Re-examining Permissive Hypercapnia in ARDS

Barnes, Tavish; Zochios, Vasileios; Parhar, Ken

DOI:
10.1016/j.chest.2017.11.010

Document Version
Peer reviewed version

Citation for published version (Harvard):
Barnes, T, Zochios, V & Parhar, K 2017, 'Re-examining Permissive Hypercapnia in ARDS: A Narrative review', *Chest*. https://doi.org/10.1016/j.chest.2017.11.010

Accepted Manuscript

Re-examining permissive hypercapnia in ARDS: A narrative review

Tavish Barnes, MD, Vasileios Zochios, MD, Ken Parhar, MD

PII: S0012-3692(17)33115-X

DOI: 10.1016/j.chest.2017.11.010

Reference: CHEST 1438

To appear in: *CHEST*

Received Date: 5 July 2017

Revised Date: 20 October 2017

Accepted Date: 13 November 2017

Please cite this article as: Barnes T, Zochios V, Parhar K, Re-examining permissive hypercapnia in ARDS: A narrative review, *CHEST* (2017), doi: 10.1016/j.chest.2017.11.010.

Word Count - Abstract: 110
Word Count – Body: 3987

Re-examining permissive hypercapnia in ARDS: A narrative review

Tavish Barnes MD[1], Vasileios Zochios MD[2], Ken Parhar MD[1]

1) Department of Critical Care Medicine, University of Calgary, Calgary, Canada
2) Department of Critical Care Medicine, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, College of Medical and Dental Sciences, University of Birmingham, Birmingham, England

Corresponding author:

Dr Ken Kuljit Singh Parhar

Department of Critical Care Medicine. University of Calgary
ICU Administration - Ground Floor - McCaig Tower
Foothills Medical Center
3134 Hospital Drive NW
Calgary, Alberta
T2N 5A1

ken.parhar@albertahealthservices.ca

Co-Author Email Addresses:
Tavish Barnes MD : tavish.barnes@ahs.ca
Vasileios Zochios MD : vasileioszochios@doctors.org.uk

Disclosures:

The authors (TB, VZ, KP) declare no conflicts of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations

Abbreviation	Definition
ABG	Arterial Blood Gas
ACP	Acute Cor Pulmonale
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
CO_2	Carbon Dioxide
CVP	Central Venous Pressure
Ees:Ea	Ratio of elastance of right ventricle to elastance of pulmonary artery system
ECLS	Extra Corporeal Life Support
HA	Hypercapnic Acidosis
HR	Heart Rate
IL-8	Interleukin 8
LPV	Lung Protective Ventilation
mPAP	Mean Pulmonary Arterial Pressure
MV	Mechanical Ventilation
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OR	Odds Ratio
PA	Pulmonary Artery
$PaCO_2$	Partial Pressure of arterial Carbon Dioxide
PaO_2	Partial Pressure of arterial Oxygen
PBW	Predicted Body Weight
PEEP	Positive End Expiratory Pressure
Ppao	Pulmonary artery Occlusion Pressure
Pplat	Plateau Pressure
PVR	Pulmonary Vascular Resistance
RV	Right Ventricle
RVEDA/LVEDA	Ratio of Right Ventricular End Diastolic Area to Left Ventricular End Diastolic Area
RVEF	Right Ventricular Ejection Fraction
RVSWI	Right Ventricular Stroke Work Index
SVR	Systemic Vascular Resistance
TEE	Trans Esophageal Echocardiography
TTE	Trans Thoracic Echocardiography
VILI	Ventilator Induced Lung Injury

Abstract

Lung protective ventilation has become the cornerstone of management in patients with ARDS. A subset of patients are unable to tolerate lung protective ventilation without significant carbon dioxide elevation. In these patients permissive hypercapnia is used. Although thought to be benign, it is becoming increasingly evident that elevated carbon dioxide 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 carbon dioxide, 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.

Keywords:

Permissive hypercapnia

Mechanical Ventilation

Acute respiratory distress syndrome

Acute cor pulmonale

Right ventricular dysfunction

1. Introduction

An improved understanding of the pathophysiology and clinical management of acute respiratory distress syndrome (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) [1]. High pressure, high tidal volume ventilation strategies were utilized to overcome densely consolidated, poorly compliant lung regions in an effort to achieve adequate arterial oxygenation and normal carbon dioxide (CO_2) levels [2,3]. This notion was disproven when the landmark ARMA trial by the ARDS Network demonstrated significant mortality benefit, (22% reduction) with pressure and volume limited LPV (6ml/kg vs 12 ml/kg PBW) [1]. LPV may improve outcomes through several mechanisms including: decreased stretch and sheer forces applied to the alveolar wall (volutrauma and barotrauma), less cyclic recruitment-derecruitment of atelectatic areas of lung (atelectrauma) and attenuation of systemic cytokine response (biotrauma) [4]. Unfortunately, mortality in severe ARDS remains high – upwards of 40% [5]. A consequence of low tidal volume ventilation is a reduced ability to clear CO_2 due to reduced minute ventilation. A subset of patients cannot tolerate LPV without significant $PaCO_2$ elevation. In these patients, a higher respiratory rate to increase minute ventilation and lower $PaCO_2$ or permissive hypercapnia to facilitate low tidal volume ventilation, are used. Although initially thought to be benign or even protective, it is becoming increasingly evident that elevated CO_2 levels have significant physiological effects that may in fact be deleterious. This review will outline both the physiological and clinical sequelae of permissive hypercapnia in ARDS.

