# Comparison of two different oxygen saturation target ranges for automated oxygen control in preterm infants: a randomised cross-over trial

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# Comparison of two different oxygen saturation target ranges for automated oxygen control in preterm infants: a randomised cross-over trial

Fleur Brouwer, Hylke H Salverda, Sophie J E Cramer, Chantal Schmeits, Jacoline van der Plas, Arjan B te Pas, Janneke Dekker

Willem-Alexander Children's Hospital, Department of Paediatrics, Division of Neonatology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands

**Correspondence to**
Mrs. Fleur Brouwer;
f.brouwer@lumc.nl

FB and HHS are joint first authors.

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## ABSTRACT

**Objective** To compare the effect of peripheral oxygen saturation ($SpO_2$) target range (TR) (either 91%–95% and 92%–96%) on the frequency and duration of hypoxic and hyperoxic episodes while on automated oxygen control using the OxyGenie controller.

**Design** Randomised cross-over study.

**Setting** Tertiary-level neonatal unit in the Netherlands.

**Patients** Infants (n=27) with a median (IQR) gestational age of 27+0 (25+5–27+3) weeks and postnatal age of 16 (10–22) days, receiving invasive or non-invasive respiratory support.

**Interventions** In both groups supplemental oxygen was titrated to a TR of 91%–95% ($TR_{low}$) or 92%–96% ($TR_{high}$) by the OxyGenie controller (SLE6000 ventilator) for 24 hours each, in random sequence. After a switch in TR, a 1-hour washout period was applied to prevent carry-over bias.

**Main outcome measures** Frequency and duration of hypoxic ($SpO_2$<80% for ≥1 s) and hyperoxic episodes ($SpO_2$>98% for ≥1 s).

**Results** Hypoxic episodes were less frequent when the higher range was targeted ($TR_{high}$ vs $TR_{low}$: 2.5 (0.7–6.2)/hour vs 2.4 (0.9–10.2)/hour, p=0.02), but hyperoxic episodes were more frequent (5.3 (1.8–12.3)/hour vs 2.9 (1.0–7.1)/hour, p<0.001). The duration of the out-of-range episodes was not significantly different (hypoxia: 4.7 (2.8–7.1) s vs 4.4 (3.7–6.5) s, p=0.67; hyperoxia: 4.3 (3.3–4.9) s vs 3.9 (2.8–5.5) s, p=0.89).

**Conclusion** Targeting a higher $SpO_2$ TR with the OxyGenie controller reduced hypoxic episodes but increased hyperoxic episodes. This study highlights the feasibility of using an automated oxygen titration device to explore the effects of subtle TR adjustments on clinical outcomes in neonatal care.

**Trial registration number** NL9662.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Automated oxygen controllers have shown promise in maintaining peripheral oxygen saturation ($SpO_2$) target range (TR) and reducing the risk of both hypoxia and hyperoxia in preterm infants, compared with manual oxygen titration.

⇒ Targeting a slightly higher TR during automated oxygen control (AOC), in light of the non-linear oxygen-haemoglobin dissociation curve, could potentially result in greater $SpO_2$ stability due to the alignment along the less steep part of the curve, thereby influencing the incidence of hypoxia and hyperoxia.

### WHAT THIS STUDY ADDS

⇒ A 1% minor change in TR from 91%–95% to 92%–96% results in a rightward shift in $SpO_2$ distribution.

⇒ Targeting a higher TR (92%–96%) during AOC reduces the frequency of hypoxic episodes but increases the risk of hyperoxia.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND POLICY

⇒ This study provides additional input for evaluating the advantages and drawbacks of shifting the TR during AOC, as well as the necessity of considering individualised approaches.

## INTRODUCTION

Supplemental oxygen is pivotal for preterm infants receiving respiratory support. However, the therapeutic range is narrow: providing too little oxygen may lead to hypoxia, which is associated with retinopathy of prematurity (ROP) and impairment of neurodevelopmental outcomes,[1 2] but too much may lead to hyperoxia, linked to bronchopulmonary dysplasia and ROP.[3 4] Consequently, oxygen must be carefully titrated and automated oxygen control (AOC) has shown to increase the proportion of time spent with peripheral oxygen saturation ($SpO_2$) within varying $SpO_2$ ranges compared with manual oxygen titration.[5–9]

The optimal target range (TR) for $SpO_2$ is unclear to date, but the general comprehension was recently refined as a result of the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) trials.[10 11] These trials showed that targeting a higher TR (91%–95%) reduced mortality and necrotizing enterocolitis (NEC) but increased the likelihood of ROP requiring treatment when compared with a lower TR (85%–89%). Remarkably, post hoc analyses of one of the NeOProM trials, Benefits Of Oxygen Saturation Targeting (BOOST)-II UK, showed that the $SpO_2$ medians achieved in preterm infants who survived and did not develop NEC or ROP were higher than originally intended by the study protocol.[12 13] These $SpO_2$ distributions were centred close to 95%, suggesting that a higher TR might be associated with improved outcomes for these infants.



