Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants

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Objective To determine the efficacy and safety of automated adjustment of the fraction of inspired oxygen (FiO_2) in maintaining arterial oxygen saturation (SpO_2) within a higher (91%-95%) and a lower (89%-93%) target range in preterm infants.

Study design Eighty preterm infants (gestational age [median]: 26 weeks, age [median] 18 days) on noninvasive (n = 50) and invasive (n = 30) respiratory support with supplemental oxygen, were first randomized to one of the SpO_2 target ranges and then treated with automated FiO_2 (A-FiO_2) and manual FiO_2 (M-FiO_2) oxygen control for 24 hours each, in random sequence.

Results The percent time within the target range was higher during A-FiO_2 compared with M-FiO_2 control. This effect was more pronounced in the lower SpO_2 target range (62 ± 17% vs 54 ± 16%, $P < .001$) than in the higher SpO_2 target range (62 ± 17% vs 58 ± 15%, $P < .001$). The percent time spent below the target or in hypoxemia (SpO_2 <80%) was consistently reduced during A-FiO_2, independent of the target range. The time spent above the target range or at extreme hyperoxemia (SpO_2 >98%) was only reduced during A-FiO_2 when targeting the lower SpO_2 range (89%-93%). These outcomes did not differ between infants on noninvasive and invasive respiratory support. Manual adjustments were significantly reduced during A-FiO_2 control.

Conclusions A-FiO_2 control improved SpO_2 targeting across different SpO_2 ranges and reduced hypoxemia in preterm infants on noninvasive and invasive respiratory support. *(J Pediatr 2015; ■: ■-■).*

Trial registration ISRCTN 56626482.

Extremely preterm infants often require supplemental oxygen to ensure adequate oxygen delivery to the tissues. The fraction of inspired oxygen (FiO_2) is usually titrated on the basis of the arterial oxygen saturation (SpO_2) measured with pulse oximetry. In addition to targeting normoxemia, avoiding both hypoxemia and hyperoxemia are important goals during oxygen supplementation, as these conditions are associated with, respectively, an increased risk of mortality and retinopathy of prematurity.[1,2] However, SpO_2 control during routine care by manually adjusting the FiO_2 is a challenging task that is often not successful. In fact, infants receiving supplemental oxygen spend approximately 50% of the time within, 30% of the time above, and 20% of the time below the intended SpO_2 range.[3,4]

With the purpose of improving oxygen targeting, an algorithm for automated adjustments of FiO_2 in response to changes in SpO_2 was developed and incorporated into a standard neonatal ventilator. This algorithm improves maintenance of oxygenation within an intended SpO_2 range compared with routine and even dedicated manual FiO_2 (M-FiO_2) control.[5-7] Studies have focused on oxygen dependent, mechanically ventilated infants with frequent episodes of hypoxemia using a single and relatively wide SpO_2 target range.

Our objective was to assess the efficacy of automated FiO_2 (A-FiO_2) control in targeting 2 different, relatively narrow SpO_2 target ranges in more stable, oxygen-dependent infants on both invasive and noninvasive respiratory support. We hypothesized that A-FiO_2 control would increase the time within the SpO_2 target range and reduce both hypoxemia and hyperoxemia compared with

A-FiO_2	Automated FiO_2
FiO_2	Fraction of inspired oxygen
M-FiO_2	Manual FiO_2
SpO_2	Arterial oxygen saturation

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M-FiO_2 control by the clinical staff during routine care, independent of the SpO_2 target range and mode of respiratory support.

Methods

This study was designed as a multicenter, randomized, cross-over clinical trial in 8 European and 1 Canadian level III and IV neonatal intensive care units. The study was approved by institutional review boards in each institution, with written parental informed consent.

Oxygen-dependent preterm infants born with a gestational age <33 weeks and weighing between 0.4 and 4 kg at the time of the study, receiving invasive mechanical ventilation or noninvasive respiratory support were considered eligible for the study. Infants with major congenital anomalies, hemodynamic instability requiring vasopressor treatment or inhaled nitric oxide, or culture proven sepsis within 72 hours prior of enrollment were excluded.

