MONASH University

CLINICAL EFFECTS AND MANAGEMENT OF HYPERCAPNIA IN MECHANICALLY VENTILATED CRITICALLY ILL PATIENTS

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A thesis submitted for the degree of Doctor of Philosophy by publication at Monash University in 2019

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Dedication

To the God for blessing me to complete this work
And
My mother for being my first and best teacher

Abstract

Hypercapnia and hypercapnic acidosis may sometimes be associated with lung protective mechanical ventilation. The implications of hypercapnia in these circumstances are unclear due to the lack of good clinical data. Furthermore, the available data does not delineate the effects of hypercapnia with and without concurrent acidosis. This lack of clinical data leads some clinicians to believe hypercapnic acidosis to be protective in reducing the lung injury and mortality, while other clinicians consider hypercapnic acidosis to be harmful with possible increase in mortality and morbidity. It is possible that hypercapnia and hypercapnic acidosis will be beneficial in some and harmful in other clinical conditions. Given the uncertainty, this project aimed to:

1. Review the published evidence on the effects of hypercapnia and hypercapnic acidosis in animal experiments as well as clinical studies.
2. Evaluate the association of hypercapnia and hypercapnic acidosis in mechanically ventilated patients on hospital mortality.
3. Review the management practices that are current available and investigate the evolving options of effective management of hypercapnia in critically ill patients.

Review of published literature on hypercapnia identified a large number of experimental studies investigating hypercapnia in animal and ex vivo models of lung injury and sepsis. Experimental data in lung injury models reported variable results, with beneficial effects shown in some models and harm in others. Similarly, the data from animal models of sepsis revealed the effects of hypercapnia to vary with benefits in some models of sepsis and harm in others. The effects also varied at different time points during the course of sepsis as well as presence or absence of acidosis with hypercapnia. There were no large clinical studies investigating the effects of hypercapnia in mechanically ventilated patients. Limited clinical data suggested hypercapnic acidosis to be potentially harmful.

To address these limitations, two large multicentre retrospective studies were conducted as part of this thesis. These included analyses of data from over 250,000 mechanically ventilated patients

from 171 intensive care units in Australia and New Zealand. This revealed hypercapnic acidosis during the first 24 hours of ICU admission to be independently associated with increased risk of hospital mortality in mechanically ventilated patients. This increased mortality was noted irrespective of the admission diagnostic category. However, compensated hypercapnia was not found to harmful in patients with acute cerebral injury caused by cardiac arrest, stroke or traumatic brain injury.

Given the increased risk of mortality associated with hypercapnia, the available and emerging options managing hypercapnia was investigated. The options to manage hypercapnic acidosis include modifications to mode of mechanical ventilation to enhance elimination of carbon-dioxide as well as buffers to normalise pH. In some patients with very severe hypercapnia that could not be managed with convention ventilation, extracorporeal techniques may be required. Hemolung RAS, a low flow, minimally invasive extracorporeal carbon dioxide removal device appeared to be an effective and safe intervention in the management of hypercapnic acidosis.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Print Name: RAVINDRANATH TIRUVOIPATI

Date: 06/02/2019

List of publications included in the thesis

1. **Tiruvoipati** R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. Anaesth Intensive Care. 2013 Mar; 41(2):157-62. Review.
2. **Tiruvoipati R**, Gupta S, Haji K, Braun G, Carney I, Botha JA. Management of severe hypercapnia post cardiac arrest with extracorporeal carbon dioxide removal. Anaesth Intensive Care. 2014 Mar;42(2):248-52
3. **Tiruvoipati R**, Haji K, Gupta S, Braun G, Carney I, Botha J. Low flow veno-venous extracorporeal carbon dioxide removal in the management of severe status asthmatics-A case report. Clin Respir J. 2014 Dec 16. doi: 10.1111/crj.12252.
4. **Tiruvoipati R**, Buscher H, Winearls J, Breeding J, Ghosh D, Chaterjee S, Braun G, Paul E, Fraser JF, Botha J. Early experience of a new extracorporeal carbon dioxide removal device for acute hypercapnic respiratory failure. Crit Care Resusc. 2016 Dec;18(4):261-269
5. **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 Apr 12. doi: 10.1097/CCM.0000000000002332.
6. **Tiruvoipati** R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury. JAMA Neurol. 2018 Mar 19. doi: 10.1001/jamaneurol.2018.0123
7. **Tiruvoipati** R, Gupta S, Pilcher D, Bailey M. Hypercapnia and hypercapnic acidosis in sepsis: Harmful, beneficial, or unclear? Crit Care Resusc. 2018 Jun;20(2):94-100.
8. **Tiruvoipati** R, Pilcher D, Bailey M. What is the Association With Dissociation?-Reply. JAMA Neurol. 2018 Oct 29. doi: 10.1001/jamaneurol.2018.3237.

9. **Tiruvoipati** R, Gupta S, Pilcher D, Bailey M. Management of hypercapnia in mechanically ventilated patients. Submitted for publication in Critical Care Medicine (CCMED-D-18-02143).

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes a combination of seven original and review papers published in peer reviewed journals, a reply letter to the editor and one article under review for publication. The core theme of the thesis is to investigate the clinical effects and management of hypercapnia in critically ill patients. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Monash University School of Public Health and Preventive Medicine under the supervision of Professors Michael Bailey and David Pilcher.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. Moreover, all studies were conceived and designed by myself. In multi-centre or multi-author studies I acted as the principal investigator. I wrote or contributed in a major way to the initial draft of all manuscripts presented in the thesis and revised them in conjunction with co-investigators and members of relevant writing committees.

In the case of chapters 2-8 and appendix 12 (that were published or under review for publication) my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** *(published, in press, accepted or returned for revision, submitted)*	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
2	Carbon dioxide clearance in critical care	*Published*	*70%. Concept and collecting data and writing first draft*	Pilcher D, Botha J and Bailey M each contributed 10% each to the drafting of manuscript	*No*
3	Hypercapnia and hypercapnic acidosis in sepsis: Harmful, beneficial, or unclear	*Published*	*70%. Concept and collecting data and writing first draft*	Gupta S, Pilcher D and Bailey M each contributed 10% each to the drafting of manuscript	*No*
4	Effects of Hypercapnia and Hypercapnic Acidosis on Hospital Mortality in Mechanically Ventilated Patients	*Published*	65%. *Concept, data analysis, interpretation and writing first draft*	Pilcher D 10% for planning analysis and drafting manuscript, Buscher H and Botha J 5% each for drafting of manuscript, Bailey M 15% for planning, supervision and assisting analysis and drafting of manuscript	*NO*
5	Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury.	*Published*	60%. *Concept, data interpretation and writing first draft*	Pilcher D 10% for planning analysis and drafting manuscript, Buscher H, Simister R, and Botha J 5% each for drafting of manuscript, Bailey M 15% for planning, supervision and assisting analysis and drafting of manuscript	*NO*
6	Management of severe hypercapnia post cardiac arrest with extracorporeal carbon dioxide removal	*Published*	75%. *Concept and collecting data and writing first draft*	Gupta S, Haji K, Braun G, Carney I and Botha JA each contributed 5% each to the drafting of manuscript	*No*
6	Low flow veno-venous extracorporeal carbon dioxide removal in the management of severe status asthmatics-A case report.	*Published*	75%. *Concept and collecting data and writing first draft*	Gupta S, Haji K, Braun G, Carney I, Botha JA each contributed 5% each to the drafting of manuscript	*No*
7	Early experience of a new extracorporeal	*Published*	64%. *Concept, collecting and data*	Buscher H, Winearls J, Breeding J, Ghosh D, Chaterjee S, Braun G,	*Paul E was a PhD student at*

	carbon dioxide removal device for acute hypercapnic respiratory failure		*analysis and writing first draft*	Fraser JF, Botha J contributed 4% each for drafting of manuscript. Paul E 4% for analysis and drafting of manuscript	*the time of drafting manuscript*
Appendix 12	What is the Association With Dissociation?- Reply.	*Published*	80%. Concept, literature search, interpretation and writing first draft	Pilcher D, and Bailey M each contributed 10% each to the drafting of manuscript	
8	Management of hypercapnia in mechanically ventilated patients	*Submitted for publication*	*70%. Concept and collecting data and writing first draft*	Gupta S, Pilcher D, and Bailey M each contributed 10% each to the drafting of manuscript	*No*

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: **Date: 06/02/2019**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: **Date:** 21/11/2018

Acknowledgements

I would like to express my sincere gratitude to my supervisors Professors Michael Bailey and David Pilcher for their supervision that helped to see this project progress through to completion. While I have learnt a lot from them while working on this project, I believe there is a lot more that I could learn from them. I wish I would have further opportunities in the near future to work with them.

My sincere thanks to Professor John Botha for being supportive of my plans to do PhD while working full time as a consultant in the Department of Intensive Care Medicine at Frankston Hospital. I am ever grateful to my dear friends and fellow consultants Dr Kavi Haji and Dr Sachin Gupta for their help and support throughout my PhD tenure. They helped me a lot by being available to swap my clinical work when I was busy with my PhD commitments. I would also like to thank my colleagues Associate Professor Ian Carney, Associate Professor Andrew Davies, Dr Ashwin Subramaniam, and Dr Mallikarjuna Reddy for their encouragement.

Part of my thesis included data from Adult Patient Database (APD) of The Australian and New Zealand Intensive Care Society. I would like to thank the clinicians, data collectors and researchers at the contributing sites that helped APD to be one of the largest and high-quality single datasets on intensive care in the world.

The other part of my thesis includes work on Hemolung RAS, a novel extracorporeal carbon dioxide removal device. Hemolung RAS was introduced to Australia at Frankston Hospital under Authorised Prescriber Scheme (section 41HC of the Therapeutic Goods Act 1989) at Frankston Hospital before Therapeutic Goods Administration (TGA) formally approved it for use in Australia. My sincere thanks Dr Gary Braun and Dr David Rankin for their support and guidance during the introduction of this device at Frankston Hospital. I am also thankful to Dr Hergen Buscher and Dr James Winearls for collaborating with me in the investigation of Hemolung RAS in management of Hypercapnia. Thanks to Lee Anne Clavarino, the research manager at Peninsula Health for all the help and guidance with ethics applications that this project required and for proof reading this thesis.

Finally, I can’t thank enough my wife Bindu and daughters Vaishnavi and Sri, for their love and affection. Without them, the completion of this thesis would not have been possible.

List of abbreviations

ANZICS	Australian and New Zealand Intensive Care Society
ANZIC RC	Australian and New Zealand Intensive Care Research Centre
ANZROD	Australian and New Zealand Risk of Death
APACHE	Acute Physiology and Chronic Health Evaluation
APD	Adult Patient Database
ARDS	Acute Respiratory Distress Syndrome
AUC	Area Under the receiver operating characteristic Curve
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CO_2	Carbon dioxide
ECMO	Extracorporeal Membrane Oxygenation
ICU	Intensive Care Unit
LOS	Length of Stay
SAPS	Simplified Acute Physiology Score
TGA	Therapeutic Goods Administration

CHAPTER 1: Introduction

Acute respiratory failure is one of the common indications for admission of patients to intensive care. Most of these patients require mechanical ventilation to assist in management of respiratory failure. Mechanical ventilation that was used in the past was aimed at maintaining blood gasses at normal ranges. This often required high inspiratory pressures and high tidal volumes (volutrauma) that were subsequently shown to worsen lung injury and respiratory failure [1-3]. A strategy of reducing inspiratory pressures and tidal volumes on mechanical ventilation appeared to reduce the mortality [4]. The current standard of care in treating patients with acute respiratory failure is to use low tidal volume and low inspiratory pressure mechanical ventilation [5]. One of the effects of such ventilation strategy is development of hypercapnia (PCO_2> 45mmHg) and hypercapnic acidosis (PCO_2> 45mmHg; pH<7.35). The use of low tidal volume ventilation was proven beyond doubt to improve survival in patients with severe respiratory failure as compared to conventional higher tidal volume ventilation [5]. However, the effects of hypercapnia and hypercapnic acidosis are not clear.

Hypercapnia and hypercapnic acidosis influence various systems including respiratory, cardiovascular, central nervous, neuromuscular and renal systems [6, 7]. There are multiple, important cardiovascular physiological effects of hypercapnia [8]. Hypercapnic acidosis was shown to increase arterial and tissue oxygenation in pre-clinical studies [9]) and in healthy humans [10] by several mechanisms. First, hypercapnic acidosis potentiates hypoxic pulmonary vasoconstriction [11] and increases alveolar ventilation [12] by inhibition of the airway tone. The net results of these changes leads to improvement in ventilation/perfusion matching and enhanced arterial oxygenation. Second, hypercapnia-mediated increases in cardiac output augment systemic oxygen delivery by several mechanisms, including sympato-adrenal mediated release of catecholamines [8].

The effects of hypercapnia and acidosis in critically ill patients are not clearly established. Some clinicians believe hypercapnic acidosis to be protective by itself independent of low tidal volume

ventilation and may aid in reducing the lung injury and mortality [13, 14]. Indeed they have hypothesised that inducing hypercapnia by supplemental carbon dioxide may be beneficial in critically ill patients with acute respiratory failure [14]. To the contrary, other clinicians consider hypercapnic acidosis harmful with possible increase in mortality and morbidity [5, 15, 16] [17-19]. This uncertainty appears to be based on data from animal experiments or clinical studies with small sample sizes. These factors also limit the validity and generalizability of these studies. Given this variability in published evidence, the management of hypercapnic acidosis varies considerably. It is possible that hypercapnia and hypercapnic acidosis may be beneficial in some clinical conditions and be harmful in other clinical conditions. To address these limitations, it is important to further evaluate the independent association of hypercapnia and hypercapnic acidosis in invasive mechanically ventilated patients on clinically important outcome measures such as mortality in different clinical situations.

Hypotheses

The effects of hypercapnia and hypercapnic acidosis will vary in different clinical situations.

- Hypercapnia and hypercapnic acidosis may be associated with reduced hospital mortality in patients with severe Acute Respiratory Distress Syndrome (ARDS) (p/f ratio < 100)
- Hypercapnia and hypercapnic acidosis may be associated with increased hospital mortality in patients with moderate (p/f ratio 100-200) and mild ARDS (p/f ratio 200 - 300)
- Hypercapnic acidosis may be associated with increased hospital mortality in specific diagnostic groups of mechanically ventilated patients including severe respiratory failure, cerebral injury, sepsis, trauma, renal failure and post-operative patients.

Aims

- Review the published evidence on the effects of hypercapnia and hypercapnic acidosis in animal experimental as well as clinical studies.

- Evaluate the adjusted independent association of hypercapnic acidosis on hospital mortality in specific diagnostic groups of mechanically ventilated patients including severe respiratory failure, cerebral injury, sepsis, trauma, renal failure and post-operative patients.
- Review the management practices that are current available and investigate the evolving options for effective management of hypercapnic acidosis in critically ill patients.

Methods

Ethics approval:

The Chairs of Monash University Human Research Ethics Committee (MUHREC) (appendix 1) reviewed this study and granted an exemption from ethical review as the proposal satisfies section 5.1.22 of the National Statement on Ethical Conduct in Human Research. The Human Research Ethics Committees of Peninsula Health (appendix 2), St Vincent's Hospital (appendix 3) and Gold Coast Health Service District (appendix 4) reviewed the study proposal and approved the reporting of data on patients where Hemolung RAS was used for management of hypercapnic respiratory failure.

Research Design and Statistical Analysis

A review was conducted to evaluate the effects of hypercapnia and hypercapnic acidosis in animal experimental as well as clinical studies. Literature search was performed on electronic databases including Cochrane Library, MEDLINE, EMBASE, Registry of Current Controlled Trials, Database of Abstracts of Review of Effects, for studies evaluating the effects of carbon-dioxide. The search was performed using the following exploded medical subject headings and text words "carbon dioxide", "hypercarbia", "hypercapnia", "acidosis", critical care", "extracorporeal membrane oxygenation", "extracorporeal life support", "acute respiratory distress syndrome", "ARDS", "acute respiratory failure", "treatment", "management" in isolation and in combination without restrictions. In addition, reference lists of all available review articles and primary studies were searched to identify studies that were not found on computerised searches. This review will aid in understanding the current literature on the effects of hypercapnic acidosis and management of hypercapnia. A further review was conducted on various techniques (conventional and extracorporeal) available in the management of hypercapnia and hypercapnic acidosis.

To evaluate the independent association of hypercapnia and hypercapnic acidosis with hospital and intensive care mortality and duration of ICU and hospital stay, data from the Australia and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) was used. The ANZICS APD is a large database of patients admitted to adult intensive care units across Australia and New Zealand. The APD currently receives data from over 180 intensive care units throughout Australia and New Zealand. This data represented more than 2,000,000 records during this study period making ANZICS APD one of the largest available single datasets on intensive care in the world. This database contains extensive data on demographics, comorbidities, diagnosis, renal, liver functions, duration of stay in ICU and hospital, mortality in hospital and ICU, highest and lowest values of carbon dioxide, pH, and HCO_3 during the first 24 hours of admission of patients to the intensive care units [20, 21]. The ANZICS APD captures physiological and laboratory data during the first 24 hours of the patient's stay in intensive care. The data from this database was used to analyse the overall adjusted independent association of hypercapnia and hypercapnic acidosis on clinically important outcome measures including hospital mortality and duration of intensive care and hospital stay. Further analysis was conducted to assess the overall adjusted independent association of hypercapnia and acidosis on hospital mortality in specific groups (Patients with admission diagnosis of ARDS, sepsis and acute cerebral injury patients).

Hemolung RAS, a novel, low flow venovenous extracorporeal carbon dioxide removal device was evaluated for safety, feasibility and efficacy of carbon dioxide clearance.

References

1. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L: Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med* 2002, 28(4):406-413.
2. Meade MO, Cook DJ: The aetiology, consequences and prevention of barotrauma: a critical review of the literature. *Clinical intensive care : international journal of critical & coronary care medicine* 1995, 6(4):166-173.
3. Vasques F, Duscio E, Cipulli F, Romitti F, Quintel M, Gattinoni L: Determinants and Prevention of Ventilator-Induced Lung Injury. *Critical care clinics* 2018, 34(3):343-356.
4. Hickling KG, Walsh J, Henderson S, Jackson R: Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994, 22(10):1568-1578.
5. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000, 342(18):1301-1308.
6. Cullen DJ, Eger EI: Cardiovascular effects of carbon dioxide in man. *Anesthesiology* 1974, 41(4):345-349.
7. Curley G, Laffey JG, Kavanagh BP: Bench-to-bedside review: carbon dioxide. *Crit Care* 2010, 14(2):220.
8. Curley GF, Laffey JG, Kavanagh BP: CrossTalk proposal: there is added benefit to providing permissive hypercapnia in the treatment of ARDS. *The Journal of physiology* 2013, 591(11):2763-2765.
9. Wang Z, Su F, Bruhn A, Yang X, Vincent JL: Acute hypercapnia improves indices of tissue oxygenation more than dobutamine in septic shock. *Am J Respir Crit Care Med* 2008, 177(2):178-183.
10. Akca O, Doufas AG, Morioka N, Iscoe S, Fisher J, Sessler DI: Hypercapnia improves tissue oxygenation. *Anesthesiology* 2002, 97(4):801-806.
11. Swenson ER, Robertson HT, Hlastala MP: Effects of inspired carbon dioxide on ventilation-perfusion matching in normoxia, hypoxia, and hyperoxia. *Am J Respir Crit Care Med* 1994, 149(6):1563-1569.
12. Domino KB, Emery MJ, Swenson ER, Hlastala MP: Ventilation heterogeneity is increased in hypocapnic dogs but not pigs. *Respiration physiology* 1998, 111(1):89-100.
13. Kavanagh BP, Laffey JG: Hypercapnia: permissive and therapeutic. *Minerva Anestesiol* 2006, 72(6):567-576.
14. Laffey JG, Kavanagh BP: Carbon dioxide and the critically ill--too little of a good thing? *Lancet (London, England)* 1999, 354(9186):1283-1286.

15. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D *et al*: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998, 158(6):1831-1838.
16. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD *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.
17. Briva A, Vadasz I, Lecuona E, Welch LC, Chen J, Dada LA, Trejo HE, Dumasius V, Azzam ZS, Myrianthefs PM *et al*: High CO2 levels impair alveolar epithelial function independently of pH. *PloS one* 2007, 2(11):e1238.
18. Vadasz I, Hubmayr RD, Nin N, Sporn PH, Sznajder JI: Hypercapnia: a nonpermissive environment for the lung. *American journal of respiratory cell and molecular biology* 2012, 46(4):417-421.
19. Vohwinkel CU, Lecuona E, Sun H, Sommer N, Vadasz I, Chandel NS, Sznajder JI: Elevated CO(2) levels cause mitochondrial dysfunction and impair cell proliferation. *The Journal of biological chemistry* 2011, 286(43):37067-37076.
20. https://www.anzics.com.au/wp-content/uploads/2018/08/ANZICS-APD-Data-Dictionary.pdf (accessed December 2017)
21. Stow PJ, Hart GK, Higlett T, George C, Herkes R, McWilliam D, Bellomo R: Development and implementation of a high-quality clinical database: the Australian and New Zealand Intensive Care Society Adult Patient Database. *Journal of critical care* 2006, 21(2):133-141.

CHAPTER 2: Review of literature on hypercapnia and hypercapnic acidosis

2.1 Chapter Introduction

To investigate the effects of hypercapnia and hypercapnic acidosis, literature was systematically searched to evaluate animal experimental and clinical studies on hypercapnia and hypercapnic acidosis. This search had a specific focus on evaluating the effects of hypercapnia associated with lung injury and mechanical ventilation. This chapter summarises

a) Physiological effects of hypercapnia on various organ systems, including respiratory, cardiovascular, renal, nervous and muscular as well as on transport and delivery of oxygen to the tissues and
b) Experimental and tissue culture models of acute lung injury.

This chapter was published as a review article in the journal of Anaesthesia and Intensive Care with an accompanying editorial (Appendix 5).

2.2 Published Manuscript

Anaesth Intensive Care 2013; **41:** 157-162

Reviews

Carbon dioxide clearance in critical care

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SUMMARY

Lung protective ventilation limiting tidal volumes and airway pressures were proven to reduce mortality in patients with acute severe respiratory failure. Hypercapnia and hypercapnic acidosis is often noted with lung protective ventilation. While the protective effects of lung protective ventilation are well recognised, the role of hypercapnia and hypercapnic acidosis remains debatable. Some clinicians argue that hypercapnia and hypercapnic acidosis protect the lungs and may be associated with improved outcomes. To the contrary, some clinicians do not tolerate hypercapnic acidosis and use various techniques including extracorporeal carbon dioxide elimination to treat hypercapnia and acidosis. This review aims at defining the effects of hypercapnia and hypercapnic acidosis with a focus on the pros and cons of clearing carbon dioxide and the modalities that may enhance carbon dioxide clearance.

Key Words: carbon dioxide, acidosis, hypercapnia, critical care

Hypercapnia occurs commonly in modern critical care practice and is usually due to reduced elimination as an effect of decreased alveolar ventilation. Decreased alveolar ventilation may be due to a reduction in minute ventilation or increased dead space ventilation. Occasionally carbon dioxide may be elevated due to increased production in conditions such as hyperpyrexia, shivering, malignant hyperthermia and neuroleptic malignant syndrome.

The management of hypercapnia may depend on whether it is acute or acute on chronic with hypercapnic acidosis or chronic with metabolic compensation. The current ventilation strategy in patients with severe acute respiratory failure is to limit tidal volumes and airway pressures that are considered 'safe'. This approach may cause mild to moderate acute hypercapnia and acidosis, but it is currently accepted as standard care.

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Accepted for publication on December 18, 2012.

The use of low volume ventilation is proven beyond a doubt to improve survival in patients with severe respiratory failure compared to conventional higher tidal volumes[1]. Some authors have suggested that hypercapnia and acidosis may be protective by itself, independent of low volume ventilation, and may aid in reducing mortality[2–5]. These authors have hypothesised that inducing hypercapnia by supplemental carbon dioxide may be beneficial in critically ill patients with acute respiratory failure[3]. Contrarily, other clinicians consider hypercapnic acidosis to be harmful[1,6,7]. Several techniques, including extracorporeal carbon dioxide elimination, are being used or evaluated to treat hypercapnic acidosis[1,7–9].

This review aims to define the effects of hypercapnia, with a focus on the pros and cons of clearing carbon dioxide and the modalities that may enhance carbon dioxide clearance.

SEARCH STRATEGY

We searched electronic databases (including Cochrane Library, MEDLINE, EMBASE, Registry of Current Controlled Trials and the Database of Abstracts for Review of Effects) for studies evaluating the effects of carbon dioxide. The search was performed using the following exploded medical subject headings and text words: "carbon dioxide", "hypercarbia", "hypercapnia", "acidosis", "critical care", "extracorporeal membrane oxygenation",

"extracorporeal life support", "acute respiratory distress syndrome", "ARDS" and "acute respiratory failure" in isolation and in combination without restrictions. In addition, reference lists of all available review articles and primary studies were searched to identify studies that were not found on computerised searches.

PHYSIOLOGICAL EFFECTS OF HYPERCAPNIA

Hypercapnia and hypercapnic acidosis influence various systems including respiratory, cardiovascular, central nervous, neuromuscular and renal systems (Table 1).

Respiratory effects

Acute hypercapnia induces air hunger and increases the respiratory drive. Hypercapnic acidosis potentiates hypoxic pulmonary vasoconstriction with a reduction in the shunt-induced decrease in PaO_2. Hypercapnia can also reduce alveolar arterial oxygen tension. A combination of these two together has relatively little effect on oxygenation[2].

Cardiovascular effects

Hypercapnia has many effects on the cardiovascular system by influencing preload, after-load and contractility. Hypercapnic acidosis decreases myocardial contractility but increases heart rate and reduces systemic vascular resistance. The net effect is an increase in systemic cardiac output[10]. Weber et al studied the effects of permissive hypercapnic acidosis on the cardiovascular system. They noted myocardial contractility to be decreased in patients with hypercapnic acidosis. Furthermore, they noted a decrease in mean arterial pressure and an increase in pulmonary arterial pressure[11].

Table 1
Physiological effects of hypercapnic acidosis

System	Effects
Respiratory	Potentiates hypoxic pulmonary vasoconstriction Augments ventilation–perfusion matching Reduces alveolar arterial oxygen tension
Cardiovascular	Decreases myocardial contractility Increases heart rate Reduces systemic vascular resistance with overall increase in cardiac output May improve tissue oxygenation by shifting oxygen-haemoglobin dissociation curve to right
Central nervous	Increases cerebral blood flow Narcosis
Renal	Reduces renal blood flow May increase need for renal replacement therapy
Neuromuscular	Impairs diaphragmatic function

Effects on tissue oxygenation

The effects of hypercapnia on oxygen carriage and oxygen dissociation is complex and not fully understood[12]. Acute hypercapnia increases oxygen transport and oxygen off-loading capacity in acute respiratory distress syndrome (ARDS) patients with normal plasma lactate, without increasing oxygen extraction[13]. Hypercapnia and acidaemia shifts the haemoglobin–oxygen dissociation curve rightwards augmenting the tissue release of oxygen[14]. The overall effect is that tissue oxygenation is usually unchanged or improved with permissive hypercapnia due to an increased cardiac output, reduced arterio-venous oxygen content difference and reduced blood lactate concentration[12,13].

Central nervous system and neuromuscular junction effects

The effects of hypercapnia on the central nervous system include an elevation of intracranial pressure due to cerebral vasodilation. Acute elevation in carbon dioxide levels may also cause carbon dioxide narcosis. It was also shown that hypercapnia may be deleterious to the neuromuscular junction depressing diaphragmatic function[15,16].

Renal effects

Hypercapnic acidosis was shown to reduce renal blood flow[17] with the possible need for increased requirement of haemodialysis[6].

EXPERIMENTAL STUDIES USING ANIMAL AND CELL CULTURE MODELS TO EVALUATE THE EFFECTS OF HYPERCAPNIA

The effects of hypercapnia and hypercapnic acidosis have been extensively investigated in various animal models of acute lung injury. The implications of hypercapnia and acidosis in acute lung injury are not clear. Some of the experimental data show beneficial effects while others suggest harmful effects.

Laffey et al showed therapeutic hypercapnia to be protective as it attenuated pulmonary inflammation and apoptosis with preserved lung mechanics in an in vivo rabbit model of ischaemia and reperfusion injury[4]. They also showed that buffering hypercapnic acidosis worsens lung injury in a rabbit model of ischaemic reperfusion injury[5]. In their rabbit model of ventilator-induced lung injury, Sinclair et al demonstrated hypercapnic acidosis to be protective[18]. Takeshita et al studied the effects of hypercapnic acidosis on a rabbit model of endotoxin-induced lung injury. They noted hypercapnic acidosis to have anti-inflammatory effects through a mechanism of inhibiting NF-kappaB activation[19]. Costello et

al evaluated the effects of hypercapnic acidosis on sepsis-induced lung injury in rats. They found that hypercapnic acidosis attenuates lung injury in both early and prolonged septic lung injury[20].

Contrary to the above experimental studies, which imply benefit from hypercapnia and hypercapnic acidosis, there are several studies confirming harmful effects of hypercapnia. Pedoto et al have demonstrated hypercapnic acidosis to worsen lung injury and cause haemodynamic instability in a rat model[21]. Lang et al, in their in vitro model of foetal rat alveolar epithelial cells, showed that hypercapnic acidosis injures alveolar epithelial cells[22]. Doerr et al evaluated the effects of hypercapnic acidosis in an ex vivo perfused rat lung model of acute lung injury and found that hypercapnic acidosis impairs wound repair in alveolar epithelial cells[23]. Similar findings were also reported by O'Toole and colleagues[24]. Briva et al found hypercapnia to impair alveolar epithelial cell function in a rat lung model[25]. O'Croinin et al found hypercapnic acidosis to worsen lung injury by exacerbating pulmonary bacterial infection in an in vivo model of acute lung injury in a rat[26]. Helenius et al reported similar findings in *Drosophila*[27]. Furthermore, elevated carbon dioxide levels were shown to cause mitochondrial dysfunction and impair cell proliferation[28].

CLINICAL STUDIES EVALUATING HYPERCAPNIA AND HYPERCAPNIC ACIDOSIS IN ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Data from clinical studies on patients with severe respiratory failure are also conflicting. Hickling et al, in their non-comparative observational study, reported improved survival in patients with ARDS where lung-protective ventilation was used with permissive hypercapnia[1,29]. Kregenow et al, in their retrospective review of an ARDS network study, found that hypercapnic acidosis was associated with reduced 28-day mortality in the 12 ml/kg predicted body weight, tidal volume group after controlling for comorbidities and severity of lung injury[30]. However, there was no survival benefit with hypercapnic acidosis when patients were ventilated with lung-protective tidal volumes (6 ml/kg predicted body weight).

Contrary to these results, prospective randomised controlled trials have raised concerns of the harmful effects of hypercapnia and hypercapnic acidosis[6,31,32]. In a multicentric randomised controlled trial, Brochard et al compared low (7 ml/kg predicted body weight, end-inspiratory pressure 25 cmH_2O) versus conventional tidal volumes (10 ml/kg predicted body weight). The results showed that both groups significantly differed in their tidal volumes (7.1±1.3 vs 10.3±1.7 ml/kg on day 1, P <0.001) and plateau pressures (25.7±5. 0 vs 31.7±6.6 cmH_2O on day 1, P <0.001), $PaCO_2$ (59.5±15.0 vs 41.3±7.6 mmHg, P <0.001) and pH (7.28±0.09 vs 7.4±0.09, P <0.001). There were no statistically significant differences in mortality, but a trend towards higher mortality was noted in patients who had hypercapnia and acidosis (46.6 vs 37.9% in control subjects, P=0.38, [relative risk=1.23]). Based on this trend of increased mortality in patients with hypercapnic acidosis, Brochard et al stopped this trial before reaching their planned sample size of 240 patients.

Stewart et al[6] reported a single centre, randomised controlled trial where pressure and volume-limited ventilation (peak inspiratory pressure ≤30 cmH_2O, tidal volume ≤8 ml/kg) was compared to conventional ventilation (peak inspiratory pressure ≤50 cmH_2O, tidal volume ≤10–15 ml/kg). The results showed that, in the limited-ventilation group, permissive hypercapnia (arterial carbon dioxide tension >50 mmHg) was more common (52 vs 28% P=0.009), more marked (54.4±18.8 vs 45.7±9.8 mmHg, P=0.002), and more prolonged (146±265 vs 25±22 hours, P=0.017) than in the control group. The numbers of patients who required paralytic agents (23 vs 13, P=0.05) and dialysis for renal failure (13 vs 5, P=0.04) were greater in the pressure and volume-limited ventilation group than in the control group. Mortality was 50% in the limited ventilation group and 47% in the control group (relative risk=1.07; 95% confidence interval, 0.72–1.57; P=0.72).

Brower et al[32] reported a multi-centric randomised controlled trial where traditional tidal volumes (tidal volume 10–12 ml/kg ideal body weight) were compared with low tidal volumes (tidal volume 5–8 ml/kg ideal body weight). The arterial carbon dioxide levels were significantly different between both groups during the first five days (40.1±1.6 and 50.3±3.5 mmHg, respectively; P=0.01). The hospital mortality was 46% in the traditional tidal volume group and 50% in the low tidal volume group.

Based on these data suggesting detrimental effects of hypercapnic acidosis associated with low volume/pressure-limited ventilation, the ARDS Network investigators[1] managed hypercapnic acidosis aggressively, aiming to keep pH >7.30 for all patients, and allowed protocol violations of the tidal volume and airway pressure limits if pH dropped below 7.15. It is interesting to note that the mean PCO_2 level in the low tidal volume ventilation group was 40 mmHg and the mean pH was 7.38 on the first day of the

study. The ARDS network authors suggest that this aggressive management of hypercapnic acidosis may be one of the causes for improved survival in their study[1].

In summary, while the effect of low volume ventilation was proved to be beneficial, the effects of hypercapnia and hypercapnic acidosis remain unclear and potentially harmful. When using low tidal volumes, most clinicians do not tolerate high carbon dioxide when the pH falls below 7.3[1,7]. Given the available evidence, it appears that mild to moderate hypercapnia (PCO_2 60–65 mmHg), especially when the pH is ≥7.3, is normally well tolerated. However, hypercapnia with hypercapnic acidosis in patients with severe lung injury and ARDS may not be well tolerated with need for sedation and paralytic agents to suppress the respiratory drive with associated adverse effects[33,34] and may be associated with increased morbidity and mortality[6,31,32].

EXTRACORPOREAL CARBON DIOXIDE CLEARANCE

In the current clinical environment, it remains via ventilation. Various extracorporeal techniques are becoming available and some are being investigated. These techniques include extracorporeal membrane oxygenation (ECMO), where oxygenation, ventilation and cardiac assist can be provided and extracorporeal carbon dioxide ($ECCO_2$) removal devices where partial extracorporeal support is provided mainly to remove carbon dioxide. Oxygenation with a membrane lung in veno-venous ECMO is mainly dependent on the blood flow and carbon dioxide clearance is primarily dependent on the fresh gas flow. It is possible to remove all metabolically produced carbon dioxide using blood flow rates between 1–2 litres/minute of venous blood flow through the membrane lung[35].

Kolobow developed a membrane lung which was shown to effectively remove carbon dioxide[36]. Indeed, this artificial carbon dioxide removal was so efficient that, when extracorporeal carbon dioxide removal approximated carbon dioxide production, alveolar ventilation could almost be ceased[37]. Clinical application of extracorporeal carbon dioxide removal was first reported in an observational study by Gattinoni et al[38] in an uncontrolled group of patients with severe ARDS. They reported encouraging results in patients with severe ARDS by using this technique as a strategy to 'rest' the lungs. The survival rate of the treated patients in this study was 49%. The blood loss was, however, significant (average blood loss 1800±850 ml/day). Subsequently, Morris et al[39] conducted a randomised clinical trial comparing pressure-controlled inverse ratio ventilation with an extracorporeal carbon dioxide removal technique in patients with ARDS. However, no significant difference in survival was found between the mechanically ventilated patients and those treated with the extracorporeal carbon dioxide removal. The use of $ECCO_2$ removal did not gain much acceptance due to its complexity and cost, as well as the implications of intervention including high blood flow rates, large cannulae and systemic anticoagulation, with its associated potential complications. Over the last two decades, several less invasive extracorporeal devices were evaluated as alternatives to ECMO support. These are less invasive and less complex devices that may be used to treat hypercapnia and acidosis.

Most of these less invasive devices provide partial extracorporeal support and are efficient in clearing carbon dioxide but do not provide significant oxygenation. The cannulae used to access blood vessels are smaller (14 F) and require minimal anticoagulation similar to renal replacement therapy circuits.

Some of the devices evaluated for extracorporeal carbon dioxide removal include the Interventional Lung Assist (NovaLung GmbH, Hechingen, Germany)[40], arterio-venous extracorporeal carbon dioxide removal[41,42], low flow veno-venous extracorporeal carbon dioxide removal[9], intra-venacaval oxygenation and carbon dioxide removal[43,44], intravascular lung assist[45], Hattler Respiratory Assist catheter[46], Decap[47] and Hemolung. Of these devices, the Interventional Lung Assist is the only device that was used in over 1800 patients with hypercapnic respiratory failure with encouraging results[48]. The Interventional Lung Assist is a sophisticated, pumpless extracorporeal arterio-venous carbon dioxide removal device that is driven by the patient's cardiac output and therefore does not require extracorporeal pump assistance.

In addition to treating hypercapnia and hypercapnic acidosis, these less invasive devices are also currently being used in conjunction with mechanical ventilation aiming for 'ultra-protective' mechanical ventilation[8,9]. Ultra-protective mechanical ventilation may be achieved in patients with ARDS with the use of low flow (0.3–0.5 litres/minute) veno-venous extracorporeal carbon dioxide removal where tidal volumes could be reduced to 4 ml/kg of predicted body weight. This was shown to be associated with superior lung protection compared with 6 ml/kg of predicted body weight[9]. This concept appears promising and

may improve the outcome in patients with severe ARDS by reducing ventilator-associated lung injury along with treating hypercapnic acidosis.

CLINICAL CONDITIONS WHERE EXTRACORPOREAL CARBON DIOXIDE REMOVAL DEVICES MAY BE OF USE

Acute respiratory distress syndrome and acute lung injury

This is by far the most common condition where extracorporeal carbon dioxide removal devices are used. The use of ECMO and $ECCO_2$ removal by Gattinoni and Morris did not prove to be effective in improving the survival in patients with severe ARDS. However, the introduction of less invasive devices, such as the Interventional Lung Assist, has prompted clinicians to use these devices, particularly in centres where ECMO is not available. To date, the published literature confirms the increasing use of these devices with encouraging results[49,50]. A prospective randomised study is currently underway to investigate the effects of a pumpless, extracorporeal interventional lung assist on the implementation of a lung-protective ventilator strategy in patients with ARDS (Registration number NCT00538928).

Exacerbations of asthma and chronic obstructive pulmonary disease

$ECCO_2$ removal devices show promise in the management of patients with exacerbated chronic obstructive pulmonary disease who fail non-invasive ventilation and who may be unsuitable or unresponsive to invasive mechanical ventilation[51–53].

Bridge to lung transplant

The use of Interventional Lung Assist devices to support patients with mild hypoxia and severe hypercapnia refractory to mechanical ventilation proved to be successful when bridging these patients to lung transplantation[54] in one series.

CONCLUSIONS

Despite inconsistent evidence as to whether high levels of carbon dioxide are independently associated with mortality, there is increasing use of devices to assist and control carbon dioxide levels reported in the literature. In conditions where lung-protective mechanical ventilation is not adequate in managing hypercapnic acidosis, extracorporeal carbon dioxide clearing devices are an option. The use of ECMO in such conditions may be beneficial, but is invasive and associated with potential complications. The use of less invasive devices, such as the Interventional Lung Assist, is increasing and several newer, less invasive devices are being introduced into clinical practice. These devices may aid in managing hypercapnic acidosis and may also play a role in instituting ultra-protective lung ventilation.

REFERENCES

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301-1308
2. Kavanagh BP, Laffey JG. Hypercapnia: permissive and therapeutic. Minerva Anestesiol 2006; 72:567-576.
3. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill—too little of a good thing? Lancet 1999; 354:1283-1286.
4. Laffey JG, Tanaka M, Engelberts D, Luo X, Yuan S, Tanswell AK et al. Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. Am J Respir Crit Care Med 2000; 162:2287-2294.
5. Laffey JG, Engelberts D, Kavanagh BP. Buffering hypercapnic acidosis worsens acute lung injury. Am J Respir Crit Care Med 2000; 161:141-146.
6. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE 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; 338:355-361.
7. Pesenti A, Patroniti N, Fumagalli R. Carbon dioxide dialysis will save the lung. Crit Care Med 2010; 38:S549-554.
8. Moerer O, Quintel M. Protective and ultra-protective ventilation: using pumpless interventional lung assist (iLA). Minerva Anestesiol 2011; 77:537-544.
9. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology 2009; 111:826-835.
10. Cullen DJ, Eger EI 2nd. Cardiovascular effects of carbon dioxide in man. Anesthesiology 1974; 41:345-349.
11. Weber T, Tschernich H, Sitzwohl C, Ullrich R, Germann P, Zimpfer M 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; 162:1361-1365.
12. Hickling KG, Joyce C. Permissive hypercapnia in ARDS and its effect on tissue oxygenation. Acta Anaesthesiol Scand Suppl 1995; 107:201-208.
13. Thorens JB, Jolliet P, Ritz M, Chevrolet JC. Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. Intensive Care Med 1996; 22:182-191.
14. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care 2010; 14:220.
15. Beekley MD, Cullom DL, Brechue WF. Hypercapnic impairment of neuromuscular function is related to afferent depression. Eur J Appl Physiol 2004; 91:105-110.
16. Shiota S, Okada T, Naitoh H, Ochi R, Fukuchi Y. Hypoxia and hypercapnia affect contractile and histological properties of rat diaphragm and hind limb muscles. Pathophysiology 2004; 11:23-30.
17. Bersentes TJ, Simmons DH. Effects of acute acidosis on renal hemodynamics. Am J Physiol 1967; 212:633-640.
18. Sinclair SE, Kregenow DA, Lamm WJE, 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; 166:403-408.

