Re-examining Permissive Hypercapnia in ARDS
A Narrative Review
Tavish Barnes, MD; Vasilios Zochios, MD; and Ken Parhar, MD

Lung-protective ventilation (LPV) has become the cornerstone of management in patients with ARDS. A subset of patients is unable to tolerate LPV without significant CO₂ elevation. In these patients, permissive hypercapnia is used. Although thought to be benign, it is becoming increasingly evident that elevated CO₂ levels have significant physiological effects. In this narrative review, we highlight clinically relevant end-organ effects in both animal models and clinical studies. We also explore the association between elevated CO₂, acute cor pulmonale, and ICU mortality. We conclude with a brief review of alternative therapies for CO₂ management currently under investigation in patients with moderate to severe ARDS.

KEY WORDS: ARDS; acute cor pulmonale; mechanical ventilation; permissive hypercapnia; right ventricular dysfunction

An improved understanding of the pathophysiology and clinical management of ARDS has led to lung-protective ventilation (LPV) becoming a cornerstone of management. Early strategies of mechanical ventilation in ARDS were tailored to achieve tidal volume ventilation of 10-15 mL/kg predicted body weight (PBW). High-pressure, high-tidal volume ventilation strategies were used to overcome densely consolidated poorly compliant lung regions in an effort to achieve adequate arterial oxygenation and normal CO₂ levels. This notion was disproved when the landmark ARMA trial by the Acute Respiratory Distress Syndrome Clinical Network demonstrated significant mortality benefit (22% reduction) with pressure- and volume-limited LPV (6 mL/kg vs 12 mL/kg PBW). LPV may improve outcomes through several mechanisms, including decreased stretch and shear forces applied to the alveolar wall (volutrauma and barotrauma), less cyclic recruitment-derecruitment of atelectatic areas of lung (atelectrauma), and attenuation of

ABBREVIATIONS: ABG = arterial blood gas; ACP = acute cor pulmonale; ALI = acute lung injury; CVP = central venous pressure; \( \text{ECCO}_2 \text{R} \) = extracorporeal venous CO₂ removal; \( \text{Ees} : \text{Ea} \) = ratio of elastance of right ventricle to elastance of pulmonary artery system; \( \text{ECLS} \) = extracorporeal life support; \( \text{HA} \) = hyperacapnic acidosis; IL-8 = interleukin 8; LPV = lung-protective ventilation; mPAP = mean pulmonary arterial pressure; \( \text{MP-KB} \) = nuclear factor kappa light chain enhancer of activated B cells; PA = pulmonary artery; PBW = predicted body weight; PEEP = positive end-expiratory pressure; \( \text{Ppso} \) = pulmonary artery occlusion pressure; \( \text{Pplat} \) = plateau pressure; PVR = pulmonary vascular resistance; \( \text{RV} \) = right ventricular; \( \text{RVEDA} / \text{LVEDA} \) = ratio of right ventricular end-diastolic area to left ventricular end-diastolic area; TEE = transesophageal echocardiography; VILI = ventilator-induced lung injury

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systemic cytokine response (biotauma). Unfortunately, mortality in severe ARDS remains high—upward of 40%. A consequence of low-tidal volume ventilation is a reduced ability to clear CO₂ due to reduced minute ventilation. A subset of patients cannot tolerate LPV without significant Paco₂ elevation. In these patients, a higher respiratory rate to increase minute ventilation and lower Paco₂ or permissive hypercapnia to facilitate low-tidal volume ventilation, is used. Although initially thought to be benign or even protective, it is becoming increasingly evident that elevated CO₂ levels have significant physiological effects that may in fact be deleterious. This review outlines both the physiological and clinical sequelae of permissive hypercapnia in ARDS.

