Automatic Control of the Inspired Oxygen Fraction in Preterm Infants
A Randomized Crossover Trial

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In preterm infants receiving supplemental oxygen, manual control of the inspired oxygen fraction is often time-consuming and inappropriate. We developed a system for automatic oxygen control and hypothesized that this system is more effective than routine manual oxygen control in maintaining target arterial oxygen saturation levels. We performed a randomized controlled crossover clinical trial in 12 preterm infants receiving nasal continuous positive airway pressure and supplemental oxygen. Periods with automatic and routine manual oxygen control were compared with periods of optimal control by a fully dedicated person. The median (range) percentage of time with arterial oxygen saturation levels within target range (87–96%) was 81.7% (39.0–99.8%) for routine manual oxygen control, 91.0% (41.4–99.3) for optimal control, and 90.5% (59.0–99.4) for automatic control (ANOVA: p = 0.01). Pairwise post hoc comparisons revealed a statistically significant difference between automatic and routine manual oxygen control (Dunnett’s test: p = 0.02). The frequency of manual oxygen adjustments was lowest in automatic control (Friedman’s test: p < 0.001). Automatic oxygen control may optimize oxygen administration to preterm infants receiving nasal continuous positive airway pressure and reduce nursing time spent with oxygen control.

Keywords: closed-loop oxygen control; continuous positive airway pressure; infants; mechanical ventilation; neonatal lung disease

Preterm infants often receive respiratory support and supplemental oxygen. These interventions, however, may lead to both hyper- and hypoxemia, which are usually detected via continuous measurements of arterial oxygen saturation by pulse oximetry (SpO2), and treated with manual adjustments of the inspired oxygen fraction (FiO2) to maintain SpO2 within a given target range.

Monitoring SpO2 values and adjusting the FiO2 accordingly, however, requires experienced staff. Inadequate FiO2 adjustments leading to periods of hyperoxemia in response to episodic hypoxemia were observed in one study (1). Such fluctuations in blood oxygen tension were found predictive of retinopathy of prematurity (ROP) and may at least in part explain differences in ROP incidences among centers (2). In addition, manual FiO2 control is a time-consuming task and response times vary widely depending on the responsibilities and motivation of the staff involved. These limitations make development of a system for automatic FiO2 control (i.e., FiO2 controller) a desirable alternative. Such a system may reduce nursing time spent to achieve adequate oxygenation, staff and shift-dependent variability in FiO2 control, and the duration and frequency of hyperoxic and/or hypoxic episodes.

Our group has recently established clinical rules for FiO2 control, leading to mathematical algorithms and software codes for a neonatal FiO2 controller (3–5). The system was configured to maintain the SpO2 within a specific target range by automatically adjusting the FiO2. The clinical rules were specifically established for preterm infants receiving nasal continuous positive airway pressure (NCPAP) and supplemental oxygen. We hypothesized that this FiO2 controller is more effective than routine manual FiO2 control by staff in maintaining SpO2 within a specific target range and reduces the need for manual FiO2 adjustments and the frequency of hypoxic episodes. Some of the results of this study have been previously reported in abstract form (6, 7).

METHODS

FiO2 Controller

The underlying algorithm of the controller software is described elsewhere (3). In short, a time-oriented data abstraction method capable of deriving steady qualitative descriptions from oscillating high-frequency data such as SpO2 values was adapted to match the demands of a neonatal FiO2 controller by incorporating clinical expert knowledge (4). The algorithm aimed to balance SpO2 fluctuations and to keep SpO2 at 87 to 96% with few adjustments of the FiO2. It was not designed to respond to acute severe hypoxic episodes. The algorithm analyzed the SpO2 data in an 180 (state analysis) and 60 seconds (trend analysis) moving time-window. The state analysis supplied five qualitative abstraction values (substantially above, above, normal range, below, substantially below). According to these values, one out of five possible FiO2 adjustments was suggested (−0.02, −0.01, −0.0, +0.02, +0.05). The trend analysis supplied three qualitative abstraction values (increasing, stable, decreasing), which could postpone intended FiO2 adjustments (e.g., trend value “increasing” postponed a “−0.02” adjustment). Each adjustment was followed by a “no action” period of 180 seconds to allow for establishing a new steady state (wait mode). In the case of “noisy” data (i.e., the SpO2 standard error exceeded a preset limit) or an acute severe hypoxic episode (i.e., <80% SpO2 for >4 seconds) the system temporarily suspended its actions (check mode) (4).