19. Takeshita K, Suzuki Y, Nishio K, Takeuchi O, Toda K, Kudo H et al. Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-[kappa]B activation. Am J Respir Cell Mol Biol 2003; 29:124-132.
20. Costello J, Higgins B, Contreras M, Chonghaile MN, Hassett P, O'Toole D et al. Hypercapnic acidosis attenuates shock and lung injury in early and prolonged systemic sepsis. Crit Care Med 2009; 37:2412-2420.
21. Pedoto A, Caruso JE, Nandi J, Oler A, Hoffmann SP, Tassiopoulos AK et al. Acidosis stimulates nitric oxide production and lung damage in rats. Am J Respir Crit Care Med 1999; 159:397-402.
22. Lang JD Jr, Chumley P, Eiserich JP, Estevez A, Bamberg T, Adhami A et al. Hypercapnia induces injury to alveolar epithelial cells via a nitric oxide-dependent pathway. Am J Physiol Lung Cell Mol Physiol 2000; 279:L994-1002.
23. Doerr CH, Gajic O, Berrios JC, Caples S, Abdel M, Lymp JF et al. Hypercapnic acidosis impairs plasma membrane wound resealing in ventilator-injured lungs. Am J Respir Crit Care Med 2005; 171:1371-1377.
24. O'Toole D, Hassett P, Contreras M, Higgins BD, McKeown STW, McAuley DF et al. Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-kappaB dependent mechanism. Thorax 2009; 64:976-982.
25. Briva A, Vadasz I, Lecuona E, Welch LC, Chen J, Dada LA et al. High CO2 levels impair alveolar epithelial function independently of pH. PLoS One 2007; 2:e1238.
26. O'Croinin DF, Nichol AD, Hopkins N, Boylan J, O'Brien S, O'Connor C et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. Crit Care Med 2008; 36:2128-2135.
27. Helenius IT, Krupinski T, Turnbull DW, Gruenbaum Y, Silverman N, Johnson EA et al. Elevated CO2 suppresses specific Drosophila innate immune responses and resistance to bacterial infection. Proc Natl Acad Sci U S A 2009; 106:18710-18715.
28. Vohwinkel CU, Lecuona E, Sun H, Sommer N, Vadasz I, Chandel NS et al. Elevated CO(2) levels cause mitochondrial dysfunction and impair cell proliferation. J Biol Chem 2011; 286:37067-37076.
29. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990; 16:372-377.
30. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. Crit Care Med 2006; 34:1-7.
31. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 1998; 158:1831-1838.
32. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 1999; 27:1492-1498.
33. McGrane S, Pandharipande PP. Sedation in the intensive care unit. Minerva Anestesiol 2012; 78:369-380.
34. Murphy GS, Vender JS. Neuromuscular-blocking drugs. Use and misuse in the intensive care unit. Crit Care Clin 2001; 17:925-942.
35. Gattinoni L, Carlesso E, Langer T. Clinical review: Extracorporeal membrane oxygenation. Crit Care 2011; 15:243.
36. Kolobow T, Gattinoni L, Tomlinson T, White D, Pierce J, Iapichino G. The carbon dioxide membrane lung (CDML): a new concept. Trans Am Soc Artif Intern Organs 1977; 23:17-21.
37. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE. Control of breathing using an extracorporeal membrane lung. Anesthesiology 1977; 46:138-141.
38. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F et al. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. JAMA 1986; 256:881-886.
39. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; 149:295-305.
40. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 2006; 34:1372-1377.
41. Brunston RL Jr, Zwischenberger JB, Tao W, Cardenas VJ Jr, Traber DL, Bidani A. Total arteriovenous CO2 removal: simplifying extracorporeal support for respiratory failure. Ann Thorac Surg 1997; 64:1599-1604.
42. Conrad SA, Zwischenberger JB, Grier LR, Alpard SK, Bidani A. Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study. Intensive Care Med 2001; 27:1340-1351.
43. Cole FJ Jr, Shouse BA. Alternative modalities of ventilation in acute respiratory failure. Surg Annu 1995; 27:55-69.
44. Terada Y. [Present status of IVOX device]. Rinsho Kyobu Geka 1994; 14:461-464.
45. Vaslef SN, Mockros LF, Anderson RW. Development of an intravascular lung assist device. ASAIO Trans 1989; 35:660-664.
46. Hattler BG, Lund LW, Golob J, Russian H, Lann MF, Merrill TL et al. A respiratory gas exchange catheter: in vitro and in vivo tests in large animals. J Thorac Cardiovasc Surg 2002; 124:520-530.
47. Gramaticopolo S, Chronopoulos A, Piccinni P, Nalesso F, Brendolan A, Zanella M et al. Extracorporeal CO2 removal—a way to achieve ultraprotective mechanical ventilation and lung support: the missing piece of multiple organ support therapy. Contrib Nephrol 2010; 165:174-184.
48. Walles T. Clinical experience with the iLA Membrane Ventilator pumpless extracorporeal lung-assist device. Expert Rev Med Devices 2007; 4:297-305.
49. Weber-Carstens S, Bercker S, Hommel M, Deja M, MacGuill M, Dreykluft C et al. Hypercapnia in late-phase ALI/ARDS: providing spontaneous breathing using pumpless extracorporeal lung assist. Intensive Care Med 2009; 35:1100-1105.
50. Bein T, Scherer MN, Philipp A, Weber F, Woertgen C. Pumpless extracorporeal lung assist (pECLA) in patients with acute respiratory distress syndrome and severe brain injury. J Trauma 2005; 58:1294-1297.
51. Garcia JP, Kon ZN, Evans C, Wu Z, Iacono AT, McCormick B et al. Ambulatory veno-venous extracorporeal membrane oxygenation: innovation and pitfalls. J Thorac Cardiovasc Surg 2011; 142:755-761.
52. Crotti S, Lissoni A, Tubiolo D, Azzari S, Tarsia P, Caspani L et al. Artificial lung as an alternative to mechanical ventilation in COPD exacerbation. Eur Respir J 2012; 39:212-215.
53. Mikkelsen ME, Woo YJ, Sager JS, Fuchs BD, Christie JD. Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. ASAIO J 2009; 55:47-52.
54. Ricci D, Boffini M, Del Sorbo L, El Qarra S, Comoglio C, Ribezzo M et al. The use of CO2 removal devices in patients awaiting lung transplantation: an initial experience. Transplant Proc 2010; 42:1255-1258.

2.3 Summary

In this chapter, review of literature on hypercapnia and hypercapnic acidosis associated with lung injury and mechanical ventilation in animal experimental, ex-vivo cell culture models and clinical studies were presented. Hypercapnia and hypercapnic acidosis was extensively investigated in animal models as well as ex-vivo cell culture models of lung injury. The effects of hypercapnia and hypercapnic acidosis was variable in different models of lung injury. It was shown to be protective in some and harmful in other models.

The clinical evaluation of hypercapnia was limited to very few studies with small sample sizes. The results of these studies were variable with some suggesting harm from hypercapnia. Despite the inconsistent evidence as to whether hypercapnia was independently associated with mortality, there was increasing use of extracorporeal devices to assist and control hypercapnia.

The accompanying editorial (Appendix 5) published on this review article titled “Hypercapnia – Keeping therapy and diagnosis distinct” highlights the ambiguity in current management strategies of hypercapnia both in mechanically ventilated as well as spontaneously breathing patients.

While this review focused on the literature pertaining to hypercapnia and hypercapnic acidosis in lung injury associated with mechanical ventilation, a significant body of literature suggests hypercapnia can modulate the pathophysiology of sepsis. The next chapter therefore reviewed the published evidence on hypercapnia and hypercapnic acidosis in sepsis.

CHAPTER 3: Review of hypercapnia in sepsis with specific focus on critically ill patients

3.1 Introduction

The previous chapter reviewed the published evidence on hypercapnia and hypercapnic acidosis in the setting of lung injury and mechanical ventilation. In addition to lung injury and mechanical ventilation, hypercapnia was also extensively investigated in the setting of sepsis. Hypercapnia is known to modulate the pathophysiology of sepsis. The effects of hypercapnia in sepsis may vary depending on the presence of acidosis (hypercapnic acidosis) or lack of acidosis (compensated hypercapnia). The effects of hypercapnia were reported to vary at different stages during evolution, progress and the source of sepsis. This article presents the biological effects of hypercapnia and hypercapnic acidosis in sepsis and its implications in sepsis evolution.

Sepsis is one of the most common reasons for admission of patients to intensive care. A clear understanding of the basic science and the effects of hypercapnia and hypercapnic acidosis in the clinical setting of sepsis may help clinicians in developing effective strategies to improve the outcomes of critically ill patients with sepsis. Hypercapnic acidosis, if proven safe and effective can be applied in mechanically ventilated patients with sepsis. On the other hand, if proven harmful, hypercapnic acidosis could be avoided or actively corrected to ensure normocapnia in patients with sepsis. This review was performed to investigate the effects of hypercapnia and hypercapnic acidosis with a specific focus on the literature pertaining to critically ill patients.

3.2 Published Manuscript

REVIEW

Hypercapnia and hypercapnic acidosis in sepsis: harmful, beneficial or unclear?

Ravindranath Tiruvoipati, Sachin Gupta,
David Pilcher and Michael Bailey

ABSTRACT

Mortality related to sepsis among critically ill patients remains high. Recent literature suggests that hypercapnia may affect the pathophysiology of sepsis. The effects of hypercapnia on sepsis are largely related to the direct effect of hypercapnic acidosis on immune function and, as a consequence, of increased cardiac output that subsequently leads to improved tissue oxygenation. Appropriate management of hypercapnia may aid in improving the outcomes of sepsis. Our aim was to review the effects of compensated hypercapnia and hypercapnic acidosis on sepsis, with a specific focus on critically ill patients.

Hypercapnic acidosis has been extensively studied in various in vivo animal models of sepsis and ex vivo studies. Published data from animal experimental studies suggest that the effects of hypercapnic acidosis are variable, with benefit shown in some settings of sepsis and harm in others. The effects may also vary at different time points during the course of sepsis. There are very few clinical studies investigating the effects of hypercapnia in prevention of sepsis and in established sepsis. It appears from these very limited clinical data that hypercapnia may be associated with adverse outcomes. There are no clinical studies investigating clinical outcomes of hypercapnic acidosis or compensated hypercapnia in sepsis and septic shock in critical care settings, thus extrapolation of the experimental results to guide critical care practice is difficult. Clinical studies are needed, especially in critically ill patients, to define the effects of compensated hypercapnia and hypercapnic acidosis that may aid clinicians to improve the outcomes in sepsis.

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Sepsis is one of the most common reasons for admission to the intensive care unit (ICU).[1] Improvement in mortality due to sepsis and septic shock was reported over the course of the past few years, but it remains high.[2-4] Some of the factors important in reducing mortality are early diagnosis, source control[5] and early administration of antibiotics.[6]

Studies investigating the effects of hypercapnia in sepsis suggest that hypercapnia may have an impact on pathophysiology in sepsis.[7,8] The effects of hypercapnia in sepsis may vary depending on the presence of acidosis (hypercapnic acidosis) or lack of acidosis (compensated hypercapnia).[9,10] Hypercapnia in the setting of sepsis was shown to have a direct effect on immune function.[11] The effects of hypercapnia were reported to vary at different stages during evolution, progress and the source of sepsis.[7,12-14] Studies reporting on the effects of hypercapnia show conflicting results, with some studies showing beneficial effects and others showing harmful effects.[15,16] In addition to affecting immunity, hypercapnia and acidosis increase the proliferation of bacteria.[17] Hypercapnia was also shown to improve cardiac output and tissue oxygenation in sepsis;[18-20] this improvement in tissue oxygenation was considered to reduce the development of surgical site infections.[21,22] Some of the studies have shown that hypercapnia in the setting of sepsis can impair vascular reactivity in cerebral circulation.[23,24]

A clear understanding of the basic science and the effects of hypercapnia and hypercapnic acidosis in the clinical setting of sepsis may help clinicians in developing attractive strategies to improve the outcomes of critically ill patients with sepsis. Hypercapnic acidosis, if proven to be safe and effective, can be applied in patients with sepsis who are mechanically ventilated. On the other hand, if it is proven to be harmful, hypercapnic acidosis could be avoided or actively corrected to ensure normocapnia in patients with sepsis.

We reviewed the literature with an aim to identify the effects of hypercapnia and hypercapnic acidosis on sepsis, with a specific focus on clinical studies investigating the effects of hypercapnic acidosis and hypercapnia in critically ill patients with sepsis.

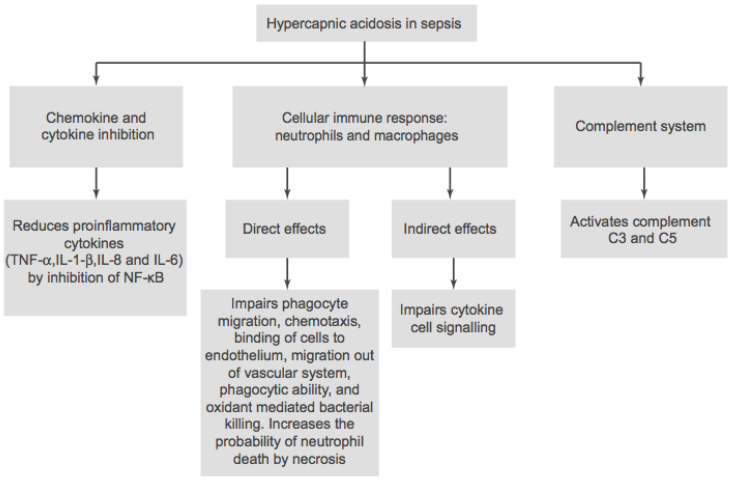
MEDLINE via PubMed (from inception to June 2017) and EMBASE (from inception to June 2017) were systematically searched. The search was performed using the following exploded medical subject headings and text words: "carbon dioxide", "hypercarbia", "hypercapnia", "acidosis", "sepsis", "septicaemia", "blood stream infection", "septic shock", "endotoxic shock", "toxic shock", "severe sepsis", "critically ill" or "critical care" in isolation and in combination without restrictions. We also

searched bibliographic references of relevant studies, irrespective of study design, with the intention of finding relevant studies to be included in this review.

Biological effects of hypercapnia and hypercapnic acidosis in sepsis

The reported effects of hypercapnia and hypercapnic acidosis in septic settings are attributed mainly to a direct effect of hypercapnia on immune function, and an indirect effect of hypercapnia and hypercapnic acidosis on cardiac output, tissue oxygenation, cerebral vascular reactivity and autoregulation.

Figure1. Effects of hypercapnic acidosis on immune function



IL = interleukin. NF-κB = *nuclear factor*-κB. TNF = tumour necrosis factor.

Effect of hypercapnia and hypercapnic acidosis on immune function

Hypercapnia and hypercapnic acidosis are well known to influence innate immunity in various animal models of sepsis, whereas data regarding impact on adaptive immune function are sparse. This influence appears to be mediated through various mechanisms, including its effect on cytokines, neutrophils, macrophage function and complements activation. The overall effect may be harmful or beneficial based on the stages during evolution, progress, source of sepsis and the duration of hypercapnia. A summary of the effects of hypercapnic acidosis on immune function[7] in sepsis is presented in Figure 1.

Harmful effects

Hypercapnic acidosis principally affects the innate immune response by inhibiting the nuclear factor-κB (NF-κB), with its main effect being anti-inflammatory.[25] It appears that the inhibition of NF-κB is independent of acidosis,[26] with hypercapnia per se noted to be an inhibitor of NF-κB activation. This may inhibit neutrophil adherence to pulmonary endothelial cells and inhibit pulmonary epithelial wound healing.[25,27] Hypercapnic acidosis may also cause inhibition of cytokine and chemokine production.[11] Acidosis is known to impair the function of immune cells by inhibiting chemotaxis, respiratory activity, bactericidal capacity in polymorphonuclear leukocytes and cytotoxicity and proliferation of lymphocytes.[28] Thus, it appears that hypercapnia may modulate immunity and host defence through pH-independent and/or pH-dependent mechanisms.

Hypercapnic acidosis can impair neutrophil function. It impairs binding of neutrophil to endothelium and migration of neutrophils out of the vascular system by inhibiting the expression of selectins, chemokines and intercellular adhesion molecules.[9,11,25] Hypercapnia has been noted to reduce the concentrations of the pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α), interleukin (IL)-1-β and the anti-inflammatory cytokine IL-10.[29] The phagocytic function of neutrophils is inhibited by hypercapnic acidosis.[13] In a murine model of *Pseudomonas aeruginosa* pneumonia, hypercapnia reduced phagocytosis of neutrophils, reduced early chemokine response (reduction of secretion of IL-6 and TNF-α and increased mortality.[30] These harmful effects of hypercapnia appear to be reversible if hypercapnia is corrected.[30] The bactericidal effects of neutrophils after phagocytosis are mediated by free radicals, such as hydrogen peroxide, superoxide and hypochlorous acid. This free radical production is reduced by acidic pH.[31] In a study by Norozian and colleagues,[32] when endotoxemic rats were treated with therapeutic hypercapnia, they noted worsening of endotoxin-induced lung injury.

Beneficial effects

While hypercapnia and acidosis appear to have detrimental effects on immune function, they have also been shown to be beneficial in early acute severe lung injury induced by endotoxin and bacterial pneumonia, possibly due to prevention of tissue injury by excessive inflammatory

response.[33-35] In an *Escherichia coli*-induced septic lung injury in rats, hypercapnic acidosis protected against worsening lung injury, attenuated the increase in airway pressure, and the impairment of lung compliance and arterial Pao_2 (arterial partial pressure of oxygen).[35] Hypercapnic acidosis was also known to reduce the magnitude of lung injury in an experimental established pneumonia model of *E. coli*-induced septic lung injury.[12] Enhancement of the protective effects of hypercapnic acidosis in septic lung injury has been noted in the presence of antibiotics.[12] Buffering of hypercapnic acidosis in acute lung injury induced by *E. coli* or endotoxin has been associated with worsening of arterial oxygenation, pulmonary compliance and structural lung damage.[10,36] The effects of hypercapnia and acidosis have been investigated further in peritoneal sepsis with a rodent model of peritoneal sepsis induced by caecal ligation puncture. Hypercapnic acidosis prevented the development or reduced severity of hypotension and lactate accumulation as compared with normocapnia.[34] There was also no increased bacterial load noted in lungs, peritoneum or blood with hypercapnic acidosis.[34]

The effects of hypercapnia appear to vary with its duration. In an animal model of experimental *E. coli* pneumonia that was studied over a 6-hour period, hypercapnia attenuated disease progression and preserved lung function.[12] In the same animal model of *E. coli* pneumonia, sustained hypercapnia over a 48-hour period worsened the lung injury.[13] The effects of hypercapnic acidosis in bacterial sepsis also appear to vary with the duration of sepsis.[11] In early sepsis, hypercapnic acidosis appears to reduce the inflammatory response and decrease bacterial toxin-mediated injury to tissues, thereby reducing the overall lung injury.[11] In contrast, prolonged or late bacterial sepsis hypercapnic acidosis appears to decrease host response to infection, which might result in unopposed bacterial proliferation with worsening lung injury.[11] These deleterious effects of hypercapnic acidosis appear to be offset by antibiotic therapy.[13] The implications of these varying effects of hypercapnia in experimental sepsis models on patients with sepsis are not known.

Effects of hypercapnia and hypercapnic acidosis on cardiac output and tissue oxygenation

The effects of hypercapnic acidosis on cardiac output and tissue oxygenation were well studied in various clinically relevant models of animal sepsis and septic shock. Stubbs and colleagues[37] studied the effects of hypercapnic acidosis and buffered hypercapnia (with normal pH) in microcirculatory oxygenation of the colon in a rodent model of peritonitis. In this experimental model, the splanchnic microcirculation was preserved, and oxygenation improved similarly under both hypercapnic acidosis and buffered hypercapnia.[37] In a rat model of lung injury induced by systemic sepsis, Higgins and colleagues[10] investigated the effects of hypercapnic acidosis and compensated hypercapnia. They found that the hypotension induced by systemic sepsis was attenuated by both hypercapnic acidosis and compensated hypercapnia. However, the severity of sepsis-induced lung injury was only reduced by hypercapnic acidosis. Wang and colleagues[19] investigated the effects of acute hypercapnic acidosis in a sheep model of faecal peritonitis and septic shock. Hypercapnic acidosis was shown to increase heart rate, cardiac output, systemic oxygen delivery and lactate clearance. Furthermore, the shunt fraction and alveolar arterial gradient reduced with hypercapnic acidosis.[19] However, there was no difference in survival times in the animals that were treated with hypercapnic acidosis as compared with those managed with normocapnia.[19]

Most of the animal experiments investigating hypercapnic acidosis targeted surrogate and short term outcome measures[12,20,30,34] and perhaps are not particularly relevant to clinical practice or understanding the effects of improved tissue oxygenation or management of hypercapnia in sepsis in clinical practice.

Hypercapnia and cerebral vascular reactivity in sepsis

Hypercapnia causes cerebral vasodilation, with a linear increase in cerebral blood volume and cerebral blood flow in rhesus monkeys.[38,39] In animal models of sepsis, this vasodilatory response to hypercapnia may be impaired. In a canine model of gram-negative endotoxic shock, cerebrovascular reactivity to hypercarnia was impaired with increased cerebral vascular resistance and reduced cerebral blood flow despite hypercapnia.[23] In a swine model of sepsis, a 4-hour infusion of group B streptococci not only affected cardiac output but also showed impaired cerebrovascular reactivity to hypercarnia, as compared with a non-septic group of piglets, despite similar reduction in cardiac output.[24]

To summarise, animal experiments on hypercapnic acidosis in sepsis have, to some extent, helped to expand our understanding, but much remains unknown, especially, the differentiating effects of compensated hypercapnia and hypercapnic acidosis.

Clinical studies on hypercapnia and hypercapnic acidosis in sepsis

Permissive hypercapnia was shown to be associated with a reduction in mortality in patients with acute respiratory distress syndrome who are mechanically ventilated.[40]

Subsequent literature, including randomised controlled trials and large observational studies, showed varying results.[41-45] Targeted hypercapnia was also shown to minimise cerebral injury in the setting of out-of-hospital cardiac arrest.[46] Studies investigating the effects of hypercapnia in clinical sepsis, especially in critically ill patients, are very limited.

The effects of hypercapnia are well studied in physiological and various pathophysiological conditions and in vitro studies including human blood. Under physiological conditions, in healthy volunteers or patients undergoing elective surgery, hypercapnia was reported to increase cardiac output[47,48] and, therefore, perfusion and oxygenation of splanchnic, myocardial and subcutaneous tissues.[21,49-51] These effects were also noted in patients with morbid obesity.[50] The effects of hypercapnia on cerebrovascular reactivity and autoregulation were investigated in a few studies.[52-56] Some studies reported hypercapnia to impair cerebrovascular reactivity and autoregulation in most but not all patients with sepsis and septic shock,[55,56] with no such impairment noted in other studies.[52,53] The clinical implications of these findings and reasons for the lack of consistent effect on cerebrovascular reactivity and autoregulation observed in different studies are not clear at this stage. Further clinical studies are required to establish the effects of hypercapnia on cerebral perfusion in patients with sepsis and septic shock.

In vitro studies investigating the effects of hypercapnia and hypercapnic acidosis on immune function in endotoxin-stimulated whole human blood suggest that hypercapnia can modulate cytokine levels in whole blood cell cultures and have a potential role in therapeutic modulation of the inflammatory cascade in sepsis.[29] Hypercapnia was shown to inhibit TNF-α and IL-6 expression in macrophages that were stimulated with lipopolysaccharide.[57] This inhibition was shown to be rapid, concentration-dependent and reversible at levels of $Paco_2$ (arterial partial pressure of carbon dioxide) that may be seen in patients with acute and chronic lung diseases. The inhibition of IL-6 is independent of acidosis.[57]

Hypercapnia and hypercapnic acidosis was investigated in clinical studies aimed at the prevention of sepsis and the association of hypercapnia with adverse clinical outcomes.

Prevention of wound infections

Mild hypercapnia was investigated as an intervention to prevent wound infection in patients undergoing elective colorectal surgery.[22] In a large randomised controlled trial that included over 1200 patients, each participant was allocated to either mild hypercapnia or normocapnia during the intra-operative period. In this study, patients who had mild hypercapnia did not have a significant reduction in wound infections. However, the authors indicated that this lack of reduction in wound infections was possibly due to inadequate sample size.[22]

Association of hypercapnia on clinical outcomes in established sepsis

The association of hypercapnia with adverse clinical outcomes was studied in patients with pulmonary sepsis due to community-acquired pneumonia. Patients presenting to emergency departments with hypercapnia were found to have an increased risk of ICU admission[58] and association with increased mortality.[58,59] Hypercapnia was shown to be independently associated with an increased risk of mortality after hospitalisation due to an acute exacerbation of chronic obstructive pulmonary disease.[60,61] Furthermore, hypercapnia was also known to be associated with increased mortality in children with lower respiratory tract infections caused by adenovirus.[62] There are no studies investigating the effects of hypercapnia in sepsis other than pulmonary sepsis.

While the data from some animal experimental models suggest benefit with hypercapnia in positively modulating the immune system and tissue oxygenation, the small number of clinical studies in non-critical care settings suggests that hypercapnia is associated with increased mortality. Hypercapnia was initially thought to be associated with improved clinical outcomes in patients who are mechanically ventilated,[40,63] but more recent studies suggest hypercapnia and hypercapnic acidosis to be independently associated with increased hospital mortality in patients who are mechanically ventilated.[44,45]

Furthermore, extracorporeal clearance of hypercapnia associated with ultraprotective lung ventilation is currently investigated in two randomised controlled trials (ClinicalTrials.gov NCT02654327, NCT02282657). Targeted hypercapnia is also currently being investigated as an intervention to minimise cerebral injury in patients (NCT03114033). Given this changing paradigm, further studies are required, particularly in critically ill patients, to define the impact of hypercapnia and hypercapnic acidosis in sepsis.

Conclusion

The effects of hypercapnic acidosis have been extensively studied in various in vivo animal models of sepsis and ex-vivo studies with varying results. Hypercapnia and hypercapnic acidosis may be beneficial in some organs sepsis and harmful in others. The effects may also vary at different time points during the course of sepsis.

Clinical data, specifically pertaining to critically ill patients, are required to further our understanding of the impact of hypercapnia and hypercapnic acidosis in sepsis, particularly given the imminent increase in modulation of carbon dioxide in these patients. Unfortunately, data of this nature are very limited.

Competing interests

None declared.

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References

1 Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014; 2: 380-6.

2 Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014; 311: 1308-16.

3 Adrie C, Alberti C, Chaix-Couturier C, et al. Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. *J Crit Care* 2005; 20: 46-58.

4 PRISM Investigators. Early, goal-directed therapy for septic shock — a patient-level meta-analysis. *N Engl J Med* 2017; 376: 2223-34.

5 Martínez ML, Ferrer R, Torrents E, et al. Impact of source control in patients with severe sepsis and septic shock. *Crit Care Med* 2017; 45: 11-19.

6 Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34: 1589-96.

7 Curley G, Contreras MM, Nichol AD, et al. Hypercapnia and acidosis in sepsis: a double-edged sword? *Anesthesiology* 2010; 112: 462-72.

8 Casalino-Matsuda SM, Nair A, Beitel GJ, et al. Hypercapnia inhibits autophagy and bacterial killing in human macrophages by increasing expression of Bcl-2 and Bcl-xL. *J Immunol* 2015; 194: 5388-96.

9 Coakley RJ, Taggart C, Greene C, et al. Ambient pCO2 modulates intracellular pH, intracellular oxidant generation, and interleukin-8 secretion in human neutrophils. *J Leukoc Biol* 2002; 71: 603-10.

10 Higgins BD, Costello J, Contreras M, et al. Differential effects of buffered hypercapnia versus hypercapnic acidosis on shock and lung injury induced by systemic sepsis. *Anesthesiology* 2009; 111: 1317-26.

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

12 Chonghaile MN, Higgins BD, Costello J, Laffey JG. Hypercapnic acidosis attenuates lung injury induced by established bacterial pneumonia. *Anesthesiology* 2008; 109: 837-48.

13 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: 2128-35.

14 The Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, 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: 1301-8.

15 Otulakowski G, Kavanagh BP. Hypercapnia in acute illness: sometimes good, sometimes not. *Crit Care Med* 2011; 39: 1581-2.

16 Tiruvoipati R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. *Anaesth Intensive Care* 2013; 41: 157-62.

17 Pugin J, Dunn-Siegrist I, Dufour J, et al. Cyclic stretch of human lung cells induces an acidification and promotes bacterial growth. *Am J Respir Cell Mol Biol* 2008; 38: 362-70.

18 Akça O. Carbon dioxide and tissue oxygenation: is there sufficient evidence to support application of hypercapnia for hemodynamic stability and better tissue perfusion in sepsis? *Intensive Care Med* 2008; 34: 1752-4.

19 Wang Z, Su F, Bruhn A, et al. Acute hypercapnia improves indices of tissue oxygenation more than dobutamine in septic shock. *Am J Respir Crit Care Med* 2008; 177: 178-83.

20 Beck C, Barthel F, Hahn AM, et al. The beneficial effects of acute hypercapnia on microcirculatory oxygenation in an animal model of sepsis are independent of K(+)ATP channels. *Microvasc Res* 2015; 99: 78-85.

21 Akça O, Doufas AG, Morioka N, et al. Hypercapnia improves tissue oxygenation. *Anesthesiology* 2002; 97: 801-6.

22 Akça O, Kurz A, Fleischmann E, et al. Hypercapnia and surgical site infection: a randomized trial. *Br J Anaesth* 2013; 111: 759-67.

23 Parker JL, Emerson TE. Cerebral hemodynamics, vascular reactivity, and metabolism during canine endotoxin shock. *Circ Shock* 1977; 4: 41-53.

24 Rudinsky BF, Lozon M, Bell A, et al. Group B streptococcal sepsis impairs cerebral vascular reactivity to acute hypercarbia in piglets. *Pediatr Res* 1996; 39: 55-63.

25 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: 124-32.

26 Cummins EP, Oliver KM, Lenihan CR, et al. NF-kappaB links CO2 sensing to innate immunity and inflammation in mammalian cells. *J Immunol* 2010; 185: 4439-45.

27 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: 976-82.

28 Lardner A. The effects of extracellular pH on immune function. *J Leukoc Biol* 2001; 69: 522-30.

29 Kimura D, Totapally BR, Raszynski A, et al. The effects of CO2 on cytokine concentrations in endotoxin-stimulated human whole blood. *Crit Care Med* 2008; 36: 2823-7.

30 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: 821-8.

31 Swallow CJ, Grinstein S, Sudsbury RA, Rotstein OD. Relative roles of Na+/H+ exchange and vacuolar-type H+ ATPases in regulating cytoplasmic pH and function in murine peritoneal macrophages. *J Cell Physiol* 1993; 157: 453-60.

32 Norozian FM, Leoncio M, Torbati D, et al. Therapeutic hypercapnia enhances the inflammatory response to endotoxin in the lung of spontaneously breathing rats. *Crit Care Med* 2011; 39: 1400-6.

33 Laffey JG, Honan D, Hopkins N, et al. Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. *Am J Respir Crit Care Med* 2004; 169: 46-56.

34 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: 2412-20.

35 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: 3135-44.

36 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: 2953-61.

37 Stübs CC, Picker O, Schulz J, et al. Acute, short-term hypercapnia improves microvascular oxygenation of the colon in an animal model of sepsis. *Microvasc Res* 2013; 90: 180-6.

38 Weinberger SE, Schwartzstein RM, Weiss JW. Hypercapnia. *N Engl J Med* 1989; 321: 1223-31.

39 Grubb RL, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in $Paco_2$ on cerebral blood volume, blood flow, and vascular mean transit time. *Stroke* 1974; 5: 630-9.

40 Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994; 22: 1568-78.

41 Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338: 347-54.

42 Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume Reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158: 1831-8.

43 Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; 27: 1492-8.

44 Nin N, Muriel A, Peñuelas O, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med* 2017; 43: 200-8.

45 Tiruvoipati R, Pilcher D, Buscher H, et al. Effects of hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients. *Crit Care Med* 2017; 45: e649-56.

46 Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation* 2016; 104: 83-90.

47 Laffey JG, Kavanagh BP. Biological effects of hypercapnia. *Intensive Care Med* 2000; 26: 133-8.

48 Kiely DG, Cargill RI, Lipworth BJ. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. *Chest* 1996; 109: 1215-21.

49 Fleischmann E, Herbst F, Kugener A, et al. Mild hypercapnia increases subcutaneous and colonic oxygen tension in patients given 80% inspired oxygen during abdominal surgery. *Anesthesiology* 2006; 104: 944-9.

50 Hager H, Reddy D, Mandadi G, et al. Hypercapnia improves tissue oxygenation in morbidly obese surgical patients. *Anesth Analg* 2006; 103: 677-81.

51 Pelletier-Galarneau M, deKemp RA, Hunter CR, et al. Effects of hypercapnia on myocardial blood flow in healthy human subjects. *J Nucl Med* 2018; 59: 100-6.

52 Matta BF, Stow PJ. Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies. *Br J Anaesth* 1996; 76: 790-4.

53 Thees C, Kaiser M, Scholz M, et al. Cerebral haemodynamics and carbon dioxide reactivity during sepsis syndrome. *Crit Care* 2007; 11: R123.

54 Bowton DL, Bertels NH, Prough DS, Stump DA. Cerebral blood flow is reduced in patients with sepsis syndrome. *Crit Care Med* 1989; 17: 399-403.

55 Bowie RA, O'Connor PJ, Mahajan RP. Cerebrovascular reactivity to carbon dioxide in sepsis syndrome. *Anaesthesia* 2003; 58: 261-5.

56 Taccone FS, Castanares-Zapatero D, Peres-Bota D, et al. Cerebral autoregulation is influenced by carbon dioxide levels in patients with septic shock. *Neurocrit Care* 2010; 12: 35-42.

57 Wang N, Gates KL, Trejo H, et al. Elevated CO_2 selectively inhibits interleukin-6 and tumor necrosis factor expression and decreases phagocytosis in the macrophage. *FASEB J* 2010; 24: 2178-90.

58 Laserna E, Sibila O, Aguilar PR, et al. Hypocapnia and hypercapnia are predictors for ICU admission and mortality in hospitalized patients with community-acquired pneumonia. *Chest* 2012; 142: 1193-9.

59 Sin DD, Man SF, Marrie TJ. Arterial carbon dioxide tension on admission as a marker of in-hospital mortality in community-acquired pneumonia. *Am J Med* 2005; 118: 145-50.

60 Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; 124: 459-67.

61 Slenter RH, Sprooten RT, Kotz D, et al. Predictors of 1-year mortality at hospital admission for acute exacerbations of chronic obstructive pulmonary disease. *Respiration* 2013; 85: 15-26.

62 Murtagh P, Giubergia V, Viale D, et al. Lower respiratory infections by adenovirus in children. Clinical features and risk factors for bronchiolitis obliterans and mortality. *Pediatr Pulmonol* 2009; 44: 450-6.

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

3.3 Chapter Summary

This review article reviewed the effects of hypercapnia and hypercapnic acidosis in the setting of sepsis. The effects of hypercapnia were reported to vary at different stages (including evolution and progress) and the source of sepsis. Published data from animal experimental studies suggest that the effects of hypercapnic acidosis are variable, with possible benefit in some settings of sepsis and harm in others.

It was apparent from this review that there are no clinical studies investigating clinical outcomes of hypercapnic acidosis or compensated hypercapnia in sepsis and septic shock in critical care settings. It highlights the need for clinical studies, especially in critically ill patients, to define the management of compensated hypercapnia and hypercapnic acidosis that may aid clinicians to improve the outcomes in sepsis.

This article was published in the journal of Critical Care and Resuscitation with an accompanying editorial entitled “The undiscovered country: therapeutic targeting of carbon dioxide levels in critically ill patients” (Appendix 6). This editorial concurs with our view on the lack of clinical studies relevant to critically ill patients and calls for clinical trials on managing hypercapnia in different diagnostic categories of critically ill patients.

Given the lack of clinical data relevant to critically ill patients, an investigation of compensated hypercapnia and hypercapnic acidosis was undertaken using ANZICS APD, a high quality data registry that receives data on critically ill patients from 171 intensive care units (during the study period) that encompassed over 80% of ICUs across Australia and New Zealand.

CHAPTER 4: Effects of hypercapnia and hypercapnic acidosis in mechanically ventilated patients.

4.1 Chapter Introduction

The review of literature described in the previous two chapters identified the lack of large high quality clinical studies in intensive care practice investigating hypercapnia and hypercapnic acidosis on clinical outcomes. The ARDS network recommended that the use of a low tidal volume lung-protective ventilation strategy in patients with ARDS could lead to hypercapnia and hypercapnic acidosis. The effects of hypercapnia and hypercapnic acidosis in critically ill patients are not clearly known. To investigate the effects of hypercapnia and hypercapnic acidosis on clinically outcomes, we conducted the largest retrospective, multicentre, binational study that included over a quarter of a million mechanically ventilated patients. This study used data from the Australian and New Zealand Intensive Care Society Adult patient database (ANZICS APD) which is recognised as a high quality clinical data registry from more than 80% of all ICUs in Australia and New Zealand. This study aimed to investigate the association of compensated hypercapnia and hypercapnic acidosis on hospital mortality in adult mechanically ventilated patients. It further assessed the association of hypercapnia and hypercapnic acidosis on specific and commonly admitted diagnostic groups of mechanically ventilated patients.

4.2 Published manuscript

Effects of Hypercapnia and Hypercapnic Acidosis on Hospital Mortality in Mechanically Ventilated Patients*

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Objectives: Lung-protective ventilation is used to prevent further lung injury in patients on invasive mechanical ventilation. However, lung-protective ventilation can cause hypercapnia and hypercapnic acidosis. There are no large clinical studies evaluating the effects of hypercapnia and hypercapnic acidosis in patients requiring mechanical ventilation.

Design: Multicenter, binational, retrospective study aimed to assess the impact of compensated hypercapnia and hypercapnic acidosis in patients receiving mechanical ventilation.

Settings: Data were extracted from the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database over a 14-year period where 171 ICUs contributed deidentified data.

Patients: Patients were classified into three groups based on a combination of pH and carbon dioxide levels (normocapnia and normal pH, compensated hypercapnia [normal pH with elevated carbon dioxide], and hypercapnic acidosis) during the first 24 hours of ICU stay. Logistic regression analysis was used to identify the independent association of hypercapnia and hypercapnic acidosis with hospital mortality.

Interventions: Nil.

Measurements and Main Results: A total of 252,812 patients (normocapnia and normal pH, 110,104; compensated hypercapnia, 20,463; and hypercapnic acidosis, 122,245) were included in analysis. Patients with compensated hypercapnia and hypercapnic acidosis had higher Acute Physiology and Chronic Health Evaluation III scores (49.2 vs 53.2 vs 68.6; $p < 0.01$). The mortality was higher in hypercapnic acidosis patients when compared with other groups, with the lowest mortality in patients with normocapnia and normal pH. After adjusting for severity of illness, the adjusted odds ratio for hospital mortality was higher in hypercapnic acidosis patients (odds ratio, 1.74; 95% CI, 1.62–1.88) and compensated hypercapnia (odds ratio, 1.18; 95% CI, 1.10–1.26) when compared with patients with normocapnia and normal pH ($p < 0.001$). In patients with hypercapnic acidosis, the mortality increased with increasing P_{CO_2} until 65 mm Hg after which the mortality plateaued.

Conclusions: Hypercapnic acidosis during the first 24 hours of intensive care admission is more strongly associated with increased hospital mortality than compensated hypercapnia or normocapnia. (*Crit Care Med* 2017; 45:e649–e656)

Key Words: hypercapnia; respiratory acidosis; respiratory failure

Acute respiratory failure is one of the common reasons why patients are admitted to ICUs. The management of acute respiratory failure often includes mechanical ventilation. The deleterious effects of mechanical ventilation with high tidal volumes and high pressures are well known (1, 2). The current recommendation in the management of patients with severe respiratory failure, particularly with acute respiratory distress syndrome (ARDS), is to practice lung-protective ventilation (1). Furthermore, some studies have claimed that "ultra" lung-protective ventilation may reduce lung injury further than that achieved by lung-protective ventilation (3).

***See also p. 1253.**

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The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000002332

The strategy of lung-protective ventilation may cause mild-to-moderate acute hypercapnia and acidosis, but it is currently accepted as standard care. The effects of hypercapnia and hypercapnic acidosis are not clearly known. Some authors have suggested that the hypercapnia and acidosis may be protective by itself, independent of low volume ventilation and may aid in reducing the mortality (4–7). Indeed they have hypothesized that inducing hypercapnia by supplemental carbon dioxide may be beneficial in critically ill patients with acute respiratory failure (5). To the contrary, other clinicians consider hypercapnic acidosis to be harmful (1, 8). There are scant clinical data to evaluate the effects of hypercapnic acidosis and compensated hypercapnia on hospital mortality.

Given the uncertainty, we aimed to review the association of hypercapnia and hypercapnic acidosis on hospital mortality in adult mechanically ventilated patients.

METHODS

We conducted a retrospective review of all mechanically ventilated patients over a 14-year period (January 2000 to December 2013) admitted to 171 ICUs in Australia and New Zealand. Data were collected from the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD). ANZCS APD is high-quality database run by ANZICS center for outcome and resource evaluation. It collates complete patient information that is required to calculate patient severity over the first 24 hours of ICU admission (9) from more than 80% of ICUs across Australia and New Zealand as part of quality assurance and benchmarking process among participating ICUs. Ethics approval was obtained from Monash University Research Ethics Committee. The ethics committee waived informed consent from the patients as the data were gathered as part of routine quality assurance benchmarking process for the participating ICUs.

Adult patients with respiratory failure, receiving mechanical ventilation during the first 24 hours of their admission to the ICU, were included in the study. For this analysis, we used the arterial blood gas that provided the highest scoring Acute Physiology and Chronic Health Evaluation (APACHE) II subscore and as such is likely to have represented the worst pH/P_{CO_2} combination in the first 24 hours of ICU admission. Patients were classified into three groups based on a combination of arterial pH and arterial carbon dioxide levels (normocapnia [P_{CO_2}, 35–45 mm Hg] and normal pH [7.35–7.45] [group 1], compensated hypercapnia [normal pH (7.35–7.45) with elevated carbon dioxide (P_{CO_2} > 45 mm Hg)] [group 2], and hypercapnic acidosis [P_{CO_2} > 45 mm Hg; pH < 7.35] [group 3]) during the first 24 hours of ICU stay. Patients with metabolic acidosis, metabolic alkalosis, and respiratory alkalosis were excluded. Patients in group 1 were considered as a reference group to which patients in groups 2 and 3 were compared. The pattern of mortality and the management of respiratory rate on mechanical ventilation (as a surrogate marker for lower tidal volume ventilation [1]) were further studied by stratifying the data into three time periods (2000–2004, 2005–2009, and 2010–2013) to enable identification of how mortality and respiratory rate have changed over time.

All analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC). Data were initially assessed for normality. Group comparisons were made using chi-square tests for equal proportion, analysis of variance for normally distributed variables, and Kruskal-Wallis tests otherwise, with results reported as percentages (*n*), means (SDs), and medians (interquartile range), respectively. To investigate the independent effect of hypercapnia and hypercapnic acidosis on hospital mortality, multivariable logistic regression models were used adjusting for a priori defined covariates (patient severity, year of admission, and site), with annual changes determined by fitting interactions between group and year of admission, with year treated initially as a categorical variable and then second as a continuous variable once linearity was established. To further determine the relationship with the severity of respiratory failure, a 12-category multivariate model was used with each of the original three groups further stratified by four P/F ratio categories (< 100, 100–200, 200–300, > 300) with the reference category being normocapnia normal pH with a P/F ratio greater than 300. Duration of stay variables (hospital and ICU length of stay) was log-transformed and analyzed using mixed linear models again adjusting for severity, year of admission, and site with results presented as geometric means (95% CI). To facilitate a measure of patient severity independent of hypercapnia, each patient's predicted risk of death was calculated in accordance with the Australia and New Zealand Risk of Death (ANZROD) methodology (9) with the components of pH and oxygen removed. ANZROD is an updated mortality prediction model specifically calibrated for use in ANZ ICUs that has been derived from components of the APACHE II and III scoring systems with additional diagnostic variables and has been shown to have significantly better calibration and discrimination than APACHE III. Given the magnitude of the dataset, in order to more closely align statistical and clinical significance, a two-sided *p* value of 0.01 was used to indicate statistically significant results.