Effects of Hypercapnic Acidosis in Animal Models

Cytokine Response

Normal CO₂ arterial tension is generally within the range of 35 to 45 mm Hg. Classification of hypercapnia is variably defined but will be referred to in this review as mild, moderate, and severe according to the ranges of 46 to 50, 50 to 75, and > 75 mm Hg, respectively. At the molecular level, hypercapnic acidosis inhibits production of proinflammatory cytokines and has been shown to attenuate inflammation related to ventilator induced lung injury (VILI) by inhibition of nuclear factor kappa light chain enhancer of activated B cells (NF-κB), and interleukin 8 (IL-8). Hypercapnic acidosis reduces oxidative reactions in the endotoxin-injured rat lung model. Hypercapnic acidosis has also been associated with less severe VILI in isolated perfused rabbit lungs ex vivo and in vivo. It has been suggested by several groups that therapeutic hypercapnia might provide benefit in ARDS, and although decreasing host oxidative injury through hypercapnic acidosis would be of benefit in many cases, it may be deleterious when the cause of ARDS is pulmonary infection, and the free radicals generated may play a role in facilitating bacterial injury and death.

At the cellular level, hypercapnia alone lowers the release of IL-8 from lipopolysaccharide-stimulated neutrophils, whereas hypercapnic acidemia attenuates lung neutrophil recruitment and function. This leads to a reduced host inflammatory response but at the cost of impaired immune-mediated bactericidal activity in the lung. The latter is also supported by a study showing that mice with Pseudomonas aeruginosa pneumonia exposed to hypercapnia develop impaired neutrophil function and have higher mortality compared with air-exposed counterparts.

Additional studies using neutrophil-depletion and Escherichia coli-mediated lung injury have found hypercapnic acidosis to be beneficial for oxygenation and lung compliance; however, there is no change in either lung inflammation or histologic damage between hypercapnia and normocapnia. Hypercapnia alone significantly enhances inflammatory reactions mediated by nitric oxide and secondary nitrating species in fetal rat lung epithelial cells exposed to lipopolysaccharide and inflammatory cytokines. The duration of hypercapnic acidosis may influence its effects, as attenuation of both histologic and physiological indices of disease severity is observed with hypercapnic acidosis of short duration (< 6 hours) and in models of acute lung injury (ALI) related to systemic sepsis. Conversely, models using pulmonary sepsis-mediated ALI demonstrate no difference in physiological or histologic indices of lung injury with hypercapnic acidosis or worsened histologic indices and higher pulmonary bacterial loads in the setting of prolonged hypercapnic acidosis (> 48 hours duration) without appropriate antimicrobial therapy.

Inhibition of Lung Epithelial Cell Repair and Function

Hypercapnic acidemia impairs pulmonary epithelial wound healing through two mechanisms. First, it slows epithelial repair of stretch-induced cell membrane injury. Second, it inhibits repair of ventilator-induced pulmonary epithelial cell injury, likely through inhibition of the NF-κB pathway, by reducing cell migration and altering matrix metalloproteinase activity. Recent clinical work lends support to these findings, as pleural hypercarbia correlates with persistent alveolar-pleural fistulas post-lung resection. Finally, short-term hypercapnia, independent of pH, has been shown to impair alveolar epithelial cell function, resulting in decreased alveolar fluid resorption.

Renal Effects

Acute hypercapnic acidosis has been shown to have several direct effects on renal vasculature in vivo. In conscious dogs, it reduces renal plasma flow, increases renal vascular resistance, stimulates robust activation of the renin-angiotensin-aldosterone system, contributes to nonsmotic release of vasopressin, and diminishes renal free water excretion. Ischemia-induced apoptosis of rat renal...
tubular cells in vitro is observed when hypercapnia and hypoxemia are present simultaneously.32 In humans, hypoxemia and severe hypercapnia have been associated with reduced renal function,33 whereas higher plasma norepinephrine levels are correlated with hypercapnia.34 There is also a potential association with an increased requirement for hemodialysis in patients using volume- and pressure-limited ventilation with hypercapnia.35

**Diaphragmatic and Skeletal Muscle Effects**

Hypercapnic acidosis has been shown to modulate rat diaphragm myogenic response through endothelium-mediated alterations to diaphragmatic arteriolar tone. Hypercapnic acidosis with CO₂ values < 80 mm Hg elicits enhancement of myogenic tone. Conversely, hypercapnic acidosis with CO₂ values of > 80 mm Hg inhibits myogenic tone through endothelium-dependent inhibitory mechanisms. CO₂ values around 100 mm Hg appear to inhibit myogenic tone by both endothelium-dependent inhibitory mechanisms and direct effects of CO₂ on arteriolar smooth muscle tone.36 In addition, skeletal muscle atrophy is associated with elevated CO₂ both in vitro and in vivo.37 This may have relevance to the subset of patients with ARDS and underlying chronic pulmonary disease in whom muscle atrophy correlates with worse clinical outcomes.

