infants in which the AOC cohort consisted almost entirely of infants treated with the $CLiO_2$ algorithm.[23] In this larger cohort around 6% of infants needed laser coagulation for ROP, similar to what is previously reported (5.9%) in a cohort of over 154.000 very preterm infants. Contrary to our results, a recent study in the Netherlands reported an increase in treatment for ROP in the more recent epoch.[24] The prevalence was 2.3% in the most recent epoch, however the upper gestational age criterion was higher (i.e. 32 weeks).[1] These figures of prevalence, combined with the relatively modest cohort size, may be indicative that the prevalence of laser coagulation for retinopathy of prematurity in the $CLiO_2$ group may be an overestimation. Nevertheless, the occurrence of laser coagulation in the Oxygenie group was much lower than our prevalence during manual treatment.

A reduction in ROP when using OxyGenie could be plausible. In a randomised crossover trial comparing OxyGenie to $CLiO_2$ we reported significantly less time above target range, tighter target range adherence (i.e. less fluctuation of oxygenation) and less frequent and shorter episodes of both hypoxaemia and hyperoxaemia while using OxyGenie.[25] Hypoxaemia, hyperoxaemia, and fluctuation of oxygenation have all been associated with an increased rate of ROP.[11, 12, 26] Early after preterm birth, a varying oxygenation of the retina might lead to decreased retinal vascular growth and blood vessel loss, leaving the retina more susceptible to damage due to hypoxia. In a later phase, this increases the risk of uncontrolled neovascularisation and retinal detachment.[27] Although our randomised trial was limited to 48 hours per studied infant, there is no reason why those results cannot be generalised largely to the rest of the admission, as the postnatal age at study was variable. We did not have data on cardiotonic medication, the other risk factors (postnatal steroids, sepsis, NEC and mechanical ventilation > 3 days) were not different between cohorts.

The applied definition of BPD [16] may prove unsuitable for infants receiving automated oxygen titration. The general consensus is that during a day supplemental oxygen should be given for at least 12 hours to be counted towards the 28 days required for the diagnosis of BPD. During automated oxygen control the administered proportion oxygen may be only intermittently be above 0.21 in a 24-hour period, and this may not be predictive of BPD, for example when these brief moments are linked to apnoeic events. Depending on what criteria are used to define BPD, significantly more infants would be classified as having BPD.

Several measures were taken to minimise the risk of bias associated with retrospective chart studies, such as missing data from patients in regional hospitals. Given that the data are relatively recent and thanks to the modest cohort size, we were able to have two independent researchers check all electronic patient records and discharge papers from regional hospitals for the outcomes. Furthermore, respiratory support data was based on automatically stored data in our patient data management system, precluding human error. In 2017 our unit changed to single room care[28], and although there have been no other major changes in standard care besides type of ventilator, we cannot rule out that there are unmeasured changes that can influence results in either direction.

Importantly, the outcomes of some outcomes were rare (for example mortality and PVL) and it should be noted that the power of the study may not be sufficient to observe a difference in these outcomes between the groups. This is reflected in the broad relative risk confidence intervals, indicative that the true effect may be markedly different. Ultimately, the retrospective nature of this study precludes us from drawing definite conclusions on the causal effect of choice of algorithm on short-term clinical outcome. Further research is warranted to replicate these findings, preferably in a large multicentre randomised trial.

Conclusion

In this observational study, the OxyGenie epoch was associated with less morbidity when compared to the $CLiO_2$ epoch. There were significantly fewer infants that received treatment for ROP, received less intensive respiratory support and although there were more supplemental oxygen days, the duration of stay in the NICU was shorter. A larger study will have to replicate these findings.

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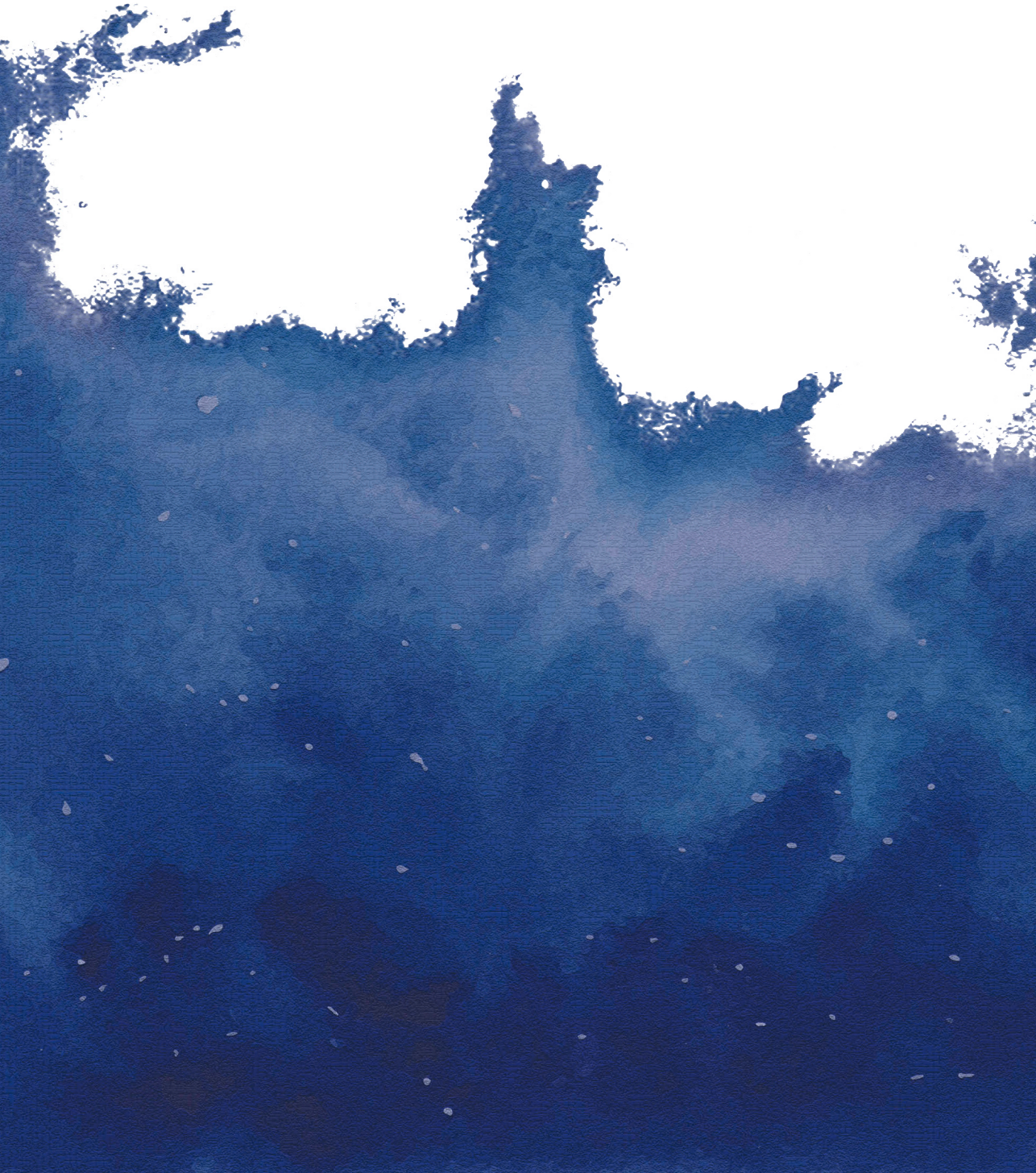
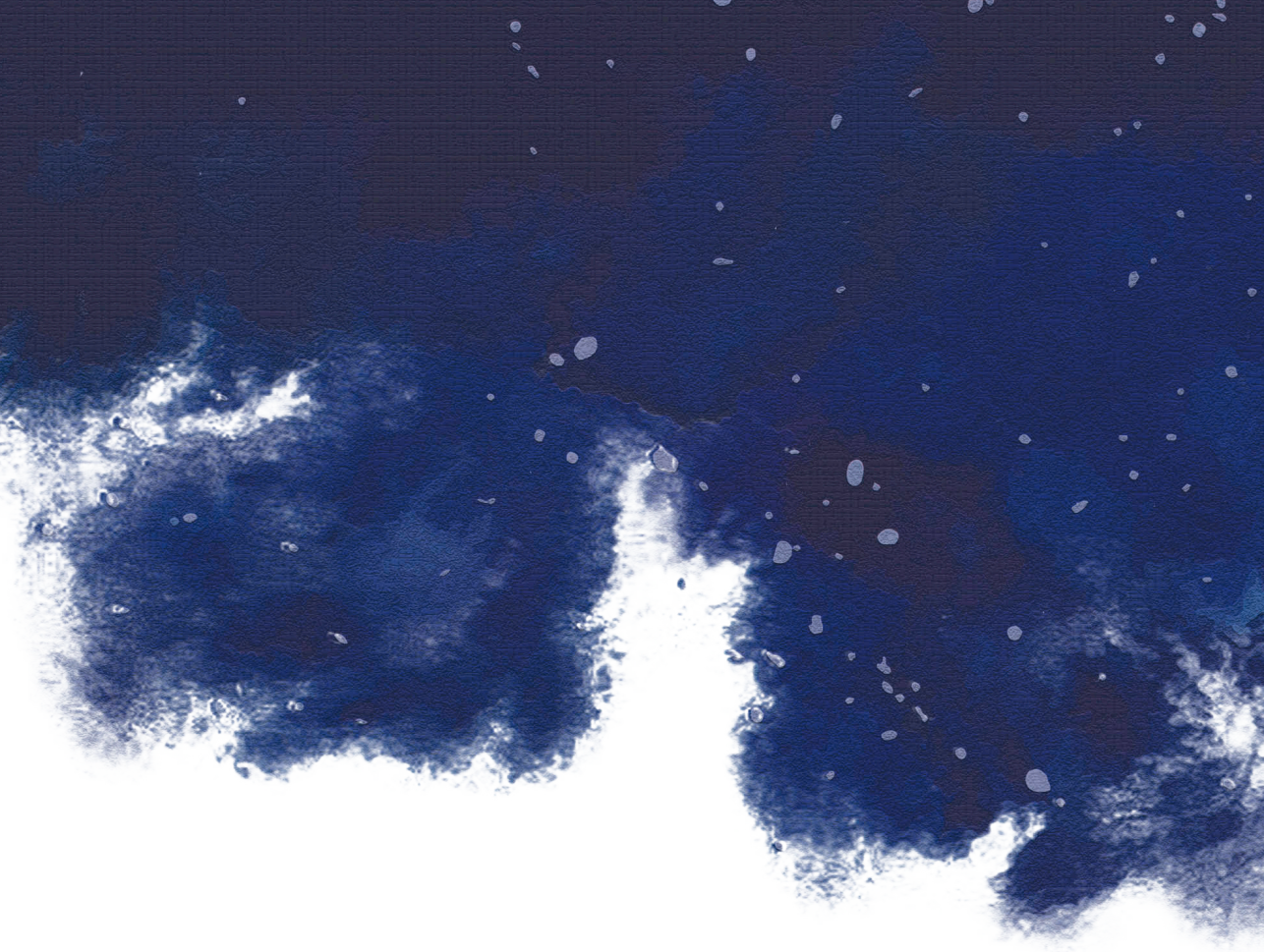


