

# Permissive Hypercapnia

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## KEYWORDS

• Permissive hypercapnia • Mechanical ventilation • Lung

Mechanical ventilation using high tidal volume (VT) and transpulmonary pressure can damage the lung, causing ventilator-induced lung injury. Several mechanisms have been offered to explain this damage. Repetitive overstretching and damage to lung tissue and cyclic alveolar recruitment may result in mechanical stress and mechano-trauma.<sup>1</sup> Increased mechanical stress may activate immune response in the lung,<sup>2</sup> with the potential for intrapulmonary inflammatory mediators and bacteria to cross an impaired alveolar-capillary barrier.<sup>3,4</sup> Therefore the use of low-lung-stretch ventilatory strategies that reduce mechanical trauma and the associated inflammatory effects is increasing.<sup>5,6</sup> Permissive hypercapnia, a ventilatory strategy for acute respiratory failure in which the lungs are ventilated with a low inspiratory volume and pressure, has been accepted progressively in critical care for adult, pediatric, and neonatal patients requiring mechanical ventilation, and it is one of the central components of current protective ventilatory strategies. Permissive hypercapnia is used to minimize lung damage during mechanical ventilation; its limitations are the resulting hypoventilation, CO<sub>2</sub> retention, and acidosis. Hypoxemia is caused by decreasing the alveolar oxygen tension and alveolar collapse during hypoventilation. The alveolar collapse can be offset in part, however, by increasing the end-expiratory volume.

## PHYSIOLOGIC EFFECTS OF HYPERCAPNIA

### *Systemic Physiologic Effects*

In healthy subjects, hypercapnia is associated with air hunger and distress. Because of decreased CO<sub>2</sub> elimination and consequent hypercapnia, respiratory acidosis occurs during hypoventilation. Laboratory studies have shown that acute hypercapnia,

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induced within 1 hour, is associated with significant increases in cardiac output, organ blood flow, and intracranial pressure.<sup>7</sup>

Systemic physiologic effects of hypercapnia in humans are respiratory (increased minute ventilation, subjective discomfort, air hunger, anxiety, fatigue), cardiovascular (increased cardiac output, tachycardia, systemic and pulmonary hypertension), neurologic (increased cerebral blood flow, headache, cerebral edema), and metabolic (endogenous catecholamines and corticosteroids release, increased tissue O<sub>2</sub> unloading, decreased effect of exogenous vasopressors). In extreme hypercapnia and in high-risk patients hypercapnia can cause myocardial depression and dysrhythmias, cerebral hemorrhage and herniation, stupor, and coma.<sup>8</sup>

The role of hypercapnia in protective lung ventilation per se, apart from the reduced lung stretch, remains unclear because of a lack of clinical data comparing the efficacy of protective lung ventilatory strategies in the presence and absence of hypercapnia. Experimental studies suggest that tissue oxygenation can be unchanged or improved during permissive hypercapnia with increased cardiac output, reduced differences in arterial and venous O<sub>2</sub> content, and reduced blood lactate concentration.<sup>9,10</sup> In dogs, permissive hypercapnia produced by inhaled CO<sub>2</sub> produced gradual and significant increases in the hemoglobin concentration and arterial oxygen content, increasing oxygen-carrying capacity.<sup>11</sup>

Animal studies of peripheral microcirculation showed that when PaCO<sub>2</sub> increases up to 80 mm Hg, vessel diameter, blood-flow velocity, and blood-flow rate increase markedly, with slight increase in cardiac output;<sup>12</sup> however, when PaCO<sub>2</sub> exceeded 100 mm Hg, all these variables decreased. In addition, hypercapnic acidosis may reduce cellular oxygen demand.<sup>13</sup>

Hypercapnic acidosis attenuated acute experimental endotoxin-induced lung injury, improving the decrement in oxygenation and lung compliance and reducing alveolar neutrophil infiltration and histologic indices of lung injury.<sup>14</sup>

One small clinical study, however, showed that acute moderate changes in PaCO<sub>2</sub> have no major effect on splanchnic perfusion and metabolism.<sup>15</sup> In another study in patients who had severe acute respiratory distress syndrome (ARDS),<sup>16</sup> the PaCO<sub>2</sub> increase from 38 to 57 mm Hg, and the pH decrease from 7.41 to 7.31 at 24 hours did not induce significant changes in arterial oxygenation, pulmonary vascular resistance, systemic vascular resistance, cardiac index, or systemic oxygen delivery and consumption.

