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

Archives of
Disease in Childhood

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

Journal:	*Archives of Disease in Childhood*
Manuscript ID	fetalneonatal-2016-312496.R2
Article Type:	Original article
Edition:	not in use
Date Submitted by the Author:	08-Aug-2017
Complete List of Authors:	van Zanten, Henriëtte; Leiden University Medical Center, Department of Pediatrics, Division of Neonatology Pauws, Steffen; Leids Universitair Medisch Centrum, Paediatrics; Tilburg University Tilburg center for Cognition and Communication Stenson, Ben; Neonatal Unit, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh, Neonatology Walther, Frans; LUMC, Neonatology lopriore, enrico; Leiden University Medical Centre, neonatology te Pas, Arjan; LUMC, Neonatology
Keywords:	preterm infant, supplemental oxygen, target range, hypoxaemia, hyperoxaemia

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

van Zanten HA[1], Pauws SC[1 2], Stenson B[3], Walther FJ[1], Lopriore E[1], te Pas AB[1]

[1] Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, Leiden, the Netherlands

[2] TiCC, Tilburg University, the Netherlands

[3] Neonatal Unit, Simpson Centre for Reproductive Health, Edinburgh Royal Infirmary, Edinburgh, UK

Key Words: preterm infant, supplemental oxygen, target range, hypoxaemia, hyperoxaemia

Word count: 2498

Corresponding author:

H. A. van Zanten

Department of Pediatrics,

Division of Neonatology

Leiden University Medical Center, J6-S,

PO Box 9600, 2300 RC Leiden, the Netherlands

Tel: +31 71 5262859

Email: h.a.van_zanten@lumc.nl

Contributors statement

Ms. H.A. van Zanten was the executive researcher of the study. She performed literature search, data collection, data analysis, data interpretation, writing and submitting of the manuscript.

Mr. S.C. Pauws was involved in data analysis, critically reviewed the manuscript and approved the final version.

Mr. B.J. Stenson was involved in interpretation of the data, critically reviewed the manuscript and approved the final version.

Mr. E. Lopriore critically reviewed the manuscript and approved the final version.

Mr. F.J. Walther critically reviewed the manuscript and approved the final version.

Mr. A.B. te Pas was the project leader and performed literature search, designed the study, and coordinated data analysis, data interpretation, writing, editing, and submitting of the manuscript.

Abbreviations

ΔFiO_2	Maximum additional FiO_2 - baseline FiO_2
ABC	Apnoea, bradycardia, cyanosis
BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
GA	Gestational age
HR	Heart rate
LUMC	Leiden University Medical Center
nCPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
PDMS	Patient data management system
SpO_2	Pulse oxygen saturation
TR	Target range

Abstract

Background

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

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

Methods:

Before and after changing the target range from 85-95% to 90-95%, infants <30 weeks of gestation receiving oxygen were compared during their admission on the NICU. For each infant distribution of SpO_2 was noted by collecting SpO_2 samples each minute, and the percentage of time spent with SpO_2 within 90-95% was calculated. Oxygen was manually adjusted. Hypoxaemic events (SpO_2<80%) where oxygen was titrated were analysed.

Results:

Data were analysed for 104 infants (57 before and 47 after the range was narrowed). The narrower range was associated with an increase in the median (IQR) SpO_2 (93 (91–96)% vs 94 (92-97)%;*p* 0.01), but no increase in median time SpO_2 within 90-95% (49.2 (39.6-59.7)% vs (46.9 (27.1-57.9)%;p 0.72). The distribution of SpO_2 shifted to the right with a significant decrease in SpO_2 <90%, but not <80%. The count of minute values for $Sp0_2$ <80% decreased while the frequency and duration of hypoxaemic events and oxygen titration was not different.

Conclusion:

Narrowing the target range from 85-95% to 90-95% in preterm infants was associated with in an increase in median SpO_2 and a rightward shift in the distribution, but no change in time spent between 90-95%.

What is already known

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

What this study adds

1. Implementing a narrower TR from 85-95% to 90-95% was not associated with a change in duration of a SpO_2 level between 90-95%.
2. The distribution of SpO_2 shifted to the right, with a decrease in SpO_2 <95%, but no effect on hypoxaemia (i.e. SpO_2 <80%).