**Pulmonary Circulation**

Hypercapnic acidosis enhances pulmonary vasoconstriction in animals.38-39 In particular, it correlates with significant elevation in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) in non-ARDS39 and ARDS porcine models,38 respectively.

**Buffered Hypercapnic Acidosis**

Preclinical studies have investigated whether hypercapnia or the associated respiratory acidemia exerts the physiological effects in models of ALI. Data from a rodent model using *E. coli* or endotoxin-induced lung injury exhibited worse lung injury and reduced wound healing in renal buffered hypercapnic acidosis in comparison with normocapnic control subjects following 6 hours of LPV.40 Additionally, sepsis-induced ALI in rodents demonstrated similar degrees of physiological and histologic injury in both bicarbonate-buffered hypercapnic acidosis and nonbuffered normocapnic control animals.41

Although evidence from preclinical animal studies provides little to support the notion that hypercapnic acidosis is directly beneficial in ALI, it does highlight the need for further studies. In addition, a strategy using prolonged hypercapnia with untreated pulmonary infection demonstrates evidence of harm without appropriate antimicrobial therapy.25

**Clinical Studies of Permissive Hypercapnia With ARDS**

**Cardiopulmonary Effects of Hypercapnia**

Hypercapnia induces physiological changes in the pulmonary and systemic circulations (Fig 1). In healthy subjects, hypercapnic acidosis induces a rightward shift of the oxygen-hemoglobin dissociation curve42 and lowers systemic vascular resistance.33 In cardiopulmonary patients who have undergone bypass surgery, hypercapnia results in globally reduced myocardial contractility; however, sympathetically driven tachycardia serves to maintain cardiac output when compensatory reserve exists.43 Right ventricular (RV) function is particularly affected in the setting of postoperative hypercapnia so that there is increased right ventricular end-diastolic volume, decreased right ventricular ejection fraction, and a significant increase in right ventricular stroke work index. These observations are in part due to increased PVR owing to the direct vasoconstrictive effects of hypercapnic acidosis on pulmonary vasculature and to the accompanying rise in mPAP.45-47 In patients with chronic pulmonary disease without ARDS, Enson et al48 demonstrated that respiratory acidosis, but not hypercapnia alone, causes elevation in PVR and mPAP. In addition, their study showed that increases in mPAP may be more sensitive to hypoxia at lower pH values. Uncertainty remains as to the relative contribution of hypercapnia and respiratory acidosis to increases in PVR and mPAP in patients with ARDS.

Additional insight into the alteration of pulmonary hemodynamics in ARDS can be obtained by studies examining coupling between the RV and pulmonary arterial circulation. The pulmonary vasculature is characterized by the arterial elastance of the pulmonary artery system synonymous with RV afterload (Ea), whereas the RV system is characterized by the RV elastance (Ees).49 The Ees:Ea is the ratio of RV to pulmonary artery (PA) elastance and reflects the mechanoenergetic aspects of RV/PA coupling, which determines RV stroke volume. When the Ees:Ea is greater than 1 (normal range 1.5-2), the system is
coupled, providing adequate RV cardiac output at minimal energy cost.\textsuperscript{50} In the context of hypercapnia, pulmonary vasoconstriction and elevated RV afterload may lead to an increase in Ea, uncoupling of the RV/PA system, and subsequent RV dysfunction.\textsuperscript{50}

\textbf{Cardiopulmonary Effects of Mechanical Ventilation in ARDS}

Studies of mechanical ventilation in patients with ARDS some 40 years ago first identified pulmonary capillary lesions leading to pulmonary hypertension, marked RV dysfunction with elevation of right ventricular stroke work index, and upward of a threefold increase in PVR.\textsuperscript{51-54} ACP represents the most severe form of RV dysfunction and has been the subject of numerous investigations in the ARDS population. It is variably defined using right heart catheterization, pulmonary artery catheterization, and echocardiography.