The study consisted of 2 consecutive periods where each enrolled infant was treated with both A-FiO_2 and M-FiO_2 control for 24 hours each. Randomization was done in 2 levels, using sequentially numbered opaque sealed envelopes. First, infants were randomized to 1 of 2 SpO_2 target ranges (89%-93% or 91%-95%), which was maintained for the entire 48-hour study period. Second, infants were randomly assigned to 1 of 2 sequences (A-FiO_2/M-FiO_2 or M-FiO_2/A-FiO_2). The randomization procedure was separate for infants on noninvasive support and those mechanically ventilated and in blocks by center.

Respiratory support was with ventilators (Avea; 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) during both A-FiO_2 and M-FiO_2. This system is approved for clinical use in the countries where the study was conducted.

A-FiO_2 Control

At the start, the A-FiO_2 function adopts the current FiO_2 as the baseline-FiO_2. This is the FiO_2 necessary to keep SpO_2 within the intended target range during relatively stable conditions. Over time, the baseline FiO_2 is slowly and automatically updated, reflecting the trend of the FiO_2 needed to maintain the SpO_2 within the target range. The actual delivered FiO_2 is automatically adjusted (up to once every second) in response to changes in SpO_2. The magnitude and rate of FiO_2 changes are determined by the difference between the actual SpO_2 and the target range, the time outside the range, the SpO_2 trend, and the baseline FiO_2. If deemed clinically necessary, the nursing staff could increase the delivered A-FiO_2 manually by 0.20 for a maximum time of 2 minutes.

SpO_2 alarms were set at 1% below and 1% above the target range with a delay time of 30 seconds. The high SpO_2 alarm could be disabled if the FiO_2 reached 0.21 and the SpO_2 remained within or above the assigned target range for more than 30 minutes. Under these circumstances, the low FiO_2 alarm could also be disabled. If FiO_2 increased again, both alarms were reinstituted. The high FiO_2 alarm was set at 1.0 and, in addition, an alarm was activated when the baseline FiO_2 increased by 0.30. In the event of poor SpO_2 signal quality or signal loss, the automated system assumed a fail-safe state, and the FiO_2 was set at the highest of the following: the current baseline-FiO_2, the median FiO_2 of the preceding 15 seconds, and the backup-FiO_2 level set by the operator.

M-FiO_2 Control

Manual adjustments of the FiO_2 to maintain the SpO_2 target range were done as part of routine care by the attending nursing staff. To limit personnel or center-dependent variability study specific guidelines for M-FiO_2 adjustments were given to the clinical staff (**Appendix**; available at www.jpeds.com). SpO_2 alarm settings were the same as those for the A-FiO_2 period.

Exit Criteria

Infants were to exit the study if they met any of the following criteria: withdrawal of parental consent, transition from invasive to noninvasive respiratory support or vice versa during the study, meeting one of the exclusion criteria during the study period, the attending physician decided it was in the best interest of the patient to exit the study, discharge, transfer to another hospital, or death.

Data and Safety Monitoring

A 3-member independent data and safety monitoring board reviewed the study at 50% enrollment and could recommend termination if adverse events suggested undue risk, the main endpoint was significantly worse during A-FiO_2, futility was demonstrated, or protocol violations compromised scientific validity. A clinical monitor oversaw compliance with the protocol and human subject research and regulatory rules. The monitor reviewed the uploaded data from each individual patient and provided periodic feedback to the sites on protocol compliance and achievement of the SpO_2 targets during manual control. Protocol deviations monitored during the study included but were not limited to inappropriate setting of the A-FiO_2 function, SpO_2 targets, monitoring alarms, or incorrect sequence of FiO_2 control mode.

Data Collection and Analyses

Demographic data including gestational age, birth weight, sex, postnatal age, and weight were collected at time of enrollment. Ventilator settings and monitored variables including SpO_2, FiO_2, pulse rate, and alarms were recorded every 5 seconds by an electronic data logger. In addition, the nurse:patient and patient care procedures that could impact SpO_2 stability were documented. The electronic data were analyzed off-line for each infant for both 24-hour periods using study dedicated software without operator intervention.