Introduction:

Oxygen therapy in preterm infants is routinely monitored by pulse oximetry during their admission in a neonatal intensive care unit (NICU). In order to prevent the risk for hypoxaemia and hyperoxaemia, neonatal caregivers in most units titrate fraction of inspired oxygen (FiO_2) manually in order to stay within the set oxygen saturation (SpO_2) target range (TR). Recent randomized trials in evaluating lower SpO_2 TR (85%-89%) versus higher SpO_2 TR (91%-95%) in preterm infants[1-3] have shown that using a higher SpO_2 TR led to a reduced mortality but increased the rate of retinopathy of prematurity (ROP) when compared to a lower SpO_2 TR.[1 3] Although the groups in the studies[1-3] had a substantial overlap in SpO_2 levels and the optimal TR remains undefined, European and Dutch guidelines now recommend a SpO_2 TR of 90–95% for preterm infants.[4]

Maintaining SpO_2 within TR during oxygen therapy requires compliance with alarm limit settings, prompt responses and careful oxygen titration of caregivers which can be a difficult task to perform.[5-7] Hyperoxaemia can easily occur, especially when extra oxygen is given after hypoxaemic events.[8] The workload of caregivers, education and awareness about the hazards of hypoxaemia and hyperoxaemia, and appropriate alarm settings, can also influence the caregivers compliance in SpO_2 targeting.[5 9 10]

Following the recommendation of European and Dutch guidelines our TR for SpO_2 was recently changed from 85-95% to 90-95%. This could lead to more intrinsic stability in infants[11] but we also recognized that complying with this smaller range could be challenging for the NICU-nurses.[5 11 12] We studied the effect of narrowing TR towards the higher end on the distribution of SpO_2 and compliance in SpO_2 targeting during oxygen therapy.

Methods:

A prospective designed pre-post implementation study was performed in the NICU of the Leiden University Medical Center (LUMC), which is a tertiary level perinatal center with a traditional open-bay NICU architecture and an average of 550 intensive care admissions per year. In the Netherlands, no ethical approval is required for anonymised studies with medical charts and patient data that were collected and noted for standard care. The LUMC Medical Ethics Committee provided a statement of no objection for obtaining and publishing the anonymised data. All preterm infants <30 weeks of gestation (GA) admitted to the NICU in LUMC between February 2014 and October 2014 (SpO_2 TR 85-95%) and November 2014 and March 2015 (SpO_2 TR 90-95%) receiving respiratory support (endotracheal and non-invasive ventilation) were included. Data was collected until infants were transferred out of the intensive care area in our unit or to a regional hospital. Preterm infants with major congenital heart disease were excluded. All infants received caffeine therapy and doxapram was added in case of refractory apnoeas.

The characteristics of each infant as well as clinical parameters and ventilator settings (including FiO_2 and SpO_2) were sampled every minute and routinely collected in the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). During both periods the heart rate and SpO_2 were collected using a Masimo pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA) integrated in a Philips bedside Intellivue monitor (Philips Healthcare Nederland, Eindhoven, The Netherlands) with an averaging time set at eight seconds. During both periods caregivers titrated the supplemental oxygen manually following local guidelines (Figure 1). In our NICU the average nurse:patient ratio was 1:2. During both periods the alarm was activated when SpO_2 was directly below or above the set TR, when FiO_2 >0.21. When no supplemental oxygen was required, no upper alarm limit was activated. We considered a washout period around changing TR setting not necessary. Before the TR was changed, all caregivers were fully informed. In addition, before the start of each shift the TR and alarm settings were checked by the nurse if they were set appropriate, which is standard care in our NICU

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

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

Statistical analyses

For this study a convenience sample was used. For the first period, infants were included that were born one month after the implementation of staff training and an oxygen titration guideline [13] until the target range was changed. For the second period, infants were included after implementing the new TR, until the time point automated oxygen control was implemented. Quantitative data are presented as median (IQR), mean (SD) or number (percentage) where appropriate. The total duration of SpO_2 levels within various ranges for FiO_2 >21% was collected for each infant individually before and after implementation of a narrowed TR and was aggregated as a percentage of recorded time