2. Effects of hypercapnic acidosis in animal models

2.1 Cytokine Response

Normal CO_2 arterial tension is generally within the range of 35– 45 mmHg. Classification of hypercapnia is variably defined but will be referred to in this review as mild, moderate and severe according to ranges of 46-50 mmHg, 50-75 mmHg and greater than 75 mmHg, respectively[6]. At the molecular level, hypercapnic acidosis inhibits production of pro-inflammatory 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) [7,8]. Hypercapnic acidosis reduces oxidative reactions in the endotoxin-injured rat lung model [9]. Hypercapnic acidosis has also been associated with less severe VILI in isolated perfused rabbit lungs ex vivo [10] and in vivo [11]. It has been suggested by several groups that therapeutic hypercapnia might provide benefit in ARDS [12-14] and while decreasing host oxidative injury via hypercapnic acidosis would be of benefit in many cases, it may be deleterious when the etiology of ARDS is pulmonary infection and free radicals generated may play a role in facilitating bacterial injury and death [15].

At the cellular level, hypercapnia alone lowers release of IL-8 from lipopolysaccharide-stimulated neutrophils [16] while 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 [14]. 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 as compared to air-exposed counterparts [17].

Additional studies using neutrophil-depletion and *E. 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 histological damage between hypercapnia and normocapnia [18]. 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 [19]. The duration of hypercapnic acidosis may influence its effects as attenuation of both histologic and physiologic indices of disease severity is observed with hypercapnic acidosis of short duration (< 6 hours) [20] and in models of acute lung injury (ALI) related to systemic sepsis [21]. Conversely, models using pulmonary sepsis-mediated ALI demonstrate no difference in physiologic or histologic indices of lung injury with hypercapnic acidosis [22] or worsened histologic indices and higher pulmonary bacterial loads in the setting of prolonged hypercapnic acidosis (>48 hrs duration) without appropriate anti-microbial therapy [23].

2.2 Inhibition of lung epithelial cell repair and function

Hypercapnic acidemia impairs pulmonary epithelial wound healing through two mechanisms [24,25]. Firstly, it slows epithelial repair of stretch-induced cell membrane injury [24]. Secondly, it inhibits repair of ventilator-induced pulmonary epithelial cell injury likely via inhibition of the NF-κB pathway by reducing cell migration and altering matrix metalloproteinase activity [25]. Recent clinical work lends support to these findings as pleural hypercarbia correlates with persistent alveolar-pleural fistulae post-lung resection[26]. Finally, short-term hypercapnia, independent of pH has been shown to impair alveolar epithelial cell function resulting in decreased alveolar fluid resorption [27].

2.3 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 [28-30], increases renal vascular resistance [30], stimulates robust activation of the renin-angiotensin-aldosterone system [30,31], contributes to non-osmotic release of vasopressin [29] and diminishes renal free water excretion [29]. Ischemia-induced apoptosis of rat renal tubular cells in vitro is observed when hypercapnia and hypoxemia are simultaneously present[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 increased requirement for hemodialysis in patients using volume and pressure limited ventilation with hypercapnia [35].

2.4 Diaphragmatic and skeletal muscle effects

Hypercapnic acidosis has been shown to modulate rat diaphragm myogenic response via endothelium-mediated alterations to diaphragmatic arteriolar tone. Hypercapnic acidosis with CO_2 values < 80 mmHg elicits enhancement of myogenic tone. Conversely, hypercapnic acidosis with CO_2 of >80 mmHg inhibits myogenic tone through endothelium-dependent inhibitory mechanisms. CO_2 values around 100 mm Hg appear to inhibit myogenic tone by both endothelium-dependent inhibitory mechanisms and direct effects of CO_2 on arteriolar smooth muscle tone [36]. In addition, skeletal muscle atrophy is associated with elevated CO_2 both in vitro and in vivo [37]. This may have relevance to the subset of ARDS patients with underlying chronic pulmonary disease in which muscle atrophy correlates with worse clinical outcomes.

2.5 Pulmonary circulation

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

2.6 Buffered hypercapnic acidosis

Pre-clinical 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 to normocapnic controls following 6 hours of lung protective ventilation [40]. Similarly, sepsis-induced ALI in rodents demonstrated similar degrees of physiologic and histologic injury in both bicarbonate-buffered hypercapnic acidosis and non-buffered normocapnic controls [41].

While evidence from pre-clinical 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 [23].

3.Clinical studies of permissive hypercapnia with ARDS

3.1 Cardio-pulmonary effects of hypercapnia

Hypercapnia induces physiological changes in pulmonary and systemic circulation (figure 1). In healthy subjects, hypercapnic acidosis induces a rightward shift of the oxygen-hemoglobin dissociation curve [42] and lowers systemic vascular resistance (SVR) [43]. In post cardiopulmonary bypass surgery patients, hypercapnia results in globally reduced myocardial contractility; however, sympathetically driven tachycardia serves to maintain cardiac output when compensatory reserve exists [44]. Right ventricular function is particularly affected in the setting of post-operative hypercapnia such that there is increased right ventricular end-diastolic volume, decreased right ventricular ejection fraction (RVEF), and a significant increase in right ventricular stroke work index (RVSWI). These observations are in part due to increased pulmonary vascular resistance (PVR) owing to the direct vasoconstrictive effects of hypercapnic acidosis on pulmonary vasculature and to the accompanying rise in mPAP [45-47]. In non-ARDS patients with chronic pulmonary disease, Enson *et al*. demonstrated that respiratory acidosis but not hypercapnia alone causes elevation in PVR and mPAP [48] . 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 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]. Ees:Ea is the ratio of RV to pulmonary

artery (PA) elastance and reflects the mechano-energetic aspects of RV/PA coupling which determines RV stroke volume. When Ees:Ea is greater than 1 (normal range 1.5 to 2), the system is coupled providing adequate RV cardiac output at minimal energy cost [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 [50].