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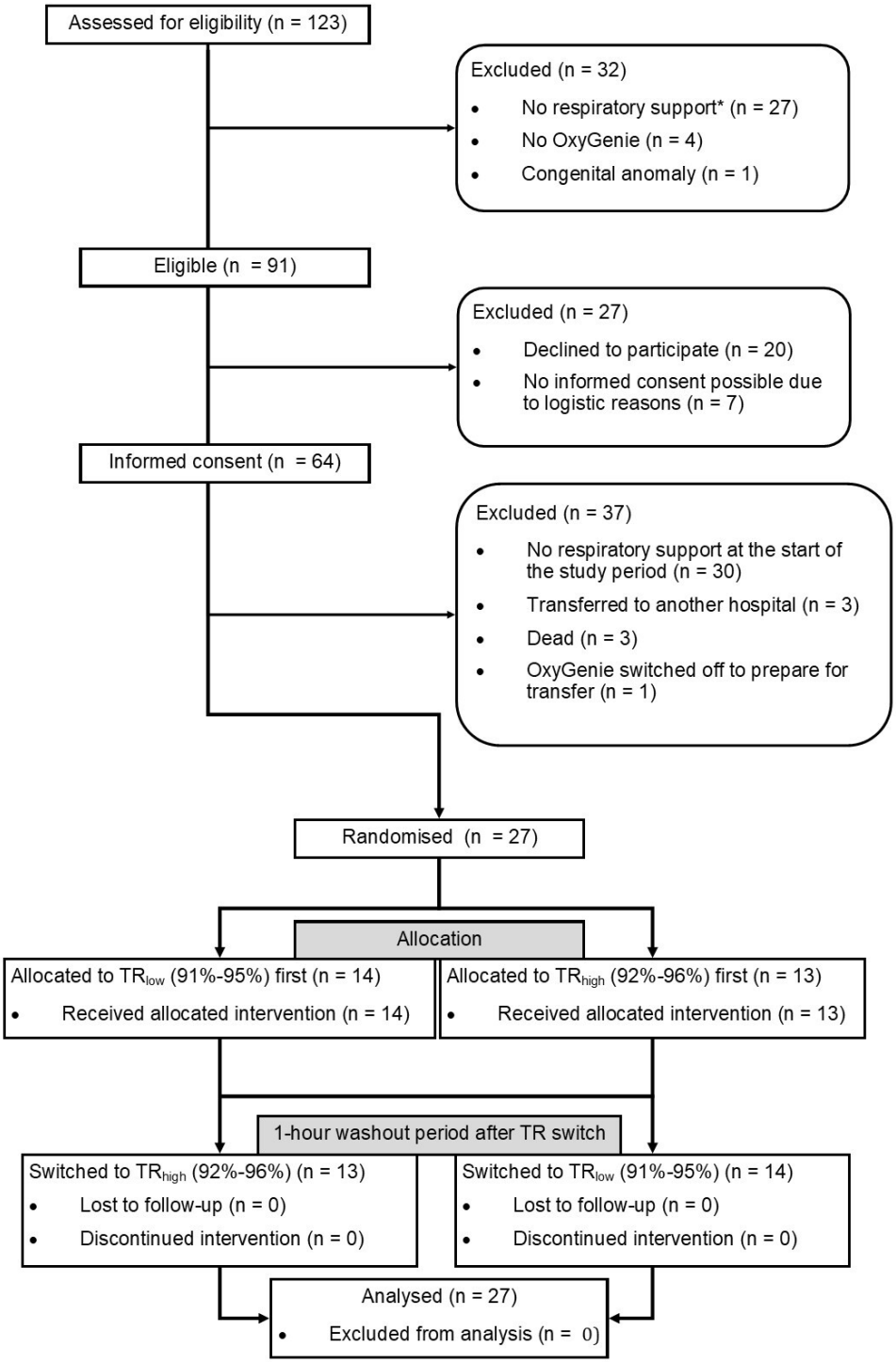


**Figure 1** Flow diagram. *Patient-triggered ventilation, high-frequency oscillatory ventilation, continuous positive airway pressure with and without backup breaths, nasal intermittent positive pressure ventilation or high flow nasal cannula. TR, target range.

Additionally, in our previous study we examined two automated oxygen controllers: OxyGenie controller of the SLE6000 ventilator (Inspiration Healthcare, South Croydon, UK) and Closed-loop Inspired Oxygen Control ($CLiO_2$) controller of the AVEA ventilator (Vyaire Medical, Yorba Linda, California, USA) within the Comparing Oxygen Controllers in Preterm Infants (COCkPIT) trial.[14] The OxyGenie has a median TR of 93% and reduced hyperoxia, while the $CLiO_2$ with a median TR of 94% decreased hypoxia. These outcomes might be attributed to the 1% TR difference, affecting their position on the oxygen-haemoglobin dissociation curve.

The oxygen-haemoglobin dissociation curve illustrates the non-linear relationship between oxygen saturation ($SaO_2$) and oxygen tension. The effect of a change in partial pressure of oxygen ($PaO_2$) on $SaO_2$ becomes smaller when the blood haemoglobin becomes more saturated with oxygen. We hypothesised that increasing the TR with 1% (from our

default 91%–95% to 92%–96%) would result in a more stable $SpO_2$, a reduction of time spent with $SpO_2$<91% and similar or less time >96%.