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

Results:

During the study period of 13 months, a total number of 104 infants born <30 weeks of gestation were admitted to our NICU. Of these infants, 57 were born before changing the SpO_2 TR, and 47 infants after this change. No infants were excluded. There were no differences in median (IQR) GA (28+3 (26+4 – 29) vs 27+5 (26+1 – 29) weeks; *p* 0.25) and BW (1000 (855 – 1206) vs 900 (740 – 1153) grams; *p* 0.17) or other characteristics (Table 1).

Effect on compliance and SpO_2 distribution

During the TR 85-95% period 630.244 data points were collected and during the TR 90-95% period 402.993 data points of SpO_2 measurements were collected during oxygen therapy. The median (IQR) number of data points per infant, were not different (2359 (377 - 14129) vs 3082 (1352 – 15024) data points;*p* 0.42).

After changing the TR, there was a slight, but significant increase in median (IQR) SpO_2 (93 (91 – 96)% vs 94 (92 - 97)%);*p*<0.02) (Figure 2), while the FiO_2 slightly decreased (28 (25-32)% vs 26 (24-30)%;*p* 0.01). Narrowing TR was not associated with an increase in median (IQR) time SpO_2 was within 90-95% (49.2 (39.6-59.7)% vs (46.9 (27.1-57.9)%;*p* 0.72). The time SpO_2 was >95% and >98% increased,

but did not reach statistical significance. Changing the TR was associated with a significant decrease in both SpO_2 <90% (15.7 (7 - 21)% vs 10.7 (8.4 - 13.7)%;*p*<0.05) and SpO_2 <85% (6.2 (2.5 - 8.0)% vs 3.5 (2.6 - 5.3)%;*p*<0.05), but SpO_2 <80% was similar (Table 2,Figure 2).

During the TR 85-95% period 471.642 data points were collected and in the TR 90-95% period 424.700 data points of SpO_2 measurements were collected when infants were breathing in air. The median (IQR) number of data points per infant, was not different (5722 (3112 - 10395) vs 8102 (3635 – 13363) data points; *p* 0.24). Changing the TR did was not associated with significant changes in SpO_2 distribution and SpO_2 <90% were similar when infants were breathing in air (Table 3, Figure 3).

Effect on hypoxaemic events and how oxygen was titrated

During non-invasive respiratory support 168 hypoxaemic events requiring extra oxygen occurred in 28/57 (49%) infants before, and 204 events in 32/47 (68%) infants after the TR was changed. There was no difference in lowest minute value and the count in minute values with bradycardia and SpO_2 <80% (Table 4). The (median (IQR) count of minute values for $Sp0_2$ <80% decreased while mean (SD) was not different. There was a non-significant increase in hyperoxaemia after the TR was changed (63% (106/168) vs 73% (148/204);*p*=0.05) (Table 4), while there was no difference in ΔFiO_2, duration of titrating oxygen down to the baseline and count in minute values with hyperoxaemia (Table 4).

Discussion

Our study demonstrated the effect of narrowing the SpO_2 TR of 85-95% towards the higher end to 90-95% on SpO_2 distribution of preterm infants when oxygen is supplied. We observed that the new, more narrow, TR was associated with a small increase in median SpO_2 and a rightward shift in the distribution. While this was associated with a decrease in the prevalence of SpO_2 < 90%, it had no effect on hypoxaemia (i.e. SpO_2 <80%). Changing TR did not affect the duration at which SpO_2 was 90-95%. However, it was associated with a non-significant increase in the occurrence of hyperoxaemia, (Figure 2). These results could indicate that the nurses attempted to comply with the

new TR, but found it difficult to titrate oxygen sufficiently to stay within the narrow TR. Nevertheless, as we managed to decrease the exposure to SpO_2 less than 90%, narrowing the TR in our unit could lead to similar beneficial effects shown in the recent trials. [1-3]

A similar effect was observed around hypoxaemic events. There was no change in occurrence and duration of hypoxaemic events and how oxygen titration was performed, but the occurrence of hyperoxaemia increased, although this raise was not significant.