3.2 Cardio-pulmonary 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 upwards of threefold increase in PVR [51-54]. Acute cor pulmonale represents the most severe form of RV dysfunction and has been the subject of numerous investigations in the ARDS patient population. It is variably defined using right heart catheterization, pulmonary artery catheterization and echocardiography.

Prior to the advent of LPV, acute cor pulmonale (defined as septal dyskinesia associated with a right ventricular to left ventricular end diastolic area ratio [RVEDA/LVEDA] greater than 0.6) was very common and could be observed in more than half of patients examined [55]. Not surprisingly, it is positively correlated with increases in plateau pressure (Pplat) during mechanical ventilation [56]. In a large pooled analysis using echocardiographic studies of patients with ARDS, the presence of acute cor pulmonale was 13%, 32% and 56% when Pplat values ranged between 18-26 cmH_2O, 27-35 cmH_2O and > 35 cmH_2O, respectively. The highest mortality was observed in the two groups with highest Pplat values and in which acute cor pulmonale

was most prevalent [56]. However, similar studies using lung protective ventilation have described significantly lower rates [57]. For example, Osman *et al.* noted that right ventricular failure (defined as the presence of: mPAP > 25mmHg, central venous pressure (CVP) > pulmonary artery occlusion pressure (Ppao) and stroke volume index < 30ml/m^2) was present in approximately 10% of ARDS patients [58], whereas Boissier *et al* and Lheritier *et al* noted prevalence of acute cor pulmonale of 22% [59] and 22.5%, respectively [60]. Driving pressure (defined as the difference between Pplat and total PEEP) is a surrogate of lung stress that has been associated with survival and risk of cor pulmonale in ARDS patients which may suggest that a 'low pressure' ventilatory strategy could be RV-protective [61]. Lower overall rates of acute cor pulmonale in more recent studies likely relates to a combination of RV-protective ventilation strategies, heterogeneity in the definition itself, and to therapeutic ventilator adjustments based on its earlier recognition.

3.3 Cardiopulmonary effects of permissive hypercapnia in ARDS

In spite of 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 non-survivors of ARDS [62]. RV dysfunction in early ARDS as defined by a higher ratio of right atrial pressure to pulmonary artery occlusive pressure (P_{RA}/Ppao) was independently associated with higher mortality [63]. 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 ARDS patients in the era following adoption of LPV also show a correlation between RV dysfunction and mortality. Boissier *et al* found significantly higher 28-day mortality in ARDS patients with severe RV dysfunction [59] and Osman *et al* found that elevated mPAP or CVP > Ppao respectively, to be

independently associated with 90-day mortality [58]. In addition, secondary analysis of ARDS patients from the Fluid and Catheter Treatment Trial (FACTT) demonstrated that elevation of transpulmonary gradient (mPAP - Ppao) or elevated pulmonary vascular resistance index, conferred a higher risk for 60-day mortality [64].

Notwithstanding LPV, permissive hypercapnia coupled with moderate to severe ARDS may exert a synergistic effect that can lead to acute cor pulmonale. Widespread use of modern 2D echocardiography has not only improved our understanding of the effects of mechanical ventilation on RV function but has facilitated a better understanding of the relationship between mechanical ventilation, permissive hypercapnia and the development of acute cor pulmonale (table 1). Mekontso-Dessap *et al* utilized transesophageal 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 [65]. Vieillard-Baron *et al* performed multivariate analysis of 75 patients with ARDS studied using transesophageal echocardiography (TEE). They found that elevated $PaCO_2$ was the sole individual predictor of acute cor pulmonale [57]. While the latter had no influence on mortality, the authors correctly identified acute cor pulmonale early in the study and introduced prone ventilation on day 3 in those patients that had $PaO_2/FiO_2 < 100$ mmHg. Such adaptions may have mitigated the mortality associated with acute cor pulmonale [66]. Lheritier *et al* utilized a combination of TTE and TEE to study 200 patients with moderate to severe ARDS < 48 hrs from admission. Elevated $PaCO_2$ was significantly associated with acute cor pulmonale and $PaCO_2 \geq 60$ mmHg was the only independent factor associated with acute cor pulmonale [60]. 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 $PaCO_2$ and was significantly higher in those patients with $PaCO_2 \geq 60$ mmHg [60]. Despite the study findings, there was no association between acute cor pulmonale at < 48 hrs from admission and 28-day mortality [60]. In a recent large prospective observational study (n=752) Mekontso-Dessap *et al* identified hypercapnia ($PaCO_2 \geq 48$ mmHg) as a respiratory variable with statistically significant correlation with cor pulmonale (assessed by TEE) in ARDS patients receiving LPV. Acute cor pulmonale was found in 22% of the cohort and severe acute cor pulmonale (defined as RVEDA/LVEDA >1) was found in 7.2 % of patients and was an independent predictor of mortality [67].

Secondary analysis of the ARDS Network Study published by Kregenow and colleagues found that the presence of hypercapnic acidosis at randomization to be associated with lower 28-day mortality in the group randomized to tidal volume of 12ml/kg (but no mortality difference in patients randomized to 6 ml/kg) [68] (table 2). This study had several limitations including being a retrospective secondary analysis, defining hypercapnic acidosis based upon a day 1 blood gas 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 proven, but only an association inferred.

In contrast to the Kregenow *et al* study, two recent studies looking at mechanically ventilated patients within the ICU have called into question the safety of hypercapnic acidosis. The first study was retrospective and included 252,812 patients admitted to ICU with respiratory failure requiring mechanical ventilation during the first 24hr of their ICU admission. It found that hypercapnic acidosis in the first 24 hours of ICU admission was associated with higher in-hospital mortality compared with

compensated hypercapnia or normocapnia [69] (table 2). Interestingly both patients with compensated hypercapnia, and hypercapnic acidosis had higher mortality rates. This effect was consistent across all types of ICU admissions. This study's strength 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 upon a day 1 ABG and did not account for adjunctive treatments such as bicarbonate infusions and extracorporeal life support (ECLS).

