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Review

Closed-loop control of inspired oxygen in premature infants

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SUMMARY

Systems for closed-loop control of inspired oxygen have been developed to improve the maintenance of oxygenation targets in premature infants and reduce hyperoxemia, hypoxemia, and exposure to high inspired oxygen levels. This review describes some of the clinical studies that have evaluated the efficacy of these systems in oxygen targeting.

1. Introduction

Supplemental oxygen is essential for the survival of premature infants with hypoxic respiratory failure. In these infants, the need for oxygen supplementation often extends beyond the acute phase of respiratory failure into a chronic oxygen dependency. Excessive and prolonged oxygen administration has been associated with the development of retinopathy of prematurity and oxidant injury to the lungs and central nervous system [1–6]. Conversely, concerns related to the association between insufficient oxygenation and increased mortality [7–9] have been raised by the findings of recent large clinical trials showing higher mortality with lower oxygen target ranges [10,11]. There are also concerns about the possible detrimental effects of insufficient oxygenation on the central nervous system, pulmonary vasculature, and other organs [12–19].

2. Targeting a prescribed oxygen target range

The goals of oxygen therapy in the premature infant are to maintain adequate oxygenation while minimizing the exposure to hypoxemia, hyperoxemia, and high concentrations of oxygen in the inspired gas. To achieve these goals, arterial oxygen saturation is usually monitored by pulse oximetry (SpO_2) and the fraction of inspired oxygen (FiO_2) is manually titrated to keep SpO_2 within a prescribed target range while trying to avoid exposure to extreme high and low SpO_2 levels. Under standard clinical conditions, these goals are only partially achieved. Because of their respiratory instability, premature infants have frequent fluctuations in SpO_2 that require constant titration of FiO_2. This is a very time-consuming task that is seldom achieved under routine clinical conditions. Thus, premature infants spend considerable periods of time with SpO_2 outside the intended ranges. Data from a study including 14 centers showed that premature infants receiving supplemental oxygen spent on average only 48% of the time with SpO_2 within the target range, 36% of the time above (5–90% between centers) and 16% of the time with SpO_2 below the target range (0–47% between centers) [20]. Similar findings were observed in premature infants receiving nasal continuous positive airways pressure [21].

Hyperoxemia in the premature infant with lung disease is almost always induced by excessive FiO_2, whereas episodes of hypoxemia are mostly spontaneous and they are often associated with increased infant activity. The severity and duration of these episodes are largely influenced by the staff's response. Hyperoxemia is frequently observed in premature infants. This is because in an attempt to avert spells of hypoxemia the FiO_2 set by the caregiver often exceeds the level required to keep SpO_2 within the target range. In other cases the increase in FiO_2 in response to hypoxemia is not followed by a prompt return to baseline after the episode resolves, leading to hyperoxemia [22].

The fluctuations in oxygenation increase with postnatal age and they are even more common in infants with chronic lung disease [23–29]. This is reflected in the time SpO_2 is within target range, which decreased from 51% of the time during week one to 44% of the time by week four [20].

The stability of oxygenation is also influenced by the targeted range of SpO_2. An observational study following a relatively minor change in the oxygen saturation target range from 90–95% to 88–94% showed that SpO_2 was maintained within the old and new target range for a similar proportion of time, but with the lower

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target range the proportion of time with SpO_2 <80% increased from 1.9% to 4.0% [30]. This was also observed in a cohort of infants enrolled in the SUPPORT trial [31], where the frequency of hypoxemia increased with postnatal age and was higher in the infants assigned to the 85–89% compared to the 91–95% target range. This is in agreement with the findings of a study where adjusting FiO_2 to keep SpO_2 within 87–91% compared to 94–96% in preterm infants increased the proportion of time with SpO_2 <85% from 1% to 17% [32]. This was also evidenced in large clinical trials where the actual SpO_2 levels did not match the target ranges, and there were clear increases in the extreme high or low tail ends of the SpO_2 distribution when targeting the higher or lower range, respectively [10,11,33,34].

Although the main factor limiting the maintenance of SpO_2 within the prescribed target range is the respiratory instability of the premature infant [24–27], multiple factors can contribute to limit the efficacy of manual titration of FiO_2 by the clinical staff in maintaining the prescribed range of SpO_2. Limited staff availability and experience further affect the maintenance of oxygenation targets during routine clinical care. Maintenance of SpO_2 within the target range declines as the nurse:infant ratio decreases [21,35]. The proportion of time with SpO_2 within the target range declined from 38% to 15% with a 1:1 compared to a 1:3 or lower nurse:infant ratio. This resulted mainly from an increase in the proportion of time spent with SpO_2 >97% from 8% to 37%. This was accompanied by a reduction in the proportion of time with SpO_2 <85% from 6% to 3% [35].