Initial evaluation studies in a bench model were promising (5). The algorithm was then implemented on a PC, connected via a serial link (RS-232) to a pulse oximeter (Radical; Masimo Inc., Irvine, CA) with a new generation motion-resistant oximeter module (Masimo’s Signal Extraction Technology, software version 3.0.3.2, 2-second-average and “Fast Sat” mode). The software was programmed to acquire SpO2 values, pulse rate, and other device parameters (e.g., signal IQ, perfusion index) from the oximeter, analyze these data, and derive suggestions for FiO2 adjustments. SpO2 values associated with a low signal IQ, a signal quality parameter indicating artifactual readings (5), were automatically excluded before entering the analysis process.

For safety reasons, the controller was initially tested in open-loop control. Thus, FiO2 adjustments suggested by the controller were displayed...
on a screen and indicated by an acoustic signal. A bedside investigator (A.H. or M.S.U.) executed the suggested adjustments if they were consistent with his/her clinical judgment. Beyond these suggested adjustments, the investigators were not allowed to change the FiO2. In contrast, the primary caregiver could make manual FiO2 adjustments at any time.

In closed-loop control, the PC containing the controller software was connected via a second serial link (RS-232) to a commercially available neonatal ventilator (Leoni; Heinen and Loewenstein GmbH, Bad Ems, Germany). The ventilator was equipped with a digital feedback-controlled oxygen blender and a serial link interface. In closed-loop control, the controller software automatically executed suggested FiO2 adjustments in directly changing the ventilator’s FiO2 setting. In addition, the FiO2 adjustments were presented on the PC screen and indicated by an acoustic signal. The ventilator itself monitored and controlled the administrated FiO2 automatically with the help of its built-in digital feedback loop. Due to the digital communication between controller and ventilator there were short response times and gas-mixing delays were comparable to other commercially available ventilators (i.e., < 20 seconds for achieving a stable FiO2 level following an adjustment). An investigator (A.H. or M.S.U.) was present throughout to correct clinically inappropriate adjustments. Again, the primary caregiver but not the investigator was allowed to make additional manual FiO2 adjustments.

**Evaluation Process and Study Design**

Three clinical trials using controllers of different stages of development were performed. First, feasibility of the controller software in open-loop control was tested in three patients (feasibility trial). Second, the FiO2 adjustments suggested by the controller in open-loop control were validated in 12 patients (validation trial). Third, efficacy of the controller in closed-loop control was finally determined in another 12 patients (efficacy trial). Based on the data obtained from the feasibility and validation trial, the software and hardware components of the controller were improved for optimal performance before entering the efficacy trial. Thus, the controller of the validation trial (open-loop control) differed substantially from the controller of the efficacy trial (closed-loop control), which made two distinct studies necessary. During the validation and efficacy trial the same crossover study design was used (Figure 1). Twelve patients underwent four different modes of FiO2 control (treatment modalities) and were studied on 1 day during five periods of 90 minutes each. Each patient was randomly assigned to one of three study groups, each of which represented a fixed order of treatment modalities (Figure 1). All trials were approved by the institutional review board and performed between July 2002 and April 2004.

**Patients**

Preterm infants admitted to the Department of Neonatology at the University Children’s Hospital of Tuebingen, Germany, were eligible for the trials. Patients were enrolled if they were < 34 weeks of gestational age at birth, required NCPAP, supplemental oxygen, and had written informed parental consent. Patients were excluded from the study if the FiO2 reached 0.21 in the course of the study and remained there for over 15 minutes. This was done because during these periods hyperoxic episodes could not be treated by a further reduction in oxygen supply. Not excluding these patients could have introduced bias.