Prior to the advent of LPV, ACP (defined as septal dyskinesia associated with a right ventricular to left ventricular end-diastolic area ratio [RVEDA/LVEDA] > 0.6) was very common and could be observed in more than half of patients examined.\textsuperscript{55} Not surprisingly, it is positively correlated with increases in plateau pressure (Pplat) during mechanical ventilation.\textsuperscript{56} In a large pooled analysis using echocardiographic studies of patients with ARDS, the presence of ACP was 13%, 32%, and 56% when Pplat values ranged between 18 and 26, 27 and 35, and > 35 cmH\textsubscript{2}O, respectively. The highest mortality was observed in the two groups with highest Pplat values, in whom ACP was most prevalent.\textsuperscript{56} However, similar studies using LPV have described significantly lower rates.\textsuperscript{57} For example,
Osman et al\(^5\) noted that RV failure (defined as the presence of mPAP > 25 mm Hg, central venous pressure (CVP) greater than pulmonary artery occlusion pressure [Ppao], and stroke volume index < 30 mL/m\(^2\)) was present in approximately 10% of patients with ARDS,\(^5\) whereas Boissier et al\(^9\) and Lheritier et al\(^6\) noted a prevalence of acute cor pulmonale of 22% and 22.5%, respectively. Driving pressure (defined as the difference between Pplat and total positive end-expiratory pressure [PEEP]) is a surrogate of lung stress that has been associated with survival and risk of cor pulmonale in patients with ARDS, which may suggest that a “low-pressure” ventilatory strategy could be protective of the right ventricle.\(^6\) Lower overall rates of ACP in more recent studies likely relates to a combination of right ventricle-protective ventilation strategies, heterogeneity in the definition itself, and therapeutic ventilator adjustments based on its earlier recognition.

**Cardiopulmonary Effects of Permissive Hypercapnia in ARDS**

Despite these improvements, RV dysfunction remains prevalent and is linked to worsened outcomes in ARDS. For example, severe RV dysfunction is shown to be more prevalent in nonsurvivors of ARDS.\(^6\) RV dysfunction in early ARDS, as defined by a higher ratio of right atrial pressure to Ppao was independently associated with higher mortality.\(^6\) The higher mortality exhibited in this study may in part be explained by the effects of mechanical ventilation in the era prior to adoption of LPV; however, studies of patients with ARDS in the era following adoption of LPV also show a correlation between RV dysfunction and mortality. Boissier et al\(^9\)

**TABLE 1** Summary of Clinical Studies Showing Correlation Between Hypercapnia, Severe RV Dysfunction/ACP, and Mortality in Mechanically Ventilated Patients With ARDS

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Study Design</th>
<th>Results</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vieillard- Baron (^7)/2001</td>
<td>Prospective single-center open design</td>
<td>Multivariate regression analysis: (\text{Paco}_2) independently associated with ACP</td>
<td>1.15 (1.05-1.25)</td>
<td>&lt; .0001</td>
<td>ACP defined as ratio of RVEDA/LVEDA &gt; 0.6 by TEE. MV: Pplat limited to &lt; 30 cm H(_2)O, tidal volume of 6-9 mL/kg (PBW), PEEP range, 3-15 cm H(_2)O.</td>
</tr>
<tr>
<td>Lheritier et al(^6)/2013</td>
<td>Prospective multicenter</td>
<td>Multivariate regression analysis: (\text{Paco}_2) &gt; 60 mm Hg strongly associated with ACP</td>
<td>3.70 (1.32-10.38)</td>
<td>.01</td>
<td>ACP defined as ratio of RVEDA/LVEDA &gt; 0.6 by TEE. MV: Pplat &lt; 30 cm H(_2)O, tidal volume and PEEP according to expert recommendations from the Societe de Reanimation de Langue Francaise.</td>
</tr>
<tr>
<td>Mekontso Dessap et al(^7)/2016</td>
<td>Prospective multicenter</td>
<td>Multivariate regression analysis: severe ACP independently associated with inhospital mortality</td>
<td>2 (1.03-3.88)</td>
<td>0.04</td>
<td>ACP and severe ACP defined as ratio of RVEDA/LVEDA &gt; 0.6 and &gt; 1 respectively with presence of septal dyskinesia by TEE. MV: Pplat &lt; 30 cm H(_2)O, tidal volume of 6-8 mL/kg (PBW), PEEP 8 ± 4 cm H(_2)O.</td>
</tr>
</tbody>
</table>

