Editorial

Permissive Hypercapnia During Mechanical Ventilation of Neonates

Mechanical ventilation improves survival of premature as well as term newborn infants with respiratory failure. However, mechanical ventilation is an expensive therapeutic option, requiring not only mechanical ventilators, humidifiers, compressed oxygen and air, but also requiring invasive and non-invasive monitoring, meticulous nursing care, frequent blood gas analysis, and expert physician supervision. Mechanical ventilation may also contribute to morbidity and mortality even when used by skilled practitioners under optimal conditions. Morbidity and subsequent mortality may occur due to acute lung injury or air leaks (PIE, pneumothorax, pneumomediastinum *etc.*) caused by mechanical ventilation.

Acute lung injury is considered to be primarily due to "volutrauma", due to the use of high tidal volumes and high end-inspiratory volumes, or due to "atelectotrauma" due to repeated collapse and re-opening of alveoli due to the use of insufficient PEEP (positive end-expiratory pressure). Attempts to decrease volutrauma by reducing tidal volume, while maintaining adequate PEEP and a constant ventilator rate, would reduce minute ventilation, thereby resulting in an elevation of arterial carbon dioxide tension ($PaCO_2$). A decrease in tidal volume will decrease alveolar minute ventilation and increase $PaCO_2$ to a greater extent, as dead space contributes to a greater proportion of tidal volume when the tidal volume is decreased. In a study being published in this issue, it has been demonstrated that a step-wise reduction in minute ventilation is associated with a corresponding increase in $PaCO_2$(1). While these results may be anticipated on physiologic grounds, they provide the necessary confirmation of our clinical practice.

It is necessary to keep in mind the goal of mechanical ventilation – achieving adequate gas exchange with the minimum possible ventilatory support. The minimum possible ventilatory support can generally be defined as the smallest necessary tidal volume with an adequate positive end-expiratory pressure, which at the very minimum can be considered to be nasal CPAP in a spontaneously breathing infant. The problem is deciding what "adequate gas exchange" is in a sick neonate. One approach in the past had been to maintain blood gas values within the normal range of non-ventilated term infants in room air. "Normal" arterial blood gas ranges are often quoted as a pH of 7.35 to 7.45, a PaO_2 of 70-100 torr, and a $PaCO_2$ of 35-45 torr. However, trying to maintain these "normal" ranges in a neonate with sick lungs may require high ventilator settings, increase the risk of volutrauma, and prolong the duration of ventilation. In addition, the "normal" range may not be physiologic for normal development of the lung, retina, brain etc. in premature infants who are normally exposed to lower PaO_2 and higher $PaCO_2$ *in utero*. Hypocapnia (a $PaCO_2$ less than 25-30 torr) is also associated with risks such as increased periventricular leukomalacia (PVL), hearing deficits, and neurodevelopmental disabilities (2). Maintaining a higher level of $PaCO_2$ (45-55 torr) in ventilated preterm neonates (601-1250 g birth weight) has been shown in a

single center randomized controlled trial to be safe and reduce the duration of mechanical ventilation in the first 96 hours(3). In a multicenter randomized trial, extremely low birth weight infants (501-1000 g) were randomized to minimal ventilation ($PaCO_2$ >52 torr) or routine ventilation ($PaCO_2$ < 48 torr) and a tapered dexamethasone course or saline placebo for 10 days, using a 2 × 2 factorial design, while maintaining pH >7.2 and PaO_2 50-80 torr(4). In this trial, the weighted average minute ventilation index was 23% lower in the minimal ventilation group as the result of a statistically significant decrease in rate, but tidal volumes were comparable (3.6 ± 0.4 mL/kg in the minimal *vs.* 3.4 ± 0.3 mL/kg in the routine ventilation group). After enrollment of 220 patients, nonrespiratory adverse events related to dexamethasone therapy were noted. There was no difference in the primary outcome of death or BPD at 36 weeks postmenstrual age in the minimal versus routine ventilation groups (Relative Risk 0.93 (95% CI, 0.77-1.12; p = 0.43)), although ventilator support at 36 weeks was 1% in the minimal versus 16% in the routine group (p <0.01)(4).