RESULTS

A total of 252,812 patients were included in the analysis (**Fig. 1**). A comparison of demographic, comorbidity, and admission diagnostic category data is presented in **Table 1**. When compared with patients with normocapnia and normal pH, patients with compensated hypercapnia and hypercapnic acidosis were older, had an increased prevalence rate of chronic respiratory, cardiovascular and renal diseases. The most common reason for admission to ICU was of cardiovascular diagnoses including post cardiac surgery, cardiac arrest, and cardiogenic shock. **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C361) presents a comparison of physiologic and laboratory variables. Patients with compensated hypercapnia and hypercapnic acidosis had a significant difference in heart rate, blood pressure, and temperature as well as the measured renal, liver function tests during the first 24 hours of their ICU admission. Significantly more patients with compensated hypercapnia and hypercapnic acidosis had lower P/F ratios and lower pH (**Supplemental Table 2**, Supplemental

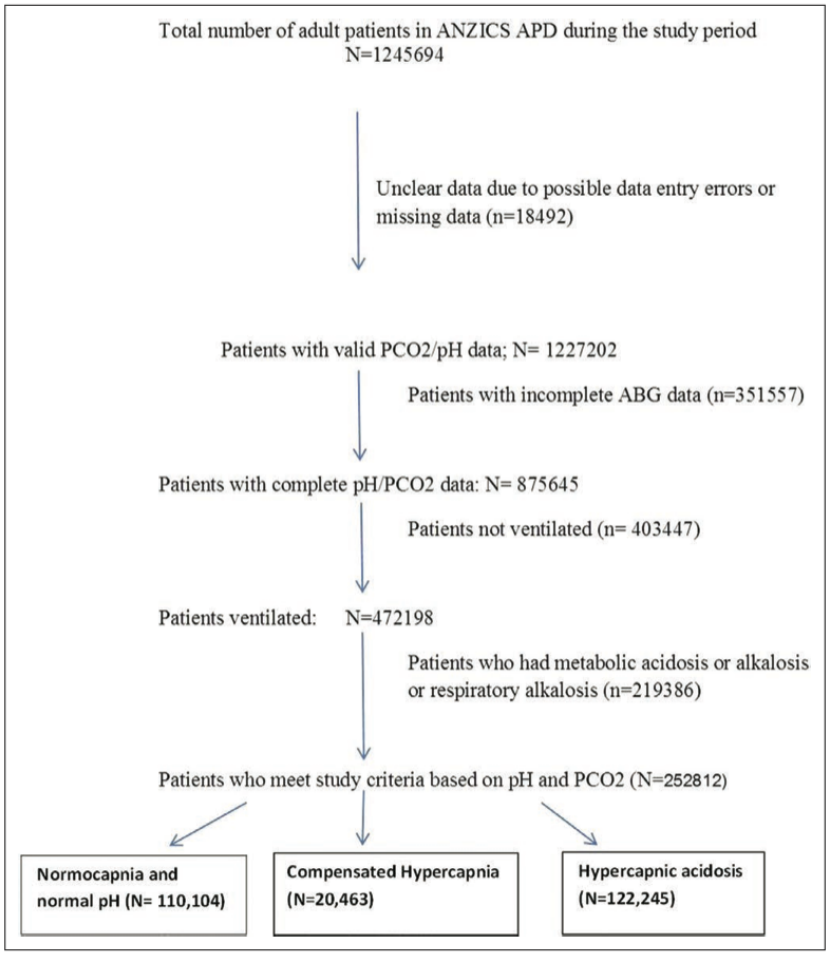

Figure 1. Study profile. ABG = arterial blood gas, ANZICS APD = Australian and New Zealand Intensive Care Society Adult Patient Database.

Digital Content 2, http://links.lww.com/CCM/C362). Hospital mortality was higher and discharge home was lower in patients with compensated hypercapnia and hypercapnic acidosis (**Table 2**). Duration of hospital stay and ICU stay was also longer in patients with compensated hypercapnia and hypercapnic acidosis (Table 2).

Multivariable logistic regression analysis revealed an increased odds ratio (OR) for hospital mortality in patients with compensated hypercapnia and hypercapnic acidosis (compensated hypercapnia: OR: 1.30, 95% CI: 1.22–1.38; hypercapnic acidosis: OR: 1.66, 95% CI: 1.60–1.72). The adjusted odds ratio for hospital mortality remained significantly higher in compensated hypercapnia and hypercapnic acidosis when compared with patients with normocapnia and normal pH irrespective of their P/F ratios (**Table 3**). This increased mortality (irrespective of P/F ratios) noted in patients with hypercapnic acidosis and compensated hypercapnia persisted during the three stratified time periods (2000–2004, 2005–2009, and 2010–2013) (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/C363). During these three stratified time periods, mechanical ventilation rates were noted to have increased after 2000–2004 (**Supplemental Table 4**, Supplemental Digital Content 4, http://links.lww.com/CCM/C364).

Subgroup analysis was further performed based on the admission diagnostic category. This showed higher adjusted odds ratio for hospital mortality in patients with compensated hypercapnia and hypercapnic acidosis in all diagnostic categories except for trauma patients where lower hospital mortality was noted in patients with compensated hypercapnia (**Supplemental Table 5**, Supplemental Digital Content 5, http://links.lww.com/CCM/C365).

In patients with compensated hypercapnia, the mortality progressively increased with an increase in P_{CO_2} till a P_{CO_2} of 65 mm Hg after which a trend toward reduction in mortality was noted. In patients with hypercapnic acidosis, the mortality increased with increasing P_{CO_2} till 65 mm Hg after which the mortality plateaued (**Fig. 2**). Over the study period, a reduction in mortality was noted in all three groups between 2000 and 2013 (**Supplemental Fig. 1**, Supplemental Digital Content 6, http://links.lww.com/CCM/C366; legend: decline in hospital mortality from 2000 to 2013 in all groups). However, there was no evidence to suggest that the decline in mortality over time differed between groups (normocapnia and normal pH: OR, 0.96 [0.96–0.97]; compensated hypercapnia: OR, 0.95 [0.94–0.96]; hypercapnic acidosis: OR, 0.96 [0.96–0.96]; $p = 0.12$).

DISCUSSION

The main results of this study show that patients with hypercapnic acidosis and compensated hypercapnia at the time of hospital admission had a higher mortality when compared with patients who had a normal pH and normocapnia. This increased mortality persisted after adjusting for the variables

TABLE 1. Comparison of Demographics Comorbidity and Admission Diagnostic Category

Variable	Normocapnia and Normal pH (n = 110,104)	Compensated Hypercapnia (n = 20,463)	Hypercapnic Acidosis (n = 122,245)	p
Age (yr)	60.8 (17.4)	60.7 (16.8)	61 (16.6)	0.002
Male gender (n, %)	74,641 (67.8)	14,023 (68.5)	82,563 (67.5)	0.017
Weight (kg)	82.1 (19.9)	87.8 (26.1)	87.5 (26.2)	< 0.001
Height (cm)	169 (14.8)	169 (21.3)	169 (21.3)	0.67
Comorbidities (n, %)				
Chronic respiratory disease	4,348 (3.9)	2,626 (12.8)	15,907 (13)	< 0.001
Chronic cardiovascular disease	13,270 (12.1)	2,616 (12.8)	16,356 (13.4)	< 0.001
Chronic liver disease	1,427 (1.3)	310 (1.5)	2,244 (1.8)	< 0.001
Chronic renal failure	1,856 (1.7)	375 (1.8)	3,415 (2.8)	< 0.001
Immune disease	1,497 (1.4)	440 (2.2)	2,309 (1.9)	< 0.001
Immunosuppression	2,382 (2.2)	665 (3.2)	4,100 (3.4)	< 0.001
Admission diagnostic category (n, %)				
Cardiovascular	55,023 (50)	7,198 (35.2)	48,553 (39.7)	<0.0001
Post coronary artery bypass grafting	29,272 (26.6)	3,194 (15.6)	18,048 (14.8)	< 0.0001
Cardiogenic shock	423 (0.3)	107 (0.5)	2,254 (1.8)	< 0.0001
Cardiac arrest	2,025 (1.8)	416 (2.0)	8,359 (6.8)	< 0.0001
Gastrointestinal	12,392 (11.3)	2,448 (12)	14,693 (12)	< 0.0001
Gynecologic	518 (0.47)	61 (0.298)	423 (0.346)	< 0.0001
Hematologic	142 (0.129)	44 (0.215)	298 (0.244)	< 0.0001
Metabolic	6,389 (5.8)	1,129 (5.5)	4,847 (4)	< 0.0001
Musculoskeletal	1,532 (1.4)	380 (1.9)	1,446 (1.2)	< 0.0001
Neurologic	13,202 (12)	1,781 (8.7)	5,820 (4.8)	< 0.0001
Renal	932 (0.846)	139 (0.679)	1,437 (1.2)	< 0.0001
Respiratory	9,551 (8.7)	5,187 (25.3)	28,134 (23)	< 0.0001
Pneumonia	2,745 (2.5)	1,477 (7.2)	8,844 (7.3)	< 0.0001
Asthma	218 (0.2)	86 (0.42)	1,857 (1.5)	< 0.0001
Chronic obstructive pulmonary disease	580 (0.5)	1,199 (5.9)	6,788 (5.6)	< 0.0001
Sepsis	1,618 (1.5)	478 (2.3)	6,668 (5.5)	< 0.0001
Trauma	7,796 (7.1)	1,365 (6.7)	8,714 (7.1)	0.06
Other	285 (0.259)	353 (0.289)	69 (0.34)	0.11

that principally contribute to hospital mortality such as severity of illness, location of the ICU, and the time frame when patients were admitted to the ICU. Furthermore, the adjusted mortality remained high for patients with compensated hypercapnia and hypercapnic acidosis irrespective of their P/F ratios. The increased association of mortality in patients with hypercapnic acidosis and compensated hypercapnia remained consistently higher during the three stratified time periods. Overall, the mortality in all three groups reduced over the 14-year study period. In patients with hypercapnic acidosis, the mortality increased with increasing P_{CO_2} till 65 mm Hg after which the mortality plateaued.

Although there are studies evaluating acute hypocapnia and hypercapnia in hospitalized patients with community-acquired pneumonia (10, 11), to the best of our knowledge, there are no large clinical studies evaluating the effect of acute hypercapnia or compensated hypercapnia in mechanically ventilated patients. The mechanisms behind the association between

TABLE 2. Comparison of Outcomes Between Patients With Normocapnia and Normal pH, Compensated Hypercapnia, and Hypercapnic Acidosis

Variable	Normocapnia and Normal pH (n = 110,104)	Compensated Hypercapnia (n = 20,463)	Hypercapnic Acidosis (n = 122,245)	p
Died in hospital (n, %)	8,610 (7.8)	2,498 (12.2)	26,507 (21.7)	< 0.001
P/F ratio < 100 (n, % died)	1,050 (12)	515 (18.7)	8,976 (36.8)	
P/F ratio 100 to < 200 (n, % died)	2,075 (8.2)	898 (14.3)	9,308 (21.8)	
P/F ratio 200 to < 300 (n, % died)	2,189 (7.3)	597 (10.9)	4,388 (15.5)	
P/F ratio ≥ 300 (n, % died)	3,296 (7.2)	488 (8.2)	3,835 (14.2)	
Discharged home (n, %)	80,435 (73.1)	13,607 (66.5)	72,515 (59.3)	< 0.001
Discharged to rehabilitation (n, %)	9,047 (8.2)	1,714 (8.4)	8,394 (6.9)	< 0.001
Discharged to other hospital (n, %)	10,739 (9.8)	2,360 (11.5)	12,379 (10.1)	< 0.001
Hospital LOS (d) (median, IQR)	10.5 (6.93–18.9)	12 (7.01–23.3)	11 (6.13–21.5)	< 0.001
Hospital LOS—survivors (d) (median, IQR)	10.7 (7–18.8)	11.9 (7.1–22.7)	12.3 (7.3–23.0)	< 0.001
Hospital LOS—deaths (d) (median, IQR)	8.9 (3.5–20.9)	13.2 (5.1–28.6)	5.4 (1.8–14.9)	< 0.001
ICU LOS—survivors (d) (median, IQR)	1.9 (1.0–3.7)	2.2 (1.2–4.9)	2.9 (1.4–6.6)	< 0.001
ICU LOS—deaths (d) (median, IQR)	3.3 (1.5–7.6)	4.3 (1.8–9.7)	2.0 (0.7–5.6)	< 0.001

IQR = interquartile range, LOS = length of stay, P/F ratio = Pao_2/Fio_2 ratio.

TABLE 3. Multivariate Analysis of Odds Ratio for Hospital Mortality Based on P/F Ratios

P/F Ratio	Normocapnia and Normal pH, OR (95% CI)	Compensated Hypercapnia, OR (95% CI)	Hypercapnic Acidosis, OR (95% CI)	p
P/F ratio, < 100	1.66 (1.50–1.84)	2.03 (1.75–2.36)	2.66 (2.51–2.82)	< 0.001
P/F ratio, 100–200	1.12 (1.40–1.20)	1.69 (1.53–1.87)	1.78 (1.69–1.88)	
P/F ratio, 200–300	1.00 (0.94–1.08)	1.20 (1.07–1.35)	1.46 (1.38–1.55)	
P/F ratio, > 300	Reference category (1.00)	1.00 (0.88–1.13)	1.37 (1.29–1.46)	

OR = odds ratio, P/F ratio = Pao_2/Fio_2 ratio.

higher mortality in patients with compensated hypercapnia and hypercapnic acidosis are unclear and are likely to be different in acute hypercapnia (generally noted in patients without chronic lung diseases) and respiratory acidosis when compared with compensated hypercapnia (usually seen in patients with chronic lung diseases) with no acidosis. It seems that the pattern of increased hospital mortality in patients with hypercapnic acidosis and compensated hypercapnia did not change over the three stratified study periods in spite of the increase in respiratory rates (a surrogate marker for the possible use of low tidal volume ventilation) during the latter part of the study period. This is perhaps due to the fact that our data are limited to the first 24 hours of ICU stay and may not reflect the management of ventilation beyond 24 hours of ICU stay.

The beneficial effects of hypercapnia are largely reported in animal experiments of lung injury and have not been confirmed in clinical studies (12). The pathophysiologic effects of hypercapnia and hypercapnic acidosis may vary across different organ systems (12). Although there are some beneficial physiologic effects associated with acute hypercapnia (13, 14), it seems from our study that there may be more harmful effects than beneficial effects that may have contributed to the overall increased hospital mortality in mechanically ventilated patients.

It is unclear from our study as to the cause for increased mortality in patients with hypercapnic acidosis and compensated hypercapnia. However, in animal experiments, hypercapnic acidosis was shown to worsen lung injury and cause hemodynamic instability, worsen injuries of alveolar epithelial cells and impair wound healing in alveolar epithelial cells (15–17). Hypercapnic acidosis was also shown to suppress both innate and adaptive immune responses. It reduces neutrophil and macrophage migration in addition to the inhibiting of phagocytosis. It was also shown to impair the release of proinflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-8, and IL-6 (18). Acidosis has been associated with bacterial proliferation in some models of infection. Acidification of culture mediums to pH 7.20

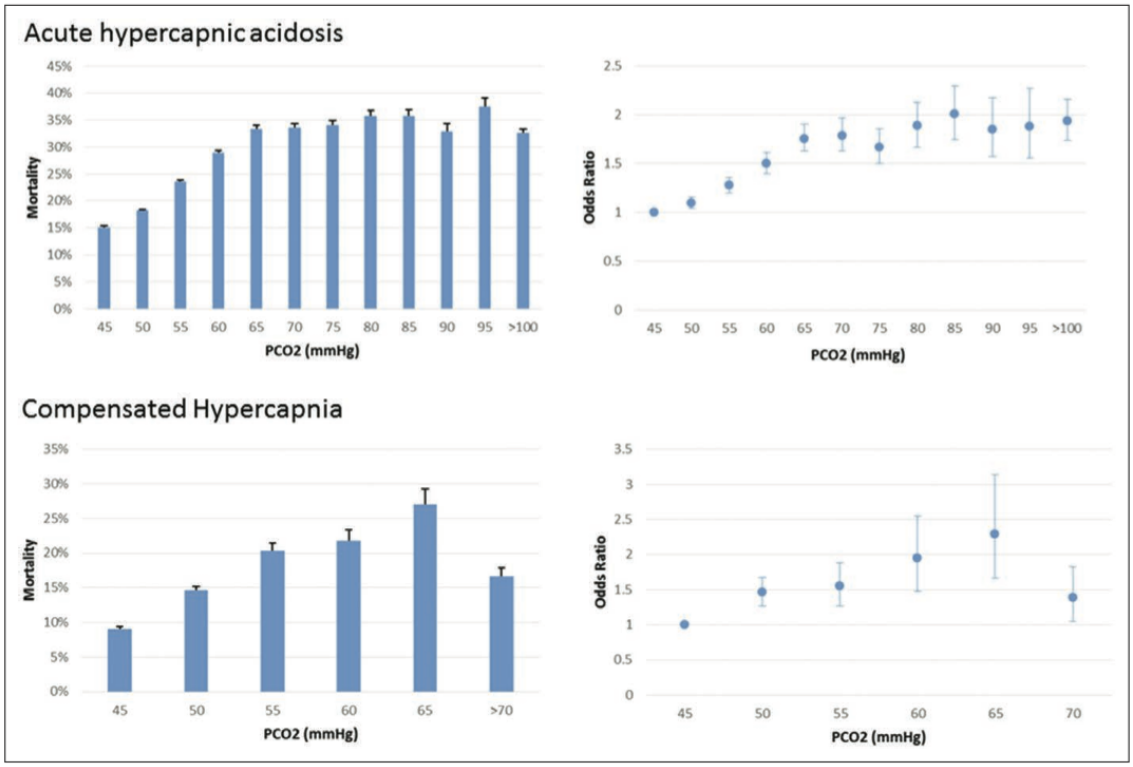

Figure 2. Hospital mortality (%) (*left*) and adjusted odds ratio (*right*) (error bars represent 95% CI).

was shown to enhance the growth of *Escherichia coli*, and a similar effect was noted across several types of bacteria (19–21). In clinical studies, acute hypercapnic acidosis was shown to reduce renal blood flow (22) with the possible need for increased requirement of hemodialysis (8). These effects may overall increase mortality and morbidity. Our study showed that acute hypercapnic acidosis within the first 24 hours was associated with higher mortality. Similar results were also noted in patients with community-acquired pneumonia where admission hypercapnia was associated with increased hospital mortality (11).

The effects of compensated hypercapnia are studied mainly in patients with chronic obstructive pulmonary disease (COPD). The results are conflicting with some studies showing compensated hypercapnia to be an independent predictor of mortality (23, 24) and others showing no such increase in mortality (25). The effects of compensated hypercapnia in the absence of COPD are not well studied. In experimentally induced compensated hypercapnia, healthy volunteers showed a reduction in oxygen uptake and an early onset of anaerobic metabolism. Furthermore, the participants with compensated hypercapnia displayed deteriorated health state and work capacity with development of compensated respiratory acidosis (26). Extrapolation of these findings to critically ill patients is difficult, and further research is required to understand the effects of compensated hypercapnia in critically ill patients.

One of the other findings in our study is that the odds ratio for hospital mortality in patients with acute hypercapnic acidosis increased with increasing P_{CO_2} up to 65 mm Hg after which it plateaued. This was different in compensated hypercapnic patients where the odds ratio for hospital mortality increased with increasing P_{CO_2} up to 65 mm Hg after which there was a trend toward a reduction in mortality. These data must be interpreted with caution given the small proportion of patients with P_{CO_2} over 65 mm Hg (13.5% in acute hypercapnic acidosis group and 4.9% in compensated hypercapnic group). The clinical implications of these trends are uncertain. Potential explanations for the progressive but nonlinear increase in mortality with increasing carbon dioxide levels include a direct adverse effects of acute hypercapnia (22, 27–29) with differential physiologic effects depending on the specific level of P_{CO_2} (see below), different pathologic processes within the body which have direct effects on mortality (e.g., through hypoxia or inflammatory cytokine release) but manifest indirectly as changes in P_{CO_2} or variation in treatment of those with higher P_{CO_2} levels (e.g., differential use of protective ventilator therapies or use of extracorporeal membrane oxygenation above or below a P_{CO_2} threshold of 65 mm Hg).

The plateauing of mortality with P_{CO_2} more than 65 mm Hg may be due to changing effects of carbon dioxide on arteriolar myogenic tone, a modulator of the microcirculation. The

study by Nagi and Ward (30) on arteriolar myogenic response to graded increase in P_{CO_2} on diaphragmatic arterioles showed that hypercapnia up to 80 mm Hg enhanced the myogenic tone. However, with hypercapnia beyond 80 mm Hg, the myogenic tone in arterioles was inhibited, an effect that was opposite to the effects of hypercapnia less than 80 mm Hg. These findings, however, were studied only in diaphragmatic arterioles. It may be possible that the arterioles in other organs may respond differently to the effects to increasing hypercapnia.

Study Significance

Acute respiratory failure is one of the common causes for admission of patients to ICUs. Although the beneficial effects of low volume and low pressure ventilation are well known, the effects of hypercapnia as a consequence of lung-protective ventilation are not clear. The results of animal experiments are conflicting (16, 17, 31–34). Furthermore, the results of small noncomparative and comparative randomized control trial are inconclusive (8, 35–37). Our study showed a strong association with increased hospital mortality in patients with acute hypercapnic acidosis. Our results further support control of C_{O_2} and pH encouraged by low tidal volume ventilation strategies used in the ARDS network study (1).

Strengths

Our study has several strengths. First, it involved more than 250,000 mechanically ventilated patients from 171 ICUs (constituting about 80% of the ICUs) in two countries making its findings highly generalizable for all ICUs in Australia and New Zealand. It is also likely the results have external validity in other developed countries with intensive care practices similar to Australia and New Zealand. The large sample size of our study enables identification of small but significant differences in outcomes. ANZICS APD is recognized as a high-quality clinical registry with extensive data quality and has been accepted internationally by high-impact journals (38, 39). Data collection from the participating ICUs is robust and quality controlled with an established data dictionary to ensure uniformity and accuracy of the data collected.

Limitations

Our study is a retrospective study with inherent limitations. The worst value of APD-Pa_{CO_2} and pH used in classifying patients to the compared groups was limited to the 24 hours following ICU admission. Thus, patients may have had more deranged blood gasses (abnormal Pa_{CO_2} and pH) prior to ICU admission or after 24 hours after ICU admission. Given the database included data collected for the first 24 hours into ICU admission, the effects of deranged blood gasses prior to ICU admission, and after 24 hours of ICU admission could not be evaluated in our study. Furthermore, the effects of mechanical ventilation on changes to pH and P_{CO_2} could not be assessed. We also did not have data available on patients who were treated with extracorporeal life supports that may have impacted on the acid base and gas exchange of the patients. The study further included all patients who were mechanically ventilated when compared with specific diagnoses which may have different outcomes. Nevertheless, even in patients with severe hypoxemia (with possible ARDS) where permissive hypercapnia may have been thought to be beneficial, our study did not show any conferred benefit of hypercapnia and hypercapnic acidosis.

CONCLUSIONS

Hypercapnic acidosis and compensated hypercapnia were associated with increased hospital mortality, prolonged duration of ICU, and hospital length of stay. The increased mortality was noted even after adjusting for severity of illness, type of the ICU, and the year in which patients were treated. A progressive increase in mortality was noted with increasing P_{CO_2} till 65 mm Hg after which the mortality plateaued. Given the retrospective, nonrandomized controlled design of our study, these results suggest an association but not causation. Prospective controlled studies may further clarify the effects of hypercapnic acidosis and compensated hypercapnia.

REFERENCES

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
2. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755
3. 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; 111:826–835
4. Kavanagh BP, Laffey JG: Hypercapnia: Permissive and therapeutic. *Minerva Anestesiol* 2006; 72:567–576
5. Laffey JG, Kavanagh BP: Carbon dioxide and the critically ill–too little of a good thing? *Lancet* 1999; 354:1283–1286
6. 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; 162:2287–2294
7. Laffey JG, Engelberts D, Kavanagh BP: Buffering hypercapnic acidosis worsens acute lung injury. *Am J Respir Crit Care Med* 2000; 161:141–146
8. 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; 338:355–361
9. Paul E, Bailey M, Pilcher D: Risk prediction of hospital mortality for adult patients admitted to Australian and New Zealand intensive care units: Development and validation of the Australian and New Zealand Risk of Death model. *J Crit Care* 2013; 28:935–941
10. Laserna E, Sibila O, Aguilar PR, et al: Hypocapnia and hypercapnia are predictors for ICU admission and mortality in hospitalized patients with community-acquired pneumonia. *Chest* 2012; 142:1193–1199
11. Sin DD, Man SF, Marrie TJ: Arterial carbon dioxide tension on admission as a marker of in-hospital mortality in community-acquired pneumonia. *Am J Med* 2005; 118:145–150
12. Tiruvoipati R, Botha JA, Pilcher D, et al: Carbon dioxide clearance in critical care. *Anaesth Intensive Care* 2013; 41:157–162
13. Cullen DJ, Eger EI 2nd: Cardiovascular effects of carbon dioxide in man. *Anesthesiology* 1974; 41:345–349
14. Curley G, Laffey JG, Kavanagh BP: Bench-to-bedside review: Carbon dioxide. *Crit Care* 2010; 14:220
15. Pedoto A, Caruso JE, Nandi J, et al: Acidosis stimulates nitric oxide production and lung damage in rats. *Am J Respir Crit Care Med* 1999; 159:397–402

16. 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:L994–1002
17. 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; 171:1371–1377
18. Coakley RJ, Taggart C, Greene C, et al: Ambient pCO2 modulates intracellular pH, intracellular oxidant generation, and interleukin-8 secretion in human neutrophils. *J Leukoc Biol* 2002; 71:603–610
19. Curley G, Contreras MM, Nichol AD, et al: Hypercapnia and acidosis in sepsis: A double-edged sword? *Anesthesiology* 2010; 112:462–472
20. Pugin J, Dunn-Siegrist I, Dufour J, et al: Cyclic stretch of human lung cells induces an acidification and promotes bacterial growth. *Am J Respir Cell Mol Biol* 2008; 38:362–370
21. Casalino-Matsuda SM, Nair A, Beitel GJ, et al: Hypercapnia inhibits autophagy and bacterial killing in human macrophages by increasing expression of Bcl-2 and Bcl-xL. *J Immunol* 2015; 194:5388–5396
22. Bersentes TJ, Simmons DH: Effects of acute acidosis on renal hemodynamics. *Am J Physiol* 1967; 212:633–640
23. Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, et al: Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: A population-based prospective study. *Respir Res* 2014; 15:30
24. Chailleux E, Fauroux B, Binet F, et al: Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. *Chest* 1996; 109:741–749
25. Oga T, Taniguchi H, Kita H, et al: Analysis of the relationship between health status and mortality in hypercapnic patients with noninvasive ventilation. *Clin Respir J* 2015 Nov 25. [Epub ahead of print]
26. Apanasenko GL, Shchegolev VS, Kuleshov VI: [Tolerance for controlled physical loading in chronic hypercapnia in man]. *Kosm Biol Aviakosm Med* 1978; 12:49–52
27. Beekley MD, Cullom DL, Brechue WF: Hypercapnic impairment of neuromuscular function is related to afferent depression. *Eur J Appl Physiol* 2004; 91:105–110
28. Juan G, Calverley P, Talamo C, et al: Effect of carbon dioxide on diaphragmatic function in human beings. *N Engl J Med* 1984; 310:874–879
29. Shiota S, Okada T, Naitoh H, et al: Hypoxia and hypercapnia affect contractile and histological properties of rat diaphragm and hind limb muscles. *Pathophysiology* 2004; 11:23–30
30. Nagi MM, Ward ME: Modulation of myogenic responsiveness by CO_2 in rat diaphragmatic arterioles: Role of the endothelium. *Am J Physiol* 1997; 272 (3 Pt 2):H1419–H1425
31. 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; 37:2412–2420
32. Sinclair SE, Kregenow DA, Lamm WJ, et al: Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. *Am J Respir Crit Care Med* 2002; 166:403–408
33. 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; 29:124–132
34. Vohwinkel CU, Lecuona E, Sun H, et al: Elevated CO(2) levels cause mitochondrial dysfunction and impair cell proliferation. *J Biol Chem* 2011; 286:37067–37076
35. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on tidal volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831–1838
36. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; 27:1492–1498
37. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
38. Kaukonen KM, Bailey M, Pilcher D, et al: Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015; 372:1629–1638
39. Kaukonen KM, Bailey M, Suzuki S, et al: Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014; 311:1308–1316

Supplemental digital content Table 1. Comparison of physiological, biochemical and haematological investigations variables*

Variable	Normocapnia and normal pH (N= 110,104)	Compensated Hypercapnia (N=20,463)	Hypercapnic acidosis (N=122,245)
Highest Body Temperature (˚C)	37.5 (0.8)	37.5 (0.8)	37.4 (1.0)
Lowest Body Temperature (˚C)	35.8 (0.9)	36.0 (0.9)	35.7 (1.2)
Highest Heart Rate (BPM)	98.3 (20.0)	102 (21.7)	108 (24.2)
Lowest Heart Rate (BPM)	70.4 (14.6)	71.9 (15.6)	74.5 (18.9)
Highest Respiratory Rate (BPM)	20.7 (6.6)	22.2 (7.9)	22.6 (8.0)
Lowest Respiratory Rate (BPM)	11.2 (3.4)	12.0 (4.0)	12.2 (4.2)
Highest Systolic BP (mmHg)	147 (24.4)	149 (25.9)	144 (27.4)
Lowest Systolic BP (mm Hg)	97.9 (16.3)	99.2 (17.5)	93.3 (19.0)
Highest Diastolic BP (mmHg)	71.4 (14.5)	73.2 (15.0)	71.2 (15.8)
Lowest Diastolic BP (mmHg)	51.3 (10.3)	52.4 (11.1)	49.9 (11.3)
Highest Mean Arterial Pressure (mmHg)	96.9 (16.1)	99 (17.0)	96 (18.0)
Lowest Mean Arterial Pressure (mmHg)	66.8 (11.0)	67.9 (11.7)	64.4 (12.4)
Highest Sodium (mmol/L)	140 (4)	140 (4)	140 (5)
Lowest Sodium (mmol/L)	137 (4)	138 (4)	137 (5)
Highest Potassium (mmol/L)	4.44 (0.6)	4.40 (0.6)	4.75 (0.8)
Lowest Potassium (mmol/L)	3.89 (0.5)	3.86 (0.5)	4.03 (0.6)
Lowest Plasma Bicarbonate (mmol/l)	23.0 (2.9)	26.6 (4.5)	22.2 (5.3)
Highest Creatinine (umol/L)	80 (66 – 100)	80 (64 – 101)	97 (74 – 144)
Lowest Creatinine (umol/L)	70 (57 – 88)	70 (56 – 88)	82 (64 – 117)
Highest Haemoglobin (g/dL)	12.6 (12.3)	12.5 (10.3)	13.1 (12.0)
Lowest Haemoglobin (g/dL)	10 (8.7 – 11.6)	10.4 (8.9 – 12.0)	10.5 (8.9 – 12.3)
Highest White Cell Count ($x10^9$/L)	13.3 (8.1)	13.6 (9.3)	16.1 (11.5)
Lowest White Cell Count ($x10^9$/L)	10.4 (6.0)	10.8 (7.3)	12.0 (8.6)
Highest Platelets ($x10^9$/L)	214 (101)	238 (118)	230 (114)
Lowest Platelets ($x10^9$/L)	185 (91)	209 (108)	192 (99)
Plasma Albumin (mmol/l)	28.7 (6.8)	28.3 (6.7)	27.5 (7.2)
Worst Plasma Bilirubin (mmol/l)	13 (9 – 19)	12 (8 – 19)	12 (8 – 19)
Plasma Glucose (mmol/l)	9.0 (3.5)	9.0 (3.9)	10.2 (4.9)

- All variables were statistically significant at $p<0.001$

Supplemental digital content Table 2. Comparison of blood gasses and severity of illness

Variable	Normocapnia and normal pH (N= 110,104)	Compensated Hypercapnia (N=20,463)	Hypercapnic acidosis (N=122,245)
PF ratio < 100 [n, %]	4,825 (4.4%)	1,824 (8.9%)	21,177 (17.3%)
PF ratio 100-<200 [n, %]	31,570 (28.7%)	8,529 (41.7%)	66,166 (54.2%)
PF ratio 200<250 [n, %]	48,394 (44%)	11,864 (58%)	83,639 (68.5%)
PF ratio 250-300 [n, %]	63,992 (58.2%)	14,573 (71.3%)	96,344 (78.9%)
Worst Inspired Oxygen Concentration (%÷100)	0.60 (0.25)	0.59 (0.25)	0.69 (0.26)
Worst Arterial Oxygen Partial Pressure (mmHg) [Median, IQR]	127 (90 – 207)	103 (76 – 167)	102 (76 – 161)
Worst Arterial CO2 Partial Pressure (mmHg)	39.5 (2.9)	52.7 (17.7)	57.7 (16.6)
Worst Arterial pH	7.39 (0.03)	7.38 (0.03)	7.22 (0.10)
Worst Plasma Bicarbonate (mmol/l)	24.3 (3.5)	28.3 (5.0)	23.5 (6.1)
APACHE II Score	14.7 (5.9)	15.6(6.5)	21.3 (8.1)
APACHE III Score	49 (22)	53 (24)	69 (33)
APACHE III ROD (with oxygen and pH component removed)	2.25 (0.61-9.0)	3.67 (0.96-13.7)	7.78 (1.6-30.4)

PF ratio: PaO2/FiO2 *ratio; IQR: Interquartile range;* APACHE: Acute Physiologic and Chronic Health Evaluation; ROD: Risk of death.
All variables were statistically significant at p<0.001

Supplemental digital content table 3: Hospital mortality patterns during specific time periods of the study

Multivariate analysis of odds ratio for hospital mortality based on p/f ratios (2000-2004)

	Normocapnia and normal pH	Compensated hypercapnia	Hypercapnic acidosis	P Value
p/f ratio <100 (OR; 95% CI)	1.67 (1.41-1.98)	2.23 (1.73-2.87)	2.69 (2.39-3.01)	<0.001
p/f ratio 100-200 (OR; 95% CI)	1.1 (0.96-1.26)	1.8 (1.47-2.2)	1.82 (1.63-2.02)	
p/f ratio 200-300 (OR; 95% CI)	0.95 (0.83-1.08)	1.16 (0.91-1.47)	1.42 (1.25-1.61)	
p/f ratio >300 (OR; 95% CI)	reference category (1.00)	1.14 (0.89-1.47)	1.44 (1.27-1.63)	

Multivariate analysis of odds ratio for hospital mortality based on p/f ratios (2005-2009)

	Normocapnia and normal pH	Compensated hypercapnia	Hypercapnic acidosis	P Value
p/f ratio <100 (OR; 95% CI)	1.82 (1.52-2.16)	1.96 (1.51-2.55)	2.62 (2.38-2.88)	<0.001
p/f ratio 100-200 (OR; 95% CI)	1.2 (1.07-1.35)	1.76 (1.5-2.07)	1.87 (1.72-2.04)	
p/f ratio 200-300 (OR; 95% CI)	1.07 (0.96-1.2)	1.24 (1.03-1.5)	1.51 (1.37-1.67)	
p/f ratio >300 (OR; 95% CI)	reference category (1.00)	0.94 (0.77-1.14)	1.52 (1.38-1.67)	

Multivariate analysis of odds ratio for hospital mortality based on p/f ratios (2010-2013)

	Normocapnia and normal pH	Compensated hypercapnia	Hypercapnic acidosis	P Value
p/f ratio <100 (OR; 95% CI)	1.63 (1.33-1.99)	2.06 (1.57-2.71)	2.81 (2.55-3.1)	<0.001
p/f ratio 100-200 (OR; 95% CI)	1.06 (0.94-1.19)	1.59 (1.34-1.88)	1.7 (1.56-1.86)	
p/f ratio 200-300 (OR; 95% CI)	0.99 (0.89-1.11)	1.2 (0.99-1.46)	1.46 (1.32-1.61)	
p/f ratio >300 (OR; 95% CI)	reference category (1.00)	0.99 (0.8-1.22)	1.19 (1.07-1.33)	

Supplemental digital content table 4: Respiratory rates on Mechanical ventilation during specific time periods of the study

Respiratory rates on mechanical ventilation in relation to p/f ratios (2000-2004)

	Normocapnia and normal pH	Compensated hypercapnia	Hypercapnic acidosis	P Value
p/f ratio <100 (Median IQR)	10 [10-18] N=4255	12 [10-23] N=1163	14 [10-25] N=8284	<0.001
p/f ratio 100-200 (Median IQR)	10 [10-20] N=6915	14 [10-25] N=1382	15 [10-24] N=9071	
p/f ratio 200-300 (Median IQR)	10 [10-20] N=7130	12 [10-24] N=1141	12 [10-22] N=5609	
p/f ratio >300 (Median IQR)	10 [10-18] N=9608	11 [10-20] N=1157	12 [10-20] N=5314	

Respiratory rates on mechanical ventilation in relation to p/f ratios (2005-2009)

	Normocapnia and normal pH	Compensated hypercapnia	Hypercapnic acidosis	P Value
p/f ratio <100 (Median IQR)	12 [10-26] N=2730	16 [10-26] N=911	20 [12-28] N=7996	<0.001
p/f ratio 100-200 (Median IQR)	14 [10-24] N=9104	18 [10-27] N=2397	18 [10-26] N=16511	
p/f ratio 200-300 (Median IQR)	11 [10-22] N=10965	16 [10-25] N=2114	16 [10-25] N=11115	
p/f ratio >300 (Median IQR)	11 [10-20] N=16829	12 [10-21] N=2389	14 [10-22] N=10840	

Respiratory rates on mechanical ventilation in relation to p/f ratios (2010-2013)

	Normocapnia and normal pH	Compensated hypercapnia	Hypercapnic acidosis	P Value
p/f ratio <100 (Median IQR)	17 [10-27] N=1624	21 [12-29] N=641	21 [12-28] N=7478	<0.001
p/f ratio 100-200 (Median IQR)	15 [10-25] N=8945	20 [10-27] N=2420	20 [10-27] N=16429	
p/f ratio 200-300 (Median IQR)	12 [10-23] N=11746	16 [10-26] N=2176	16 [10-25] N= 11173	
p/f ratio >300 (Median IQR)	11 [10-20] N=19085	12 [10-22] N=2344	13 [10-23] N=10522	

Supplemental digital content table 5: Subgroup analysis comparing adjusted odds of mortality based on admission diagnostic category.

Subgroup	**Normocapnia and normal pH** Adjusted Odds ratio, 95%CI	**Compensated Hypercapnia** Adjusted Odds ratio, 95%CI	**Hypercapnic acidosis** Adjusted Odds ratio, 95%CI	**P Value**
CABG (N= 50,514)	reference category (1.00)	1.32 (0.9-1.93)	1.99 (1.65-2.39)	< 0.001
Cardiovacular, cardiogenic shock and cardiac arrest (N= 60,260)	reference category (1.00)	1.26 (1.08-1.47)	1.87 (1.74-2.02)	< 0.001
Respiratory (COPD/Asthma) (N=10,728)	reference category (1.00)	1.55 (1.12-2.15)	1.96 (1.48-2.59)	< 0.001
Respiratory (Pneumonia) (N=32,144)	reference category (1.00)	1.38 (1.22-1.57)	1.54 (1.41-1.68)	<0.001
Gastrointestinal (N= 29,533)	reference category (1.00)	1.32 (1.11-1.55)	1.71 (1.56-1.87)	< 0.001
Neurological (N= 20,803)	reference category (1.00)	1.05 (0.89-1.22)	1.26 (1.15-1.38)	< 0.001
Sepsis (N= 8,764)	reference category (1.00)	1.37 (1.01-1.84)	1.82 (1.55-2.14)	< 0.001
Chronic renal failure (N=5,646)	reference category (1.00)	1.24 (0.89-1.74)	1.52 (1.28-1.81)	< 0.001
Acute renal failure (N=14,816)	reference category (1.00)	1.24 (0.95-1.63)	1.77 (1.56-2.01)	< 0.001
Trauma (N= 17,875)	reference category (1.00)	0.76 (0.57-1.01)	1.3 (1.15-1.48)	< 0.001

4.3 Chapter summary

This study aimed to investigate the association of compensated hypercapnia and hypercapnic acidosis on hospital mortality in adult mechanically ventilated patients. A total of 252,812 mechanically ventilated patients were included in this study making this the largest study published so far on evaluating independent association of hypercapnia and hospital mortality. The results of the study showed that hypercapnic acidosis and compensated hypercapnia during the first 24 hours of intensive care admission is associated with increased hospital mortality compared to normocapnia. The adjusted odds of hospital mortality increased with increasing hypercapnia. The increased mortality noted with hypercapnic acidosis was consistent across all the diagnostic groups. The effects of compensated hypercapnia however, differed according to diagnosis with neurological, renal, trauma and post cardiac surgery failing to display an increased risk in mortality. The retrospective nature of this study could have prevented accurate correction for disease severity. Disease severity may be a cause of elevated carbon dioxide levels, and poor outcomes in this group

This study was published in the journal of Critical Care Medicine, which is ranked 3rd among 27 titles in the Critical Care Medicine category of the Journal Citation Reports. This article was well received and was published with an accompanying editorial and has created a significant discussion in critical care community. This article has an Altmetric Attention Score of 17 and is in the 93rd percentile of all the research articles Altmetric has tracked so far (November 2018). The editorial (Appendix 7) on this study titled “A Climate Change in Mechanical Ventilation?*” discuss the implications of the published study along with the limitations of the retrospective nature of the study. As stated in the editorial, hypercapnic acidosis can have potentially dangerous side effects, especially in patients with advanced comorbidity and should be avoided or limited whenever possible with extracorporeal devices where required.

CHAPTER 5: Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury

5.1 Chapter Introduction

The previous chapter reported the independent association of hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients. Hypercapnic acidosis was associated with increased risk of hospital mortality in mechanically ventilated patients. This was consistent across all the pre-specified diagnostic groups. Overall compensated hypercapnia was also found to be independently associated with increased risk of hospital morality. However, in some diagnostic groups, compensated hypercapnia was not seen to be associated with an increased risk of hospital mortality. One of the important groups are patients with neurological and trauma diagnosis. This included patients with acute cerebral injury caused by traumatic brain injury, stroke and cardiac arrest. Preventing secondary brain injury is an important aspect of intensive care management in such patients. Secondary brain injury could be caused by low cerebral blood flow, hypoxia, fever, seizures, or hypo and hyperglycaemia. Arterial partial pressure of CO_2 regulates cerebral blood flow and is one of the important intensive care management targets in preventing secondary brain injury. Hypercapnia and hypocapnia are known to be associated with adverse outcomes in patients with cerebral injury. The current guidelines on management of these patients recommend normocapnia (PCO_2 35-45 mmHg) with no specific target of pH based on low quality evidence. All studies evaluating the outcomes in cerebral injury patients so far focused on the changes in PCO_2 and pH in isolation but have not evaluated the effects of PCO_2 and pH in conjunction. Changes in PCO_2 however are inextricably linked to changes in pH.

In this chapter, we investigated the independent association of hypercapnic acidosis and compensated hypercapnia on hospital mortality in patients with acute cerebral injury.

This is the first study of its kind where PCO_2 and pH association on clinical outcomes were assessed in conjunction. This is also the largest retrospective study of mechanically ventilated acute cerebral injury patients published so far that included over 30,000 patients.