ACP = acute cor pulmonale; MV = mechanical ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; RVEDA/LVEDA = ratio of right ventricular end-diastolic area to left ventricular end diastolic area; TEE = transesophageal echocardiography.
found significantly higher 28-day mortality in patients with ARDS and severe RV dysfunction, and Osman et al found that elevated mPAP or CVP greater than Ppao, respectively, was independently associated with 90-day mortality. In addition, secondary analysis of patients with ARDS from the Fluid and Catheter Treatment Trial (FACTT) demonstrated that elevation of transpulmonary gradient (mPAP – Ppao) or elevated PVR index, conferred a higher risk for 60-day mortality.64

Notwithstanding LV, permissive hypercapnia coupled with moderate to severe ARDS may exert a synergistic effect that can lead to ACP. Widespread use of modern two-dimensional echocardiography not only has improved our understanding of the effects of mechanical ventilation on RV function but also has facilitated a better understanding of the relationship between mechanical ventilation, permissive hypercapnia, and the development of ACP (Table 1). Mekontso Dessap et al used transeosophageal echocardiography (TEE) in patients with severe ARDS to demonstrate that induction of hypercapnic acidosis with low-tidal volume ventilation and increasing PEEP at constant plateau pressure directly impaired RV function independent of the effects of PEEP.55 Veillard-Baron et al performed a multivariate analysis in 75 patients with ARDS studied using TEE. They found that elevated Paco2 was the sole individual predictor of ACP. Although the latter had no influence on mortality, the authors correctly identified ACP early in the study and introduced prone ventilation on day 3 in those patients with a Paco2/Fio2 < 100 mm Hg. Such adaptations may have mitigated the mortality associated with ACP. Lheriter et al used a combination of transthoracic echocardiography and TEE to study 200 patients with moderate to severe ARDS < 48 hours after admission. Elevated Paco2 was significantly associated with ACP, and Paco2 ≥ 60 mm Hg was the only independent factor associated with ACP.64 The study also found that the systolic pressure gradient between the right ventricle and right atrium (ΔPmax), an indirect measurement of pulmonary vascular tone, correlated with Paco2 and was significantly higher in patients with a Paco2 ≥ 60 mm Hg.64 Despite the study findings, there was no association between ACP at < 48 hours after admission and 28-day mortality.65 In a recent large prospective observational study (N = 752), Mekontso Dessap et al identified hypercapnia (Paco2 ≥ 48 mm Hg) as a respiratory variable with a statistically significant correlation with cor pulmonale (assessed by TEE) in patients with ARDS receiving LPV. ACP was found in 22% of the cohort, and severe ACP (defined as RVEDA/LVEDA > 1) was found in 7.2% of patients and was an independent predictor of mortality.

Secondary analysis of the ARDS Network study published by Kregenow et al found that the presence of hypercapnic acidosis at randomization was associated with lower 28-day mortality in the group randomized to a tidal volume of 12 mL/kg (but no mortality difference in patients randomized to 6 mL/kg) (Table 2). This study had several limitations, including being a retrospective secondary analysis, defining hypercapnic acidosis based on a day 1 blood gas measurement rather than sustained hypercapnic acidosis over time, as well as having very few patients in the hypercapnic acidosis group. As this was a secondary analysis, there was no causality proved but only an association inferred.