There are some additional potential benefits for maintaining a higher level of $PaCO_2$, and this topic has been reviewed recently(5). A disproportionate increase in minute ventilation is required for a lowering of $PaCO_2$. A higher $PaCO_2$ increases the amount of CO_2 in the alveolar gas, which enhances the CO_2 elimination for the same minute ventilation. $PaCO_2$ is also a stimulator of the respiratory drive, and a higher $PaCO_2$ may improve spontaneous respiratory effort while infants who are hyperventilated with a low $PaCO_2$ often have a poor spontaneous respiratory effort, further prolonging their ventilation. In addition, due to the Bohr effect, with increasing $PaCO_2$, the oxygen affinity of hemoglobin decreases, resulting in a shift to the right of the oxygen dissociation curve. This would improve peripheral unloading of oxygen in the circulation. Hypercapnic acidosis is also protective in the setting of lung injury. Induction of hypercapnic acidosis by addition of CO_2 to inspired gas has been shown to reduce ventilator-induced lung injury(6), endotoxin-induced(7), and ischemia-reperfusion-induced lung injury(8) in animal models. This attenuation of inflammation occurs due to hypercapnic acidosis at multiple levels (systemic, end-organ, cellular, and molecular levels)(5), and there is evidence from animal studies that hypercapnic acidosis is more protective than metabolic acidosis, and that buffering of hypercapnic acidosis with sodium bicarbonate reduces this protective activity(9). In another study using a preterm lamb model of RDS, CO_2 added to the ventilator circuit to maintain a $PaCO_2$ of 95+5 torr did not result in physiologic compromise for the six hours of the study, and animals with the higher $PaCO_2$ had reduced lung injury as compared to control animals with a $PaCO_2$ of 40-50 torr(10).

The potential hazards of hypercapnia, such as an increase in cerebral blood flow and an increase in the risk of intraventricular hemorrhage, have not been seen in clinical trials to date(3,4). On the contrary, avoidance of hypocapnia by targeting higher $PaCO_2$ levels may actually reduce PVL. In immature animal models, hypercapnia has been shown to reduce hypoxic-ischemic brain damage (11).

What level of oxygen saturation or oxygen tension (PaO_2) should we target? We echo the words of Tin, *et al.* who wrote: "We do not even know what level of arterial oxygen tension we should be aiming for"(12). There is some evidence that a transcutaneous PaO_2

>80 torr is associated with an increasing incidence and severity of retinopathy of prematurity(13). Tin, *et al*. in a retrospective study of 295 infants <28 weeks gestational age noted that babies nursed with a monitor set to alarm if oxygen saturation fell outside the range 70-90% had a 6.2% (95% confidence interval 1.7 to 15.0%) chance of developing retinopathy severe enough to need cryotherapy while those nursed with a monitor set to maintain a saturation of 88-98% had a 27.7% (17.3 to 40.2%) chance of developing this degree of retinopathy(12). In this study, there was no difference in the incidence of death or cerebral palsy but the duration of ventilation (31.4 days vs. 13.9 days) and supplemental oxygen (96 days vs. 40 days) was longer in infants at the higher target saturation (88-98%) as compared to the lower oxygen saturation(12). In the STOP-ROP trial, an oxygen saturation target of 96-99% vs. 89-94% was associated with an increase in oxygen supplementation, need for diuretics and other adverse respiratory events(14). Askie, *et al*. in a randomized controlled trial on 358 infants <30 weeks' gestation dependent on oxygen at 32 weeks postmenstrual age also noted that a higher saturation target (95-98%) as compared to a lower range (91-94%) in infants resulted in no benefit(15). The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; p <0.001), had a significantly higher rate of supplemental oxygen at 36 weeks of postmenstrual age, a significantly higher frequency of home-based oxygen therapy, and showed no significant benefit with respect to growth and development(15).

In summary, there is much evidence that hypocapnia and hyperoxia are undesirable in neonates. While extreme hypercapnia and hypoxemia are also dangerous, there may be benefit in "permissive hypercapnia" ($PaCO_2$ 50-55 torr) and avoidance of hyperoxemia (maintaining oxygen saturation 80-90% in preterm infants, with PaO_2 <80 torr) in combination with "gentle ventilation" techniques targeted at reducing ventilator-induced lung injury. Rather than targeting ventilator settings or tidal volumes, it may be more important to maintain physiologic stability with minimal ventilator settings, and attempt to extubate infants from mechanical ventilation as soon as possible, or not to ventilate them if at all possible.

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