5.2 Published Manuscript

JAMA Neurology | Original Investigation

Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury

Ravindranath Tiruvoipati, FCICM; David Pilcher, FCICM; John Botha, FCICM; Hergen Buscher, FCICM; Robert Simister, PhD; Michael Bailey, PhD

IMPORTANCE Clinical studies investigating the effects of hypercapnia and hypercapnic acidosis in acute cerebral injury are limited. The studies performed so far have mainly focused on the outcomes in relation to the changes in partial pressure of carbon dioxide and pH in isolation and have not evaluated the effects of partial pressure of carbon dioxide and pH in conjunction.

OBJECTIVE To review the association of compensated hypercapnia and hypercapnic acidosis during the first 24 hours of intensive care unit admission on hospital mortality in adult mechanically ventilated patients with cerebral injury.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, binational retrospective review of patients with cerebral injury (traumatic brain injury, cardiac arrest, and stroke) admitted to 167 intensive care units in Australia and New Zealand between January 2000 and December 2015. Patients were classified into 3 groups based on combination of arterial pH and arterial carbon dioxide (normocapnia and normal pH, compensated hypercapnia, and hypercapnic acidosis) during the first 24 hours of intensive care unit stay.

MAIN OUTCOMES AND MEASURES Hospital mortality.

RESULTS A total of 30 742 patients (mean age, 55 years; 21 827 men [71%]) were included. Unadjusted hospital mortality rates were highest in patients with hypercapnic acidosis. Multivariable logistic regression analysis and Cox proportional hazards analysis in 3 diagnostic categories showed increased odds of hospital mortality (cardiac arrest odds ratio [OR], 1.51; 95% CI, 1.34-1.71; stroke OR, 1.43; 95% CI, 1.27-1.6; and traumatic brain injury OR, 1.22; 95% CI, 1.06-1.42; P <.001) and hazard ratios (HR) (cardiac arrest HR, 1.23; 95% CI, 1.14-1.34; stroke HR, 1.3; 95% CI, 1.21-1.4; traumatic brain injury HR, 1.13; 95% CI, 1-1.27), in patients with hypercapnic acidosis compared with normocapnia and normal pH. There was no difference in mortality between patients who had compensated hypercapnia compared with patients who had normocapnia and normal pH. In patients with hypercapnic acidosis, the adjusted OR of hospital mortality increased with increasing partial pressure of carbon dioxide, while no such increase was noted in patients with compensated hypercapnia.

CONCLUSIONS AND RELEVANCE Hypercapnic acidosis was associated with increased risk of hospital mortality in patients with cerebral injury. Hypercapnia, when compensated to normal pH during the first 24 hours of intensive care unit admission, may not be harmful in mechanically ventilated patients with cerebral injury.

Editorial

Supplemental content

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JAMA Neurol. doi:10.1001/jamaneurol.2018.0123
Published online March 19, 2018.

Cerebral injury may be caused by traumatic brain injury, stroke, and cardiac arrest. Hypercapnia and hypocapnia are avoided in such patients to prevent secondary brain injury.[1] Clinical studies investigating the effects of hypocapnia and hypercapnia on traumatic brain injury and cardiac arrest revealed that hypocapnia and hypercapnia were associated with increased in-hospital mortality.[2-6] Clinical studies evaluating the effects of arterial partial pressure of carbon dioxide (Pco_2) derangements in stroke are very few.[7-9] Two studies investigated the effect of hypocapnia, with differing results.[7,8] A retrospective observational study in patients with subarachnoid hemorrhage showed higher mortality with hypocapnia,[8] and a randomized clinical trial with a sample size of 50 patients with pituitary apoplexy reported no difference in mortality when hypocapnia was compared with normocapnia.[7] The study by Westermaier et al[9] in patients with aneurysmal subarachnoid hemorrhage found benefit in outcome with hypercapnia.

In addition to Pco_2, pH level appears to have a significant effect on clinical outcomes in patients with acute cerebral injury. Acidic pH has been shown to have an increased risk of mortality and unfavorable outcomes in patients with severe traumatic brain injury,[10] out-of-hospital cardiac arrest,[11] and ischemic stroke.[12,13]

All these studies have mainly focused on the changes in Pco_2 and pH in isolation and have not evaluated the effects of Pco_2 and pH in conjunction. To our knowledge, no study has investigated for differences in outcomes between compensated hypercapnia and hypercapnic acidosis. Given this limited data and lack of evaluation of the outcomes in combination of Pco_2 and pH, we aimed to review the effects of compensated hypercapnia and hypercapnic acidosis during the first 24 hours of intensive care unit (ICU) admission on clinical outcomes in adult mechanically ventilated patients with cerebral injury caused by cardiac arrest, stroke, and traumatic brain injury.

Key Points

Question What is the association between compensated hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients with acute cerebral injury?

Findings In this cross-sectional study including 30 742 patients with cerebral injury admitted to intensive care units in Australia and New Zealand, hospital mortality was higher in patients with hypercapnic acidosis compared with patients with compensated hypercapnia or normocapnia. In patients with hypercapnic acidosis, the adjusted odds ratio for hospital mortality increased with increasing partial pressure of carbon dioxide, while in patients with compensated hypercapnia, the adjusted odds did not change with increasing partial pressure of carbon dioxide.

Meaning In mechanically ventilated patients with cerebral injury, hypercapnic acidosis is associated with increased mortality, and compensated hypercapnia appears to have no such association.

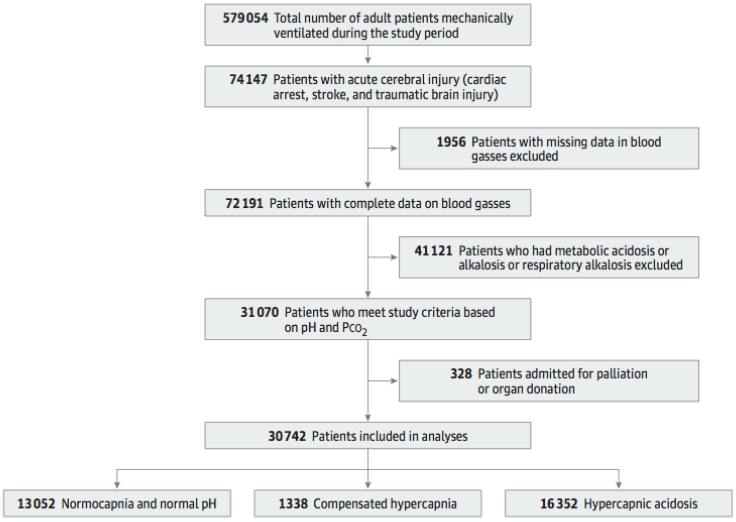
Methods

We conducted a retrospective review of all patients who had cerebral injury and were mechanically ventilated during a 16-year period (January 2000 to December 2015) admitted to 167 ICUs in Australia and New Zealand. Data were collected from the Australian and New Zealand Intensive Care Society Adult Patient Database. The Australian and New Zealand Intensive Care Society Adult Patient Database is a high-quality database run by the Australian and New Zealand Intensive Care Society Center for Outcome and Resource Evaluation. It collates complete patient information that is required to calculate patient severity during the first 24 hours of ICU admission from more than 80% of ICUs across Australia and New Zealand as part of quality assurance and benchmarking process among participating ICUs. Ethics approval was obtained from Monash University research ethics committee. The ethics committee waived informed consent from the patients because the data were gathered as part of routine quality assurance benchmarking process for the participating ICUs.

Adult patients with cerebral injury receiving mechanical ventilation during the first 24 hours of their admission to the ICU were included in the study. Cerebral injury was diagnosed if the patients had admission diagnosis of 1 of 3 diagnostic categories: traumatic brain injury, cardiac arrest, or stroke (including intracerebral hemorrhage, subdural, subarachnoid hemorrhage, and ischemic stroke). For this analysis, we used the arterial blood gas that provided the highest scoring Acute Physiology, Age, Chronic Health Evaluation III subscore and as such is likely to have represented the worst pH/Pco_2 combination in the first 24 hours of ICU admission. Patients were classified into 3 groups based on a combination of arterial pH and arterial carbon dioxide levels: normocapnia (Pco_2, 35-45 mm Hg) and normal pH (7.35-7.45) (group 1), compensated hypercapnia (normal pH [7.35-7.45] with elevated carbon dioxide [Pco_2 >45 mm Hg]) (group 2), and hypercapnic acidosis (Pco_2 >45 mm Hg and pH <7.35) (group 3) during the first 24 hours of ICU stay. Patients with metabolic acidosis, metabolic alkalosis, and respiratory alkalosis were excluded because the focus of the study was to investigate the effects of compensated hypercapnia and hypercapnic acidosis on the outcomes after cerebral injury. Patients in group 1 were considered a reference group to which patients in group 2 and 3 were compared. The primary outcome measure included hospital mortality. Secondary outcome measures included ICU mortality, duration of ICU and hospital stay, and survival to discharge home.

All analysis was performed using SAS, version 9.4 (SAS Institute Inc). Data were initially assessed for normality. Group comparisons were made using χ^2 tests for equal proportion, analysis of variance for normally distributed variables, and Kruskal-Wallis tests otherwise, with results reported as number values (percentages), means (SDs), and medians (interquartile range), respectively. Given the retrospective nature of this study, to account for differing patient characteristics, logistic regression models were constructed using all available baseline information that related to the patient (age, sex, and chronic comorbidities) or hospital (location, level, admission source, and time of admission) to identify each patient's probability (propensity) of presenting to the ICU with either hypercapnic acidosis or compensated hypercapnia (eTables 1

Figure 1. Study Profile



and 2 in the Supplement). These models were constructed using both stepwise selection and backward elimination techniques, with only variables that were significant ($P < .01$) from both methods included. To investigate the independent effect of hypercapnia and hypercapnic acidosis on hospital mortality, hierarchical multivariable regression models were used using logistic regression for hospital death and Cox proportional hazards regression for time to death. These models adjusted for patient severity, propensity to be hypercapnic, propensity to be hypercapnic acidotic, baseline Glasgow Coma Scale (GCS) Score stratified into 3 groups (GCS score 3-7, 8-12, and 13-15), and year of admission, with patients nested in sites and sites treated as a random effect. Subgroup analysis relating to diagnosis, neurological severity (baseline GCS score), and operative status were performed using hierarchical multivariable logistic regression models. To determine whether the association between hypercapnic status and mortality differed according to the 3 diagnostic categories (diagnostic subgroup, neurological severity [baseline GCS score], or operative status), interaction terms with hypercapnic status were fitted. Duration of survivals have been presented as Kaplan-Meier curves with log-rank tests comparing equality of strata. Duration of stay variables (hospital and ICU length of stay) were log-transformed and analyzed using hierarchical mixed linear modeling, again adjusting for the covariates outlined here, with results presented as geometric means (95% CI). To account for survival bias, duration variables were further stratified by survival status. To facilitate a measure of patient severity independent of hypercapnia and neurological severity, each patient's predicted risk of death was calculated in accordance with the Australia and New Zealand Risk of Death methods,[14] with the components of pH, oxygen, and GCS score removed. Australia and New Zealand Risk of Death is an updated mortality prediction model specifically calibrated for use in Australia and New Zealand ICUs that has been derived from components of the Acute Physiology, Age, Chronic Health Evaluation II and III scoring systems, with additional diagnostic variables, and has been shown to have significantly better calibration and discrimination than Acute Physiology, Age, Chronic Health Evaluation III. To further ensure that our observed results were not driven by imbalances in patient severity, an additional matched sensitivity analysis was performed with patients from each of the 3 hypercapnic diagnostic categories matched for patient severity. Given the magnitude of the data set, to more closely align statistical and clinical significance, a 2-sided P value of .01 was used to indicate statistically significant results.

Results

A total of 30 742 patients were included in the study (**Figure 1**). A comparison of demographics, comorbidities, physiological and laboratory variables, and ICU admission diagnostic category data are presented in **Table 1**. Patients with normocapnia and normal pH were younger and had lower comorbidities compared with other groups. Patients with compensated hypercapnia and hypercapnic acidosis differed from patients with normocapnia and normal pH levels in heart rate, blood pressure, and temperature, as well as renal and liver function test results during the first 24 hours of their ICU admission. Plasma glucose levels were higher in the hypercapnic acidosis group. Lower Pa_{O_2} and higher P_{CO_2} levels were noted in patients with compensated hypercapnia and hypercapnic

Table 1. Comparisons of Demographics, Comorbidities, and Physiological and Laboratory Data

Variable	No. (%) Normocapnia and Normal pH (n = 13 052)	Compensated Hypercapnia (n = 1338)	Hypercapnic Acidosis (n = 16 352)	*P* Value
Age, y, mean (SD)	53.1 (20.2)	54.9 (19.9)	56.2 (18.9)	<.001
Men	8949 (68.6)	996 (74.4)	11929 (73)	<.001
Worst GCS score, mean (SD)	8.15 (4.44)	8.47 (4.66)	6.27 (4.55)	<.001
GCS score 3-7	6462 (50)	630 (47)	11125 (68)	<.001
GCS score 8-12	3237 (25)	398 (30)	2925 (18)	<.001
GCS score 13-15	3170 (24)	290 (22)	1935 (12)	<.001
Missing data on GCS score	183 (1.4)	20 (1.5)	367 (2.2)	<.001
Comorbidities				
Chronic respiratory disease	245 (1.9)	72 (5.4)	1119 (6.8)	<.001
Chronic cardiovascular disease	773 (5.9)	123 (9.2)	1620 (9.9)	<.001
Chronic liver disease	117 (0.9)	22 (1.6)	171 (1)	.03
Chronic renal failure	169 (1.3)	25 (1.9)	472 (2.9)	<.001
Immunosuppression	149 (1.1)	18 (1.3)	312 (1.9)	<.001
Physiological data				
Highest body temperature, °C	37.5 (0.9)	37.6 (0.9)	37 (1.4)	<.001
Highest heart rate, bpm	95.7 (22.8)	98.5 (23.9)	107 (25.7)	<.001
Highest respiratory rate, PM	19.1 (6.3)	20.4 (7.1)	21.4 (7.3)	<.001
Highest mean arterial pressure, mm Hg	105 (18)	106 (19)	101 (21)	<.001
Laboratory data				
Lowest sodium, mEq/L	138 (4.05)	139 (4.59)	138 (4.75)	<.001
Highest, mEq/L	4.19 (0.526)	4.23 (0.582)	4.69 (0.86)	<.001
Lowest potassium plasma, mEq/L	22.4 (2.9)	25.3 (3.9)	19.8 (4.8)	<.001
Highest creatinine, mg/dL, median (IQR)	0.85 (0.70-1.04)	0.80 (0.74-1.17)	1.18 (0.88-1.75)	<.001
Worst inspired oxygen concentration, %/100	0.53 (0.24)	0.548 (0.25)	0.729 (0.26)	<.001
Worst arterial oxygen partial pressure, mm Hg, median, (IQR)	127 (92-205)	107 (78-164)	104 (76-174)	<.001
Worst arterial CO2 partial pressure, mm Hg	39 (2.8)	52.2 (18.3)	56.7 (14.8)	<.001
Worst arterial pH	7.4 (0.03)	7.39 (0.03)	7.19 (0.13)	<.001
Highest hemoglobin, g/dL	12.5 (2.0)	12.6 (2.2)	13.1 (2.5)	<.001
Highest white blood cell count, /μL	14 100 (7800)	13 900 (11 500)	17 800 (11 600)	<.001
Lowest platelets, × 10^3/μL	203 (79)	201 (90)	197 (88)	<.001
Plasma albumin, mmol/L	31.3 (5.9)	30.9 (6.0)	29.8 (6.9)	<.001
Worst plasma bilirubin, mmol/L, median (IQR)	13 (9-18)	13 (9-18)	12 (8-18)	<.001
Plasma glucose, mg/dL	161.08 (63.06)	159.28 (64.86)	209.01 (106.31)	<.001
Severity of illness at ICU admission				
APACHE III Score	57.9 (28)	61.8 (30.5)	91.4 (37.3)	<.001
ANZROD, %	29.3	33.8	51.3	<.001
Diagnostic category				
Traumatic brain injury (n = 9507)	4902 (37.6)	482 (36)	4123 (25.2)	<.001
Cerebrovascular accidents (n = 9477)	6219 (47.6)	548 (41)	2710 (16.6)	<.001
Cardiac arrest (n = 11 785)	1931 (14.8)	308 (23)	9519 (58.2)	<.001

Abbreviations: ANZROD, The Australian and New Zealand Risk of Death; APACHE, Acute physiology and chronic health evaluation; bpm, beats per minute; GCS, Glasgow Coma Scale; ICU, intensive care unit; IQR, interquartile range.

SI conversion factor: To convert creatine to millimoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555; hemoglobin to grams per liter, multiply by 10; sodium to micromoles per liter, multiply by 1; potassium to millimoles per liter, multiply by 1; platelets to × 10^9 per liter, multiply by 1; white blood cell count to × 10^9 per liter, multiply by 0.001.

acidosis (Table 1). Acute Physiology, Age, Chronic Health Evaluation III scores and customized Australia and New Zealand Risk of Death were lower in patients with normocapnia and normal pH levels (Table 1). Unadjusted hospital mortality was higher, and discharge home was lower in patients with hypercapnic acidosis (Table 2). Patients with compensated hyper-

Table 2. Comparison of Outcomes in Patients With Cerebral Injury Based on Their pH and Carbon Dioxide (Unadjusted) and of Hospital Mortality (Unadjusted) Based on Diagnostic Categories

Variable	Normocapnia and Normal pH (n = 13052)	Compensated Hypercapnia (n = 1338)	Hypercapnic Acidosis (n = 16352)	*P* Value
Status at discharge, No. (%)				
Died in hospital	3614 (27.7)	400 (29.9)	8223 (50.3)	NA
Discharged home	4757 (36.4)	505 (37.7)	5064 (31)	NA
Discharged to rehabilitation	2224 (17)	205 (15.3)	1300 (8)	NA
Discharged to other hospital	2368 (18.1)	221 (16.5)	1697 (10.4)	NA
Duration of stay				
Hospital LOS, d, median (IQR)	8.9 (8.2-9.6)	8 (7.2-8.8)	7 (6.4-7.5)	<.001
Hospital LOS, survivors, d, geometric mean (95% CI)	10.9 (9.9-12)	10 (8.9-11.2)	10.6 (9.6-11.6)	.016
Hospital LOS, deaths, d, geometric mean (95% CI)	4.9 (4.5-5.4)	4.3 (3.7-5)	3.5 (3.2-3.9)	<.001
ICU LOS, d, geometric mean (95% CI)	3.1 (2.9-3.3)	2.8 (2.5-3)	2.8 (2.6-2.9)	<.001
ICU LOS, survivors, d, geometric mean (95% CI)	3.5 (3.3-3.8)	3.2 (2.9-3.5)	4.2 (3.9-4.5)	<.001
ICU LOS, deaths, d, geometric mean (95% CI)	2.5 (2.2-2.7)	2.2 (1.9-2.6)	1.7 (1.5-1.8)	<.001
Diagnostic category, No./Total No. (%)				
Traumatic brain injury (n = 9507)	535/4908 (10.9)	36/480 (7.5)	852/4116 (20.7)	<.001
Stroke (n = 9477)	2321/6223 (37.3)	234/548(42.7)	1589/2712 (58.6)	<.001
Cardiac arrest (n = 11758)	758/1929 (39.3)	130/308 (42.2)	5782/9526 (60.7)	<.001

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay, NA, not applicable.

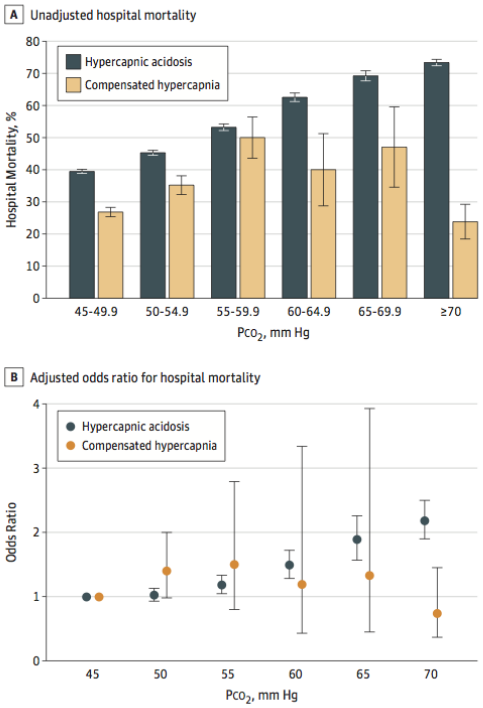
capnia had a higher discharge home rate compared with patients with hypercapnia acidosis or normocapnia and normal pH (Table 2). Unadjusted hospital mortality rates were highest in patients with hypercapnic acidosis in all 3 diagnostic categories (eFigures 1-4 in the Supplement and Table 2). Hospital mortality increased in patients with hypercapnic acidosis with increasing P_{CO_2} (**Figure 2**). No such increased mortality was noted in patients with compensated hypercapnia. In patients with traumatic brain injury, lower hospital mortality was noted in patients with compensated hypercapnia (eFigure 4 in the Supplement and Table 2).

Multivariable analysis using both logistic regression (hospital mortality) and Cox proportional hazards regression (time to death) confirmed patients with hypercapnic acidosis had an increased risk of death compared with patients with normocapnia and normal pH levels (**Table 3**). While this increased risk of death was evident across the 3 diagnostic categories, there was a statistically significant interaction between hypercapnic status and diagnosis indicating that the increase in risk of hospital mortality for patients with hypercapnic acidosis did differ according to diagnostic category, with the greatest risk for patients with cardiac arrest (odds ratio [OR], 1.51; 95% CI, 1.34-1.71); stroke (OR, 1.43; 95% CI, 1.27-1.6); and traumatic brain injury (OR, 1.22; 95% CI, 1.06-1.42; *P* <.001) (Table 3). Patients with compensated hypercapnia did not have an increased risk of hospital mortality compared with patients with normocapnia and normal pH levels (Table 3). These findings were subsequently confirmed from sensitivity analysis matching patients for baseline severity eTable 3 in the Supplement.

In subgroup analysis based on baseline GCS score, patients with hypercapnic acidosis had consistent increased risk of hospital mortality for patients with cardiac arrest and stroke, with no significant evidence that the nature of the association between hypercapnic status and mortality differed according to baseline GCS score (eTable 4 in the Supplement). Patients with traumatic brain injury with hypercapnic acidosis had increased risk of hospital mortality (compared with normocapnia and normal pH levels) in patients with GCS score between 3-7; this was not the case for those with GCS score 8-12 and 13-15, with the interaction between hypercapnic status and GCS score not statistically significant (eTable 4 in the Supplement).

In further subgroups, analyses based on diagnostic subgroups (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, subdural or extradural hemorrhage, isolated traumatic brain injury, and traumatic brain injury associated with other injuries), patients with hypercapnic acidosis consistently had an increase in risk (compared with normocapnia and normal pH levels) and there were no significant interactions among patients with stroke or patients with traumatic brain injury to indicate that the nature of the association between hypercapnic status and mortality differed according to diagnostic subgroup (eTable 5 in the Supplement). Patients with compensated hypercapnia had no increased risk of hospital mortality compared with patients who had normocapnia and normal pH levels. Finally, in the subgroup analyses, based on the requirement of surgical intervention, patients with hypercapnic acidosis retained the highest risk of hospital mortality with no significant interactions between the

Figure 2. Hospital Mortality With Increasing Partial Pressure of Carbon Dioxide in Patients With Hypercapnic Acidosis and Compensated Hypercapnia



Hospital mortality with increasing partial pressure of carbon dioxide (Pco_2) in patients with hypercapnic acidosis and compensated hypercapnia unadjusted (A) and adjusted odds ratio for hospital mortality (B). Error bars represent 95% CI. $P = .008$ for interaction between hypercapnic status and Pco_2.

requirement or nonrequirement of surgical intervention in patients with stroke or traumatic brain injury (eTable 6 in the Supplement).

The adjusted odds ratio of hospital mortality significantly differed between patients who had hypercapnic acidosis and compensated hypercapnia with increasing Pco_2 (Figure 2). In patients with hypercapnic acidosis, the adjusted odds ratio of hospital mortality increased with increasing Pco_2. In patients with compensated hypercapnia, the adjusted odds of hospital mortality did not change with increasing Pco_2 (Figure 2).

Discussion

The main results of this study show that hospital mortality in patients with cerebral injury is higher in patients with hypercapnic acidosis compared with patients who had normocapnia or compensated hypercapnia. This increased mortality was consistent across all the 3 diagnostic categories and persisted after adjusting for the variables that principally contribute to hospital mortality. While mortality increased with increasing Pco_2 in patients with hypercapnic acidosis, it did not increase in patients with compensated hypercapnia.

The effects of hypercapnia in acute cerebral injury have been described in several studies.[15-20] Most suggest normocapnia after cerebral injury is associated with better clinical outcomes, and hypocapnia and hypercapnia are associated with poor clinical outcomes.[2,6,15,16,19] However, in patients with cerebral injury secondary to cardiac arrest, there is some evidence to suggest that mild hypercapnia may be beneficial. Experimental studies have demonstrated mild to moderate hypercapnia to be neuroprotective after transient global cerebral ischemia reperfusion injury, while severe hypercapnia resulted in worsening of cerebral edema.[20] The study by Schneider et al[5] showed that in patients admitted to ICUs after cardiac arrest, presence of hypercapnia during the first 24 hours of ICU stay was associated with a greater likelihood of discharge home among survivors.[5] A pilot randomized clinical trial showed induction of mild hypercapnia after cardiac arrest reduced neuron-specific enolase, a biomarker of cerebral injury, compared with normocapnia.[17] Hypercapnia has been shown to increase cerebral blood flow in patients who were successfully resuscitated after cardiac arrest and in patients with subarachnoid hemorrhage.[9,18,21] Hypercapnia was also shown to have anticonvulsive[22] and antiinflammatory properties[23] that may be helpful to improve neurological recovery after cerebral injury. The results of our study show that compensated hypercapnia was not associated with an increase in adverse outcomes and that patient outcomes are comparable with those in patients with normocapnia and normal pH levels. However, in our study, we did not find improved outcomes in the compensated hypercapnia group compared with the normocapnic group. Further, prospective studies will be required to evaluate whether compensated hypercapnia may be beneficial in a subcategory of patients with cerebral injury.

The effect of pH on clinical outcomes was predominantly studied in patients with out-of-hospital cardiac arrest.[11,24] A pH of at least 7.05 was found to be an independent predictor for a favorable outcome.[11] However, this study did not differentiate acidosis caused by carbon dioxide (hypercapnic acidosis) and metabolic acidosis. The study by Takaki et al[24] investigating the predictors of neurologic recovery in patients resuscitated after cardiac arrest found that blood pH had a stronger predictive power than CO_2 in patients after out-of-hospital cardiac arrest.[24]

In patients with ischemic stroke, acidosis is common and has been demonstrated to be associated with toxic calcium influx into the cell and programmed cell death[25] and poorer outcomes.[12,13] Although our data do not provide information about the level of acidosis at the time of onset of the acute cerebral injury, prolonged acidosis into the first 24 hours of intensive care admission is likely to represent significant exposure to this mechanism for neuronal influx of calcium ions and higher levels of consequent injury caused by the excitotoxic action of glutamate release triggered by high intracellular levels of calcium 2.[26] Our data are also lim-

Table 3. Adjusted Hospital Mortality (Logistic Regression and Cox-Proportional Hazards) in Patients With Cerebral Injury

	Logistic Regression Analysis[a]		Cox Proportional Hazards[b]	
Diagnostic Category	OR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Cardiac arrest				
Hypercapnic group				
Normocapnia and normal pH	1.00 [Reference]		1.00 [Reference]	
Compensated hypercapnia vs normocapnia and normal pH	1.04 (0.78-1.38)	<.001	0.98 (0.81-1.19)	<.001
Hypercapnic acidosis vs normocapnia and normal pH	1.51 (1.34-1.71)		1.23 (1.14-1.34)	
Stroke				
Hypercapnic group				
Normocapnia and normal pH	1.00 [Reference]		1.00 [Reference]	
Compensated hypercapnia vs normocapnia and normal pH	0.98 (0.8-1.21)	<.001	1.04 (0.9-1.2)	<.001
Hypercapnic acidosis vs normocapnia and normal pH	1.43 (1.27-1.6)		1.3 (1.21-1.4)	
Traumatic brain injury				
Hypercapnic group				
Normocapnia and normal pH	1.00 [Reference]		1.00 [Reference]	
Compensated hypercapnia vs normocapnia and normal pH	0.74 (0.5-1.11)	.004	0.85 (0.6-1.21)	.07
Hypercapnic acidosis vs normocapnia and normal pH	1.22 (1.06-1.42)		1.13 (1-1.27)	

Abbreviations: HR, hazard ratio; OR, odds ratio.

[a] *P* value for interaction between diagnostic group and hypercapnic group: *P* < .001.

[b] *P* value for interaction between diagnostic group and hypercapnic group: *P* < .001.

ited with respect to time at onset or pattern of brain injury for the patients with cardiac arrest and brain hemorrhage. However, although not reported in the literature, it is possible that similar mechanisms of secondary injury might be active in the cardiac arrest group experiencing prolonged periods of critically low brain blood flow and acidosis secondary to anaerobic metabolism and in the hemorrhage group in the context of mass effect or vasospasm causing focal ischemia.

Strengths

This study has several strengths. First, it involved more than 30 000 mechanically ventilated patients with cerebral injury from 167 ICUs (constituting about 80% of ICUs) in 2 countries, making its findings highly generalizable for all ICUs in Australia and New Zealand. This study specifically aimed to delineate the effects of hypercapnia with and without the effects of concurrent acidosis, which, to our knowledge, has not been studied in any earlier studies. It is likely that our findings have external validity in other developed countries with intensive care practices similar to Australia and New Zealand. To our knowledge, this is the largest study relating hypercapnic status to mortality published thus far, and the large sample size of our study enables identification of small but significant differences in outcomes. The Australian and New Zealand Intensive Care Society Adult Patient Database is recognized as a high-quality clinical registry with excellent data quality. Analyses arising from this data have been published in multiple high-impact journals.[27,28] Data collection from the participating ICUs is robust and quality-controlled, with an established data dictionary to ensure uniformity and accuracy of the data collected.

Limitations

Our study is a retrospective study with inherent limitations. The worst value of Adult Patient Database Pco_2 and pH used in classifying patients was limited to the 24 hours after ICU admission. Thus, patients may have had more deranged blood gasses (abnormal Pco_2 and pH) prior to ICU admission or after 24 hours after ICU admission, and the absence of this data precluded evaluation of association of hypercapnic status before or after 24 hours of ICU admission on hospital mortality. However, most studies published thus far have also evaluated the association of hypercapnia on clinical outcomes using data during the first 24 hours of patient's hospital presentation. Our results are therefore comparable with existing literature.[2,5,11,24,29] Some patients presenting with compensated hypercapnia and hypercapnic acidosis may have had renal compensation prior to the ICU admission. From the data available, it was not possible to evaluate the proportion of patients with prior renal compensation before admission to ICU with cerebral injury or the etiology of hypercapnic acidosis that could have contributed to the increased mortality. We also did not have data on physiological indices, such as cerebral blood flow or intracranial pressure measurement, and neuroimaging data that could have helped in understanding the possible mechanisms in the increased mortality noted in patients with hypercapnic acidosis patients. The outcomes of patients with cerebral injury is known to be dependent on several factors such as duration and type of cardiac arrest,[30] pattern or severity of brain injury, volume of intracerebral blood, GCS score, and computed tomography characteristics.[31,32] Given the retrospective nature of our study, we did not have data on some of these variables that could have further aided in understanding the association of compensated hypercapnia and hypercapnic acidosis on hospital mortality. Further-

more, retrospective studies such as this could have unknown confounders that may have accounted for the observed differences in the outcomes. Nevertheless, the current ICU severity scoring system used in Australia and New Zealand[14] is known to have excellent calibration and discrimination in intensive care patients, particularly in patients with cerebral injuries. This may have compensated for the lack of availability of some known severity markers.

Conclusions

Hypercapnic acidosis was associated with increased risk of hospital mortality in patients with cerebral injury. Hypercapnia when compensated to normal pH during the first 24 hours of ICU admission may not be harmful in mechanically ventilated patients with cerebral injury.

ARTICLE INFORMATION

Accepted for Publication: December 3, 2017.

Published Online: March 19, 2018. doi:10.1001/jamaneurol.2018.0123

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Administrative, technical, or material support: Pilcher.
Supervision: Pilcher, Botha, Bailey.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank clinicians, data collectors. and researchers at the following contributing sites: Royal Darwin Hospital; Bathurst Base Hospital; Alice Springs Hospital; Canberra Hospital; Albury Base Hospital; Ashford Community Hospital; The Queen Elizabeth (Adelaide, Australia); Royal North Shore Hospital; Warringal Private Hospital; Royal Perth Hospital; Royal Prince Alfred Hospital; Box Hill Hospital; St George Hospital (Sydney, Australia); Austin Hospital; Christchurch Hospital; Royal Brisbane and Women's Hospital; Brisbane Private Hospital; Dunedin Hospital; Dandenong Hospital; Greenslopes Private Hospital; Cairns Base Hospital; Knox Private Hospital; Ballarat Health Services; Tauranga Hospital; Auburn Hospital and Community Health Services; John Hunter Hospital; Calvary Wakefield Hospital (Adelaide, Australia); Gosford Hospital; Epworth Hospital (Richmond, Australia); Bendigo Health Care Group; Wellington Hospital; The Valley Private Hospital; Mater Adults Hospital (Brisbane, Australia); Redcliffe Hospital; Sutherland Hospital & Community Health Services; Mater Private Hospital (Brisbane, Australia); Flinders Medical Centre; Liverpool Hospital; Coffs Harbour Health Campus; Mount Druitt Hospital and Community Health Services; The Prince Charles Hospital; Prince of Wales Hospital; Concord Hospital (Sydney, Australia); Goulburn Valley Health; Orange Base Hospital; Rockhampton Hospital; Northeast Health Wangaratta; Taranaki Health; Calvary Hospital (Lenah Valley, Australia); Royal Adelaide Hospital; Fremantle Hospital; Lismore Base Hospital; Alfred Hospital; Blacktown Hospital; Nepean Hospital; Timaru Hospital; Launceston General Hospital; Sydney Adventist Hospital; Calvary Mater Newcastle; Lyell McEwin Hospital; Toowoomba Hospital; Tweed Heads District Hospital; Port Macquarie Base Hospital; Hornsby Ku-ring-gai Hospital; St Andrew's Hospital(Adelaide, Australia); Logan Hospital; Mackay Base Hospital; Bankstown-Lidcombe Hospital; St John Of God Hospital (Murdoch, Australia); Repatriation General Hospital (Adelaide); Wollongong Hospital; St George Private Hospital; Cabrini Hospital; Monash Medical Centre-Clayton Campus; Prince of Wales Private Hospital; Royal Hobart Hospital; Nambour General Hospital; North Shore Private Hospital; Westmead Hospital; The Northern Hospital; Geelong Hospital; Mater Private Hospital (Sydney); Wagga Wagga Base Hospital and District Health; North West Regional Hospital (Burnie, Australia); Gold Coast University Hospital; St Vincent's Hospital (Sydney); John Flynn Private Hospital; Maroondah Hospital; The Townsville Hospital; Cairns Private Hospital; Ipswich Hospital; Sir Charles Gairdner Hospital; Manly Hospital & Community Health; St Vincent's Private Hospital (Sydney); St Andrew's War Memorial Hospital; Tamworth Base Hospital; John Fawkner Hospital; Hawkes Bay Hospital; Westmead Private Hospital; St Vincent's Hospital (Melbourne, Australia); Calvary Hospital (Canberra); FigTree Private Hospital; Latrobe Regional Hospital; Frankston Hospital; The Memorial Hospital (Adelaide, Australia); St Andrew's Hospital Toowoomba; Bundaberg Base Hospital; Mount Hospital; Royal Melbourne Hospital; The Wesley Hospital; Nelson Hospital; Shoalhaven Hospital; Mersey Community Hospital; Calvary North Adelaide Hospital; Grafton Base Hospital; Melbourne Private Hospital; St Vincent's Hospital (Toowoomba, Australia); Footscray Hospital; Peter MacCallum Cancer Institute; Epworth Freemasons Hospital; Mater Private Hospital (Townsville, Australia); St John Of God Hospital (Geelong, Australia); Modbury Public Hospital; Caboolture Hospital; Waikato Hospital; Dubbo Base Hospital; Holy Spirit Northside Hospital; Campbelltown Hospital; Mildura Base Hospital; Central Gippsland Health Service; Queen Elizabeth II Jubilee Hospital; Manning Rural Referral Hospital; Flinders Private Hospital; Wimmera Health Care Group (Horsham, Australia); Norwest Private Hospital; Hollywood Private Hospital; Calvary John James Hospital; Armidale Rural Referral Hospital; Princess Alexandra Hospital; Hervey Bay Hospital; Rotorua Hospital; St John Of God Health Care (Subiaco, Australia); Whangarei Area Hospital, Northland Health Ltd; Gosford Private Hospital; Joondalup Health Campus; Hutt Hospital; Western District Health Service (Hamilton, Australia); Griffith Base Hospital; Auckland City Hospital; Allamanda Private Hospital; South West Healthcare (Warrnambool); Sunshine Hospital; Pindara Private Hospital; North Shore Hospital; Mount Isa Hospital; Middlemore Hospital; St Vincent's Private Hospital Fitzroy; Noosa Hospital; The Sunshine Coast Private Hospital; Epworth Eastern Private Hospital; Robina Hospital; Wyong Hospital; Macquarie University Private Hospital; Rockingham General Hospital; Armadale Health Service; Peninsula Private Hospital; and St George Hospital (Sydney, Australia).

REFERENCES

1. Maas AI, Dearden M, Teasdale GM, et al; European Brain Injury Consortium. EBIC-guidelines for management of severe head injury in adults. *Acta Neurochir (Wien)*. 1997;139(4):286-294.

2. Davis DP, Idris AH, Sise MJ, et al. Early ventilation and outcome in patients with moderate to severe traumatic brain injury. *Crit Care Med*. 2006;34(4):1202-1208.

3. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. *Circulation*. 2013;127(21):2107-2113.

4. Roberts BW, Kilgannon JH, Chansky ME, Trzeciak S. Association between initial prescribed minute ventilation and post-resuscitation partial pressure of arterial carbon dioxide in patients with post-cardiac arrest syndrome. *Ann Intensive Care*. 2014;4(1):9.

5. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation*. 2013;84(7):927-934.

6. Warner KJ, Cuschieri J, Copass MK, Jurkovich GJ, Bulger EM. The impact of prehospital ventilation on outcome after severe traumatic brain injury. *J Trauma*. 2007;62(6):1330-1336.

7. Christensen MS, Paulson OB. Prolonged artificial hyperventilation in severe cerebral apoplexy. Clinical results and cerebrospinal fluid findings in a controlled study. *Eur Neurol*. 1972;8(1):137-141.

8. Solaiman O, Singh JM. Hypocapnia in aneurysmal subarachnoid hemorrhage: incidence and association with poor clinical outcomes. *J Neurosurg Anesthesiol*. 2013;25(3):254-261.

9. Westermaier T, Stetter C, Kunze E, et al. Controlled transient hypercapnia: a novel approach for the treatment of delayed cerebral ischemia after subarachnoid hemorrhage? *J Neurosurg*. 2014;121(5):1056-1062.

10. Gupta AK, Zygun DA, Johnston AJ, et al. Extracellular brain pH and outcome following severe traumatic brain injury. *J Neurotrauma*. 2004;21(6):678-684.

11. Momiyama Y, Yamada W, Miyata K, et al. Prognostic values of blood pH and lactate levels in patients resuscitated from out-of-hospital cardiac arrest. *Acute Med Surg*. 2017;4(1):25-30.

12. Katsura K, Ekholm A, Asplund B, Siesjö BK. Extracellular pH in the brain during ischemia: relationship to the severity of lactic acidosis. *J Cereb Blood Flow Metab*. 1991;11(4):597-599.

13. Nedergaard M, Goldman SA, Desai S, Pulsinelli WA. Acid-induced death in neurons and glia. *J Neurosci*. 1991;11(8):2489-2497.

14. Paul E, Bailey M, Pilcher D. Risk prediction of hospital mortality for adult patients admitted to Australian and New Zealand intensive care units: development and validation of the Australian and New Zealand Risk of Death model. *J Crit Care*. 2013;28(6):935-941.

15. McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. *Resuscitation*. 2017;111:116-126.

16. Roberts BW, Karagiannis P, Coletta M, Kilgannon JH, Chansky ME, Trzeciak S. Effects of PaCO2 derangements on clinical outcomes after cerebral injury: A systematic review. *Resuscitation*. 2015;91:32-41.

17. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation*. 2016;104:83-90.

18. Vaahersalo J, Bendel S, Reinikainen M, et al; FINNRESUSCI Study Group. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. *Crit Care Med*. 2014;42(6):1463-1470.

19. Warner KJ, Cuschieri J, Copass MK, Jurkovich GJ, Bulger EM. Emergency department ventilation effects outcome in severe traumatic brain injury. *J Trauma*. 2008;64(2):341-347.

20. Zhou Q, Cao B, Niu L, et al. Effects of permissive hypercapnia on transient global cerebral ischemia-reperfusion injury in rats. *Anesthesiology*. 2010;112(2):288-297.

21. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: the impact of hypercapnia. *Resuscitation*. 2016;102:11-16.

22. Tolner EA, Hochman DW, Hassinen P, et al. Five percent CO_2 is a potent, fast-acting inhalation anticonvulsant. *Epilepsia*. 2011;52(1):104-114.

23. O'Croinin D, Ni Chonghaile M, Higgins B, Laffey JG. Bench-to-bedside review: permissive hypercapnia. *Crit Care*. 2005;9(1):51-59.

24. Takaki S, Kamiya Y, Tahara Y, Tou M, Shimoyama A, Iwashita M. Blood pH is a useful indicator for initiation of therapeutic hypothermia in the early phase of resuscitation after comatose cardiac arrest: a retrospective study. *J Emerg Med*. 2013;45(1):57-64.

25. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. *Neuron*. 2010;67(2):181-198.

26. Gao J, Duan B, Wang DG, et al. Coupling between NMDA receptor and acid-sensing ion channel contributes to ischemic neuronal death. *Neuron*. 2005;48(4):635-646.

27. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med*. 2015;372(17):1629-1638.

28. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311(13):1308-1316.