In contrast to the Kregenow et al study, two recent studies looking at mechanically ventilated patients in the ICU have called into question the safety of hypercapnic acidosis. The first study was retrospective and included 252,812 patients admitted to ICUs with respiratory failure requiring mechanical ventilation during the first 24 hours of their ICU admission. It found that hypercapnic acidosis in the first 24 hours of ICU admission was associated with higher inhospital mortality compared with compensated hypercapnia or normocapnia (Table 2). Interestingly, both patients with compensated hypercapnia and those with hypercapnic acidosis had higher mortality rates. This effect was consistent across all types of ICU admissions. This study’s strengths were the large number of patients included and the longitudinal nature of the data collection (data over a 14-year period from 171 ICUs). This study classified patients based on a day 1 arterial blood gas (ABG) measurement and did not account for adjunctive treatments such as bicarbonate infusions and extracorporeal life support (ECLS).

The second study was a secondary analysis of 1,899 patients from three prospective noninterventional cohort studies on patients with ARDS. It demonstrated that severe hypercapnia, as defined by a Paco2 ≥ 50 mm Hg, was associated with higher ICU mortality in a population with moderate to severe ARDS (Table 2). The authors used propensity matching to conduct a sensitivity analysis to demonstrate that hypercapnia independent of acidosis was associated with increased mortality, whereas both had independent additive effects on increasing mortality. This study...
<table>
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<tbody>
<tr>
<td>Kregenow et al(^{10})/2006</td>
<td>Retrospective secondary analysis of ARMA trials (ARDS Network) multicenter RCT (2000) N = 861</td>
<td>Multivariate regression analysis Lower 28-d mortality associated with hypercapnic acidosis at 12 mL/kg (PBVW) No reduction in 28-d mortality associated with hypercapnic acidosis in low-tidal volume ventilation group (6 mL/kg PBV)</td>
<td>0.14 (adjusted) (0.03-0.70)</td>
<td>.016</td>
<td>HA based on day 1 ABG measurement only; too few patients with sustained HA to analyze Significant number of patients missing day 1 ABG measurement No data collected on IV bicarbonate infusion use</td>
</tr>
<tr>
<td>Tiruvpilati et al(^{11})/2017</td>
<td>Retrospective multicenter international study N = 252,612</td>
<td>Multivariate regression analysis Higher hospital mortality for patients with hypercapnic acidosis, and compensated hypercapnia, (adjusted for severity of illness) OR compared with normocapnia with normal pH 1.74 (1.62-1.88 and 1.18 (1.10-1.26), respectively</td>
<td>&lt;.001</td>
<td></td>
<td>Strength of this study was the high number of patients included Used only day 1 ABG data to classify No data collected on use of IV bicarbonate infusion or extracorporeal life support</td>
</tr>
<tr>
<td>Nin et al(^{12})/2017</td>
<td>Secondary analysis of 3 prospective noninterventional cohort studies (multicenter international) N = 1,899</td>
<td>Multivariate regression analysis Significantly higher ICU mortality in patients with maximum PaCO(_2) of ≥ 50 mm Hg (severe hypercapnia) during the first 48 h of MV</td>
<td>1.93 (1.32-2.81)</td>
<td>.001</td>
<td>Strength is a secondary analysis of multinational multicenter cohort from ICUs in 40 countries Used worst PaCO(_2) from ABGs within 48 h of initiation of MV</td>
</tr>
<tr>
<td>Nin et al(^{12})/2017</td>
<td>Secondary analysis of 3 prospective noninterventional cohort studies (multicenter international) N = 1,899</td>
<td>Additional binomial logistic model omitting acidosis: PaCO(_2) of ≥ 50 mm Hg independently associated with a higher risk of ICU mortality</td>
<td>2.40 (1.67-3.46)</td>
<td>&lt;.001</td>
<td>11.5% of patients excluded due to missing ABG data No data collected on use of IV bicarbonate infusion or extracorporeal life support</td>
</tr>
<tr>
<td>Nin et al(^{12})/2017</td>
<td>Secondary analysis of 3 prospective noninterventional cohort studies (multicenter international) N = 1,899</td>
<td>Higher rates of organ failure and complications with PaCO(_2) of ≥ 50 vs &lt; 50 mm Hg</td>
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<tr>
<td>Nin et al(^{12})/2017</td>
<td>Secondary analysis of 3 prospective noninterventional cohort studies (multicenter international) N = 1,899</td>
<td>Cardiovascular failure</td>
<td></td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Nin et al(^{12})/2017</td>
<td>Secondary analysis of 3 prospective noninterventional cohort studies (multicenter international) N = 1,899</td>
<td>Renal failure</td>
<td></td>
<td>.013</td>
<td></td>
</tr>
<tr>
<td>Nin et al(^{12})/2017</td>
<td>Secondary analysis of 3 prospective noninterventional cohort studies (multicenter international) N = 1,899</td>
<td>Barotrauma</td>
<td></td>
<td>.011</td>
<td></td>
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ABG = arterial blood gas; HA = hypercapnic acidosis. See Table 1 legend for expansion of other abbreviations.
included patients from 927 ICUs in 40 countries. The
investigators used the worst ABG measurement in the first
48 hours of mechanical ventilation to stratify patients.
Some of the weaknesses of this study included a high
number of patients being excluded due to missing ABG
data (11.5%) and no data collection on the use of adjunctive
therapies such as bicarbonate infusions and ECIS.