The second study was a secondary analysis of 1899 patients from three prospective non-interventional cohort studies on ARDS patients. It demonstrated that severe hypercapnia, as defined by a $PaCO_2 \geq 50$ mmHg, was associated with higher ICU mortality in a population with moderate to severe ARDS [70] (table 2). The authors used propensity matching to conduct a sensitivity analysis to demonstrate that hypercapnia independent of acidosis was associated with increased mortality while both had independent additive effects at increasing mortality. This study included patients from 927 ICUs in 40 countries. The investigators used the worst ABG 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 ECLS.

3.3 Hypercapnia and organ dysfunction

Not surprisingly, the harmful effects of severe hypercapnia extend beyond the cardiopulmonary system. In the study by Nin *et al*, hypercapnic acidosis was associated with higher ventilator-associated complication rates (such as barotrauma) and more

organ failures including renal and cardiovascular dysfunction [70]. Further studies will be required to externally validate and elucidate the pathophysiologic basis for these findings and whether they share similarities to those described in animal models.

4. Strategies of LPV when severe hypercapnia is present

4.1 LPV, dead space and hypercapnia

Hypercapnia in ARDS patients 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 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 employed but carry risk. Firstly, adequate lung recruitment to facilitate ventilation in ARDS often necessitates finding optimal PEEP but care must be used to avoid alveolar overdistention which can negatively affect pulmonary hemodynamics and RV function [67]. Secondly, titrating PEEP and driving pressure to achieve a desired tidal volume and $PaCO_2$ threshold during LPV is a complex process. For instance, Amato *et al* demonstrated in observational post hoc analysis of nine randomized controlled trials of patients with ARDS, that decreases in tidal volume or increases in PEEP are beneficial only when associated with decreased driving pressure [61]. Lastly, 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 $PaCO_2$ can be associated with significant harm and their use must be weighed against the risks associated with permissive hypercapnia.

4.2 Prone Positioning

Placing patients with severe ARDS in prone position has been demonstrated to improve oxygenation, compliance and early institution improves mortality [73]. Some studies, however, have suggested that it is the decrease in $PaCO_2$ associated with a reduction in alveolar dead space rather than increased PaO_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 (PROSEVA) did not directly evaluate alveolar recruitment with prone positioning [73]. In addition, a retrospective analysis of PROSEVA by Albert et al, demonstrated that increased survival with proning was not predicted by improvement in gas exchange as determined by blood gas analysis.[76] Nonetheless, prone positioning can lower $PaCO_2$ and unload the RV in selected groups of ICU patients and is an important tool to improve patient outcomes in severe ARDS.[77]

4.3 Extracorporeal veno-venous CO_2 removal ($ECCO_2R$)

Debate continues over the role of extracorporeal devices in the management of ARDS. Specifically, there has been renewed interest in extracorporeal veno-venous CO_2 removal ($ECCO_2R$) which offers efficient CO_2 removal with relatively low blood flow rates. A recent experimental porcine model by Morimont *et al* sought to determine whether using $ECCO_2R$ during LPV could improve pulmonary hemodynamics and RV function in early ARDS [38]. Institution of $ECCO_2R$ effectively corrected acidosis and hypercapnia during LPV. In addition, PVR and mPAP were significantly reduced and RV-pulmonary arterial (Ees:Ea) coupling was improved. Changes in both pH and $PaCO_2$ were highly correlated with changes in mPAP. Whether findings from this study are

translatable into 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 $ECCO_2R$ to normalize pH and CO_2 in conjunction with current standards of LPV.

4.4 Ultralow tidal volume ventilation and maintenance of normocapnia

Several recent trials have examined ultra-low tidal volume ventilation (3-4 ml/kg) in combination with $ECCO_2R$ to determine its feasibility and whether additional benefit beyond current lung protective ventilation exists [78-80]. In theory, ultra-low tidal volume ventilation lowers the risk of alveolar over-distension that can still occur despite our current use of LPV [81]. It prevents the hemodynamic changes (acute cor pulmonale and/or RV failure) and it facilitates a 'least damaging' ventilatory approach (substantially lower Pplat and driving pressure values) that some have speculated would confer survival benefit [82]. While the study by Bein *et al* 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 (PaO_2/FiO_2 < 150 mmHg) had a significantly shorter ventilation period as assessed by higher 60-day ventilator free days [78]. Additional studies on this front are underway (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 respective groups.

4.5 The role of buffers in management of ARDS

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

5. Summary

Pre-clinical studies of ARDS have provided insight into the physiologic effects of hypercapnic acidosis; however, the relative contribution of hypercapnia on mortality in animal models remains uncertain except in the context of active untreated pulmonary infection where it is associated with worsened outcomes.

Clinical studies in patients with ARDS have shown an association between severe hypercapnia, acute cor pulmonale and mortality. Severe hypercapnia has also been associated with higher rates of non-cardiovascular organ dysfunction and ICU mortality in patients with moderate to severe ARDS.

Ultra lung protective ventilation with maintenance of normocapnia using extracorporeal CO_2 removal offers potential advantages over current standards of lung protective ventilation. It remains uncertain, however, whether this strategy should be applied to patients with moderate ARDS, severe ARDS, or both. Furthermore, it remains to be determined whether this strategy offers additional benefit in either of these patient groups as compared to LPV with maintenance of normocapnia.

6. 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 such that $PaCO_2$ be kept below 50mmHg in line with current evidence [83]. In addition to examining ultra low tidal volume ventilation with $ECCO_2R$, 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 $ECCO_2R$ versus permissive hypercapnia is warranted.

