Automated control of inspired oxygen (FiO_2) in preterm infants

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Background

Oxygen is likely the most used medication in preterm infants.[1] For these patients, oxygen-therapy is a life-saving drug and at the same time a risk-factor for the development of severe complications such as bronchopulmonary dysplasia (BPD)[2] and retinopathy of prematurity (ROP).[3] Therefore, the continuous monitoring of supplemental oxygen is very important; in preterm infants it is performed measuring the oxygen pulse saturation (SpO_2). Recently, the American Academy of Pediatrics suggested that a 90-95% SpO_2 represents a reasonable target[4] in substantial agreement with European guidelines that suggest a 90-94% SpO_2 target.[5] In fact, low (85-89%) target increases mortality and the risk of necrotizing enterocolitis (NEC), while a high target (91-95%) increases the risk of ROP.[6]

However, it is not easy to maintain the optimal SpO_2 target. In fact, the most important randomized controlled trials on this issue[7-10] reported that patients spend a high percentage of time outside the planned target, ranging from 9.1[7] to 27.4%[9] with SpO_2<85%, and from 11.1[10] to 33%[11] with SpO_2 >95%. This occurs due to the respiratory instability of very preterm infants which causes SpO_2 fluctuations and the ineffective manual adjustments of FiO_2 by caregivers which can be late and defective, or prolonged and excessive. The consequence is patient exposure to recurrent episodes of hypoxia (and associated bradycardia) and hyperoxia that can be detrimental for their outcome.[2,3,11]

In fact, premature infants present with frequent episodes of spontaneous intermittent hypoxemia (SIH) which are more prevalent in infants who require prolonged mechanical ventilation and increase their frequency with postnatal age and with progressing chronic lung disease. A common mechanism triggering intermittent hypoxemia (SIH) is contractions of the abdominal muscles that opposes the respiratory activity of patients resulting in decreased lung volume, impaired lung mechanics, and hypoventilation. It has been observed that limited staff availability can further compromise SpO_2 targeting during routine clinical care enhancing the effect of SIH and that education of the clinical staff induces a relevant increase of time spent within the SpO_2 target range, decreases episodes of hyperoxia but, paradoxically, increases episodes of hypoxia.

The management of SIH include ventilator strategies and supplemental oxygen therapy. To increase high positive end-expiratory pressure (PEEP) allows to increase lung volume and basal oxygenation levels but is only partially effective in preventing SIH caused by active exhalations. In fact, the rise in intrathoracic pressure during forceful contraction of the abdominal muscles exceeds the level of PEEP considerably.

High peak inspiratory pressure (PIP) or ventilator frequency can limit SIH, but this strategy might provide excessive support during periods when the infant is not presenting with episodic hypoxemia and induce lung injuries.[12] Volume-targeted ventilation, which automatically adjusts the ventilator PIP to maintain a set tidal volume, can contribute to attenuate SIH compared with conventional pressure-controlled (PC) ventilation but is ineffective in preventing them. However, this requires setting a target tidal volume (TV) that was larger than the TV delivered during mechanical ventilation, possibly exposing the infants to excessive TV and PIP during periods when ventilation is stable. High basal levels of SpO_2 can attenuate the frequency or severity of SIH, but this increases the exposure to high FiO_2 and hyperoxemia. It usually occurs that caregivers increase FiO_2 when SpO_2 decreases and, subsequently, maintain high FiO_2 to prevent SIH, but this strategy is ineffective in the medium- and long-term and SIH reappears soon.

Systems allowing the automated control of FiO_2

The aforementioned considerations represent the basis for development of systems allowing the automated control of FiO_2 patient delivery to maintain SpO_2 within a target range limiting episodes of both hypoxia and hyperoxia and decreasing the workload of nurses. These systems include a pulse oximeter, a non-invasive or invasive respiratory support (i.e. mechanical ventilator), and the algorithm that regulates the FiO_2 adjustments in relationship to SpO_2 changes.

Fathabadi et al. detailed the main characteristics of algorithms developed for automation of inspired oxygen control in preterm infants and classified them in four categories: rule-based (fuzzy or non-fuzzy algorithms), proportional-integral-derivative (PID), adaptive, and robust (this algorithm is not available in the clinical practice)[13]. Among the most diffuses systems, the Predictive Intelligent Control of Oxygenation (PRICO®) uses a rule-based non-fuzzy control algorithm (see figure 1) ;

