

Quicker response results in better SpO₂ control – a comparison of 3 FiO₂-titration strategies in ventilated preterm infants

Maria Wilinska¹, Thomas Bachman², Janusz Swietlinski³, Grzegorz Jakiel⁴

¹ Medical Centre of Postgraduate Education, Warsaw, Poland

² Czech Technical University of Prague

³ Silesia Institute of Mother and Newborn, Chorzów, Poland

⁴ I Department of Obstetrics and Gynecology, Medical Centre of Postgraduate Education, Warsaw, Poland

Wilinska M, Bachman T, Swietlinski J, Wasko A. Quicker response results in better SpO₂ control – a comparison of 3 FiO₂-titration strategies in ventilated preterm infants. *Ann Agric Environ Med*. 2015; 22(4): 708–712. doi: 10.5604/12321966.1185781

Abstract

Introduction. The impact of SpO₂ target ranges (TR) has been carefully studied; however, reports suggest a wide variation among infants and centres in maintaining the intended range. Little is known about the effectiveness of different approaches to manual control. Auto-SpO₂ controllers are now available which show promise.

Objective. The aim was to compare two different protocol-driven manual strategies with different response requirements to each other, and a faster automated system (AveaCLiO₂, Yorba Linda, CA, USA).

Materials and methods. In a crossover design, each of the three FiO₂/SpO₂ approaches was implemented in three randomly assigned consecutive 2.5-hour runs. The two manual strategies (Attentive and Observational) were implemented by a trained operator. The primary endpoints were time in 1) SpO₂ TR, 2) < 80% SpO₂ and 3) >98% SpO₂.

Results. Fifteen studies were completed. All three approaches resulted in good control, with time in the target range >60%. CLiO₂ use reflected reduced exposure at the two SpO₂ extremes. *Post hoc* analysis determined that the differences were more marked in the infants with more frequent desaturations. Likewise, in this group, the Attentive strategy performed better than the Observative.

Conclusions. All three approaches provided excellent control of SpO₂ in infants with infrequent desaturations, significantly better than typical routine care. In hard to manage infants with frequent desaturations, faster response appeared to result in better control. The potential of automating the tedious error prone FiO₂ adjustment offers significant promise. If manual titration of FiO₂ is to remain the usual method of care, additional studies are needed to identify optimal approaches.

Key words

newborn, clinical study, saturation targeting

INTRODUCTION

Pulse oximetry has been the standard for care in neonatology for more than two decades. While originally used primarily to monitor hypoxaemia, the need to utilize an SpO₂ target range (SpO₂-TR) that also avoided hyperoxaemia became apparent a decade ago [1, 2, 3]. Controlled trials have shown that an SpO₂-TR that reduces hyperoxaemia result in significant reductions in pulmonary and retinal morbidity [3, 4, 5]. However, trials have also suggested that lowering the SpO₂-TR too far may increase mortality [4, 5]. While it is clear that the SpO₂-TR of a decade ago were too high, there is no consensus on the ideal range. A prospectively designed evaluation of the data for the three largest SpO₂-TR trials will provide much needed information [6], but the application of that insight will be complicated by the marked variation of manual adjustment of FiO₂ in routine care.

Another very large controlled trial suggests that these changes in outcomes are also related to the actual SpO₂ exposure and not the intended target range [7]. Reports suggest that infants on respiratory support spent only about half of the time in the target range, and also that there is

considerable variability among infants as well as centres [8, 9]. In recent large controlled trials, the median SpO₂ was often outside the intended target range [3, 4, 5, 7]. Many studies have also documented serious problems with staff compliance with unit policy in SpO₂ targeting [10, 11, 12, 13]. While some have suggested benefits of not aggressively adjusting FiO₂ [1, 14, 15] there is a paucity of literature describing or evaluating protocol driven FiO₂-titration strategies. Clearly, these practical considerations complicate the selection of the best clinical SpO₂-TR.

Computer control of the delivered volume and synchronization of respiratory support are common in neonatal ventilators. Several have reported on the feasibility of automatically adjusting FiO₂ in response to SpO₂ [16, 17, 18]. Automation makes possible FiO₂ adjustments much more frequently than practical during routine care, and also is attentive 24 hours per day. One such system is now commercially available [19, 20].

OBJECTIVE

The aim of the study was to explore the differences among two different protocol-driven FiO₂ titration control strategies implemented with a trained operator and an automated control system. It is believed that a quicker response to values outside the intended SpO₂-TR will result in better control.

