Outcomes after automated oxygen control for preterm infants

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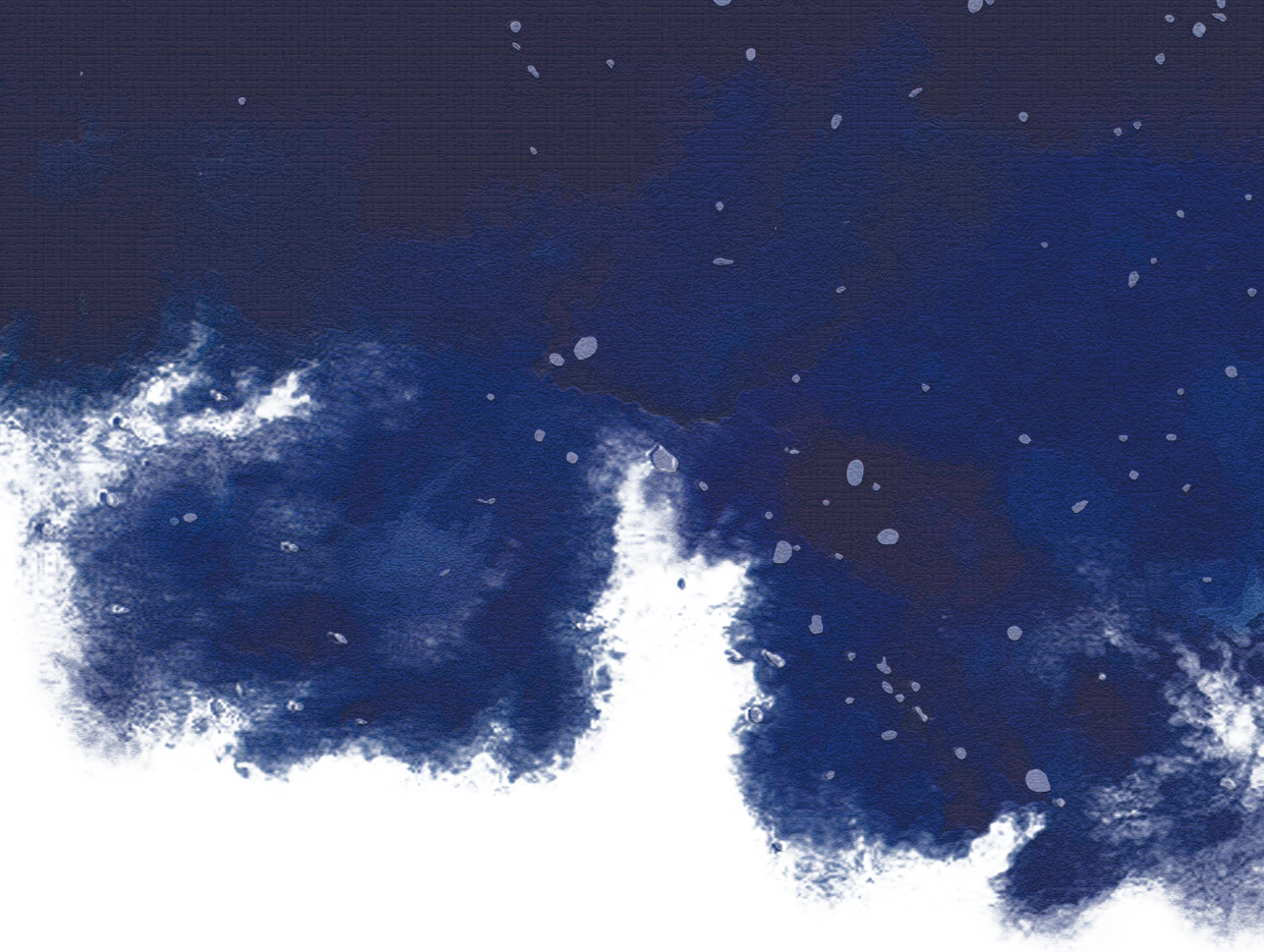
Part V

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.