The primary endpoint was defined as the proportion of time with SpO_2 within the assigned target range plus the

time spent above this target while FiO_2 was set at 0.21. Secondary endpoints included the proportion of time below or above the SpO_2 target range, the frequency of prolonged episodes (>1 minute) with SpO_2 <80%, <70%, and >98% (excluding time when the FiO_2 was 0.21). In addition, the analysis software counted the number of episodes with SpO_2 <80% (for at least 10 seconds) that were followed by a SpO_2 overshoot during both automated and manual control. An overshoot was defined as SpO_2 readings above the target range for at least 60 seconds over the 2 minutes following the desaturation. Histograms and median SpO_2 and mean FiO_2 levels during each of the two 24-hour periods were calculated for every infant and averaged for all infants. We also calculated the number of M-FiO_2 adjustments during each 24-hour study period.

Sample Size

Based on a previous study showing an 8.2 ± 9.3% increase in the primary endpoint, an estimated enrollment of 80 infants would enable detection of at least a 4.2% difference in the primary endpoint between A-FiO_2 and M-FiO_2 with an alpha of 5% and a beta of 10%. The total enrollment of 80 infants for a sample size of 40 infants assigned to each of the 2 SpO_2 target ranges would enable detection of at least a 5.9% difference in the primary endpoint between A-FiO_2 and M-FiO_2 within each of 2 target range groups.

Statistical Analyses

Primary analysis of the entire study population used a linear mixed model with fixed effects for assigned target range with the intervention (A-FiO_2 and M-FiO_2) as a repeated measure. The linear mixed model with fixed effects was also used to explore the effects of mode of respiratory support and assigned sequence. Dependent variables with skewed distribution were log transformed to align with the distribution assumption of ANOVA. Post hoc analysis assessed the interaction of the intervention (A-FiO_2 and M-FiO_2) and the assigned target range.

Descriptive and secondary analyses included within-subject comparisons of A-FiO_2 vs M-FiO_2 by paired *t* tests or Wilcoxon signed rank test, depending on their distribution. Results are reported as mean and SD or median and IQR. These analyses were conducted using SAS v 9.3 (SAS Institute, Cary, North Carolina) and SigmaXL v 6.1 (SigmaXL, Inc, Toronto, Canada) statistical software. A *P* value of <.05 was considered statistically significant.

Results

Ninety-one infants were enrolled in the study between April 2013 and February 2014. Of these, 11 infants were excluded for the following reasons: electronic data logging failure (n = 2), change in respiratory support mode (n = 5), sepsis (n = 2), hemodynamic instability (n = 1), and need for inhaled nitric oxide (n = 1).

Eighty infants, of whom 30 received invasive mechanical ventilation and 50 noninvasive support, were included in the final analysis (Table I). Ventilator settings during the 24-hour periods of M-FiO_2 and A-FiO_2 control were comparable. One patient was changed from nasal continuous positive airway pressure to nasal intermittent positive pressure ventilation.

Protocol deviations consisted mainly of inappropriate SpO_2 alarm setting. This occurred in 6 infants during M-FiO_2, in 1 infant during A-FiO_2, and in 17 infants during both M-FiO_2 and A-FiO_2. The randomization order was incorrectly applied in 1 infant. In 2 infants assigned to the higher SpO_2 target range (91%-95%), the target range was incorrectly set (90%-96% and 91%-98%) during A-FiO_2 control. In 1 patient, automated control was turned off for 2 hours. Most of these violations were transient and once noticed, corrected by the staff. In 6 patients, the alarm settings were incorrect for the entire 48-hour study period.

Multivariate analysis of the primary endpoint in all 80 infants showed that the proportion of time with SpO_2 within the target range was significantly higher during A-FiO_2 control (62 ± 17%) compared with M-FiO_2 control (57 ± 16%, $P < .001$). The time spent in hypoxemia (SpO_2 <80%) was significantly less during A-FiO_2 (0.9 [0.3-1.9] %) than during M-FiO_2 (2.2 [1.0-4.4] %, $P < .001$) control. The time spent in hyperoxemia (SpO_2 >98%) was also reduced during A-FiO_2 (0.4 [0.1-1.4] %) compared with M-FiO_2 control (0.9 [0.3-2.6] %, $P < .05$).