## METHODS

### Study design

This randomised cross-over trial was conducted at the 21-bed tertiary-level neonatal intensive care unit (NICU) of the Leiden University Medical Centre. AOC using the OxyGenie controller is routine care for preterm infants receiving respiratory support at our NICU, aiming for a TR of 91%–95%. Detailed information on the algorithm of the OxyGenie can be found elsewhere.[15 16]

### Study population

Preterm infants born between 24 and 32 weeks of gestation receiving either invasive or non-invasive respiratory support were assessed for eligibility. Preterm infants were included if they met one of the following criteria: (1) receiving supplemental oxygen (defined as fraction of inspired oxygen ($FiO_2$)≥0.25) for at least 18 hours during the previous 24 hours or (2) having a coefficient of variation in $FiO_2$≥0.1 in the preceding 24 hours. Preterm infants were excluded in case of major congenital anomalies or arterial hypotension requiring vasopressor therapy within 48 hours prior to enrolment.

### Study procedures

Preterm infants underwent two consecutive study periods of 24 hours each in random sequence, one with a TR of 91%–95% ($TR_{low}$), and the other with a TR of 92%–96% ($TR_{high}$). Web-based randomisation (Castor EDC, Amsterdam, The Netherlands) was used for randomisation using permuted blocks of 4–6. After a switch in TR, a 1-hour washout period was applied to prevent carry-over bias. After the study period, the TR was changed back or remained 91%–95%.

If either recorded period was <18 hours due to instability or a change in the mode of respiratory support, the data were excluded from further analysis. All treatments during the study period were conform routine care and ventilation settings were adjusted at the discretion of the caregiver.

### Data collection and analysis

Baseline characteristics were collected from our patient data management system (PDMS Metavision, IMDsoft, Tel Aviv, Israel) at the time of enrolment. Collected data included demographics, such as gestational age, postnatal age, birth weight, gender, corticosteroids prior to birth and prior to the study, mode of delivery and Appearance, Pulse, Grimace, Activity and Respiration (Apgar) score at 1, 5 and 10 min. $SpO_2$ alarms and vital parameters, including $SpO_2$, $FiO_2$ and heart rate were collected at 1 Hz throughout study participation using Philips Data Warehouse Connect software.

The primary outcomes were the frequency and duration of hypoxic episodes ($SpO_2$<80% for ≥1 s) and hyperoxic episodes ($SpO_2$>98% for ≥1 s). Secondary outcomes included: the proportion of time spent in the allocated TR, the proportion of time spent in various degrees of hypoxia and hyperoxia while receiving supplemental oxygen, the coefficient of variation for $SpO_2$ and $FiO_2$, the average $FiO_2$, frequencies and mean durations of bradycardic episodes (HR <100 beats per minute for ≥10 s) and $SpO_2$ alarms.

**Table 1** Baseline characteristics

| Characteristic (n=27) | Definition | Statistics | Results |
|---|---|---|---|
| Gestational age | Weeks+days | Median (IQR) | 27+0 (25+5–27+3) |
| Postnatal age | Days | Median (IQR) | 16 (10–22) |
| Birth weight | Grams | Median (IQR) | 880 (730–998) |
| Gender | Male | N (%) | 15 (55.6) |
| Ventilation mode | PTV | N (%) | 4 (14.8) |
| | HFOV | | 0 (0) |
| | NIPPV | | 1 (3.7) |
| | CPAP with backup breaths | | 6 (22.2) |
| | CPAP without backup breaths | | 16 (59.3) |
| | HFNC | | 0 (0) |
| Weight at study entry | Grams | Median (IQR) | 940 (855–1204) |
| Allocation at study entry | 91%–95% first<br>92%–96% first | N | 14<br>13 |
| Antenatal corticosteroids | Complete treatment | N (%) | 22 (81.5) |
| | Incomplete treatment | | 4 (14.8) |
| | None | | 1 (3.7) |
| Postnatal corticosteroids before study commencement | | N (%) | 4 (14.8) |
| Caesarean delivery | | N (%) | 17 (63.0) |
| Multiple pregnancy | | N (%) | 11 (40.7) |
| Surfactant | | N (%) | 26 (96.3) |
| NSAIDs | | N (%) | 4 (14.8) |
| Diuretics | | N (%) | 4 (14.8) |
| Number of blood transfusions before study commencement | | Median (IQR) | 0 (0–2) |
| Number of blood transfusions during study period | | N (%) | 0 (0) |
| Apgar score | At 1 min | Median (IQR) | 5 (3–7) |
| | At 5 min | | 8 (6–8) |
| | At 10 min | | 8 (6–8) |

Apgar, Appearance, Pulse, Grimace, Activity and Respiration; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; HFOV, high frequency oscillatory ventilation; IQR, Interquartile Range; NIPPV, nasal intermittent positive pressure ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; PTV, patient-triggered ventilation.