Part V

General discussion and summary



Chapter 9

General discussion and future perspectives

Introduction

Very preterm infants have an immature respiratory system leading to inadequate ventilation and gas exchange, eventually resulting in hypoxia. Supplemental oxygen is therefore often provided to prevent damage associated with hypoxia.[1-3] In response to hypoxic episodes the concentration of supplemental oxygen is increased but, when not titrated down promptly after resolution of the event, can lead to iatrogenic hyperoxia. Both hypoxia and hyperoxia have been associated with organ injury.[4-8] To guide titration of supplemental oxygen the infant's oxygen saturation (SpO_2) is used, in an attempt to minimise the occurrence of episodes outside the intended range. Despite best efforts with manual titration, the therapeutic range is narrow and preterm infants still spent up to 50% of the time outside this intended therapeutic oxygen saturation target range.[9]

Maintaining a stable oxygenation within the narrow therapeutic range is hampered by a multiplicity of reasons: (1) The neonatal oxygenation physiology is unstable, exemplified by respiratory pauses also called apnoea of prematurity. (2) The infant's response to a therapeutic change in supplemental oxygen is non-linear, and there is a significant time delay between a change in the concentration of inhaled oxygen (FiO_2) and a change in the infant's SpO_2.[10] (3) Workload of bedside staff may limit continuous titration to the infants need[11] and there appears to be a tendency to accept a higher oxygen saturation by bedside staff, possibly because the infants are believed to be more stable and temporary hyperoxia may be considered less harmful.[12, 13] The contribution of some of these issues to morbidity and mortality may be reduced by using an automated oxygen controller (AOC) for titration of supplemental oxygen, rather than manual titration by bedside staff.

Although the concept was already thought of in the 1940s, automated oxygen titration has only become booming in the last decade. A recent survey in the UK by Kaltsogianni et al. showed that 10% of the surveyed units have embraced AOC, with the majority of those units using it in routine clinical care. In the last two decades, over 20 studies reported a comparison of manual titration with an automated oxygen controller in preterm infants.[14-20] Six devices are commercially available at the time of writing, which are discussed in **chapter 2**.

Automated oxygen titration by a device reduces time outside of the target range[14, 21] by providing a more prompt response to deviations from the target range, and as such may help reduce associated morbidity and mortality. Several basic approaches are employed and combined by the available automated oxygen titration algorithms:

rule-based (**chapter 2 figure 1**), resembling an if-this-then-do-that mechanism; proportional-integral-derivative control (**chapter 2 figure 2**), a mathematical combination combining the current, past and future oxygenation; and adaptive control (**chapter 2 figure 3**), which tailors the algorithms response to the individual infant, for example to the severity of lung disease in the infant. Besides using these components in different degrees, algorithms also differ in the promptness of their response and what is targeted (i.e. the middle or the limits of the target range).

All commercially available algorithms were demonstrated to achieve higher proportions of time within target range when compared to manual titration, however which algorithm is most effective is unknown, as is the effect on clinical outcome. Comparing these algorithms purely based on the available literature is difficult, considering a variation in choice of target range, pulse oximeter settings, ventilator mechanics, choice of inclusion/exclusion criteria, modes of respiratory support and the aims of the studies. Direct 'head-to-head' comparisons of AOCs are required, so clinicians know what to expect when using a specific automated oxygen controller.

The aim of this thesis was to evaluate outcomes after using automated oxygen control. We set out to describe currently available devices and their differences, we will start to discuss our data on oxygenation in the NICU while using automated oxygen control, and will thereafter discuss clinical and long-term outcome.

Effectivity of automated oxygen control algorithms on oxygenation of preterm infants in the NICU

The preferred way to compare two automated oxygen control algorithms would be to compare the algorithms within the same patients at the same time. In this way, the only changing condition would be the ventilator with the built-in automated oxygen controller, while most other aspects remain equal. This thesis describes the first comparative study between automated oxygen controllers within the same infants. The lack of evidence in this regard may be explained by the difficulties met when performing such a study. First of all, researchers (temporarily) need to have a running stock of two different brands of ventilators, including disposable materials required to use these machines. Staff would need to be competent to work with both ventilators, including not only bedside staff but also supportive staff such as technicians. Secondly, actual execution of the study includes switching between ventilators in (sometimes invasively) supported babies. Preparing and switching ventilators increases the workload for already busy bedside staff. Even though it is unlikely a patient would notice a change in ventilator, parents may be reluctant

to consent to this procedure. Finally, the respiratory condition of the infant under study may change rapidly due to unforeseen events such as sepsis, meaning the time window in which such a study can be done is short.

In the LUMC we were in the unique situation that caregivers were trained to work with the AVEA system, which incorporates the $CLiO_2$ controller, and at the same time in the process of acquiring and training caregivers for SLE6000 ventilators. In **chapter 3** we describe a crossover study comparing the OxyGenie and $CLiO_2$ algorithm in preterm infants. We observed that OxyGenie was better at maintaining oxygen saturation within the target range, preventing hyperoxaemia and severe hypoxaemia. This was accompanied by an increase in overall mild hypoxaemia during OxyGenie control. The OxyGenie algorithm appeared more responsive, as 30 second and 60 second deviations from the target range were less frequent, indicating that although infants may venture under the target range more frequently during OxyGenie control, they did return to the target range more promptly than during $CLiO_2$ control. These results make it apparent that choice of algorithm, with its inherent design and responsiveness, will largely influence the success of SpO_2 targeting.

For this thesis, the first head-to-head comparison between two different ventilators incorporating AOC algorithms was performed. Achieved proportions of time within target range were similar to other studies when either OxyGenie or $CLiO_2$ was compared against manual control.[18, 20, 22-29] There were two previous studies that compared an updated version of an AOC algorithm ($CLAC_{fast}$ versus $CLAC_{slow}$[17], $SPOC_{new}$ versus $SPOC_{old}$[30]), rather than two different algorithms, in a crossover study. In both studies the update changed the responsiveness in a way, mostly making them act quicker in the case of target range deviations. While no significant differences between algorithm versions were found, superiority of automated oxygen control was demonstrated when compared to manual titration.

The mild increase in time under target range during OxyGenie control was unexpected. Explaining this finding is hampered by limited availability of data on the exact working of the $CLiO_2$ algorithm, but it may be related to a higher median SpO_2 achieved during $CLiO_2$ control. A higher median SpO_2 corresponds to a more gradual part of the oxygen-haemoglobin dissociation curve.[31] On a more gradual slope, a change in partial pressure of oxygen will have a smaller effect on the oxygen saturation, possibly resulting in a more stable oxygen saturation. Indeed, this could explain the experience of our nurses finding preterm infants' oxygen saturation more stable when a slightly higher saturation is accepted. The relevance of higher median

SpO_2 was implied in a post-hoc analysis of the BOOST-II UK, where infants that died had a lower median SpO_2 when compared to survivors in their own group (Died: 90% in the 85%-89% group, 94% in the 91%-95% group. Survived: 94% in 85%-89% group, 95% in 91-95% group). [32]

Although **chapter 3** provides causality through a randomised crossover study on which algorithm performs best, it should be noted that it remains unclear how generalisable the results are for a preterm infant's full stay in the NICU. Different clinical conditions, which are certain to arise during the long stay of a very preterm infants, may demand different strategies or configurations. For example, a more responsive strategy may be more appropriate when apnoea of prematurity occurs frequently, which increases in frequency at a later postnatal age,[33] whereas an infant with chronic lung disease may benefit from a slower weaning strategy. Moreover, in the first days after birth when respiratory insufficiency is often related to a surfactant deficiency, it will be necessary for an automated oxygen controller to quickly adapt when exogenous surfactant is administered, as this likely leads to a change in oxygen requirement. An algorithm which is programmed to be resistant to large changes could provide too much oxygen leading to hyperoxia.

