Effects of Automated Adjustment of the Inspired Oxygen on Fluctuations of Arterial and Regional Cerebral Tissue Oxygenation in Preterm Infants with Frequent Desaturations

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Objective To assess the effect of automated adjustment of the inspired oxygen fraction (FiO_2) on arterial oxygen saturation (SpO_2) and cerebral tissue oxygen saturation ($SctO_2$) in very low birth weight infants with frequent fluctuations in oxygenation.

Study design Fifteen infants (median gestational age, 25 weeks [range, 23-28 weeks]; median age, 34 days [range, 19-74 days]) were assigned in random sequence to 24 hours of automated adjustment of FiO_2 or manual adjustment of FiO_2. Primary outcome measurements were time within the SpO_2 target range and the area under the curve above and below a defined $SctO_2$ range.

Results Percentage of time within the SpO_2 target range increased during automated FiO_2 control (76.3% ± 9.2% vs 69.1% ± 8.2% for manual; $P < .01$). Prolonged episodes with SpO_2 <88% of >60 seconds duration (median, 115 episodes [range, 67-240] vs 54 episodes [range, 7-184]; $P < .01$) and of >180 seconds duration (median, 13 episodes [range, 6-39] vs 2 episodes [range, 0-5]; $P < .01$) decreased significantly during the automated period. Percentage of time with SpO_2 >96% decreased during automated control (6.6% ± 4.4% vs 10.4% ± 3.3%; $P < .02$). There was no significant difference in FiO_2 exposure. The area (deviation × time) below and above the defined $SctO_2$ threshold did not differ between the 2 periods (median, 59.7%*seconds [range, 17.2%-208.3%] for manual vs 49.0%*seconds [range, 4.3%-193.7%] for automated; $P = .36$).

Conclusion Automated FiO_2 control in preterm infants with frequent SpO_2 fluctuations significantly increased the time within the SpO_2 target range and reduced the incidence of prolonged hypoxemic events compared with manual FiO_2 adjustment, but did not significantly affect cerebral tissue oxygenation. *(J Pediatr 2015;166:240-4)*.

Intermittent fluctuations in arterial oxygen saturation (SpO_2) frequently occur in very preterm infants. These episodes may contribute to retinopathy of prematurity,[1] sleep-disordered breathing,[2] impaired growth,[3] and poor neurodevelopmental outcome.[4] Treatment of apnea, bradycardia, and intermittent hypoxemia, especially in extremely low birth weight infants, remains a challenge, given that some of the interventions of choice may cause serious side effects. Based on the multifactorial pathophysiology of these events,[5] therapeutic approaches include invasive and noninvasive ventilation, caffeine administration, as well as carefully adjusted oxygen supplementation to maintain SpO_2 within a target range.

Clinically, fluctuations in SpO_2 are detected by pulse oximetry. Ideally, the occurrence of hypoxemic or hyperoxemic events should be followed by an immediate response from the attendant caregiver, which typically includes a transient increase or decrease in inspired oxygen fraction (FiO_2). Frequent fluctuations in SpO_2 increase the workload of staff members, and because personnel resources are limited, caregivers are often unable to titrate FiO_2 to individual patients' needs. The incidence of hypoxemic events in preterm infants may increase with postnatal age to more than 600 events per week.[1] As a result, the caregiver's response may be delayed, leading to prolonged time with hypoxemia and/or hyperoxemia. Based on the high incidence of these hypoxemic events, it is not surprising that some preterm infants requiring supplemental oxygen are within the SpO_2 target range only one-half of the time.[6,7] Automated FiO_2 adjustments may limit SpO_2 fluctuations in preterm infants with intermittent hypoxemia.[8-12] Moreover, in a short-term study, the automated FiO_2 adjustment improved maintenance of SpO_2 within the intended range and reduced hyperoxemic episodes and exposure to supplemental oxygen in preterm infants.[11] Intermittent hypoxemia, especially when accompanied by bradycardia, may affect cerebral perfusion and tissue oxygenation as well.[13] To date, no published study has assessed the effect of automated FiO_2 adjustment on fluctuations in cerebral tissue oxygenation in

AUC	Area under the curve
FiO_2	Fraction of inspired oxygen
SpO_2	Arterial oxygen saturation
$SctO_2$	Cerebral tissue oxygen saturation

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Funded by the German Bundesministerium für Wirtschaft und Technologie (KF3031901MD2). The authors declare no conflicts of interest.

Registered with ClinicalTrials.gov: NCT01942473.

http://dx.doi.org/10.1016/j.jpeds.2014.10.007

preterm infants. We evaluated the efficacy of automated FiO_2 adjustment in maintaining SpO_2 within a target range and its influence on fluctuations of cerebral tissue oxygenation in preterm infants with intermittent hypoxemia.