Continuous data are presented as median (IQR) or mean±SD as appropriate, with standard tests for normality. For each preterm infant, the time spent within specific $SpO_2$ ranges was collected and expressed as a proportion of the complete study period. Differences in time within, under or above TR and other outcomes were assessed with the Wilcoxon matched-pairs tests. Post hoc analysis was performed to examine the difference in hypoxic and hyperoxic episodes between respiratory stable preterm infants (≤3 hypoxic episodes/hour) and unstable preterm infants (>3 hypoxic episodes/hour). The intention-to-treat principle was applied. Statistical analyses were performed by IBM SPSS Statistics V.25 (IBM, Armonk, New York, USA). P values <0.05 were considered statistically significant.

Sample size calculation was based on data from the COCkPIT trial.[14] During the COCkPIT trial, preterm infants

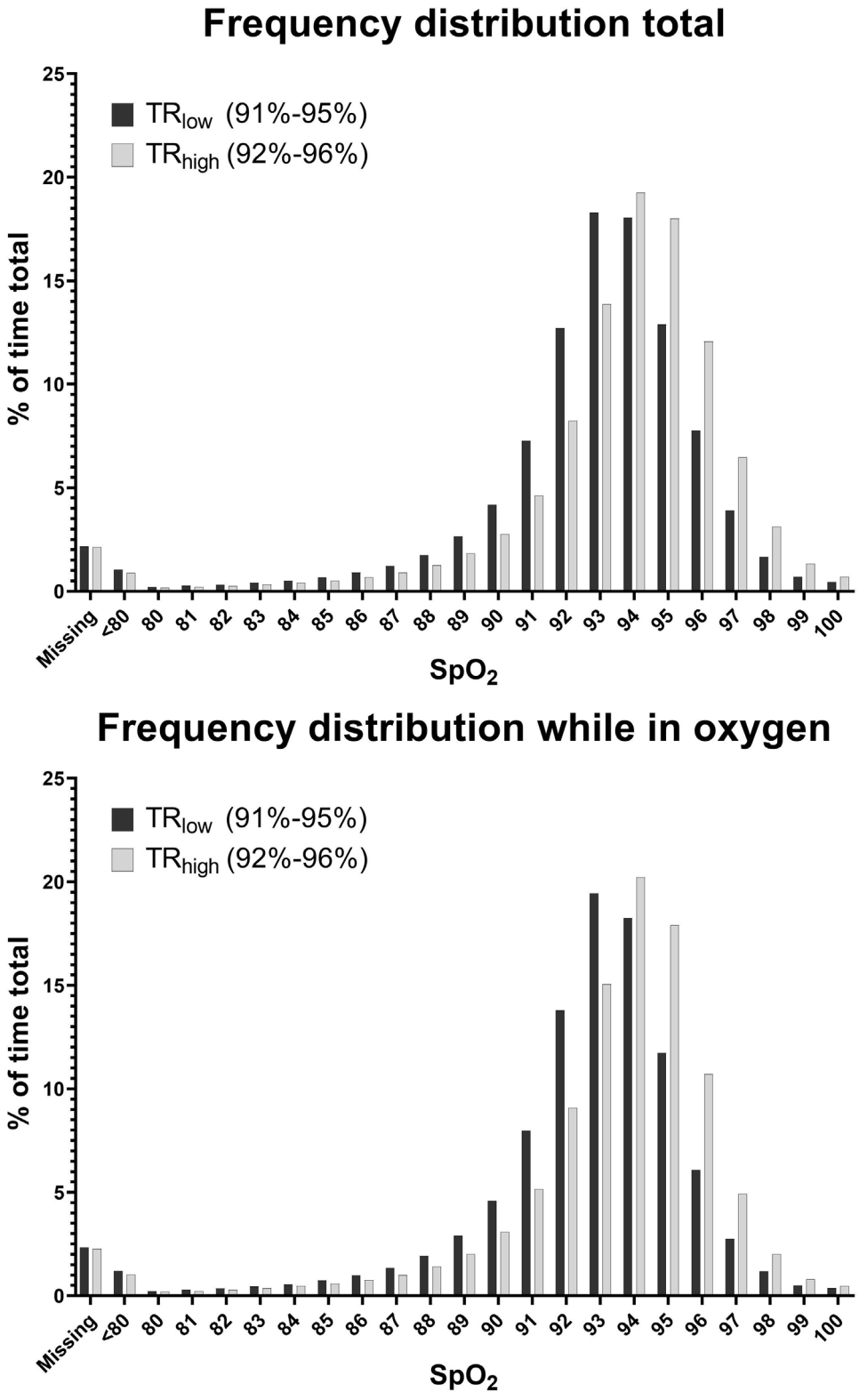


**Figure 2** $SpO_2$ histograms. Time spent per $SpO_2$ value as a proportion of the total study period while receiving supplemental oxygen and ambient air (total) or while only receiving supplemental oxygen. $SpO_2$, peripheral oxygen saturation; TR, target range.

receiving respiratory support had an average of 5.1±5.6 episodes/hour with $SpO_2$<80% during OxyGenie control, with a median $SpO_2$ of 93%. During $CLiO_2$ control, where a median $SpO_2$ of 94% was achieved, the mean frequency of episode/hour with $SpO_2$<80% was 1.0±1.0. Using a sample size calculation for paired statistical testing and assuming the same SD of 5.6 for the control group, 23 preterm infants would be needed to detect 4.1 fewer episodes/hour with 90% power and an α of 0.05. As a non-parametric test was used, a 15% addition was made to the sample size, as described by Lehmann[17], resulting in a total of 27 preterm infants.

