Closed-Loop Automatic Oxygen Control (CLAC) in Preterm Infants: A Randomized Controlled Trial

WHAT'S KNOWN ON THIS SUBJECT: In preterm infants receiving supplemental oxygen, manual control of the inspired oxygen fraction is often difficult and time consuming, which may increase the risk of complications. We developed a system for automatic oxygen control and proved its efficacy in the past.

WHAT THIS STUDY ADDS: A multicenter study adds evidence for the proposed automatic oxygen control system to significantly improve oxygen administration to preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure while reducing workload compared with routine manual oxygen control.

BACKGROUND AND OBJECTIVE: In preterm infants receiving supplemental oxygen, routine manual control (RMC) of the fraction of inspired oxygen (FIO2) is often difficult and time consuming. We developed a system for closed-loop automatic control (CLAC) of the FIO2 and demonstrated its short-term safety and efficacy in a single-center study. The objective of this study was to test the hypothesis that this system is more effective than RMC alone in maintaining arterial oxygen saturation within target levels when evaluated over 24 hours under routine conditions and with different target levels.

METHODS: We performed a multicenter, randomized controlled, crossover clinical trial in 34 preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure and supplemental oxygen. Twenty-four-hour periods with RMC were compared with 24-hour periods of RMC supported by CLAC.

RESULTS: The median (range) percentage of time with arterial oxygen saturation levels within target range was 61.4 (31.5–99.5) for RMC and 71.2 (44.0–95.4) for CLAC (P < .001). The median (range) number of manual FIO2 adjustments was reduced from 77.0 (0.0–224.0) for RMC to 52.0 (10.0–317.0) for CLAC (P = .007).

CONCLUSIONS: CLAC may improve oxygen administration to preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure while reducing workload related to RMC. Pediatrics 2014;133:e379–e385
Preterm infants frequently require supplemental oxygen (O2). The goal of this therapy is to deliver sufficient O2 to the tissues while minimizing O2 toxicity and oxidative stress, which may result from too high or too widely fluctuating O2 levels. Although the optimal level of arterial pulse oximeter saturation (SpO2) is still debated, there is evidence that wide fluctuations in SpO2 should in any case be avoided.1-3 This may be difficult to achieve, however, under routine clinical conditions.4

Thus, automatic titration of the fraction of inspired oxygen (FiO2) by using a closed-loop FiO2 controller (FiO2C) seems attractive. The first attempts at automating O2 delivery to patients date back to the 1970s, but only recently, with the advance of motion-resistant pulse oximetry, sophisticated systems have been developed that seem to be suitable for clinical use in preterm infants requiring respiratory support.5,6 In a group of preterm infants receiving nasal continuous positive airway pressure (CPAP), we previously tested an FiO2C that was able to maintain SpO2 within target for 91% of the time.7 Another system, tested in mechanically ventilated infants, maintained SpO2 within target for 40% of the time.6 With both systems, automatic was better than manual control in maintaining SpO2 within the desired range.

The underlying algorithm is based on a time-oriented data abstraction method. This method is capable of deriving steady qualitative descriptions from oscillating high-frequency data, such as SpO2 values. The algorithm tends to level out SpO2 fluctuations, thereby keeping SpO2 in a predefined target range. Its conceptual design is not aimed at treating acute severe hypoxic episodes, as these may require individual intervention by caregivers.

SpO2 data are analyzed in time windows and qualified as outlined in Table 1. The target range is further subdivided into “upper target range,” “middle target range,” and “lower target range.” According to this qualification, 5 different FiO2 adjustments are suggested (−0.02, −0.01, 0, +0.02, +0.05). Each adjustment is followed by a wait-and-see period of 180 seconds during which the FiO2C software does not effect further changes. In the case of low SpO2 values, the algorithm changes into an “alarm” mode, signals this condition, and suspends further adjustments until the SpO2 values are again above this critical limit.