Address for correspondence: Maria Wilinska, Medical Centre of Postgraduate Education, Czerniakowska 205/5, 00-436 Warsaw, Poland
E-mail: wilinska.maria@gmail.com

Received: 22 August 2013; accepted: 06 January 2014

MATERIALS AND METHOD

The study was conducted in the NICU of the Medical Centre of Postgraduate Education in Warsaw Poland. It was approved by the institution's Bioethics Committee, and required informed consent.

Intubated infants were eligible for the study if they exhibited 4 or more significant desaturations (<80% SpO₂) in the 8 hours prior to enrollment, and were expected to be able to complete the three 8-hour studies. Eligible infants were enrolled if the Avea-CLiO₂ and research staff were available.

This study used a leading neonatal ventilator (Avea, CareFusion, Yorba Linda CA) with a new option (CLiO₂) designed to automatically adjust the FiO₂ towards maintaining an operator set SpO₂-TR. During the study, prior to and following the study, this device was in routine use in the NICU. The system and its performance has been previously described [19, 20].

CLiO₂ utilizes a sophisticated patented multi-parameter control system. While monitoring SpO₂ virtually continuously, CLiO₂ compares the SpO₂ to the clinician selected target range. Every second, it considers a change to the FiO₂. The FiO₂ change is based not only on the duration and magnitude/depth of the episode, but also on the trajectory of the SpO₂. Adjustments are not linearly related to the size, but rather the severity (magnitude, duration and acceleration) of the excursion. CLiO₂ considers a baseline FiO₂ level to facilitate returning to the target range as quickly as possible and minimizing overshoot beyond the target range. The baseline FiO₂ is initially set by the clinician and updated automatically based on the infant's course. The time constant of the update is based on the infant's SpO₂ stability; the more stable, the more quickly the baseline is changed. In addition, when the SpO₂ is within the desired target range, the FiO₂ is slowly wound down, not up, to bring it towards the middle of the desired range. Finally, in addition to traditional SpO₂ alarms, CLiO₂ also offers two other safety features. First, should CLiO₂ need to increase FiO₂ significantly to maintain SpO₂ in the target range, an alert is provided to the clinician. Second, should the oximeter signal drop out, or signal be of poor quality, CLiO₂ returns the FiO₂ to the baseline FiO₂ or the most recent FiO₂, or the backup FiO₂ set by the operator, whichever is higher.

The three control approaches were labeled Attentive, Observational and CLiO₂. The prescribed SpO₂ target range for all three was 87%-93% SpO₂. Prior to any FiO₂ adjustment, consideration was given to oximeter sensor integrity, the need for patient stimulation and other potential issues. A clinician dedicated to FiO₂-titration, with no other clinical responsibilities, implemented the two manual approaches. The response guideline for the Attentive strategy was to respond within 0.5 minutes when SpO₂ was <80% or greater than 98%. For the Observative strategy, the intended response was 1 and 3 minutes. The Attentive approach was intended to result in much more responsive management than is practical in routine care. The Observational was intended to be similar to typical, but vigilant, routine care. FiO₂ adjustments were to be in 0.10 increments in response to severe, otherwise smaller episodes. The time guidelines applied to the initial response to an episode, and also to the delay following an adjustment, prior to making an additional adjustment.

Following enrollment and randomization, the infants were studied 3 times, each for 3 consecutive 2.5-hour periods, on

different days. The order of the 3 FiO₂-control interventions for each day was decided by a pre-determined randomized sequence.

There were three prospective primary endpoints: percent of study time:

- 1) within the SpO₂-TR, including time above it when the FiO₂ was 0.21;
- 2) hypoxaemia (SpO₂ <80%);
- 3) hyperoxaemia (SpO₂ >98%, excluding the time when the FiO₂ was at 0.21). Descriptive endpoints included the median SpO₂, median FiO₂, distribution of SpO₂ exposure and manual response times to episodes outside the SpO₂-TR.

Analysis indicated that 15 2.5-hour studies of each of the three strategies would be well-powered (>95% power, p<0.01) to detect the differences in the percent time in the TR seen in other studies comparing CLiO₂ with manual FiO₂ control.

A wide variation was observed in the number of severe desaturations seen among the 2.5-hour study epochs, and an apparent relationship between that rate and the relative effectiveness of SpO₂ control. Therefore, on a *post hoc* basis, the studies were stratified at the median with the rate of desaturations (2.5 <80% SpO₂/hour) to evaluate the relative difference in effectiveness among the 3 strategies.