Although the time spend within the target range was significantly increased during A-FiO_2 control in both SpO_2 target ranges, the mean within subject difference was significantly ($P < .05$) larger in the 89%-93% target group (Δ8%) compared with the 91%-95% target group (Δ4%) (Table II).

The proportion of time spent above the target range was smaller during A-FiO_2 compared with M-FiO_2 control in the 89%-93% but not the 91%-95% SpO_2 target range. The proportion of time spent in severe hyperoxemia (SpO_2 >98%) and the number of episodes of prolonged (>1 minute) hyperoxemia were significantly reduced in favor of A-FiO_2 control in the infants assigned to the 89%-93%, but not the 91%-95% target range (Table II).

Table I. Patient characteristics

Variables	N = 80
Gestational age (wk)	26 (25-28)*
Birth weight (g)	794 (674-950)*
Male sex, no. (%)	38 (48)
Age at data collection (d)	18 (10-29)*
Noninvasive support mode, no. (%)	50 (63)
Mechanical ventilation mode, no. (%) mod (%) malformations	30 (37)
Nurse:patient	1:2 (1:2-1:3)*
FiO_2	0.28 (0.25-0.35)
Number assigned to high/low SpO_2 target	40/40
Number A-FiO_2/M-FiO_2 during first 24 h	45/35

SpO_2 measured with pulse oximetry.
*Median and IQR.

Table II. Time and episodes of normoxemia, hypoxemia, and hyperoxemia for each SpO_2 target group

	SpO_2 target 89%-93% (n = 40)		SpO_2 target 91%-95% (n = 40)	
	M-FiO_2 control	A-FiO_2 control	M-FiO_2 control	A-FiO_2 control
% time in SpO_2 range	54 ± 16	62 ± 17§	58 ± 15	62 ± 17**
% time >SpO_2 range*	25 ± 10	21 ± 13§	19 ± 8	22 ± 13
% time <SpO_2 range	21 ± 8	17 ± 11¶	23 ± 9	17 ± 10§
% time SpO_2 >98%†	0.7 (0.1-1.6)	0.2 (0.0-0.8)§	1.7 (0.7-4.3)	0.7 (0.2-2.1)
% time SpO_2 <80%†	2.6 (1.0-4.3)	1.2 (0.2-2.1)§	2.0 (0.9-5.0)	0.8 (0.3-2.1)§
Episodes SpO_2 >98%, >1 min (n/24 h)†	5 (1-13)	1 (0-4)§	10 (4-27)	4 (1-16)
Episodes SpO_2 <80%, >1 min (n/24 h)†	15 (5-24)	4 (1-12)§	13 (3-24)	4 (1-11)§
Episodes SpO_2 <70%, >1 min (n/24 h)†	1 (0-5)	0.5 (0-1)¶	2 (1-6)	0.5 (0-3)§
SpO_2 (%)‡	91.8 ± 0.8	91.9 ± 1.3	93.5 ± 1.0	93.9 ± 1.0
FiO_2	0.30 ± 0.09	0.31 ± 0.08	0.33 ± 0.09	0.35 ± 0.11**

SpO_2 measured with pulse oximetry.
*Periods with FiO_2 = 0.21 excluded.
†Median and IQR.
‡Mean of the hourly medians.
§$P < .001$ vs M-FiO_2.
¶$P < .01$ vs M-FiO_2.
**$P < .05$ vs M-FiO_2.

In both high and low target range groups, the proportion of time spent with SpO_2 below the target range and the proportion of time in hypoxemia (SpO_2 <80%) were significantly reduced during A-FiO_2 compared with M-FiO_2 control. Furthermore, in both target range groups, the number of prolonged episodes of hypoxemia and severe hypoxemia (SpO_2 <70%) were significantly reduced during A-FiO_2.

