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## Oxygen titration and compliance with targeting oxygen saturation in preterm infants

Zanten, H.A. van

### Citation

Zanten, H. A. van. (2017, March 15). *Oxygen titration and compliance with targeting oxygen saturation in preterm infants*. Retrieved from <https://hdl.handle.net/1887/46692>

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**Note:** To cite this publication please use the final published version (if applicable).

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**Author:** Zanten, Henriëtte van

**Title:** Oxygen titration and compliance with targeting oxygen saturation in preterm infants

**Issue Date:** 2017-03-15

# Chapter 6

The effect of implementing an automated oxygen control  
on oxygen saturation in preterm infants

Henriëtte A. van Zanten

Kristel L.A.M. Kuypers

Ben J. Stenson

Tom E. Bachman

Steffen C. Pauws

Arjan B. te Pas

*Arch Dis Child Fetal Neonatal Ed 2016 Accepted*  
*doi:10.1136/archdischild-2016-312172*



## ABSTRACT

**Objective:** To evaluate the effect of implementing automated oxygen control as routine care in maintaining oxygen saturation ( $\text{SpO}_2$ ) within target range (TR) in preterm infants.

**Methods:** Infants <30 weeks gestation in LUMC before and after the implementation of automated oxygen control were compared. The percentage (%) of time spent with  $\text{SpO}_2$  within and outside TR (90-95%) was calculated.  $\text{SpO}_2$  values were collected every minute and included for analysis when infants received supplemental oxygen.

**Results:** In a period of 9 months, 42 preterm infants (21 manual, 21 automated) were studied. In the automated period the median (IQR) time spent with  $\text{SpO}_2$  within TR increased (manual vs automated: 48.4 (41.5 - 56.4)% vs 61.9 (48.5 - 72.3)%;  $p < 0.01$ ) and time  $\text{SpO}_2 > 95\%$  decreased (41.9 (30.6 - 49.4)% vs 19.3 (11.5 - 24.5)%;  $p < 0.001$ ). The time  $\text{SpO}_2 < 90\%$  increased (8.6 (7.2 - 11.7)% vs 15.1 (14.0 - 21.1)%;  $p < 0.0001$ ), while  $\text{SpO}_2 < 80\%$  was similar (1.1 (0.4 - 1.7)% vs 0.9 (0.5 - 2.1)%; ns).

**Conclusion:** During oxygen therapy, preterm infants spent more time within the  $\text{SpO}_2$  TR after implementation of automated oxygen control, with a significant reduction in hyperoxaemia, but not hypoxaemia

### What is already known on this topic

1. The frequency and duration of hypoxaemia and hyperoxaemia in preterm infants influence survival and long term outcome.
2. Titrating oxygen manually to maintain oxygen saturation within a narrow target range can be challenging.
3. Randomized trials have shown that automated oxygen control is effective, but this has only been measured for short periods.

### What this study adds

1. After implementation of automated oxygen control for daily care, preterm infants spent more time with their oxygen saturation within the target range.
2. After implementation, hyperoxaemia significantly decreased during oxygen therapy, but there was no effect on hypoxaemia.

## INTRODUCTION

To prevent hypoxaemia and hyperoxaemia in preterm infants, nurses manually titrate the fraction of inspired oxygen ( $\text{FiO}_2$ ) in order to maintain peripheral oxygen saturation ( $\text{SpO}_2$ ) within a set target range (TR). Studies have shown that compliance with  $\text{SpO}_2$  targets is low and there is a tendency for nurses to accept higher  $\text{SpO}_2$ .<sup>18 30 31 40 41</sup> Manual titration of oxygen is challenging, especially during hypoxaemic and bradycardic events related to apnoea of prematurity.<sup>10 24</sup> We recently demonstrated that manual titration of oxygen therapy in preterm infants during these hypoxaemic and bradycardic events, led to unintended hyperoxaemia ( $\text{SpO}_2 >95\%$ ).<sup>24</sup> Both hypoxaemia and hyperoxaemia are associated with morbidity (impaired growth, bronchopulmonary dysplasia, retinopathy of prematurity, cerebral injury) and mortality. Reducing periods of hypoxaemia and hyperoxaemia may improve survival and neurodevelopmental outcome.<sup>9-15</sup>

