**Time Required for Effective FiO2-Titration in Preterm Infants: a Comparison**

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**Introduction**

Proper targeting of SpO2 in preterm infants has become a topic of increasing interest over the last decade. Prior to that time, the pulse oximeter was used primarily to alert nurses to episodes of severe desaturations, or slow deterioration of oxygenation. Subsequently, reports confirmed the physiological rationale that lowering SpO2 target levels would result in significant reductions in pulmonary and retinal morbidity without apparent increases in developmental and neurological outcomes or mortality. As part of a massive research effort to determine the optimum SpO2 target range, two recently concluded mega RCTs found that dropping the target range too low (85%-89%), while further improving retinal and pulmonary morbidity, resulted in increased mortality. Recommendations for SpO2 targeting are expected to adjust and monitor to implement each of the three FiO2-titration approaches.

The aim of this analysis is to determine the nursing time needed for adjustment and monitoring to implement each of the three FiO2-titration approaches.

**Methods**

Nursing time associated with FiO2-titration includes the time to adjust the FiO2 and observe the infants response, as well as time to observe persistent alarms, even when adjustment of FiO2 is not deemed necessary. This need is applicable not only to the manual methods, but also to CLiO2. We defined, what was to our thinking, optimal practice guidelines. We made the following baseline assumptions: 1) alarms were set for silence for 20 seconds; 2) when the FiO2 was changed the nurse would stay with the patient and observe its response for 3 minutes if the SpO2 was at extremes (<80% or >98%), and 2 minutes if just outside the target range; 3) for alarms that persisted for 1 minute or more but did not result in an FiO2 adjustment, 1 minute of time was allocated for observation; and, 4) for less persistent alarms, 30 seconds was allocated for observation.

Our previous study identified two distinct groups of infants. The first group experienced frequent severe desaturations (average 4 per hour). They spent about half of the time in the intended target range and during manual control more than 10% of the time at extreme saturations (either above 98% or below 80% SpO2). The second group with less frequent severe desaturations (average 1 per hour) spent about three-quarters of the time in the intended target range. During manual control they spent less than 5% of the time at extreme saturations. In all cases we found CLiO2 tended to result in better control. Our database includes FiO2 and SpO2 readings for every 5 seconds for 113 hours of monitoring of 8 infants. We analyzed this database to determine the frequency, duration and magnitude of episodes outside the SpO2 target range and tabulated it for the two categories of infants.

In our previous study a dedicated operator implemented the two manual titration strategies. They were labeled Attentive and Observative. In both, response to episodes of SpO2<80% or >98% was faster than to small SpO2 excursions (Attentive within 30 sec and 1 min, Observative within 2 min and 3 min, respectively).

We built an Excel (Microsoft, Redmond, WA) model based on the frequency, magnitude and duration of the episodes for each of

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Automated FiO2 control systems for neonates have been tested and show promise of improved SpO2 control. Moreover, the potential for labor savings associated with automation is of great interest. One system is commercially available outside the US (CLiO2 option for the Anea ventilator, CareFusion, Yorba Linda, CA). We recently compared CLiO2 with two different, strictly applied, manual FiO2-titration strategies. We found CLiO2 generally more effective and safer than either of the manual strategies.

Evaluation of these studies and selection of the best SpO2 target range is, however, complicated by several factors. Disordered breathing and changes in extrapulmonary shunt result in episodes of significant desaturation, in addition to continual wandering of the SpO2 outside of the desired target range. Staff training and workload have both been shown to be barriers to effective SpO2 management of preterm infants. The oxygen saturation of many preterm infants is quite unstable. As a result, studies have shown that preterm infants receiving respiratory support spend only about half of the time within the intended target range.

There is very little in the literature describing or testing the relative effectiveness of specific FiO2-titration strategies for infants during respiratory support. FiO2-titration strategies should consider not only the timing and magnitude of an increase in FiO2 needed to address SpO2 levels below the target range, but also the timing and magnitude of response to SpO2 levels above the target range, the latter being either a result of either improving oxygenation or a need to wean a previous FiO2 increase. Some have suggested that many desaturations resolve quickly and unless prolonged are not addressed. This thinking is intended to avoid the frequent need to wean FiO2 to mitigate hyperoxemia. This delayed approach also has the advantage of reducing the amount of time required by nursing staff to address SpO2 alarms. Regardless of approach, it is generally accepted that an effective clinical strategy includes nursing observation of the infant with a persistent alarm or following an FiO2 adjustment.
the categories of infants. It calculated the nursing time required to implement, with the defined oversight, for the three control methods.