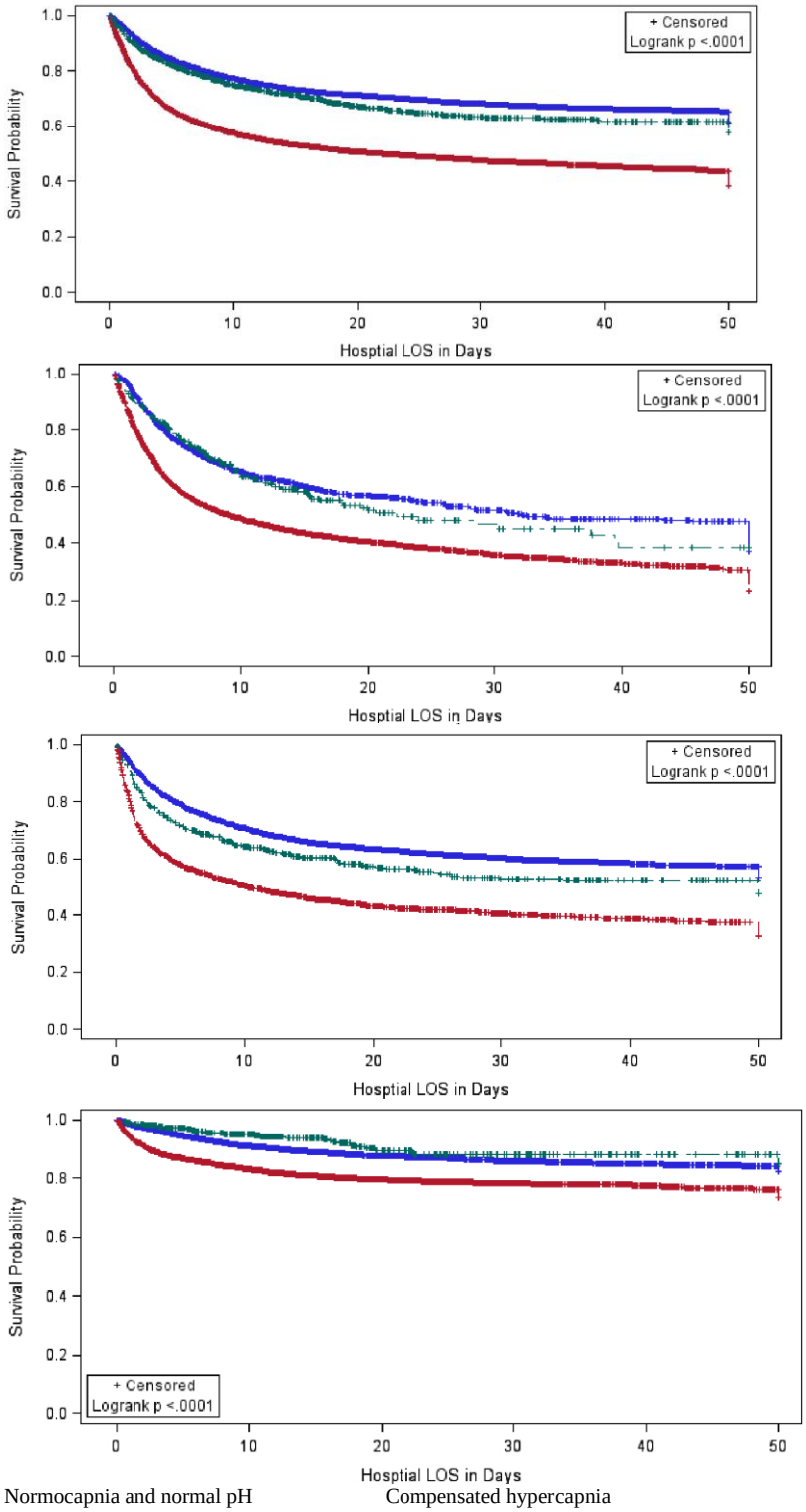
29. Bennett KS, Clark AE, Meert KL, et al; Pediatric Emergency Care Medicine Applied Research Network. Early oxygenation and ventilation measurements after pediatric cardiac arrest: lack of association with outcome. *Crit Care Med*. 2013;41(6):1534-1542.

30. Sathianathan K, Tiruvoipati R, Vij S. Prognostic factors associated with hospital survival in comatose survivors of cardiac arrest. *World J Crit Care Med*. 2016;5(1):103-110.

31. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24(7):987-993.

32. Murray GD, Butcher I, McHugh GS, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24(2):329-337.

eFigure 1 : *Kaplan-Meier* survival curves for (1) All cerebral injury patients (Top). (2) cardiac arrest (upper middle) , (3)Cerebrovascular accident(Lower middle), and (4) traumatic brain injury (bottom)



e Table 1. Prediction model to determine each patient's probability to present to intensive care units with hypercapnic acidosis

Category	Hypercapnic Acidosis		Odds Ratio
	No	**Yes**	**95%CI**
Age			
1.<=44	33.8%(4891)	26.8%(4448)	1
2.45-64	30.4%(4406)	33.6%(5566)	1.29(1.21-1.37)
3.65-84	32.1%(4643)	35.6%(5911)	1.18(1.11-1.26)
4.>=85	3.8%(544)	4%(661)	1.09(0.96-1.24)
Chronic renal failure			
No	98.7%(14290)	97.1%(16110)	1
Yes	1.3%(194)	2.9%(476)	1.78(1.49-2.13)
Diabetes			
No	98.7%(14292)	97.6%(16181)	1
Yes	1.3%(192)	2.4%(405)	1.46(1.21-1.75)
Immune therapy			
No	98.8%(14317)	98.1%(16273)	1
Yes	1.2%(167)	1.9%(313)	1.58(1.29-1.92)
Gender			
Female	30.9%(4470)	27.1%(4502)	1
Male	69.1%(10014)	72.9%(12084)	1.28(1.22-1.35)
Admission Source			
Chronic care	0.6%(85)	0.8%(138)	0.97(0.73-1.30)
Home	53%(7677)	67.8%(11239)	1
Other Hospital	31.9%(4626)	22.6%(3749)	0.55(0.52-0.58)
Other ICU	3.5%(510)	1.7%(287)	0.38(0.33-0.45)
Unknown	11%(1586)	7.1%(1173)	0.82(0.71-0.94)
Hospital Level			
Metropolitan	8%(1153)	17%(2815)	2.10(1.56-2.82)
Private	3%(435)	2.8%(462)	1
Rural	4.4%(643)	8.9%(1476)	1.97(1.46-2.66)
Tertiary	84.6%(12253)	71.3%(11833)	1.04(0.79-1.38)
*All variables were significant p<0.0001 AUC=0.682 (0.677-0.688)			
Hosmer Lemmeshow p=0.33			

eTable 2. Prediction model to determine each patient's probability to present to intensive care units with compensated hypercapnia

Variable	Compensated Hypercapnia		Odds Ratio
	No	Yes	(95%CI)
Diagnosis			
Cardiovascular	38.7%(11492)	22.9%(310)	1
Neurological	30.7%(9122)	41.3%(559)	2.42(2.08-2.81)
Trauma	30.6%(9104)	35.7%(483)	2.13(1.82-2.49)
Day Shift admission			
No	55.4%(16470)	53%(716)	0.86(0.77-0.96)
Yes	44.6%(13248)	47%(636)	1
Admission Source			
Chronic Care	0.7%(211)	0.9%(12)	1.51(0.84-2.73)
Home	61.2%(18181)	54.4%(735)	1
Other Hosp	26.7%(7933)	32.7%(442)	1.27(1.12-1.44)
Other ICU	2.5%(740)	4.2%(57)	1.78(1.34-2.37)
Unknown	8.9%(2653)	7.8%(106)	0.86(0.68-1.08)
Hospital Type			
Metropolitan	12.8%(3797)	12.6%(171)	1.25(0.87-1.8)
Private	2.9%(857)	3%(40)	1
Rural	6.8%(2026)	6.9%(93)	1.16(0.79-1.71)
Tertiary	77.5%(23038)	77.5%(1048)	0.87(0.62-1.21)
Indigenous status			
No	68.2%(20269)	66.2%(895)	1
Yes	5.3%(1563)	3.6%(49)	0.75(0.56-1.02)
Unknown	26.5%(7886)	30.2%(408)	1.28(1.12-1.45)
Location (Australian states and New Zealand)			
ACT	3.1%(922)	3.1%(42)	1.61(1.09-2.36)
NSW	25.6%(7621)	28.8%(389)	1.82(1.43-2.32)
NT	1.3%(399)	1%(13)	0.93(0.5-1.72)
NZ	10%(2958)	7%(94)	1
QLD	15.5%(4617)	13.2%(178)	1.31(1-1.71)
SA	10.9%(3229)	13.1%(177)	1.97(1.51-2.57)
TAS	2.3%(679)	2.6%(35)	1.63(1.09-2.44)
VIC	25.6%(7613)	26.7%(361)	1.64(1.29-2.08)
WA	5.7%(1680)	4.7%(63)	1.4(0.99-1.98)
Gender			
Female	29%(8625)	25.7%(347)	1
Male	71%(21093)	74.3%(1005)	1.22(1.07-1.39)
*All variables were significant p<0.01 AUC=0.631 (0.616-0.646)			
Hosmer Lemmeshow p=0.38			

5.3 Chapter summary

This multicentre, binational study examined the relationship between compensated hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients with acute cerebral injury. This is the largest retrospective study ever published so far evaluating hypercapnia and hypercapnic acidosis in patients with acute cerebral injury. The main results of this study are that the hospital mortality in patients with cerebral injury is higher in patients with hypercapnic acidosis as compared to patients who had normocapnia or compensated hypercapnia. The increased hospital mortality was consistent across all three diagnostic categories (traumatic brain injury, stroke and cardiac arrest) and persisted after adjusting for the variables that principally contribute to hospital mortality. While mortality increased with increasing PCO_2 in patients with hypercapnic acidosis, it did not increase in patients with compensated hypercapnia.

The important finding of this study is that compensated hypercapnia, irrespective of the level of elevation in PCO_2 did not confer an increased risk of hospital mortality as compared to normocapnia and normal pH. This finding did not change when adjusted for potential confounders and relevant subgroups defined by individual diagnostic categories and subcategories defined by baseline clinical severity as well as Glasgow Coma Scale. These findings suggest that targeting absolute PCO_2 values without considering pH status of the patients, may lead to hyperventilation and alkalosis that is known to worsen secondary brain injury. Furthermore, hyperventilation may need higher driving pressures and tidal volumes on mechanical ventilation that could cause or worsen lung injury.

This chapter was published in the journal of JAMA Neurology that currently (2018) has an impact factor of 11.5 accompanied by an editorial (appendix 8), two media releases and a Comment & Response (Appendices 9 -12). The article was well received by clinicians across the world with Altmetric Attention Score of 63 (November 2018) bringing this to the top 5% of all research outputs ever tracked by Altmetric.

The editorial (appendix 8) titled “Arterial Partial Pressure of Carbon Dioxide and Secondary Brain Injury—6 Degrees of Separation?” discusses the current management guidelines not recommending a target pH while managing hypercapnia and the importance of interpreting and managing arterial PCO_2 in conjunction with pH.

Two media releases, one from MEDPAGE TODAY (Appendix 9) (https://www.medpagetoday.com/neurology/generalneurology/71889) and one from Monash University (http://ccsmonash.blogspot.com/2018/04/monash-study-reveals-insights-into.html) (Appendix 10) were published describing the importance of the study.

Following the publication of this article a letter to editor (Appendix 11) was written titled "What is the Association with Dissociation?" where the implications of acidosis on oxygen dissociation curve on oxygen delivery was questioned. The authors of this letter argue that hypercapnic acidosis may have beneficial effects in patients with cerebral injury. We have responded to the letter (Appendix 12) stating that the clinical data that is available (including our paper) suggests acidosis is harmful and should be avoided or actively managed and that PCO_2 should be interpreted in conjunction with pH. We believe further guidelines on management of cerebral injury patients may consider the results of our study and recommend a pH target while managing hypercapnia.

Our investigation on the association of hypercapnia and hypercapnic acidosis in mechanically ventilated patients showed an increased hospital mortality risk associated with hypercapnic acidosis. Similar studies were also published by other investigators suggesting an increased mortality with hypercapnia and hypercapnic acidosis in patients with ARDS. The studies that are published in the recent past are retrospective and has shown an association of hypercapnic acidosis with increased mortality. Nevertheless based on these findings, it appears that hypercapnia and hypercapnic acidosis must be prevented or actively managed.

Hypercapnia may be controlled with modifications in the techniques of conventional mechanical ventilation. However, in some patients this may not be possible while instituting lung protective ventilation. Over the recent past extracorporeal carbon dioxide removal devices were introduced to clinical practice to manage hypercapnia associated with lung protective ventilation. This research programme investigated one of the novel low flow venovenous extracorporeal carbon dioxide removal device (Hemolung RAS) for safety, feasibility and efficacy in management of hypercapnic acidosis. This was the first evaluation of this device in Australia and New Zealand.

CHAPTER 6: Evaluation of a HEMOLUNG RAS - a novel extracorporeal device in the management of hypercapnic acidosis

6.1 Chapter introduction

Hypercapnic acidosis was thought to be benign and possibly beneficial in mechanically ventilated patients. However, the recently published data including our studies (presented in chapters 4 and 5) showed an increased risk of hospital mortality and other adverse events. Based on these findings hypercapnic acidosis should be prevented or managed actively.

Several extracorporeal carbon dioxide removal devices were recently introduced to treat severe hypercapnic acidosis that may be seen with low volume lung protection ventilation. As part of this research programme, one of the novel low flow venovenous extracorporeal carbon-dioxide removal devices called Hemolung RAS was investigated for safety and feasibility in management of hypercapnic acidosis in mechanically ventilated patients. This was the first evaluation of such a device in Australia and New Zealand.

The chapter contains three subsections; the first subsection describes Hemolung RAS and its introduction to clinical practice at our hospital, the second subsection a case report on the first use of Hemolung RAS in Australia on a patient with severe COPD and the third subsection a case report on its use in a patient with severe status asthmaticus.

6.2 Evaluating safety and feasibility of Hemolung RAS at Frankston Hospital

Introduction

Acute hypercapnic respiratory failure is one of the common causes for admission to intensive care unit. This may be caused by exacerbation of reactive or chronic obstructive airway disease. The management of such patients include identifying and treating the precipitating cause and providing supportive care until the lung function recovers. Supportive care in such patients includes provision of non-invasive as well as invasive mechanical ventilation. Most of these patients recover with such management. However, in some patients the respiratory failure may worsen and in such patients, the respiratory function may not be adequately supported with mechanical ventilation. Some patients while on mechanical ventilation for acute lung injury or acute respiratory distress syndrome, may develop acute hypercapnia when lung protective ventilation strategies are used. These patients may be treated with more invasive treatments such as extracorporeal membrane oxygenation (ECMO). The use of ECMO, while may be beneficial, is invasive, expensive and it is not widely available. Furthermore, the expertise required to use ECMO is limited. Given these factors, the use of ECMO is currently limited to only a small proportion of patients.

There have been some technological developments in the recent past in management of patients with severe hypercapnic respiratory failure. One of these advances includes the development of a minimally invasive extracorporeal carbon dioxide removal device called Hemolung RAS (Hemolung® Respiratory Assist System, ALung Technologies, Pittsburgh, PA). This technology is the least invasive devices available to remove carbon dioxide, with efficient carbon dioxide removal at blood flows of 400- 600 ml/ minute. The Hemolung RAS is a simple, venovenous extracorporeal lung support device, which is intended for partial extracorporeal respiratory support in the treatment of acute hypercapnic respiratory failure. The Hemolung RAS removes carbon dioxide and delivers oxygen directly to the blood utilizing a simple extracorporeal circuit, small venous catheter, and techniques similar to haemodialysis which is routinely used in intensive care units. By providing gas exchange independently of the lungs, the Hemolung RAS supports the respiratory system, giving the patient's lungs time to rest and heal. The Hemolung RAS is comprised of three

main devices with the following key characteristics: Hemolung cartridge, Hemolung controller and Hemolung catheter.

Hemolung (Hemolung® Respiratory Assist System, ALung Technologies, Pittsburgh, PA):

Hemolung Cartridge

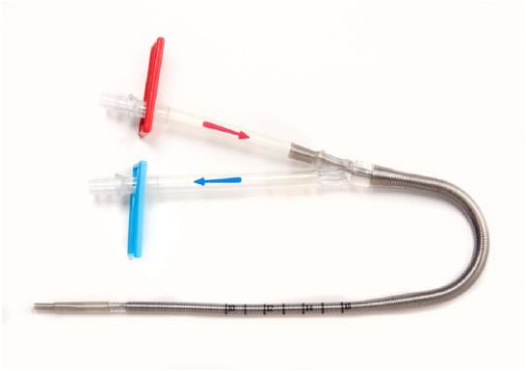
- Integrated pump/oxygenator provides extracorporeal gas exchange while simultaneously pumping blood allowing for veno-venous operation.
- Minimal membrane surface area (0.59 m2)
- CO2 removal of at least 50 mL/min at blood flows of 350 – 550 mL/min

Hemolung Controller

- Controls the Hemolung Cartridge pump speed and gas flow
- Provides real-time monitoring of CO2 removal and blood flow, bubble detection, and other alarms

Hemolung Catheter

- 15.5 Fr dual lumen venous catheter
- Percutaneous, single-stick venous access
- Femoral (26 cm) and jugular (17 cm) available (dual lumen venous catheter with insertion accessories). These are similar to the catheters used for haemodialysis in ICU.



The Hemolung removes carbon dioxide and delivers oxygen directly to the blood utilizing a simple extracorporeal circuit and a small venous catheter. This technique is less complex than ECMO and very similar to haemodialysis that is routinely performed in most ICUs. By providing gas exchange independently of the lungs, Hemolung reduces the burden of ventilation on lungs, giving them time to rest and heal.

Inclusion criteria

- Adult patients with hypercapnic respiratory failure who are not responsive to non-invasive mechanical ventilation or on invasive mechanical ventilation and cannot be treated with lung protective mechanical ventilation due to hypercapnia.
- Can consent or have next of kin to provide assent.

Exclusion Criteria:

- Patients who have contraindication for limited anticoagulation
- Patients who have allergy to heparin or have heparin induced thrombocytopenia
- Patients with hemodynamic instability or uncontrolled arrhythmia
- Platelet count of less than 75,000/mm^3
- Patients who are not for active management

Protocol:

Hemolung was used if patients had

a) severe hypercapnic respiratory failure and on non-invasive mechanical ventilation for at least one hour and not responsive to non-invasive mechanical ventilation as defined by pH < 7.25 and pCO_2 >55 and /or have a high likelihood of requiring invasive mechanical ventilation.

b) Patients on invasive mechanical ventilation but cannot be ventilated with lung protective ventilation (tidal volumes </= 6 ml/Kg of ideal body weight) due to hypercapnic respiratory failure (pH< 7.2)

Clinical Governance in introduction of Hemolung RAS to Frankston Hospital: At the time of initiation of Hemolung RAS at Frankston Hospital, this device did not have Therapeutic Goods Administration (TGA) approval for use in Australia. Hence, application and approval from TGA was obtained to use this device as an authorised prescriber (Appendix 13). Approval from New Technology Committee at Frankston Hospital was acquired, as this device had never been used at Frankston Hospital or anywhere in Australia before (Appendix 14). Consent was obtained from the eligible patients or their next of kin as appropriate (Appendix 15).

Technique: Hemolung was set up and used as per the recommendations by the manufacturer. The principles of cannulation to access blood vessels and anticoagulation are very similar to haemodialysis routinely performed in intensive care. An Intensivist was available on-site during

days and was readily available on call during nights. Intensive care registrars, nursing and allied health staff in intensive care assisted the Intensivist in management of these patients.

A specifically designed dual lumen catheter was inserted under aseptic precautions into femoral or jugular veins as per the standard protocol of our ICU. Ultrasound guidance was used to minimise the risk of injury to other structures. After establishing the cannula, patients were connected to Hemolung. Heparin was used for anticoagulation as per the manufacturer's recommendations and an aPTT of 50-70 seconds. Blood flow through the catheter was maintained at 300-600 ml/ min to achieve a CO2 clearance rate of >50ml/min. The blood flow and CO2 clearance rate were continuously monitored and recorded. Baseline blood samples were collected for measurement of arterial blood gasses, haematological, biochemical and coagulation parameters at the initiation of Hemolung. Subsequent measurements were based on clinical indication. Hemolung was used for up to 7days depending on the response of recovery of the patients.

Hemolung was successfully used in 2 patients with severe hypercapnic acidosis to test the safety of feasibility of using this device. Details of these patients were published as case reports.

6.3 Published manuscript

Anaesth Intensive Care 2014; **42: 248-252**

Case Reports

Management of severe hypercapnia post cardiac arrest with extracorporeal carbon dioxide removal

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SUMMARY

Normocapnia is recommended in intensive care management of patients after out-of-hospital cardiac arrest. While normocapnia is usually achievable, it may be therapeutically challenging, particularly in patients with airflow obstruction. Conventional mechanical ventilation may not be adequate to provide optimal ventilation in such patients. One of the recent advances in critical care management of hypercapnia is the advent of newer, low-flow extracorporeal carbon dioxide clearance devices. These are simpler and less invasive than conventional extracorporeal devices. We report the first case of using a novel, extracorporeal carbon dioxide removal device in Australia on a patient with out-of-hospital cardiac arrest where mechanical ventilation failed to achieve normocapnia.

Key Words: cardiac arrest, hypercapnia, respiratory acidosis, extracorporeal

Patients are usually admitted to the intensive care unit (ICU) after out-of-hospital cardiac arrest (OHCA) if return of spontaneous circulation is achieved after resuscitation. Their mortality remains high despite improvements in pre-hospital management and intensive care post cardiac arrest. Therapeutic hypothermia has improved neurological outcome[1,2] and the recommendations are to maintain $PaCO_2$ between 40 and 45 mmHg[3,4]. While normocapnia is usually achievable, it may be therapeutically challenging, particularly in patients with airflow obstruction or increased physiological dead space. Conventional mechanical ventilation may not be adequate to provide optimal ventilation in such patients. One of the recent advances in the critical care management of hypercapnia is the advent of newer extracorporeal carbon dioxide clearance devices[5,6]. These are simpler and less invasive than conventional extracorporeal membrane oxygenation (ECMO) devices. These low blood-flow carbon dioxide clearance devices are effective in the removal of carbon dioxide without contributing significantly to oxygenation.

We report the first use of a novel extracorporeal carbon dioxide removal (ECCO2-R) device in Australia in managing a patient with OHCA where mechanical ventilation failed to achieve normocapnia. The severe hypercapnic acidosis was managed by ECCO2-R using the Hemolung® Respiratory Assist System (RAS) (ALung Technologies Inc., Pittsburgh, PA, USA).

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Accepted for publication on December 2, 2013

CASE REPORT

Ethics approval and consent

The Human Research and Ethics Committee of Peninsula Health approved the use of Hemolung® in our ICU. Approval was also obtained from the Australian Therapeutic Goods Administration (TGA approval number 2013-123) for using Hemolung®. Consent from the family was obtained to allow reporting of this case.

Figure 1: Hemolung® Respiratory Assist System.

A 58-year-old male was found unconscious by his wife at 3.00 am. She had last seen him at about 10.00 pm the preceding day. Following instructions provided by the paramedical team, she performed chest compressions until the arrival of the paramedical personnel, who found the patient in pulseless electrical activity. They initiated cardiopulmonary resuscitation as per the Advanced Life Support guidelines and continued this for ten minutes until the return of spontaneous circulation. During resuscitation the patient was intubated and a needle thoracostomy performed for a suspected tension pneumothorax.

The patient had a history of severe chronic obstructive pulmonary disease (COPD), secondary to a more than 40 pack-year history of cigarette smoking, with forced expired volume in one second of 0.41 l (16% of predicted for his age and sex) and diffusing capacity of the lung for carbon monoxide 7.4 ml/min/mmHg (33% of predicted). There was confirmed asbestos exposure in the past but no radiological evidence of parenchymal or pleural disease as a consequence. He was independent with his activities of daily living but with a markedly reduced exercise tolerance, limited to 50 metres on flat ground. He had been admitted to hospital twice in the two weeks preceding this admission with exacerbations of COPD and was awaiting lung transplantation.

On arrival at the emergency department he had decreased breath sounds bilaterally with no evidence of a pneumothorax or new infiltrates on a bedside anterior-posterior chest radiograph. The patient was on a pressure control mode of ventilation with a peak airway pressure target of 35 cmH_2O, an inspiratory to expiratory time ratio of 1:3.7 and a respiratory rate of 12/minute. He was treated with nebulised salbutamol, ipratropium and high-dose intravenous hydrocortisone, and therapeutic hypothermia[1] was instituted. His endotracheal tube had minimal secretions.

He did not have any evidence of acute intracranial pathology on the plain computed tomography scan of his brain. Computed tomography pulmonary angiogram was not suggestive of pulmonary thromboembolism, pneumothorax or airspace consolidation.

Initial arterial blood gas analysis revealed a $PaCO_2$ of 82 mmHg and a pH of 7.20. The $PaCO_2$ was significantly higher than his baseline $PaCO_2$ of about 50 mmHg when well. He was sedated with morphine and midazolam and paralysed with cisatracurium by infusion to facilitate mechanical ventilation.

Over the next few hours he became increasingly difficult to ventilate, with increased intrinsic positive end-expiratory pressure, decreased alveolar ventilation and an arterial $PaCO_2$ increasing to 94 mmHg with worsening respiratory acidosis on admission to intensive

Figure 2: 15.5 French double-lumen catheter.

care. In light of severe hypercapnia and increasing respiratory acidosis not responding to conventional mechanical ventilation, ECCO2-R with Hemolung® RAS (Figure 1) was initiated to prevent lung injury and secondary brain injury.

A detailed description of Hemolung® has been published previously[7,8]. Extracorporeal circulation was achieved through a 15.5 French double-lumen catheter (Figure 2), and the device consisted of a controller and an integrated pump/gas-exchange cartridge. The priming volume of the cartridge is 144 ml and the blood tubing 115 ml (total priming volume of the circuit is 259 ml). The cartridge and circuit are recommended to be used for up to seven days. The cost of using this device in Australia is about A$10,000.

The right internal jugular vein was cannulated under ultrasound guidance. Limited heparinisation was established with intravenous injection of 80 units of heparin per kilogram body weight. Following limited heparinisation (aiming for an activated clotting time of 150 to 180 seconds), extracorporeal carbon dioxide clearance was initiated. Following the introduction of Hemolung®, it was possible to decrease both the minute ventilation and respiratory rate and optimise the inspiratory to expiratory time ratio to minimise the risk of barotrauma. Excellent clearance of carbon dioxide was achieved through the extracorporeal device.

Over the next three days the improvement in respiratory function facilitated weaning from mechanical ventilation followed by removal of the Hemolung® (Table 1). However, the patient remained mechanically ventilated. The average blood-flow during the course of treatment was 454 ml/minute. The carbon dioxide clearance during the first 24, 48 and 72 hours was 87, 66 and 36 ml/minute, respectively. There were no major complications noted while the patient was on Hemolung®. There was a drop in platelet count from 223×10^9/l at the initiation of Hemolung® to 103×10^9/l, and the platelet count remained stable throughout the course on Hemolung®. There was minor oozing from the cannulation site on the first day which resolved by the second day. There was no requirement for transfusion of blood or platelets during the course of treatment.

After liberation from the Hemolung®, the patient started to show clinical signs of significant hypoxic brain injury, including recurrent generalised myoclonic jerks which were refractory to very high doses of benzodiazepine and propofol infusions, levetiracetam and sodium valproate. His electroencephalogram, obtained three days after the event, revealed suppressed background rhythm and generalised epileptiform discharges. His brainstem reflexes were preserved but a magnetic resonance imaging scan of the brain five days after admission confirmed significant hypoxic ischaemic brain injury. Despite aggressive, multiple anti-epileptic therapies, his myoclonic seizures remained sustained and unresponsive to treatment. By day eight, on the basis of continued myoclonic jerks and significant hypoxic ischaemic brain injury on brain magnetic resonance imaging scan, the neurological prognosis was considered to be extremely poor. The decision to withdraw all life-sustaining therapies and

offer palliation was reached after a family meeting. Consistent with the patient's wishes of being an organ donor he progressed to donation after cardiac death and his kidneys were considered suitable for organ donation.

DISCUSSION

In our patient with severe hypercapnic respiratory failure, the use of Hemolung® was successful and safe in achieving satisfactory carbon dioxide clearance. We used ECCO2-R in our patient, who had an unwitnessed OHCA and end-stage obstructive airway disease as he was on the waiting list for lung transplantation and a short time to return of spontaneous circulation after the initiation of cardiopulmonary resuscitation. Furthermore, the ECCO2-R was minimally invasive. We noted an excellent carbon dioxide clearance soon after initiation of Hemolung®, with carbon dioxide levels approximating normal values despite the reduction in minute ventilation (Table 1). Despite its first use in our ICU, no reported complications were observed during the running of the extracorporeal circuit. Our patient was hypothermic during deployment of the device and pleasingly we did not note any untoward haemorrhagic complications.

Despite the novel approach to carbon dioxide clearance, this patient had several poor prognostic features at presentation. These included an unwitnessed arrest, pulseless electrical activity, severe COPD and hypercapnic acidosis, which may have contributed to the poor outcome[4,9,10]. Patients with COPD who present to hospital with OHCA are known to have a higher mortality than OHCA patients without COPD. COPD was also found to be an independent predictor of mortality in patients presenting with OHCA[10]. The presence of either hypocapnia or hypercapnia is common after cardiac arrest and is independently associated with poor neurological outcome[4]. While the outcome of this patient was unfavourable, we believe ECCO2-R, and other extracorporeal life assist devices in general, may play a vital role in cardiopulmonary resuscitation and post-resuscitation care in some difficult situations.

This report suggests that the use of less invasive low-flow extracorporeal devices is practical and safe in the setting of a metropolitan ICU. The initiation and use of the Hemolung® RAS was accomplished by staff with a limited period of education, and the extracorporeal therapy was delivered without complications. The clearance of carbon dioxide was adequate at about 90 ml/minute during the first 24 hours of use, during

Table 1

Blood gases and Hemolung® RAS parameters

	At initiation	1 hour	6 hours	Day 1	Day 2	Day 3	At removal	24 hours post
pH	7.18	7.26	7.3	7.42	7.41	7.35	7.31	7.36
PaO_2 mmHg (kPa)	470 (62.6)	140 (18.6)	58 (7.7)	94 (12.5)	122 (16.2)	77.5 (10.3)	86 (11.4)	95 (12.6)
$PaCO_2$ mmHg (kPa)	78 (10.4)	53 (7)	51 (6.7)	53 (7)	42 (5.5)	48 (6.3)	57 (7.5)	59 (7.8)
HCO_3 (mmol/l)	23.4	22.1	24.7	24.8	26.2	25.5	28	30.2
Base excess	-1.3	-2.8	0.4	1.1	2	1.2	0.7	6.5
SaO_2 (%)	99.4	98.8	94.6	97	98.7	94.7	98.6	94.7
FiO_2	100	50	60	50	40	30	30	30
Minute ventilation (l/min)	7	6	3	3.5	5.3	4.6	6.4	6.4
PIP (cm H_2O)	38 (PC)	31 (PC)	28 (PC)	29 (PC)	25 (PC)	35 (PC)	17 (PRVC)	31 (PC)
Tidal volume (ml)	380	250	198	263	377	413	335	447
Respiratory rate (/min)	18	12	16	16	12	15	14	14
Hemolung® flow (ml/min)	–	450	480	450	470	390	–	–
Hemolung® sweep (l/min)	–	1.5	10	5.5	5.3	1.1	–	–
CO_2 clearance (ml/min)	–	58	98	81	68	30	–	–
HR (/min)	70	70	55	60	85	90	100	95
MBP (mmHg)	70	70	95	75	75	100	80	90
Noradrenaline (μg/min)	7	6	4	5	1	0	0	0

RAS=respiratory assist system, PIP=peak inspiratory pressure, HR=heart rate, MBP=mean blood pressure, PC=pressure controlled ventilation, PRVC=pressure regulated volume controlled.

which time ventilation was difficult. This permitted optimal conditions for prevention of secondary brain, as well as lung, injury.

In adult patients with severe respiratory failure the use of an ECMO-based protocol was shown to improve survival without severe disability[11]. However, the use of ECMO and conventional extracorporeal carbon dioxide clearance devices is often limited to a few centres because of the cost associated with its establishment, availability of a multidisciplinary team including cardiac surgeons and perfusionists to maintain the circuit, and the training requirements of the attending medical, nursing and paramedical personnel. In addition to costs and complexities, there are also serious potential complications due to the use of large intravascular catheters, systemic anticoagulation and high blood-flow rates[12], which can limit the applicability of these conventional extracorporeal devices only to specialised ICUs.

Several low-flow extracorporeal devices have been introduced to clinical practice in the last two decades[8,13,14]. These devices appear to be effective in reducing arterial carbon dioxide, less invasive and able to provide partial respiratory support. They may, therefore, have a role in managing patients with severe respiratory failure when mechanical ventilation alone is inadequate. As such, these devices are increasingly used in centres that are not capable of initiating ECMO, and may ultimately prove to be preferable to ECMO in the management of severe hypercapnic respiratory failure not responding to mechanical ventilation. Although these devices may aid in lung ultra-protective mechanical ventilation, further studies are required to define whether these devices can reduce mortality and morbidity of patients with refractory hypercapnic respiratory failure.

CONCLUSION

The low-flow ECCO2-R devices are minimally invasive and may be useful in the management of severe hypercapnic respiratory failure refractory to mechanical ventilation.

ACKNOWLEDGEMENTS

We would like to thank Sue Reaper, Emily Vegt, Angelique Clarke and all the nursing staff involved in supporting our patient on Hemolung® RAS during his ICU stay.

CONFLICT OF INTEREST

None of the authors have a commercial association or financial involvement that might pose a conflict of interest in connection with this report. The manufacturers of Hemolung® RAS had no role or influence in the writing of this report. They provided technical assistance and education to the intensive care nurses while the patient was treated with Hemolung® RAS.

REFERENCES

1. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346:557-563.
2. Lindner TW, Langorgen J, Sunde K, Larsen A, Kvaloy J, Heltne J et al. Factors predicting the use of therapeutic hypothermia and survival in unconscious out-of-hospital cardiac arrest patients admitted to the ICU. Crit Care 2013; 17:R147.
3. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122:768-786.
4. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. Circulation 2013; 127:2107-2113.
5. Lund LW, Federspiel WJ. Removing extra CO_2 in COPD patients. Curr Respir Care Rep 2013; 2:131-138.
6. Cove ME, Maclaren G, Federspiel WJ, Kellum JA. Bench to bedside review: Extracorporeal carbon dioxide removal, past present and future. Crit Care 2012; 16:232.
7. Batchinsky AI, Jordan BS, Regn D, Necsoiu C, Federspiel WJ, Morris MJ et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO_2 removal. Crit Care Med 2011; 39:1382-1387.
8. Burki NK, Mani RK, Herth FJF, Schmidt W, Teschler H, Bonin F et al. A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. Chest 2013; 143:678-686.
9. Weaver WD, Cobb LA, Hallstrom AP, Fahrenbruch C, Copass MK, Ray R. Factors influencing survival after out-of-hospital cardiac arrest. J Am Coll Cardiol 1986; 7:752-757.
10. Blom MT, Warnier MJ, Bardai A, Berdowski J, Koster RW, Souverein PC. Reduced in-hospital survival rates of out-of-hospital cardiac arrest victims with obstructive pulmonary disease. Resuscitation 2013; 84:569-574.
11. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009; 374:1351-1363.
12. Tiruvoipati R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. Anaesth Intensive Care 2013; 41:157-162.
13. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 2006; 34:1372-1377.
14. Gramaticopolo S, Chronopoulos A, Piccinni P, Nalesso F, Brendolan A, Zanella M et al. Extracorporeal CO_2 removal–a way to achieve ultraprotective mechanical ventilation and lung support: the missing piece of multiple organ support therapy. Contrib Nephrol 2010; 165:174-184.

6.4 Published manuscript

The Clinical Respiratory Journal CASE REPORT

Low-flow veno-venous extracorporeal carbon dioxide removal in the management of severe status asthmatics: a case report

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Abstract

Status asthmaticus is a life-threatening condition that requires intensive care management. Most of these patients have severe hypercapnic acidosis that requires lung protective mechanical ventilation. A small proportion of these patients do not respond to conventional lung protective mechanical ventilation or pharmacotherapy. Such patients have an increased mortality and morbidity. Successful use of extracorporeal membrane oxygenation (ECMO) is reported in such patients. However, the use of ECMO is invasive with its associated morbidity and is limited to specialised centres. In this report, we report the use of a novel, minimally invasive, low-flow extracorporeal carbon dioxide removal device in management of severe hypercapnic acidosis in a patient with life threatening status asthmaticus.

Please cite this paper as: Tiruvoipati R, Haji K, Gupta S, Braun G, Carney I and Botha J. Low-flow veno-venous extracorporeal carbon dioxide removal in the management of severe status asthmatics: a case report. *Clin Respir J* 2015; ••: ••–••. DOI:10.1111/crj.12252.

Key words
extracorporeal – hypercapnia – respiratory acidosis – status asthmatics

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Received: 21 May 2014
Revision requested: 18 November 2014
Accepted: 07 December 2014

DOI:10.1111/crj.12252

Authorship and contributorship

RT: Conception and design, acquisition of data, and interpretation of data, drafting the manuscript or revising it critically for important intellectual content; have given final approval of the version to be published.
KH: Acquisition of data, and interpretation of data, revising manuscript critically for important intellectual content; have given final approval of the version to be published.
SG: Revising manuscript critically for important intellectual content; have given final approval of the version to be published.
GB: Revising manuscript critically for important intellectual content; have given final approval of the version to be published.
IC: Revising manuscript critically for important intellectual content; have given final approval of the version to be published.
JB: Revising manuscript critically for important intellectual content; have given final approval of the version to be published.

Ethics

The Human Research and Ethics Committee of Peninsula Health approved the use of Hemolung in our intensive care unit. Approval was also obtained from the Therapeutic Goods Administration (TGA) Australia for using Hemolung. Consent from the patient was obtained to allow reporting of this case.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Introduction

Status asthmaticus, or acute severe asthma, is the term used to refer to an exacerbation of asthma that does not respond to usual pharmacotherapy. Patients with severe asthma are often admitted to intensive care units (ICUs) for observation and management that may include non-invasive mechanical ventilation. However, a small proportion do not respond to these measures and will require invasive mechanical ventilation (IMV). Although precise epidemiology figures are lacking, it is estimated that about 30% of medical ICU

admissions for acute severe asthma require intubation and mechanical ventilation. The mortality of these patients on mechanical ventilation is increased with a mortality of 8% in published studies (1). Several ventilator strategies have been adopted to help minimise complications such as barotrauma and auto-positive end-expiatory pressure, leading to dynamic hyperinflation. While these strategies have reduced these complications, they are not always effective. Extracorporeal membrane oxygenation as an adjunct to mechanical ventilation for status asthmaticus was first reported in 1981 (2), and a number of subsequent reports have shown positive outcomes with this therapy (3–5).

We report a novel minimally invasive veno-venous extracorporeal carbon dioxide removal ($ECCO_2R$) technique that was used in treating a patient with life-threatening, refractory status asthmatics when mechanical ventilation was unsuccessful.

Case report

A 44-year-old male with a history of asthma presented to his general practitioner with acute shortness of breath. His asthma had been well controlled in the past, and he had not been previously admitted to hospital with an exacerbation of asthma. He was a known smoker and had experienced symptoms suggestive flu for a few days prior to presentation. After clinical examination, his general practitioner suspected an exacerbation of asthma with a possible pneumothorax. Because of severe dyspnoea and significant desaturation, the patient was immediately transferred to the Frankston Hospital emergency department (ED) via ambulance. Shortly after presentation to the ED, he suffered respiratory arrest. A short period of resuscitation included endotracheal intubation, IMV and decompression of a tension pneumothorax via placement of a left chest drain. Following a brief period of improvement, he again deteriorated and a second tension pneumothorax was identified in the patient's right side, requiring placement of an additional chest drain. Admission to the ICU followed. While in intensive care, he required a third chest drain due to worsening pneumothorax in the right chest consequent to poor drainage of air from the existing chest drain.

Over the next 48 h in the ICU, the patient continued to deteriorate with the development of significant subcutaneous emphysema and ongoing air leaks. By the third day, he had become very difficult to ventilate with uncontrollable hypercapnia (arterial CO_2 tension, $PaCO_2$ was 73 mmHg, with pH 7.22) and worsening

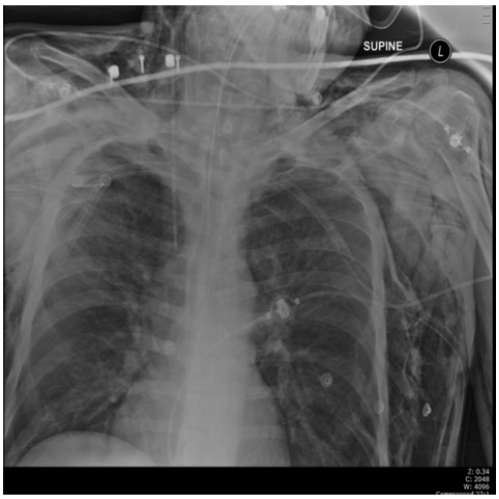

Figure 1. Chest X ray prior to initiation of Hemolung showing extensive surgical emphysema and multiple chest drains.

surgical emphysema (Fig. 1) despite optimal medical management including the use of corticosteroids, nebulised (salbutamol and ipratropium) and intravenous bronchodilators (aminophylline), magnesium, ketamine and muscle relaxants. $ECCO_2R$ was indicated to control the hypercapnia and facilitate de-escalation of IMV.

$ECCO_2R$ with Hemolung RAS^R (ALung Technologies, Inc., Pittsburgh, PA, USA) was initiated to facilitate carbon dioxide clearance and reduce barotrauma. A detailed description of Hemolung has been published previously (6, 7). The application of this device consisted of a 15.5 French double lumen catheter, a controller and an integrated pump/gas-exchange cartridge. The right internal jugular vein was cannulated under ultrasound guidance. Intravenous heparin (80 U/Kg) was given to aim for limited heparinisation (aiming for an ACT of 150 to 180 s). The Hemolung RAS circuit was then connected to the catheter, and $ECCO_2R$ was initiated. Extracorporeal blood flow was established at 470 mL/min, and the sweep gas was gradually increased to 10 L/min to provide $ECCO_2R$ of approximately 100 mL/min as measured by the Hemolung Controller (Table 1). Following the introduction of Hemolung, it was possible to decrease the support on mechanical ventilation while maintaining satisfactory gas exchange and allowing to withdraw the use of muscle relaxants. Excellent clearance of carbon dioxide was achieved through the extracorporeal device.

Table 1. Blood gasses and Hemolung RAS parameters

	Before initiation	At initiation	1 h	6 h	Day 1	Day 2	Day 3	At removal	24 h post-removal
pH	7.22	7.24	7.28	7.33	7.31	7.39	7.44	7.42	7.39
PaO2 (mmHg)	96	92.5	77.1	65.9	62.1	66.9	87.4	76.9	77.2
PaCO2 (mmHg)	73	68.1	60.6	53.6	57.5	64.7	57.1	45.2	60
HCO3	25	25.1	25.3	28.9	26.6	36	38.5	34.4	34
Base excess	0.6	0.6	1.0	2.0	2.6	12.9	14.7	8.8	9.2
SaO2	98	97.1	95.4	95.3	92.9	94.9	98.7	96.1	95
FiO2	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.55	0.4
Mode of mechanical ventilation	Bi-level	Bi-level	Bi-level	Bi-level	Bi-level	Bi-level	SIMV VC	SIMV VC	SIMV VC
Minute ventilation (L)	5.5	5.7	5.1	5.2	4.9	4.8	5.1	8.9	8.4
Peak inspiratory pressures	34	34	34	32	32	26	27	28	30
Tidal vol	460	460	450	450	449	455	420	497	480
Resp rate	12	12	12	12	10	10	14	18	18
Hemolung flow (mL/min)		470	540	540	540	530	550	540	
Hemolung sweep (L/min)		6	10	10	10	10	10	4.1	
Carbon dioxide clearance (mL/min)		75	105	94	100	105	101	81	
Heart rate	77	75	65	65	67	90	80	100	105
Mean blood pressure (mmHg)	78	85	100	92	95	105	90	92	75

Tidal volume and minute ventilation may not be accurate because of air leaks from three chest drains.
SIMV, synchronised intermittent mandatory ventilation; VC, volume control.