**Table 2** Hypoxic and hyperoxic events

| | $TR_{low}$ (91%–95%) | $TR_{high}$ (92%–96%) | P value |
|---|---|---|---|
| Hypoxic events | | | |
| Episodes $SpO_2$<80% (/hour) | 2.4 (0.9–10.2) | 2.5 (0.7–6.2) | 0.02 |
| Average duration episode (s) | 4.4 (3.7–6.5) | 4.7 (2.8–7.1) | 0.67 |
| Episodes $SpO_2$<80% over 10 s (/hour) | 0.3 (0.0–0.8) | 0.2 (0.0–0.9) | 0.50 |
| Hyperoxic events | | | |
| Episodes $SpO_2$>98% (/hour) | 2.9 (1.0–7.1) | 5.3 (1.8–12.3) | <0.001 |
| Average duration episode (s) | 3.9 (2.8–5.5) | 4.3 (3.3–4.9) | 0.89 |
| Episodes $SpO_2$>98% over 10 s (/hour) | 0.2 (0.0–0.7) | 0.5 (0.1–1.2) | 0.002 |

Data in median (IQR).
$SpO_2$, peripheral oxygen saturation; TR, target range.

**Table 3** Hypoxic and hyperoxic events between respiratory unstable and stable preterm infants

| | $TR_{low}$ (91%–95%) | $TR_{high}$ (92%–96%) | P value |
|---|---|---|---|
| Respiratory unstable preterm infants* (n=11) | | | |
| Episodes $SpO_2$<80% (/hour) | 12.4 (6.2–17.1) | 9.2 (4.5–11.2) | 0.04 |
| Episodes $SpO_2$>98% (/hour) | 9.2 (4.3–12.4) | 12.4 (5.3–15.7) | 0.03 |
| Respiratory stable preterm infants† (n=16) | | | |
| Episodes $SpO_2$<80% (/hour) | 1.3 (0.5–2.0) | 1.0 (0.2–1.7) | 0.12 |
| Episodes $SpO_2$>98% (/hour) | 1.9 (0.6–2.9) | 3.6 (0.8–7.1) | 0.007 |

Data in median (IQR).
* Respiratory unstable preterm infants = hypoxic episodes > 3 /hour.
† Respiratory stable preterm infants = hypoxic episodes ≤ 3 /hour. Threshold of 3 is derived from the national recommendations for apnoea in preterm infants.
$SpO_2$, periheral oxygen saturation; TR, target range.

## RESULTS

During the study period (October 2021 to May 2022), informed consent was sought from 91 parent couples, of which 64 agreed to participate (figure 1). After obtaining informed consent, 37 preterm infants were excluded because they no longer had respiratory support (n=30), were transferred to another hospital (n=3), had died (n=3) or the OxyGenie controller was switched off to prepare for transfer (n=1). All included infants completed the cross-over study comparison (n=27) and all study periods were included in the analysis. The primary allocation involved 14 preterm infants in $TR_{low}$ (91%–95%) and 13 preterm infants in $TR_{high}$ (92%–96%).

Fifteen preterm infants were male (56%), the median gestational age at birth was 27+0 (25+5–27+3) weeks, the postnatal age was 16 (10-22) days and the median birth weight of the preterm infants was 880 (730–998) grams (table 1).