Compliance in  $\text{SpO}_2$  targeting can be improved by training and implementation of guidelines.<sup>37 48-50</sup> Additionally,  $\text{FiO}_2$  can be titrated automatically.<sup>86 87</sup> Randomised trials comparing automated  $\text{FiO}_2$  systems with manual titration for short periods, demonstrated an increase in the percentage of time spent with  $\text{SpO}_2$  within TR varying between 8-24%.<sup>35 36 38 39</sup> Automated  $\text{FiO}_2$  control also decreased the required nursing time in preterm infants with frequent severe desaturations.<sup>35 88 89</sup> However, the use of automated  $\text{FiO}_2$  control for longer periods has not been investigated.

In the neonatal intensive care unit (NICU) in Leiden University Medical Centre (LUMC) an automated  $\text{FiO}_2$  control system (Closed Loop of inspired Oxygen, Avea-CLiO<sub>2</sub>, CareFusion, Yorba Linda, California) was implemented and routinely used since August 2015 in order to improve targeting  $\text{SpO}_2$ . We performed an observational study in preterm infants to evaluate automated  $\text{FiO}_2$  control when it was used as standard care and thus for a longer period. The aim was to compare the effectiveness of the automated  $\text{FiO}_2$  system versus manual titration of  $\text{FiO}_2$  in maintaining the  $\text{SpO}_2$  within the intended TR.

## METHODS

A prospective observational study was performed in the NICU of the LUMC, which is a tertiary level perinatal centre in the Netherlands with an average of 650 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 born <30 weeks of gestation (GA) admitted to the NICU before and after the implementation of the automated  $\text{FiO}_2$  control in August 2015

(May 2015 - January 2016) receiving respiratory support (endotracheal and non-invasive ventilation) using the AVEA ventilator (CareFusion, Yorba Linda California) were included. Preterm infants with major congenital heart disease were excluded.

The characteristics, of each infant as well as clinical parameters and ventilator settings (including  $\text{FiO}_2$  and  $\text{SpO}_2$ ) 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  $\text{SpO}_2$  was collected using a neonatal pulse oximeter (Masimo Radical, Masimo Corporation, Irvine CA, USA) with an averaging time set at 8 seconds. Data were included until the infants reached a GA of 32 weeks. After 32 weeks most infants are transferred out of the intensive care area in our unit or to a regional hospital, where no automated  $\text{FiO}_2$  control is available.

During the manual and the automated  $\text{FiO}_2$  control periods,  $\text{SpO}_2$  was measured using a neonatal pulse oximeter integrated into the AVEA ventilator. During the manual period the nurses manually titrated the supplemental oxygen following local guidelines. During the automated period, an automated  $\text{FiO}_2$  control device integrated in the ventilator was used (CLiO<sub>2</sub>), in addition to manual adjustments. The CLiO<sub>2</sub> function is a Closed-Loop controller, designed to regulate  $\text{FiO}_2$  levels for preterm infants receiving support and oxygen from a mechanical ventilator. The  $\text{FiO}_2$  is automatically adjusted to maintain the  $\text{SpO}_2$  within the TR set by the clinician.<sup>34</sup> The CLiO<sub>2</sub> was turned off during episodes where  $\text{SpO}_2$  remained 100% for more than 30 minutes when  $\text{FiO}_2$  was 0.21 as recurrent alarms would occur. In case extra oxygen was needed again, the CLiO<sub>2</sub> was switched on, and data analysis continued. The episodes without supplemental oxygen were not included in the analysis. In this study, for both manual and automated  $\text{FiO}_2$  control periods, the  $\text{SpO}_2$  TR was 90% to 95% during oxygen therapy. The alarm was activated if  $\text{SpO}_2$  was below 90% or above 95%.