Over the next 48 h, the patient showed signs of improvement with a substantial decrease in the surgical emphysema. However, the air leaks from the three chest drains continued. On the third day on $ECCO_2R$, the chest drain on the left side blocked and the drain was replaced to resolve another tension pneumothorax. Bleeding within the chest was noted as evidenced by a fall in haemoglobin and haziness on the chest X-ray. This was managed by blood transfusion (three units) and a reduction of systemic anticoagulation. $ECCO_2R$ was continued for a total of 7 days until respiratory function had substantially improved. Following the discontinuation of $ECCO_2R$, the patient had video-assisted thoracoscopic surgery for evacuation of haematoma in left pleural cavity and was tracheostomised to assist in weaning from IMV. He was weaned off from mechanical ventilation and was discharged to a ward after 23 days of ICU stay. He was transferred to a rehabilitation facility 3 days later and ultimately discharged home.

Discussion

We report the successful use of a novel low flow $ECCO_2R$ device in the management of severe hypercapnia and barotrauma in a patient with life threatening status asthmaticus. In most cases of bronchial asthma, maintenance of oxygenation is not difficult. However, hypercapnia secondary to alveolar hypoventilation and gas trapping cause severe respiratory acidosis and may increase mortality and morbidity.

This patient had severe asthma that precipitated respiratory arrest soon after arrival to our ED. The asthma was resistant to conservative measure including the use of bronchodilators, steroids and lung protective ventilation. The barotrauma this patient sustained was so profound that it ultimately precluded mechanical ventilation, making $ECCO_2R$ the only remaining treatment option. Extracorporeal membrane oxygenation (ECMO) may have been beneficial in this patient, and several reports have confirmed the use of ECMO in managing severe hypercapnic respiratory failure (2, 8, 9). Furthermore, the use of ECMO is increasing, and the complications associated with the use of ECMO is reduced with modern ECMO cannulae and circuts (10). Nevertheless, the use of ECMO is still limited to specialised centres and requires a multidisciplinary approach for a successful outcome. The availability of ECMO in only specialised centres usually requires the transfer of patients who have severe respiratory failure with associated risks.

Successful reports of other less invasive devices such as Novalung iLA (Novalung GmbH, Heilbronn, Germany) were reported (4, 5). Novalung iLA is driven

by the patient's cardiac output and therefore does not require extracorporeal pump assistance. However, the use of such devices implies a more invasive approach than the use of Hemolung as it requires cannulation of femoral artery. The reported rate of lower limb ischemia is over 24%, making this device less attractive in the management of hypercapnic respiratory failure (11). These devices are also not indicated in patients with inadequate cardiac output.

Contrary to these devices, the use of Hemolung appears to be minimally invasive with excellent carbon dioxide clearance. It does not require larger cannulae as for ECMO or arterial cannulation for iLA. However, Hemolung does not improve oxygenation. In status asthmaticus patients with severe hypoxemia, ECMO remains the only management option. The only complication we noted in our patient after initiation of Hemolung was a haemothorax occurring after drainage of a tension pneumothorax. As this was a medical emergency, it was not possible to reduce anticoagulation, which may have reduced the risk of haemothorax substantially.

To conclude, the use of low-flow venovenous $ECCO_2R$ was successful in treating severe hypercapnia in our patient with status asthmatics. Such devices are simpler to use than ECMO and may reduce the need of ECMO in patients with severe hypercapnia. Awareness and appropriate use of such devices may improve the mortality and morbidity of patients with status asthmaticus.

Acknowledgements

We would like to thank Sue Reaper, Emily Vegt, Angelique Clarke and all the nurses involved in supporting our patient on Hemolung RAS during his ICU stay. The manufactures of Hemolung RAS have no role or influence in the writing this report. They provided technical assistance and education to the intensive care nurses while the patient was treated with Hemolung RAS

References

1. McFadden ER Jr. Acute severe asthma. Am J Respir Crit Care Med. 2003;168: 740–59.
2. MacDonnell KF, Moon HS, Sekar TS, Ahluwalia MP. Extracorporeal membrane oxygenator support in a case of severe status asthmaticus. Ann Thorac Surg. 1981;31: 171–5.
3. Brenner K, Abrams DC, Agerstrand CL, Brodie D. Extracorporeal carbon dioxide removal for refractory status asthmaticus: experience in distinct exacerbation phenotypes. Perfusion. 2014;29: 26–8.
4. Aravantagi A, Patra KP, Shekar S, Scott LK. Pumpless arteriovenous carbon dioxide removal: a novel simplified strategy for severe asthma in children. Indian J Crit Care Med. 2011;15: 224–6.
5. Lobaz S, Carey M. Rescue of acute refractory hypercapnia and acidosis secondary to life-threatening asthma with extracorporeal carbon dioxide removal ($ECCO_2R$). JICS. 2011;12: 140–2.
6. Batchinsky AI, Jordan BS, Regn D, *et al.* Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal. Crit Care Med. 2011;39: 1382–7.
7. Burki NK, Mani RK, Herth FJ, *et al.* A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. Chest. 2013;143: 678–86.
8. Peek GJ, Mugford M, Tiruvoipati R, *et al.* Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374: 1351–63.
9. Shapiro MB, Kleaveland AC, Bartlett RH. Extracorporeal life support for status asthmaticus. Chest. 1993;103: 1651–4.
10. Tiruvoipati R, Botha J, Peek G. Effectiveness of extracorporeal membrane oxygenation when conventional ventilation fails: valuable option or vague remedy? J Crit Care. 2012;27: 192–8.
11. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX, Butz B, Birnbaum D, Taeger K, Schlitt HJ. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med. 2006;34: 1372–7.

6.5 Chapter summary

This chapter presented the initial use of Hemolung RAS for feasibility and safety as an extracorporeal carbon dioxide removal device. From the initial experience it appeared that Hemolung use is feasible in a centre such as Frankston Hospital that currently does not have the capabilities of using extracorporeal membrane oxygenation (ECMO). The case reports define the first use of this device in Australia. The first case report was published with an editorial (Appendix 16) titled *"Extracorporeal respiratory support: breaking conventions?* This editorial discusses and highlights the possible expanding use of extracorporeal therapies in intensive care practice in achieving a short-term physiological target as well as the need for more experience on case selection to achieve the best possible outcomes with the use of these devices.

To investigate Hemolung RAS further, we collaborated with three other centres that started using Hemolung RAS to evaluate the generalisability of the use of Hemolung RAS in hypercapnic respiratory failure.

CHAPTER 7: Early experience of a novel extracorporeal device in management of hypercapnic acidosis

7.1 Chapter Introduction

In the previous chapter the feasibility and safety of Hemolung RAS was presented. This chapter provides details on the use of Hemolung RAS in two further centres to evaluate its feasibility, safety, efficacy and generalisability in treating hypercapnic acidosis. Each of these three centres had different expertise in the use of extracorporeal life support systems. This study provides the combined experience of using Hemolung RAS in acute hypercapnic acidosis.

7.2 Published Manuscript

Early experience of a new extracorporeal carbon dioxide removal device for acute hypercapnic respiratory failure

Ravindranath Tiruvoipati, Hergen Buscher, James Winearls, Jeff Breeding, Debasish Ghosh, Shimonti Chaterjee, Gary Braun, Eldho Paul, John F Fraser and John Botha

ABSTRACT

Background: Recent advances in the technology of extracorporeal respiratory assist systems have led to a renewed interest in extracorporeal carbon dioxide removal (ECCOR). The Hemolung is a new, low-flow, venovenous, minimally invasive, partial ECCOR device that has recently been introduced to clinical practice to aid in avoiding invasive ventilation or to facilitate lung-protective ventilation.

Objective: We report our early experience on use, efficacy and safety of the Hemolung in three Australian intensive care units.

Methods: Retrospective review of all patients with acute or acute-on-chronic respiratory failure (due to chronic obstructive pulmonary disease [COPD] with severe hypercapnic respiratory failure when non-invasive ventilation failed; acute respiratory distress syndrome; COPD; or asthma when lung-protective ventilation was not feasible due to hypercapnia) for whom the Hemolung was used.

Results: Fifteen patients were treated with ECCOR. In four out of five patients, the aim of avoiding intubation was achieved. In the remaining 10 patients, the strategy of instituting lung-protective ventilation was successful. The median duration for ECCOR was 5 days (interquartile range, 3–7 days). The pH and P_{CO_2} improved significantly within 6 hours of instituting ECCOR, in conjunction with a significant reduction in minute ventilation. The CO_2 clearance was 90–100 mL/min. A total of 93% of patients survived to weaning from ECCOR, 73% survived to ICU discharge and 67% survived to hospital discharge.

Conclusion: Our data shows that ECCOR was safe and effective in this cohort. Further experience is vital to identify the patients who may benefit most from this promising therapy.

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Clinical application of extracorporeal carbon dioxide removal (ECCOR) for acute hypercapnic respiratory failure was first reported in 1979.[1] Initial reports on patients with severe acute respiratory distress syndrome (ARDS) who were not responding to conventional ventilation and were treated using ECCOR appeared to be encouraging.[2,3] However, when subjected to a randomised controlled trial, ECCOR appeared to offer no benefit compared with conventional ventilation.[4] Several reasons were proposed for this lack of benefit, including the complexity of the technology of ECCOR, the circuit design, anticoagulation management and case selection.[5] These factors have restricted the use of ECCOR in routine clinical practice until recently.

Several minimally invasive extracorporeal respiratory support systems with substantial improvements in technology have recently been introduced into clinical practice. These aim to enable lung-protective ventilation while preventing hypercapnic acidosis in patients with ARDS.[6-9] Minimally invasive extracorporeal systems usually have a short, heparin-coated circuit with an integrated centrifugal pump, an efficient gas exchanger and a small priming volume to avoid haemodilution.[10] They are distinguished from more invasive extracorporeal membrane oxygenation (ECMO) by reduced blood flow (0.4–0.6 L/min v 3–5 L/min), smaller cannulae (14–15.5 Fr v 21–31 Fr) and avoidance of arterial cannulation and its associated complications.

Abbreviations

ACT	activated clotting time
APACHE	Acute Physiology and Chronic Health Evaluation
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
BOS	bronchiolitis obliterans syndrome
COPD	chronic obstructive pulmonary disease
ECCOR	extracorporeal carbon dioxide removal
ECMO	extracorporeal membrane oxygenation
ICC	intercostal catheter
ICU	intensive care unit
IQR	interquartile range
LPV	lung-protective ventilation
PIP	peak inspiratory pressure
RAS	Respiratory Assist System
TGA	Therapeutic Goods Administration
VATS	video-assisted thoracoscopic surgery

The use of ECCOR has been reported to facilitate ultra-protective lung ventilation, with tidal volume reduced to less than 6 mL/kg — an outcome that could not be achieved with mechanical ventilation alone.[8,9] It has been suggested that these devices could have a positive impact on the management of refractory acute respiratory failure.[11,12]

The Hemolung Respiratory Assist System (RAS) (ALung Technologies) is a new, minimally invasive, low-flow ECCOR device. Other ECCOR devices were introduced as an adjunct to ARDS management, but the clinical use of the Hemolung was first reported in a series of 20 patients with chronic obstructive pulmonary disease (COPD) and failure to wean from mechanical ventilation.[13] That report only showed data until 30 days and provided no hospital discharge data.

The use of compl ex extracorporeal respiratory support systems, such as ECMO, has traditionally been restricted to large centres with a cardiothoracic service. However, the currently available, minimally invasive extracorporeal respiratory assist systems may be successfully used in intensive care units that do not have cardiac surgical services but are familiar with other extracorporeal therapies, such as renal replacement therapy.

With this clinical context, we retrospectively analysed the data on the use of the Hemolung in three Australian ICUs with varying casemixes and expertise in extracorporeal therapies. We analysed the data to assess the efficacy of the Hemolung in CO_2 clearance, and feasibility and safety in managing patients with acute or acute-on-chronic hypercapnic respiratory failure.

Methods

Ethics approval and consent

The human research and ethics committees of all ICUs approved the use of the Hemolung. Approval was also obtained from the Australian Therapeutic Goods Administration (TGA) for 11 patients, as these patients were treated with the Hemolung before formal TGA approval of this device in Australia. The human research ethics committees of Peninsula Health (QA/16/PH/4), St Vincent's Hospital (file number 10/218) and Gold Coast Health Service District (HREC/16/QGC/78) reviewed the study proposal and waived the requirement for full ethics committee application. This was because the study was seen as a retrospective audit of data routinely collected for patient care and was not experimental research. Consent from individual patients was not required, as the research was limited to the use of information previously collected in the course of normal care and the patients were not identifiable.

Centres

The three centres where the Hemolung was used were Frankston Hospital, Melbourne, Australia (Centre 1), which is a metropolitan hospital with no cardiac surgery or ECMO services; St Vincent's Hospital, Sydney, Australia (Centre 2), where cardiac surgery and ECMO services are available; and the Gold Coast University Hospital, Gold Coast, Australia (Centre 3), which offers cardiac surgery services but no ECMO service (at the time of the study).

Patients

We included all patients with acute or acute-on-chronic hypercapnic respiratory failure who were managed with ECCOR in the three ICUs. The Hemolung was used either to avoid intubation or to institute lung-protective ventilation.

Patients were managed with the Hemolung at the discretion of the intensivist if they had severe hypercapnic respiratory failure, were on non-invasive mechanical ventilation for at least 1 hour and were not responsive to non-invasive mechanical ventilation (defined as having a pH < 7.25, P_{CO_2} > 55 mmHg and/or a high likelihood of requiring invasive mechanical ventilation).

We also included patients who were on invasive mechanical ventilation but could not be ventilated with lung-protective ventilation (tidal volumes ≤ 6 mL/kg of ideal body weight) due to hypercapnic respiratory failure (pH < 7.2).

Contraindications to ECCOR included:

- limited anticoagulation (heparinisation to achieve an activated partial thromboplastin time [APTT] of 50–70 seconds or an activated clotting time [ACT] of 150–180 seconds)
- platelet count < 75 000/mm^3
- patients who had treatment limitations in place.

Outcome measures

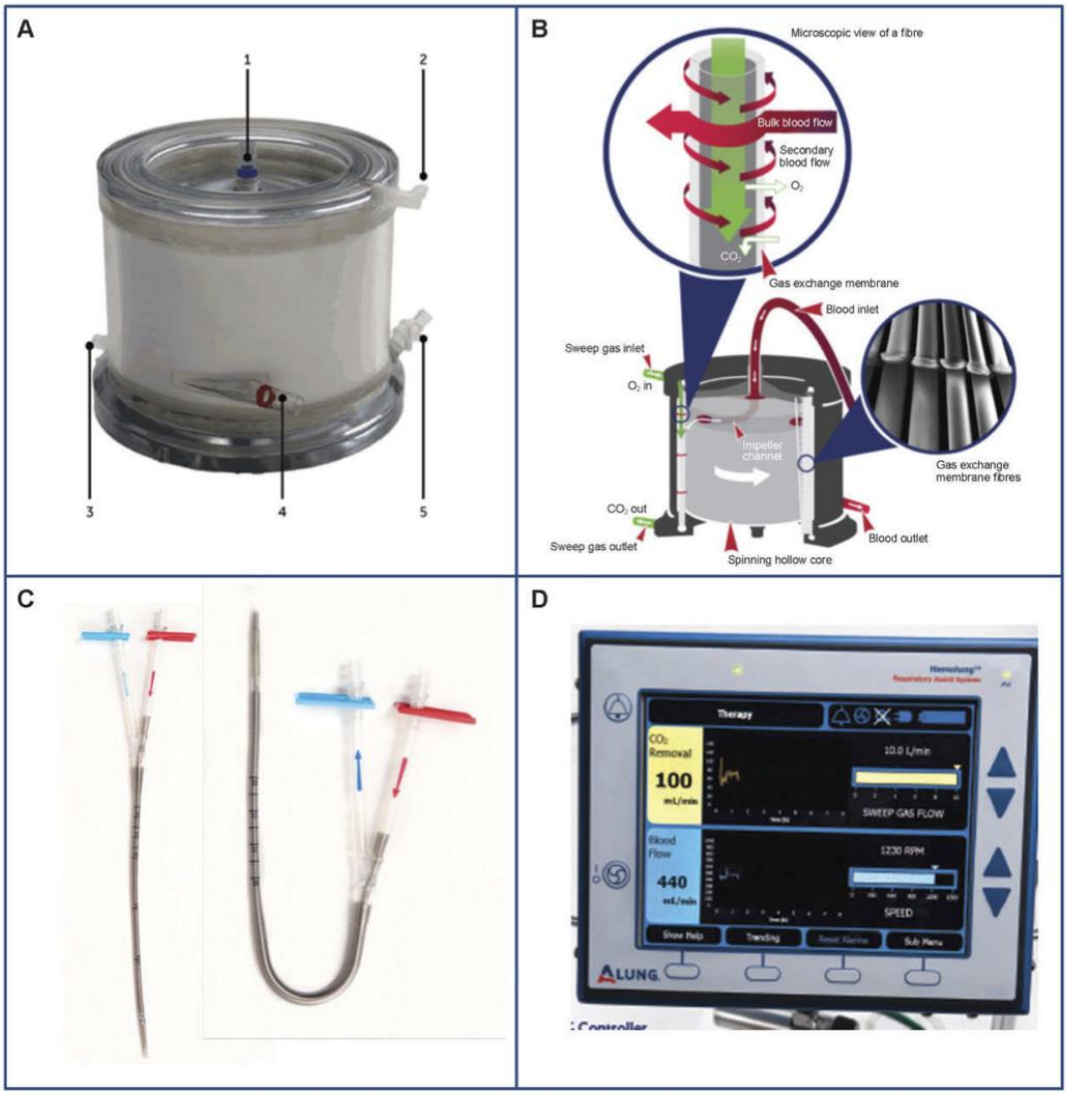
The primary outcome measure was clearance of CO_2 and change in pH with the use of ECCOR. Secondary outcome measures included complications associated with Hemolung use, survival to weaning from Hemolung, and survival to ICU and hospital discharge.

Equipment

The Hemolung RAS is a minimally invasive partial ECCOR device including an integrated gas exchanger, centrifugal blood pump, and low prime volume circuit with a dual lumen 15.5 Fr venous access cannula. A detailed description of Hemolung and its management has been published previously.[6,13] The device consists of three main components including a catheter, cartridge and controller (Figure 1).

A 15.5 Fr double-lumen catheter (Figure 1) that could be inserted via the jugular vein (catheter length, 17 cm) or the femoral vein (catheter length, 26 cm) was used. The Hemolung cartridge consists of an integrated pump and a membrane that facilitates gas exchange. The hollow-core pump spins within a cylindrical bundle of hollow-fibre membranes, integrating pump and gas exchanger within a single component. This design aims to offer simplicity

Figure 1. Components of Hemolung Respiratory Assist System



A. Cartridge: (1) blood flow inlet, (2) sweep gas inlet, (3) sweep gas outlet, (4) blood flow outlet, (5) seal flush port with one-way valve.
B. Cross-section of cartridge showing blood flow and gas exchange in cartridge. C. Femoral catheter (15.5 Fr, 17 cm) on left; jugular catheter (15.5 Fr, 26 cm) on right. D. Controller.

Source: ALung Technologies.

with no need for a heat exchanger and a more efficient gas exchange than the traditional extracorporeal respiratory support devices. The controller shows pump speed, blood flow rate, gas flow and the amount of CO_2 that is being cleared, as real-time data. Two control settings are available, one to change pump speed to adjust the blood flow rate, and a second one to adjust sweep gas flow (0–10 L of air or oxygen) that determines the amount of CO_2 removal.

Patient management

Catheter insertion was performed using real-time ultrasound guidance. Heparin was used for anticoagulation, aiming for an APTT of 50–70 seconds or an ACT of 150–180 seconds. The Hemolung circuit was then connected to the catheter and ECCOR was initiated. Blood flow was established at a rate between 450 mL/min and 550 mL/min. Sweep gas was gradually increased to 10 L/min to provide ECCOR of about 90–100 mL/min, as measured by the Hemolung controller. The sweep gas was subsequently titrated to ensure adequate CO_2 clearance, as determined by the patient's blood gas levels and the ventilator settings. After lung recovery (at the discretion of the treating clinician), Hemolung weaning was initiated by reduction in sweep gas flow, thereby reducing the amount of CO_2 removal to zero. After confirming adequate respiratory function without sweep gas flow, the Hemolung was disconnected from the patient and the cannula removed.

There was no pre-specified protocol for management of mechanical ventilation across the three centres, but all centres used low-volume, low-pressure ventilation for patients with ARDS.[14] Mechanical ventilation for asthma was provided with a low tidal volume (5–7 mL/kg), a low respiratory rate (10–12 breaths/min) and a short inspiratory time associated with prolonged expiratory time to avoid dynamic hyperinflation.

Statistical analysis

All data analyses were performed using SAS, version 9.4 (SAS Institute) and SPSS, version 22 (IBM SPSS). We assessed changes in pH, P_{CO_2}, P_{O_2}, peak inspiratory pressure (PIP) and minute ventilation from baseline values before initiation of Hemolung and at successive time points. To account for repeat measures, data were analysed using the PROC MIXED procedure in SAS, with each patient treated as a random effect. Results are presented as means and standard errors. Time was treated as a categorical variable to facilitate specific comparisons. A two-sided $P < 0.05$ was chosen to indicate statistical significance.

Results

Fifteen patients were treated in three intensive care units, and their data are shown in Table 1. The primary diagnoses were ARDS in five patients and COPD in five patients, with acute severe asthma in two patients, cardiac arrest due to COPD in one patient, cardiac arrest due to asthma in one patient, and bronchiolitis obliterans syndrome (BOS) in one patient.

In five patients (four with COPD and one with BOS), the indication was to avoid intubation, and this was achieved in four patients. In 10 patients (five with acute lung injury or ARDS, three with asthma and two with COPD), the indication was to institute lung-protective ventilation, and this strategy was successful in all patients, as shown by a reduction in PIP, tidal volume and minute ventilation. The median age of patients was 61.5 years (interquartile range [IQR], 44.7–68.7 years) and 12 patients (80%) were men. The median Acute Physiology and Chronic Health Evaluation III score was 85 (IQR, 44–98), and the most common access site was the jugular vein (10 patients, 67%). The median duration of ECCOR was 5 days (IQR, 3–7 days). Six patients were on concurrent renal replacement therapy.

The clearance of CO_2 and return of P_{CO_2} to near-normal levels was achieved within 6 hours (Table 2, Figure 2). The pH correction matched the return of the P_{CO_2} level to normal. With the institution of the Hemolung, a significant reduction in minute ventilation and peak airway pressures was achieved (Figure 3, Table 2). There was no significant change in P_{O_2} (Table 2, Figure 2). The CO_2 clearance was 90–100 mL/min and the blood flow rates were about 450 mL/min (Figure 4).

Complications

Haemorrhage occurred in seven patients, most of which was minor and stopped with reduction of anticoagulant agents and administration of blood products. Haemorrhages included catheter site insertion bleeding, haematuria, gastrointestinal bleeding, and a haemothorax that required video-assisted thoracoscopic surgery for drainage. Packed red cells were used in 12 patients (80%), with a median transfusion volume of two packed cell units (IQR, 1–7 units).

Four patients had thrombocytopenia requiring platelet transfusion. Haemodynamic instability was noted at the time of initiation of ECCOR in two patients, both of whom required inotropic support that they were subsequently weaned off.

One patient developed compartment syndrome during Hemolung support and associated anticoagulation therapy, after a cannulation attempt of the brachial artery for arterial access.

Survival

Overall, 93.3% of the patients survived to discontinuation of ECCOR, 73.3% to ICU discharge and 66.6% to hospital discharge. All patients treated for ARDS and acute severe asthma were discharged from hospital. Three out of five patients treated for COPD (60%) were discharged from hospital. Both patients who had a cardiac arrest were successfully weaned from ECCOR support but both patients died in hospital due to severe anoxic brain injury. The patient with BOS could not be weaned from the Hemolung and died while on Hemolung support (see Table 1). No patient died due to a complication from the Hemolung.

Table 1. Summary of data for patients managed with Hemolung Respiratory Assist System

Centre no.	Age (years)	Diagnosis	ECCOR indication	Intubated	ECCOR duration (days)	ECCOR complications	Survival to ECCOR removal	Survival to ICU discharge	Survival to hospital discharge	Cause of death
1	74	COPD exac.	AI	No	8.4	Catheter site bleeding	Yes	No	No	COPD
2	59	COPD exac.	AI	No	4.0	NA	Yes	Yes	Yes	–
2	37	Stage 3 BOS	AI	No	1.0	Seizure	No	No	No	BOS
2	63	COPD exac.	AI	No	2.1	NA	Yes	Yes	Yes	–
1	68	COPD exac.	AI	Yes	5.7	Haematuria	Yes	Yes	Yes	–
1	60	Asystolic cardiac arrest secondary to COPD	LPV	Yes	2.7	NA	Yes	No	No	Severe anoxic brain injury
1	44	Asthma exac.	LPV	Yes	5.8	Haemothorax after ICC insertion requiring VATS	Yes	Yes	Yes	–
1	49	Cardiac arrest secondary to asthma	LPV	Yes	2.6	NA	Yes	Yes	No	Severe anoxic brain injury
1	66	Resp. arrest with COPD exac.	LPV	Yes	6.2	NA	Yes	No	No	Candida sepsis and multi-organ failure
1	23	Aspiration pneum.	LPV	Yes	1.9	Gastric bleeding	Yes	Yes	Yes	–
2	–	ARDS, pneum.	LPV	Yes	4.0	NA	Yes	Yes	Yes	–
2	45	Influenza B, asthma	LPV	Yes	5.0	Compartment syndrome, haematoma	Yes	Yes	Yes	–
3	64	ARDS, pneum.	LPV	Yes	6.9	NA	Yes	Yes	Yes	–
3	71	ARDS, pneum.	LPV	Yes	9.7	Haemorrhage, thrombocytopenia	Yes	Yes	Yes	–
3	71	ARDS, pneum.	LPV	Yes	6.6	Haemorrhage	Yes	Yes	Yes	–

ECCOR = extracorporeal carbon dioxide removal. ICU = intensive care unit. COPD = chronic obstructive pulmonary disease. exac. = exacerbation. AI = avoiding intubation. NA = not applicable. BOS = bronchiolitis obliterans syndrome. LPV = lung-protective ventilation prevented by management of severe hypercapnia. ICC = intercostal catheter. VATS = video-assisted thoracoscopic surgery. Resp. = respiratory. pneum. = pneumonia. ARDS = acute respiratory distress syndrome.

Discussion

In our study, we discuss the use of the Hemolung in 15 patients in three ICUs with different expertise in the management of extracorporeal support systems. Our primary aim was to assess the efficiency of CO_2 clearance. This ECCOR device was effective in correcting hypercapnia and improving pH, in conjunction with a significant reduction in minute ventilation and PIPs.

In our limited experience, its use appears to be safe and it appears to have no major complications (such as circuit clotting due to inadequate anticoagulation, or fatal retroperitoneal bleeding during catheterisation, as in earlier reports[12]). Most of the complications we noted were minor and did not require withdrawal from the Hemolung.

Intracranial bleeding is one of the most serious complications of extracorporeal life supports. A recent study by Luyt and colleagues,[15] on neurological events during venovenous ECMO, showed an association between rapid reduction in Pco_2 and intracranial bleeding. Given the limited experience with the Hemolung and other similar low-flow extracorporeal devices, it is difficult to ascertain such association with these devices. No patients in our cohort suffered intracranial bleeding.

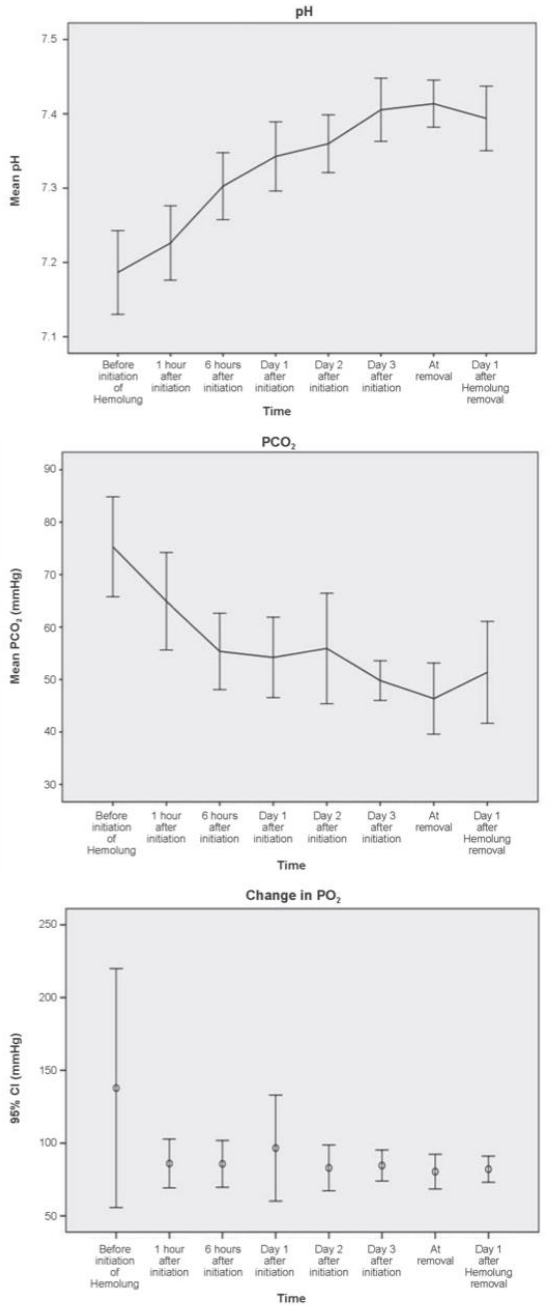
The proportion of patients who required blood transfusions was 80% (median volume, 2 units of packed red cells). While this proportion appeared to be lower than blood transfusion requirements reported with comparable low-flow partial respiratory support systems,[16] further experience in the use of the Hemolung and anticoagulation management is essential to reduce the need for blood and blood products. Furthermore, six of our patients were on renal replacement therapy concurrently with the Hemolung. Replacement of circuits during renal replacement therapy is known to be associated with blood loss,[17] and this may have contributed to the requirement for blood transfusions.

The prediction of potential reversibility is an important aspect in patient selection when instituting advanced

Table 2. Estimated mean changes in minute ventilation, peak inspiratory pressure, $Paco_2$, Pao_2 and pH before initiation and at successive time points

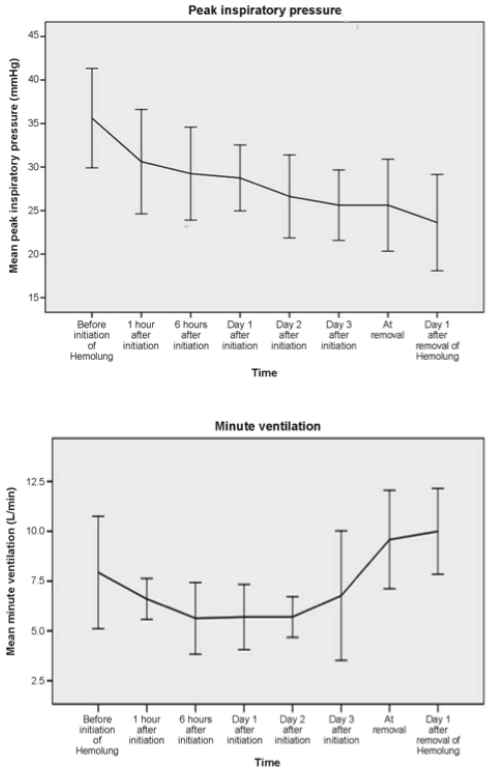
Variable	Estimated change from before initiation	Standard error	*P*
Minute ventilation			
1 hour	3.145	1.188	0.010
6 hours	3.632	1.214	0.004
Day 1	3.618	1.230	0.005
Day 2	3.454	1.231	0.007
Day 3	2.126	1.271	0.099
At removal	–0.407	1.216	0.739
24 hours after removal	–1.981	1.231	0.113
Peak inspiratory pressure			
1 hour	3.429	2.256	0.134
6 hours	4.070	2.347	0.088
Day 1	4.602	2.402	0.060
Day 2	7.562	2.465	0.003
Day 3	6.023	2.538	0.021
At removal	6.220	2.465	0.014
24 hours after removal	9.723	2.621	< 0.0001
$Paco_2$			
1 hour	9.653	3.515	0.007
6 hours	19.844	3.590	< 0.0001
Day 1	18.967	3.515	< 0.0001
Day 2	19.077	3.670	< 0.0001
Day 3	24.826	3.869	< 0.0001
At removal	27.916	3.590	< 0.0001
24 hours after removal	23.771	3.672	< 0.0001
Pao_2			
1 hour	44.287	27.381	0.110
6 hours	37.502	27.471	0.176
Day 1	33.700	27.381	0.222
Day 2	44.538	27.567	0.110
Day 3	40.537	27.815	0.149
At removal	45.180	27.471	0.104
24 hours after removal	43.663	27.571	0.117
pH			
1 hour	–0.029	0.018	0.112
6 hours	–0.096	0.019	< 0.0001
Day 1	–0.131	0.018	< 0.0001
Day 2	–0.167	0.019	< 0.0001
Day 3	–0.211	0.021	< 0.0001
At removal	–0.219	0.019	< 0.0001
24 hours after removal	–0.212	0.019	< 0.0001

Figure 2. Changes in pH, Pco_2 and Po_2 before initiation and at successive time points



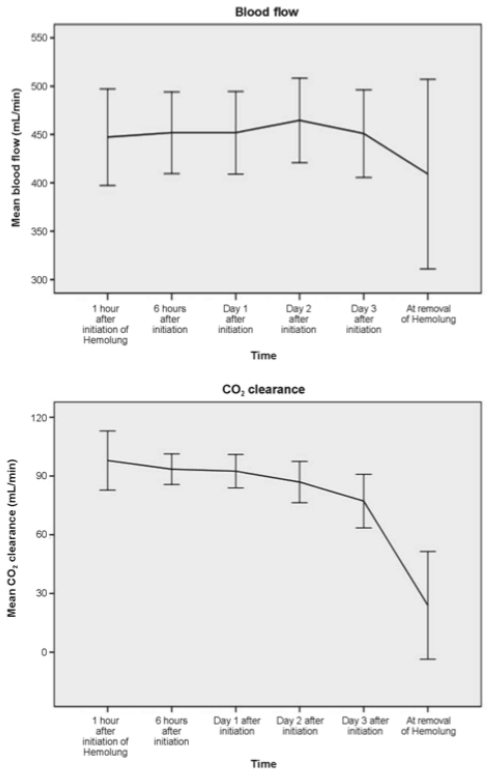
Error bars: 95% CIs.

Figure 3. Changes in peak inspiratory pressure and minute ventilation before initiation of Hemolung and at successive time points



Error bars: 95% CIs.

Figure 4. Changes in blood flow and CO_2 clearance before initiation of Hemolung and at successive time points



Error bars: 95% CIs.

respiratory support systems such as ECMO and ECCOR. The use of ECMO for ARDS over the past three decades, in conjunction with established registries (such as the Extracorporeal Life Support Organization), have contributed to intensivists gaining significant experience in patient selection. This experience has led to the development of scoring systems that may be useful in predicting the appropriateness of these devices for patients with ARDS.[5,18,19] Therefore, the use of extracorporeal respiratory support devices such as ECCOR may now prove to be more successful than previously reported devices. The use of ECCOR in patients with COPD and other chronic respiratory conditions is very limited, and further experience is vital to understand the role of ECCOR in COPD and other causes of acute-on-chronic respiratory failure.

The mortality of patients with ARDS is reducing with modern intensive care practice,[20] but mortality is still high.[20,21] Further mortality and morbidity reduction appears to be feasible if driving pressures and tidal volume ventilation can be reduced.[9,22] Technologies working in conjunction with mechanical ventilation may be required to achieve this reduction. In severe ARDS, the introduction of ECMO has been shown to improve outcome.[5] In the context of mild-to-moderate ARDS, such treatment is not indicated because of its invasiveness and the associated risk of complications. Minimally invasive and effective devices such as the Hemolung may aid in lung-protective ventilation with a lower risk. It is encouraging to note that none of our patients with ARDS died, and no device-related complications were reported.

The use of the Hemolung and other similar ECCOR systems has been reported in patients with chronic respiratory failure such as COPD.[13,23] Although the reports are early and further data are vital to evaluate the role of the Hemolung

in COPD management, we believe this system has the potential to influence the management of exacerbations of COPD patients in whom prolonged mechanical ventilation may increase mortality and morbidity.[24] The use of the Hemolung may aid in avoiding intubation, facilitate lung-protective ventilation and hasten liberation of patients from mechanical ventilation. An observational study by Del Sorbo and colleagues[23] suggests that the risk of intubation could be reduced, compared with a propensity score-matched historic control. Kluge and colleagues reported similar results in their retrospective series.[25] Furthermore, a retrospective ancillary cost analysis of using arteriovenous ECCOR in COPD patients suggests that the costs are comparable to conventional management, due to shorter ICU and hospital lengths of stay when ECCOR is used.[26] However, the retrospective nature of these studies only provides limited evidence, and further experience is vital for patient selection to evaluate the role of ECCOR in this population.

Acute asthma that is refractory to conventional therapies may necessitate the use of ECMO,[27] but the use of ECMO is invasive and not available in most centres. Two of our patients had severe asthma that was resistant to conventional pharmacological and mechanical ventilation management and could have potentially required the use of ECMO (not available at that centre). In both patients, ECCOR was successfully instituted with no requirement for transfer to an ECMO centre. More data are needed to establish the role of low-flow ECCOR in asthma treatment, but it appears from our results that ECCOR use may prevent the need for ECMO in patients with severe asthma, especially if the patients are not profoundly hypoxic.

In this study, the Hemolung was used in two patients with cardiac arrest when the severity of anoxic brain injury could not be assessed at the time of instituting the Hemolung. Both patients had severe hypercapnic respiratory failure associated with severe respiratory acidosis, and it was considered vital to treat the severe hypercapnia to optimise neuroprotection.[28,29] The use of the Hemolung ameliorated severe hypercapnia and respiratory acidosis and aided in reducing the time to assess the brain injury by avoiding prolonged use of sedation and muscle relaxants, which would have been required in these difficult-to-ventilate patients. The earlier clinical assessment probably led to a reduced duration of ICU stay for these patients, thus reducing prolonged futile treatment and associated health care costs.

Conclusion

The Hemolung appears to be effective, safe and feasible for managing hypercapnic respiratory failure of various aetiologies. Further experience is vital to identify the types of patients who may benefit most from this promising therapy. Considering the minimally invasive nature of the Hemolung, in conjunction with its efficient removal of CO_2, we believe it has a promising place in the management of hypercapnic respiratory failure.

Acknowledgements

We thank the nursing staff in our ICUs for supporting participating patients on the Hemolung. We thank Cameron Green for assistance with data collection and compilation. ALung Technologies, the manufacturer of Hemolung RAS, had no role in or influence on the writing of our article. They provided technical assistance and education to the ICU nurses while some of the patients were treated with the Hemolung RAS.

Competing interests

Hergen Buscher was an invited speaker at an Alung Technologies-sponsored meeting in 2014.

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References

1 Gattinoni L, Kolobow T, Agostoni A, et al. Clinical application of low frequency positive pressure ventilation with extracorporeal CO2 removal (LFPPV-ECCO2R) in treatment of adult respiratory distress syndrome (ARDS). *Int J Artif Organs* 1979; 2: 282-3.

2 Gattinoni L, Agostoni A, Pesenti A, et al. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO2. *Lancet* 1980; 2: 292-4.

3 Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. *JAMA* 1986; 256: 881-6.

4 Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 149: 295-305.

5 Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; 374: 1351-63.

6 Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal. *Crit Care Med* 2011; 39: 1382-7.

7 Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 2006; 34: 1372-7.

8 Gramaticopolo S, Chronopoulos A, Piccinni P, et al. Extracorporeal CO2 removal — a way to achieve ultraprotective mechanical ventilation and lung support: the missing piece of multiple organ support therapy. *Contrib Nephrol* 2010; 165: 174-84. doi: 10.1159/000313757.

9 Terragni PP, Del SL, Mascia L, et al. Tidal volume lower than 6 mL/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009; 111: 826-35.

10 Anastasiadis K, Antonitsis P, Ranucci M, et al. Minimally invasive extracorporeal circulation (MiECC): towards a more physiologic perfusion. *J Cardiothorac Vasc Anesth* 2016; 30: 280-1.

11 Del Sorbo L, Ranieri VM. We do not need mechanical ventilation any more. *Crit Care Med* 2010; 38 (10 Suppl): S555-8.

12 Pesenti A, Patroniti N, Fumagalli R. Carbon dioxide dialysis will save the lung. *Crit Care Med* 2010; 38 (10 Suppl): S549-54.

13 Burki NK, Mani RK, Herth FJ, et al. A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest* 2013; 143: 678-86.

14 The Acute Respiratory Distress Syndrome Network. 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: 1301-8.

15 Luyt CE, Brechot N, Demondion P, et al. Brain injury during venovenous extracorporeal membrane oxygenation. *Intensive Care Med* 2016; 42: 897-907.

16 Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (about 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: 847-56.

17 Gattas DJ, Rajbhandari D, Bradford C, et al. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. *Crit Care Med* 2015; 43: 1622-9.

18 Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302: 1888-95.

19 Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The respiratory extracorporeal membrane oxygenation survival prediction (RESP) score. *Am J Respir Crit Care Med* 2014; 189: 1374-82.

20 Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest* 2008; 133: 1120-7.

21 Luecke T, Muench E, Roth H, et al. Predictors of mortality in ARDS patients referred to a tertiary care centre: a pilot study. *Eur J Anaesthesiol* 2006; 23: 403-10.

22 Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372: 747-55.

23 Del Sorbo L, Pisani L, Filippini C, et al. Extracorporeal CO2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015; 43: 120-7.

24 Nevins ML, Epstein SK. Predictors of outcome for patients with COPD requiring invasive mechanical ventilation. *Chest* 2001; 119: 1840-9.

25 Kluge S, Braune SA, Engel M, et al. Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. *Intensive Care Med* 2012; 38: 1632-9.

26 Braune S, Burchardi H, Engel M, et al. The use of extracorporeal carbon dioxide removal to avoid intubation in patients failing non-invasive ventilation — a cost analysis. *BMC Anesthesiol* 2015; 15: 160.

27 Mikkelsen ME, Woo YJ, Sager JS, et al. Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. *ASAIO J* 2009; 55: 47-52.

28 Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 — American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122 (18 Suppl 3): S768-86.

29 Roberts BW, Kilgannon JH, Chansky ME, et al. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. *Circulation* 2013; 127: 2107-13. ❑

7.3 Chapter summary

This chapter presented the data on the safety and efficacy of Hemolung RAS in management of acute hypercapnic respiratory failure in three different hospitals. Hemolung RAS appeared to be effective, safe and feasible in managing hypercapnic respiratory failure of various aetiologies. Given the minimally invasive nature in conjunction with efficient removal of carbon dioxide, Hemolung RAS has a promising place in the management of hypercapnic respiratory failure. Further data however, will be required to know the effectiveness of Hemolung RAS in reducing mortality and morbidity as well as cost effectiveness of this intervention.