In the current study, a laptop computer (Eee PC 900; Asus, Taipei, Taiwan) executing the FiO2C software was connected via serial links to a motion-resistant pulse oximeter (Radical 7; Masimo Inc, Irvine, CA; “Fast-sat” mode with 2-second averaging, ASCII-1 data output mode) and a commercially available neonatal ventilator (Leoni plus; Heinen & Loewenstein GmbH, Bad Ems, Germany). Study oximeter alarms were muted but displays were not shielded.

The FiO2C software was programmed to acquire SpO2 values, pulse rate, and other parameters (eg, signal IQ, perfusion index) from the pulse oximeter, analyze these data, and derive FiO2 adjustments. SpO2 values associated with a low signal IQ (a signal quality parameter indicating potentially artifactual readings) were automatically excluded. The ventilator was equipped with a digital feedback-controlled O2 blender. The FiO2C software automatically executed its FiO2 adjustments by directly changing the ventilator’s FiO2 setting.

**Study Design and Progress**

This study was designed as a multicenter, randomized controlled, crossover clinical trial at 3 German level-III NICUs (University Children’s Hospital Tuebingen, University Children’s Hospital Ulm, and University Children’s Hospital Freiburg). However, recruitment of patients took longer than expected, and a fourth study center (Children’s Hospital, Klinikum am Steinenberg; Reutlingen, Germany) was involved 2 years after study initiation. In addition, study funding ran out after 3 years and the study had to be terminated prematurely.

After a run-in phase of 3 hours, each patient underwent 2 different modes of FiO2 control (treatment modalities: RMC alone versus RMC supported by CLAC).

**METHODS**

**Technical Solutions**

The underlying algorithm, the software solution, and the hardware setup have been described elsewhere.7-9

Table:

<table>
<thead>
<tr>
<th>Range</th>
<th>Center 1</th>
<th>Center 2</th>
<th>Center 3</th>
<th>Center 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above target range</td>
<td>96–100</td>
<td>95–100</td>
<td>94–100</td>
<td>95–100</td>
</tr>
<tr>
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<td>83–93</td>
<td>85–94</td>
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<td>90–92</td>
<td>91–93</td>
<td>92–94</td>
</tr>
<tr>
<td>Middle target range</td>
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<tr>
<td>Lower target range</td>
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<td>80–83</td>
<td>83–86</td>
<td>85–87</td>
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<tr>
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</tr>
<tr>
<td>Alarm range</td>
<td>&lt;80</td>
<td>&lt;70</td>
<td>&lt;73</td>
<td>&lt;75</td>
</tr>
</tbody>
</table>

SpO2 values were qualified into 4 main ranges: above target, target, below target, and alarm. The target range was further subdivided into upper target, middle target, and lower target. According to this qualification, different FiO2 adjustments were performed (−0.02 for above target, −0.01 for upper target, ±0 for middle target, +0.02 for lower target, and +0.05 for below target). Alarm range was a condition in which the system suspends further adjustments until the SpO2 values were again above this critical limit.
Each treatment phase lasted 24 hours, leading to a total study duration per patient of 51 hours. For group allocation, a computer-generated list of random numbers was used with a 1:1 allocation by using random block sizes of 9. This list was prepared by an investigator without clinical involvement in the trial (M.S.U.). After recruitment, infants were randomly assigned by a senior doctor to 1 of 2 study groups by opening corresponding sequentially numbered and sealed opaque envelopes. Each group represented a fixed order of treatment modalities.

The trial was approved by the institutional review board (project 7/2006) and registered in the German Clinical Trials Register (DRKS00000157). The device setup was approved by the local department of biomedical engineering and written informed parental consent was obtained for each infant.