Before the start of each shift the set TR of the CLiO<sub>2</sub> and alarm settings were checked by the nurse. Also backup- $\text{FiO}_2$  was checked before the start of each shift or when a procedure was performed (e.g. surfactant administration) and was adjusted if necessary. High  $\text{FiO}_2$  alarm was set at 70% with a delay of 60 seconds. All preterm infants received, as part of standard care, a loading dose of 10mg/kg caffeine base followed by 5 mg/kg/day. Dopram (2 mg/kg/hr) was added in case of refractory apnoeas.

The primary outcome was the percentage of time spent with  $\text{SpO}_2$  within the intended TR (90-95%) when  $\text{FiO}_2$  was  $>0.21$ . Also the percentage of time spent with  $\text{SpO}_2 >95\%$ ,  $>98\%$ ,  $<90\%$ ,  $<85\%$  and  $<80\%$  were calculated. Hypoxaemia was defined as  $\text{SpO}_2 <80\%$  and hyperoxaemia as  $\text{SpO}_2 >95\%$ .

## Statistical analyses

Quantitative data are presented as median (IQR), mean  $\pm$  SD or number (percentage) where appropriate. Time with SpO<sub>2</sub> within various ranges for FiO<sub>2</sub> >0.21 were collated for each infant, and aggregated as percentages of the recorded time (median and IQR). A Kruskal-Wallis rank sum test was used to compare the percentage of time that SpO<sub>2</sub> was within TR (SpO<sub>2</sub>-wtr) of 90-95% between the manual period and the automated period. 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. Statistical analyses were performed by IBM SPSS Statistics version 23 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/>).

An increase of 10% in time that SpO<sub>2</sub> was within the intended TR when using the automated FiO<sub>2</sub> control was considered clinically relevant. Based on a previous study, we estimated a standard deviation of 10%.<sup>67</sup> Therefore, 21 patients in each arm were required to detect a change of 10% SpO<sub>2</sub>-wtr between the periods with an 80% power and a significance level of 0.05.

## RESULTS

In a nine months period 42 infants with a GA <30 weeks were admitted and supported using the AVEA-ventilator, of which 21 infants <30 weeks in four months before the implementation of the automated FiO<sub>2</sub> control and 21 infants in five months after implementation (characteristics Table 1). In one patient the CLiO<sub>2</sub> was turned off for three days and during that period SpO<sub>2</sub> data points were excluded from the analysis. In total, 234.541 data points (minute values) during the manual period and 392.211 data points (minute values) during the automated period were collected when FiO<sub>2</sub> >0.21. The median (IQR) number of data points per infant were not significantly different (manual vs. automated period: 4805 (1238 -16980) vs 16527 (1324 – 33625) data points; ns). The total number of days preterm infants were on respiratory support (with or without extra oxygen) were not different 16 (10-22) vs 14 (3-28) days; ns).

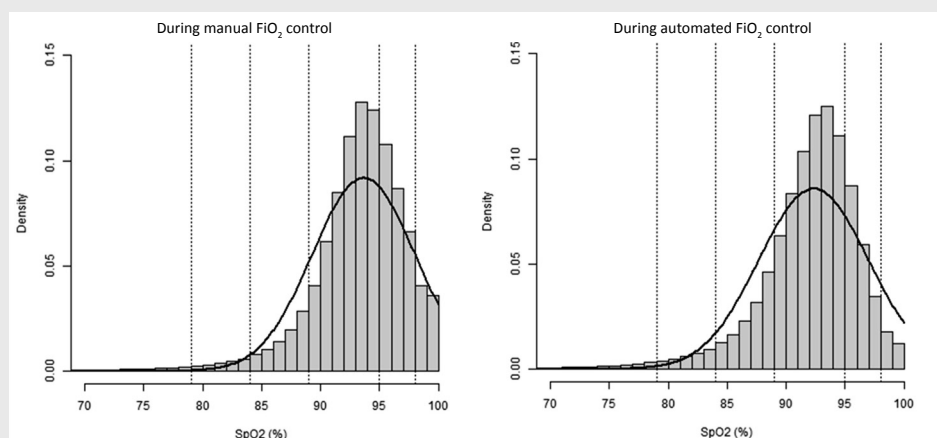
After implementation of the automated FiO<sub>2</sub> control, there was a slight, but significant decrease in median (IQR) SpO<sub>2</sub> (manual vs automated: 94 (92 - 96)% vs 93 (91 - 95)%; $p<0.001$ ) (Figure 1), while the FiO<sub>2</sub> used increased (0.25 (0.24-0.29) vs 0.27 (0.25-0.32); $p< 0.009$ ) (Figure 2).