In **chapter 4** we further investigated the differences between algorithms during the admission, throughout the entire range of postnatal age and postmenstrual age, by comparing oxygenation data of infants treated with OxyGenie or $CLiO_2$. In this chapter we report on data collected from the six years we either used $CLiO_2$ or OxyGenie as standard of care. We observed that with the Oxygenie better control of oxygenation was carried throughout all postnatal ages on the NICU. Infants treated with OxyGenie had spent significantly lower proportions of time spent in hyperoxia and hypoxia while the average FiO_2 and group characteristics were not significantly different. Combined, the studies in **chapter 3** and **4** provide clear evidence that for better control of oxygenation in the NICU, OxyGenie should be preferred over $CLiO_2$.

When we included periods where no supplemental oxygen was given, the difference in achieved target range time was smaller, but still significantly different. Both controllers achieved a very high proportion of time within target range (OxyGenie 92.5%, $CLiO_2$ 90.2%) when considering all pulse-oximetry data (i.e. periods with and periods without supplemental oxygen). As a result, one could question the clinical relevance of the observed difference between $CLiO_2$ and OxyGenie. However, it is likely that oxygenation-related morbidity and mortality mostly has its genesis in days of respiratory instability. For example, a higher incidence of retinopathy of prematurity is found to be associated with intermittent hypoxia[34] as well as hyperoxia,[35] both

of which occur more often in unstable respiratory periods.[36] We therefore deem it appropriate to limit a comparison to episodes of supplemental oxygen when viewing the entire admission, limiting the diluting effect of respiratory stability when no supplemental oxygen is given.

Vital signs such as heart rate and SpO_2 can change rapidly on a second-to-second basis. Researchers using vital signs in studies should carefully consider at what rate these vital signs should be recorded. In general, it can be said that a higher resolution, or higher sampling frequency, is preferred so no fluctuations can be missed. However, data storage performance restrictions or high costs associated with data storage may justify lower frequencies for routine care. In **chapter 5**, data from our patient data management system recorded at a frequency of one sample per minute was used. It was unclear whether this lower frequency data could be sufficient for the purpose of descriptive statistics such as time within target range. For this reason, we compared data recorded at a 1 per second rate with sampled data once per minute in **chapter 5**. We processed this data in such a way that it is comparable to how data is stored by our patient data management system. In this study we assessed the difference between data derived with a low vs a high sampling rate with regard to oxygenation outcomes (f.e. proportion of time within target range, proportion of SpO_2<80%, average FiO_2). We found no significant differences in these oxygenation outcomes when comparing one-per-second data to one-per-minute data. This increased the validity of using one-per-minute data in descriptive statistics for retrospective studies. One-per-minute data collected for routine care is often relatively easy to acquire, and reduces the burden for parents, infants and researchers.

Clinical and long-term outcome after using automated oxygen controllers for preterm infants during NICU stay.

Currently, there is very little data on the effect of AOC on morbidity and mortality in preterm infants. In **chapter 6** and **7**, we were the first to report on clinical and long term outcome after using automated oxygen control during the stay of preterm infants of the NICU. (**chapter 6**). Besides observing that the use of AOC was associated with a shift toward more non-invasive ventilation, we were unable to demonstrate an effect on clinical outcome at hospital discharge (mortality; retinopathy of prematurity, ROP; Necrotising enterocolitis, NEC; Bronchopulmonary dysplasia, BPD, **chapter 6**). We could also not demonstrate an effect of AOC on neurodevelopmental outcome at two years of age (**chapter 7**).

Although no effect on short and long term outcome could be detected, we could also

not demonstrate a possible harmful effect of using AOC as standard care. Although there has been no report of an adverse effect in any of the trials comparing automated oxygen titration with manual titration, concerns for masking clinical deterioration have frequently been expressed.[23, 37] On the contrary, after training of clinical staff in our unit, assessment of basal oxygen requirement combined with the magnitude and frequency of interventions by the AOC device was used as an additional, objective indicator of clinical status.

Although it has become clear that AOC greatly reduces hypoxia and hyperoxia, which are known to be injurious, there are several (unmeasured) confounding factors that can influence outcome in very preterm infants until hospital discharge. Preterm infants may experience many other potentially harmful sequelae before birth, during their admission (e.g. sepsis, intraventricular haemorrhage) and after discharge, on which automated oxygen control is unlikely to have influence. Also, as demonstrated in the oxygenation studies of this thesis, the gain in time within target range was mostly attributable to a reduction in mild hypoxia and hyperoxia, and we have no data on the duration of hypoxic events. A lack of reducing (long lasting) hypoxic events could have reduced the effect on clinical outcome. In addition, neonatal care is a rapidly changing field with frequent changes to standard care, which may influence outcomes of cohort studies in either direction, and may have negated the effect of automated oxygen control. For example, we also changed the lower limit of the target range to 90% instead of 85%. While we used large cohorts for the observational studies in this thesis, it is likely that an appropriately powered RCT is needed to measure an effect on important clinical outcomes.

Currently, the FiO2-C trial -a large multicentre trial aiming to include 2340 patients- randomises between automated oxygen control or manual titration during the entire admission, and will compare the effect on clinical and neurodevelopmental outcome at 24 months of corrected age.[38] There are four different AOCs allowed for the study, which will likely not be equally effective at maintaining SpO_2 within TR. We demonstrated in this thesis that there can be a large difference in impact between AOCs. While using all available AOCs in a trial has likely been a pragmatic choice, the AOC with the best oxygenation control will have the largest treatment effect.

Indeed, an example of the difference in impact by AOCs is given in **chapter 8**, where the OxyGenie group developed less morbidity compared to the $CLiO_2$ group in a matched cohort study. Significantly fewer infants received treatment for ROP, infants received less intensive respiratory support and, although there were more supplemental oxygen days, the duration of stay in the NICU was shorter. Other short-

term clinical outcomes were not significantly different between the two groups, and neurodevelopmental outcome at two years is not yet available.

The reduction in retinopathy of prematurity is plausible. In this thesis we reported tighter target range adherence (i.e. less fluctuation of oxygenation) and less frequent and shorter episodes of both hypoxaemia and hyperoxaemia while using OxyGenie.[39] Hypoxaemia, hyperoxaemia, and fluctuation of oxygenation have all been associated with an increased rate of ROP.[34, 40, 41] Early after preterm birth, a varying oxygenation of the retina might lead to decreased retinal vascular growth and blood vessel loss, leaving the retina more susceptible to damage due to hypoxia. In a later phase, this increases the risk of uncontrolled neovascularisation and retinal detachment.[35] Less frequent and shorter episodes of hyperoxaemia during OxyGenie control may also contribute to the reduction in ROP. We did not have data on cardiotonic medication, but the other known risk factors (postnatal steroids, sepsis, NEC and mechanical ventilation > 3 days) for ROP were not different between cohorts.

Limitations

Although there are currently no alternatives available, the use of a pulse oximeter is a limitation when performing studies to measure the effect of tighter control of oxygenation. A proxy for oxygenation status, oxygen saturation measured with pulse oximetry (SpO_2), is used in **chapter 3**, **chapter 4**, and **chapter 5** for continuous non-invasive monitoring of oxygenation, but is limited in accuracy.[42-44] The FiO_2-SpO_2 relationship shows substantial intra-subject variability in the change of the infants' SpO_2 following an adjustment in FiO_2.[10] Many factors will influence the SpO_2 response, including for example, the changes in the oxygen-dissociation relationship during transition from foetal to adult haemoglobin. This shift will be quite pronounced in preterm infants who receive transfusions of adult blood.

In **chapter 3**, **chapter 4**, and **chapter 8** we compared two ventilators rather than purely the effect of the AOC algorithms on outcome. It is possible that ventilator mechanics also played a role in the effectiveness of oxygen control, as well as other aspects of ventilator function including the circuit flow characteristics.[45] However, this was a pragmatic choice as license agreements precluded us from implementing two algorithms in one ventilator.

Several measures were taken to minimise the risk of bias associated with retrospective chart studies as reported in **chapter 4**, **chapter 6**, **chapter 7**, and **chapter 8**. For all respiratory support data we used automatically stored data in our patient data

management system, precluding human error and recall bias. For clinical outcome we were able to have two independent researchers check all electronic patient records, in which data is collected prospectively as part of standard care.

While the current standard definition of BPD [46] in **chapter 6** and **chapter 8** has been used, this definition does not take into account the use of AOC. The general consensus is that during a day supplemental oxygen should be given for at least 12 hours to be counted towards the 28 days required for the diagnosis of BPD. During automated oxygen control the administered fraction of oxygen may only intermittently be above 0.21 in a 24-hour period, and this may not be predictive of BPD, for example when these brief moments are linked to apnoeic events. Depending on what criteria are used to define BPD, significantly more infants would be classified as having BPD. Thus, the standard BPD definition may be unsuitable when AOC is used as standard care.