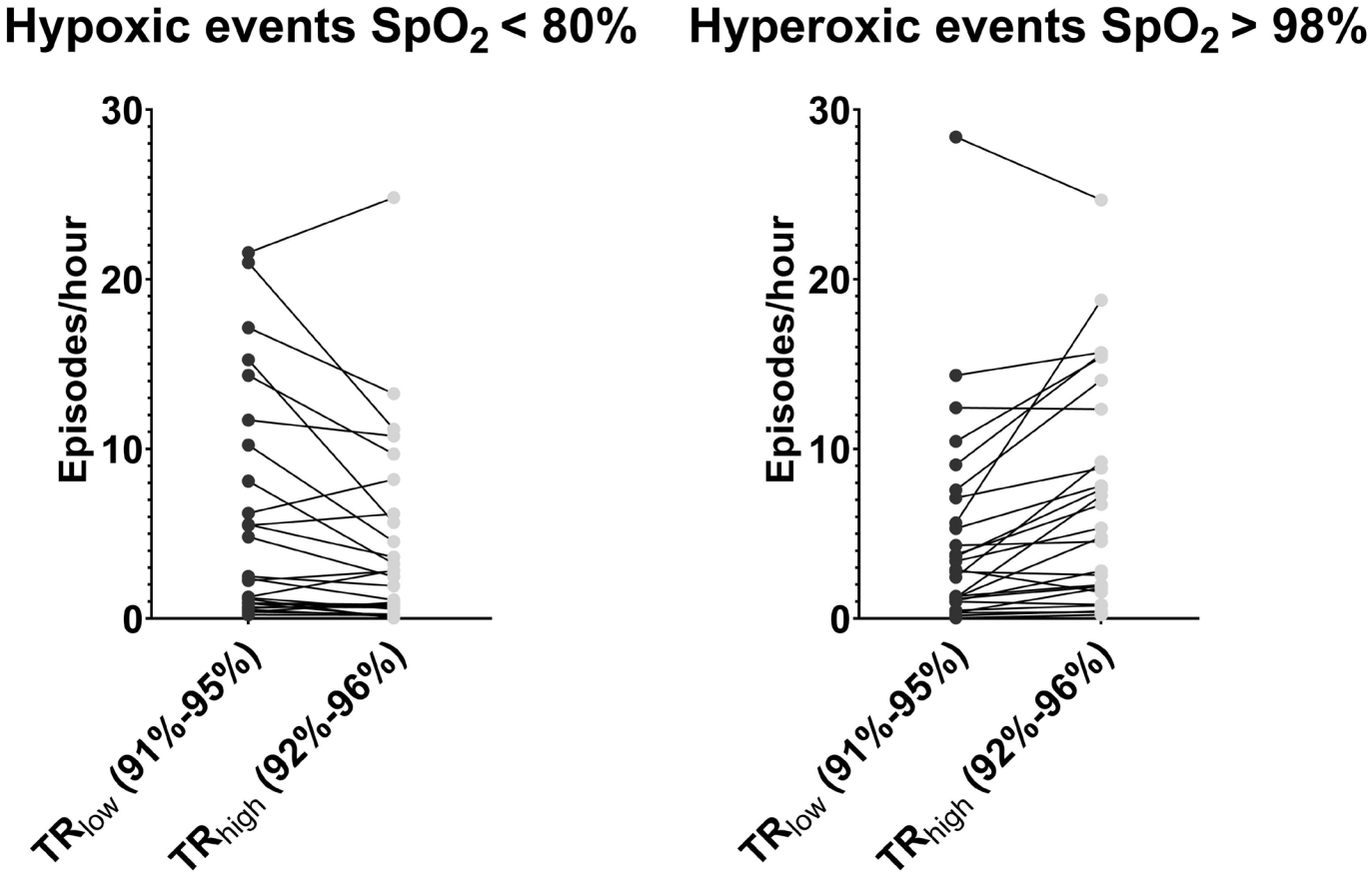


**Figure 3** Comparison between the frequency of hypoxic episodes ($SpO_2$<80% for ≥1 s) and hyperoxic episodes ($SpO_2$>98% for ≥1 s). $SpO_2$, peripheral oxygen saturation; TR, target range.

**Table 4** Secondary outcomes regarding oxygenation, incidence of bradycardia and $SpO_2$ alarms

| | $TR_{low}$ (91%–95%) | $TR_{high}$ (92%–96%) | P value |
|---|---|---|---|
| Proportion of time within $SpO_2$ ranges | | | |
| $SpO_2$ 91%–95% | 76.3 (68.9–86.4) | 70.6 (61.5–87.3) | 0.002 |
| $SpO_2$ 91%–96% | 81.3 (74.7–89.9) | 80.6 (73.0–91.0) | 0.17 |
| $SpO_2$ 92%–96% | 74.0 (64.5–81.3) | 75.9 (68.9–87.2) | 0.001 |
| $SpO_2$<80% | 0.5 (0.1–1.3) | 0.4 (0.1–1.5) | 0.14 |
| $SpO_2$ 80%–84% | 1.4 (0.4–2.7) | 1.2 (0.4–2.3) | 0.01 |
| $SpO_2$ 85%–89% | 8.2 (4.3–10.1) | 5.5 (2.8–7.6) | <0.001 |
| $SpO_2$ 85%–90% | 12.6 (8.0–14.7) | 8.4 (5.2–10.9) | <0.001 |
| $SpO_2$<91% | 15.5 (8.5–20.0) | 10.3 (5.3–14.7) | <0.001 |
| $SpO_2$<92% | 23.2 (17.0–27.1) | 16.7 (9.8–19.5) | <0.001 |
| $SpO_2$>95% | 8.1 (4.8–14.2) | 16.2 (8.8–24.7) | <0.001 |
| $SpO_2$>96% | 2.6 (1.6–5.7) | 6.8 (2.4–11.3) | <0.001 |
| $SpO_2$ 96%–98% | 7.4 (4.2–13.5) | 15.3 (8.7–22.6) | <0.001 |
| $SpO_2$ 97%–98% | 2.4 (1.4–5.1) | 5.9 (2.3–9.9) | <0.001 |
| $SpO_2$>98% | 0.4 (0.1–0.9) | 0.9 (0.3–1.5) | 0.005 |
| Coefficient of variation | | | |
| $SpO_2$ (%) | 1.5 (1.1–1.8) | 1.4 (1.1–1.7) | 0.68 |
| $FiO_2$ (%) | 2.0 (1.7–2.5) | 2.0 (1.5–2.7) | 0.27 |
| Average $FiO_2$* | | | |
| Average $FiO_2$* (%) | 29.8 (25.6–37.3] | 30.6 (26.1–36.5) | 0.006 |
| Bradycardic episodes (<100 bpm for ≥10 s) | | | |
| Frequency (/24 hours) | 4.0 (1.0–9.0) | 3.0 (1.0–6.0) | 0.97 |
| Mean duration (s) | 17.0 (11.0–23.6) | 16.0 (11.7–22.9) | 0.92 |
| $SpO_2$ alarms† | | | |
| Frequency (/24 hours) | 52.0 (26.8–75.3) | 55.5 (27.8–121.3) | 0.66 |
| Mean duration (s) | 7.2 (6.3–8.2) | 7.4 (6.0–8.3) | 0.89 |

Data in median (IQR).
*Average $FiO_2$ is based on measured $FiO_2$.
†Data were available for 24 preterm infants.
$FiO_2$, fraction of inspired oxygen; $SpO_2$, periheral oxygen saturation; TR, target range.