To our knowledge this is the first report of the effect when the TR is significantly narrowed to only the upper part of the original TR when oxygen is manually titrated. Laptook *et al*. reported the effect of changing the SpO_2 TR, but the change in range was much smaller (from 90-95% to 88-94%) when compared to ours.[14] It is difficult to compare our results with their findings, but they also reported no change in the time SpO_2 spent within the TR. They observed also no difference in the mean percentage of time spent within the TRs, but this might be attributed to the small change in TR.[14] Mills *et al*. reported a lower compliance when a narrow TR for SpO_2 was used, except when preterm infants participated in a trial comparing TRs.[12]

Changing the TR did not lead to a change in SpO_2 distribution when infants were breathing in air and there was no decrease in lower SpO_2. This finding, together with the observation that the time SpO_2 was 90-95% did not change when oxygen was given, could indicate that the nurses already had the tendency to keep SpO_2 in the higher end of the intended target range when 85-95% was used. This is in line with previous observation that nurses were less compliant in the upper alarm limits.[5 6 11 15] Indeed, the clinical trials comparing lower vs higher SpO_2 TR also reported that the median levels of oxygen saturations were higher than intended TR in both treatment groups.[1-3] It is likely that caregivers favour SpO_2 closer to the higher end of the target range because infants are intrinsically more stable in the higher SpO_2 region, resulting in less FiO_2 fluctuations.

We observed a decrease in time SpO_2 spent <90% when oxygen was given, which is comparable to the findings of recent trials comparing low (85-89%) vs high TR (91-95%). These trials showed that a TR above 90% led to a decrease in mortality.[1-3] A low SpO_2 TR has been associated with an increased rate of hypoxaemic events.[14 16] However, we did not observe a change in hypoxaemia, or hypoxaemic events and how these were handled, after we increased the lower limit of the TR. This lack of effect is probably also a consequence of how nurses titrated oxygen before the TR was changed. Changing the TR towards the higher end led to a non-significant increase in hyperoxaemia and more often hyperoxaemia after an hypoxaemic event. This has also been observed in previous studies, as also in the trials comparing lower and higher TRs,[1-3] which could then potentially lead to an increase in ROP.

Titrating oxygen when using a smaller target range in instable premature infants with fluctuating SpO_2 requires constant nursing intervention.[8] It has been reported that a narrower TR leads to an inevitable increase of SpO_2 alarms.[17] These alarms contribute to all other alarms on a NICU where a high number of alarms are false.[18] Excessive exposure to alarms can effect response from caregivers and lead to alarm fatigue, which is potentially harmful to patients.[19 20] Although we have not measured the number of alarms in our study, this can affect the compliance in TR negatively.

While maintaining SpO_2 within a narrow TR is a difficult task to perform when oxygen needs to titrated manually, automated oxygen regulation could be more effective and lead to the desired compliance in keeping SpO_2 within the narrow range.[21-25] However, when Wilinska *et al.* used automated oxygen control and compared the TR 87-93% with a more narrow TR (90-93%), similar results as in our study were observed. The narrow range of 90-93%, resulted in less time with lower SpO_2 (80-86%), but more time with higher SpO_2 (94-98%). In addition, there were also no differences in the amount and duration of hypoxaemic events.[26]

The non-randomized character of this study is a limitation. Although the compared groups were not different in basic characteristics and there were no further policy changes occurred during the study period, bias could have been introduced by conditions we did not record or measure. The Masimo oximeter algorithm could not be updated in the Philips monitors that we used in our unit, which is reflected by the well described dip[27] in the frequencies of SpO2 87-90%. However, the same oximeters and monitors were used in both groups and thus did not influence the observed distributions when comparing the groups. Furthermore, we did not adjust for the contribution of the number of hypoxic events of each patient, but we considered every hypoxaemic event as an independent event because all events are handled similar for each infant. We could only compare SpO_2 values that were routinely sampled every minute and the value is an average of 8 seconds, which is less frequent than reported in other studies.[28 29 30] It is possible that in both groups we missed SpO_2 fluctuations and hypoxaemic events in between the samples taken. These limitations indicate that the results have to be interpreted with caution, this study was not designed to compare morbidity and mortality.