**Patients**

Preterm infants admitted to participating study centers were eligible if they had a gestational age at birth of <37 weeks, required mechanical ventilation or nasal CPAP, and needed an FiO₂ of at least 0.25. Patients were excluded if they had congenital diaphragmatic hernia, cyanotic heart disease, or another medical condition necessitating a deviation from the usual SpO₂ target range. Individual exclusion criteria were reached in case of resuscitation, termination of both mechanical ventilation and CPAP, and withdrawal of parental consent. Extubation (and switch to nasal CPAP), changes in ventilator settings, and no further need of additional O₂ (ie, switch to room air) were no exclusion criteria.

**Protocol**

Twenty-four-hour periods with RMC were compared with 24-hour periods of RMC supported by CLAC. During the whole study period, the nurse on duty remained responsible for any FiO₂ adjustments necessary and the patient remained on the standard monitoring system throughout (SpO₂ averaging time was 8 seconds in 1 center and 10 seconds in the remaining centers). Nurses were encouraged to ignore the readings of the study oximeters and to adjust the FiO₂ according to the readings of the standard monitor. The patient-to-nurse ratio was 2:1 or 3:1 at that time.

O₂ administration policy was determined according to clinical experience of the bedside nurse and was not further specified for the current study. To comply with routine conditions in participating study centers, we left the center-specific SpO₂ target levels (ranging from 80% to 95%; Table 1) unchanged. Changes in ventilator settings and body position, as well as routine nursing procedures, were allowed throughout.

**Data Acquisition and Analysis**

The patient’s SpO₂ and pulse rate, other SpO₂-related variables (eg, signal IQ, perfusion index), and the number of FiO₂ adjustments executed by nurses and/or the FiO₂C were digitally recorded by the FiO₂C software. Data were analyzed and visualized by using standard data handling and plotting software by 1 of the investigators (W.H.) who was blinded to group assignment. SpO₂ values associated with low signal IQ (ie, artifactual readings) were excluded from analysis. Recordings were excluded if more than 10% of SpO₂ values of a study phase were missing or the amount of artifactual readings was more than 10% of a study phase. According to the center-specific SpO₂ target levels (Table 1), SpO₂ values were qualified as above target range, within target range, and below target range. During time periods in which patients did not need additional O₂ (ie, FiO₂ = 0.21), SpO₂ values qualified as above target range were requalified as within target range, because in this situation, further FiO₂ reduction is not an option.

**Sample Size and Statistical Analysis**

The primary study variable was the proportion of time (expressed as percentage) spent within target range (Target%). The sample size calculation was based on pilot data from our previous trial and the assumption that no carryover effects would occur. An increase of 2 percentage points in Target % was judged as clinically relevant. We calculated that 18 study participants would be sufficient to detect improvement with 0.05 type-I error and 0.1 type-II error (ie, 90% power) and this was the lower limit of sample size for the current study. We assumed that the presence of different conditions among study centers potentially influences the assumptions made for sample size calculation. Consequently, and as a secondary goal, we initially powered the study to detect significant differences for each individual study center. Hence, we decided to enroll 18 patients in each participating center (ie, 54 in total) and to perform a center-stratified secondary analysis. However, at study termination, only 1 center had reached its center-specific sample size (n = 18) and we decided against center-stratified secondary hypothesis testing and calculated center-specific treatment effects only.

Secondary study variables were the percentage of time spent above target range and below target range, as well as the number of manual FiO₂ adjustments performed by bedside personnel. Descriptive statistics (n and percentage, as well as median, minimum, and maximum) were used to summarize demographic and clinical characteristics, as well as primary and secondary study variables. As Target% was normally distributed in our sample, treatment effects across modalities were calculated as the mean of the individual
differences between CLAC and RMC and its 95% confidence interval (CI). For confirmatory analysis, comparisons between means of Target% across treatment modalities were performed using a linear mixed model with the patient as random factor. The model was adjusted for center, study phase, and carryover effects (expressed as interaction term between treatment and study phase). For confirmatory analysis, $P < .05$ was considered statistically significant. For exploratory analysis, secondary study variables were compared across treatment modalities by using the nonparametric 2-tailed Wilcoxon signed-rank test. For exploratory analysis, corrections for multiple testing were not performed and $P$ values were given for descriptive reasons only. Analyses were done with statistical software (IBM SPSS Statistics 20; IBM Corporation, Chicago, IL).