### ***Anti-inflammatory Action***

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Hypercapnic acidosis may interfere with the coordination of the immune response. In one *in vitro* study,<sup>17</sup> CO<sub>2</sub> produced profound reversible inhibition of lipopolysaccharide-stimulated cytokine release by peritoneal macrophages, possibly explaining the lack of systemic inflammation after laparoscopic surgery with CO<sub>2</sub>. Macrophages incubated in CO<sub>2</sub> produced significantly less tumor necrosis factor and interleukin (IL)-1 in response to lipopolysaccharide compared with those incubated in air or helium;<sup>18</sup> the authors attributed this finding to cellular acidification.

According to other authors, neutrophils respond to hypercarbia by decreasing intracellular oxidant production and the release of IL-8 from lipopolysaccharide-stimulated cells.<sup>19</sup> This hypothesis suggests that CO<sub>2</sub> can modify neutrophil activity significantly by altering pH. Extracellular acidosis may intensify acute inflammatory responses by inducing neutrophil activation, delaying spontaneous apoptosis, and extending neutrophil functional lifespan.<sup>20</sup> Hypercapnic acidosis may increase neutrophil CD18 expression and enhance neutrophil adhesion.<sup>21</sup> There is a direct positive correlation between the intracellular pH value and the locomotor response of neutrophils to a chemotactic gradient.<sup>22</sup>

Spreading and several functions of neutrophils were inhibited at an acidic pH.<sup>23</sup> This observation indicates that neutrophils release superoxide upon spreading, generating a burst of intracellular acid production, and the coordinated activation of intracellular pH regulatory mechanisms along with the oxidase is essential for sustained microbicidal activity.

Hypercapnic acidosis can have anti-inflammatory effects through a mechanism that inhibits activation of nuclear factor- $\kappa$ B,<sup>24</sup> leading to down-regulation of intercellular adhesion molecule-1 and IL-8, which in turn inhibit neutrophil adherence to pulmonary endothelial cells.<sup>25</sup>

Hypercapnic acidosis seems to attenuate free radical production and may attenuate tissue injury following pulmonary ischemia and reperfusion.<sup>26</sup> The production of superoxide radicals by chemotactic factor-stimulated human neutrophils *in vitro* was decreased at acidic pH.<sup>27</sup> There are, however, concerns regarding the formation of nitration products from peroxynitrite, a potent free radical.<sup>28,29</sup>

In general, the available experimental data are inconclusive as to whether hypercapnic acidosis interferes with the coordination of the immune response.

#### IMPLEMENTATION OF PERMISSIVE HYPERCAPNIA

Implementation of permissive hypercapnia requires ventilation with decreased VT and low alveolar pressure.<sup>8</sup> The VT should be reduced gradually to 7 mL/kg or less<sup>30</sup> to allow a progressive rise in the PaCO<sub>2</sub>, not to exceed 10 mm Hg/h, to a maximum of 80 to 100 mm Hg, to maintain the static peak airway pressure at less than 40 cm H<sub>2</sub>O and arterial oxygen saturation (SaO<sub>2</sub>) greater than 90%.<sup>31</sup>

The strategies of permissive hypercapnia are continuing to develop. The initial approach aimed at avoiding end-inspiratory lung trauma by using small VTs, limiting the plateau airway pressure to 30 to 35 cm H<sub>2</sub>O, and allowing a slow rise of PaCO<sub>2</sub>.<sup>32-36</sup> It has been suggested that the use of small VTs that avoid tissue overdistention and the acceptance of the consequent elevation of PaCO<sub>2</sub> minimize the risk of barotrauma in patients who have asthma and ARDS.<sup>36</sup> Adoption of the ARDS Network low-VT protocol for routine ventilator management was associated with lower mortality in 292 patients who had acute lung injury (ALI)/ARDS than seen in recent historical controls.<sup>37</sup>

Further development of this strategy emphasized the importance of alveolar recruitment to avoid the end-expiratory lung trauma by applying positive end-expiratory pressure (PEEP) and optimizing gas exchange.<sup>38,39,40</sup>

Although in most patients PEEP induces alveolar hyperinflation during mechanical ventilation with conventional VT, at low VT a significant alveolar collapse is present, and PEEP is able to expand these units, improving gas exchange and hemodynamics.<sup>38</sup> In patients who have ALI, a PEEP of at least 15 cm H<sub>2</sub>O is needed to prevent the decay of respiratory system compliance because of low VT ventilation.<sup>40</sup>

