Outcomes after automated oxygen control for preterm infants

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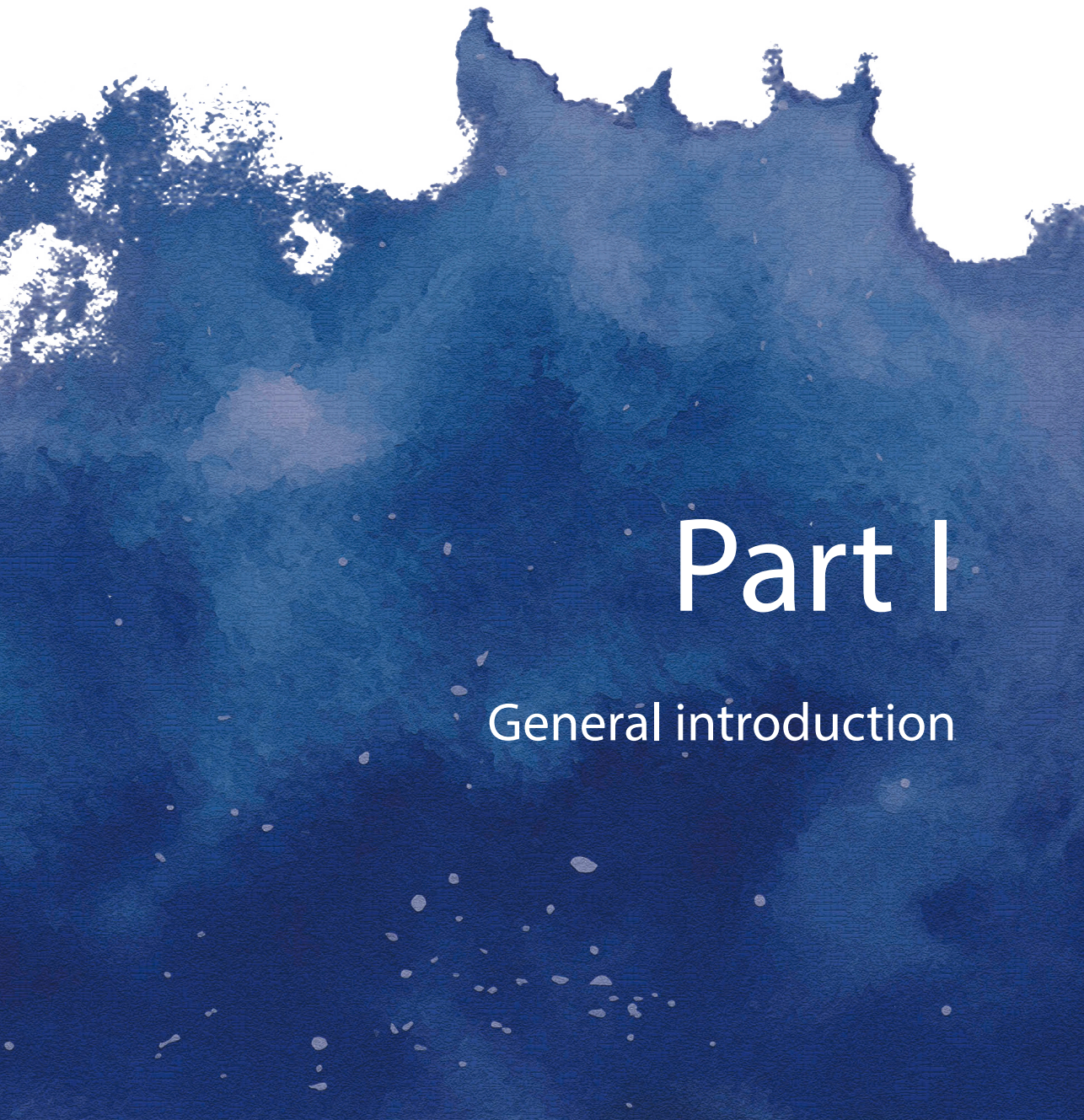