**RESULTS**

**Patients**

Between April 2009 and March 2012, 52 infants were approached and 44 were enrolled and randomized (Fig 1). Of these, 6 had to be later excluded because of protocol nonadherence (severe apnea of prematurity requiring changing the ventilator, $n = 1$; change of the desired $SpO_2$ target range, $n = 1$; ventilator failure, $n = 2$ [leading to adverse event, $n = 1$]; premature termination of ventilation, $n = 1$; clinical deterioration requiring changing the ventilator, $n = 1$) and 4 were later excluded because of incomplete oximetry data (ie, more than 10% of data were missing for either study phase). The final sample size stratified by center was 4, 5, 7, and 18. Demographic and clinical characteristics of the 34 included study participants are shown in Table 2. Patients received predominantly nasal CPAP. During the run-in phase, 2 infants were extubated and remained on nasal CPAP, and 1 received surfactant. All 3 infants remained in the study.

**Saturation Target Results**

The $FiO_2$C software performed well throughout the trial and all infants tolerated the study procedures well. There was no study interruption or termination related to failures of the $FiO_2$C software. In every single patient, Target% was higher during CLAC compared with RMC. Regarding the total sample, results for primary and secondary study variables are given in Table 3. A box-and-whisker plot of Target% is presented in Fig 2. Target% increased substantially during CLAC compared with RMC; the mean treatment effect (95% CI) of CLAC compared with RMC was +11.1 percentage points (+6.6 to +15.6). This was higher than what we had defined as clinically relevant (ie, +2 percentage points). In the linear mixed model, the main effect of the treatment modality was highly significant ($P < .001$), whereas there were no significant study phase or carryover effects ($P = .979$ and .164, respectively). There was also a reduction in percentage of time spent below target range in CLAC compared with RMC. In contrast, the percentage of time spent above target range did not differ between treatment modalities. In addition, the number of manual $FiO_2$ adjustments executed by nurses was reduced in CLAC compared with RMC.

**Center-Specific Treatment Effects**

Results of the center-stratified secondary analysis for Target% are shown in Table 4. Mean Target% for CLAC was higher throughout, compared with RMC. Because of the small sample size, CIs for the mean treatment effect were large in some centers, including 0 in 1 center. However, in 3 of 4 centers, the lower limit of the 95% CI for the mean treatment effect was $>2$ percentage points, which was our cutoff value for a clinically relevant improvement.

**DISCUSSION**

In this multicenter, randomized controlled trial, the evaluated $FiO_2$C significantly increased the proportion of time with $SpO_2$ levels within a predefined target range. We found that the treatment effect was $\sim$11 percentage points (ie, an improvement in Target% from 61% to 72%). This is in line with previous studies from our group as well as other groups, and indicates the potential of an $FiO_2$C to optimize $O_2$ therapy. Such a system may help to avoid unnecessarily high or low $O_2$ exposure, sustained hypoxemic and/or hyperoxemic episodes, and large fluctuations in $SpO_2$ levels, all related to adverse clinical outcomes. Moreover, the proposed $FiO_2$C decreased the frequency of manual $FiO_2$ adjustments executed by bedside personnel, which could reduce workload resulting from $SpO_2$ monitoring and $FiO_2$ control.

Strengths of the study included that the $FiO_2$C was tested under routine conditions in different NICUs and for 24 hours. Hence, the $FiO_2$C was handled solely by routine clinical staff. Different ventilation modes were allowed and each study center's given $SpO_2$ target range was not influenced by the study protocol. Even under these conditions, a significant improvement in maintaining a predefined target level could be achieved by using the $FiO_2$C. This indicates a high external validity of the trial findings.