Loss to follow up is unfortunately common in follow-up research and may lead to bias.[47] In **chapter 7** there was a relatively high rate of missing data due to loss to follow-up (pre-AOC 6.9%, post-AOC 10.6%). The majority of missing children were transferred to another NICU in the neonatal period and had subsequent follow-up there, therefore we expect them to be missing at random and not related to neurodevelopmental outcome. However, children lost to follow-up may be under treatment in a special care facility and therefore not missing at random. Parents may be less inclined to present their child for follow-up when they already receive regular tests in such a facility. To prevent biased results due to missing such children, we requested data for all children tested elsewhere. The strength of this study was that the children are always tested by trained professionals as part of a standardized national follow-up programme, improving the repeatability and reliability of the assessment of neurodevelopmental outcome.

General conclusion

Automated oxygen control is evolving and the technology holds promise. It increases time spent within the prescribed oxygen saturation target range, decreases hypoxia and hyperoxia, and reduces workload. This thesis is the first to show that these oxygenation outcomes are influenced by choice of automated oxygen controller. The OxyGenie controller was more effective in keeping oxygen saturation within the target range and preventing hyperoxaemia when compared to the $CLiO_2$ controller. We confirmed that these findings also apply during the entire NICU stay. Ultimately, our results demonstrated that OxyGenie is a better choice than $CLiO_2$ for oxygenation targeting.

The influence of automated oxygen control on mortality, morbidities and neurodevelopmental outcome at two years corrected age is not yet clear. However, OxyGenie control was associated with better clinical outcome than $CLiO_2$ control, strengthening the suggestion of controller influence on outcome. The retrospective nature of the studies precludes us from drawing definite conclusions on the causal effect of choice of algorithm on outcome, but the data from the studies performed are pointing in the same direction.

Future perspectives

Several automated oxygen control algorithms are embedded in commercially available ventilators, each of which has its own design and strategy. [15, 16, 48-51] Choice of design will influence how successful oxygen titration will be. As the influence on clinical effect of better titration may be small, the most effective algorithm should be used. Direct head-to-head comparison can be performed using a cross-over design in preterm infants, but changes in respiratory condition would likely preclude testing more than two algorithms at a time. Direct comparison of all algorithms would entail testing them under the same circumstances. A bench test incorporating a model of a preterm infant could be used, against which each oxygen control algorithm could be tested. We are in the process of developing such a model. The strength of this design is that each ventilator would be tested against the same 'typical' patients, which is helpful in informing clinicians exactly what to expect when using an algorithm/ventilator combination.

To date it remains unclear what the least harmful range to target is, which could be dependent on what technique is used control the titration of oxygen. As was seen in the NeOProM studies[52] and during another study[27], during manual titration

bedside staff tend to accept a slightly higher oxygen saturation, whereas a machine will always follow its programmed instructions. Titration by a machine may lead to stricter adherence of the target range, and can therefore lead to a different median SpO_2 and spread around the median. The NeOProM studies included a significant overlap in the achieved oxygen saturation distribution. This may have diluted the effect of choice in target range on clinical outcomes such as ROP, NEC and mortality. Strict titration by automated technology can aid in finally solving the puzzle of the most appropriate range to target. We are currently conducting a study comparing an SpO_2 TR of 91%-95% with an SpO_2 TR of 92%-96% during automated oxygen control. We expect that a set target range of 92%-96% will result in a more stable SpO_2 and reduction of hypoxic episodes (SpO_2 <80%) due to the position at the oxygen-haemoglobin dissociation curve.

Finally, further research is warranted to elucidate the effect of AOC on clinical outcome, preferably in a very large, carefully designed randomised controlled trial with continuous automated oxygen control from the most effective device during the entire admission.

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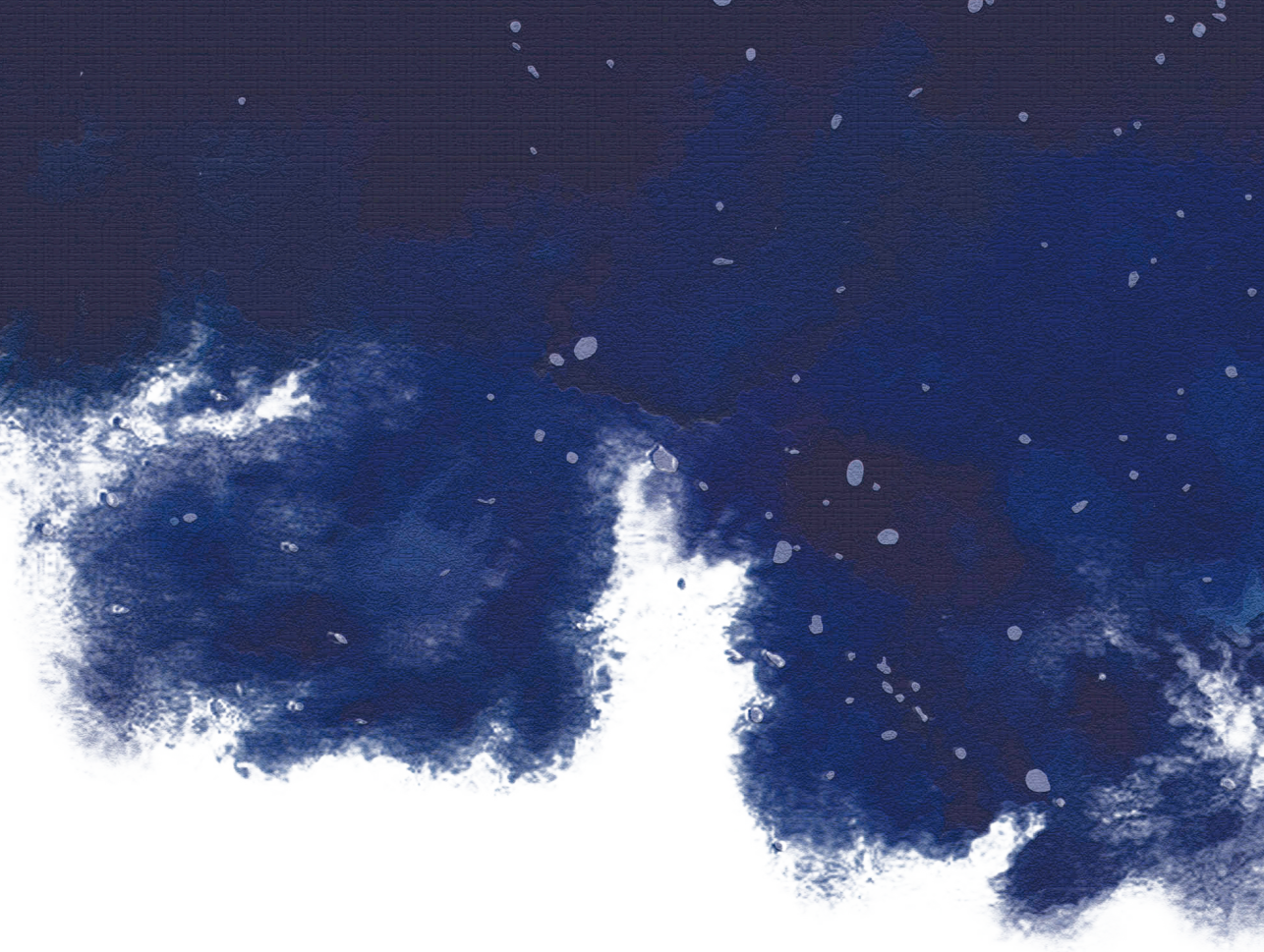


Chapter 10

Summary

Introduction

This thesis consists of studies that relate to outcomes of preterm infants after using automated oxygen control (AOC). Supplemental oxygen is an important tool in battling hypoxia related to prematurity but can be harmful. Hyperoxia resulting from inappropriate oxygen administration can lead to morbidities such as bronchopulmonary dysplasia, retinopathy of prematurity and neurodevelopmental impairment. Therefore, supplemental oxygen must be carefully titrated within a therapeutic range. An automated oxygen controller has been proven to be more successful than manual control in titrating oxygen within this range. In this thesis, a review is given of which algorithms are available, and how they work. Thereafter, we report on the effectivity of two automated oxygen controllers used in the NICU, followed by clinical and long-term outcomes after using AOC. We conclude with a general discussion of this thesis.

Currently available automated oxygen control algorithms

In **chapter 2**, we described the six automated oxygen control systems which are currently commercially available for use in the NICU. All systems are discussed in light of their algorithm, strategy and, if known, effect. Our goal was to provide guidance to clinicians seeking to comprehend AOC and those possibly seeking to implement this technology in their practice. We explained the basic approaches applied, namely rule-based, proportional-integral-derivative and the adaptive approach. Also, we gave an overview of how each of the six algorithms work and, where available, we gave an overview of clinical effect. When compared to manual titration, all these commercially available algorithms have shown a beneficial effect on the proportion of time that oxygen saturation of preterm infants is within the set target range, and they all demonstrate a decrease in hyperoxia and severe hypoxia. AOC may also reduce the workload for bedside staff. Although not reported to date, there is a concern that these devices may mask clinical deterioration. So far, trials involving different algorithms were heterogeneous in design and no head-to-head comparisons have been made, making it difficult to differentiate which algorithm is most effective and what clinicians can expect from algorithms under certain conditions.