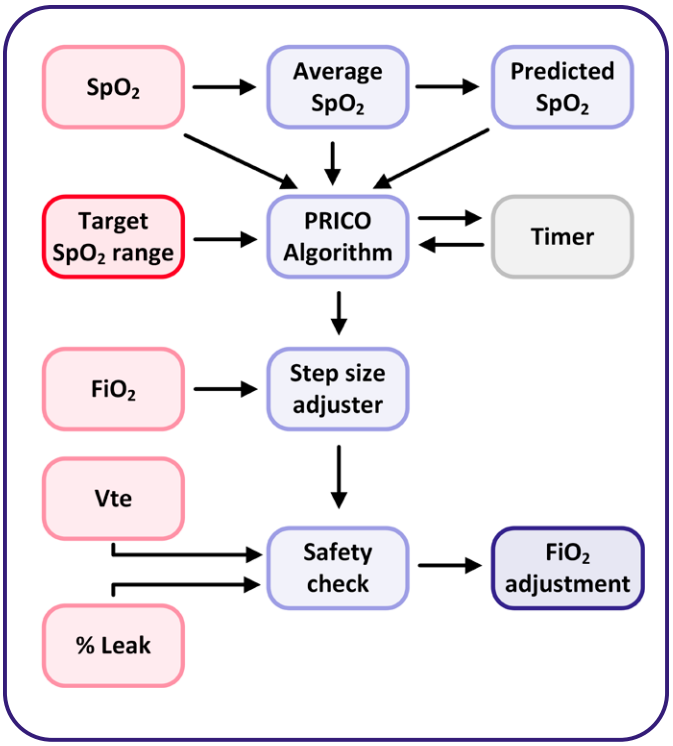

Figure 1 Flow scheme of PRICO algorithm, Hütten et al.[15]

Neonatal ventilators	Company	Algorithm
Fabian H™FO	Acutronic, Hirzel, Switzerland	PRICO®
SLE6000	SLE Limited, South Croydon, UK	OxyGenie®
Avea™	Vyaire Medical, CA, USA	CLiO2™
Sophie	Fritz Stephan GmbH, Gackenbach Germany	SPO2C®
Leoni plus	Heinen & Loewenstein GmbH, Bad Ems, Germany	CLAC®

Table 1 Largely diffused neonatal ventilators and integrated algorithms for automated control of fiO_2 delivery.

OxyGenie® system use a PID algorithm; and the AVEA™-CLiO2™ uses an adaptive algorithm.[14,15]

Thus, it is noteworthy to underline that different clinical effects of systems for automated control of FiO_2 in preterm infants may depend on many variables, such as study population, type of respiratory support, and chosen target range, but also reflect the effectiveness of the algorithm itself.

Clinical studies

Most studies compared the effectiveness of automated control for FiO_2 delivery versus manual control. Although they are heterogeneous for design, population size, duration, and device used, demonstrate that automated systems are significantly more effective than manual control in maintaining target SpO_2.[14] Automated control has also been associated with less time spent with SpO_2 higher than the target in comparison with manual control. See Figure 2 below as an example by Dani et al.[18]

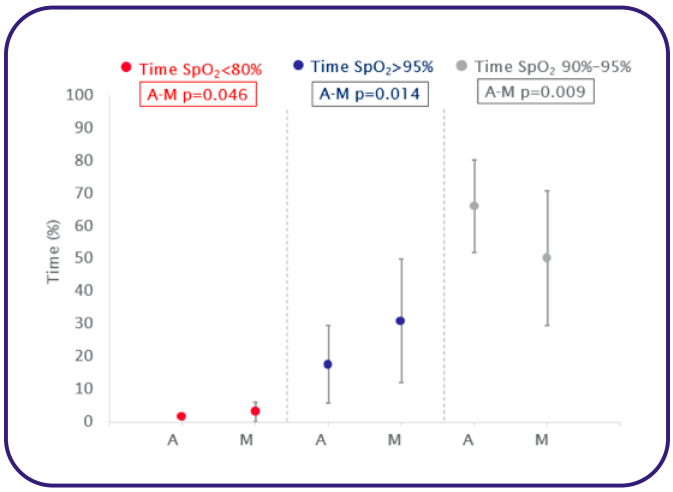

Figure 2 Comparison of the SpO_2 outcome measurement during automated (with PRICO) (A) and manual (M) control of FiO_2. Time spent with SpO_2 90%–95% was higher during the automatic than manual control of FiO_2, while time spent with SpO_2 <80% or>95% was lower.

This advantage has not always been observed for the time spent with SpO_2 lower than the target. Thus, it is possible that automated control is more effective in preventing hyperoxia than hypoxia in comparison with manual control.[14] To explain why automated systems might perform less favourably with hypoxia, we must remember that closed loop systems can respond to episodes of oxygen desaturation but are ineffective in preventing them. Moreover, it is possible that the automatic increase of FiO_2 can attenuate the severity of hypoxemia but it is unlikely that it produces an immediate recovery of the episode. However, very recent studies by Dijckman et al.[16] and Dani et al.[17] found that PRICO® system was more effective of manual control in maintaining SpO_2 within target range, but also decreased the duration of hypoxemia in preterm infants with frequent desaturations suggesting that some algorithms might be more effective of others in correcting low values of SpO_2.