**Study Protocol**

During the validation trial, treatment modalities were baseline periods (Periods 1 and 5), open-loop control, and two different modes of manual FiO2 control (optimal and routine manual control). During the efficacy trial, treatment modalities were baseline, closed-loop control, and optimal and routine manual control.

In optimal manual control, an investigator (A.H. or M.S.U.) was constantly present at the patient’s side and fully dedicated to manual FiO2 control. The primary caregiver could make additional FiO2 adjustments at any time. In routine manual control, the nurse on duty, who was informed about the study aims and the desired SpO2 target range, was exclusively responsible for any FiO2 adjustments. The patient to nurse ratio was 2:1 at that time. The only difference between baseline periods and routine manual control was the fact that an investigator was present during routine manual control for documentation purposes. No written oxygen administration policy was used as a basis for FiO2 control, neither for the optimal nor for the routine manual control. Instead, the FiO2 was adjusted according to the clinical experience of the investigators (optimal manual control) and nurses (routine manual control). There was, however, agreement among investigators and nurses about a strict avoidance of overshooting FiO2 adjustments.

During all study periods (manual and automatic FiO2 control modes) the desired SpO2 target range was 87 to 96%. This range was chosen in accordance to a previous publication on automatic FiO2 control and to enable comparability with this study (8). Ventilator settings (i.e., gas flow and NCPAP level) and body position remained unchanged unless clinically indicated. No routine nursing procedures (e.g., changing the diaper or suctioning) were performed during study periods. During baseline periods, open-loop control, optimal manual control, and routine manual control, NCPAP and oxygen were administered using a standard ventilator (Stephanie; Stephanie GmbH, Gackenbach, Germany); during closed-loop control, the study ventilator described above was used.

**Data Acquisition and Analysis**

The number of manual FiO2 adjustments executed by nurses were documented during routine manual control, optimal manual control, and open-loop control/closed-loop control. During open-loop and closed-loop control the FiO2 adjustments suggested by the controller were also documented. The patients’ SpO2 and pulse rate and other SpO2-related variables (e.g., signal IQ, perfusion index) were digitally recorded at a sampling rate of 1 Hz using a new generation oximeter (Radical, software version 3.0.3.2, 2 seconds average and Fast Sat mode; Masimo Inc., Irvine, CA) and proprietary recording software (DIPLOG; Masimo Inc.). The oximeter sensor was usually attached to the right foot. If not, this was documented. The oximeter was equipped with a serial link interface cable that enabled the simultaneous acquisition of SpO2 data by the controller and the recording software on two different PCs. Following acquisition, recorded data were exported as an ASCII file. Data were analyzed and visualized using standard data handling and plotting software by one of the investigators (W.H.), who was blinded to group assignment.

The percentage of time each infant spent within the SpO2 target range (i.e., 87–96%; target time [TT]) was the primary outcome variable for the validation and the efficacy trial. For the validation trial, the secondary outcome variable was the frequency of manual FiO2 adjustments executed by the nurses (i.e., total number of increases and decreases) per hour study time. For the efficacy trial, secondary outcome variables were the mean and standard deviation of the SpO2, the frequency of hypoxic (i.e., < 87% SpO2 for > 5 seconds) and hyperoxic episodes (i.e., > 96% SpO2 for > 5 seconds) per hour study time, the average duration (seconds) of hypoxic and hyperoxic episodes, the frequency of overshooting episodes (i.e., a long-term hyperoxic episode [≥ 96% SpO2 for ≥ 60 seconds] occurring during the 2 minutes after the resolution of a hypoxic episode [i.e., < 87% SpO2 for ≥ 5 seconds])
per hour study time (8), and the frequency of manual $F_{O_2}$ adjustments per hour study time.