In a study of the hemodynamic effects of hypercapnia in adult patients who have ARDS,<sup>41</sup> the acute combined use of permissive hypercapnia, VT less than 6 mL/kg, distending pressures above PEEP of less than 20 cm H<sub>2</sub>O, and PEEP 2 cm H<sub>2</sub>O above the lower inflection point resulted in an immediate increase in heart rate, cardiac output, oxygen delivery, and mixed venous partial pressure of oxygen. The mean pulmonary arterial pressure increased markedly (by 8.8 mm Hg), but the pulmonary vascular resistance did not change. A multivariate analysis suggested that these acute hyperdynamic effects were related to respiratory acidosis, with no depressant effects ascribed to high PEEP levels,<sup>41</sup> and transitory pulmonary hypertension and high cardiac output were attenuated significantly within 36 hours.

In patients who had ARDS, adding increased PEEP to low VT resulted in improved survival at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma than seen with conventional ventilation.<sup>42</sup> In another study in patients who had ARDS, a high PEEP/low VT ventilatory strategy also improved ICU mortality, hospital mortality, and ventilator-free days at day 28 as compared with patients receiving conventional ventilation.<sup>43</sup>

Higher levels of sedation may be required to manage patients with permissive hypercapnia. In a study by Vinayak and colleagues,<sup>44</sup> higher doses of propofol but not midazolam were required to sedate patients managed with permissive hypercapnia. Hypercapnia should be avoided in trauma patients who have evidence of brain injury, because it can worsen intracranial pressure.<sup>31</sup>

### ***Clinical Studies***

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A growing body of evidence supports the use of permissive hypercapnia in ALI and ARDS, status asthmaticus, and neonatal respiratory failure.

#### ***Acute lung injury and acute respiratory distress syndrome***

Patients who have ALI and ARDS require ventilatory support, and ALI/ARDS are complicated further by ventilator-induced lung injury. The causes of the ALI and ARDS include pneumonia, sepsis or generalized infection, aspiration, shock, trauma/multiple fractures, acute pancreatitis, multiple transfusions, inhalation injury, burns, pulmonary contusion, and drug overdose.<sup>32,34,42,45</sup>

Protective ventilation involving end-expiratory pressures above the lower inflection point on the static pressure-volume curve, a VT of less than 6 mL/kg, driving pressures of less than 20 cm H<sub>2</sub>O above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes resulted in improved survival at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in 29 patients who had ARDS;<sup>42</sup> however, this treatment was not associated with a higher rate of survival to hospital discharge.

A further large, multicenter, randomized trial in 861 patients who had ALI and ARDS<sup>32</sup> demonstrated that ventilation with a lower VT, which involved an initial VT of 6 mL/kg predicted body weight and a plateau pressure of 30 cm H<sub>2</sub>O or less, significantly decreased mortality (31% vs. 40%) and increased the number of days without ventilator use during the first 28 days (12 ± 11 days vs. 10 ± 11 days). A high-PEEP/low-VT ventilatory strategy improved outcome in 53 patients who had persistent ARDS compared with 50 control patients receiving conventional ventilation.<sup>43</sup> ICU mortality (53% vs. 32%), hospital mortality (56% vs. 34%), and ventilator-free days at day 28 (6 vs. 11) all favored the low-VT strategy, and the number of organ failures was higher in the control group.

One hundred and twenty patients at high risk for ARDS were assigned randomly to pressure- and volume-limited ventilation, with the peak inspiratory pressure maintained at 30 cm H<sub>2</sub>O or less and the VT at 8 mL/kg body weight or less, or to conventional ventilation (control group).<sup>34</sup> In the limited-ventilation group, permissive hypercapnia (defined as PaCO<sub>2</sub> > 50 mm Hg) was more common (52% vs. 28%), more marked (54 ± 19 mm Hg vs. 46 ± 10 mm Hg), and more prolonged (146 ± 265 hours vs. 25 ± 22 hours) than in the control group. Permissive hypercapnia did not seem to reduce mortality and might increase morbidity, however, the incidence of barotrauma, the multiple-organ dysfunction score, and the number of episodes of organ failure were similar in the two groups, and more patients in the limited-ventilation group than in the control group required paralytic agents and dialysis for renal failure.<sup>34</sup> A study comparing traditional versus reduced VT ventilation conducted in 52