**Table 1.** Patient characteristics, manual vs automated oxygen titration period.

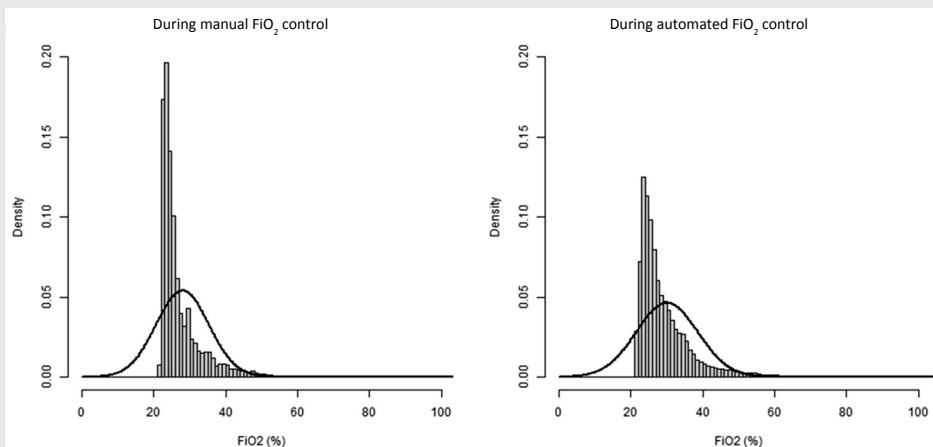
Patients characteristics N=42	Manual N=21	Automated N=21	p Value
Gestational age in weeks, median (IQR)	27+6 (26+3 – 28+4)	27+3 (26 – 28+2)	0.2 <sup>a</sup>
Birth weight in grams, median (IQR)	966 (843-1235)	940 (825-1242)	0.6 <sup>a</sup>
Males, n (%)	10 (48)	12 (57)	0.5 <sup>b</sup>
Apgar score 5 min, median (IQR)	7 (6-9)	8 (6-9)	0.9 <sup>a</sup>
Caesarean delivery, n (%)	10 (47.6)	7 (33.3)	0.3 <sup>b</sup>
Singletons, n (%)	15 (71.4)	10 (47.6)	0.1 <sup>b</sup>
Invasive ventilated days, median (IQR)	1 (0-8)	2 (0-7)	0.8 <sup>a</sup>
Use of dopram, n(%)	7 (33)	6 (28)	0.7 <sup>b</sup>
Mortality, n (%)	0 (0)	3 (14)	0.2 <sup>c</sup>

<sup>a</sup> Statistical analysis comprised nonparametric Mann Whitney U test; <sup>b</sup> Statistical analysis comprised Chi square test; <sup>c</sup> Statistical analysis comprised Fisher's Exact Test.

The time spent with SpO<sub>2</sub> within TR increased during the automated period (48.4 (41.5 - 56.4)% vs 61.9 (48.5 – 72.3)%;*p*<0.01) (distribution is given in Figure 1). The time spent with SpO<sub>2</sub>>95% significantly decreased during the automated period (41.9 (30.6 - 49.4)% vs 19.3 (11.5- 24.5)%;*p*<0.001) as did SpO<sub>2</sub>>98% 10.1 (3.7 - 14.4)% vs 2.1(0.7 - 3.1)%;*p*<0.0005) (Table 2). The time spent with SpO<sub>2</sub><90% significantly increased during the automated period (8.6 (7.2 - 11.7)% vs 15.1 (14.0 - 21.1)%;*p*<0.0001), which was mostly influenced by an increase in time SpO<sub>2</sub> was between 85% and 89% (Table 2). There was no significant difference in time spent with SpO<sub>2</sub><85% (2.7 (1.4 - 4.0)% vs 3.2 (1.8 - 5.1)%; ns), or % time with SpO<sub>2</sub><80% (1.1 (0.4 – 1.7)% vs 0.9 (0.5 - 2.1)%; ns).