It is interesting to evaluate if the width of the SpO_2 target range (i.e.: > or > 6%) can affect the effectiveness of the automated system for FiO_2 control but available data do not seem to support this hypothesis.[14] However, it seems reasonable to avoid too much wide target range which might mask worrying fluctuations in patients' oxygen need.

On the other hand, it would be interesting to compare the effectiveness of various algorithms but to date there are not many published studies on this topic. So far only Salverda et al. compared two different systems for automated control of FiO_2 delivery and found significant difference between them[18] confirming that different algorithms can be associated with different results.

Clinical studies on effects of automated control of FiO_2 on tissue oxygenation

Some researchers investigated if a better control of SpO_2 results in an improvement of tissue oxygenation. Waitz et al. studied 15 very low birth weight infants who were randomly assigned to 24 h of automated (AVEA-CLiO2™, Vyaire Medical, Mettawa IL, USA) or manual adjustment of FiO_2.[19] They found that automated and manual FiO_2 control were associated to similar values and fluctuations of cerebral oxygenation.[19] Gajdos et al. studied 12 very low birth weight infants who were randomly assigned to 24 h of automated (SPO2C®, Sophie Respirator, Fritz Stephan GmbH Medizintechnik GmbH, Gackenbach, Germany) or manual adjustment of FiO_2.[20] They confirmed that automated and manual FiO_2 control were associated to similar values and fluctuations of cerebral, renal and hepatic rSO_2.[20] More recently, we studied 20 infants with gestational age <32 weeks who were randomly assigned to 24 h of automated (PRICO®, fabian HFO®, Acutronic Medical System AG, Hirzel, Switzerland) or manual adjustment of FiO_2 and, in agreement with previous studies, we found that cerebral and splanchnic oxygenation were similar during automatic and manual control of FiO_2.[21]

To explain why the more stable SpO_2 guaranteed by automated system of FiO_2 delivery did not improve cerebral oxygenation, we can speculate that endogenous mechanisms of cerebral compensation and autoregulation, which concur to maintain adequate cerebral blood perfusion and oxygenation despite abnormal arterial oxygenation, are per sè very effective. Therefore, it is difficult that an automated FiO_2 control is able to further improve the stability of cerebral oxygenation. It is more difficult to explain the lack of effects of automated FiO_2 control on oxygenation of hepatic, renal and splanchnic tissues, since these district does not benefit from an autoregulation system that safeguards its blood perfusion. However, some explanations can be speculated: during the studies patients were in stable clinical condition and this might have helped limit fluctuations of tissue oxygenation;[19-21] baseline values of hepatic, renal and splanchnic oxygenation are lower than those of cerebral oxygenation and, therefore, it is possible that significant changes can occur only for deep and prolonged changes of SpO_2 that both automated and manual control of FiO_2 can prevent.

Clinical studies on effects of automated control of FiO_2 on outcome of preterm infants.

No large studies investigated whether automated control of FiO_2 can affect outcome in preterm infants, and recently it has been questioned the actual possibility of these devices of beneficially influencing their neurodevelopment.[22] In fact, it has been demonstrated that the correlation between SIH and neurodevelopment in preterm infants becomes significant at 6-10 weeks of postnatal age when oxygen supplementation and respiratory support are often absent or mild[23] and, consequently, the role of automated control of FiO_2 might be smaller than expected.

However, Salverda et al. have recently reported in a retrospective study that the implementation in their center of the automated oxygen control (CLiO2 and OxyGenie® systems) did not change mortality and morbidity of patients but decreased the duration of mechanical ventilation.[24] This result is promising because prolonged mechanical ventilation is a risk factor for severe complications, such as bronchopulmonary dysplasia (BPD), and has been directly associated with poor neurodevelopmental outcome.

Conclusions

Automated devices are significantly more effective than manual control in maintaining SpO_2 within selected ranges and in preventing hyperoxia and to lesser extent hypoxia, although they do not improve tissue oxygenation. However, automated control can safely decrease the workload of nurses. Large studies are required to assess the actual effects of automated control of FiO_2 on infants' outcome. These RCTs should assess the effect of automated control of FiO_2 on short and long-term outcome in preterm infants including neurodevelopment at 2 years of life and later. Moreover, further clinical studies comparing the effectiveness of various algorithms would be useful to assess their most effective settings.

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