While Hemolung RAS and other extracorporeal carbon dioxide removal devices may be efficient and effective in managing hypercapnic respiratory failure, these devices are invasive, currently not widely available and are expensive. Some of the techniques that are commonly available on mechanical ventilation may be sufficient in some patients to manage hypercapnia. The following chapter presents a review of current management options available for management of hypercapnia.

CHAPTER 8: Management of hypercapnia in critically ill adult patients

8.1 Chapter Introduction

The last two chapters (Chapter 6 and 7) described the use of Hemolung RAS, novel low flow venovenous carbon dioxide removal device to treat hypercapnic acidosis. While extracorporeal devices such as Hemolung RAS may be effective in active management of hypercapnic acidosis, these devices are invasive, expensive and are generally not widely available. Their underlying cost and clinical effectiveness have yet to be fully evaluated. There are techniques on conventional ventilators as well as options such as prone position ventilation that could be effective in treatment of acute hypercapnia in many patients with hypercapnic acidosis.

This chapter reviews the management options (conventional and extracorporeal) managing hypercapnia in mechanically ventilated patients.

8.2 Manuscript submitted for publication

Abstract

The use of lower tidal volume ventilation was shown to reduce mortality in mechanically ventilated patients with acute respiratory distress syndrome. A similar strategy was also shown to be beneficial in other diagnostic categories of mechanically ventilated patients. One of the associated effect of low tidal volume ventilation is the development of hypercapnia and hypercapnic acidosis. Some data from animal experiments suggested that hypercapnia and hypercapnic acidosis may be beneficial. However most of the clinical data suggest an increased mortality with hypercapnia and hypercapnic acidosis. This was noted across several diagnostic categories in mechanically ventilated patients. Given the current available evidence, acute hypercapnia and hypercapnic acidosis may be avoided or treated to ensure normocapnia and normal pH. We aimed to review the available treatment options including extracorporeal techniques that may be used to manage acute hypercapnia acidosis in the current critical care practice.

Introduction

Acute respiratory failure is one of the common indications for admission of patients to intensive care. Most of these patients require mechanical ventilation to assist in management of respiratory failure. Mechanical ventilation that was used in the past was aimed at maintaining blood gasses at normal ranges. This often required high inspiratory pressures that were subsequently shown to worsen lung injury and respiratory failure [1,2]. A strategy of reducing inspiratory pressures on mechanical ventilation appeared to reduce the mortality[3]. The current standard of care in treating patients with acute respiratory failure is to use low tidal volume and low inspiratory pressure mechanical ventilation[4]. One of the effects of such ventilation strategy is development of hypercapnia and hypercapnic acidosis.

Hypercapnia and hypercapnic acidosis influence various systems including respiratory, cardiovascular, central nervous, neuromuscular and renal systems [5-7]. The effects of hypercapnia and acidosis in critically ill patients are not clearly established. Some clinicians believe hypercapnic acidosis to be protective by itself independent of low volume ventilation and may aid in reducing the lung injury and mortality[8,9]. Indeed they have hypothesised that inducing hypercapnia by supplemental carbon dioxide may be beneficial in critically ill patients with acute respiratory failure [8]. To the contrary other clinicians consider hypercapnic acidosis to be harmful with possible increase in mortality and morbidity [4,10,11]. This uncertainty appears to be based on data from animal experiments or clinical studies with small sample sizes. These factors also limit the validity and generalizability of these studies.

Over the recent past several large studies evaluated hypercapnia and hypercapnic acidosis in various clinical settings. Our group investigated the effects of hypercapnia and hypercapnic acidosis during the first 24 hours of intensive care admission in over 250,000 mechanically ventilated patients[12]. In this study the adjusted hospital mortality of patients with compensated hypercapnia and hypercapnic acidosis was significantly higher than those patients who had normocapnia and normal pH. Furthermore, the adjusted odds of hospital mortality increased with increasing hypercapnia[12]. The study by Nin and colleagues[13] investigating the effects of hypercapnia during the first 48 hours of intensive care admission in patients with ARDS showed that severe hypercapnia, as defined by PCO_2 > 50mmHg, was independently associated with increased ICU mortality, and higher complications including barotrauma, renal dysfunction, and cardiovascular dysfunction[13,14]. Hypercapnic acidosis was also found to be independently associated with increased mortality in various diagnostic categories of mechanically ventilated patients including acute cerebral injury, trauma, sepsis, cardiac, respiratory, gastrointestinal, renal causes of admission to ICU[12,15,16]. From these data it appears that severe hypercapnia especially when associated with acidosis should be avoided or actively managed [12,13,15,17]. We performed a

review of published literature to identify the therapeutic options that are currently available to manage acute hypercapnia in critically ill patients requiring invasive mechanical ventilation.

Search Strategy:
MEDLINE via PubMed (from inception to June 2018) and EMBASE (from inception to June 2018) were systematically searched. The search was performed using the following exploded medical subject headings and text words “carbon dioxide”, “hypercarbia”, “hypercapnia”, “acidosis”, “critically ill” or “critical care” or “management” or “treatment” in isolation and in combination without restrictions. Studies including animals or tissues were excluded from the review. We also searched bibliographic references of relevant studies, irrespective of study design with the intention of finding relevant studies to be included in this review.
The possible options include optimising the use of mechanical ventilation to enhance carbon dioxide elimination while avoiding practices such as lung recruitment manoeuvres, where possible that could lead to hypercapnic acidosis, buffers such as sodium bicarbonate and Tris-hydroxymethyl aminomethane (THAM) to correct acidosis, airway pressure release ventilation, high frequency oscillation ventilation, early use of prone position ventilation, use of extracorporeal treatments including extracorporeal membrane oxygenation (ECMO) or other less invasive low flow extracorporeal carbon dioxide removal devices.

Mechanical ventilation: The efficacy of lower tidal volume ventilation to improve mortality was initially shown in observational studies[3]. This was considered to be due to a reduction in lung injury with low tidal volumes as well as the associated hypercapnia with lower tidal volume ventilation[18]. In randomised controlled trials a strategy of low volume ventilation when associated with hypercapnia demonstrated a trend towards increased mortality[10]. However when low volume ventilation was performed while ensuring normocapnia the mortality was significantly reduced [4]. Optimal management of mechanical ventilation should remain the primary modality of prevention or correcting hypercapnic acidosis. Hypercapnia that develops with low volume ventilation may be managed by simple modifications to the ventilator circuit such as connecting Y-piece directly to endotracheal tube to reduce the dead space in ventilator circuit [19]. Changes to the circuit in mechanical ventilation including removal of heat and moisture exchanger and using heated humidifier was also shown to reduce hypercapnia without the need for increase in the need for increasing tidal volumes or the rate [20]

Changes in delivery of conventional mechanical ventilation including the settings such as increasing respiratory rate (and minute ventilation) or pharmacological agents such as bicarbonate infusions as recommended by the ARDS network [4] may further help in management of hypercapnic acidosis. The increase in respiratory rates may be associated with dynamic

hyperinflation and right ventricular dysfunction without clearance of hypercapnia[21]. End-inspiratory pause prolongation was shown to increase clearance of hypercapnia in ARDS patients. By increasing end-inspiratory pause prolongation from 0.1 to 0.7 Bermeo et al. demonstrated a significant decrease in PCO_2 from 54±9 to 50±8 mmHg[22]. They showed that the decrease in PCO_2 was due to a reduction in physiological dead space[22]. Some of the treatments that are used in patients with severe ARDS such as lung recruitment to improve oxygenation and reduce ventilator induced lung injury are shown to cause severe hypercapnia during the first 24 hours of institution [23]. Lung recruitment manoeuvres were investigated for reducing the incidence of ventilator-induced lung injury and improving survival in patients with ARDS. The strategy of lung recruitment manoeuvre and PEEP titration according to the best respiratory–system compliance was recently investigated by Cavalcanti and colleagues in a large multinational, multicentre randomised controlled trial[23]. This study showed a higher 28-day and 6 month all-cause mortality in patients who were treated with lung recruitment. Higher mortality noted with lung recruitment was attributed to several factors including changes in driving pressure and lung over distention, breath stacking, need for neuromuscular blockade and haemodynamic compromise[23]. It is important to note that in the lung recruitment group, hypercapnia and acidosis during the first hour of randomisation was observed, which is known to be associated with higher mortality in mechanically ventilated patients[12,13].

Buffers in the management of hypercapnic acidosis: The use of buffers in the management of hypercapnic acidosis remains controversial[24]. Sodium bicarbonate and THAM were both used in clinical practice to buffer hypercapnic acidosis [4 25-27]. Kallet et al.[27] demonstrated THAM improving arterial pH and base deficit, and a reduction in PCO_2 that could not be fully accounted for by ventilation. Weber and colleagues investigated the use of THAM in ARDS patients where permissive hypercapnia was implemented for 2 hours aiming for a target PCO_2 of 80 mm Hg. In their randomised controlled trial of 12 patients with ARDS, the use of THAM buffering attenuated depression of myocardial contractility and hemodynamic alterations during rapid permissive hypercapnia institution [25]. The ARDS network trial recommended the use of sodium bicarbonate when pH was lower than 7.1[4]. However bicarbonate should not be administered in hypoxemic and lactic acidosis [26].

Some patients with severe ARDS will be hypercapnic in spite of best possible conventional ventilation. In such patients other modalities in addition to conventional ventilation may be required. These include high frequency oscillatory ventilation, prone position ventilation and airway pressure release ventilation.

High frequency oscillation ventilation (HFOV): HFOV is a ventilatory technique where using an oscillatory pump, breathing frequencies of 180 –900 breaths/min (3–15 Hz) are used with very

small tidal volumes (1-4 ml/kg) at a constant airway pressure potentially reducing volutrauma, decrease anatomical dead space, and improving ventilation-perfusion matching. HFOV was used as a mode of lung protective ventilation. The initial experience esp. with neonatal patients was encouraging [28]. However, use in adult patients was restricted to a few centres. The recent studies on adult patients with ARDS showed no significant benefit and with possible increase in mortality [29]. It may be of benefit in group of patients with more severe ARDS (PaO2/FiO2 <64 mmHg) where hypercapnia is unresponsive to conventional ventilation [30] . Friesecke et al reported the use of HFOV in patients with hypercapnic acidosis not responsive to conventional ventilation[31]. In their cohort of 26 patients, 24 patients responded to HFOV with improvement in hypercapnia and acidosis at 24 hours of initiating HFOV. It is however important to note that the routine use of HFOV was not recommended due to lack of mortality benefit and a potential for harm with the use of HFOV as compared to conventional ventilation with low tidal volumes [32].

Prone position ventilation: Prone position reduces the heterogeneity of ventilation of dorsal to ventral lung regions as compared to supine position, increasing homogeneity of stress and strain as a result[33] . By virtue of ventral de-recruitment exceeding dorsal recruitment, or reduction in hyper inflated ventral regions, prone position ventilation can result in reduction in dead space. Indeed, prone position ventilation was shown to decrease hypercapnia in patients with ARDS[34,35] especially with those who are responders to prone position ventilation [34]. Prone ventilation was also shown to improve oxygenation and improve mortality in patients with ARDS [36]. Prone position ventilation aids in recruitment of previously excluded alveoli reducing the dead space ventilation [35].

Airway pressure release ventilation (APRV): APRV entails continuous positive airway pressure at a high level, with intermittent time cycled release, to maintain alveolar recruitment and lung volume. Patients can breathe spontaneously, independent of the phase of respiration, through a biphasic positive pressure circuit [37]**.** APRV was initially described as a spontaneous mode of ventilation to treat patients with acute lung injury with aim of maintaining lower airway pressure and to allow unrestricted spontaneous ventilation. While it is not commonly used in patients with acute lung injury there are some reports suggesting that APRV may prevent progression of acute lung injury in high-risk trauma patients [38]. APRV was shown to be effective in reducing CO2 as well as improving oxygenation without increasing minute ventilation [39] in conjunction with a reduction in peak and mean airway pressures [40]. This improvement in gas exchange is related to the reduction in dead space ventilation [41]. The use of APRV however is not widespread and this mode is not available in all commercially available ventilators [42].

Some patients may have severe hypercapnia that could not be managed with mechanical ventilation alone. In such patients extracorporeal carbon dioxide removal needs to be considered.

Extracorporeal management of hypercapnia

Extracorporeal management include ECMO and other newer low flow devices specifically introduced to support clearance of carbon dioxide.

Extracorporeal membrane oxygenation (ECMO): ECMO provides oxygenation, ventilation and cardiac assist can be provided. Oxygenation with a membrane lung in veno-venous ECMO is mainly dependent on the blood flow and CO_2 clearance is primarily dependent on the fresh gas flow. It is possible to remove all metabolically produced CO_2 from blood flow rates between 1 to 2 L per minute of venous blood flow through the membrane lung[43].

Removal of carbon dioxide was considered in 1970s when Kolobow developed a membrane lung which was shown to remove carbon dioxide effectively[44]. Indeed this artificial CO_2 removal was so efficient that when extracorporeal CO_2 removal approximated CO_2 production, alveolar ventilation could almost be ceased[45]. Clinical application of extracorporeal carbon-dioxide removal was first reported in an observational study by Gattinoni et al [46] in an uncontrolled group of patients with severe ARDS. They reported encouraging results in patients with severe ARDS by using this technique as a strategy to "rest" the lungs. The survival rate of the treated patients in this study was 49%. The blood loss was however significant (average blood loss 1800 +/- 850 mL/day). Subsequently Morris et al[47] conducted a randomized clinical trial comparing pressure controlled inverse ratio ventilation with an extracorporeal CO_2 removal technique in patients with ARDS. However, no significant difference in survival was found between the mechanically ventilated patients and those treated with the extracorporeal CO_2 removal. The use of ECCO2 removal did not gain much acceptance due to complexity, costs and implications of intervention including high blood flow rates, large cannulas and systemic anticoagulation with its associated potential complications. More recently the use of ECMO had gained momentum with improvements in technology, advances in intensive care practice especially of the anticoagulation while patients were managed on extracorporeal circulation. CESAR trial [48], incorporating such advances in equipment and clinical practice investigated the use of ECMO in ARDS patients with hypoxic or had hypercapnic acidosis with respiratory failure. The results of CESAR showed that an ECMO-based management protocol to significantly improve survival without severe disability. However only a small proportion (about 5%) of patients in this trial had hypercapnic acidosis and the results may not support the routine use of ECMO in patients with hypercapnic acidosis. These results may not therefore be generalisable in managing patients with hypercapnic acidosis. Furthermore, the availability of ECMO is limited to very few centres.

Low flow extracorporeal carbon dioxide removal devices:

Over the last 2 decades several less invasive extracorporeal devices were evaluated as alternatives to ECMO support. These are less invasive and less complex devices that may be used to treat hypercapnia and acidosis.

Most of these less invasive devices provide partial extracorporeal support where they are efficient in clearing carbon dioxide, but do not provide significant oxygenation. The cannulas used to access blood vessels are smaller and require minimal anticoagulation similar to renal replacement therapy circuits.

Some of these devices evaluated for extracorporeal carbon dioxide removal include Interventional Lung Assist (ILA) (NovaLung GmbH, Hechingen, Germany)[49], arteriovenous extracorporeal CO2 removal (AVCO2R) [50,51], low flow venovenous extracorporeal carbon dioxide removal[52], intra-venacaval oxygenation and CO2 removal (IVOX) device[53,54], Decap [55], hemolung[56,57] and prismalung [57,58].

Of these devices ILA is the only device that was used in over 1800 patients with hypercapnic respiratory failure with encouraging results[48]. ILA is a sophisticated pumpless extracorporeal arteriovenous carbon dioxide removal device that is driven by the patient's cardiac output and therefore, do not require extracorporeal pump assistance. ILA was shown to be effective in clearing hypercapnia when tidal volumes as low as 3 ml/kg predicted body weight was used[59]. However, the need for arterial cannulation increases morbidity with complications such as limb ischaemia and arterial pseudoanneurysms[59].

Low flow veno-venous devices such as hemolung and prismalung appears to be more promising in being minimally invasive (avoiding arterial cannulation). Initial results mainly of case reports[60,61] and feasibility observational studies[56,58] while encouraging need further investigation. The results of currently ongoing randomised controlled trials currently investigated in randomised controlled trials(REST and SUPERNOVA) [62,63] may further define the efficacy of these low flow veno venous extracorporeal carbon dioxide removal devices in management of hypercapnic respiratory failure.

Conclusions

Recent evidence suggest hypercapnic acidosis is associated with increased risk mortality and should be prevented or actively managed. The options to manage hypercapnic acidosis include modifications to mode of mechanical ventilation to enhance CO2 clearance as well as buffers to normalise pH. In patients where hypercapnic acidosis could not be managed with mechanical ventilation, extracorporeal techniques may be used. The newer low flow extracorporeal devices are minimally invasive and are effective in clearing hypercapnia. These devices are currently being investigated in randomised controlled trials to further define their role not only in clearing hypercapnia but to improve clinical outcomes.

References

1. Meade MO, Cook DJ. The aetiology, consequences and prevention of barotrauma: a critical review of the literature. Clinical intensive care : international journal of critical & coronary care medicine 1995;6:166-73.
2. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. Intensive Care Med 2002;28:406-13.
3. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 1994;22:1568-78.
4. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301-8.
5. Cullen DJ, Eger EI. Cardiovascular effects of carbon dioxide in man. Anesthesiology 1974;41:345-9.
6. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care 2010;14:220.
7. Tiruvoipati R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. Anaesth Intensive Care 2013;41:157-62.
8. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill--too little of a good thing? Lancet (London, England) 1999;354:1283-6.
9. Kavanagh BP, Laffey JG. Hypercapnia: permissive and therapeutic. Minerva Anestesiol 2006;72:567-76.
10. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 1998;158:1831-8.
11. 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;338:355-61.
12. 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:e649-e56.
13. Nin N, Muriel A, Peñuelas O, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Medicine 2017;43:200-8.
14. 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;42:862-70.

15. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury. JAMA neurology 2018;75:818-26.
16. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation 2013;84:927-34.
17. Barnes T, Zochios V, Parhar K. Re-examining Permissive Hypercapnia in ARDS: A Narrative Review. Chest 2018;154:185-95.
18. Hickling KG, Joyce C. Permissive hypercapnia in ARDS and its effect on tissue oxygenation. Acta anaesthesiologica Scandinavica Supplementum 1995;107:201-8.
19. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. The New England journal of medicine 2010;363:1107-16.
20. Prin S, Chergui K, Augarde R, Page B, Jardin F, Vieillard-Baron A. Ability and safety of a heated humidifier to control hypercapnic acidosis in severe ARDS. Intensive Care Med 2002;28:1756-60.
21. 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;30:1407-12.
22. Aguirre-Bermeo H, Moran I, Bottiroli M, et al. End-inspiratory pause prolongation in acute respiratory distress syndrome patients: effects on gas exchange and mechanics. Annals of intensive care 2016;6:81.
23. Cavalcanti AB, Suzumura EA, Laranjeira LN, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. Jama 2017;318:1335-45.
24. Gattinoni L, Taccone P, Carlesso E. Respiratory acidosis: is the correction with bicarbonate worth? Minerva Anestesiol 2006;72:551-7.
25. 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;162:1361-5.
26. Kallet RH, Liu K, Tang J. Management of acidosis during lung-protective ventilation in acute respiratory distress syndrome. Respiratory care clinics of North America 2003;9:437-56.
27. Kallet RH, Jasmer RM, Luce JM, Lin LH, Marks JD. The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). Am J Respir Crit Care Med 2000;161:1149-53.
28. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. The New England journal of medicine 2002;347:643-52.

29. Sud S, Sud M, Friedrich JO, et al. High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. The Cochrane database of systematic reviews 2016;4:Cd004085.
30. Meade MO, Young D, Hanna S, et al. Severity of Hypoxemia and Effect of High-Frequency Oscillatory Ventilation in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2017;196:727-33.
31. Friesecke S, Stecher SS, Abel P. High-frequency oscillation ventilation for hypercapnic failure of conventional ventilation in pulmonary acute respiratory distress syndrome. Crit Care 2015;19:201.
32. Goligher EC, Munshi L, Adhikari NKJ, et al. High-Frequency Oscillation for Adult Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Annals of the American Thoracic Society 2017;14:S289-s296.
33. Gattinoni L, Taccone P, Carlesso E, Marini JJ. Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. Am J Respir Crit Care Med 2013;188:1286-93.
34. Gattinoni L, Vagginelli F, Carlesso E, et al. Decrease in $PaCO_2$ with prone position is predictive of improved outcome in acute respiratory distress syndrome. Crit Care Med 2003;31:2727-33.
35. Charron C, Repesse X, Bouferrache K, et al. $PaCO_2$ 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:R175.
36. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. The New England Journal of Medicine 2013;368:2159-68.
37. Dries DJ, Marini JJ. Airway pressure release ventilation. Journal of burn care & research : official publication of the American Burn Association 2009;30:929-36.
38. Andrews PL, Shiber JR, Jaruga-Killeen E, et al. Early application of airway pressure release ventilation may reduce mortality in high-risk trauma patients: a systematic review of observational trauma ARDS literature. The journal of trauma and acute care surgery 2013;75:635-41.
39. Maung AA, Luckianow G, Kaplan LJ. Lessons learned from airway pressure release ventilation. The journal of trauma and acute care surgery 2012;72:624-8.
40. Rasanen J, Cane RD, Downs JB, et al. Airway pressure release ventilation during acute lung injury: a prospective multicenter trial. Crit Care Med 1991;19:1234-41.
41. Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe acute respiratory failure. Chest 1991;100:460-3.
42. Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? Respiratory care 2012;57:282-92.
43. Gattinoni L, Carlesso E, Langer T. Clinical review: Extracorporeal membrane oxygenation. Crit Care 2011;15:243.

44. Kolobow T, Gattinoni L, Tomlinson T, White D, Pierce J, Iapichino G. The carbon dioxide membrane lung (CDML): a new concept. Trans Am Soc Artif Intern Organs 1977;23:17-21.
45. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE. Control of breathing using an extracorporeal membrane lung. Anesthesiology 1977;46:138-41.
46. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. Jama 1986;256:881-6.
47. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295-305.
48. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet (London, England) 2009;374:1351-63.
49. Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 2006;34:1372-7.
50. Brunston RL, Jr., Zwischenberger JB, Tao W, Cardenas VJ, Jr., Traber DL, Bidani A. Total arteriovenous CO2 removal: simplifying extracorporeal support for respiratory failure. The Annals of thoracic surgery 1997;64:1599-604; discussion 604-5.
51. Conrad SA, Zwischenberger JB, Grier LR, Alpard SK, Bidani A. Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study. Intensive Care Med 2001;27:1340-51.
52. 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;111:826-35.
53. Cole FJ, Jr., Shouse BA. Alternative modalities of ventilation in acute respiratory failure. Surgery annual 1995;27:55-69.
54. Terada Y. [Present status of IVOX device]. Rinsho kyobu geka = Japanese annals of thoracic surgery 1994;14:461-4.
55. Gramaticopolo S, Chronopoulos A, Piccinni P, et al. Extracorporeal CO2 removal--a way to achieve ultraprotective mechanical ventilation and lung support: the missing piece of multiple organ support therapy. Contributions to nephrology 2010;165:174-84.
56. Tiruvoipati R, Buscher H, Winearls J, et al. Early experience of a new extracorporeal carbon dioxide removal device for acute hypercapnic respiratory failure. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine 2016;18:261-9.
57. Winiszewski H, Aptel F, Belon F, et al. Daily use of extracorporeal CO2 removal in a critical care unit: indications and results. Journal of intensive care 2018;6:36.
58. Schmidt M, Jaber S, Zogheib E, Godet T, Capellier G, Combes A. Feasibility and safety of low-flow extracorporeal CO2 removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. Crit Care 2018;22:122.

59. 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;39:847-56.
60. Tiruvoipati R, Gupta S, Haji K, Braun G, Carney I, Botha JA. Management of severe hypercapnia post cardiac arrest with extracorporeal carbon dioxide removal. Anaesthesia and intensive care 2014;42:248-52.
61. Tiruvoipati R, Haji K, Gupta S, Braun G, Carney I, Botha J. Low-flow veno-venous extracorporeal carbon dioxide removal in the management of severe status asthmatics: a case report. The clinical respiratory journal 2016;10:653-6.
62. Strategy of UltraProtective Lung Ventilation With Extracorporeal CO2 Removal for New-Onset Moderate to seVere ARDS (SUPERNOVA). (Accessed 26th January, 2018,
63. REST Trial. (Accessed 26 Jan, 2018,

8.3 Chapter summary

This chapter summaries that management options including conventional ventilation modifications, buffers, prone ventilation, high frequency oscillatory ventilation, airway pressure release ventilation, and extracorporeal techniques that are currently available to actively manage hypercapnic acidosis. The manuscript of this chapter is under review for publication in Critical Care Medicine (CCMED-D-18-02143).

Chapter 9: Conclusions

9.1 Chapter Introduction

This chapter provides summary of key findings of this thesis and context for future directions in evaluation of the effects and management options of hypercapnia in critically ill patients requiring mechanical ventilation. This chapter also outlines the strengths and limitations of this thesis.

9.2 Summary of key findings

Hypercapnia and hypercapnic acidosis were considered benign and potentially beneficial in mechanically ventilated patients with severe respiratory failure (1, 2). This was largely based on small retrospective cohort studies (3) or post hoc analysis of prospective trials where higher tidal volumes were used than recommended in current practice (4). These findings were supported by some animal experimental data (5, 6). However, some animal data also showed that hypercapnia was harmful (7, 8). Extrapolation of these animal experimental data to clinical practice is difficult. With lack of data relevant to management of hypercapnia in critically ill patients, the management practices varied with some clinicians believing hypercapnia was beneficial and other harmful. This thesis contributes significantly to the understanding of the association of hypercapnia and hypercapnic acidosis as well as the management of hypercapnia in adult mechanically ventilated patients. To the best of our knowledge, this is the first study investigating the effects of hypercapnia with or without acidosis. In other words, this work attempts to delineate the association of hypercapnia to that of acidosis caused by hypercapnia on clinically important endpoints.

This thesis describes the conduct of a carefully planned research schedule investigating the effects and management of hypercapnia and hypercapnic acidosis in adult mechanically ventilated patients. This included three review articles (Chapters 2,3 and 8), two of the largest, binational retrospective studies published so far investigating the association of hypercapnia and hypercapnic acidosis in mechanically ventilated patients (Chapter 4 and 5) and implementation of a novel low flow minimally invasive extracorporeal carbon dioxide removal device (Chapter 6 and 7).

The three review articles provide a concise summary of published data on effects of hypercapnia and management options for hypercapnia (9, 10). However, the most significant contribution to the literature arising from this thesis was from the publication of the two largest retrospective studies (11, 12). The study presented in Chapter four, highlights the fact that hypercapnia may have different effects based on the presence or absence of acidosis as well as the diagnostic clinical condition. It shows a strong association of hypercapnic acidosis with hospital mortality across all diagnostic categories. The subsequent study presented in Chapter five provides evidence that compensated hypercapnia may not be harmful in cerebral injury patients. This study is extremely important and contributes to the growing body of evidence on management of hypercapnia to prevent secondary brain injury. This study suggest that PCO_2 should not be managed in isolation, but in conjunction with arterial pH. The evaluation of Hemolung RAS shows that this device is effective in clearing hypercapnia in a range of clinical conditions and different health care settings with variable experiences in the use of extracorporeal life support systems (13-15).

9.3 Strengths and limitations

This section presents the overall strengths and limitations of this thesis. A detailed description of strengths and limitations are presented in individual studies as appropriate.

Strengths

This thesis has several strengths. Firstly, this work is first of its kind on clinical evaluation of hypercapnia in conjunction with pH. Carbon dioxide changes are inextricably linked to the changes in pH. So far, clinical studies that investigated the effects carbon dioxide relevant to critically ill patients have focussed on evaluation based on carbon dioxide alone, without relation to the associated changes in pH with changing carbon dioxide. The research presented in this thesis attests to the fact that hypercapnia has different effects depending on pH. This is particularly important in managing patients with acute cerebral injury. Furthermore, this thesis focused on investigating the effects of hypercapnia in mechanically ventilated patients. This is an important aspect, because manipulation of carbon dioxide is achievable in mechanically ventilated patients as compared to spontaneously breathing patients. A clear understanding of the basic science and the effects of hypercapnia and hypercapnic acidosis in clinical practice may help clinicians in

targeting specific levels of hypercapnia in different diagnostic categories that could improve the outcomes of critically ill mechanically ventilated patients.

Secondly, in addition to presenting the overall effects of hypercapnia and hypercapnic acidosis in mechanically ventilated patients, this thesis investigated the effects of compensated hypercapnia and hypercapnic acidosis on the commonly admitted diagnostic categories of critically ill patients, providing an understanding on different effects of hypercapnia and hypercapnic acidosis on different diagnostic conditions.

Thirdly, this thesis includes two of the largest retrospective studies published so far on hypercapnia and hypercapnic acidosis. The large sample size (252,812 and 30 742 patients) in these studies enabled identification of small but clinically significant differences in outcomes.

Fourthly, ANZICS APD data (used in retrospective studies used in this thesis) is recognised as a high quality clinical registry with excellent data quality. Publications arising from this data analysis have been published in multiple journals with highest impact factor including the New England Journal of Medicine and The Journal of the American Medical Association (16, 17). Data collection from more than 80% of the participating intensive care units in Australia and New Zealand is robust and quality controlled with an established data dictionary to ensure uniformity and accuracy of the data collected. Finally, it is likely that our findings have external validity in other developed countries with intensive care practices similar to Australia and New Zealand.

Limitations

The limitations of this thesis include the evaluation of clinical outcomes of hypercapnia largely in retrospective studies. Our study showed an association of increased risk of adverse outcomes with hypercapnia but not causation given the retrospective nature of our study. Retrospective studies generally provide inferior level of evidence compared with prospective randomised controlled studies and could have confounding variables that could be not be controlled by statistical techniques. Hence, there is a possibility that reverse causation may be a factor in the presented findings. Data on some of the important variables such as cerebral blood flow or intracranial pressure measurement and neuroimaging data that are vital to understand the mechanism of

secondary brain injury were not available. Furthermore, we did not have specific data pertaining to mechanical ventilation such as driving pressures, tidal volumes and compliance that could have aided in interpreting the relation of hypercapnia to mechanical ventilation supports. A further limitation is that the worst value of APD-PCO_2 and pH used to classify patient's hypercapnic status was limited to the 24 h following ICU admission. Thus, patients may have had more deranged blood gasses (abnormal PCO_2 and pH) prior to ICU admission or after 24 h following ICU admission and the absence of this data precluded evaluation of association of hypercapnic status before or after 24 hours of ICU admission on hospital mortality.

9.4 Future directions

Hypercapnia was investigated extensively in animal experimental studies in two main areas, one in relation to mechanical ventilation and lung injury and the other as a tool to modulate pathophysiology of sepsis (18). Clinical studies in both these areas were limited prior to the publication of studies presented in this thesis.

Hypercapnia was extensively investigated in experimental sepsis and to some extent in clinical sepsis of different sources mostly in patients who are not critically ill or mechanically ventilated. Published data from animal experimental studies suggest that the effects of hypercapnic acidosis are variable with benefit shown in some settings of sepsis and harm in others (19). The effects may also vary at different time points during the course of sepsis as well as presence or absence of acidosis with hypercapnia (20).This thesis investigated the effects of hypercapnia and hypercapnic acidosis in mechanically ventilated patients with sepsis. However, it did not characterise the specific association of hypercapnia on different sources of sepsis and the relation of hypercapnia during the different stages on sepsis evolution in critically ill patients. Further studies are required to assess hypercapnia in such settings.

Hypercapnia is likely to change over the course of patient's intensive care stay. Given the lack of data beyond 24 hours in ICU, in our studies (16, 17) further studies are required to investigate the course of hypercapnia beyond 24 hours and its relation to outcomes.

Future studies should also evaluate the impact of compensated hypercapnia on outcomes in acute cerebral injury patients. Mild hypercapnia (PCO_2 45–55 mmHg) was investigated in patients with cardiac arrest (21). It appears that mild hypercapnia may increase the cerebral blood flow in patients with cerebral injury caused by cardiac arrest (21). Whether increased blood flow translates to better clinical outcomes in cerebral injury patients with cardiac arrest as well as other diagnostic categories such as stroke and traumatic brain injury remains to be evaluated.

Extracorporeal devices, especially minimally invasive and low flow devices such as Hemolung RAS may have a significant role in managing hypercapnic acidosis associated with low and ultra-low tidal volume ventilation. However, whether this management of hypercapnic acidosis improve clinical outcomes by reducing mortality and morbidity as well as the cost effectiveness of these interventions remains to be addressed.

9.5 Concluding remarks

The implications of hypercapnia in critically ill patients were unclear at the conception of this research project. This research project contributes to the body of evolving literature in this area to better understand the association of hypercapnia and clinical outcomes as well as the management of hypercapnia in critically ill patients. These studies have contributed to a change in paradigm on the approach and management of hypercapnia in critically ill patients (22-25).

The main conclusion of this thesis is that hypercapnic acidosis is associated with increased risk of hospital mortality in mechanically ventilated patients. Compensated hypercapnia may not be associated with increased risk of hospital mortality in some diagnostic groups of patients such as with acute cerebral injury but may be associated with higher risk of mortality in other diagnostic categories. Extracorporeal devices may have a role in effective management of hypercapnic acidosis.

References

1. Kavanagh BP, Laffey JG. Hypercapnia: permissive and therapeutic. Minerva Anestesiol. 2006;72(6):567-76.

2. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill--too little of a good thing? Lancet (London, England). 1999;354(9186):1283-6.

3. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med. 1994;22(10):1568-78.

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

5. Costello J, Higgins B, Contreras M, Chonghaile MN, Hassett P, O'Toole D, et al. Hypercapnic acidosis attenuates shock and lung injury in early and prolonged systemic sepsis. Crit Care Med. 2009;37(8):2412-20.

6. 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):403-8.

7. Lang JD, Jr., Chumley P, Eiserich JP, Estevez A, Bamberg T, Adhami A, 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.

8. Pedoto A, Caruso JE, Nandi J, Oler A, Hoffmann SP, Tassiopoulos AK, et al. Acidosis stimulates nitric oxide production and lung damage in rats. Am J Respir Crit Care Med. 1999;159(2):397-402.

9. Tiruvoipati R, Gupta S, Pilcher D, Bailey M. Hypercapnia and hypercapnic acidosis in sepsis: harmful, beneficial or unclear? Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2018;20(2):94-100.

10. Tiruvoipati R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. Anaesth Intensive Care. 2013;41(2):157-62.

11. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury. JAMA neurology. 2018;75(7):818-26.

12. 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-e56.

13. Tiruvoipati R, Buscher H, Winearls J, Breeding J, Ghosh D, Chaterjee S, et al. Early experience of a new extracorporeal carbon dioxide removal device for acute hypercapnic respiratory failure. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2016;18(4):261-9.

14. Tiruvoipati R, Gupta S, Haji K, Braun G, Carney I, Botha JA. Management of severe hypercapnia post cardiac arrest with extracorporeal carbon dioxide removal. Anaesthesia and intensive care. 2014;42(2):248-52.

15. Tiruvoipati R, Haji K, Gupta S, Braun G, Carney I, Botha J. Low-flow veno-venous extracorporeal carbon dioxide removal in the management of severe status asthmatics: a case report. The clinical respiratory journal. 2016;10(5):653-6.

16. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372(17):1629-38.

17. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311(13):1308-16.

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

19. Curley G, Contreras MM, Nichol AD, Higgins BD, Laffey JG. Hypercapnia and acidosis in sepsis: a double-edged sword? Anesthesiology. 2010;112(2):462-72.

20. 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):1317-26.

21. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. Resuscitation. 2016;102:11-6.

22. Barnes T, Zochios V, Parhar K. Re-examining Permissive Hypercapnia in ARDS: A Narrative Review. Chest. 2018;154(1):185-95.

23. Mekontso Dessap A, Boissier F, Charron C, Begot E, Repesse X, Legras A, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. Intensive Care Med. 2016;42(5):862-70.

24. Nin N, Muriel A, Peñuelas O, Brochard L, Lorente JA, Ferguson ND, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. Intensive Care Medicine. 2017;43(2):200-8.

25. Barnes T, Parhar K, Zochios V. Hypercapnia vs normocapnia in patients with acute respiratory distress syndrome. British journal of hospital medicine (London, England : 2005). 2018;79(2):118.

APPENDICES

APPENDIX 1 Monash University Human Research Ethics Committee Approval

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

11 August 2014

Dear Researchers

Project Number:	**CF14/2340 - 2014001281**
Project Title:	**Clinical Effects and Management of Hypercapnia in Critically Ill patients**
Chief Investigator:	**Assoc Prof Michael Bailey**

The above application has been reviewed by the Chairs of the Monash University Human Research Ethics Committee (MUHREC) who determined that the proposal satisfies section 5.1.22 of the National Statement on Ethical Conduct in Human Research.

Therefore, the Committee has granted an exemption from ethical review for the research as described in your proposal.

Thank you for your assistance.

Professor Nip Thomson
Chair, MUHREC

cc: Dr Ravindranath Tiruvoipati, Assoc Prof David Pilcher

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
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ABN 12 377 614 012 CRICOS Provider #00008C

APPENDIX 2 Human Research Ethics Committee approval Peninsula Health

Peninsula Health

CONFIRMATION OF APPROVAL

Office for Research
Frankston Hospital
2 Hastings Road
PO Box 52
Frankston VIC 3199
Telephone (03) 9784 2680

24 January 2019

Evaluation of extracorporeal carbon dioxide removal in the critically ill using the Hemolung device

Reference Number: QA/16/PH/4

This is to confirm that the project detailed above was approved as an Audit Activity on 19 February 2016. Human Research Ethics Committee approval was not required.

Dr Timothy Williams
Executive Director Medical Services
Executive Sponsor Research

APPENDIX 3 Human Research Ethics Committee approval St Vincent's Hospital

St Vincent's Hospital

A facility of St Vincent's
& Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 054 038 872
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19 November 2015

Dr Andrew Jackson
Department of Anaesthesia
St Vincent's Hospital
Darlinghurst NSW 2010

Dear Andrew

SVH File Number: 10/218
Project Title: Establishment of a database of all patients treated with Extracorporeal Membrane Oxygenation in St Vincent's Hospital
HREC Reference Number: insert number: N/A

Thank you for submitting a request for an extension of HREC approval for the above project. The project was first approved by St Vincent's Hospital HREC on **16 December 2010**. This HREC has been accredited by NSW Ministry of Health as a Lead HREC under the model for single ethical and scientific review and Certified by the NHMRC under the National model for Harmonisation of Multicentre Ethical Review (HoMER).This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

I am pleased to advise that the Committee at an Executive meeting on **17 November 2015** has granted an extension of ethical and scientific approval until **17 November 2020.**

If the project is expected to continue beyond this date a new submission is required to be submitted to the HREC prior to **17 November 2020.**Please contact the Research Office to discuss your project and submission requirements.

You are reminded that this letter constitutes *ETHICAL* and *SCIENTIFIC* approval only. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at **St Vincent's Hospital, Sydney**

Please note the following conditions of approval:

- The Co-ordinating Investigator is required to notify the HREC 6 months prior to the **17 November 2020.**if the project is expected to extend beyond the extended approval date at which time the HREC will advise of the requirements for ongoing approval of the study.
- The Co-ordinating Investigator will continue provide an annual progress report, to the HREC as well as a final study report at the completion of the project in the specified format.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by study participants regarding the conduct of the study.
- Proposed changes to the research protocol, conduct of the research, or length of HREC approval will be provided to the HREC for review, in the specified format.
- The HREC will be notified, giving reasons, if the project is discontinued before the expected date of completion.

- Projects that are undertaken by Investigators holding an academic appointment (including conjoint appointments) or by students as part of a University course may also be required to notify the relevant University HREC.

Please note that only an electronic copy of this letter will be provided, if you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries about your project please contact the Research Office, Tel: 8382-2075, email SVHS.Research@svha.org.au The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office website: https://svhs.org.au/home/research-education/research-office

Yours sincerely

Sarah Charlton
HREC Executive Officer
St Vincent's Research Office
L6 deLacy Building

cc: Serene Yoke Wei Leow
TRIM REF: D/2015/64259

APPENDIX 4 Human Research Ethics Committee approval Gold Coast Health Service District

Gold Coast Health
Building a healthier community

Queensland Government

Enquiries to: HREC Coordinator
Phone: 07 5687 3879
E-mail GCHEthics@health.qld.gov.au
Our Ref: HREC/16/QGC/78

14 March 2016

Dr James Winearls
Intensive Care Unit
Gold Coast University Hospital
1 Hospital Boulevard
SOUTHPORT QLD 4215

Dear Dr Winearls

HREC Reference: HREC/16/QGC/78
Project title: Evaluation of extracorporeal membrane oxygen and carbon dioxide removal in critically ill adults.

The above proposal was submitted to the Chair of Gold Coast Health Service District Human Research Ethics Committee (HREC) for advice/opinion regarding ethical and scientific review on 11 March 2016.

I wish to acknowledge that the proposal does not require full HREC review on the basis that the project is recognised as not being research in accordance with the definition of Research on page 6 of the *National Statement on Ethical Conduct in Human Research (2007) Updated May 2015*. This study has been categorised as a **Quality Activity/Clinical Audit**.

Should you require any further information, please contact the HREC Coordinator, Vanessa Druett at GCHEthics@health.qld.gov.au or on 07 5687 3879.

Yours sincerely

Vanessa Druett
HREC Coordinator
On Behalf of
E/Prof Drew Nesdale
Chair of HREC
Gold Coast Hospital and Health Service

APPENDIX 5 Editorial on "Carbon dioxide clearance in critical care"

Anaesth Intensive Care 2013; **41:** 149-150

Editorial

Hypercapnia: keeping therapy and diagnosis distinct

Some aspects of intensivists' thinking on arterial carbon dioxide tension ($PaCO_2$) have changed dramatically over the past 30 years, while other facets are unaltered[1]. As a Fellow in critical care, I spent considerable time manipulating the ventilator to ensure that my patients' $PaCO_2$ remained within the normal range. Any increase in $PaCO_2$ above 45 mmHg was assumed to be harmful and evidence of laziness on the part of the fellow.

This thinking was overturned by a revolutionary study published in 1984 by Darioli and Perret[2]. Analysing a retrospective dataset collected in patients with status asthmaticus receiving mechanical ventilation, they found that the use of lower tidal volumes, with inevitable increase in $PaCO_2$, resulted in better survival. A few years later, Hickling et al[3] applied a similar approach in patients with the acute respiratory distress syndrome. A retrospective dataset again revealed better survival with use of permissive hypercapnia. A randomised controlled trial undertaken by Amato et al[4] corroborated the Perret-Hickling hypothesis; additional support subsequently came from a randomised trial conducted by the Acute Respiratory Distress Syndrome Network[5]. These studies and other research that address carbon dioxide clearance are reviewed by Tiruvoipati et al in the current issue of *Anaesthesia and Intensive Care*[6]. The authors note that there is little evidence that hypercapnia is harmful to critically ill patients; indeed, there is much evidence that hypercapnia can aid lung-repair mechanisms in certain circumstances[7].