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

References

1. 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. doi: 10.1056/NEJMoa0911781 [published Online First: 2010/05/18]

2. Schmidt B, Whyte RK, Asztalos EV, et al. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA* 2013;309(20):2111-20.

3. Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. *The New England Journal of Medicine* 2013;368(22):2094-104. doi: 10.1056/NEJMoa1302298 [published Online First: 2013/05/07]

4. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. *Neonatology* 2013;103(4):353-68. doi: 10.1159/000349928 [published Online First: 2013/06/06]

5. Clucas L, Doyle LW, Dawson J, et al. Compliance with alarm limits for pulse oximetry in very preterm infants. *Pediatrics* 2007;119(6):1056-60. doi: 10.1542/peds.2006-3099 [published Online First: 2007/06/05]

6. 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. doi: 10.1542/peds.2005-0413 [published Online First: 2006/10/04]

7. Lim K, Wheeler KI, Gale TJ, et al. Oxygen saturation targeting in preterm infants receiving continuous positive airway pressure. *The Journal of Pediatrics* 2014;164(4):730-36.e1. doi: 10.1016/j.jpeds.2013.11.072 [published Online First: 2014/01/18]

8. van Zanten HA, Tan RN, Thio M, et al. The risk for hyperoxaemia after apnoea, bradycardia and hypoxaemia in preterm infants. *Archives of Disease in Childhood Fetal and Neonatal edition* 2014 doi: 10.1136/archdischild-2013-305745 [published Online First: 2014/03/29]

9. Armbruster J, Schmidt B, Poets CF, et al. Nurses compliance with alarm limits for pulse oximetry: Qualitative study. *Journal of Perinatology* 2010;30(8):531-34. doi: 10.1038/jp.2009.189

10. Sink DW, Hope SA, Hagadorn JI. Nurse:patient ratio and achievement of oxygen saturation goals in premature infants. *Archives of Disease in Childhood Fetal and Neonatal edition* 2011;96(2):F93-8. doi: 10.1136/adc.2009.178616 [published Online First: 2010/11/03]

11. Jones JG, Lockwood GG, Fung N, et al. Influence of pulmonary factors on pulse oximeter saturation in preterm infants. *Archives of Disease in Childhood Fetal and Neonatal edition* 2016;101(4):F319-22. doi: 10.1136/archdischild-2015-308675 [published Online First: 2015/11/26]

12. Mills BA, Davis PG, Donath SM, et al. Improving compliance with pulse oximetry alarm limits for very preterm infants? *Journal of Paediatrics and Child Health* 2010;46(5):255-8. doi: 10.1111/j.1440-1754.2009.01680.x [published Online First: 2010/03/27]

13. van Zanten HA, Pauws S.C, Beks E.C., Stenson, B.J., Lopriore E., te Pas A.B. Selected Abstracts of the 1st Congress of joint European Neonatal Societies (jENS 2015); Budapest (Hungary); September 16-20, 2015; Session "Pulmonology". *Journal of Pediatric and Neonatal Individualized Medicine* 2015;4(2):e040213-e13. doi: 10.7363/040213

14. Laptook AR, Salhab W, Allen J, et al. Pulse oximetry in very low birth weight infants: can oxygen saturation be maintained in the desired range? *Journal of Perinatology* 2006;26(6):337-41. doi: 10.1038/sj.jp.7211500 [published Online First: 2006/04/07]

15. Greenspan JS, Goldsmith JP. Oxygen therapy in preterm infants: hitting the target. *Pediatrics* 2006;118(4):1740-1. doi: 10.1542/peds.2006-1834 [published Online First: 2006/10/04]

16. Di Fiore JM, Walsh M, Wrage L, et al. Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia. *The Journal of Pediatrics* 2012;161(6):1047-52. doi: 10.1016/j.jpeds.2012.05.046 [published Online First: 2012/06/29]