Histograms of pooled $SpO_2$ data during the two TR periods, while receiving supplemental oxygen and ambient air (total) and only while receiving oxygen, are shown in figure 2. These histograms have the same shape and demonstrate a rightward shift in the distribution of $SpO_2$ values during the $TR_{high}$ period. The proportion of missing signal was 2.2% during $TR_{low}$ and 2.1% during $TR_{high}$ while receiving supplemental oxygen and ambient air (total) and 2.3% during $TR_{low}$ and 2.3% during $TR_{high}$ while receiving oxygen.

The frequency of hypoxic episodes in $TR_{high}$ was lower compared with $TR_{low}$, but the duration was not significantly different (table 2). Conversely, there was an increase in the frequency of hyperoxic episodes in the higher TR, and again the duration was not significantly different.

Of the 27 patients, 20 (74%) had more hypoxic episodes in the $TR_{low}$ group and 22 patients (81%) had more hyperoxic events in the $TR_{high}$ group (figure 3).

For the post hoc analysis, infants that were defined as being respiratory unstable had significantly fewer hypoxic episodes in $TR_{high}$ compared with $TR_{low}$, but a significant increase in the number of hyperoxic episodes. While the TR did not affect the number of hypoxic episodes in infants who were considered respiratory stable, $TR_{high}$ again resulted in a significant increase in the number of hyperoxic episodes (table 3).

The proportions of time within the TR, hypoxic ranges and hyperoxic ranges are shown in table 4. While there were no differences in time with $SpO_2$<80% between the groups, the duration of time spent in other hypoxic ranges was all significantly shorter in the $TR_{high}$ group. Additionally, the $TR_{high}$ group showed significantly higher durations in the hyperoxic ranges compared with the $TR_{low}$ group. The coefficient of variation for $FiO_2$ and $SpO_2$ was similar for both TR periods. The average delivered $FiO_2$ was higher during the $TR_{high}$ period. There was no significant difference between the frequencies and mean durations of bradycardic episodes and $SpO_2$ alarms between the two TR periods.

## DISCUSSION

This randomised cross-over study demonstrated that targeting a TR of 92%–96% led to fewer episodes of hypoxia but more episodes of hyperoxia when compared with a TR of 91%–95%. The difference is also apparent from the $SpO_2$ histogram which displays a rightward shift in the $SpO_2$ distribution when targeting the higher TR, resulting in less time spent in the hypoxic ranges and more time spent in the hyperoxic ranges. These results suggest that a small change in TR during AOC can reduce the frequency of hypoxic episodes but increases the risk of hyperoxia.

The rationale of the study was to increase the TR by 1% as demonstrated in the COCkPIT trial.[14] We hypothesised that targeting a higher TR using AOC would result in less time spent under the TR due to the non-linear relationship between $SaO_2$ and $PaO_2$ as depicted in the oxygen-haemoglobin dissociation curve. The transition from fetal haemoglobin (HbF) to adult haemoglobin (HbA) shifts this curve leftward due to HbF's higher oxygen affinity.[18] Transfusions can further alter this by increasing HbA concentration, requiring higher $PaO_2$ for the same $SpO_2$, and increasing oxygen toxicity risk.[19–21] HbF percentages were not measured in this study, but their impact seemed minimal, as each preterm infant served as their own control within the relatively short 49–50 hours study period, with no transfusions. However, the variation in results, where not all preterm infants showed reduced hypoxia and increased hyperoxia during the $TR_{high}$ period, could potentially be influenced by the HbF differences. This could be due to the varying postmenstrual ages and the fact that 13 patients (48.1%) had received transfusions prior to the study period.

An intriguing finding of our subanalysis was that differences in episodes, both with too much and too little oxygen, were significantly more pronounced in infants who initially experienced relatively frequent episodes of intermittent hypoxia. It could be speculated that, especially for this subgroup, the slightly higher TR could be beneficial. Importantly, the observed differences among infants may be influenced by variations in HbF but also by the likelihood that infants with a history of more hypoxaemic episodes beforehand have distinct oxygenation needs. This emphasises the importance of considering individual variations and needs when establishing oxygen targets for preterm infants.