The number of episodes of SpO_2 <80% that were followed by an SpO_2 overshoot did not differ between automated and manual control in the high (6 [2-16] vs 5 [1-14]) and low (8 [2-26] vs 7 [1-19]) SpO_2 target range.

The histograms of SpO_2 values during the manual and automatic control periods showed a left shift in the SpO_2 distribution in the lower compared with the higher target range group during both manual and automatic FiO_2 control (**Figure**).

The median SpO_2 values of the entire 24-hour period did not differ between A-FiO_2 and M-FiO_2 control in both SpO_2 target range groups (**Table II**). The median SpO_2 values were near the center of the assigned target range during both automatic and M-FiO_2 control periods.

In the higher SpO_2 target range group, the mean FiO_2 over the 24-hour period was slightly but consistently higher during A-FiO_2 control than during M-FiO_2 control. In contrast, mean FiO_2 values did not differ between A-FiO_2 and M-FiO_2 control in the low target range group (**Table II**).

The number of M-FiO_2 adjustments per 24 hours was significantly lower during A-FiO_2 control compared with M-FiO_2 in both the 89%-93% SpO_2 target range (1 [0-3] vs 102 [73-173], $P < .001$) and the 91%-95% SpO_2 target range (1 [0-3] vs 109 [79-156], $P < .001$).

There were no statistically significant effects associated with sequence of FiO_2 control. Furthermore, post hoc analyses revealed no differences in treatment effects of A-FiO_2 vs M-FiO_2 control in the subgroups of infants receiving noninvasive and invasive respiratory support (**Tables III** and **IV**; available at www.jpeds.com).

Discussion

Automated control of the FiO_2 in preterm infants receiving invasive and noninvasive respiratory support results in more time spend within the intended SpO_2 target range. This effect is present across different, relatively narrow SpO_2 target ranges and during both invasive and noninvasive respiratory support.

Our finding that A-FiO_2 control improves SpO_2 targeting is consistent with previous studies using the same and other automated systems.[5-8] However, the treatment effect in terms of time spent within the SpO_2 target range is smaller than previously reported.[5,7] This may be, in part, explained by the fact that previous studies only included infants on mechanical ventilation requiring supplemental oxygen and with frequent episodes of hypoxemia. In our study, eligibility was based solely on the need for supplemental oxygen, resulting in the inclusion of more stable infants as also reflected by higher mean gestational age and the lower FiO_2 at the time of the study. The increased stability probably also explains the relatively higher proportion of time within the intended SpO_2 target during both M-FiO_2 and A-FiO_2 control compared with previous studies. Furthermore, and in contrast to previous studies, the nursing staff received clear guidelines on how to titrate the FiO_2, which may have improved the efficacy of manual control.

Previous studies with the same automated system showed that improved SpO_2 targeting was mainly the result of a reduction in the time above the target range.[5-7] In 2 of these studies, the time below the target range was increased during A-FiO_2 compared with M-FiO_2 control.[6,7] Interestingly, in the present study A-FiO_2 significantly decreased the time below the target range compared with M-FiO_2 control, and the time above the SpO_2 target range during A-FiO_2 was similar or lower compared with M-FiO_2 control in the 91%-95% and 89%-93% target range group, respectively. Reassuringly, the proportion of time and the number of