17. Ketko AK, Martin CM, Nemshak MA, et al. Balancing the Tension Between Hyperoxia Prevention and Alarm Fatigue in the NICU. *Pediatrics* 2015;136(2):e496-504. doi: 10.1542/peds.2014-1550

18. Sola A, Golombek SG, Montes Bueno MT, et al. Safe oxygen saturation targeting and monitoring in preterm infants: can we avoid hypoxia and hyperoxia? *Acta Paediatrica (Oslo, Norway : 1992)* 2014;103(10):1009-18. doi: 10.1111/apa.12692 [published Online First: 2014/05/20]

19. Bitan Y, Meyer J, Shinar D, et al. Nurses' reactions to alarms in a neonatal intensive care unit. *Cogn Tech Work* 2004;6(4):239-46. doi: 10.1007/s10111-004-0162-2

20. Cvach M. Monitor alarm fatigue: an integrative review. *Biomed Instrum Technol* 2012;46(4):268-77. doi: 10.2345/0899-8205-46.4.268

21. 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-E83.

22. 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. [published Online First: 2001/05/23]

23. Hallenberger A, Poets CF, Horn W, et al. Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. *Pediatrics* 2014;133(2):e379-85. doi: 10.1542/peds.2013-1834 [published Online First: 2014/01/29]

24. 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. doi: 10.1164/rccm.200407-929OC [published Online First: 2004/09/07]

25. Zapata J, Gomez JJ, Araque Campo R, et al. A randomised controlled trial of an automated oxygen delivery algorithm for preterm neonates receiving supplemental oxygen without mechanical ventilation. *Acta Paediatrica (Oslo, Norway : 1992)* 2014;103(9):928-33. doi: 10.1111/apa.12684 [published Online First: 2014/05/13]

26. Wilinska M, Bachman T, Swietlinski J, et al. Automated FiO2-SpO2 control system in neonates requiring respiratory support: a comparison of a standard to a narrow SpO2 control range. *BMC Pediatrics* 2014;14:130. doi: 10.1186/1471-2431-14-130 [published Online First: 2014/06/03]

27. Johnston ED, Boyle B, Juszczak E, et al. Oxygen targeting in preterm infants using the Masimo SET Radical pulse oximeter. *Archives of Disease in Childhood Fetal and Neonatal edition* 2011;96(6):F429-33. doi: 10.1136/adc.2010.206011 [published Online First: 2011/03/08]

28. 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. doi: 10.1001/jama.2015.8841 [published Online First: 2015/08/12]

29. 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. *The Journal of Pediatrics* 2015;166(2):240-4 e1. doi: 10.1016/j.jpeds.2014.10.007

30. Vagedes J, Poets CF, Dietz K. Averaging time, desaturation level, duration and extent. *Archives of Disease in Childhood Fetal and Neonatal edition* 2013;98(3):F265-6. doi: 10.1136/archdischild-2012-302543 [published Online First: 2012/09/11]

Table 1. Patient characteristics

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

[a] Independent samples Mann-Whitney U test

[b] Chi square

Table 2. Time in different saturation ranges when breathing oxygen

	TR 85-95%	TR 90-95%	*p*-value*
Data points per patient, median (IQR)	2359 (377 - 14129)	3082 (1352 – 15024)	0.42
SpO_2 <80%	1.7 (0.8-2.6)	1.5 (0.8 - 2.1)	0.55
SpO_2 <85%,	6.2 (2.5 - 8.0)	3.5 (2.6 - 5.3)	<0.05
SpO_2 <90%	15.7 (7 - 21)	10.7 (8.4 - 13.7)	<0.05
SpO_2 90-95%,	49.2 (39.6 - 59.7)	46.9 (27.1 - 57.9)	0.72
SpO_2 >95	30.8 (22.6 - 44.5)	39.0 (28.8 - 59.2)	0.07
SpO_2 >98%,	6.1 (2.3 - 12.1)	8.9 (3.3 - 17.9)	0.15

Time with SpO_2 within various ranges were collated for each infant individually and aggregated as proportions of recorded time (Median (IQR).

