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ORIGINAL ARTICLE

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

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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 thast 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.

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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 H20	19 (17–25)
PEEP – cm H20	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

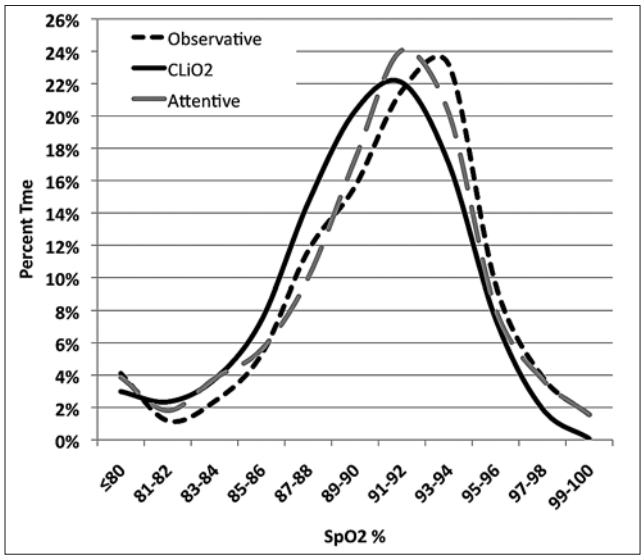

Figure 1. Histogram of SpO2 Exposure. Polled distribution of SpO2 in 2 % bins for each of the 3 control strategies

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 end points. 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.

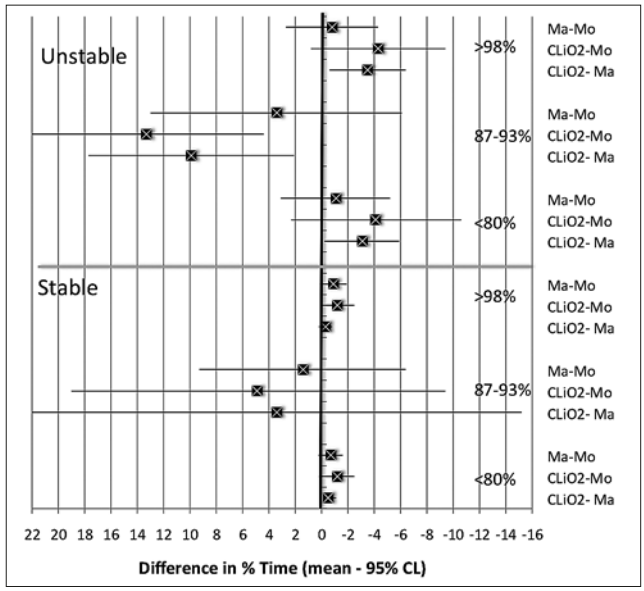

Figure 2. Difference among the 3 control strategies according to infant stability. The box is the pooled mean difference, and the whiskers represent the 95% confidence limits of the difference. Infants below the mean rate of severe desaturation of 2.5/hr were categorized as stable.
Ma – Attentive manual 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 meet 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 Claure, et al. [20, personal communication]. The difference was most marked for episodes of high SpO2. Laptook 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 thist 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 hypooxaemia.

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