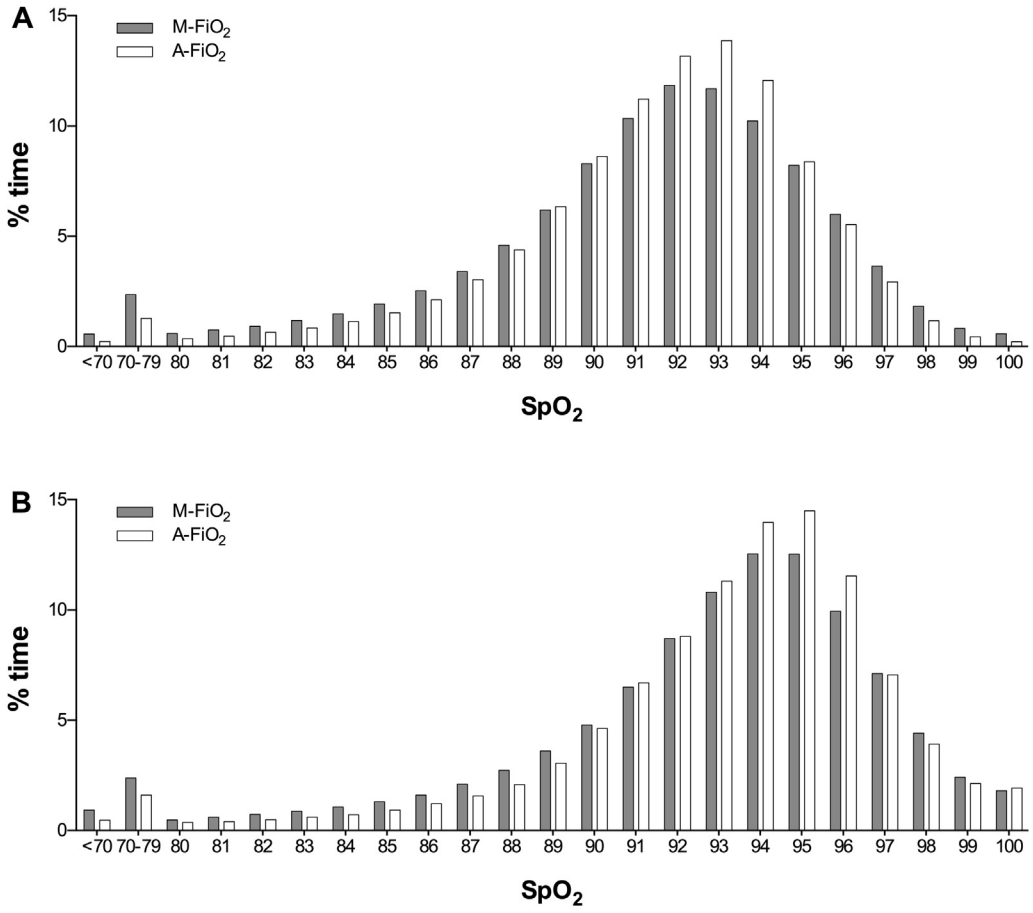

Figure. Histograms of SpO_2 measured with pulse oximetry during 24 hours of M-FiO_2 and A-FiO_2 control in the groups of infants assigned to the SpO_2 target range of **A,** 89%-93% and **B,** 91%-95%. Data obtained while receiving 21% inspired oxygen are included in the histograms.

episodes of severe hyperoxemia (SpO_2 >98%) tended to be lower during A-FiO_2 control in both SpO_2 subgroups. Again, these differences with prior studies may be explained by the inclusion of more stable patients and the guidelines given to the nursing staff for manual control. The later may have resulted in more consistent weaning of FiO_2 in case of hyperoxemia compared with what would normally occur during routine care.

Although A-FiO_2 consistently increased the time within both target ranges, the treatment effect was more prominent in the lower SpO_2 target range (Δ8%) than in the higher SpO_2 target range (Δ4%) group. Interestingly, this difference in treatment effect appears to be caused by less effective M-FiO_2 control to keep the lower SpO_2 target range. A more detailed analysis showed that the reduced efficacy of manual control to keep the lower SpO_2 target range resulted from an increased time above the target range and in spite of the use of specific guidelines. This is in agreement with SpO_2 distribution data from recent trials on oxygen targeting, which showed a right sided tendency that is more evident in the lower target range groups.[1,2,9] The reasons why it is harder to manually maintain a lower target range are not entirely clear. Increased frequency of fluctuations in oxygenation with the lower SpO_2 target ranges has been reported.[10] It is possible that the FiO_2 increases in response to hypoxemia might have been unnecessarily long resulting in hyperoxemia[11] or that some degree of tolerance of high SpO_2 existed during manual control in an attempt to prevent or attenuate the episodes of hypoxemia.