References

1. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000; 342(18):1301-1308.

2. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis. 1988; 137(5):1159-1164.

3. Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. Lancet. 2007; 369(9572):1553-1564.

4. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013; 369(22):2126-2136.

5. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012; 307(23):2526-2533.

6. Bautista AF, Akca O. Hypercapnia: is it protective in lung injury? Med Gas Res. 2013; 3(1):23.

7. Contreras M, Ansari B, Curley G, et al. Hypercapnic acidosis attenuates ventilation-induced lung injury by a nuclear factor-kappaB-dependent mechanism. Crit Care Med. 2012; 40(9):2622-2630.

8. Takeshita K, Suzuki Y, Nishio K, et al. Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-[kappa]B activation. Am J Respir Cell Mol Biol. 2003; 29(1):124-132.

9. Nichol AD, O'Cronin DF, Naughton F, Hopkins N, Boylan J, McLoughlin P. Hypercapnic acidosis reduces oxidative reactions in endotoxin-induced lung injury. Anesthesiology. 2010; 113(1):116-125.

10. Broccard AF, Hotchkiss JR, Vannay C, et al. Protective effects of hypercapnic acidosis on ventilator-induced lung injury. Am J Respir Crit Care Med. 2001; 164(5):802-806.

11. Sinclair SE, Kregenow DA, Lamm WJ, Starr IR, Chi EY, Hlastala MP. Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. Am J Respir Crit Care Med. 2002; 166(3):403-408.

12. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? Am J Respir Crit Care Med. 1994; 150(6 Pt 1):1722-1737.

13. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill--too little of a good thing? Lancet. 1999; 354(9186):1283-1286.

14. Laffey JG, Tanaka M, Engelberts D, et al. Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. Am J Respir Crit Care Med. 2000; 162(6):2287-2294.

15. Curley G, Hayes M, Laffey JG. Can 'permissive' hypercapnia modulate the severity of sepsis-induced ALI/ARDS? Crit Care. 2011; 15(2):212.

16. Coakley RJ, Taggart C, Greene C, McElvaney NG, O'Neill SJ. Ambient pCO2 modulates intracellular pH, intracellular oxidant generation, and interleukin-8 secretion in human neutrophils. J Leukoc Biol. 2002; 71(4):603-610.

17. Gates KL, Howell HA, Nair A, et al. Hypercapnia impairs lung neutrophil function and increases mortality in murine pseudomonas pneumonia. Am J Respir Cell Mol Biol. 2013; 49(5):821-828.

18. Ni Chonghaile M, Higgins BD, Costello JF, Laffey JG. Hypercapnic acidosis attenuates severe acute bacterial pneumonia-induced lung injury by a neutrophil-independent mechanism. Crit Care Med. 2008; 36(12):3135-3144.

19. Lang JD, Jr., Chumley P, Eiserich JP, et al. Hypercapnia induces injury to alveolar epithelial cells via a nitric oxide-dependent pathway. Am J Physiol Lung Cell Mol Physiol. 2000; 279(5):L994-1002.

20. Chonghaile MN, Higgins BD, Costello J, Laffey JG. Hypercapnic acidosis attenuates lung injury induced by established bacterial pneumonia. Anesthesiology. 2008; 109(5):837-848.

21. Costello J, Higgins B, Contreras M, et al. Hypercapnic acidosis attenuates shock and lung injury in early and prolonged systemic sepsis. Crit Care Med. 2009; 37(8):2412-2420.

22. O'Croinin DF, Hopkins NO, Moore MM, Boylan JF, McLoughlin P, Laffey JG. Hypercapnic acidosis does not modulate the severity of bacterial pneumonia-induced lung injury. Crit Care Med. 2005; 33(11):2606-2612.

23. O'Croinin DF, Nichol AD, Hopkins N, et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. Crit Care Med. 2008; 36(7):2128-2135.

24. Doerr CH, Gajic O, Berrios JC, et al. Hypercapnic acidosis impairs plasma membrane wound resealing in ventilator-injured lungs. Am J Respir Crit Care Med. 2005; 171(12):1371-1377.

25. O'Toole D, Hassett P, Contreras M, et al. Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-kappaB dependent mechanism. Thorax. 2009; 64(11):976-982.

26. Bharat A, Graf N, Mullen A, et al. Pleural Hypercarbia After Lung Surgery Is Associated With Persistent Alveolopleural Fistulae. Chest. 2016; 149(1):220-227.

27. Briva A, Vadasz I, Lecuona E, et al. High CO2 levels impair alveolar epithelial function independently of pH. PLoS One. 2007; 2(11):e1238.

28. C E Rose J, D P Kimmel, R L Godine, Jr, D L Kaiser and R M Carey. Synergistic effects of acute hypoxemia and hypercapnic acidosis in conscious dogs. Renal dysfunction and activation of the renin-angiotensin system. Circulation Research. 1983; 53(2):202 - 213.

29. C. E. Rose Jr RJA, R. M. Carey. Antidiuresis and vasopressin release with hypoxemia and hypercapnia in conscious dogs. American Journal of Physiology. 1984; 247(1):127 - 134.

30. Rose CE, Jr., Peach MJ, Carey RM. Role of angiotensin II in renal vasoconstriction with acute hypoxemia and hypercapnic acidosis in conscious dogs. Ren Fail. 1994; 16(2):229-242.

31. Anand IS, Chandrashekhar Y, Ferrari R, et al. Pathogenesis of congestive state in chronic obstructive pulmonary disease. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. Circulation. 1992; 86(1):12-21.

32. Hotter G, Palacios L, Sola A. Low O2 and high CO2 in LLC-PK1 cells culture mimics renal ischemia-induced apoptosis. Lab Invest. 2004; 84(2):213-220.