Differences in the means and proportions of percent time in the respective ranges between the three strategies were evaluated using a two-tailed paired t-test. P<0.05 was considered statistically significant. 95% confidence limits were used rather than explicit calculation of probability of difference (p) to explore difference in the *post hoc* strata, because it was felt that the knowledge of the uncertainty of the means and proportions was more useful and appropriate for a small exploratory evaluation. Confidence limits that did not overlap were considered to infer statistical significance. Mean, standard deviation, median and range, as appropriate, were calculated for the descriptive variables. All analysis was conducted using Excel (v 12.3.2 Microsoft Redmond, WA, USA)

RESULTS

Between April – October 2011, 5 infants successfully completed the 3 days of study. The data from one epoch (CLiO₂) was corrupted during recording and not available for analysis. Thus, 44 epochs representing 110 hours of SpO₂ control were analyzed (37.5 hours for both Observative and Attentive, and 35 hours for CLiO₂). Characteristics of the infants are summarized in Table 1.

To characterize the implementation of the 2 manual FiO₂ strategies, the length of episodes that were not addressed with an adjustment and also the time response of adjustments when made were reviewed we reviewed (Tab. 2). Most of the SpO₂ episodes outside the target range that were not associated with an adjustment were very short. There was a clear difference, as intended, between the time to respond for the 2 strategies.

A histogram of the SpO₂ exposure during the 3 strategies is presented in Figure 1. The histogram suggests that all 3 approaches to FiO₂-titration resulted in good control of SpO₂, although the difference in the median SpO₂ and extreme SpO₂s is apparent.

Table 1. Patient characteristics

	median (range)
EGA – weeks	27 (24–36)
age at entry – days	8 (3–23)
study weight – grams	0.94 (0.70–2.06)
PIP – cm H2O	19 (17–25)
PEEP – cm H2O	5 (5–5)
Respiratory rate – /min	55 (35–65)
FiO2	0.31 (0.23–0.40)
SpO2 %	94 (92–94)

All the baseline demographic and physiological parameters are presented as median and (range)

Table 2. Manual strategy response

	Attentive	Observative
Unadjusted Episodes (sec)	20	45
Time to Adjustment		
SpO2 <80% or >98% (sec)	40	130
SpO2 <87% or >93% (sec)	75	195

Response times are the 75th percentile

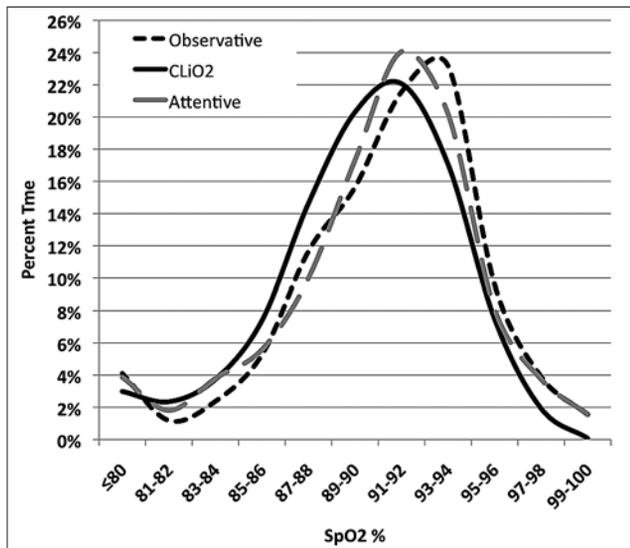
**Figure 1.** Histogram of SpO2 Exposure. Polled distribution of SpO2 in 2% bins for each of the 3 control strategies

Table 3. presents the tabulation of the endpoints. They confirm good control, as reflected not only by the percent time in the SpO2-TR (>60%), but also in the low percent time spent at the extreme SpO2s. During the use of CLiO2, the time with SpO2>98% and V80% was significantly lower.

The differences in the 3 endpoints categorized into the 2 strata based on frequency of severe desaturations are shown in Figure 2. Twenty-three of the 44 2.5-hours epochs were above the median frequency of severe desaturations. (6 Observative, 9 Attentive and 8 CLiO2). The differences among approaches in this group with more frequent desaturations were clinically relevant for all 3 endpoints. In the 21 more stable epochs, the differences were probably not clinically relevant; the trend, however, was similar.