This study showed that keeping the higher target range required a higher FiO_2 and resulted in an increase in significant hyperoxemia, regardless of the method of FiO_2 control. Therefore, even a small change in target range, if carefully applied, results in potential clinically relevant increases in hyperoxemia and oxygen exposure. In the present study, this was particularly evident during M-FiO_2 control, and it is likely to be even more striking during routine care.

At first glance the improvement in SpO_2 targeting during A-FiO_2 might seem modest. However, it is important to emphasize that A-FiO_2 was only studied for 24 hours, even though most preterm infants remain oxygen-dependent for months. The extrapolation of the results to a long time frame does result in a significant and clinically relevant improvement in SpO_2 targeting.

The present study has some limitations. The efficacy of A-FiO_2 control was evaluated during a 48-hour study period, which may not be representative of the many weeks that most preterm infants require supplemental oxygen. Also, the nursing staff received specific guidelines to manually adjust the FiO_2 in response to hypoxemia and hyperoxemia, and they were not blinded to the mode of FiO_2 control and were aware of the recordings made for study purposes. For these reasons, the study conditions may not represent routine care and, instead, represent improved care. Finally, because of the cross-over design, the infants that were included in the analysis had to be clinically stable during the entire 48-hour study period. For this reason, 9 patients exited the study because including these infants in the analysis might obscure or augment the true treatment effect of A-FiO_2 control on SpO_2 targeting.

Despite these limitations, this study has important clinical implications. Based on the reported increase in mortality when targeting a lower SpO_2 range (85%-89%), it has recently been suggested to keep the SpO_2 within the relatively narrow range of 90%-95% in preterm infants with a gestational age less than 28 weeks.[12] However, the oxygen targeting trials also showed that infants only spent approximately 45% of the time within the target SpO_2 range of 91%-95% during M-FiO_2 control, whereas the time these infants spent in severe hyperoxemia (SpO_2 >98%) or hypoxemia (SpO_2 <80%) was nearly 4%. Using the same target range of 91%-95%, the present study shows that A-FiO_2 control maintained the SpO_2 within the target range 62% of the time while reducing the time in severe hypoxemia or hyperoxemia to less than 1%.

An important finding of this study is that tighter SpO_2 control during A-FiO_2 control can be achieved with significantly less workload for the nursing staff. The number of M-FiO_2 adjustments was dramatically reduced by almost 100%. This additional benefit of A-FiO_2 control may be especially important in clinical settings where staffing resources are limited.

This study confirmed that A-FiO_2 control is feasible and effective during mechanical ventilation but also documented its feasibility and efficacy in a large group of patients on noninvasive respiratory support, which nowadays is the most widely used mode of support in preterm infants. These findings are similar to those reported in a recent study where most infants were receiving noninvasive support.[13] In conclusion, this study shows that A-FiO_2 control improves SpO_2 targeting across different SpO_2 target ranges and during different modes of respiratory support in preterm infants. Future studies need to investigate if these beneficial effects will also translate into improved clinical outcome. ■

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Appendix. Guidelines for manual adjustment of FiO_2 to maintain target range of SpO_2

a) If SpO_2 >target range
   i. Reduce FiO_2 by 0.02-0.1 within 5 minutes or sooner if SpO_2 >98%.
   ii. Repeat within 5 minutes as long as SpO_2 remains above target range or sooner if SpO_2 >98%.
b) If SpO_2 <target range, assess the infant within 30-120 seconds and if required:
   i. Increase FiO_2 by 0.05-0.20 manually using the FiO_2 dial or using the "Increase O_2" button in Avea (preset to 0.20). It is not necessary to increase FiO_2 if SpO_2 is trending up.
   ii. Increase FiO_2 every 30-120 seconds according to response and as long as SpO_2 remains below the target range. It is not necessary to increase FiO_2 if SpO_2 is trending up.
   iii. If SpO_2 <80%, assess the infant and increase FiO_2 by 0.20-0.40 or by a greater amount if bradycardia is concurrently observed.
   iv. Continue to assess infant until SpO_2 returns to assigned range and when this occurs, return FiO_2 to the level before the decrease in SpO_2.
c) Notify clinical attending team if there is a persistent increase in FiO_2 >0.30 from baseline over a 2 hours period needed to maintain the SpO_2 in the target range. If SpO_2 >target range, see a) above.