References

1. Avery ME, Oppenheimer EH. Recent increase in mortality from byaline membrane disease. *The Journal of pediatrics* 1960;57(4):553-59.
2. Bolton DPG, Cross KW. FURTHER OBSERVATIONS ON COST OF PREVENTING RETROLENTAL FIBROPLASIA. *The Lancet* 1974;303(7855):445-48.
3. Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004;113(2):394-6.
4. Cohen PJ. Oxygen and intracellular metabolism. *International anesthesiology clinics* 1981;19(3):9-19.
5. Giannone PJ, Bauer JA, Schanbacher BL, et al. Effects of hyperoxia on postnatal intestinal development. *Biotechnic & histochemistry : official publication of the Biological Stain Commission* 2007;82(1):17-22.
6. Hellstrom A, Perruzzi C, Ju M, et al. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98(10):5804-8.
7. Liu Y, Jiang P, Du M, et al. Hyperoxia-induced immature brain injury through the TLR4 signaling pathway in newborn mice. *Brain research* 2015;1610:51-60.
8. Poets CF, Roberts RS, Schmidt B, et al. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. *Jama* 2015;314(6):595-603.
9. Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics* 2006;118(4):1574-82.
10. Sadeghi Fathabadi O, Gale TJ, Lim K, et al. Characterisation of the Oxygenation Response to Inspired Oxygen Adjustments in Preterm Infants. *Neonatology* 2016;109(1):37-43.
11. van Zanten HA, Tan RN, van den Hoogen A, et al. Compliance in oxygen saturation targeting in preterm infants: a systematic review. *European journal of pediatrics* 2015;174(12):1561-72.
12. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1959-69.
13. Kaufman DA, Zanelli SA, Gurka MJ, et al. Time outside targeted oxygen saturation range and retinopathy of prematurity. *Early human development* 2014;90 Suppl 2:S35-40.
14. Mitra S, Singh B, El-Naggar W, et al. Automated versus manual control of inspired oxygen to target oxygen saturation in preterm infants: a systematic review and meta-analysis. *Journal of Perinatology* 2018:1-10.
15. Gajdos M, Waitz M, Mendler MR, et al. Effects of a new device for automated closed loop control of inspired oxygen concentration on fluctuations of arterial and different regional organ tissue oxygen saturations in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2018
16. Reynolds PR, Miller TL, Volakis LI, et al. Randomised cross-over study of automated oxygen control for preterm infants receiving nasal high flow. *Archives of disease in childhood Fetal and neonatal edition* 2019;104(4):F366-F71.
17. Schwarz CE, Kidszun A, Bieder NS, et al. Is faster better? A randomised crossover study

comparing algorithms for closed-loop automatic oxygen control. *Archives of disease in childhood Fetal and neonatal edition* 2019:fetalneonatal-2019-317029.
18. Sturrock S, Ambulkar H, Williams EE, et al. A randomised crossover trial of closed loop automated oxygen control in preterm, ventilated infants.n/a(n/a)
19. Ali SK, Jayakar RV, Marshall AP, et al. Preliminary study of automated oxygen titration at birth for preterm infants. *Archives of disease in childhood Fetal and neonatal edition* 2022
20. Dargaville PA, Marshall AP, Ladlow OJ, et al. Automated control of oxygen titration in preterm infants on non-invasive respiratory support. *Archives of disease in childhood Fetal and neonatal edition* 2022;107(1):39-44.
21. Dargaville PA, Marshall AP, McLeod L, et al. Automation of oxygen titration in preterm infants: Current evidence and future challenges. *Early human development* 2021;162:105462.
22. Plottier GK, Wheeler KI, Ali SK, et al. Clinical evaluation of a novel adaptive algorithm for automated control of oxygen therapy in preterm infants on non-invasive respiratory support. *Arch Dis Child Fetal Neonatal Ed* 2017;102(1):F37-F43.
23. Claure N, Bancalari E, D'Ugard C, et al. Multicenter crossover study of automated control of inspired oxygen in ventilated preterm infants. *Pediatrics* 2011;127(1):e76-83.
24. Claure N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial. *J Pediatr* 2009;155(5):640-5 e1-2.
25. Claure N, Gerhardt T, Everett R, et al. Closed-loop controlled inspired oxygen concentration for mechanically ventilated very low birth weight infants with frequent episodes of hypoxemia. *Pediatrics* 2001;107(5):1120-4.
26. van Kaam AH, Hummler HD, Wilinska M, et al. Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants. *J Pediatr* 2015;167(3):545-50 e1-2.
27. Van Zanten HA, Kuypers K, Stenson BJ, et al. The effect of implementing an automated oxygen control on oxygen saturation in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2017;102(5):F395-F99.
28. Waitz M, Schmid MB, Fuchs H, et al. Effects of automated adjustment of the inspired oxygen on fluctuations of arterial and regional cerebral tissue oxygenation in preterm infants with frequent desaturations. *J Pediatr* 2015;166(2):240-4 e1.
29. Lal M, Tin W, Sinha S. Automated control of inspired oxygen in ventilated preterm infants: crossover physiological study. *Acta Paediatr* 2015;104(11):1084-9.
30. Schwarz CE, Kreutzer KB, Langanky L, et al. Randomised crossover trial comparing algorithms and averaging times for automatic oxygen control in preterm infants. *Archives of disease in childhood Fetal and neonatal edition* 2021
31. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. *Journal of applied physiology: respiratory, environmental and exercise physiology* 1979;46(3):599-602.
32. Stenson BJ. Achieved Oxygenation Saturations and Outcome in Extremely Preterm Infants. *Clinics in perinatology* 2019;46(3):601-10.
33. Lorch SA, Srinivasan L, Escobar GJ. Epidemiology of apnea and bradycardia resolution in premature infants. *Pediatrics* 2011;128(2):e366-73.