patients who had ARDS in eight ICUs demonstrated the safety of the reduced-VT strategy.<sup>45</sup> There were, however, no significant differences in requirements for PEEP, fluid intakes/outputs, requirements for vasopressors, sedatives, or neuromuscular-blocking agents, percentage of patients who achieved unassisted breathing, ventilator days, or mortality.<sup>45</sup> Another multicenter trial compared 116 patients who had ARDS and no organ failure (other than the lung) ventilated with different VTs ( $7.1 \pm 1.3$  vs.  $10.3 \pm 1.7$  mL/kg at day 1) and plateau pressure resulting in different  $\text{PaCO}_2$  ( $60 \pm 15$  vs.  $41 \pm 8$  mm Hg) and pH ( $7.28 \pm 0.09$  vs.  $7.4 \pm 0.09$ ) but with a similar level of oxygenation.<sup>33</sup> In this trial, mortality at day 60, the duration of mechanical ventilation, the incidence of pneumothorax, and the secondary occurrence of multiple organ failure were not reduced.<sup>33</sup>

A meta-analysis of six trials involving 1297 adult patients who had ALI or ARDS, comparing ventilation using either lower VT or low airway driving pressure versus ventilation with VT in the range of 10 to 15 mL/kg, found that mortality at day 28 and at the end of hospital stay was reduced significantly by lung-protective ventilation allowing hypercapnia.<sup>30</sup>

Kregenow and colleagues<sup>46</sup> tested the hypothesis that hypercapnic acidosis is associated with reduced mortality in patients who have ALI, independent of changes in mechanical ventilation in a previously conducted randomized, multicenter trial ( $n = 861$ ) comparing 12 mL/kg with 6 mL/kg.<sup>32</sup> After controlling for comorbidities and severity of lung injury, they found that hypercapnic acidosis was associated with reduced 28-day mortality in the group treated with VTs of 12 mL/kg predicted body weight.

Despite data supporting the use of protective ventilatory strategies and permissive hypercapnia in patients who have ALI and ARDS, many clinicians do not use these strategies. A survey of experienced ICU nurses and respiratory therapists has shown that clinicians had used lung-protective ventilation in a median of 20% (interquartile range, 10%–50%) patients who had ALI or ARDS.<sup>47</sup> Barriers to using lung-protective ventilation were physician unwillingness to relinquish control of ventilator, physician recognition of ALI or ARDS, and physician perceptions of patient contraindications to low VTs. Barriers to continuing patients on lung-protective ventilation were concerns about patient discomfort and tachypnea and concerns about hypercapnia, acidosis, and hypoxemia.<sup>47</sup>

### **Status asthmaticus**

Controlled hypoventilation with permissive hypercapnia is a relatively safe strategy in the ventilatory management of asthma,<sup>48</sup> and it may reduce morbidity and mortality compared with conventional normocapnic ventilation in the management of status asthmaticus.<sup>49</sup> The aim of controlled hypoventilation with permissive hypercapnia in status asthmaticus is to reduce potentially life-threatening side effects such as lung barotrauma and cardiovascular collapse by using low minute ventilation ( $\leq 10$  L/min), low VT (6–10 mL/kg), and low respiratory rate (10–14 cycles/min), taking care that expiratory time be sufficient ( $\geq 4$  seconds).<sup>49</sup> A low incidence of barotrauma and no mortality were reported with a ventilation strategy involving permissive hypercapnia in patients who had near-fatal asthma in an inner-city hospital.<sup>50</sup> Hypercapnia and associated acidosis are well tolerated in the absence of contraindications such as pre-existing intracranial hypertension;<sup>48</sup> however, inhalation anesthesia may be necessary. Pressure-controlled ventilation is an effective ventilatory strategy in severe status asthmaticus in children and represents a therapeutic option in their management.<sup>51</sup>

### **Neonatal respiratory failure**

Permissive hypercapnia seems to be an effective and safe approach to decrease morbidity from bronchopulmonary dysplasia in premature infants.<sup>52</sup> Retrospective studies

reported a lower incidence of bronchopulmonary dysplasia in infants whose  $\text{PaCO}_2$  values were higher during the first 4 days after birth.<sup>53,54</sup> Kamper and colleagues<sup>55</sup> have shown that ventilatory treatment in 407 extremely premature and extremely low-birth-weight infants based on the principle of permissive hypercapnia and early nasal continuous positive airway pressure supplemented with surfactant resulted in a lower incidence of chronic lung disease than reported with conventional treatment, with comparable survival rates and sensorineural outcomes. Application of a treatment protocol using gentle ventilation and permissive hypercapnia for congenital diaphragmatic hernia produced a significant increase in survival and a concomitant decrease in morbidity; the rate of pneumothorax also was decreased significantly.<sup>56</sup>