There are frequent gaps between unit policies and actual clinical practice during routine care. An observational study reported that the high SpO_2 alarm limits used to monitor premature infants receiving supplemental oxygen were set incorrectly in more than 75% of cases [36]. A survey of nearly 3000 nurses from 59 centers in the USA found that only 40% of them were able to identify their center's SpO_2 goals and policies [37]. Education and training of the clinical staff have been shown to be effective tools for improving the maintenance of the target range of SpO_2 from 20% to approximately 40% of the time [38]. This was largely the result of a reduction in the proportion of time with SpO_2 above the target from 78% to 37%. These interventions also reduced the proportion of time with SpO_2 $\geq$98% from 30% to 10%, but were also accompanied by a noticeable increase in the proportion of time spent with SpO_2 <85% from 1% to 13%.

These studies reflect the fact that in spite of a concerted effort and the clear evidence of the harmful effects of hyperoxemia, maintenance of SpO_2 within a target is only partially achieved and tolerance of high SpO_2 is prevalent in routine neonatal intensive care. It is also evident that efforts to limit exposure to high SpO_2 levels often lead to an increased time in the lower tail end of SpO_2 and vice-versa. This is even more widespread in preterm infants who present with large fluctuations in oxygenation.

During routine care, SpO_2 levels above the target range are frequently tolerated to reduce hypoxemia, but this practice increases the exposure to extremely high SpO_2. Conversely, changes in practice to target lower SpO_2 ranges to avoid hyperoxemia can increase exposure to very low SpO_2 levels. Tolerance of high SpO_2 to avert hypoxemia spells or targeting low SpO_2 ranges to avoid hyperoxemia may not be necessary if the maintenance of the intended SpO_2 range could be improved and exposure to extreme high or low SpO_2 minimized by automated control.

3. Systems for oxygen saturation targeting using closed-loop FiO_2 control

Systems for closed-loop FiO_2 control have been developed to overcome the shortcomings of routine manual control and to improve the balance between adequate oxygenation and excessive oxygen exposure in preterm infants. These systems aim at maintaining SpO_2 within a range selected by the clinicians while minimizing oxygen exposure.

Closed-loop FiO_2 control systems available for clinical or experimental use generally consist of a device to monitor oxygenation (e.g., pulse oximeter), gas delivery device (e.g., ventilator) and the algorithm that determines the timing and size of the FiO_2 adjustments. FiO_2 is reduced when SpO_2 exceeds the target range or increased when SpO_2 declines below the range. The magnitude of these adjustments is proportional to the deviation of the measured SpO_2 from the set target range. These algorithms can also include adjustments in FiO_2 based on upward or downward trends in SpO_2 or the time during which SpO_2 is out of the target range.

4. Effects on oxygen saturation targeting

The efficacy of closed-loop FiO_2 systems has been compared to manual FiO_2 control by routine care or a fully dedicated caregiver in single and multicenter clinical studies [39–54]. These studies showed that closed-loop FiO_2 control systems were consistently more effective than manual control in maintaining the oxygenation targets and were similar or better than a caregiver fully dedicated to FiO_2 titration (Table 1).

These studies were conducted on populations of premature infants of various gestational and postnatal ages and receiving different forms of invasive and non-invasive respiratory support. They included groups of infants who presented with very frequent fluctuations in oxygenation in whom maintenance of oxygenation targets was particularly challenging for both the caregivers and the automated systems. These studies provided the proof of principle and documented the feasibility of this approach in the care of these infants.

5. Effects on hyperoxemia and oxygen exposure

The improved oxygenation targets achieved by closed-loop FiO_2 control was in part the result of reductions in hyperoxemia (Table 2). This effect appears to be largely related to the tolerance of high SpO_2 levels during routine care. Studies in which closed-loop FiO_2 control was compared to a fully dedicated nurse or where the clinical staff diligently avoided hyperoxemia showed a smaller relative reduction in the amount of time spent with high SpO_2 levels. This may be one of the most important advantages of closed-loop FiO_2 control systems by reducing the deleterious effects of hyperoxemia on the eye, brain, and other organs.

In these studies, closed-loop systems achieved a reduction in FiO_2 (Table 3). In premature infants with respiratory insufficiency, hyperoxemia is mainly induced by administration of excessive FiO_2. The reduction in FiO_2 by automated systems may also have an important beneficial impact on the prevention of oxidant lung injury. This reduction in FiO_2 during closed-loop FiO_2 control is illustrated in Fig. 1.

6. Effects on hypoxemia

The proportion of time infants spent below the target range of SpO_2 in the different studies was not consistently decreased by closed-loop FiO_2 control compared to routine or dedicated staff. In fact, in some studies it actually increased (Table 4). However, when the proportion of time spent at more severe ranges of hypoxemia is examined, there is a consistent tendency towards a decrease in time spent in the low ranges of oxygenation during closed-loop compared to manual FiO_2 control.

This is in agreement with the paradoxical observations of an increased frequency of episodes of SpO_2 below the target range but