### Statistical Methods

Sample size calculations, based upon the three patients of the feasibility trial, revealed that 12 study participants would be sufficient to detect a 2% increase in TT with 0.05 type I and 0.2 type II error, assuming a mean TT of 92% for the routine manual control and an SD of 2.2% for the difference in TT between routine manual control and open-loop/closed-loop control.

Descriptive statistics (mean and SD or median and range) were used to summarize demographic characteristics and outcome variables. TT was transformed to achieve a normally distributed test variable. Because Mauchly’s criterion, used to test for sphericity, was not significant ($p > 0.05$), comparisons between means of the transformed TT across $F_{O_2}$ control modes (baseline 1 and 2, routine manual control, optimal manual control, open-loop/closed-loop control) were done using mixed-model ANOVA with the patient as random factor. Models were adjusted for study period effects and cofactors (body position, oximeter sensor site). Dunnett’s test was used for pairwise post hoc analysis using routine manual control as reference $F_{O_2}$ control mode.

Comparisons between means of secondary outcome variables were done using nonparametric tests for paired data where appropriate (Friedman's test and Wilcoxon's test). No correction for multiple testing was performed. A $p$ value of $< 0.05$ was considered statistically significant. Analyses were done with statistical software (Statistical Package for the Social Science, release 11.5 for Windows; SPSS, Chicago, IL).

### RESULTS

Results are presented for the validation and the efficacy trial. Demographic characteristics of study participants in both trials are shown in Table 1.

#### Validation Trial

Thirteen infants were enrolled; one infant was excluded because $F_{O_2}$ was 0.21 for more than 15 minutes (Table 2). The controller software performed well throughout the study and all infants tolerated the open-loop control procedures. During open-loop control, 101 $F_{O_2}$ adjustments were executed. Thirty-one adjustments (30.7% of all executed adjustments; median, range per infant: 2, 0–8) were performed by the primary caregiver although not suggested by the controller. Seventy-four adjustments were suggested by the controller and 70 (69.3% of all executed adjustments; median, range per infant: 7, 0–17) were executed by the bedside investigator (i.e., acceptance of 95% of suggested adjustments). Four out of the 74 $F_{O_2}$ adjustments suggested by the controller were refused by the investigator. Three could not be executed because the controller suggested a decrease in $F_{O_2}$ while the infant had already reached $F_{O_2}$ 0.21 (due to a lack of feedback from the ventilator at this stage of development). The software withdrew the fourth recommendation before it could be executed. According to the protocol, there were no additional $F_{O_2}$ adjustments executed by the bedside investigator.

The frequency of manual $F_{O_2}$ adjustments executed by the nurses differed significantly between modes of $F_{O_2}$ control (Friedman’s test; $p < 0.001$). There were significantly more $F_{O_2}$ adjustments per hour study time during optimal manual control compared with routine manual control and open-loop control (Wilcoxon’s test; $p < 0.005$ for both). The difference in manual $F_{O_2}$ adjustments between open-loop control and routine manual control was not statistically significant. TT varied widely, ranging from 22.0 to 97.8%. Compared with routine manual control, median TT was 6.1% and 5.4% higher during optimal manual control and open-loop control (ANOVA: $p > 0.05$).

#### Efficacy Trial

Thirteen infants were enrolled and one infant was excluded again because $F_{O_2}$ was 0.21 for more than 15 minutes (Table 3). All infants tolerated the study procedures well. The $F_{O_2}$ controller executed a total of 132 $F_{O_2}$ adjustments (median, range per infant: 11.5, 4–19) and none had to be corrected by the investigator. The number of manual $F_{O_2}$ adjustments executed by the nurses (not including the automatic $F_{O_2}$ adjustments by the controller) varied significantly (Friedman’s test; $p < 0.001$), being lowest in closed-loop control. Pairwise comparisons revealed statistically significant differences between routine manual control and closed-loop control (Wilcoxon’s test; $p = 0.004$), routine manual control and optimal manual control (Wilcoxon’s test; $p = 0.032$), and optimal manual control and closed-loop control (Wilcoxon’s test; $p = 0.002$).