Moreover, we were able to show positive treatment effects of CLAC compared with RMC for each center, although convincingly so for only 3 of the 4. In fact, center-specific mean treatment effects differed considerably between centers, ranging from +4.8 to +22.9 percentage points, with large overlaps in the respective 95% CIs. This large variation may be explained by differences in patients enrolled and by the small sample size in 3 of 4 centers. Furthermore, the effect of CLAC may be influenced by different $SpO_2$ target ranges. The lowest effect (ie, +4.8 percentage points) was observed in the center with the lowest $SpO_2$ target range (ie, 80% to 92% $SpO_2$).
Low target ranges may predispose infants to hypoxemic episodes and cerebral desaturations due to respiratory instability associated with low SpO2 values. However, a preliminary post hoc analysis did not suggest that the target range affected the efficacy of the FIO2C in a relevant manner (data not shown).

It has been suggested by recent large multicenter trials that extremely low gestational age infants may best be maintained within a relatively narrow range of SpO2 values (e.g., 91%–95% SpO2). Given the workload associated with keeping infants within such a narrow SpO2 target range, reducing this workload by means of an FIO2C seems even more relevant.

In a recent study evaluating a different FIO2C in 32 infants, Target% increased significantly during CLAC periods compared with RMC periods. In contrast, the improvement in Target% in the current study was predominantly accomplished via a reduction in hypoxemic episodes, whereas at the same time, undesired hyperoxemic periods or overshooting O2 delivery could be avoided.

We explicitly aimed at avoiding hypoxemic episodes with the proposed FIO2C. Therefore, we subdivided the target range into 3 areas (upper target, middle target, lower target) and added FIO2 adjustments of −0.01 for upper target and +0.02 for lower target. In other words, our FIO2C is proactive in avoiding hypoxemic episodes by adjusting FIO2 while the SpO2 is still

TABLE 2 Demographic and Clinical Characteristics (n = 34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
<th>Statistics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/female</td>
<td>n</td>
<td>23/11</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Grams</td>
<td>Median (range)</td>
<td>840 (410–2460)</td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>Weeks</td>
<td>Median (range)</td>
<td>26.4 (23.0–35.3)</td>
</tr>
<tr>
<td>Age at study entry</td>
<td>Weeks</td>
<td>Median (range)</td>
<td>29.9 (26.0–35.6)</td>
</tr>
<tr>
<td>FIO2 at study entry</td>
<td>Fraction</td>
<td>Median (range)</td>
<td>0.32 (0.25–0.63)</td>
</tr>
<tr>
<td>Ventilation mode at study entry</td>
<td>Mechanical ventilation/CPAP</td>
<td>n</td>
<td>11/23</td>
</tr>
</tbody>
</table>

study, however, time with SpO2 < 87% increased significantly during CLAC periods, with more frequent episodes of SpO2 ranging from 80% to 86%. In contrast, the improvement in Target% in the current study was predominantly accomplished via a reduction in hypoxemic episodes, whereas at the same time, undesired hyperoxemic periods or overshooting O2 delivery could be avoided.

We explicitly aimed at avoiding hypoxemic episodes with the proposed FIO2C. Therefore, we subdivided the target range into 3 areas (upper target, middle target, lower target) and added FIO2 adjustments of −0.01 for upper target and +0.02 for lower target. In other words, our FIO2C is proactive in avoiding hypoxemic episodes by adjusting FIO2 while the SpO2 is still
within (lower) target range. The resulting reduction in hypoxemic episodes may be important in terms of potential sequelae of hypoxemic episodes in preterm infants.1,3,14–16

We assumed different conditions among study centers and aimed at detecting significant improvements concerning Target% for each single study by enrolling 18 infants per center. Unfortunately and despite considerable effort, we failed to reach this projected sample size in 3 of 4 centers. This did not allow us to perform center-stratified formal statistical hypothesis testing. However, on a descriptive basis we found mean treatment effects with 95% CIs not including the null in 3 of 4 centers. In our opinion, this is sufficient evidence to assume that the FIO2C will be effective in its present form in diverse settings. This should be further assessed by postmarketing surveillance studies.