Effectivity of automated oxygen control algorithms on oxygenation of preterm infants in the NICU

In **chapter 3**, we compared the effect of two different automated oxygen control devices on target range time and occurrence of hypoxic and hyperoxic episodes in a randomised cross-over trial in the Leiden University Medical Center. We included fifteen preterm infants born between 24 weeks and 29 weeks and 6 days of gestation, receiving invasive or non-invasive respiratory support. Inspired oxygen concentration was titrated by the OxyGenie controller (SLE6000 ventilator) and the CLiO$_2$ controller (AVEA ventilator) for 24 hours each in a random sequence with the respiratory support mode kept constant. The main outcome was time spent within the set oxygen saturation target range (TR; 91%-95% with supplemental oxygen, 91%-100% without supplemental oxygen). The infants in the study had a median gestational age of 26 weeks and 4 days (interquartile range (IQR) 25 weeks 3 days - 27 weeks 6 days) and a post-natal age of 19 (IQR 17-24) days. Time spent within the TR was higher during OxyGenie control (80.2 (IQR 72.6–82.4) % vs 68.5 (IQR 56.7–79.3) %, $p<0.005$). Less time was spent above TR while receiving supplemental oxygen (6.3 (IQR 5.1-9.9) % vs 15.9 (IQR 11.5-30.7) %, $p<0.005$) but more time was spent below TR during OxyGenie control (14.7 (IQR 11.8-17.2) % vs 9.3 (IQR 8.2-12.6)

%, p<0.05). There was no significant difference in time with SpO_2 <80% (0.5 (IQR 0.1-1.0) % vs 0.2 (IQR 0.1-0.4) %, p=0.061). Long-lasting SpO_2 deviations occurred less frequently during OxyGenie control. The OxyGenie control algorithm was more effective in keeping the oxygen saturation within TR and preventing hyperoxaemia, and equally effective in preventing hypoxaemia (SpO_2<80%), albeit at the cost of a small increase in mild hypoxaemia.

Chapter 4 is a continuation on comparing these two different automated oxygen control devices in preterm infants on time spent in different oxygen saturation ranges. Contrary to **chapter 3,** the entire stay in the NICU was investigated in a retrospective cohort study. Preterm infants (OxyGenie 75 infants, $CLiO_2$ 111 infants) born under 30 weeks of gestation receiving at least 72 hours of supplemental oxygen during respiratory support between October 2015 and November 2020 were studied. Inspired oxygen concentration was titrated by the OxyGenie controller between February 2019 and November 2020 and the $CLiO_2$ controller between October 2015 and December 2018 as standard of care. Time spent within the SpO_2 TR was higher during OxyGenie control (median 71.5 [IQR 64.6–77.0] % vs 51.3 [47.3–58.5] %, p<0.001). Infants under OxyGenie control spent less time in hypoxic and hyperoxic ranges (SpO_2 <80%: 0.7 [0.4–1.4] % vs 1.2 [0.7–2.3] %, p<0.001; SpO_2 >98%: 1.0 [0.5-2.4] % vs 4.0 [2.0-7.9] %, p<0.001). Both groups received a similar fraction of inspiratory oxygen (29.5 [28.0 – 33.2] % vs 29.6 [27.7-32.1] %, p=non-significant). Again, oxygen saturation targeting was better in the Oxygenie cohort, which resulted in less hypoxia and hyperoxia.

To conclude this part, we report what the effect is of using one-per-second or one-per-minute data in **chapter 5**. Large amounts of data are collected in neonatal intensive care units which could be used for research. It is unclear whether this data, usually sampled at a lower frequency, is sufficient for retrospective studies. We investigated what to expect when using one-per-minute data for descriptive statistics. One-per-second fraction of inspiratory oxygen and oxygen saturation data was processed to one-per-minute data and compared on average, standard deviation, target range time, hypoxia, days of supplemental oxygen, and missing signal. Outcomes calculated from data recordings (one-per-minute=92, one-per-second=92) showed very little to no difference. Neither did sub-analyses of recordings under 100 and 200 hours. In this study descriptive statistics of one-per-minute data were comparable to one-per-second and could be used for retrospective analyses. Comparable, routinely collected one-per-minute data could be used to develop algorithms or finding associations retrospectively.

Clinical and long-term outcome after using automated oxygen controllers for preterm infants during NICU stay

Several studies demonstrated an increase in time spent within target range when AOC is used, however the effect on clinical outcome remains unclear. In **chapter 6** we compared clinical outcomes of preterm infants born before and after implementation of AOC as standard of care. In a retrospective pre-post implementation cohort study of outcomes for infants of 24-29 weeks gestational age receiving respiratory support before (2012-2015) and after (2015-2018) implementation of AOC as standard of care were compared. Outcomes of interest were mortality and complications of prematurity, number of ventilation days and length of stay in the Neonatal Intensive Care Unit (NICU). A total of 588 infants were included (293 pre- vs 295 in the post-implementation cohort), with similar gestational age (27.8 weeks pre- vs 27.6 weeks post-implementation), birth weight (1033 grams vs 1035 grams) and other baseline characteristics. Mortality and rate of complications related to prematurity were not different between the groups. Length of stay in NICU was not different, but duration of invasive ventilation was shorter in infants who received AOC (6.4 ±10.1 days vs 4.7 ±8.3 days, p=0.029). In this pre-post comparison, the implementation of AOC did not lead to a change in mortality or morbidity during admission.

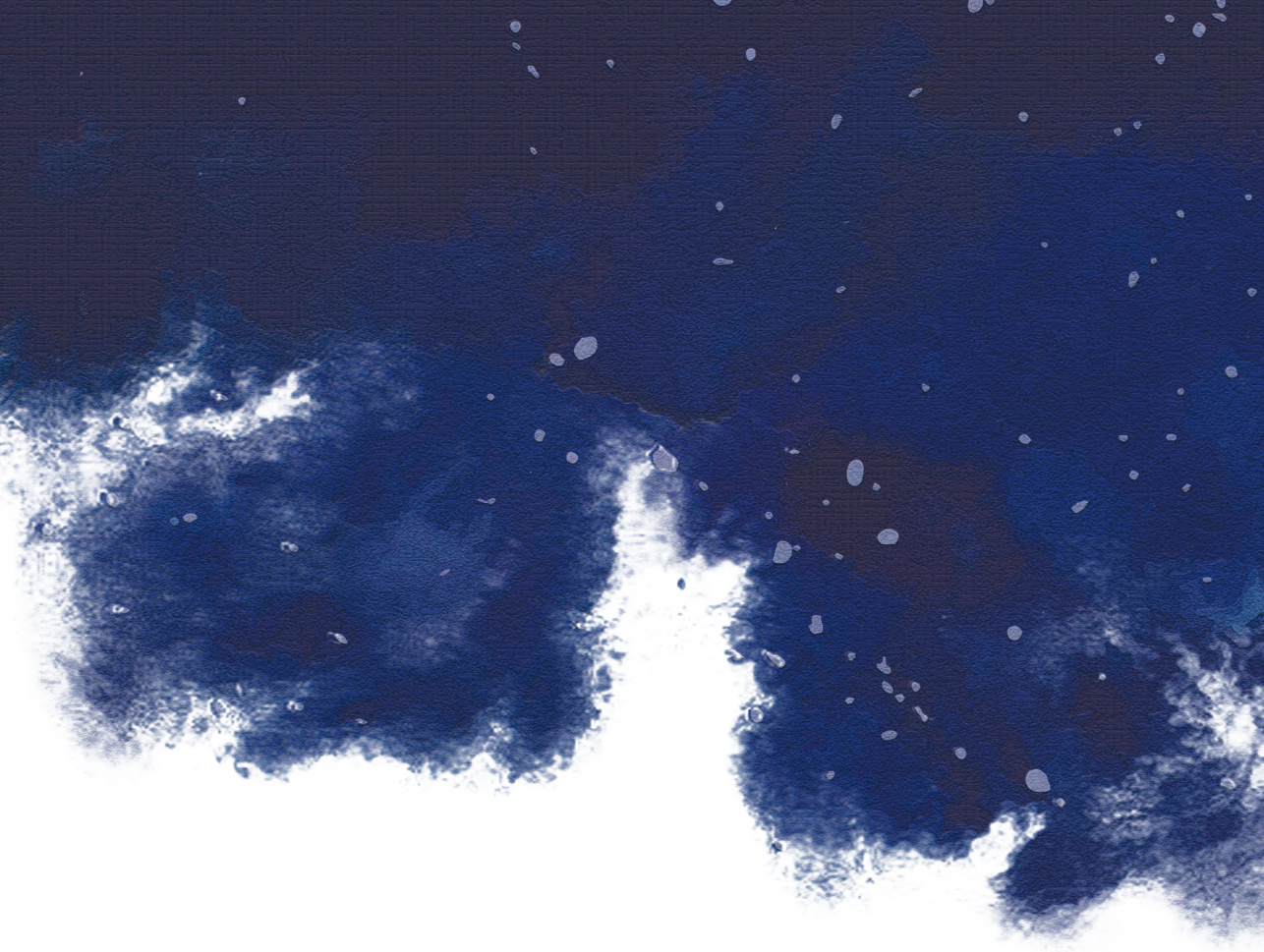
Faster resolution of hypoxaemic or hyperoxaemic events in preterm infants may reduce long-term neurodevelopmental impairment. Automatic titration of inspiratory oxygen increases time within the oxygen saturation target range and may provide a prompter response to hypoxic and hyperoxic events. In **chapter 7** we assessed routinely performed follow-up at two years of age after implementation of AOC as standard care and compared this with a historical cohort. Neurodevelopmental outcomes at two years of age were compared for infants born at 24-29 weeks gestational age before (2012-2015) and after (2015-2018) implementation of AOC as standard of care. Primary outcome was a composite of mortality or neurodevelopmental impairment (NDI), other outcomes assessed were mild-moderate NDI, Bayley-III composite scores, cerebral palsy and problem behaviour scores. 289 infants were eligible in the pre-AOC epoch and 292 in the post-AOC epoch. Baseline characteristics were not significantly different. 51 infants were lost to follow-up (pre-AOC 6.9% (20/289), post-implementation 10.6% (31/292)). The composite outcome of mortality or severe NDI was observed in 17.9% pre-AOC (41/229) vs. 24.0% (47/196) post-AOC (p=0.12). No significant differences were found for the secondary outcomes such as mild-moderate NDI, Bayley-III composite scores, cerebral palsy GMFCS and problem behaviour scores, with the exception of parent-reported readmissions until moment of follow-up which was less frequent post-AOC than pre-AOC. In this cohort study,

implementation of automated oxygen control in our NICU as standard of care for preterm infants led to no statistically significant difference in neurodevelopmental outcome at two years of age.