**Figure 1.** Time with SpO<sub>2</sub> within various ranges collated over all infants and aggregated as total proportion of recorded time





**Figure 2.** Time with  $\text{FiO}_2$  within various ranges were collated over all infants and aggregated as total proportion of recorded time.

**Table 2.** Median (IQR) time with  $\text{SpO}_2$  values within and outside TR with  $\text{FiO}_2 > 0.21$

	Percentage of time, %		p-value*
	Manual	Automated	
$\text{SpO}_2 < 80\%$	1.1 (0.4 - 1.7)	0.9 (0.5 - 2.1)	ns
$\text{SpO}_2 < 85\%$	2.7 (1.4 - 4.0)	3.2 (1.8 - 5.1)	ns
$\text{SpO}_2 < 90\%$	8.6 (7.2 - 11.7)	15.1 (14.0 - 21.1)	$< 0.0001$
$90\% \leq \text{SpO}_2 \leq 95\%$	48.4 (41.5 - 56.4)	62.0 (56.4 - 68.6)	$< 0.01$
$\text{SpO}_2 > 95\%$	41.9 (30.6 - 49.4)	19.3 (11.5 - 24.5)	$< 0.001$
$\text{SpO}_2 > 98\%$	10.1 (3.7 - 14.4)	2.1 (0.7 - 3.1)	$< 0.0005$

\*Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test.  $\text{SpO}_2$ , pulse oxygen saturation;  $\text{FiO}_2$ , fraction of inspired oxygen.

## DISCUSSION

We observed that preterm infants spent significantly more time with  $\text{SpO}_2$  within their intended TR and less time with  $\text{SpO}_2$  above their intended TR, while  $\text{FiO}_2$  used was higher after implementing automated  $\text{FiO}_2$  control for routine care. Although the infants spent more time with  $\text{SpO}_2$  between 80% and 90% during automated control, no significant effect on the time spent with hypoxaemia ( $\text{SpO}_2 < 80\%$ ) was observed. It is likely that automatic  $\text{FiO}_2$  control had little effect on the infants' intrinsic stability, but rather that correction of fluctuations in  $\text{SpO}_2$  were faster than during manual oxygen titration and with less overshoot.

Furthermore, the use of an automated device precludes the tendency of nurses to maintain the SpO<sub>2</sub> in the higher end of TR, which could lead to more hyperoxaemia.<sup>18 30 31 40 41</sup> The effect of an increased time that SpO<sub>2</sub> was between 80% and 90% is unclear, while the reduction in hyperoxaemia may reduce the risk of major morbidities.<sup>9-15 24 34</sup> Routine use of automated oxygen control has the potential to improve outcome in preterm infants.

Randomised and non-randomised studies have compared short periods using automated FiO<sub>2</sub> with manual titration.<sup>11 34-36 38 39 67 90</sup> This is the first study reporting the impact when an automated FiO<sub>2</sub> was implemented in routine care for longer periods. Although the previous studies showed that automated FiO<sub>2</sub> control improved time spent with SpO<sub>2</sub> within the intended TR, the short study periods may have increased the risk for a Hawthorne effect.<sup>11 34-</sup>

<sup>36 38 39 67 90</sup> We compared automated FiO<sub>2</sub> with manual titration for a much longer period and observed a bigger increase in time SpO<sub>2</sub> was within the TR than has been observed in other studies. This is important as it supports that in routine use, the potential for improvement of automated FiO<sub>2</sub> is higher. This was not a randomised trial but our results reflect the effect of the automated FiO<sub>2</sub> control when there was less risk of influencing the attentiveness of caregivers by participating in a study. It is likely that the results of this study can be extrapolated to other level III NICU centers.