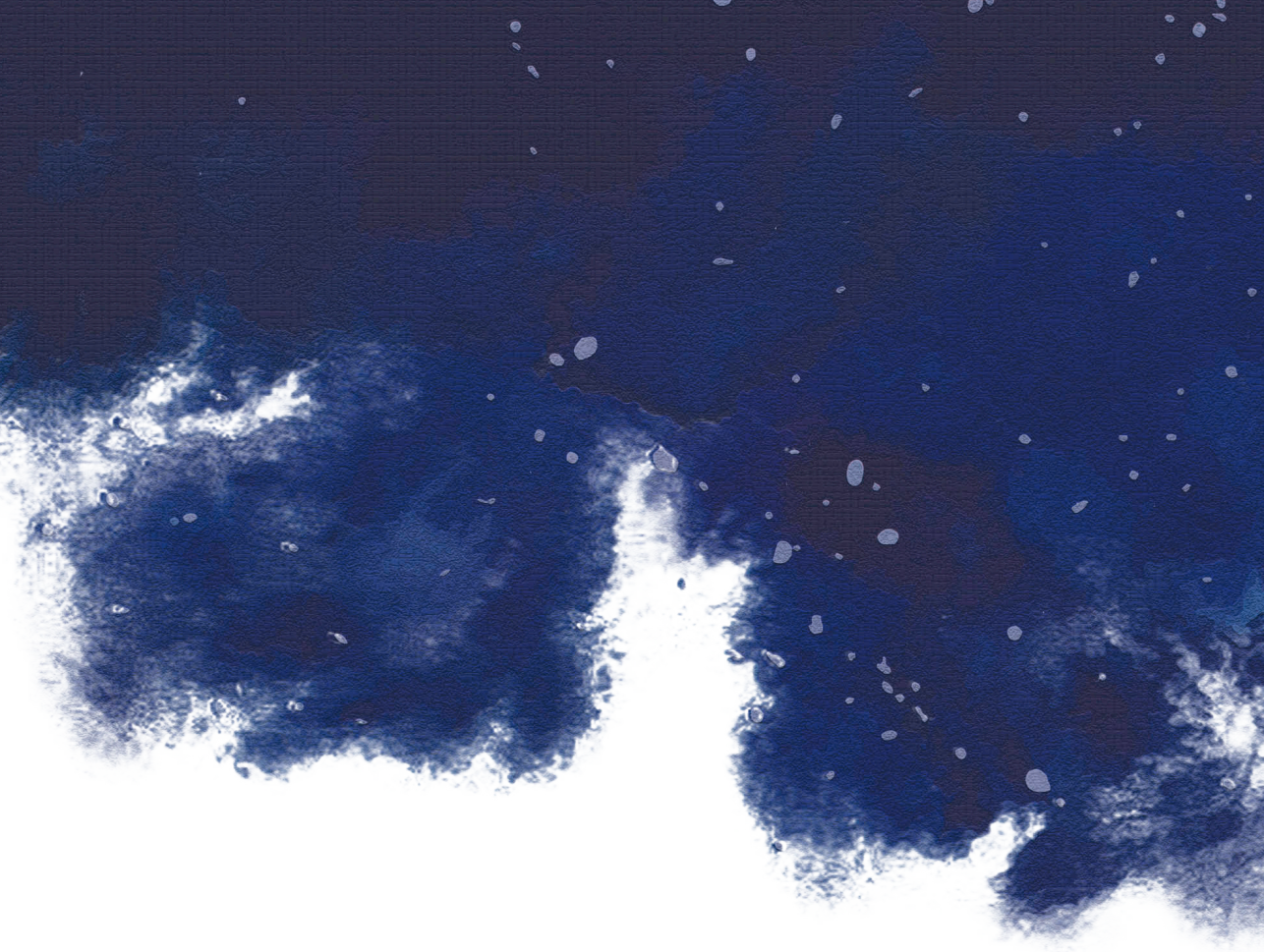


Part I

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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