Optimal Target Range of Closed-Loop Inspired Oxygen Support in Preterm Infants: A Randomized Cross-Over Study

Maria Elisabeth Nicoletta van den Heuvel, MD[1], Henriette A. van Zanten, PhD[2], Tom E. Bachman, MSc[3], Arjan B. te Pas, MD, PhD[2], Anton H. van Kaam, MD, PhD[1], and Wes Onland, MD, PhD[1]

Objective To investigate the effect of different pulse oximetry (SpO_2) target range settings during automated fraction of inspired oxygen control (A-FiO_2) on time spent within a clinically set SpO_2 alarm range in oxygen-dependent infants on noninvasive respiratory support.

Study design Forty-one preterm infants (gestational age [median] 26 weeks, age [median] 21 days) on FiO_2 >0.21 receiving noninvasive respiratory support were subjected to A-FiO_2 using 3 SpO_2 target ranges (86%-94%, 88%-92%, or 89%-91%) in random order for 24 hours each. Before switching to the next target range, SpO_2 was manually controlled for 24 hours (washout period). The primary outcome was the time spent within the clinically set alarm limits of 86%-94%.

Results The percent time within the 86%-94% SpO_2 alarm range was similar for all 3 A-FiO_2 target ranges (74%). Time spent in hyperoxemia was not significantly different between target ranges. However, the time spent in severe hypoxemia (SpO_2 <80%) was significantly reduced during the narrowed target ranges of A-FiO_2 (88%-92%; 1.9%, 89%-91%; 1.7%) compared with the wide target range (86%-94%; 3.4%, $P < .001$). There were no differences between the 88%-92% and 89-91% target range.

Conclusions Narrowing the target range of A-FiO_2 to the desired median ±2% is effective in reducing the time spent in hypoxemia, without increasing the risk of hyperoxemia. *(J Pediatr 2018;■■:■■-■■).*

Trial registration www.trialregister.nl: NTR4368.

Preterm infants often require supplemental oxygen to prevent hypoxemia, a condition that has been associated with organ damage and an increased mortality.[1-3] However, too much oxygen supplementation resulting in hyperoxemia may lead to systemic oxidative stress and long-term complications such as retinopathy of prematurity.[4,5] For these reasons, oxygen saturation is continuously measured in preterm infants with pulse oximetry (SpO_2) aiming to keep it within a safe range by manually titrating the fraction of inspired oxygen (FiO_2). However, studies in preterm infants have shown that SpO_2 targeting is a clinical challenge with patients spending only 50% of the time within their intended SpO_2 range because of clinical instability and the limited time nurses have to adjust the amount of oxygen.[6,7] To improve SpO_2 targeting, systems for automated FiO_2 (A-FiO_2) control have been developed.

These closed-loop A-FiO_2 systems are increasingly incorporated into standard neonatal ventilators and consist of an oxygenation monitoring device (pulse oximeter), gas (air/oxygen mixing) delivery device, and an algorithm that determines the timing and magnitude of the FiO_2 adjustments. Previous studies have shown that these algorithms improve maintenance of oxygenation within an SpO_2 target range compared with routine or dedicated manual FiO_2 (M-FiO_2) control.[8-12] However, in these studies, the SpO_2 target set in the A-FiO_2 arm was relatively wide and the SpO_2 alarm setting was identical to the setting used during normal clinical care. This approach may not use the full potential of the closed-loop A-FiO_2 systems. The aggressiveness of adjustments is proportional to the deviation of the measured SpO_2 from the set SpO_2 limits. Therefore, narrowing the SpO_2 target range during A-FiO_2 might increase the time spent within the SpO_2 alarm limits even further and make the algorithm more effective.

This study aimed to investigate the effect of different SpO_2 target range settings during A-FiO_2 on time spent within a (wider) clinically desired SpO_2 range in oxygen-dependent infants on noninvasive respiratory support. We hypothesized that narrowing the upper and lower limits of the A-FiO_2 target range would result in an increased proportion of time spent within the (wider) clinically set SpO_2 alarm limits and reduced episodes of both hypoxemia and hyperoxemia.

A-FiO_2	Automated FiO_2
FiO_2	Fraction of inspired oxygen
M-FiO_2	Manual FiO_2
SpO_2	Pulse oximetry

From the [1]Department of Neonatology, Emma Children's Hospital, Academic Medical Center Amsterdam; [2]Department of Pediatrics, Division of Neonatology, Leiden University Medical Center, Leiden, The Netherlands; and [3]Faculty of Biomedical Engineering, Czech Technical University in Prague, Kladno, Czech Republic

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Methods

This study was designed as a multicenter, randomized, crossover clinical trial (www.trialregister.nl: NTR4368) in 2 level III neonatal intensive care units in The Netherlands (Emma Children's Hospital Academic Medical Center, Amsterdam; Leiden University Medical Center, Leiden). The study was approved by the institutional review boards, and written parental informed consent was obtained before enrollment.