Two trials<sup>57,58</sup> involving 269 newborn infants were included in a Cochrane meta-analysis of permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants.<sup>59</sup> There was no evidence that permissive hypercapnia reduced the incidence of death or chronic lung disease at 36 weeks, grade 3 or 4 intraventricular hemorrhage, or periventricular leukomalacia. There were no differences in any other reported outcomes when permissive hypercapnia was compared with routine ventilation in newborn infants. One trial, however, reported that permissive hypercapnia reduced the incidence of chronic lung disease in the subgroup of newborns weighing 501 to 750 g.<sup>58</sup> A recent randomized, controlled trial in 86 extremely preterm infants under 28 weeks' gestational age with optimized ventilation including continuous tracheal gas insufflation, prophylactic surfactant administration, low oxygen saturation target, and moderate permissive hypercapnia resulted in a very gentle ventilation; the rate of survival without bronchopulmonary dysplasia was remarkably high for the whole population (78%) and for the subgroup of infants weighing less than 1000 g at birth (75%).<sup>60</sup>

There are, however, concerns regarding the use of permissive hypercapnia in ventilated very-low-birth-weight infants during the first week of life, because impaired autoregulation during this period may be associated with increased vulnerability to brain injury.<sup>61</sup> A retrospective cohort study of 574 very-low-birth-weight infants has shown that, in addition to traditional risk factors, the maximum  $\text{PaCO}_2$  during the first 3 days of life seems to be a dose-dependent predictor of severe intraventricular hemorrhage.<sup>62</sup> According to Fabres and colleagues,<sup>63</sup> both the extremes of arterial  $\text{CO}_2$  pressure and the magnitude of fluctuations in arterial  $\text{CO}_2$  pressure are associated with severe intraventricular hemorrhage in preterm infants, and it may be prudent to avoid extreme hypocapnia and hypercapnia during the period of risk for intraventricular hemorrhage. Although managing ventilatory support to keep  $\text{PaCO}_2$  values above 40 mm Hg in preterm infants seems to be beneficial and safe,<sup>52</sup> ventilatory strategies targeting high levels of  $\text{PaCO}_2$  (> 55 mm Hg) should be undertaken only in the context of well-designed, controlled clinical trials to establish the safe range for  $\text{CO}_2$  in ventilated newborns and to examine the role of protective ventilatory techniques in achieving this target.<sup>59</sup>

A study of physical outcome and school performance in a cohort of very-low-birth-weight infants treated with early nasal continuous positive airway pressure and a minimal handling regimen with permissive hypercapnia<sup>64</sup> found a relatively low incidence of handicaps and impairments, with near-average school performances that were not different from their siblings', indicating that these infants fare at least as well as survivors after conventional treatment.

#### PERMISSIVE HYPERCAPNIA IN SEPSIS

Sevransky and colleagues,<sup>65</sup> in their review of mechanical ventilation in sepsis-induced ALI/ARDS, recommend using permissive hypercapnia. A large prospective

study (n = 861)<sup>32</sup> of ventilation with lower VTs as compared with traditional VTs for ALI and ARDS, which included patients who had sepsis (27%) and pneumonia (34%), showed that mechanical ventilation with a lower VT results in decreased mortality and increases the number of days without ventilator use. O’Croinin and colleagues,<sup>66</sup> however, argue that the potential for hypercapnia to exert deleterious effects in the context of sepsis and to result in significant adverse consequences is clear. Although hypercapnic acidosis has been shown to be protective against experimental endotoxin-induced lung injury,<sup>14</sup> and the potential for CO<sub>2</sub> to inhibit bacterial growth and metabolism has been demonstrated,<sup>67</sup> several concerns regarding the safety of hypercapnia in sepsis exist, based on experimental studies. Hypercapnic acidosis may inhibit the chemotactic and bactericidal activity of neutrophils and macrophages,<sup>22,23,66,68</sup> render some antibiotics less effective,<sup>69</sup> and potentially increase tissue destruction through neutrophil necrosis.<sup>19</sup> In addition, a study by Stewart and colleagues,<sup>34</sup> which included 42% patients who had pneumonia and 39% who had sepsis, suggested that permissive hypercapnia did not seem to reduce mortality and might increase morbidity. The multiple-organ dysfunction scores and the number of episodes of organ failure were similar in the two groups; the number of patients who required dialysis for renal failure was greater in the limited-ventilation group.<sup>34</sup>

In contrast, another study of protective ventilation involving permissive hypercapnia conducted in 53 patients who had ARDS (with sepsis in 86% of the group receiving protective ventilation and 79% of the group receiving conventional ventilation)<sup>42</sup> resulted in improved survival at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in patients receiving protective ventilation.