Hypercapnia and Organ Dysfunction

Not surprisingly, the harmful effects of severe
hypercapnia extend beyond the cardiopulmonary
system. In the study by Nin et al,^{20} hypercapnic acidosis
was associated with higher ventilator-associated
complication rates (such as barotrauma) and more
organ failure, including renal and cardiovascular
dysfunction. Further studies will be required to
externally validate and elucidate the pathophysiological
basis for these findings and whether they share
similarities to those described in animal models.

Strategies of LPV When Severe Hypercapnia Is
Present

LPV, Dead Space, and Hypercapnia

Hypercapnia in patients with ARDS can be an
unintended consequence of LPV but may also be the
result of higher dead space associated with increasing
disease severity. This is important to identify early in the
disease process, as a higher dead space fraction in early
ARDS is independently associated with higher
mortality.^{71} Strategies aimed at reducing alveolar dead
space along with the severity of hypercapnia can be used
but carry risk. First, adequate lung recruitment to
facilitate ventilation in ARDS often necessitates finding
optimal PEEP levels, but care must be used to avoid
alveolar overdistention, which can negatively affect
pulmonary hemodynamics and RV function. Second,
titrating PEEP and driving pressure to achieve a desired
tidal volume and PaCO\textsubscript{2} threshold during LPV is a
complex process. For instance, in an observational post
hoc analysis of nine randomized controlled trials of
patients with ARDS, Amato et al^{61} demonstrated that
decreases in tidal volume or increases in PEEP are
beneficial only when associated with decreased driving
pressure. Finally, higher respiratory rates to correct
hypercapnia are not tolerated in some patients with
ARDS due to the development of dynamic
hyperinflation and significant RV dysfunction.^{72} In
summary, strategies to lower PaCO\textsubscript{2} can be associated
with significant harm, and their use must be weighed
against the risks associated with permissive hypercapnia.

Prone Positioning

Placing patients with severe ARDS in the prone position
has been demonstrated to improve oxygenation and
compliance, and early institution improves mortality.^{75}
Some studies, however, have suggested that it is the
decline in PaCO\textsubscript{2} associated with a reduction in alveolar
dead space rather than increased PaO\textsubscript{2} that might best
reflect the degree of functional lung recruited with prone
positioning.^{74,75} Unfortunately, the only prospective
randomized controlled trial to demonstrate mortality
benefit with prone positioning (Proning Severe ARDS
Patients [PROSEVA]) did not directly evaluate alveolar
recruitment with prone positioning.^{73} In addition, a
retrospective analysis of PROSEVA by Albert et al,^{76}
demonstrated that increased survival with prone
positioning was not predicted by improvement in gas
tension as determined by blood gas analysis.
Nonetheless, prone positioning can lower PaCO\textsubscript{2} and
unload the right ventricle in selected groups of patients
in the ICU and is an important tool to improve patient
outcomes in severe ARDS.^{77}