Boxplots of the TT stratified by modes of $F_{O_2}$ control are presented in Figure 2. No obvious differences were observed between routine manual control and the two baseline periods, suggesting that the routine manual control periods were representative of the usual patient care. On average, TT was higher in optimal manual control and closed-loop control compared with routine manual control and baseline periods. These differences were statistically significant (ANOVA: $p = 0.01$). Pairwise post hoc comparisons revealed a statistically significant difference between routine manual control and closed-loop control (Dunnett’s test: $p = 0.02$) but no statistically significant differences between routine manual control and optimal manual control (Dunnett’s test: $p = 0.06$). Although not statistically significant, there was a trend (Friedman’s test: $p = 0.05$) toward fewer hyperoxic episodes during optimal manual control/closed-loop control compared with routine manual control/baseline periods. Other outcome variables did not differ statistically significantly across study periods.

### DISCUSSION

This clinical evaluation process aimed to test the efficacy of a $F_{O_2}$ controller designed for preterm infants receiving noninvasive respiratory support and supplemental oxygen. We observed a 11% increase in the proportion of time spent within SpO_2 target

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**TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE TWO STUDY SAMPLES**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
<th>Validation Trial (n = 12)</th>
<th>Efficacy Trial (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M n (%)</td>
<td>5 (42)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>wk Median (range)</td>
<td>24.5 (24–28)</td>
<td>25.5 (24–33)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>g Median (range)</td>
<td>7.35 (420–1,060)</td>
<td>800 (600–2,490)</td>
</tr>
<tr>
<td>Age at study enrollment</td>
<td>d Median (range)</td>
<td>21 (8–57)</td>
<td>20.5 (4–78)</td>
</tr>
<tr>
<td>$F_{O_2}$ at study enrollment</td>
<td>Fraction Median (range)</td>
<td>0.31 (0.23–0.43)</td>
<td>0.29 (0.23–0.34)</td>
</tr>
<tr>
<td>Positive end-expiratory pressure</td>
<td>Millbar Median (range)</td>
<td>5.5 (4.0–7.0)</td>
<td>6.0 (4.0–7.0)</td>
</tr>
</tbody>
</table>
Recent studies suggested that not only the target range of SpO2, but also the extent of the fluctuations in blood oxygen tension (38) was poor, ranging from 16 to 71%, and varied substantially above intended target range. These data indicate the need for educational efforts to improve manual FiO2 control. In our study, both hypoxemia and hyperoxemia occur frequently during routine manual FiO2 control (1), suggesting that differences in clinical practice may account for different incidences of ROP.

A recent study reported a major reduction in the incidence of ROP following the implementation of a strict protocol for oxygen administration (18), including a switch to new-generation oximeters and strict avoidance of hyperoxemia and repeated episodes of hypoxygen-hyperoxemia (i.e., “overshooting”). Despite several limitations, this report supports the hypothesis that a change in the policy of oxygen administration may result in reduced oxygen-associated morbidity such as ROP. In our study, we observed a 50 to 70% reduction in hyperoxia episodes and a 14 to 21% reduction in SpO2 fluctuations (expressed as the standard deviation of SpO2) during closed-loop automatic FiO2 control compared with routine manual FiO2 control. Our study was not designed to detect differences in these outcome variables, but we speculate that automatic FiO2 control could lead to a significant reduction in both hyperoxemia and SpO2 fluctuations and may hence lower the incidence of ROP.