34. Di Fiore JM, Bloom JN, Orge F, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr* 2010;157(1):69-73.
35. Hellström A, Hård AL. Screening and novel therapies for retinopathy of prematurity - A review. *Early human development* 2019;138:104846.
36. van Zanten HA, Tan RN, Thio M, et al. The risk for hyperoxaemia after apnoea, bradycardia and hypoxaemia in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2014;99(4):F269-73.
37. Claure N, Bancalari E. Automated closed loop control of inspired oxygen concentration. *Respir Care* 2013;58(1):151-61.
38. University Hospital Tubingen. Effects of Closed-loop Automatic Control of FiO2 in Extremely Preterm Infants 2018 [updated October. Available from: https://ClinicalTrials.gov/show/NCT03168516.
39. Salverda HH, Cramer SJE, Witlox R, et al. Comparison of two devices for automated oxygen control in preterm infants: a randomised crossover trial. *Archives of disease in childhood Fetal and neonatal edition* 2021
40. Imanishi Y, Hirata K, Nozaki M, et al. Effect of fluctuation of oxygenation on the development of severe retinopathy of prematurity in extremely preterm infants. *J Perinatol* 2020;40(3):515-21.
41. Martin RJ, Wang K, Koroglu O, et al. Intermittent hypoxic episodes in preterm infants: do they matter? *Neonatology* 2011;100(3):303-10.
42. Nitzan M, Romem A, Koppel R. Pulse oximetry: fundamentals and technology update. *Med Devices (Auckl)* 2014;7:231-9.
43. Sahni R. Continuous noninvasive monitoring in the neonatal ICU. *Current opinion in pediatrics* 2017;29(2):141-48.
44. Tin W, Lal M. Principles of pulse oximetry and its clinical application in neonatal medicine. *Seminars in Fetal and Neonatal Medicine* 2015;20(3):192-97.
45. Schwarz CE, Lightbody G, Müller-Hansen I, et al. In vitro evaluation of delays in the adjustment of the fraction of inspired oxygen during CPAP: effect of flow and volume. 2020:fetalneonatal-2020-319058.
46. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *American journal of respiratory and critical care medicine* 2001;163(7):1723-9.
47. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? *European journal of epidemiology* 2004;19(8):751-60.
48. Urschitz MS, Horn W, Seyfang A, et al. Automatic control of the inspired oxygen fraction in preterm infants: a randomized crossover trial. *Am J Respir Crit Care Med* 2004;170(10):1095-100.
49. Claure N, Gerhardt T, Everett R, et al. Closed-Loop Controlled Inspired Oxygen Concentration for Mechanically Ventilated Very Low Birth Weight Infants With Frequent Episodes of Hypoxemia. *Pediatrics* 2001;107:1120-24.
50. Hutten MC, Goos TG, Ophelders D, et al. Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs. *Pediatric research* 2015;78(6):657-63.
51. Dargaville PA, Sadeghi Fathabadi O, Plottier GK, et al. Development and preclinical testing of an adaptive algorithm for automated control of inspired oxygen in the preterm

infant. *Arch Dis Child Fetal Neonatal Ed* 2017;102(1):F31-F36.
52. Askie LM, Darlow BA, Finer N, et al. Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. *Jama* 2018;319(21):2190-201.