Extracorporeal Venovenous CO\textsubscript{2} Removal

Debate continues over the role of extracorporeal devices
in the management of ARDS. Specifically, there has been
renewed interest in extracorporeal venovenous CO\textsubscript{2}
removal (ECCO\textsubscript{2}R), which offers efficient CO\textsubscript{2} removal
with relatively low blood flow rates. A recent
experimental porcine model used by Morimont et al^{38}
sought to determine whether ECCO\textsubscript{2}R during LPV
could improve pulmonary hemodynamics and RV
function in early ARDS. Institution of ECCO\textsubscript{2}R
effectively corrected acidosis and hypercapnia during
LPV. In addition, PVR and mPAP were significantly
reduced and right ventricle-P(A) (Ep:Ea) coupling was
improved. Changes in both pH and PaCO\textsubscript{2} were highly
correlated with changes in mPAP. Whether findings
from this study are translatable to human patients with
ARDS is unknown. At minimum, it provides rationale
to initiate prospective studies in patients with moderate to
severe ARDS using early institution of ECCO\textsubscript{2}R to
normalize pH and CO\textsubscript{2} in conjunction with current
standards of LPV.

Ultralow-tidal Volume Ventilation and Maintenance
of Normocapnia

Several recent trials have examined ultralow-tidal
volume ventilation (3-4 ml/kg) in combination with
ECCO\textsubscript{2}R to determine its feasibility and whether
additional benefit beyond current LPV exists.^{78-80} In
theory, ultralow-tidal volume ventilation lowers the risk

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of alveolar overdistention that can still occur despite our current use of LPV.81 It prevents the hemodynamic changes (ACP or RV failure, or both) and it facilitates a “least damaging” ventilatory approach (substantially lower Pplat and driving pressure values) that some have speculated would confer survival benefit.82 Although the study by Bein et al78 did not show an overall difference in 28- or 60-day ventilator-free days between groups, a post hoc analysis demonstrated that patients with severe hypoxemia at randomization (PaO2/ FiO2 < 150 mm Hg) had a significantly shorter ventilation period as assessed by higher 60-day ventilator-free days. Additional studies on this front are under way (SUPERNOVA and REST). Yet despite these trials, it remains unclear whether the “least damaging” ventilation approach with ultralow-tidal volume ventilation and maintenance of normocapnia should be applied to patients with moderate ARDS or severe ARDS and whether it confers benefit over current standards of LPV with maintenance of normocapnia in either of these groups.

The Role of Buffers in the Management of ARDS

There is substantial uncertainty over the role of buffers in the management of respiratory acidosis associated with LPV. Although the ARMA trial permitted sodium bicarbonate infusions in the low-tidal volume protocol when pH fell to < 7.15,1 their use warrants caution. A reasonable approach would be to use a strategy similar to the protocol used in the low-tidal volume ventilation group of the ARMA trial.1

Conclusions

Preliminary studies of ARDS have provided insight into the physiological effects of hypercapnia acidosis; however, the relative contribution of hypercapnia on mortality in animal models remains uncertain except in the context of active untreated pulmonary infection in which it is associated with worsened outcomes. Clinical studies in patients with ARDS have shown an association between severe hypercapnia, ACP, and mortality. Severe hypercapnia has also been associated with higher rates of noncardiovascular organ dysfunction and ICU mortality in patients with moderate to severe ARDS. 

Ultra-LPV with maintenance of normocapnia using extracorporeal CO2 removal offers potential advantages over current standards of LPV. It remains uncertain, however, whether this strategy should be applied to patients with moderate ARDS or severe ARDS, or both.

Furthermore, it remains to be determined whether this strategy offers additional benefit in either of these patient groups compared with LPV with maintenance of normocapnia.

Final Thoughts

Severe hypercapnia has deleterious consequences in patients with moderate to severe “Berlin criteria” ARDS. For clinicians managing such patients, we suggest controlling severe hypercapnia so that PaCO2 is kept at < 50 mm Hg in line with current evidence.83 In addition to examining ultralow-tidal volume ventilation with ECCO2R, it is time to reassess current LPV strategies in patients with moderate to severe ARDS. A larger adequately powered randomized study using LPV comparing maintenance of normocapnia with ECCO2R vs permissive hypercapnia is warranted.

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References