In **chapter 8** we compared short-term clinical outcomes after using two different automated oxygen controllers (OxyGenie and $CLiO_2$) in a propensity score matched retrospective observational study. Preterm infants (OxyGenie n=121, $CLiO_2$ n=121) born between 24+0-29+6 weeks of gestation were included. Median [IQR] gestational age in the OxyGenie cohort was 28+3 [26+3.5–29+0] versus 27+5 [26+5–28+3] in the $CLiO_2$ cohort, respectively 42% and 46% of infants were male and mean (SD) birth weight was 1034 (266) grams vs 1022 (242) grams. Again, inspired oxygen was titrated by OxyGenie (SLE6000) or $CLiO_2$ (AVEA) during respiratory support. We compared mortality, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotising enterocolitis and found that fewer infants in the OxyGenie group received laser coagulation for ROP (1 infant vs 10; risk ratio 0.1 (95%-CI 0.0 – 0.7); p=0.008), and infants had a shorter admittance in the NICU (28 [15-42] vs 40 [25-61] days; median difference 13.5 days (95%-CI 8.5 – 19.5); p<0.001). Infants in the OxyGenie group had fewer days on continuous positive airway pressure (8.4 [4.8-19.8] days vs. 16.7 [6.3-31.1]; p<0.001) and a significantly lower number of days on invasive ventilation (0 [0-4.2] days vs. 2.1 [0-8.4]; p=0.012). There were no statistically significant differences between all other morbidities. In this propensity score matched retrospective study, the OxyGenie epoch was associated with less morbidity when compared to the $CLiO_2$ epoch. There were significantly fewer infants that received treatment for ROP, received less intensive respiratory support and, although there were more supplemental oxygen days, the duration of stay in the NICU was shorter. A larger study will have to replicate these findings.

Finally, this thesis concludes with discussing the results of our studies. Automated oxygen control is up and coming and improves oxygen targeting by reducing hypoxia, hyperoxia and workload. This thesis provides the first evidence that the success of oxygen targeting is influenced by choice of AOC device. The OxyGenie controller was more effective than the $CLiO_2$ controller, both in a controller crossover study as well as during the entire admission under routine clinical care. Ultimately our result demonstrated that OxyGenie is a better choice than $CLiO_2$ for oxygenation targeting. The effect on clinical outcome of these devices is not yet clear. OxyGenie control was associated with better clinical outcome than $CLiO_2$ control, but the retrospective nature of the studies performed precludes us from inferring causality. Nevertheless, all data in this thesis are pointing in the same direction.

In the future research on this topic will involve a direct head-to-head comparison of all ventilators, preferably under the same conditions. This could be achieved by testing all available algorithms against a model of a preterm infant. This will allow us to inform clinicians what to expect when using an algorithm/ventilator combination. Directly following my PhD, I started this project at the University of Tasmania in Australia under supervision of Prof Peter Dargaville with a team of clinicians and engineers. Furthermore, automated oxygen control gives us the tool to elucidate what the least harmful range to target is. Previous studies have struggled to provide this evidence as during significant overlap between the compared target ranges occurred, reducing discriminative power. Automated oxygen control will provide strict titration and prevent this overlap. We are currently testing an SpO_2 target range of 91%-95% against one of 92%-96%. Finally, further research should be done to provide strong evidence on the effect of automated oxygen control on clinical outcome, preferably using the most effective automated oxygen controller.



Chapter 11

Nederlandse samenvatting

Introductie

Dit proefschrift bestaat uit studies die betrekking hebben op uitkomsten na het gebruik van automatische zuurstof titratie (AZT) bij prematuur geboren kinderen, ofwel prematuren. Het geven van extra zuurstof is een belangrijk middel om prematuriteits-gerelateerde hypoxie te bestrijden, maar extra zuurstof kan ook schadelijk zijn. Hyperoxie bij het geven van te veel zuurstof kan leiden tot ziektes als bronchopulmonaire dysplasie, prematurenretinopathie en een neurologische ontwikkelingsstoornis. Daarom moet extra zuurstof precies getitreerd worden binnen het therapeutische bereik. Het is bewezen dat een automatische zuurstof controller dit beter kan dan handmatige afstelling. In dit proefschrift geven we een overzicht van welke algoritmes er beschikbaar zijn die automatische zuurstof controle mogelijk maken en hoe ze werken. Daarna rapporteren we over de effectiviteit van twee automatische zuurstof controllers die gebruikt werden in de Neonatale Intensive Care Unit (NICU), gevolgd door de klinische en lange termijn uitkomsten na het gebruik van AZT. We eindigen met een algemene discussie van dit proefschrift.

Momenteel beschikbare automatische zuurstof controllers

In hoofdstuk 2 beschreven we zes automatische zuurstof controllers die momenteel commercieel verkrijgbaar zijn voor het gebruik in de NICU. Alle systemen worden beschreven vanuit het perspectief van hun algoritme, strategie en, als bekend, uitkomsten bij gebruik in de NICU. Ons doel was om handvaten te bieden voor clinici die AZT willen begrijpen en voor clinici die de technologie mogelijk willen implementeren in hun praktijk. We bespraken de basisprincipes die toegepast worden in de algoritmen, namelijk de *rule-based*, *proportional-integral-derivative* en *adaptive* principes. We gaven een overzicht van hoe ieder van de zes algoritmen werkte, en waar beschikbaar, gaven we een overzicht van het klinische effect. Al deze commercieel verkrijgbare systemen hebben een voordeel laten zien ten opzichte van manuele titratie op de tijd dat de zuurstofsaturatie (SpO_2) van prematuren binnen het ingestelde doelgebied is, en ze hebben allemaal een afname laten zien van hyperoxie en diepe hypoxie. AZT geeft mogelijk ook minder werkdruk voor zorgpersoneel. Onder sommige wetenschappers bestaat een bezorgdheid over het maskeren van klinische achteruitgang bij het gebruik van deze technologie, hoewel dit nergens in de tot op het moment van schrijven beschikbare medische literatuur beschreven wordt. Ten slotte kon geconcludeerd worden dat de beschikbare studies waarin de verschillende algoritmes gebruikt worden verschillend in ontwerp zijn en er zijn geen directe vergelijkende studies tussen algoritmes gedaan. Dit maakt het moeilijk om te bepalen welk algoritme het meest effectief is en wat clinici kunnen verwachten van deze systemen onder verschillende condities.

Effectiviteit van automatische zuurstof controller algoritmes op oxygenatie van prematuren in de NICU

In **hoofdstuk 3** vergeleken we het effect van twee verschillende automatische zuurstof controllers op de tijd binnen het zuurstofsaturatie doelgebied en het optreden van hypoxische en hyperoxische episodes in een gerandomiseerde cross-over studie in het Leids Universitair Medische Centrum. We includeerden vijftien premature kinderen geboren tussen de 24 weken en 29 weken en 6 dagen zwangerschapsduur. Allen kregen ofwel invasieve ofwel niet-invasieve respiratoire ondersteuning. De concentratie zuurstof werd zowel getitreerd door de OxyGenie controller (SLE6000-beademingsmachine) als de $CLiO_2$ controller (AVEA-beademingsmachine) in willekeurige volgorde voor 24 uur per controller, waarbij de respiratoire ondersteuning zo ver mogelijk constant werd gehouden. De primaire uitkomst was de tijd binnen het ingestelde zuurstofsaturatie doelgebied (DG; 91%-

95% wanneer extra zuurstof gegeven werd, 91%-100% zonder extra zuurstof). De kinderen in de studie hadden een mediane gestatieduur bij geboorte van 26 weken en 5 dagen (interkwartielbereik (IQR) 25 weken 3 dagen – 27 weken en 6 dagen) en een postnatale leeftijd van 19 dagen (IQR 17-24 dagen). De tijd doorgebracht in het DG was hoger tijdens OxyGenie controle (80,2 (IQR 72,6–82,4) % vs. 68,5 (IQR 56,7–79,3) %, p<0,005). Minder tijd werd doorgebracht boven het DG terwijl extra zuurstof gegeven werd (6,3 (IQR 5,1-9,9) % vs. 15,9 (IQR 11,5-30,7) %, p<0,005), maar meer tijd werd doorgebracht onder het DG tijdens OxyGenie controle (14,7 (IQR 11,8-17,2) % vs. 9,3 (IQR 8,2-12,6) %, p<0,05). Er was geen significant verschil in tijd met een SpO_2 <80% (0,5 (IQR 0,1-1,0) % vs. 0,2 (IQR 0,1-0,4) %, p=0,061). Lange periodes buiten het DG kwamen minder vaak voor tijdens OxyGenie controle. Het OxyGenie algoritme was effectiever in het houden van de zuurstofsaturatie binnen het DG en het voorkomen van hyperoxie. OxyGenie was net zo effectief in het voorkomen van diepe hypoxie (SpO_2 <80%), tegen de prijs van een kleine toename van milde hypoxie.