Methods

This study was a randomized cross-over clinical trial comparing 2 treatment phases, clinical routine and automated adjustment of FiO_2, each of 24 hours duration. Infants were recruited in the neonatal intensive care unit of the children's hospital at Ulm University Medical Center. Inclusion criteria were gestational age <30 weeks, receipt of nasal/nasopharyngeal continuous positive airway pressure or mechanical ventilation (including nasopharyngeal intermittent mandatory ventilation), more than 4 episodes of hypoxemia (SpO_2 <80%) during an 8-hour period within the 24 hours before the study, and informed consent from the parents or legal guardian. Infants with major congenital anomalies, clinical evidence of seizures, or ongoing sepsis (C-reactive protein >10 mg/L or positive blood culture, receipt of catecholamines) during study were excluded.

Randomization of the sequence of the 2 study phases was carried out using sealed envelopes. Infants were changed to a specific ventilator device approved for clinical use for neonates in Germany, which is capable of automatically adjusting the FiO_2 based on readings of an incorporated SpO_2 monitoring device (respirator: AVEA; CareFusion, Hoechberg, Germany; pulse oximeter: Radical; Masimo, Irvine, California; averaging time, 8 seconds). After randomization, the infants were exposed to the first study phase (clinical routine or automated FiO_2 adjustment) for 24 hours, then switched to the alternate mode for another 24 hours. The ventilator's SpO_2 monitor was used for clinical SpO_2 monitoring during the study. The SpO_2 sensor was attached to the right arm. An additional sensor was attached to the infants' forehead for continuous measurement of cerebral tissue oxygen saturation ($SctO_2$) using absolute oximetry by near-infrared spectroscopy with a laser-light source using four different wavelengths (Fore-Sight; Casmed, Branford, Connecticut). SpO_2 values, FiO_2 values, ventilator settings, and heart rate as determined by electrocardiography (Dash 4000 Pro patient monitor; GE Medical Systems, Freiburg, Germany) were recorded every 2 seconds with an electronic data logger. The selected target range for preductal SpO_2 was 88%-96% at the ventilator during automated FiO_2 control, and alarm limits for interventions were selected at 87% (lower limit) and 97% (upper limit). The study was done with routine neonatal intensive care unit care with no investigator at the bedside. The physicians and nursing staff were advised to follow specific standard guidelines (**Table I**; available at www.jpeds.com) on FiO_2 adjustments during the manual period. The trial was approved by the University of Ulm's Institutional Review Board.

The first primary outcome was the time (ie, percentage of the total recording time) within the SpO_2 target range (88%-96%). For the detection of fluctuations in cerebral tissue oxygenation, a second primary outcome was defined as the area under the curve (AUC; %*second) below and above the individual median $SctO_2$ range (defined as ±5% of the individual $SctO_2$ median of each infant during each period; **Figure 1**). Secondary outcomes included the total time (ie, proportion of the total recording time) with SpO_2 <80%, <70%, and >96%, the number of episodes below the SpO_2 target range (defined as episodes with a duration of >10, >60, or >180 seconds), mean SpO_2 and variability of SpO_2 (coefficient of variation), number of bradycardic events (heart rate <100/minute for >10 seconds), and mean FiO_2 during each phase of the study. Secondary $SctO_2$ outcomes included median $SctO_2$, variability of $SctO_2$ (coefficient of variation), proportion of time with $SctO_2$ <55%, and time as percentage of total recording time and number of events of >2 seconds duration with $SctO_2$ below and above the defined $SctO_2$ range.

A sample size was calculated based on findings from a previous study[13] that measured the effects of 2 different SpO_2 target ranges (80%-92% vs 85%-96%) on the time that infants remained within that range. The mean difference in time with SpO_2 within the target range was 71.6 ± 56.3 minutes. Based on an α error of 0.05 and a β error of 0.10 (power of 90%), a sample size of 9 patients was needed to demonstrate the same difference. Because of 2 primary outcomes, Bonferroni adjustment was applied (α = 0.05/2 = 0.025). With the Bonferroni adjustment, a total of 10 patients was calculated. Given the potential for loss of data (defined as a signal loss of >25% during the study period), we studied 15 patients. All data were continuous variables, and the paired t test or Wilcoxon signed-rank test, as appropriate, was used for statistical comparisons. Results are reported as mean ± SD or median (range). A P value <.025 for the 2 primary outcome measures was considered statistically significant. All other measures were compared in a descriptive manner, and the level of significance for these comparisons was $P < .05$.

Results

A total of 15 preterm infants with intermittent hypoxemia were included from February 2012 through June 2013. Characteristics of the study group are summarized in **Table II**.

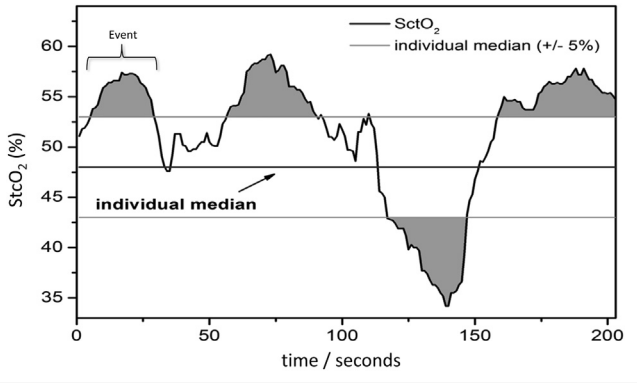

Figure 1. Threshold for detection of $SctO_2$ fluctuations.