*Statistical analysis comprised a Mann-Whitney U test

Table 3. Time with SpO_2 within various ranges when breathing in air

	TR 85-95%	TR 90-95%	*p*-value*
Data points per patient, median (IQR)	5722 (3112 – 10395)	8102 (3635 – 13363)	0.24
SpO_2 <80%	0.3 (0.1-0.9)	0.3 (0.1 – 0.9)	0.49
SpO_2 <85%,	1.1 (0.5 – 2.9)	1.2 (0.7 – 2.7)	0.65
SpO_2 <90%	3.6 (1.6 – 11.7)	4.5 (2.1 – 7.9)	0.97
SpO_2 90-95%,	29.8 (14.7 – 49.8)	36.5(20.7 – 46.1)	0.50
SpO_2 >95%	60.1 (39.5 – 83.2)	58.2 (41.1 – 76.6)	0.35
SpO_2 >98%,	14.9 (5.8 – 42.8)	13.9 (6.2 – 27.3)	0.57

Time with SpO_2 within various ranges were collated for each infant individually and aggregated as proportions of recorded time (Median (IQR).

*Statistical analysis comprised a Mann-Whitney U test.

Table 4. Hypoxaemic events; Apnoea Bradycardia Cyanosis characteristics requiring oxygen therapy

	TR 85-95% (ABC= 168)	TR 90-95% (ABC = 204)	***p*-value***
ABC with occurrence of SpO_2 >95% after administration of extra oxygen	64%	73%	0.057[a]
Lowest minute value during bradycardia, bpm (depth)	69 (61-75)	70 (62-75)	0.63[b]
Count minute values with bradycardia, min (duration)	1 (1-1)	1 (1-1)	0.073[b]
Lowest minute value during SpO_2 <80, % (depth)	72 (61-77)	73 (63-77)	0.57[b]
Count minute values SpO_2 <80%, min (duration) Median (IQR) Mean (SD)	 1 (1-2) 1.73 (1.1)	 1 (1-2) 1.47 (0.8)	 0.004[b] 0.006
ΔFiO_2 (Maximum increase – baseline FiO_2), %	19 (6-21)	19 (7-21)	0.93[b]
Count minute values of FiO_2 titration to baseline oxygen concentration, min	3 (2-7)	2 (2-6)	0.10[b]

count minute value with SpO_2 >95%, min	1 (1-3)	1 (0-2)	0.27[b]

Data are expressed as median (IQR)

[a] Chi-square test

[b] Independent samples Mann-Witney U test

Data is sampled every minute, every hypoxaemic event (ABC) where extra oxygen was titrated was evaluated by documenting the following characteristics: lowest stored minute value (depth) and count in low minute values (duration) of HR <80 bpm, lowest stored minute value (depth) and the count in low minute values (duration) of SpO_2 <80%, ΔFiO_2 (maximum additional FiO_2 minus baseline FiO_2), the count in minute values with additional oxygen, occurrence and count in minute values with SpO_2 >95%. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%.

Figure 1. Oxygen titration guideline

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

Figure 3. Time with SpO_2 within various ranges collated over all infants and aggregated as total proportion of recorded time