In the above study, the authors also reported that their new policy met with some resistance from staff, possibly related to fear of an increased workload (18). This problem may be most likely solved by closed-loop automatic FiO2 control. We observed a significant reduction in FiO2 adjustments done by staff during automatic FiO2 control. Thus, workload will be clearly reduced by a FiO2 controller, which would enhance acceptance of a policy of FiO2 control aimed at reducing fluctuations in FiO2. “Nonuniform” acceptance of staff has also been found in a preliminary multicenter study on intended versus actual SpO2 values (C. Cole, personal communication). Compliance with intended policies was poor, ranging from 16 to 71%, and varied substantially among participating centers. Most noncompliance occurred above intended target range. These data indicate the need for educational efforts to improve manual FiO2 control. In our study,

### TABLE 2. VALIDATION TRIAL

<table>
<thead>
<tr>
<th>Study Variable</th>
<th>Baseline 1</th>
<th>Routine Manual Control</th>
<th>Optimal Manual Control</th>
<th>Open-loop Control</th>
<th>Baseline 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of manual FiO2 adjustments/h</td>
<td>n.a.</td>
<td>1.7 (0.0–10.0)</td>
<td>11.7 (4.7–22.0)</td>
<td>1.3 (0.0–5.3)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Percentage of time within SpO2 target range</td>
<td>75.3 (37.3–94.8)</td>
<td>79.7 (22.0–95.2)</td>
<td>85.8 (55.9–97.1)</td>
<td>85.1 (69.9–97.8)</td>
<td>79.4 (66.5–97.4)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: n.a. = not available; SpO2 = arterial oxygen saturation measured by pulse oximetry. Results are given as median and range.*

### TABLE 3. EFFICACY TRIAL

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Baseline 1</th>
<th>Routine Manual Control</th>
<th>Optimal Manual Control</th>
<th>Closed-loop Control</th>
<th>Baseline 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of time within SpO2 target range*</td>
<td>82.9 (49.5–99.3)</td>
<td>81.7 (39.0–99.8)</td>
<td>91.0 (41.4–99.3)</td>
<td>90.5 (59.0–99.4)</td>
<td>81.2 (46.5–98.5)</td>
</tr>
<tr>
<td>SpO2 mean</td>
<td>92.0 (91.0–94.0)</td>
<td>91.9 (89.0–94.2)</td>
<td>91.3 (86.9–93.7)</td>
<td>92.3 (90.9–92.9)</td>
<td>92.6 (88.0–94.7)</td>
</tr>
<tr>
<td>SpO2 SD</td>
<td>3.9 (1.7–27.7)</td>
<td>3.6 (1.5–8.2)</td>
<td>3.1 (1.4–10.6)</td>
<td>3.1 (1.9–7.7)</td>
<td>3.1 (1.6–14.7)</td>
</tr>
<tr>
<td>No. of hypoxic episodes/h</td>
<td>9.7 (0.0–24.7)</td>
<td>9.3 (0.0–46.7)</td>
<td>4.0 (0.0–15.3)</td>
<td>4.7 (0.0–20.0)</td>
<td>16.0 (0.0–26.7)</td>
</tr>
<tr>
<td>Average duration of hypoxic episodes, s</td>
<td>24.7 (0.0–117.0)</td>
<td>19.3 (0.0–79.2)</td>
<td>16.4 (0.0–41.3)</td>
<td>10.1 (0.0–43.2)</td>
<td>17.4 (0.0–39.8)</td>
</tr>
<tr>
<td>No. of hyperoxic episodes/h</td>
<td>10.0 (0.0–26.0)</td>
<td>12.7 (0.0–34.0)</td>
<td>8.7 (0.0–30.7)</td>
<td>9.3 (0.0–22.0)</td>
<td>8.7 (0.0–24.0)</td>
</tr>
<tr>
<td>Average duration of hyperoxic episodes, s</td>
<td>20.2 (0.0–57.5)</td>
<td>19.0 (0.0–39.0)</td>
<td>16.4 (0.0–71.0)</td>
<td>12.4 (0.0–59.9)</td>
<td>19.1 (0.0–136.0)</td>
</tr>
<tr>
<td>No. of overshooting episodes/h</td>
<td>0.0 (0.0–0.7)</td>
<td>0.0 (0.0–2.7)</td>
<td>0.0 (0.0–3.5)</td>
<td>0.0 (0.0–2.0)</td>
<td>0.0 (0.0–0.7)</td>
</tr>
<tr>
<td>No. of manual FiO2 adjustments/h†</td>
<td>n.a.</td>
<td>3.0 (0.7–8.7)</td>
<td>7.7 (1.3–19.3)</td>
<td>3.0 (0.4–4.7)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