33. Kilburn KH, Dowell AR. Renal function in respiratory failure. Effects of hypoxia, hyperoxia, and hypercapnia. Arch Intern Med. 1971; 127(4):754-762.

34. Henriksen JH, Christensen NJ, Kok-Jensen A, Christiansen I. Increased plasma noradrenaline concentration in patients with chronic obstructive lung disease: relation to haemodynamics and blood gases. Scand J Clin Lab Invest. 1980; 40(5):419-427.

35. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med. 1998; 338(6):355-361.

36. Nagi MM, Ward ME. Modulation of myogenic responsiveness by CO2 in rat diaphragmatic arterioles: role of the endothelium. Am J Physiol. 1997; 272(3 Pt 2):H1419-1425.

37. Jaitovich A, Angulo M, Lecuona E, et al. High CO2 levels cause skeletal muscle atrophy via AMP-activated kinase (AMPK), FoxO3a protein, and muscle-specific Ring finger protein 1 (MuRF1). J Biol Chem. 2015; 290(14):9183-9194.

38. Morimont P, Guiot J, Desaive T, et al. Veno-venous extracorporeal CO2 removal improves pulmonary hemodynamics in a porcine ARDS model. Acta Anaesthesiol Scand. 2015; 59(4):448-456.

39. Stengl M, Ledvinova L, Chvojka J, et al. Effects of clinically relevant acute hypercapnic and metabolic acidosis on the cardiovascular system: an experimental porcine study. Crit Care. 2013; 17(6):R303.

40. Nichol AD, O'Cronin DF, Howell K, et al. Infection-induced lung injury is worsened after renal buffering of hypercapnic acidosis. Crit Care Med. 2009; 37(11):2953-2961.

41. Higgins BD, Costello J, Contreras M, Hassett P, D OT, Laffey JG. Differential effects of buffered hypercapnia versus hypercapnic acidosis on shock and lung injury induced by systemic sepsis. Anesthesiology. 2009; 111(6):1317-1326.

42. Kavanagh BP, Laffey JG. Hypercapnia: permissive and therapeutic. Minerva Anestesiol. 2006; 72(6):567-576.

43. Cardenas VJ, Jr., Zwischenberger JB, Tao W, et al. Correction of blood pH attenuates changes in hemodynamics and organ blood flow during permissive hypercapnia. Crit Care Med. 1996; 24(5):827-834.

44. Weber T, Tschernich H, Sitzwohl C, et al. Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2000; 162(4 Pt 1):1361-1365.

45. Puybasset L, Stewart T, Rouby JJ, et al. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. Anesthesiology. 1994; 80(6):1254-1267.

46. Ranieri VM, Mascia L, Fiore T, Bruno F, Brienza A, Giuliani R. Cardiorespiratory effects of positive end-expiratory pressure during progressive tidal volume reduction (permissive hypercapnia) in patients with acute respiratory distress syndrome. Anesthesiology. 1995; 83(4):710-720.

47. Viitanen A, Salmenpera M, Heinonen J. Right ventricular response to hypercarbia after cardiac surgery. Anesthesiology. 1990; 73(3):393-400.

48. Enson Y, Giuntini C, Lewis ML, Morris TQ, Ferrer MI, Harvey RM. The Influence of Hydrogen Ion Concentration and Hypoxia on the Pulmonary Circulation. J Clin Invest. 1964; 431146-1162.

49. Morimont P, Lambermont B, Ghuysen A, et al. Effective arterial elastance as an index of pulmonary vascular load. Am J Physiol Heart Circ Physiol. 2008; 294(6):H2736-2742.

50. Vanderpool RR, Pinsky MR, Naeije R, et al. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart. 2015; 101(1):37-43.

51. Jardin F, Gurdjian F, Fouilladieu JL, Goudot B, Margairaz A. Pulmonary and systemic haemodynamic disorders in the adult respiratory distress syndrome. Intensive Care Med. 1979; 5(3):127-133.

52. Villar J, Blazquez MA, Lubillo S, Quintana J, Manzano JL. Pulmonary hypertension in acute respiratory failure. Crit Care Med. 1989; 17(6):523-526.

53. Zapol WM, Kobayashi K, Snider MT, Greene R, Laver MB. Vascular obstruction causes pulmonary hypertension in severe acute respiratory failure. Chest. 1977; 71(2 suppl):306-307.

54. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med. 1977; 296(9):476-480.

55. Jardin F, Gueret P, Dubourg O, Farcot JC, Margairaz A, Bourdarias JP. Two-dimensional echocardiographic evaluation of right ventricular size and contractility in acute respiratory failure. Crit Care Med. 1985; 13(11):952-956.

56. Jardin F, Vieillard-Baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. Intensive Care Med. 2007; 33(3):444-447.

57. Vieillard-Baron A, Schmitt JM, Augarde R, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med. 2001; 29(8):1551-1555.

58. Osman D, Monnet X, Castelain V, et al. Incidence and prognostic value of right ventricular failure in acute respiratory distress syndrome. Intensive Care Med. 2009; 35(1):69-76.

59. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. Intensive Care Med. 2013; 39(10):1725-1733.

60. Lheritier G, Legras A, Caille A, et al. Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. Intensive Care Med. 2013; 39(10):1734-1742.

61. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015; 372(8):747-755.

62. Steltzer H, Krafft P, Fridrich P, Hiesmayr M, Hammerle AF. Right ventricular function and oxygen transport patterns in patients with acute respiratory distress syndrome. Anaesthesia. 1994; 49(12):1039-1045.

63. Monchi M, Bellenfant F, Cariou A, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. Am J Respir Crit Care Med. 1998; 158(4):1076-1081.