Nurses did not get any study-specific additional instructions on how to make their routine manual FIO2 adjustments. Giving such instructions might have improved FIO2 control in both RMC and CLAC periods.4 Thus, in a setting of perfectly instructed nurses, the additional benefit of an FIO2C may be smaller than seen here. Despite the advice to ignore the readings of the study oximeter, nurses may have been influenced in their routine care by these readings. However, the consideration of the readings had, if any, rather improved RMC periods (due to a double feedback about SpO2 status). This likely translated into a conservative (toward the null) bias. We speculate that shielding the oximeter displays would have led to an even larger beneficial effect of the FIO2C during CLAC periods.

The efficacy of FIO2C in maintaining SpO2 within target has yet been tested for only 2 devices.5–7 Thus, results cannot be generalized to other devices, which should therefore undergo similar evaluation before recommending them for clinical use in this vulnerable patient population.

CONCLUSIONS
The FIO2C tested here increased the proportion of time with SpO2 levels within a desired range, while at the same time decreased the number of hypoxemic episodes. This was associated with a reduction in manual FIO2 adjustments executed by bedside personnel. The device might help to reduce morbidity resulting from intermittent hypoxemia or large fluctuations in SpO2 levels, such as retinopathy of prematurity, brain injury, or other organ damage and may help to improve neurodevelopmental outcome. Furthermore, the system may reduce workload related to FIO2 control and may help to decrease the level of noise and stress for nursing staff members and patients alike.

ACKNOWLEDGMENTS
Members of the CLAC Study Group were Silvia Miksch (Vienna University of Technology, Vienna, Austria); Ingo Mueller-Hansen

### TABLE 3 Results for Primary and Secondary Study Variables (n = 34)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics</th>
<th>Treatment Modality</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Time within target range, %</td>
<td>Mean (SD)</td>
<td>RMC 61.0 (15.2)</td>
<td>72.1 (13.6)</td>
</tr>
<tr>
<td>Time above target range, %</td>
<td>Median (range)</td>
<td>16.0 (0.0–60.0)</td>
<td>15.9 (1.9–34.8)</td>
</tr>
<tr>
<td>Time below target range, %</td>
<td>Median (range)</td>
<td>15.0 (0.5–39.6)</td>
<td>9.1 (1.9–24.2)</td>
</tr>
<tr>
<td>Number of manual FIO2 adjustments</td>
<td>Median (range)</td>
<td>77 (0–224)</td>
<td>52 (10–317)</td>
</tr>
</tbody>
</table>

### FIGURE 2
Box-and-whisker plot of the primary outcome variable: percentage of time spent within the SpO2 target range (Target%). Comparison between RMC of the inspired oxygen fraction and CLAC of the inspired oxygen fraction.

### TABLE 4 Results of the Center-Stratified Secondary Analysis for Target% (n = 34)

<table>
<thead>
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<th>Center</th>
<th>n</th>
<th>Treatment Modality</th>
<th>Mean Treatment Effect (95%CI)</th>
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<tr>
<td></td>
<td></td>
<td>RMC</td>
<td>CLAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean % (SD)</td>
<td>Mean % (SD)</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>62.7 (16.6)</td>
<td>71.4 (15.3)</td>
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<td>7</td>
<td>64.3 (9.1)</td>
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<td>3</td>
<td>4</td>
<td>42.9 (9.1)</td>
<td>65.8 (6.0)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>64.9 (13.3)</td>
<td>83.9 (8.2)</td>
</tr>
</tbody>
</table>
REFERENCES


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Randomized Controlled Trial

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Antonietta Hallenberger, Christian Friedrich Poets, Werner Horn, Andreas Seyfang
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