Hoofdstuk 4 is een voortzetting van het vergelijken van de doorgebrachte tijd in verschillende SpO_2 gebieden bij het gebruik van deze twee AZT-systemen bij prematuren. In tegenstelling tot **hoofdstuk 3** werd bij deze studie het hele verblijf op de NICU onderzocht in een retrospectieve cohortstudie. Prematuren (OxyGenie 75 kinderen, $CLiO_2$ 111 kinderen) tussen oktober 2015 en november 2020 met een gestatieduur bij geboorte onder de 30 weeks werden geïncludeerd indien ze tenminste 72 uur extra zuurstof toegediend kregen tijdens respiratoire ondersteuning. Toegediende zuurstof werd getitreerd door de OxyGenie controller tussen februari 2019 en november 2020, de $CLiO_2$ controller werd gebruikt voor standaard zorg tussen oktober 2015 en december 2018. De tijd in het SpO_2 doelgebied was hoger tijdens OxyGenie controle (mediaan 71,5 [IQR 64,6–77,0] % vs. 51,3 [47,3–58,5] %, p<0,001). De zuurstofsaturatie van kinderen in het OxyGenie cohort was minder vaak in hypoxische en hyperoxische gebieden (SpO_2 <80%: 0,7 [0,4–1,4] % vs. 1,2 [0,7–2,3] %, p<0,001; SpO2 >98%: 1,0 [0,5-2,4] % vs. 4,0 [2,0-7,9] %, p<0,001). Beide groepen kregen een vergelijkbare concentratie zuurstof 29,5 [28,0 – 33,2] % vs. 29,6 [27,7-32,1] %, p=non-significant). Opnieuw was de SpO_2 beter gereguleerd bij kinderen in het OxyGenie cohort, wat gepaard ging met minder hypoxie en hyperoxie.

In het laatste hoofdstuk van dit deel (**hoofdstuk 5**), rapporteren we wat het effect is van het gebruik van één-per-seconde of één-per-minuut data. In de NICUs worden continue grote hoeveelheden data verzameld welke gebruikt zouden kunnen worden voor onderzoek. Het is onduidelijk of deze data, vaak verzameld met een frequentie

van 1 waarde per minuut, voldoende is om retrospectieve studies op te baseren. We onderzochten wat men kan verwachten als één-per-minuut data gebruikt wordt voor beschrijvende statistiek. Verzamelde één-per-seconde toegediende zuurstofconcentratie en SpO_2 waarden werden verwekt tot één-per-seconde waarden. Hierna vergeleken we deze data op gemiddelde, standaarddeviatie, DG-tijd, hypoxie, aantal dagen extra toegediende zuurstof, en het optreden van missend signaal. Uitkomsten werden berekend van data-opnames (één-per-minuut=92, één-per-seconde=92) en toonden weinig tot geen verschil. Ook sub-analyses van data-opnames met een duur van minder dan 100 en 200 uur toonden weinig tot geen verschil. In deze studie bleek omschrijvende statistiek van één-per-minuut data vergelijkbaar met die van één-per-seconde data en zou gebruikt kunnen worden voor retrospectieve analyses. Vergelijkbare, routinematig verzamelde één-per-minuut data zou gebruikt kunnen worden om nieuwe algoritmes te ontwikkelen of om associaties retrospectief te onderzoeken.

Klinische en lange termijn uitkomsten na het gebruik van automatische zuurstof titratie voor prematuren in de NICU.

Verschillende studies hebben laten zien dat de tijd binnen het SpO_2 DG toeneemt wanneer AZT gebruikt wordt in plaats van manuele titratie, maar de effecten op klinische uitkomsten waren nog niet onderzocht. In **hoofdstuk 6** vergeleken we klinische uitkomsten van prematuren die geboren werden voor (2012-2015) met prematuren geboren na implementatie van AZT in de standaard zorg (2015-2018). Data over mortaliteit, complicaties van prematuriteit, aantal dagen invasieve beademing en duur van verblijf in de NICU werden verzameld voor alle prematuren geboren tussen de 24 tot en met 29 weken en 6 dagen zwangerschapsduur voor een retrospectieve pre-post implementatie studie. In totaal werden 588 prematuren geïncludeerd (293 pre- vs. 295 in het post-implementatie cohort), die vergelijkbare zwangerschapsduren hadden bij geboorte (27,8 weken pre- vs. 27,6 weken post-implementatie), vergelijkbare geboortegewichten (1033 gram vs. 1035 gram) en ook andere onderzochte baseline karakteristieken waren vergelijkbaar. Mortaliteit en het optreden van complicaties gerelateerd aan prematuriteit waren niet verschillend tussen de twee cohorten. De duur van opname in de NICU was niet verschillend, maar de duur van invasieve beademing was korter in het cohort waarin kinderen AZT kregen (gemiddeld 6.4 standaard deviatie (SD) ±10,1 vs. gemiddeld 4,7 SD ±8,3, p=0,029). In deze pre-post vergelijking leidde de implementatie van AZT niet tot een verandering in mortaliteit of morbiditeit tijdens opname.

Het sneller oplossen van hypoxische of hyperoxische episodes bij prematuren zou mogelijk lange termijn neurologische ontwikkelingsstoornissen kunnen verminderen. Automatische titratie van zuurstof verhoogd de tijd binnen het SpO_2 DG en kan een snellere reactie geven op hypoxische en hyperoxische episodes dan wanneer manueel getitreerd wordt. Prematuur geboren kinderen krijgen routinematig follow-up onderzoek op een leeftijd van 2 jaar, waarbij ook neurologische ontwikkeling getest wordt. In **hoofdstuk 7** vergeleken we dit routinematig deze follow-up van prematuren geboren voor implementatie (2012-2015) met prematuren geboren na implementatie (2015-2018) van AZT in de standaard zorg. Neurologische uitkomsten op een (gecorrigeerde) leeftijd van twee jaar werden vergeleken voor prematuren geboren tussen de 24 tot en met 29 weken en 6 dagen zwangerschapsduur. De primaire uitkomst was samengesteld uit mortaliteit en ernstige neurologische ontwikkelingsachterstand; andere uitkomsten waren milde-matige neurologische ontwikkelingsachterstand, Bayley-III composite scores, cerebral palsy, en probleemgedrag scores. 289 kinderen kwamen in aanmerkingen voor inclusie in het pre-AZT-cohort en 292 kinderen in het post-AZT-cohort. Baseline karakteristieken waren niet significant verschillend tussen de twee cohorten. Er was een lost-to-follow-up van 51 kinderen (pre-AZT-cohort 6,9% (20/289), post-AZT-cohort 10,6% (31/292)). De samengestelde uitkomst van mortaliteit en ernstige neurologische ontwikkelingsachterstand werd gevonden in 17,9% pre-AZT-cohort (41/229) vs. 24,0% (47/196) post-AZT-cohort (p=0,12). We vonden geen significante verschillende voor de secundaire uitkomsten als milde-matige neurologische ontwikkelingsachterstand, cerebral palsy, en probleemgedrag scores, met uitzondering van het aantal heropnames gerapporteerd door ouders wat minder frequent was in het post-AZT-cohort. In deze cohortstudie leidde implementatie van AZT in de standaard zorg in onze NICU niet tot een statistisch significant verschil in neurologische uitkomsten op twee jarige leeftijd

In **hoofdstuk 8** vergeleken we korte-termijn klinische uitkomsten na het gebruiken van de OxyGenie controller en de $CLiO_2$ controller in een *propensity-score-matched* retrospectieve studie. Prematuren (OxyGenie n=121, $CLiO_2$ n=121) geboren bij een zwangerschapsduur tussen de 24 tot en met 29 weken en 6 dagen werden geïncludeerd. De mediane [IQR] gestatieduur in het OxyGenie cohort was 28 weken en 3 dagen [26 weken 3,5 dag – 29 weken] vs. 27 weken en 5 dagen [26 weken en 5 dagen – 28 weken en 3 dagen] in het $CLiO_2$ cohort, respectievelijk was 42% en 46% van het mannelijk geslacht en het gemiddelde (SD) geboortegewicht was 1034 (±266) vs. 1022 (±242) gram. Opnieuw werd zuurstof getitreerd door ofwel de OxyGenie controller ofwel de $CLiO_2$ controller tijdens respiratoire ondersteuning. We vergeleken mortaliteit, prematurenretinopatie, bronchopulmonaire dysplasia, en necrotische enterocolitis en vonden dat minder prematuren in het OxyGenie cohort