64. Bull TM, Clark B, McFann K, Moss M, National Institutes of Health/National Heart L, Blood Institute AN. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. Am J Respir Crit Care Med. 2010; 182(9):1123-1128.

65. Mekontso Dessap A, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. Intensive Care Med. 2009; 35(11):1850-1858.

66. Vieillard-Baron A, Jardin F. Why protect the right ventricle in patients with acute respiratory distress syndrome? Curr Opin Crit Care. 2003; 9(1):15-21.

67. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. Intensive Care Med. 2016; 42(5):862-870.

68. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. Crit Care Med. 2006; 34(1):1-7.

69. Tiruvoipati R, Pilcher D, Buscher H, Botha J, Bailey M. Effects of Hypercapnia and Hypercapnic Acidosis on Hospital Mortality in Mechanically Ventilated Patients. Crit Care Med. 2017; 45(7):e649-e656.

70. Nin N, Muriel A, Penuelas O, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Med. 2017; 43(2):200-208.

71. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002; 346(17):1281-1286.

72. Vieillard-Baron A, Prin S, Augarde R, et al. Increasing respiratory rate to improve CO2 clearance during mechanical ventilation is not a panacea in acute respiratory failure. Crit Care Med. 2002; 30(7):1407-1412.

73. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368(23):2159-2168.

74. Gattinoni L, Vagginelli F, Carlesso E, et al. Decrease in PaCO2 with prone position is predictive of improved outcome in acute respiratory distress syndrome. Crit Care Med. 2003; 31(12):2727-2733.

75. Charron C, Repesse X, Bouferrache K, et al. PaCO2 and alveolar dead space are more relevant than PaO2/FiO2 ratio in monitoring the respiratory response to prone position in ARDS patients: a physiological study. Crit Care. 2011; 15(4):R175.

76. Albert RK, Keniston A, Baboi L, Ayzac L, Guerin C, Proseva I. Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2014; 189(4):494-496.

77. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. Chest. 2007; 132(5):1440-1446.

78. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med. 2013; 39(5):847-856.

79. Fanelli V, Ranieri MV, Mancebo J, et al. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress sindrome. Crit Care. 2016; 2036.

80. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology. 2009; 111(4):826-835.

81. Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. Am J Respir Crit Care Med. 2007; 176(8):761-767.

82. Hager DN, Krishnan JA, Hayden DL, Brower RG, Network ACT. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005; 172(10):1241-1245.

83. Repesse X, Vieillard-Baron A. Hypercapnia during acute respiratory distress syndrome: the tree that hides the forest! J Thorac Dis. 2017; 9(6):1420-1425.

Tables

Citation	Study Design	Results	Comments
Vieillard-Baron et al [57] (2001)	Prospective single center, open design n = 75	Multivariate regression analysis: $PaCO_2$ independently associated with ACP. OR 1.15, 95% CI 1.05–1.25, p < .0001 Mortality not influenced by presence of ACP	ACP defined as ratio of RVEDA/LVEDA > 0.6 by TEE MV: Pplat limited to ≤ 30 cm H_2O, tidal volume of 6 –9 mL/kg (PBW), PEEP range 3–15 cm H_2O
Lheritier et al [60] (2013)	Prospective multi-center n = 200	Multivariate regression analysis: $PaCO_2$ > 60 mmHg strongly associated with ACP. OR 3.70, 95% CI 1.32–10.38, p = 0.01 ACP not independently associated with mortality	ACP defined as ratio RVEDA/LVEDA > 0.6 by TEE MV: Pplat ≤ 30 cm H_2O, tidal volume and PEEP according to expert recommendations from the Societe de Reanimation de Langue Francaise
Mekontso-Dessap et al [67] (2016)	Prospective multi-center n = 752	Multivariate regression analysis: Severe ACP independently associated with in hospital mortality. OR 2.00, 95% CI 1.03–3.88, p= 0.04 $PaCO_2$ > 48 mmHg associated with ACP. OR 2.39, CI 1.62–3.52, p<0.01	ACP and severe ACP defined as ratio of RVEDA/LVEDA > 0.6 and > 1.0 respectively with presence of septal dyskinesia by TEE MV: Pplat ≤ 30 cm H_2O, tidal volume of 6–8 ml/kg (PBW), PEEP 8 ± 4 cm H_2O