Table III. M-FiO_2 and A-FiO_2 control in infants receiving noninvasive respiratory support

	SpO_2 target 89%-93% (n = 25)		SpO_2 target 91%-95% (n = 25)	
	M-FiO_2 control	A-FiO_2 control	M-FiO_2 control	A-FiO_2 control
% time in SpO_2 range	51 ± 14	60 ± 17§	57 ± 16	61 ± 18¶
% time >SpO_2 range*	26 ± 10	24 ± 14	19 ± 8	21 ± 14
% time <SpO_2 range	23 ± 7	17 ± 11§	24 ± 9	18 ± 10§
% time SpO_2 >98%†	0.9 (0.2-1.5)	0.3 (0.1-0.8)¶	2.0 (0.8-4.6)	1.1 (0.2-4.5)
% time SpO_2 <80%†	3.4 (1.7-4.3)	1.4 (0.4-2.0)§	2.0 (1.2-4.5)	0.9 (0.3-2.0)§
Episodes SpO_2 >98%, >1 min (n/24 h)†	6 (1-10)	1 (0-6)§	12 (5-31)	4 (2-18)
Episodes SpO_2 <80%, >1 min (n/24 h)†	15 (8-24)	6 (2-11)§	12 (4-23)	4 (1-11)§
Episodes SpO_2 <70%, >1 min (n/24 h)†	2 (0-5)	1 (0-1)¶	2 (1-6)	0 (0-3)¶
SpO_2 (%)‡	91.7 ± 0.8	92.1 ± 1.2	93.5 ± 1.1	93.9 ± 1.3
FiO_2	0.28 ± 0.08	0.30 ± 0.09**	0.31 ± 0.08	0.34 ± 0.11¶

SpO_2 measured with pulse oximetry.
*Periods with FiO_2 = 0.21 excluded.
†Median and IQR.
‡Mean of the hourly medians.
§$P < .001$ vs M-FiO_2.
¶$P < .01$ vs M-FiO_2.
**$P < .05$ vs M-FiO_2.

Table IV. M-FiO_2 and A-FiO_2 control in infants receiving invasive respiratory support

	SpO_2 target 89%-93% (n = 15)		SpO_2 target 91%-95% (n = 15)	
	M-FiO_2 control	A-FiO_2 control	M-FiO_2 control	A-FiO_2 control
% time in SpO_2 range	58 ± 18	66 ± 16¶	60 ± 15	63 ± 17
% time >SpO_2 range*	23 ± 11	17 ± 10	19 ± 8	22 ± 13
% time <SpO_2 range	18 ± 8	17 ± 11	21 ± 9	15 ± 9§
% time SpO_2 >98%†	0.2 (0.1-2.7)	0.1 (0.0-0.9)**	0.7 (0.4-3.7)	0.6 (0.2-1.6)
% time SpO_2 <80%†	0.8 (0.6-4.3)	0.4 (0.2-2.7)**	2.3 (0.7-6.2)	0.6 (0.3-2.5)¶
Episodes SpO_2 >98%, >1 min (n/24 h)†	2 (0-18)	1 (0-4)**	6 (3-14)	4 (1-11)
Episodes SpO_2 <80%, >1 min (n/24 h)†	7 (3-33)	3 (1-22)	13 (2-33)	3 (2-11)¶
Episodes SpO_2 <70%, >1 min (n/24 h)†	1 (0-10)	0 (0-3)	2 (1-13)	1 (0-3)¶
SpO_2 (%)‡	91.9 ± 0.9	91.6 ± 1.3	93.5 ± 8.2	94.0 ± 1.1**
FiO_2	0.33 ± 0.10	0.33 ± 0.07	0.36 ± 0.11	0.36 ± 0.10

SpO_2 measured with pulse oximetry.
*Periods with FiO_2 = 0.21 excluded.
†Median and IQR.
‡Mean of the hourly medians.
§$P < .001$ vs M-FiO_2.
¶$P < .01$ vs M-FiO_2.
**$P < .05$ vs M-FiO_2.