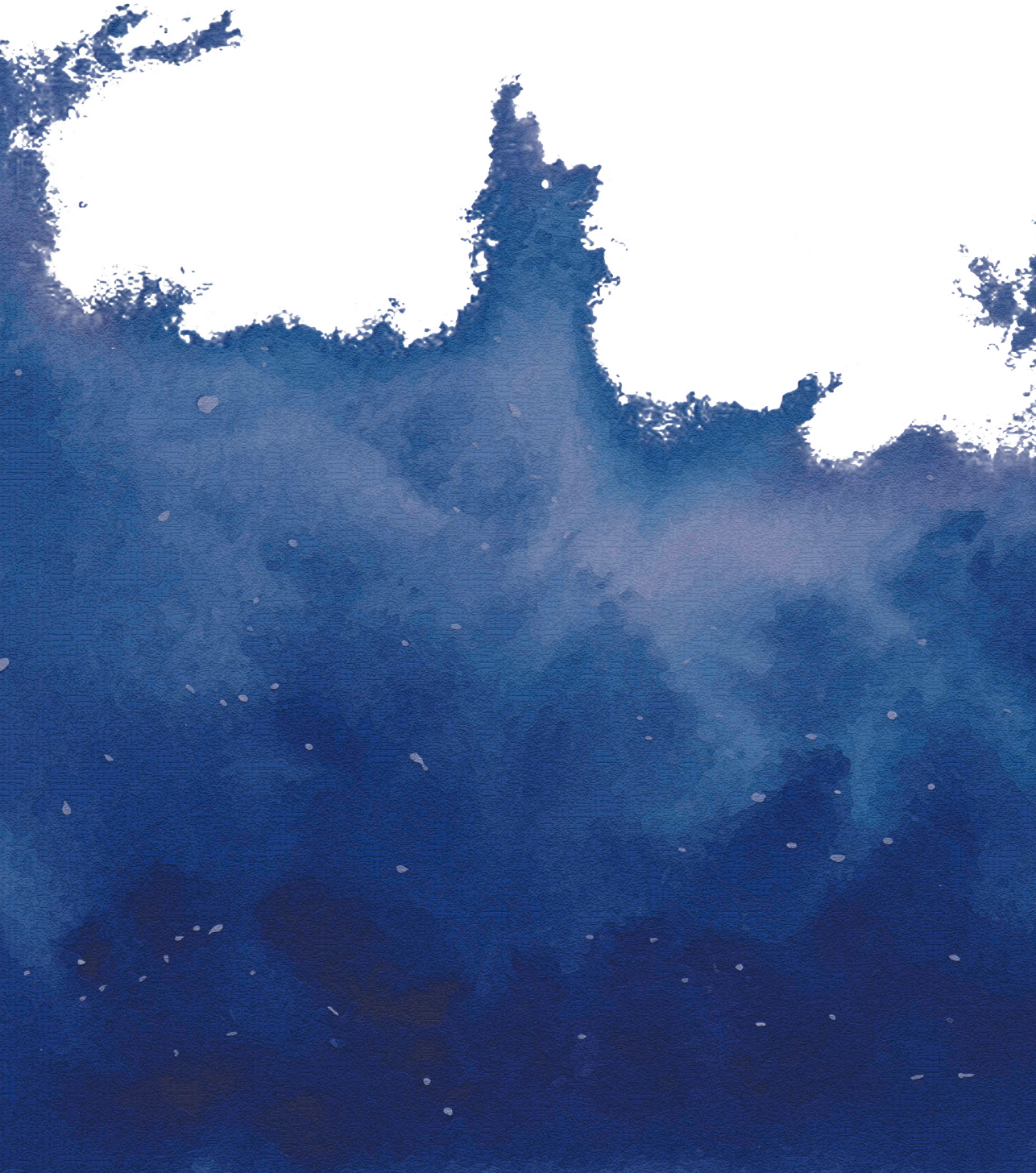
lasertherapie nodig hadden voor prematurenretinopathie (1 kind vs. 10; risk ratio 0,1 (95%-CI 0 – 0,7); p=0,008), en kinderen hadden een kortere opnameduur op de NICU (28 [15-42] vs. 40 [25-61] dagen; mediaan verschil 13.5 dagen (95%-CI 8,5 – 19,5); p<0,001). Prematuren in de OxyGenie groep lagen minder dagen aan de respiratoire ondersteuningsmodus 'continuous positive airway pressure' (8,4 [4,8-19,8] dagen vs. 16,7 [6,3-31,1]; p<0,001) en een significant aantal dagen minder aan de invasieve beademing (0 [0-4,2] dagen vs. 2,1 [0-8,4]; p=0,012). Geen van de andere morbiditeiten toonde significante verschillen. In deze retrospectieve studie was het OxyGenie tijdperk geassocieerd met minder morbiditeit wanneer vergeleken met het $CLiO_2$ tijdperk. Er waren significant minder kinderen die behandeling nodig hadden voor prematurenretinopathie, ze kregen minder invasieve respiratoire ondersteuning en, hoewel er meer dagen zuurstof gegeven werd, was de duur van opname in de NICU korter. Een grotere studie is nodig om deze bevinden te repliceren.

Ten slotte concludeert dit proefschrift met het bespreken van de resultaten van onze studies. Automatische zuurstof titratie is aan het opkomen en verbetert titratie van zuurstof met het voorkomen van hypoxie, hyperoxie en werkdruk. Dit proefschrift geeft het eerste bewijs dat de keuze van welke AZT-controller gebruikt wordt beïnvloed hoe succesvol zuurstoftitratie zal zijn. De OxyGenie controller was effectiever dan de $CLiO_2$ controller, zowel in een gerandomiseerde cross-over studie als tijdens een gehele opname met standaard zorg.

Uiteindelijk laten onze resultaten zien dat de OxyGenie controller een betere keuze is dan de $CLiO_2$ controller voor zuurstof titratie. Het effect op klinische uitkomsten van deze apparaten is nog niet duidelijk. OxyGenie was geassocieerd met een betere klinische uitkomst dan $CLiO_2$, maar vanwege het retrospectieve karakter van de uitgevoerde studies kunnen we geen causaliteit afleiden. Desalniettemin wijst alle data in dit proefschrift in dezelfde richting.

In de toekomst zal onderzoek over dit onderwerp zich richten op een directe vergelijking van alle beademingsapparaten met AZT-controller, bij voorkeur onder de exact zelfde omstandigheden. Dit kan bereikt worden door alle beschikbare algoritmes te testen met een gecomputeriseerd model van een prematuur. Dit zal ons in staat stellen om clinici te informeren over wat ze kunnen verwachten wanneer ze een bepaald combinatie van algoritme/beademingsapparaat gebruiken. Meteen volgend op mijn promotietraject ben ik dit project begonnen aan de University of Tasmania in Australië onder supervisie van professor Peter Dargaville met een team van clinici en ingenieurs. Verder zou AZT ons kunnen helpen te verhelderen wat het minst schadelijke SpO_2 doelgebied is. Eerdere studies zijn er niet volledig in geslaagd

dit bewijs te geven aangezien er in de praktijk significante overlap was tussen de vergeleken doelgebieden. AZT biedt strikte titratie en voorkomt zulke overlap. We vergelijken momenteel een SpO_2 DG van 91%-95% met een van 92%-96% in een gerandomiseerde cross-over studie. Ten slotte zal toekomstig onderzoek gedaan moeten worden om sterk bewijs te verzamelen over de effecten van AZT op klinische uitkomsten, bij voorkeur met de meeste effectieve automatische zuurstof controller.



Part VI

Appendices

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Abbreviations

AOC - Automated oxygen controller
BPD – Bronchopulmonary dysplasia
BSID-III-NL - Bayley Scales of Infant and Toddler Development - Third Edition - NL
CBCL - Child Behaviour CheckList
ETROP - Early Treatment of Retinopathy of Prematurity
FiO_2 – Fraction of inspiratory oxygen
GMFCS - Gross Motor Function Classification System
HFNC – High Flow Nasal Cannula
HFO - High Frequency Oscillation
IVH – Intraventricular haemorrhage
LUMC – Leiden University Medical Center
NDI – Neurodevelopmental impairment
NEC – Necrotising enterocolitis
NICU – Neonatal intensive care unit
NS - Non Significant
PID – Proportional-integral-derivative
PVL – Periventricular leukomalacia
ROP – Retinopathy of prematurity
SpO_2 – Oxygen saturation measured by pulse-oximetry
TR – Target range

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Curriculum Vitae

Hylke Salverda was born in Alkmaar, the Netherlands in 1988. After finishing secondary school at the Berger Scholen Gemeenschap in Bergen, the Netherlands, he studied Computer Science for two and a half years at the University of Amsterdam starting in 2007. In 2010 he switched majors and started his degree in Medicine. During his studies, he worked in the Clinical Epidemiology department. At the beginning of his Masters he did a research internship in the Otolaryngology department investigating complications after vestibular schwannomas. After being awarded cum laude as a MSc, Hylke worked for over a year in the HMC Bronovo hospital as a senior house officer in Paediatrics. To combine his technical interests and his passion for Neonatology, Hylke applied for a PhD program investigating closed-loop oxygenation and ventilation under the supervision of Prof. dr. Arjan te Pas from Leiden University Medical Center and Prof. dr. Peter Dargaville from the University of Tasmania.

During the PhD program, Hylke has had the opportunity to conduct several randomized clinical trials at the Leiden University Medical Center, and perform multiple cohort studies using clinical data from infants treated with automated oxygen control. In 2020, he laid the foundations for a bench-top study comparing all commercially available automated oxygen controllers. From mid-2022 he will work as a postdoctoral research fellow at the University of Tasmania to continue working on the bench-top study. In the future he hopes to continue using his experience with large data sets and apply his research skillset to improve healthcare as a general practitioner and researcher.

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- *Hylke*