Finding the optimal TR has been the subject of many studies. The NeOProM trials showed good evidence that a TR of 91%–95% for preterm infants is associated with improved outcomes when compared with a lower TR.[10 11] The BOOST-II UK trial indicated that preterm infants who survived and did not develop NEC had $SpO_2$ distributions centred close to 95%.[12 13] This suggests a potential, yet unrecognised, survival advantage with a slight increase in TR, but the risks and benefits of higher TRs remain unknown. Christie *et al* conducted the

first investigation of $SpO_2$ stability in preterm infants by manually targeting the $SpO_2$ in the range of 92%–97%, as compared with the standard TR of 91%–95%.[22] This study showed that targeting in a range of 92%–97% resulted in a rightward shift in $SpO_2$ distribution, reducing the time spent at SpO2 levels <90% and increasing time spent with $SpO_2$>97%.

However, the NeOProM trials and Christie *et al* used manual oxygen titration, whereas AOC has demonstrated its ability to improve $SpO_2$ targeting across different $SpO_2$ ranges, resulting in reduced time spent in hypoxic ranges and a decreased number of hypoxic events when compared with manual oxygen control.[5–9] Our study, using AOC, showed high percentages of time within the set TRs, making it a trial that is able to demonstrate differences in clinical presentation regarding the set TR. Furthermore, the notably higher percentage of time spent in each TR for their respective allocations emphasises the effectiveness of the OxyGenie controller. This outcome strongly supports the success of AOC implementation in our NICU.

So far, two studies examined different TRs while using an AOC algorithm, namely the $CLiO_2$ of the AVEA ventilator.[23 24] Narrowing the TR during AOC (from 87%–93% to 90%–93%[23] and 86%–94% to 89%–91%[24]) reduces the time spent in hypoxic ranges, but the risk of hyperoxia may depend on the set TR and corresponding median $SpO_2$. Our study is the first study that investigated the effect of two TRs (91%–95% and 92%–96%) on AOC on the $SpO_2$ stability in preterm infants. Our findings align with Christie *et al*,[22] showing a rightward shift in the $SpO_2$ distribution, reducing time in hypoxic ranges and increasing time in hyperoxic ranges. Even our subanalysis showed that respiratory unstable patients had fewer hypoxic episodes but more hyperoxic episodes during the higher TR of 92%–96%. Similarly, Kelly *et al* explored the relationship between $PaO_2$ (using intermittent arterial blood gasses) and $SpO_2$ in preterm infants and showed that $PaO_2$ values >10.7 kPa are uncommon with $SpO_2$ readings <98%.[25] These results suggest that higher TRs could be studied in clinical trials without a substantial likelihood of hyperoxia. However, the different AOC algorithms vary in their functioning and approach to maintain $SpO_2$ levels within the set TR,[16] leading to different outcomes in managing the risks of hypoxia and hyperoxia as represented in the COCkPIT trial.[14]

This study has some limitations. First, the effects of the two TRs during AOC were evaluated during a relatively short period of 49–50 hours which may not be representative of the many weeks that most preterm infants require supplemental oxygen. Additionally, preterm infants were also included at different times after admission and postmenstrual ages. Furthermore, our study population consisted of very preterm infants. Older infants have a lower oxygen demand and more stable respiratory periods, which typically occur at a postmenstrual age of 30 weeks or older,[14] making them challenging to include in the study. Moreover, during the study period, the only altered variable was the TR, while standard care for all treatments remained consistent. Therefore, the comparison of the two TRs did not include other factors that might also impact $SpO_2$, such as positive end-expiratory pressure levels or caffeine usage.

In conclusion, targeting a 1% higher TR (from 91%–95% to 92%–96%) resulted in fewer hypoxic episodes but more hyperoxic episodes in preterm infants. Not all infants showed reduced hypoxia and increased hyperoxia during the $TR_{high}$ period. Our study creates further rationale to determine the benefits and risks of shifting the TR and whether an individual approach is needed.

**Contributors** FB: collected the data (with HS and JD), compiled the data (with HHS, SJEC, JvdP, CS and JD), analysed the data (with HHS and JD), interpreted the data (with JD), wrote the first draft of the manuscript and approved the final version of the manuscript. HHS: co-conceived the study (with ABtP and JD), conducted the study (with JD), collected the data (with FB and JD), compiled the data (with FB, SJEC, JvdP, CS and JD), analysed the data (with FB and JD), reviewed and edited the manuscript and approved the final version of the manuscript. SJEC: compiled the data (with FB, HHS, JvdP, CS and JD), reviewed and edited the manuscript and approved the final version of the manuscript. JvdP and CS: compiled the data (with FB, HHS, SJEC and JD), reviewed the manuscript and approved the final version of the manuscript. ABtP: co-conceived the study (with HHS and JD), had full responsibility for the conduct of the study, had access to the data, reviewed and edited the manuscript and approved the final version of the manuscript.JD: co-conceived the study (with HHS and ABtP), oversaw the study conduct, conducted the study (with HHS), collected the data (with FB and HHS), compiled the data (with FB, HHS, SJEC, JvdP and CS), interpreted the data (with FB), reviewed and edited the manuscript and approved the final version of the manuscript.

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**ORCID iDs**
Fleur Brouwer http://orcid.org/0000-0003-0365-3974
Hylke H Salverda http://orcid.org/0000-0001-9355-5993
Sophie J E Cramer http://orcid.org/0000-0001-5725-0594
Arjan B te Pas http://orcid.org/0000-0001-7831-8797
Janneke Dekker http://orcid.org/0000-0002-6710-3587

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