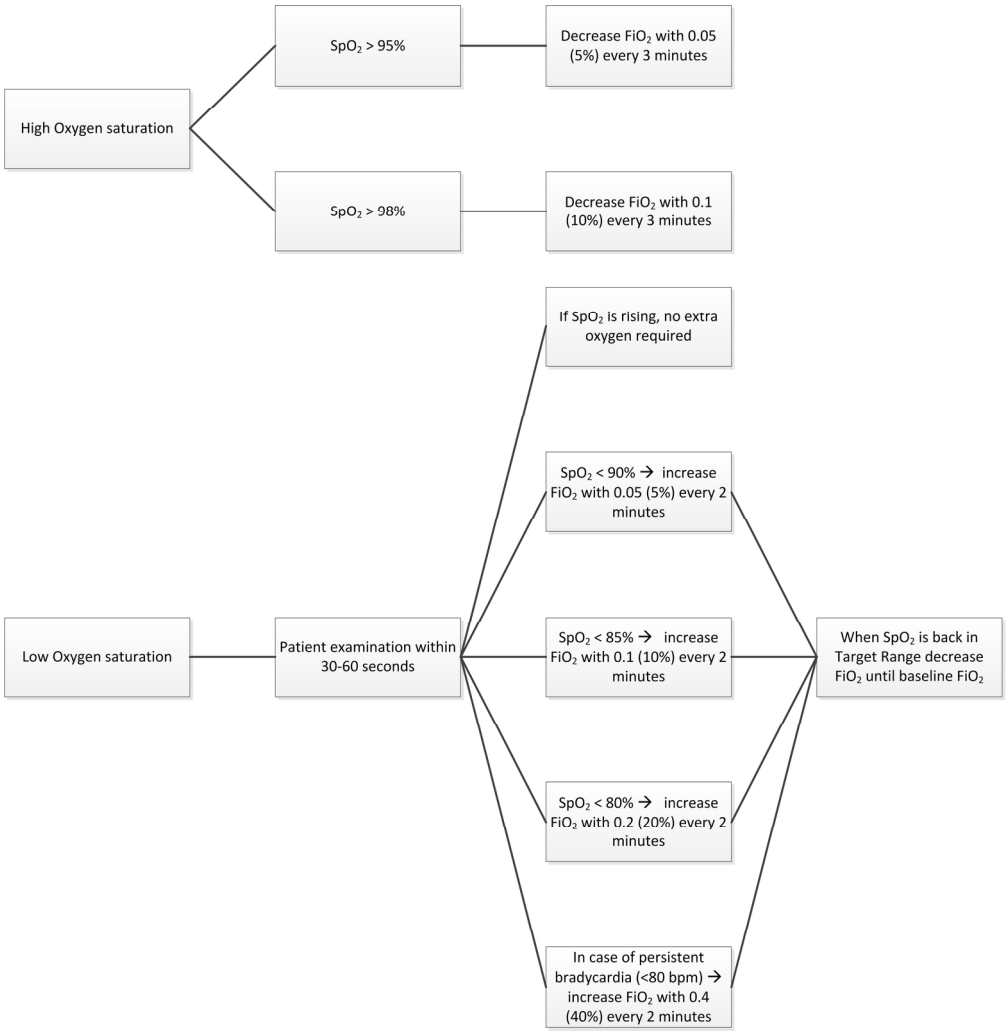

Figure 1. Oxygen titration guideline

179x184mm (300 x 300 DPI)

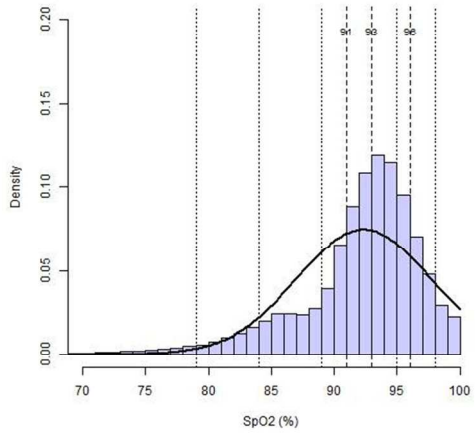

Figure 2; Histogram Target range 85-95%‼ ┼

254x190mm (96 x 96 DPI)

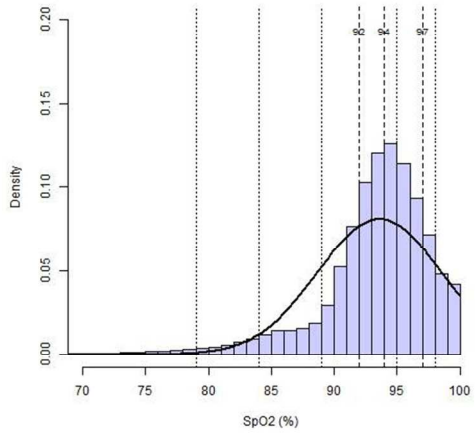

Figure 3;Histogram Target Range 90-95%

254x190mm (96 x 96 DPI)