Results
Infants with infrequent severe desaturations spend about three-quarters of the time within the target range, experiencing episodes outside the target range an average of every 4.4 minutes. About half of these did not trigger an audible alarm, and an adjustment was only required once or twice per hour (Observative, Attentive respectively). In contrast the infants with frequent severe desaturations spent about half the time in the target range, with episodes outside the target range every 1.2 minutes. About half of these did not trigger an audible alarm, but an adjustment was only required every 13 (Observative) or 9 minutes (Attentive). Our previous study showed that during CLiO2 control no FiO2 adjustments were required and that persistent episodes were less frequent.

The charts of FiO2 and SpO2 shown in Figure 1a, b illustrate a typical test run of 7.5 hours for the three control methods for each of the two infant stability categories. The contrast between the stable and unstable oxygenation groups is apparent in these two infants. In the more stable infant group we found the percent time below and above the Target range (87%-93% SpO2) were similar, though favoring CLiO2 slightly. (12%/11% CLiO2, 19%/9% Observative, and 15%/11% Attentive). In the less stable group the difference >93% SpO2 is more marked (15%/22% CLiO2, 30%/21% Observative, 21%/23% Attentive).16

The amount of estimated nursing time needed per hour to implement the three strategies is shown in Figure 2. For the more stable group of infants it is modest (4.3 minutes per hour for CLiO2 and 6.8 minutes per hour for Observative and 8.3 minutes per hour for Attentive). For the unstable group the time requirements become excessive for the two manual approaches (33 minutes per hour for Observative and 45.5 minutes per hour for Attentive), but not for CLiO2 (9.5 minutes per hour).

Nearly three quarters of the time projected for the two manual strategies in managing the unstable infants was associated with observation following adjustments. That was also the case during the Attentive strategy in stable patients, while it reflected only about one third of the time during the Observational strategy.

Discussion
Our model of the time requirement to implement an ideal practice of FiO2-titration suggests that use of an automated system would require 10 minutes of nursing time per hour in the most unstable group of infants. This, in itself, is an important finding, as automated FiO2 control is not an autopilot, but rather requires oversight.

In contrast to CLiO2, the two manual approaches would require 30 and 45 minutes per hour, respectively, to ideally manage the unstable patient. This amount of time is clearly not practical, even with a 1:1 nursing patient ratio.

Our previous study suggests better control with CLiO2 than either of these strategies in stable and unstable infants.14,15 Claire et al also reported, in a group of 32 relatively unstable infants, better control with CLiO2 that with routine care over a 24-hour period.15 In that study, routine care required an adjustment every 13 minutes and CLiO2 only every 150 minutes. This is consistent with our model for unstable infants (every 9-13 minutes). However, Claire’s report did not address the time associated with observing the infant with a persistent alarm or following an FiO2 adjustment.

This factor of how quickly one responses to an unacceptably persistent SpO2 can be characterized as attentiveness. Included in attentiveness is the necessary time to observe the infant’s
response. In contrast to attentiveness is vigilance. Our model assumes constant vigilance; 60 minutes per hour, 24 hours a day. This is a significant benefit of an effective automated approach. Claire et al reported significantly more prolonged episodes of low saturations during routine care. Our report of the two manual strategies, implemented with a dedicated operator and excellent vigilance, suggested better maintenance of a target range and less time in extreme saturations than generally reported in routine care. These two observations tend to confirm the benefit of attentiveness and vigilance with an automated system. Some have reported more frequent desaturations with lower target ranges. Others have reported an important difference in the time in extreme saturations with relatively small shifts in target range. We speculate that these three issues might also be associated with or exacerbated by a lack of vigilance.

Our analysis, while provocative, clearly has limitations. Other manual FiO2-titration strategies would have different results. Certainly a more permissive approach to observing the persistent alarm conditions or timing of FiO2 adjustments would require less time. Nevertheless, we previously reported that more attentive response led to better SpO2 control, albeit with an impractical time requirement. Thus it is reasonable to expect a significantly more permissive approach, while reducing time requirements, would likely result in poorer SpO2 control. It is not clear, however, what level of actual SpO2 control is necessary for optimal outcomes.

We conclude that, in infants with frequent severe desaturations, the time demands of optimal saturation management, without automatic control, are impractical in the NICU. In contrast, in those more stable infants the time savings of automatic control are not significant, and its only advantage would be improved SpO2 control as a result of vigilance. Finally we suggest the need for further evaluation of the limitations of effectiveness of manual SpO2 control approaches. This should address both attentiveness and vigilance. Attentiveness relates to staffing and practical guidelines suited for manual FiO2 adjustments and SpO2 targeting. It is also important to understand what degree a lack of vigilance plays in shortfalls in achieving desired SpO2 control in the routine environment.

References