*For definition of abbreviations see Table 2. Results are given as median and range.*

†p = 0.001.
routine manual FiO₂ control achieved desired SpO₂ values on average for 75 to 82% of the time. Although these results were already considered as good, they were further improved by closed-loop automatic FiO₂ control, reaching target levels for > 90% of the time. Thus, automatic FiO₂ control may substantially decrease variations in FiO₂ control across different shifts and centers.

Limitations

Patients of the present study were preterm infants receiving NCPAP. This is the preferred mode of respiratory support for preterm infants recovering from respiratory distress syndrome in this country. We, therefore, developed automatic FiO₂ control specifically for this mode. This, however, precludes generalizability of our results to more unstable preterm infants receiving invasive ventilation and/or being exposed to higher levels of oxygen. This will be the subject of further studies.

As digital communications were used with the pulse oximeter as well as with the ventilator, the system is functioning only with those specific devices. It is, however, possible to adapt the system to every pulse oximeter and ventilator equipped with serial link interfaces. Unfortunately, ordinary commercially available ventilators are rarely equipped with such interfaces. It was hard for the authors to find usable devices. The industry is thus encouraged to equip their systems with such interfaces, which would enable researchers to develop closed-loop automatic FiO₂ control.

The main problem with automatic FiO₂ control is the lack of a generally accepted policy for optimal oxygen administration and FiO₂ control. To date, there is still an ongoing debate on the optimal SpO₂ target range and other aspects of oxygen administration (19). As long as knowledge on optimal FiO₂ control is lacking, a completely safe and effective automatic FiO₂ control cannot be achieved. Thus, more studies on the best policy for oxygen administration are needed.

We used a target range of 87 to 96% SpO₂, which is higher than that suggested from recent studies (20). This range was selected to enable comparability with a previous study on automatic FiO₂ control (8). The upper limit has been used in our institution for many years, and our incidence of severe ROP (> stage 2) was found to be significantly lower than that in a neighboring university hospital adopting a target range of 80 to 90% (21). Whatever the optimal target range, it is freely configurable with this particular FiO₂ controller software and can thus be adapted to any clinical demand.

The FiO₂ controller was designed not to respond to sudden falls in SpO₂, which may be related to apnea of prematurity or tube disconnection. Increasing the FiO₂ automatically during such events may be inappropriate and could bear the risk for “overshooting” and thus increased SpO₂ fluctuations. A manual intervention (e.g., stimulation for apnea cessation, reconnection of tubes), however, may be a better choice. As apneas were relatively frequent in our patients, this may explain why the controller had little effect on the number of hypoxic episodes. Despite this, a 35% reduction in the length of hypoxic episodes was observed during automatic FiO₂ control compared with routine manual FiO₂ control, indicating the capability of the system for an early intervention in hypoxic episodes. There are, however, increasing suggestions how to treat acute hypoxic episodes without increasing the risk for overshooting (8, 18). They could be the basis for a further improvement of the system presented here.

CONCLUSIONS

The FiO₂ controller used in the current study significantly increased the proportion of time oxygen saturation levels were within a desired range. Further studies are needed to test the hypothesis that this device will not only reduce workload due to SpO₂ monitoring and FiO₂ control, but can also help to reduce morbidity resulting from unnecessarily high exposure to oxygen or large fluctuations in oxygen levels.

Conflict of Interest Statement: M.S.U. received a travel grant in 2001 and a research support grant in 2004 from Masimo Inc.; W.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; I. M.-H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.F.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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