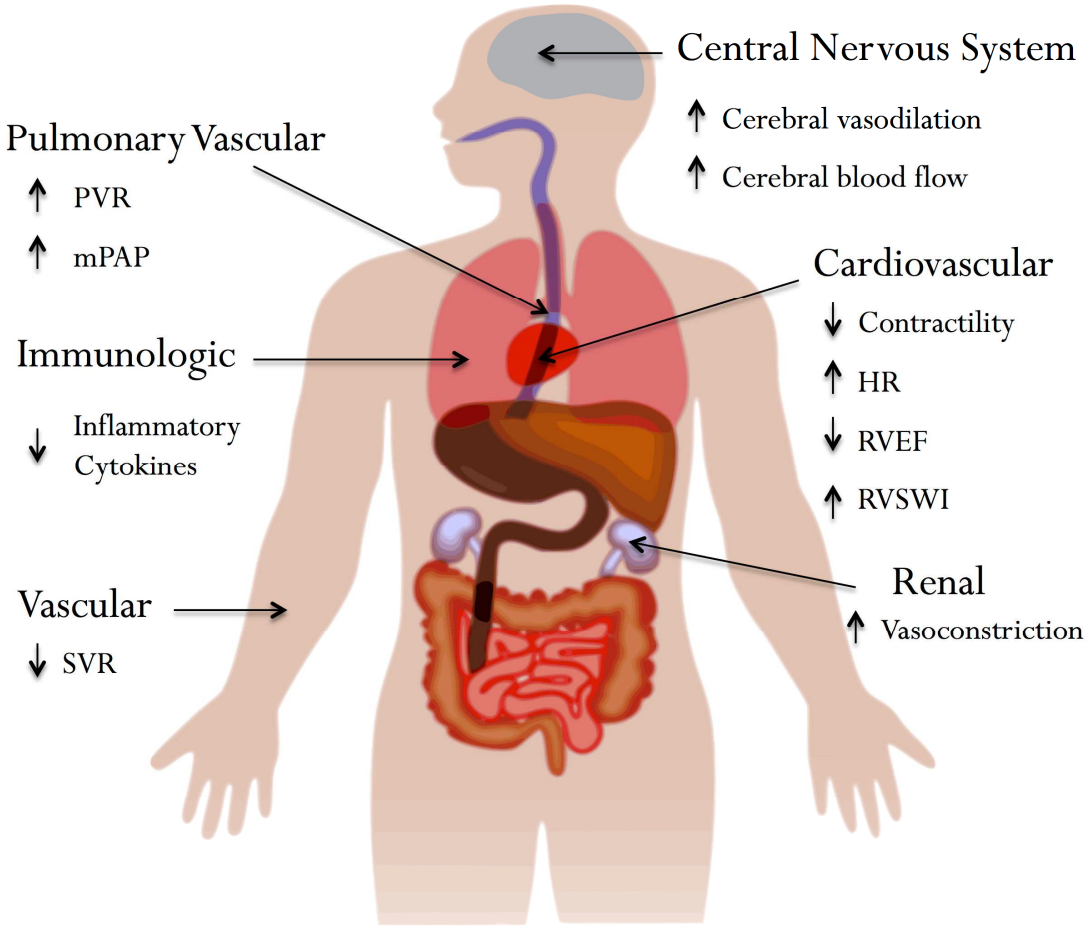
Table 1 - Summary of clinical studies showing correlation between hypercapnia, severe RV dysfunction/acute cor pulmonale and mortality in mechanically ventilated patients with ARDS. ACP = Acute cor pulmonale, CI = Confidence interval, MV = Mechanical ventilation, OR = Odds ratio, $PaCO_2$ = Partial pressure of arterial carbon dioxide, Pplat = plateau pressure, PEEP = Positive end expiratory pressure, PBW = Predicted body weight, RVEDA/LVEDA = Ratio of right ventricular end diastolic area to left ventricular end diastolic area, TEE = Trans esophageal echocardiography

Citation	Study Design	Results	Comments
Kregenow et al [68] (2006)	Retrospective secondary analysis of ARMA trial (ARDS Network) multi-center RCT (2000) n = 861	Multivariate regression analysis: Lower 28 day mortality associated with hypercapnic acidosis in 12 ml/kg (PBW). Adjusted odds ratio 0.14, 95% CI 0.03–0.70, p = .016 No reduction in 28 day mortality associated with hypercapnic acidosis in low tidal volume ventilation group (6ml/kg PBW)	HA based on day 1 ABG measurement only. Too few patients with sustained HA to analyze Significant number of patients missing day 1 ABG No data collected on intravenous bicarbonate infusion usage
Tiruvoipati et al [69] (2017)	Retrospective multi-center international study n = 252,812	Multivariate regression analysis: Higher hospital mortality for patients with hypercapnic acidosis, and compensated hypercapnia, adjusted (for severity of illness) OR 1.74, 95% CI, 1.62–1.88 and 1.18; 95% CI, 1.10–1.26 respectively, as compared to normocapnia with normal pH, p < 0.001	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 intravenous bicarbonate infusion or extracorporeal life support
Nin et al [70] (2017)	Secondary analysis of three prospective non-interventional cohort studies (multi-center \international) n = 1899	Multivariate regression analysis: Significantly higher ICU mortality in patients with maximum $PaCO_2$ of ≥ 50 mmHg (severe hypercapnia) during the first 48 h of MV, OR 1.93, 95% CI 1.32–2.81, p = 0.001 Additional binomial logistic model omitting acidosis: $PaCO_2$ of ≥ 50 mmHg independently associated with a higher risk of ICU mortality, OR 2.40, 95% CI 1.67–3.46, p < 0.001 Higher rates of organ failure and complications with $PaCO_2$ of ≥ 50 vs < 50 mmHg: Cardiovascular failure (p = .001), renal failure (p = 0.013), barotrauma (p = .001)	Strength is a secondary analysis of multinational, multicenter cohort from ICUs in 40 countries Used worst $PaCO_2$ from ABGs within 48 hours of initiation of MV 11.5% of patients excluded due to missing ABG data No data collected on use of intravenous bicarbonate infusion or extracorporeal life support

Table 2: Summary of clinical studies showing effects of hypercapnia and hypercapnic acidosis on mortality in mechanically ventilated patients with ARDS. ABG = arterial blood gas, CI = Confidence interval, HA = Hypercapnic acidosis, MV = Mechanical ventilation, OR = Odds ratio, $PaCO_2$ = Partial pressure of arterial carbon dioxide, PBW = predicted body weight

Figure Legends

Figure 1 - Systemic effects of hypercapnia. HR = heart rate, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, RVEF = right ventricular ejection fraction, RVSWI = right ventricular stroke work index, SVR = systemic vascular resistance


Central Nervous System
↑ Cerebral vasodilation
↑ Cerebral blood flow
Pulmonary Vascular
↑ PVR
↑ mPAP
Cardiovascular
↓ Contractility
↑ HR
↓ RVEF
↑ RVSWI
Immunologic
↓ Inflammatory Cytokines
Renal
↑ Vasoconstriction
Vascular
↓ SVR