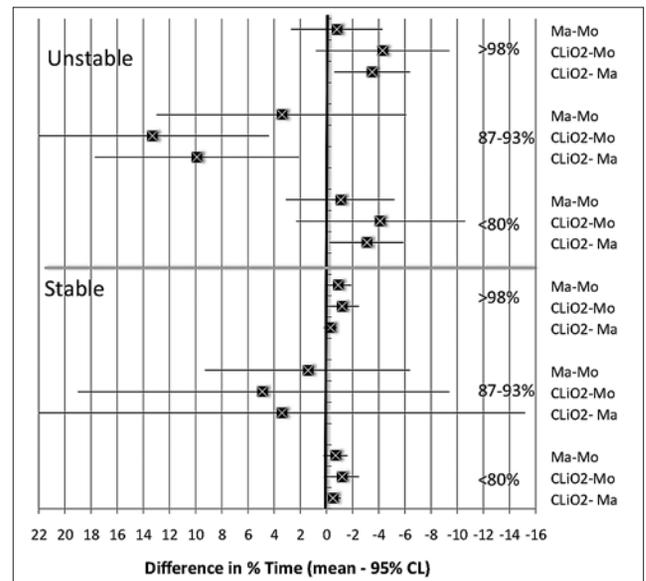
Table 3. SpO2 control parameters

	Attentive	Observative	CLiO2
Primary Endpoints			
% time target range	65.4% (15.8)	62.7% (14.9)	66.3% (18.8)
% time hyperoxaemia	1.3% (1.8)	1.7% (2.6)	0.2% (0.3)*
% time hypoxemia	3.2% (2.9)	3.9% (4.0)	2.2% (2.3)**
Descriptive Endpoints			
SpO2 %	90.9 (0.8)	91.3(1.1)	90.3 (2.4)
FiO2	.333 (0.040)	.326(0.085)	.317 0.069)
SpO2<80% /hr	3.1 (3.2)	2.6 (2.5)	(3.1)

All data presented as mean and stdev. Hypoxaemia is defined as SpO2 <80%, SpO2 >98% excluding time when FiO2 is room air. Target range includes SpO2 87–93% and SpO2>93% when the FiO2 is room air.

*Differences between Attentive (0.022) and Observational (0.025).

**Difference with Observative (0.044); other differences were not significant <0.05.

**Figure 2.** Difference among the 3 control strategies according to infant stability. The box is the pooled mean difference, and the whiskers represent the 95% confidence limits of the difference. Infants below the mean rate of severe desaturation of 2.5/hr were categorized as stable.

Ma – Attentive manual strategy; Mo – Observative manual strategy.

DISCUSSION

The presented study compared 3 FiO2-titrations strategies in ventilated preterm infants experiencing periodic severe desaturations. One strategy was an automated system (CLiO2) which made reasoned FiO2 adjustments every second. The other 2 were manual strategies implemented by a trained clinician, that made protocol-driven adjustments within a minute or several minutes, respectively. All 3 approaches were effective. It was found that the use of CLiO2 resulted in significantly decreased time with SpO2 at SpO2 extremes. In periods with more frequent desaturations, CLiO2 use also markedly increased time in the intended target range. There were also potentially clinically relevant differences in the effectiveness between the 2 manual strategies in periods with more frequent desaturations, favouring the Attentive. In the aggregate, these findings support the authors' premise that faster response to episodes outside the intended range, whether provided by an attentive operator or automatically, results in better SpO2 control.

To the best of the authors' knowledge, the presented study is the first to compare the impact of FiO₂-titration strategies on SpO₂ control. It was found that a quicker approach to responding, especially as seen with CLiO₂, resulted in clinically important increases in effectiveness. This finding is logical, but in contrast to some reports of improved outcomes associated with more permissive SpO₂ targeting strategies implemented in routine care [1, 14, 15]. These reports speculated that frequent increases to FiO₂ in response to drops in SpO₂ are often not met with equally attentive reductions in FiO₂ in the face of high SpO₂. This is probably correct, and highlights the importance of pragmatic issues associated with selecting optimal approaches for manual SpO₂ control. In a related analysis, the authors of the current study reported that the time to manage either of their manual strategies was not practical, even with 1:1 nursing, in patients with frequent desaturations [21].