Whether there was a decrease in time SpO<sub>2</sub> was above or below TR or both, varied between previous reported studies.<sup>11 34-36 38 39 67 90</sup> We observed a decrease in time with SpO<sub>2</sub> above TR which was comparable with previous studies.<sup>11 34-36 39 90</sup> While some studies of automated control observed a decrease in time spent with SpO<sub>2</sub> below TR,<sup>36 38 67 90</sup> we observed an increase. This has also been reported by others.<sup>34 35</sup> Explaining this conflicting finding is complicated by differences in methodology used (devices, study period, TR).<sup>36 38 67</sup> We observed the largest increase in time spent just below TR (85%-90%) with no increase in hypoxaemia (< 80%), consistent with others.<sup>34 35</sup> The CliO<sub>2</sub> algorithm has been designed to prevent hyperoxaemia when overshoot occurs when the oxygen is increased. It is also known that nurses tend to give more liberal oxygen during desaturation resulting in a shorter duration with SpO<sub>2</sub> below TR, but longer duration with time above TR. Indeed, in a previous study we reported that there is more awareness for alarms for SpO<sub>2</sub> below TR than above.<sup>24</sup> Comparable to most previous studies, we could not detect a decrease in the total time with hypoxaemia when automated FiO<sub>2</sub> was implemented. This likely reflects the aversion of caregivers to very low SpO<sub>2</sub> values.<sup>11 34 35 39</sup> Apparently the occurrence and depth of hypoxaemia is not prevented, but infants profit from a faster response provided by an automated FiO<sub>2</sub> device when a hypoxaemic event occurs. Likewise, the gradual but constant downward titration of oxygen of the automated FiO<sub>2</sub> control explains of the decrease in hyperoxaemia. It is possible that other devices for auto FiO<sub>2</sub> control give different results as the algorithms can differ.<sup>91</sup>

In considering the results of our study and others, it is clear that the SpO<sub>2</sub> distribution achieved using manual control differs from that achieved using automated control, even when the intended TR is the same.<sup>84</sup> Others have also shown the effect of shifting automated control ranges.<sup>84</sup> For that reason selecting the best TR for use with automated control should consider the likely SpO<sub>2</sub> exposure and not just an adoption of the optimum standard of practice for manual control.

This study was performed as an audit after implementation of automated FiO<sub>2</sub> control as standard care in our unit. The results reflect the real situation as data were collected for the duration infants were admitted, while nurses taking care of them, with varying workload. Although the characteristics of the groups were similar, this was not a randomised study and it is possible that there were differences between the group of infants admitted during the observed periods. We compared SpO<sub>2</sub> values that were routinely sampled every minute and although the value is an average of 8 seconds, it is possible we missed SpO<sub>2</sub> fluctuations in between the samples taken.<sup>92</sup> However, our findings and distribution of SpO<sub>2</sub> in the compared groups are similar when higher sample rates were used<sup>43 44</sup> and it is likely that this is an accurate reflection of the SpO<sub>2</sub> of the infants admitted.

Reducing the occurrence and duration of hypoxaemia and hyperoxaemia is known to reduce the related morbidity and mortality. Currently randomised trials are planned to determine the effect of automated FiO<sub>2</sub> on clinical outcome in preterm infants.<sup>93</sup> In anticipation of these upcoming trials, we implemented the automated FiO<sub>2</sub> as standard care for all infants receiving respiratory support in the NICU as part of a quality improvement in our unit. Although difficult to measure, during evaluations nurses reported that after implementation of the automated FiO<sub>2</sub> control their workload was less and they would be very reluctant to go back to the manual titration. Studies have reported that automated FiO<sub>2</sub> control decreased the required nursing time in preterm infants with frequent severe desaturations.<sup>35 88 89</sup> However, thresholds should be set very carefully in order not to mask deterioration of a patient and nurses need to stay attentive as well as the automated FiO<sub>2</sub> control should give a warning if the FiO<sub>2</sub> baseline rises above a predefined level.

In conclusion, implementation of automated FiO<sub>2</sub> control led to an increased compliance of maintaining SpO<sub>2</sub> within the intended TR during oxygen therapy, with a decrease in the time in which SpO<sub>2</sub>>95% and SpO<sub>2</sub>>98%. Although the observed effects of the automated FiO<sub>2</sub> control have the potential to improve outcome, this study was not designed to demonstrate this. Randomised studies are needed to confirm the beneficial effects of the automated FiO<sub>2</sub> control on the outcome of preterm infants.