Patients

Preterm infants, born with a gestational age between 24 and 32 weeks, and a weight at study entry between 0.5 and 4 kg, receiving nasal continuous positive airway pressure or nasal intermittent positive pressure ventilation with a FiO_2 >0.21 for more than 18 hours per day and expected to require this noninvasive support for the 5-day study period were considered eligible for the study.

Infants with major congenital anomalies, hemodynamic instability requiring vasopressor treatment within 48 hours prior to enrollment, or culture proven sepsis within 72 hours prior to enrollment were excluded.

Study Protocol

Respiratory support was provided by means of Avea ventilator (CareFusion, Yorba Linda, California) with a built-in A-FiO_2 adjustment function. A neonatal pulse oximeter (Radical, Masimo Corporation, Irvine, California) integrated in the ventilator was used to measure SpO_2 (normal sensitivity, averaging time 8 seconds). The algorithm determines the timing and size of the FiO_2 adjustments, if needed, every second. FiO_2 is reduced when SpO_2 exceeds the target range or increased when SpO_2 falls below it. The magnitude of these adjustments is proportional to the deviation of the measured SpO_2 from the set high or low SpO_2 limit as well as the time the SpO_2 has been out of the target range. The algorithm calculates the SpO_2 response to hypoxemia and hyperoxemia in relation to the lower and upper limits of the target range, respectively. It includes adjustments in FiO_2 based on upward or downward trends in SpO_2 that are tied to the midpoint of the target range. In addition, when in the target range, but above the midpoint, the FiO_2 is weaned slowly. Therefore, a narrow target range leads to an amplification of the FiO_2 response, for a given SpO_2 value in the hypoxemic or hyperoxemic zone. When the oximeter identifies a condition that renders the SpO_2 measurement invalid or unreliable, in addition to creating a high priority alarm, the FiO_2 is set to a fallback level. Additional details of the A-FiO_2 function can be found elsewhere.[13] This system is approved for clinical use in The Netherlands. At the time of the study, both sites aimed to keep the SpO_2 between 86% and 94% during normal clinical practice and this SpO_2 range was also adopted for outcome assessment in this study and is here from referred to as the SpO_2 alarm range. This SpO_2 alarm range was similar for all 3 target ranges.

Enrolled infants underwent three 24-hour study periods of A-FiO_2 control using 3 different SpO_2 target ranges with a fixed midpoint of 90%: (1) 86%-94%; (2) 88%-92%; and (3) 89%-91%. The order of SpO_2 targeting was randomly assigned, using sequentially numbered opaque sealed envelopes. To minimize a possible effect of the previously assigned target range, infants received 24 hours of standard M-FiO_2 care after the first and second target range study period, resulting in a total study time of 120 hours. The nursing staff was unaware that data were recorded during both M-FiO_2 periods.

Demographic data including gestational age, birth weight, sex, postnatal age, and weight were collected at time of enrollment. Ventilator settings and monitored measures including SpO_2, FiO_2, pulse rate, and alarms were recorded every 5 seconds during the study period by an electronic data logger.

Off-line computerized analysis was used to evaluate the recorded data for each infant for all five 24-hour periods (3 A-FiO_2 and 2 M-FiO_2). Intention-to-treat analysis was applied to all recorded data during A-FiO_2 (ie, periods when the automated function was paused or the target range intermittently set incorrectly were not excluded).

The primary outcome was defined as the proportion of time spent within the (clinically) intended SpO_2 alarm range of 86%-94%, plus time with SpO_2 above 94% and FiO_2 was set at 0.21. Secondary outcomes included the proportion of time below or above the 86%-94% SpO_2 alarm range, the proportion of time below SpO_2 <80% and above SpO_2 >98%, and the frequency of prolonged episodes (>1 minute) with SpO_2 <80% and >98% (excluding time when the FiO_2 was 0.21). Data collection continued during the 2 days of M-FiO_2 to evaluate M-FiO_2 during usual care as a secondary outcome. Histograms and median SpO_2 and FiO_2 levels in each of the 24-hour periods were calculated for each infant and averaged for all infants.

Statistical Analyses

Our hypothesis was that narrowing the target range of the A-FiO_2 adjustment to 88%-92%, and 89%-91% would increase the proportion of time within the SpO_2 alarm range of 86%-94% by 7%, and 10%, respectively.[13] A sample size of 41 subjects achieves 80% power to detect this increase with a significance level of 0.05. The power calculation was performed using Nquery (Statistical Solutions Ltd, Cork, Ireland).

The primary analysis of the entire study population used a linear mixed model with fixed effect for sequence and with the interventions (3 A-FiO_2 and 2 M-FiO_2) as within subject repeated measures. Descriptive and secondary analyses included within-subject comparisons with paired *t* tests for normally distributed data or nonparametric Wilcoxon signed-rank tests. Results are reported as mean and SD or median and IQR. These analyses were conducted with XLSTAT v 6.01 (XLSTAT, Paris, France) software. *P* values of <.05 were considered statistically significant.

Results

Forty-three infants requiring supplemental oxygen by noninvasive respiratory support were enrolled between January 2014 and October 2015. Six infants exhibited clinical deterioration shortly after the start of the study needing intubation and

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