In general, caution is advised in using permissive hypercapnia in patients who have sepsis, although most clinical data support its use.

## ADVERSE EVENTS

Although moderate hypercapnia has beneficial effects, these benefits may be counterbalanced by a potential for adverse effects of hypercapnic acidosis at high levels. Permissive hypercapnia, via the combined effects of increased cardiac output and decreased alveolar ventilation, can increase pulmonary shunt and impair pulmonary gas exchange in ARDS.<sup>70</sup> An experimental study demonstrated that severe hypercapnia produced by 15% CO<sub>2</sub> worsened neurologic injury compared with normocapnia (3% CO<sub>2</sub>) or 12% CO<sub>2</sub>,<sup>71</sup> presumably because of more severe cardiovascular depression that leads to greater cerebral ischemia and ultimate brain damage. Two other laboratory studies reported that intestinal lesions<sup>72</sup> and lung inflammation and injuries<sup>73</sup> were induced in rats by experimentally created severe acidosis, which is unlikely in the clinical setting.

Therefore correction of acidosis is important, and most authors prefer to correct it by increasing the mechanical respiratory rate.<sup>8</sup> It has been shown that in patients who have severe ARDS treated with permissive hypercapnia increasing the respiratory rate and reducing instrumental dead space during conventional mechanical ventilation is as efficient as expiratory washout in reducing PaCO<sub>2</sub>.<sup>74</sup> pH as low as 7.15 can be tolerated before the administration of intravenous buffering agents (bicarbonate or tromethamine) is initiated.<sup>31</sup>

## PHARMACOLOGIC BUFFERING OF HYPERCAPNIC ACIDOSIS

In critically ill patients, subjective discomfort caused by hypercapnic acidosis can be mitigated with the appropriate buffering and sedation. A slowly established hypercapnia, in which acidosis is buffered, would have minimal adverse effects.<sup>8</sup> There are

concerns, however, that the protective effects of hypercapnic acidosis in ALI result from the acidosis rather than  $\text{CO}_2$ , and that buffering hypercapnic acidosis may worsen ALI, causing pulmonary vasodilation.<sup>26</sup>

Hypercapnia at normal pH also may enhance cell injury, as evidenced by the impairment of monolayer barrier function and increased induction of apoptosis<sup>28</sup> via modifying nitric oxide-dependent pathways. In addition,  $\text{CO}_2$  can enhance nitration of surfactant protein A by activated alveolar macrophages and decrease its function.<sup>29</sup>

Buffering with bicarbonate raises systemic  $\text{CO}_2$  levels and may worsen an intracellular acidosis.<sup>66,75</sup> Although intracellular acidification occurs after the addition of sodium bicarbonate to a suspension of human leucocytes in vitro, the effect is minimal when the conditions approximate those seen in clinical practice.<sup>75</sup> Another option is the use of tromethamine acetate,<sup>76,77</sup> which does not increase  $\text{CO}_2$  production. Tromethamine buffer may attenuate the reversible depression of myocardial contractility and hemodynamic alterations during rapid permissive hypercapnia<sup>78</sup> and allow the benefit of decreased airway pressures to be realized while minimizing the adverse hemodynamic effects of hypercapnic acidosis. The initial loading dose of tromethamine acetate is 0.3 mol/L, and the maximum daily dose is 15 mmol/kg for an adult;<sup>76</sup> in large doses, it may induce respiratory depression and hypoglycemia, which will require ventilatory assistance and glucose administration.

## SUMMARY

Permissive hypercapnia is one of the central components of current protective ventilatory strategies in critical care for adult, pediatric, and neonatal patients requiring mechanical ventilation. Moderate permissive hypercapnia seems to be effective and safe in ALI and ARDS, status asthmaticus, and neonatal respiratory failure. Patients at risk include those who have head trauma, high intracranial pressure, hemodynamic instability, and myocardial dysfunction. The optimal ventilatory strategy for hypercapnia remains to be established.

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