Both manual strategies, as planned, were more responsive than those observed in the multicentre trial by Claire, et al. [20, personal communication]. The difference was most marked for episodes of high SpO₂. Laptok reported on experience with 72 infants during their course of treatment, and found that the time in the SpO₂-TR was less than 50% in about a quarter of the infants [8]. Hagadorn reported dramatic differences in a sample of 84 infants from 14 centres [9]. Looking at individual infants, the interquartile ranges for time in, above and below the SpO₂-TR, were wide (6–75%, 5–90%, 0–47%, respectively) [9]. These suggest that the 2 manual FiO₂ strategies in the presented study resulted in better control of SpO₂ than is typical in routine FiO₂ titration.

Significant problems in compliance and application of SpO₂ targeting have been reported in the results of major trials, specifically a bias in routine care that results in a median SpO₂ at the top or above the intended target range [4, 5, 20]. It is not clear whether this bias is a result of lapses in attentiveness to high SpO₂, or a tendency to keep SpO₂ higher to avoid desaturations, with the unintentional consequence of increasing hyperoxaemia. In the current study, a small upward shift in median SpO₂ above the midpoint of the TR was observed in the 2 protocol-driven strategies, but this was not of the same magnitude as reported in the other studies. Better compliance is no surprise when considering the use of a trained operator. The obtained results suggest that an important part of this problem is related to attentiveness in addressing high SpO₂ readings.

Of course, median SpO₂ is the first, but only a crude measure of SpO₂ exposure. It was found that the time in the extreme ranges of SpO₂ (<80% >98%) were relatively low for all 3 strategies, although better with CLiO₂. The BOOST trial reported improved outcomes with increased time in a lower SpO₂-TR, and less time at very high SpO₂s (SpO₂>98% reduced from >20% – <10%) [3]. Similar exposure data is not yet available from the SUPPORT, BOOSTII or COT trials. However, it has been reported that poorer survival in the SUPPORT trial was associated with increased time <80% SpO₂ [22]. All 3 of the presented FiO₂ titration strategies resulted in an average SpO₂ near the midpoint of the target range, and markedly less time in hyperoxaemia than reported in other studies.

The presented results are consistent with other studies of CLiO₂. In a single centre pilot study, CLiO₂ performed better than a trained operator not using a specific strategy guideline

[18]. A recent multicentre trial of CLiO₂, compared to routine care in 32 infants over two 24-hour periods, reported that the infants were in the target SpO₂ range for 47% of the time during CLiO₂ and 40% during routine care. The trial studied a group of relatively unstable infants [20] and reported that the primary reason for the CLiO₂ increased time in the target range was a reduction in the percent time above the target range. In that study, the infants averaged about 4.5 significant desaturations per hour. They also reported, consistent with our findings, a reduction in time in severe hyperoxaemia (>98% SpO₂) associated with CLiO₂. In that study as well as in the current one, the percent time >98% SpO₂ was less than 1% during use of CLiO₂. However, the trial results also reported an increase in the time associated with SpO₂ below the Target Range during use of CLiO₂, as compared to manual use. This effect was not apparent in the presented study. It is believed that this different finding was a result of the higher median SpO₂ (about 2% SpO₂) in routine care, a finding not seen during either of the manual strategies.

Only infants who had experienced 4 or more severe desaturations in the 8 hours before entry were studied. About a half of these infants experienced more than 10 times that many desaturations.

However, some comments about the more stable epochs are warranted. While during all 3 FiO₂-control methods the percent time at extreme SpO₂ was very small, the infants still spent a significant amount of the time, more than a quarter, outside the SpO₂-TR, with such episodes occurring every 5 minutes. This is hardly stable. It is therefore suggested that a less attentive approaches to FiO₂-control, typical of routine care, would result in much more time outside the target range, as referred to in reports cited above [8, 9].

Limitations of the study. Primarily, only 5 subjects were studied over a short period of time. Nevertheless, it is encouraging that the general trends of relative effectiveness were consistent with that shown in a larger study over longer periods of time [19]. The shorter length runs were necessitated by the need for a trained operator. Furthermore, the results reflect only the 2 FiO₂-titration strategies tested. Other strategies might implement different response times and magnitudes of FiO₂ changes. A less responsive approach might also have demonstrated greater difference in relative effectiveness. Studies comparing CLiO₂ to less responsive routine care suggest this to be the case [19, 20]. Finally our *post hoc* categorization of patient stability could introduce bias. A more careful study directed at this issue may be warranted.

CONCLUSIONS

In conclusion, there appears to be clinically relevant differences in the presented SpO₂ control approaches. Quicker responses to episodes outside the intended SpO₂ range resulted in better control. The differences were more pronounced in infants who experienced more frequent severe desaturations, which were certainly clinically relevant. The potential for automating the tedious and error prone manual titration of FiO₂ offers significant promise of improved SpO₂ control and significant labour savings. There is a need for further evaluation of actual FiO₂ management and its association with SpO₂ exposure.

What is known to-date about this subject:

- shifts in SpO₂ exposure markedly effect neonatal outcome, but the optimal desired range is unknown;
- clinician titration of FiO₂ to maintain desired SpO₂ ranges is not highly effective as a result of problems with compliance and attentiveness;
- automated FiO₂ controllers offer promise of better effectiveness and labour savings.

The presented study therefore adds a more timely reasoned response to episodes of SpO₂ excursion which result in better SpO₂ control, whether provided automatically or manually, and a quicker automated control may significantly reduce both hyper- and hypoxaemia.

REFERENCES

1. Tin W, Milligan WA, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 2001; 84: 106–10.
2. Deulofeut R, Critz A, Adams Chapman I, Sola A, et al. Avoiding hyperoxia in infants < 1250 g is associated with improved short term and long term outcomes. *J Perinatology* 2006;26:700–05.
3. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen saturation targets and outcomes in extremely preterm infants. *N Engl J Med.* 2003; 349: 959 –67.
4. The BOOSTII United Kingdom, Australia, New Zealand Collaborative Groups. Oxygen saturation and outcomes in preterm infants. *N Engl J Med.* 2013; 368(22): 2094–104.
5. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD, Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010; 362: 1959–69.
6. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. Askie LM, Brocklehurst P. *BMC Pediatrics* 2011; 11(6): 1–9.
7. Schmidt B, Whyte R, Aszalos, et al. Effects of targeting higher vs lower oxygenation saturations on death or disability in extremely preterm infants. *JAMA* 2013; 309(20): 2111–20.
8. Laptook AR, Salhab W, Allen J, et al. Pulse oximetry in very low birth weight infants: Can oxygen saturation be maintained in the desired range? *J Perinatol.* 2006; 26: 337–41.
9. Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics* 2006; 118: 1574–82.
10. Bitan Y, Meyer J, Shinar D, Zmora E. Nurses' reactions to alarms in a neonatal intensive care unit. *Cogn Tech Work.* 2004; 6: 239–46.
11. Armbruster J, Schmidt B, Poets CF, Bassler D. Nurses' compliance with alarm limits for pulse oximetry: qualitative study. *J Perinat.* 2009; 189: 1–4.
12. Clucas L, Doyle LW, Dawson J, et al. Compliance with alarm limits for pulse oximetry in very preterm infants. *Pediatrics* 2007; 119: 1056–60.
13. Nghiem TH, Hagadorn JI, Terrin N, et al. Nurse opinions and pulse oximeter saturation target limits for preterm infants. *Pediatrics* 2008; 121: 1039–46.
14. Chow LC, Wright KW, Sola A, et al. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003; 111: 339–45.
15. Ford SP, Leick-Rude MK, Meinart KA, et al. Overcoming barriers to oxygenation saturation targeting. *Pediatrics* 2006; 118: s177–86.
16. Urschitz MS, Horn W, Seyfang A, et al. Automatic control of the inspired oxygen fraction in preterm infants: a randomized crossover trial. *Am J Respir Crit Care Med.* 2004; 170: 1095–100.
17. Null D, Gerstman DL. Clinical evaluation of a closed loop oxygen controller for neonatal respiratory care. *Clinical Trials.gov.* February 2010.
18. Claire N, Gerhardt T, Everett R, et al. Closed loop controlled inspired oxygen concentration for mechanically ventilated very low birth weight infants with frequent episodes of hypoxemia. *Pediatrics* 2001; 107: 1120–4.
19. Claire N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial. *J Pediatr.* 2009; 155: 640–5.
20. Claire N, Bancalari E, D'Ugard C, et al. Automated adjustment of inspired oxygen in mechanically ventilated preterm infants: a multicenter crossover trial. *Pediatrics* 2011; 127: e76–3.
21. Wilinska M, Bachman T, Swietlinski. Time required for effective FiO₂ titration in preterm infants: a comparison. *Neonatal IC* 2012; 25(5): 44–6.
22. Carlo WA, Finer NN, Gantz MG. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010; 363(13): 1285–1286.