Also in the current issue of *Anaesthesia and Intensive Care*, Joseph et al report the findings of a study undertaken to determine whether use of a tracheostomy achieves physiological benefits in mechanically ventilated patients[8]. Specifically, does a tracheostomy enhance carbon dioxide clearance compared with use of an endotracheal tube? And does it lower airway resistance? They answer 'no' to both questions.

Common sense would dictate that use of a tracheostomy, which bypasses a large portion of the upper airways, should reduce dead space. Studies conducted in cadavers reveal that a tracheostomy decreases anatomical dead space volume by about half[9]. But Joseph et al found that a tracheostomy had no effect on dead space to tidal volume ratio: 41±12.6% before and 40±14.6% after tracheotomy (P=0.75). Likewise, $PaCO_2$ did not budge: 35.4±6.96 mmHg before tracheotomy and 36.8±8.86 mmHg afterwards (P=0.55).

Why did the investigators not find a decrease in dead space? Here we need to distinguish geometric volume, as measured by filling an airway with water, and functional volume or physiologic dead space. Physiological dead space is defined as that part of the tidal volume that does not participate in gas exchange, a mixture of anatomic dead space in the conducting airways and pathologic alveolar dead space resulting from lung disease. If we form a mental picture of ventilation being achieved by bulk flow—with air moving down the trachea (and bronchi) and occupying the entire width of the airway—we expect a tracheostomy to decrease total dead space. Back in 1915, however, Henderson et al showed that this commonsensical picture of CO_2 clearance is wrong. In the days before technetium scans and radioactive labelling, Henderson blew tobacco smoke down a glass tube and found that smoke did "not move along the tube in a cylindrical column, filling the tube from side to side, but in the form of a very thin spike"[10]. When the investigator stopped the puff by placing his tongue against the opening of the tube, "the spike breaks instantly everywhere; and the tube is seen to be filled from side to side with a mixture of smoke and air". Henderson's demonstration that dead space operates as a thin spike, rather than an unvarying volume occupying the entire width of the airway, explains why Joseph et al failed to find a decrease in $PaCO_2$ following a tracheotomy.

The papers by Joseph et al and Tiruvoipati et al have one message in common: physicians should not devote undue efforts to lowering $PaCO_2$ in most critically ill patients. At first blush, this might suggest that intensivists should not bother themselves too much about hypercapnia. That interpretation would be dangerous. Here we need to make a distinction between diagnosis and therapy. In many instances, therapeutic manoeuvres designed to lower $PaCO_2$ may cause more harm than benefit. In contrast, $PaCO_2$ is vitally important in diagnosis, acting as a harbinger of impending disaster.

Interpretation of $PaCO_2$ readings in a spontaneously breathing patient needs to be grounded in an

understanding of the respiratory control system. The respiratory controllers—respiratory centres, neurons and muscles that produce alveolar ventilation—maintain a stable $PaCO_2$ across wide fluctuations in CO_2 production[11]. CO_2 production can vary tenfold during exercise, yet $PaCO_2$ remains virtually unchanged. This stability is achieved by the exquisite sensitivity of the chemoreceptor system, typically assessed by measuring the change in minute ventilation as a patient rebreathes CO_2. The normal range in healthy adults is 0.5–8.0 litre/minute/mmHg (1.5–5.0 in 80% of subjects)[11]. Thus, an increase in $PaCO_2$ of 3 mmHg should cause minute ventilation to increase by about 10 litres per minute (or double). Failure to observe such an increase signifies significant respiratory impairment, either because the patient won't breathe secondary to significant depression of respiratory motor output or the patient can't breathe consequent to increased mechanical load or respiratory muscle weakness.

The need for prudent interpretation of $PaCO_2$ readings in a spontaneously breathing patient is illustrated by a case on which I recently consulted. A young woman was admitted to a medical ward with acute pancreatitis for which she was receiving morphine at frequent intervals. Five days after admission, the patient experienced a cardiac arrest that resulted in irreversible hypoxic brain injury. An arterial blood gas obtained two days before the arrest revealed the following values: pH 7.29, $PaCO_2$ 44 mmHg, PaO_2 76 mmHg, bicarbonate 18 mEq/litre and oxygen saturation 93%. In the progress notes, the medical resident noted "Patient saturating well on two litres of oxygen with nasal cannula. PCO_2 levels within normal limits. Continue present management".

It is true that the patient's PCO_2 was within the normal range, but the recorded $PaCO_2$ signalled considerable compromise. The marked metabolic acidosis was producing substantial stimulation of the central chemoreceptors[11]. Consequently, the patient's $PaCO_2$ should have been much lower than 44 mmHg—more like 35–37 mmHg. The $PaCO_2$ of 44 mmHg represented significant respiratory depression. When the staff further increased the dosage of morphine, they markedly increased the patient's susceptibility to further respiratory depression, hypoventilation and hypoxaemia.

When thinking about $PaCO_2$ in critically ill patients, intensivists may adopt a laissez-faire approach towards hypercapnia in the ventilated patient, but a different mindset—more alert, and even a little radical—is needed when assessing $PaCO_2$ in a spontaneously breathing patient.

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REFERENCES

1. Tobin MJ. Preface. In: Tobin MJ (ed). Principles and Practice of Mechanical Ventilation, 3rd ed. New York: McGraw-Hill Inc., 2012, p. xxi-xxii.
2. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 1984; 129:385-387.
3. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990; 16:372-377.
4. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347-354
5. The Acute Respiratory Distress Syndrome Network. 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; 342:1301-1308.
6. Tiruvoipati R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. Anaesth Intensive Care 2013; 41:157-162.
7. Laffey JG, Kavanagh BP. Permissive hypercapnia. In: Tobin MJ (ed). Principles and Practice of Mechanical Ventilation, 3rd ed. New York: McGraw-Hill Inc., 2012, p. 377-401.
8. Joseph MJ, Khoury A, Mendoza AE, Adams S, Short KA, Charles AG. Tracheostomy in the critically ill: the myth of dead space. Anaesth Intensive Care 2013; 41:216-221
9. Nunn JF, Campbell EJM, Peckett BW. Anatomical subdivisions of the volume of respiratory dead space and effect of position of the jaw. J Appl Physiol 1959; 14:174-176.
10. Henderson Y, Chillingworth FP, Whitney JL. The respiratory dead space. Am J Physiol 1915; 38:1-19
11. Tobin MJ, Laghi F, Jubran A. Ventilatory failure, ventilator support and ventilator weaning. Comprehensive Physiology (Handbook of Physiology, American Physiological Society) 2012; 2:2871-2921.

APPENDIX 6 Editorial on "Hypercapnia and hypercapnic acidosis in sepsis: Harmful, beneficial, or unclear?"

EDITORIAL

The undiscovered country: therapeutic targeting of carbon dioxide levels in critically ill patients

Alistair D Nichol

In the current issue of *Critical Care and Resuscitation*, there are two complementary articles: one reviewing the biological effects of hypercapnia in sepsis[1] and another reporting the tidal volume delivery (including the effects on carbon dioxide [CO_2] levels) in patients without acute respiratory distress syndrome (ARDS) in Victoria, Australia.[2] These manuscripts highlight the profound and commonly unrecognised effects that altered CO_2 levels may have on our patients, and show how routine care in the intensive care unit (ICU) may significantly alter CO_2 homeostasis. It is important for bedside clinicians to appreciate both the physiological and the immunological effects of hyper- and hypocapnia but also for researchers seeking an easily inducible therapeutic agent with the potential to change patient outcomes. Given the ease by which CO_2 levels can be altered in critically ill ventilated patients, it is somewhat surprising to note the limited clinical data examining the long term effects of targeted CO_2 management in the ICU population to date.

First, Tiruvoipati and colleagues[1] review the extensive basic science and limited clinical studies describing the effects of hypercapnic acidosis and buffered hypercapnia (hypercapnia with a normal pH) in clinical practice.[3] This review highlights the current limits of our understanding, but also shows that hyerpcapnic acidosis has the potential to be a potent immunomodulator with immune suppressant effects in critically ill patients, including those with sepsis. Some animal models have suggested that this immunomodulator effect may be beneficial in sterile models of tissue injury but may be detrimental in live bacterial models (ie, with lack of adequate source control).[4] However, our current understanding is that hypercapnia is not detrimental in the presence of appropriate antibiotic therapy, suggesting it may be a safe therapeutic intervention.[4,5] This review summarises the growing body of evidence that hypercapnia, in addition to its profound physiological effects (ie, increasing heart rate, pulmonary vascular resistance etc), has potent immunomodulatory effects. More clinical studies of therapeutic hypercapnia are clearly needed.

Secondly, Eyeington and colleagues[2] describe the Victorian practice of mechanical ventilation management in patients without ARDS. This statewide observational study indicates a worrying "one size fits all" approach to mechanical ventilation in this cohort. While this article describes the delivery of tidal volumes in many patients far greater than what is currently recommended, it is interesting to examine the effects this "hyperventilation" has on CO_2 levels and acid base balance. Despite a prevailing trend towards tolerance of elevated levels of CO_2 in patients with ARDS to permit safe, low tidal volume ventilation (so-called permissive hypercapnia), this study would suggest that the opposite (ie, hypocapnia) is common in ICU patients without ARDS. It is likely that the potential immunological effects of this inadvertent alteration in CO_2 level are not appreciated in this cohort of patients.

It is difficult to think of another example of our practice where we would use an agent with the potential for chronotropic, inotropic, systemic vasodilator and pulmonary vasoconstrictor effects combined with the potential for immunomodulation without thoughtful consideration. Furthermore, while there are situations (ie, traumatic brain injury, right-sided heart failure, pulmonary hypertension etc) where we assess and tightly control CO_2 levels due to unwanted physiological effects, or situations where we tolerate hypercapnia to minimise lung stretch (ie, severe ARDS), in the majority of patients, we continue not to value or study the therapeutic potential of hypercapnia. Hopefully, the two studies reported in this issue of the Journal will help trigger more research in this field.

We are starting to see the targeting of CO_2 levels to alter long term outcomes, so-called therapeutic hypercapnia, for the first time. The TAME (Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest) study (ClinicalTrials.gov identifier NCT03114033) a large (n = 1700) randomised controlled trial of comatose patients after out-of-hospital cardiac arrest aims to randomly assign patients to normocapnic or hypercapnic management for 24 hours after promising phase 2 work.[6]

It is clear from the two studies in this issue of *Critical Care and Resuscitation* that we need to consider how we manage CO_2 levels in many different patient populations in the ICU, and that we need to consider a broader role for therapeutic hypercapnia. Further studies and clinical trials in this field are an important additional research agenda in critical care medicine.

Competing interests

I am an investigator in the TAME study.

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References

1 Tiruvoipati R, Gupta S, Pilcher D, Bailey M. Hypercapnia and hypercapnic acidosis in sepsis: harmful, beneficial or unclear? *Crit Care Resusc* 2018; 20: 94-100.

2 Eyeington CT, Glassford NJ, Darvall J, et al. Ventilation management in Victorian intensive care unit patients without acute respiratory distress syndrome. *Crit Care Resusc* 2018; 20: 101-108.

3 Curley G, Contreras MM, Nichol AD, Higgins BD, Laffey JG. Hypercapnia and acidosis in sepsis: a double-edged sword? *Anesthesiology.* 2010 Feb; 112(2): 462-72. doi: 10.1097/ALN.0b013e3181ca361f. Review. PMID: 20068449

4 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: 2128-35.

5 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: 2953-61.

6 Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic hypercapnia after cardiac arrest: a phase II multi-centre randomized controlled trial. *Resuscitation* 2016; 104: 83-90. ❑

APPENDIX 7 Editorial on "Effects of hypercapnia and hypercapnic acidosis in mechanically ventilated patients".

transmission (10). The data on the inequality of healthcare provider risk support greater inclusion of therapy providers in prevention programs. The number of therapy providers on duty may be too few to truly cohort MDRAB-colonized patient care. Alternative means of cohorting, such as providing services to these patients at the end of shift, may serve to reduce transmission risk using existing staffing. Finally, active surveillance for *Acinetobacter* (and other pathogens) is designed to identify patients who serve as a reservoir for transmission (3). Even with active surveillance, colonized patients are not always recognized. Universal prevention measures (such as gowning and gloving, increased environmental cleaning, and chlorhexidine bathing) may lend additional control to transmission from unknown reservoirs.

This study is small, single center, and limited by the lack of genomic typing. Nevertheless, it contributes to our understanding of MDRAB transmission by supporting components of previously reported control bundles. Further studies are needed into how MDRAB and other resistant pathogens are transmitted, including studies carefully structured to weigh the value of individual interventions. Future bundle approaches to *Acinetobacter* control must be targeted and effective, rather than too little prevention too late or too much too soon.

REFERENCES

1. Villegas MV, Hartstein AI: *Acinetobacter* outbreaks, 1977–2000. *Infect Control Hosp Epidemiol* 2003; 24:284–295
2. Nelson RE, Schweizer ML, Perencevich EN, et al: Costs and mortality associated with multidrug-resistant healthcare-associated *Acinetobacter* infections. *Infect Control Hosp Epidemiol* 2016; 37:1212–1218
3. Rodríguez-Baño J, García L, Ramírez E, et al: Long-term control of hospital-wide, endemic multidrug-resistant *Acinetobacter baumannii* through a comprehensive "bundle" approach. *Am J Infect Control* 2009; 37:715–722
4. Palmore TN, Michelin AV, Bordner M, et al: Use of adherence monitors as part of a team approach to control clonal spread of multidrug-resistant *Acinetobacter baumannii* in a research hospital. *Infect Control Hosp Epidemiol* 2011; 32:1166–1172
5. Wright MO, Hebden JN, Harris AD, et al: Aggressive control measures for resistant *Acinetobacter baumannii* and the impact on acquisition of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* in a medical intensive care unit. *Infect Control Hosp Epidemiol* 2004; 25:167–168
6. Munoz-Price LS, Carling P, Cleary T, et al: Control of a two-decade endemic situation with carbapenem-resistant *Acinetobacter baumannii*: Electronic dissemination of a bundle of interventions. *Am J Infect Control* 2014; 42:466–471
7. Cheon S, Kim MJ, Yun SJ, et al: Controlling endemic multidrug-resistant *Acinetobacter baumannii* in intensive care units using antimicrobial stewardship and infection control. *Korean J Intern Med* 2016; 31:367–374
8. Ray A, Perez F, Beltramini AM, et al: Use of vaporized hydrogen peroxide decontamination during an outbreak of multidrug-resistant *Acinetobacter baumannii* infection at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2010; 31:1236–1241
9. Thom KA, Rock C, Jackson SS, et al: Factors Leading to Transmission Risk of *Acinetobacter baumannii*. *Crit Care Med* 2017; 45:e633–e639
10. Harris AD, Pineles L, Belton B, et al; Benefits of Universal Glove and Gown (BUGG) Investigators: Universal glove and gown use and acquisition of antibiotic-resistant bacteria in the ICU: A randomized trial. *JAMA* 2013; 310:1571–1580
11. Wetzker W, Bunte-Schönberger K, Walter J, et al: Compliance with hand hygiene: Reference data from the national hand hygiene campaign in Germany. *J Hosp Infect* 2016; 92:328–331
12. Espinal P, Martí S, Vila J: Effect of biofilm formation on the survival of *Acinetobacter baumannii* on dry surfaces. *J Hosp Infect* 2012; 80:56–60

A Climate Change in Mechanical Ventilation?*

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In the healthy human being, the P_{CO_2} and the corresponding pH value are kept stable in a small physiologic range. Although a pronounced deviation of the pH will most likely lead to systemic disturbances, it remains a matter of debate whether hypercapnia itself is dangerous. Prior to the routine measurement of exhaled $_{CO_2}$ concentration during anesthesia, hypercapnia could occur accidentally in anesthetized patients. Several case studies in humans report a surprisingly good tolerance of increased P_{CO_2} and respiratory acidosis despite the well-known fact that hypercapnia can cause a variety of negative effects on a multitude of physiologic functions including cerebral blood flow, pulmonary arterial tension, myocardial contractility, heart rhythm, and the autonomic nervous system (1). Predicting the precise reaction to hypercapnia is complicated by the fact that $_{CO_2}$ can either act directly or indirectly through the concomitant respiratory acidosis and that its effects on different physiologic systems can be opposed and dose dependant.

Hypercapnia occurs frequently in the acute respiratory distress syndrome (ARDS). It is believed to be the result of alveolar hypoventilation (2) and of an increased dead space probably due to lesions of the pulmonary vasculature including thrombotic and inflammatory mechanisms (3). In a recent observational study on 2,377 patients with ARDS, Bellani et al (4) found a mean Pa_{CO_2} of 46.0 mm Hg (95% CI, 45.4–46.6) corresponding to a mean pH of 7.33 (95% CI, 7.32–7.33). In the subgroup of 557 patients with severe ARDS according to the Berlin definition, mean Pa_{CO_2} was further increased to 52.2 mm Hg (95% CI, 50.7–53.7) with a mean pH of 7.27 (95% CI, 7.26–7.29).

***See also p. e649.**

Key Words: carbon dioxide; mechanical ventilation; permissive hypercapnia; respiratory acidosis

Dr. Max has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000002398

The recommended use of a lung-protective ventilation strategy with reduced tidal volumes in patients with ARDS may further increase $Paco_2$. Using a mean tidal volume of 348 ± 6 mL, a mean positive end-expiratory pressure of 16.4 ± 0.4 cm H_2O, and intermittent recruitment maneuvers, Amato et al (5) observed a gradual increase of mean $Paco_2$ from 38.1 ± 1.6 to 55.0 ± 1.2 mm Hg after 36 hours of mechanical ventilation with a concomitant decrease of the arterial pH from 7.32 ± 0.02 to 7.25 ± 0.01. In this study, the so-called "permissive hypercapnia" did not produce any clinically detectable side effects, and the slight respiratory acidosis was considered negligible regarding the significant improvement of survival when this ventilator strategy was used.

Whether hypercapnia and respiratory acidosis could even exert beneficial effects in patients with ARDS, inter alia through a down-regulation of the release and activity of pro-inflammatory mediators as shown in experimental studies, is yet unclear (for a comprehensive review, see [6]). Kregenow et al (7) studied the impact of hypercapnia ($Paco_2$, > 40 to < 65 mm Hg) and respiratory acidosis (pH, < 7.40 to > 7.15) during the first 31 hours of mechanical ventilation in a post hoc analysis of a study investigating the effect of higher versus lower tidal volumes in patients with acute lung injury and ARDS (8). In the group ventilated with a tidal volume of 12 mL/kg body weight, the authors found that hypercapnia and respiratory acidosis were associated with a decrease of the adjusted odds ratios for 28-day mortality when compared to patients with a normal $Paco_2$ (35–40 mm Hg) and pH (7.40–7.45) and to patients with respiratory alkalosis ($Paco_2$, < 35 mm Hg; pH, > 7.45) (7). This effect was most pronounced in patients with the highest $Paco_2$ and the lowest pH. In the group of patients submitted to lung-protective ventilation with a tidal volume of 6 mL/kg body weight, hypercapnia and respiratory acidosis had no effect on survival. The authors speculated that hypercapnic acidosis may have a protective effect and may mitigate lung injury in the presence of a more injurious form of mechanical ventilation with larger tidal volumes. However, the small number of patients included in the study make a valid interpretation difficult.

In late ARDS, the $Paco_2$ can increase as a consequence of structural changes in the lung (9). These changes are characterized by the appearance of emphysema-like lesions with a decrease of respiratory compliance and an increase of dead space, which shows a significant correlation with an increase of mortality (3). A correlation between a decrease in $Paco_2$ and an increase of the survival rate was shown for patients with ARDS ventilated in the prone position (10). Subsequent investigations were able to show that the prone position induced a recruitment of nonaerated lung tissue, a decrease of the physiologic dead space ratio, and an increase of the amount of normally ventilated lung (10–12). These studies suggest that an increase of $Paco_2$ may serve as a marker for the severity of lung parenchymal lesions in ARDS and that a decrease of $Paco_2$ may indicate a reduction of alveolar consolidation and dead space, for example, through alveolar recruitment and a less injurious ventilation, that will ultimately correlate with an improved survival rate.

In this issue of *Critical Care Medicine*, Tiruvoipati et al (13) present a retrospective analysis aimed to assess the impact of compensated hypercapnia and hypercapnic acidosis on hospital mortality in 252,812 patients receiving mechanical ventilation. $Paco_2$ and pH data for each patient were derived from a single arterial blood gas analysis, taken during the first 24 hours after admission to the ICU. Patients were divided into three predefined subgroups: 1) patients with a normal acid-base balance ($Paco_2$, 35–45 mm Hg; pH, 7.35–7.45); 2) patients with compensated hypercapnia ($Paco_2$, > 45 mm Hg; pH, 7.35–7.45); and 3) patients with respiratory acidosis ($Paco_2$, > 45 mm Hg; pH, < 7.35). The authors found that hospital mortality was higher in the groups with compensated hypercapnia and respiratory acidosis, and this finding persisted after adjusting for several risk factors that are usually associated with increased hospital mortality. However, given the retrospective and observational design of their study, the authors conclude that their finding may only suggest an association but not causation between hypercapnia and mortality.

The results of Tiruvoipati et al (13) match the results of other recent observational studies, which also show an increased mortality in hypercapnic patients with respiratory failure (14). However, due to limitations of the study design and patient characterization, it may be impossible to draw conclusions for clinical practice. The most important question is the etiology of hypercapnia and respiratory acidosis. Between one third and half of the patients in each of the three predefined groups were patients after cardiovascular surgery. In this subgroup, hypercapnia and respiratory acidosis can be an indicator for a more severe cardiac dysfunction, especially in patients after cardiac arrest and in cardiogenic shock. Similarly, the development of hypercapnia and respiratory acidosis in patients with chronic respiratory insufficiency may indicate a more advanced state of the chronic pulmonary disease with increased odds of death. The severity of preexisting comorbidity may vary, although the patients are classified in the same subgroup (e.g., chronic respiratory disease). Although the authors suggest that different degrees of disease severity and mortality risk are equally distributed between the three study groups, one could argue that hypercapnia is a marker for disease severity, indicating that the sickest patients with the highest mortality are accumulated in the groups with hypercapnia and respiratory acidosis. This would be supported by the finding of Tiruvoipati et al (13) that hypercapnia and mortality show a good correlation and is in accordance with the results of the above-mentioned studies showing a good correlation between a decrease in $Paco_2$ and survival (10, 12). However, none of the two hypotheses can be substantiated by the data presented by Tiruvoipati et al (13).

The question, whether ventilation with low tidal volumes combined, if necessary, with permissive hypercapnia is a clinically important cause for the development of hypercapnia and respiratory acidosis remains unanswered by the authors as well in the absence of any ventilator data. An increased $Paco_2$ could be the result of a more severe lung injury or of

a distinct ventilator strategy. However, it seems unlikely that any clinician would accept severe hypercapnia and respiratory acidosis due to ventilator management, unless the severity of pulmonary disease does not allow a different respiratory setting. Although permissive hypercapnia has been largely adopted in clinical practice, therapeutic hypercapnia, which is the arbitrary increase of $Paco_2$ in otherwise normocapnic patients, has never become a standard therapeutic procedure, and it seems justified to exclude the possibility that this experimental approach has influenced the results of the presented study. This raises the question what conclusions for the clinical practice can be drawn from the presented study. Hypercapnia can have potentially dangerous side effects, especially in patients with advanced comorbidity and should be avoided or limited whenever possible without doing harm. Permissive hypercapnia as a consequence of low tidal volume ventilation, one of the rare interventions that has been consistently associated with an improved survival, should be accepted and seems safe in certain limits. Severe hypercapnia and respiratory acidosis may require the use of extracorporeal gas exchange, but further studies are necessary to unveil, which $Paco_2$ and pH will be beneficial in clinical practice.

REFERENCES

1. Prys-Roberts C, Smith WD, Nunn JF: Accidental severe hypercapnia during anaesthesia. A case report and review of some physiological effects. *Br J Anaesth* 1967; 39:257–267
2. Hubmayr RD: Perspective on lung injury and recruitment: A skeptical look at the opening and collapse story. *Am J Respir Crit Care Med* 2002; 165:1647–1653
3. 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; 346:1281–1286
4. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
5. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
6. Ismaiel NM, Henzler D: Effects of hypercapnia and hypercapnic acidosis on attenuation of ventilator-associated lung injury. *Minerva Anestesiol* 2011; 77:723–733
7. Kregenow DA, Rubenfeld GD, Hudson LD, et al: Hypercapnic acidosis and mortality in acute lung injury. *Crit Care Med* 2006; 34:1–7
8. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
9. Gattinoni L, Bombino M, Pelosi P, et al: Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994; 271:1772–1779
10. Gattinoni L, Vagginelli F, Carlesso E, et al; Prone-Supine Study Group: Decrease in PaCO2 with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003; 31:2727–2733
11. Vieillard-Baron A, Rabiller A, Chergui K, et al: Prone position improves mechanics and alveolar ventilation in acute respiratory distress syndrome. *Intensive Care Med* 2005; 31:220–226
12. Protti A, Chiumello D, Cressoni M, et al: Relationship between gas exchange response to prone position and lung recruitability during acute respiratory failure. *Intensive Care Med* 2009; 35:1011–1017
13. Tiruvoipati R, Pilcher D, Buscher H, et al: Effects of Hypercapnia and Hypercapnic Acidosis on Hospital Mortality in Mechanically Ventilated Patients. *Crit Care Med* 2017; 45:e649–e656
14. Nin N, Muriel A, Penuelas O, et al; VENTILA Group: Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory Distress syndrome. *Intensive Care Med* 2017; 43:200–208

Early Electroencephalography for Neurologic Prognostication After Cardiac Arrest: More Optimization Before Generalization?*

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***See also p. e674.**

Key Words: cardiac arrest; coma; diagnostic techniques, neurologic; electroencephalography; prognosis

Dr. Gaspard has disclosed that he does not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000002419

Cardiac arrest (CA) is the most common cause of natural deaths in Western countries. Although an increasing number of patients achieve a return of spontaneous circulation (ROSC) and are admitted alive to the hospital, no more than one-third of them will eventually be discharged with a good neurologic recovery, underscoring the importance of early neurologic prognostication to guide patient care. Current guidelines recommend that prognostication relies on a combination of methods, in particular clinical neurologic examination, somatosensory-evoked potentials (SSEPs), and electroencephalography (EEG) (1).

Studies using continuous EEG have shown that EEG had the best prognostic accuracy at 12 and 24 hours after ROSC, with a normal voltage, continuous EEG devoid of periodic or epileptiform discharges ("benign" EEG) at 12 hours being most often associated with good recovery and suppressed (< 10 μV) with

APPENDIX 8 Editorial on “Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with Cerebral Injury”

EDITORIAL

Arterial Partial Pressure of Carbon Dioxide and Secondary Brain Injury—6 Degrees of Separation?

J. Claude Hemphill III, MD, MAS

Secondary brain injury (SBI) occurs when tissue made vulnerable by a primary brain injury (eg, traumatic brain injury [TBI], stroke, or global cerebral ischemia), is exposed to additional insults, such as low blood flow, hypoxia, fever, seizures, or glucose concentration extremes. The prevention and treatment of SBI forms the basis for these conditions' neurocritical care management; guidelines emphasize maintaining parameters associated with blood pressure and ventilation thought to limit SBI. Cerebral blood flow (CBF) is regulated by a complex interplay of neurovascular coupling, pressure autoregulation, arterial blood gases, and other elements.[1] Changes in arterial partial pressure of carbon dioxide (Pco_2) result in changes to cerebral blood volume (CBV) and CBF, with an acute excess of carbon dioxide (hypercapnia) associated with an increase in CBV, CBF, and intracranial pressure (ICP) and its opposite, hypocapnia, associated with decreasing ICP, possibly at the expense of CBF.[2] Balancing these 2 potential concerns has led to clinical acute ventilation strategy recommendations of a Pco_2 range of 35 to 45 mm Hg after resuscitation from cardiac arrest and avoidance of prolonged hyperventilation to a Pco_2 level of 25 mm Hg or less in patients with TBI.[3,4] There is an inextricable link between Pco_2 and pH levels through bicarbonate production and buffering (normal serum bicarbonate concentration is 25 mmol/L, normal serum pH is 7.4, and normal Pco_2 is 40 mm Hg). Interestingly, these recommendations do not include a pH target.

Related article

In this context, the study by Tiruvoipati et al[5] is interesting, specifically regarding the relative importance of hypercapnia with or without acidosis on outcomes after acute brain injury. Using a large, prospective database from most intensive care units (ICU) in Australia and New Zealand, they studied more than 30 000 mechanically ventilated patients who had TBI, resuscitation from cardiac arrest, or stroke (of any subtype). They defined normocapnia as a Pco_2 level of 35 to 45 mm Hg, hypercapnia as a Pco_2 level greater than 45 mm Hg, a normal pH as 7.35 to 7.45, and acidosis as a pH of less than 7.35. Using the single arterial blood gas with the worst combination of pH and Pco_2 (based on Acute Physiology and Chronic Health Evaluation III scoring) in the 24 hours after ICU admission, they divided the cohort into 3 subgroups: those with normocapnia and normal pH, those with compensated hypercapnia (involving a normal pH level), and those with hypercapnic acidosis. Patients with metabolic acidosis or alkalosis associated with respiratory or metabolic causes were excluded, narrowing the cohort to address the association of Pco_2 and pH levels. The primary outcome was in-hospital mortality, which is a limitation given that long-term functional outcome is usually the most important outcome after acute brain injury; however, in-hospital mortality was reliably available in their large database. Extensive statistical analyses adjusted for potential confounders and assessed subgroups defined by individual diagnostic categories and subcategories defined by baseline clinical severity per the Glasgow Coma Scale.

The principal finding was that patients with acute cerebral injury and hypercapnic acidosis had a higher risk of mortality than those with acute cerebral injury, normocapnia, and normal pH.[5] This confirms studies that have found acidosis associated with worsened outcomes in patients with acute brain injuries. Perhaps most interestingly, Tiruvoipati et al[5] found that patients with compensated hypercapnia (characterized by elevated Pco_2 level and normal pH level) did not have increased mortality risk, but rather the same likelihood of mortality as those with normocapnia and a normal pH. This is a potentially important finding that suggests that any impact of a single value of elevated Pco_2 early after acute brain injury needs to be considered in the context of the patient's acid-base status (ie, pH value). Extensive subgroup analyses did not find substantial interactions altering the conclusions for the compensated hypercapnia group. Hypercapnic acidosis did seem to have the greatest risk for poor outcomes in patients who had had cardiac arrest and patients with TBI who had very low Glasgow Coma Scale scores. Also, in the absence of compensation, the higher the Pco_2 level, the higher the risk of death.

Notably, the group with compensated hypercapnia was quite small, composing only 4.4% of the cohort.[5] Reasons for this early compensation (within the first day in the ICU) were unavailable. Also, despite extensive statistical adjustment, residual confounding could exist, especially with respect to the hypercapnic acidosis group. Although patients with metabolic acidosis were excluded, the values presented by Tiruvoipati et al[5] for lowest plasma bicarbonate level, worst Pco_2 level, and worst pH level (Table 1) suggest that some of these patients may have had a component of metabolic acidosis, perhaps because of other metabolic derangements, that could be associated with outcomes. Ultimately, it may be that this cohort overall divides into 2 groups: people who are very sick and those who are not as sick, with the compensated hypercapnia group in the healthier group. Even so, these limitations do not change the similarity of the outcome of the compensated hypercapnia group with patients with normal pH and Pco_2 levels and its dissimilarity to patients with low pH and high Pco_2 levels.

Why would this matter to clinical practitioners? Clinicians in the ICU who desire guidance on ventilating patients with acute brain injury generally find recommendations to target an absolute P_{CO_2} level within a certain range, without attention to pH level.[3,6,7] Adhering to that approach would lead clinicians to purposefully hyperventilate a patient with compensated hypercapnia to lower the P_{CO_2} level, even if it resulted in alkalosis. Also, these suggested approaches are not limited to the first day of hospital admission. This likely results in multiple changes to ventilatory parameters during an ICU stay to keep the patient's absolute P_{CO_2} parameter within range. Since the presumptive reason to care about the P_{CO_2} level in patients with acute brain injury is the association of this level with CBF and SBI, it is worth examining if this approach makes sense. Additionally, the use of induced hypercapnia as a therapeutic intervention for postcardiac arrest brain injury has been considered with some supporting evidence derived from an analysis of the same database in this current study.[8,9]

It has long been established that an acute increase in P_{CO_2} levels decreases cerebrovascular resistance and increases CBF, with an acute decrease in P_{CO_2} resulting in the opposite.[10] This is thought to be primarily because of a change in cerebrospinal fluid pH, which leads to vasodilation (acute hypercapnia) of pial arterioles, or vasoconstriction (acute hypocapnia).[11] However, over time (sometimes even within a few hours), the buffering capacity of the extracellular fluid in the brain attenuates this effect, even with a persistently low P_{CO_2} level. In a clinical trial on TBI used as an example of potential harm or at least lack of efficacy for acute hyperventilation, cerebrospinal fluid bicarbonate progressively decreased, and P_{CO_2} levels in cerebrospinal fluid normalized despite ongoing low levels of arterial P_{CO_2}.[12] In addition to pH-dependent mechanisms, P_{CO_2}-dependent mechanisms have been postulated, perhaps involving nitric oxide.[13] Thus, P_{CO_2} influences extracellular pH, which then influences cerebrovascular resistance, which influences CBV, which is associated with CBF, which partially determines the cerebral metabolic rate of oxygen utilization, which then determines whether sufficient oxygen is delivered to meet cellular metabolic demand. If what we care about is limiting secondary brain injury by ensuring adequate oxygen delivery to the brain, then it seems an absolute arterial P_{CO_2} level is many steps removed. Several of these steps may be associated with other factors, including concurrent hypotension, arterial P_{O_2}, systemic acid-base status, and neurovascular coupling. We have probably oversimplified ventilation in patients with brain injury, which is quite complex and difficult to accurately access by just measuring arterial P_{CO_2} level and adjusting ventilator settings. While Tiruvoipati et al[5] did not include changes in arterial blood gases over time or report on the ventilator management paradigms used in their patients, they do support the notion that the association between pH and P_{CO_2} is important in acute brain injury.

If not by regulating P_{CO_2}, then how to target ventilation in acute brain injury? First, it is important to distinguish between an absolute P_{CO_2} value and a change in that value. Change is probably most important, although it might be difficult to interpret the importance on SBI from a single absolute value, especially in the setting of metabolic compensation. Actively changing the acute P_{CO_2} for a short period or avoiding change might make sense in the management of a patient with a brain injury. Second, pH matters and acidosis should be treated by targeting the underlying respiratory or metabolic derangement. If the pH level is normal, it may be fine to leave well enough alone. Finally, if SBI management is the goal, then monitoring and measuring parameters such as ICP, brain tissue oxygen tension, CBF, and cerebral microdialysis, which give more direct information into a patient's status, may help rationally drive therapy. Reducing the degrees of separation between what we measure and what we care about may be the real lesson in transitioning from a one size fits all approach to personalized medicine.

ARTICLE INFORMATION

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Published Online: March 19, 2018. doi:10.1001/jamaneurol.2018.0003

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol*. 2014;592(5):841-859.

2. Stocchetti N, Maas AI, Chieregato A, van der Plas AA. Hyperventilation in head injury: a review. *Chest*. 2005;127(5):1812-1827.

3. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(18)(suppl 2):S465-S482.

4. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6-15.

5. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Impact of hypercapnia and hypercapnic acidosis on clinical outcomes in mechanically ventilated patients with cerebral injury [published online March 19, 2018]. *JAMA Neurol*. doi:10.1001/jamaneurol.2018.0123.

6. Haddad SH, Arabi YM. Critical care management of severe traumatic brain injury in adults. *Scand J Trauma Resusc Emerg Med*. 2012;20:12.

7. Puntis M, Smith M. Critical care management of adult traumatic brain injury. *Anaesth Intensive Care Med*. 2017;18(5):233-238.

8. Eastwood GM, Nichol A, Wise MP. Targeted therapeutic mild hypercapnia after cardiac arrest. *Crit Care*. 2017;21(1):196.

9. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation*. 2013;84(7):927-934.

10. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. *Stroke*. 1972;3(5):566-575.

11. Lassen NA. Brain extracellular pH: the main factor controlling cerebral blood flow. *Scand J Clin Lab Invest*. 1968;22(4):247-251.

12. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. 1991;75(5):731-739.

13. Yoon S, Zuccarello M, Rapoport RM. pCO(2) and pH regulation of cerebral blood flow. *Front Physiol*. 2012;3:365.

APPENDIX 9 Media Release by MEDPAGE TODAY

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Compensated Hypercapnia Tied to Lower Mortality Odds

— Study looked at ICU patients with cerebral injury on mechanical ventilation

by Judy George, Contributing Writer, MedPage Today
March 20, 2018

Hypercapnia, when compensated to normal pH during the first 24 hours of ICU admission, may not be harmful in mechanically ventilated patients with acute cerebral injury, a retrospective study in Australia and New Zealand found.

In patients with cerebral injury, hypercapnic acidosis was associated with increased hospital mortality, but compensated hypercapnia was associated with the same likelihood of mortality as normocapnia and normal pH, reported Ravindranath Tiruvoipati, MBBS, FCICM, of Frankston Hospital in Victoria, Australia, and colleagues.

Mortality odds also increased with increasing partial pressure of arterial carbon dioxide (PCO_2 or $PaCO_2$) in patients with hypercapnic acidosis, but not in patients with compensated hypercapnia, they wrote in JAMA Neurology.

High PCO_2 (hypercapnia) can be associated with a low pH (hypercapnic acidosis) or a normal pH (compensated hypercapnia). "Many studies have investigated the effects of PCO_2 and pH in critically ill patients with cerebral injury. These studies have shown that hypercapnia and low pH are harmful for patients," Tiruvoipati told MedPage Today. "All these studies investigated the effects of PCO_2 and pH in isolation. PCO_2 and pH, however, are interrelated, where changes in PCO_2 will influence the pH."

Secondary brain injury occurs when tissue weakened by a primary injury -- such as traumatic brain injury (TBI), global cerebral ischemia, or stroke -- is exposed to additional insults like hypoxia, low blood flow, or other elements. Hypercapnia is

The researchers reviewed all patients who had cerebral injury from cardiac arrest, stroke, and TBI who were mechanically ventilated at 167 ICUs in Australia and New Zealand from 2000 to 2015, excluding patients with metabolic acidosis or alkalosis associated with a respiratory or metabolic cause. They looked at 30,742 patients who had an average age of 55; 71% were men. The primary outcome was in-hospital mortality, which was more reliably available in patient records than other measures like long-term functional outcome.

The researchers defined normocapnia as a PCO_2 level of 35 to 45 mm Hg, hypercapnia as a PCO_2 level greater than 45 mm Hg, a normal pH as 7.35 to 7.45, and acidosis as a pH of less than 7.35. Using the single arterial blood gas with the worst combination of pH and PCO_2 during the first 24 hours of ICU stay, they classified patients into three groups: normocapnia and normal pH, compensated hypercapnia, and hypercapnic acidosis.

Patients with hypercapnic acidosis had the highest unadjusted mortality rates. Compared with patients with normocapnia and normal pH, hypercapnic acidosis patients showed increased adjusted odds of mortality in all three diagnostic categories: cardiac arrest (odds ratio 1.51), stroke (OR 1.43), and TBI (OR 1.22).

The researchers saw no difference in mortality between patients who had compensated hypercapnia compared with patients who had normocapnia and normal pH.

Patients with hypercapnic acidosis had increased odds of hospital mortality with increasing PCO_2, but no similar increase in mortality occurred in patients with compensated hypercapnia. This was consistent across all three groups of patients with cerebral injury.

This finding suggests that any effect of a single value of elevated PCO_2 early after acute brain injury needs to be considered in the context of the patient's acid-base status, noted J. Claude Hemphill III, MD, of the University of California in San Francisco, in an accompanying editorial.

"This paper shows that patients with compensated hypercapnia are a different group of patients than ones with hypercapnia and acidosis," he told MedPage Today.

hyperventilate a patient with compensated hypercapnia to lower the PCO_2 level, even if it resulted in alkalosis.

"It's not just the $PaCO_2$ that is important," Hemphill said. "It's the $PaCo_2$ and the pH and their relationship that's going to help define the factor of cerebral blood flow and perfusion. If the pH level is normal, it may be fine to leave well enough alone."

The group with compensated hypercapnia in this study was small, representing only 4.4% of the cohort, and reasons why they compensated on their first day in the ICU were unavailable. The researchers did not have cerebral blood flow, intracranial pressure, or neuroimaging data to evaluate possible mechanisms associated with increased mortality among hypercapnic acidosis patients. Despite extensive statistical adjustment, residual confounding could have existed, especially in the hypercapnic acidosis group.

Tiruvoipati and co-authors, as well as Hemphill, disclosed no relevant relationships with industry.

Reviewed by Robert Jasmer, MD *Associate Clinical Professor of Medicine, University of California, San Francisco and Dorothy Caputo, MA, BSN, RN, Nurse Planner*

LAST UPDATED 03.21.2018

Primary Source
JAMA Neurology
Source Reference: *Tiruvoipati R, et al "Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury" JAMA Neurol 2018; DOI:10.1001/jamaneurol.2018.0123.*

Secondary Source
JAMA Neurology
Source Reference: *Hemphill JC "Arterial partial pressure of carbon dioxide and secondary brain injury -- 6 degrees of separation?" JAMA Neurol 2018 DOI:10.1001/jamaneurol.2018.0003.*

APPENDIX 10 Media Release by Monash University

Monash study reveals insights into brain injury, blood carbon dioxide levels and hospital deaths

ccsmonash.blogspot.com.au/2018/04/monash-study-reveals-insights-into.html

by Anne Crawford

A large multi-centre study has made an important finding about the relationship between hypercapnia (high carbon dioxide or CO2) in the blood of patients with acute brain injury and hospital mortality. CO2 makes your blood more acidic which, if not adjusted, can affect your outcomes for the worse.

Professor Ravi Tiruvoipati

Professor Ravindranath Tiruvoipati, Adjunct Clinical Professor at the Peninsula Clinical School, Monash University and Intensive Care Specialist at Frankston Hospital, Peninsula Health, was first author on the paper, published in JAMA Neurology.

Professor Tiruvoipati looked at data from 30,742 patients with acute cerebral injury admitted to 167 intensive care units in Australia and New Zealand between January 2000 and December 2015 aiming to unravel the complex relationship between blood CO2 (PCO2), blood acidosis (pH) and hospital mortality.

High carbon dioxide levels set in due to several causes in patients who are critically ill.

Many studies have investigated the effects of partial pressure of arterial carbon dioxide (PCO2) and pH in critically ill patients with cerebral injury, showing that high PCO2 or low pH is harmful for patients. However, they all investigated the effects of PCO2 and pH in isolation – PCO2 and pH are interrelated. A high PCO2 can be associated with a low pH (hypercapnic acidosis) or a normal pH (compensated hypercapnia).

The researchers investigated the association of PCO2 and pH in conjunction to differentiate the association of hypercapnic acidosis and compensated hypercapnia in patients with acute cerebral injury caused by cardiac arrest, stroke and traumatic brain injury.

As such, it is the first and largest study relating blood carbon dioxide and pH status to mortality in such patients.

Patients with brain injury admitted to ICU for mechanical ventilation were classified into three groups based on a combination of arterial pH and arterial carbon dioxide levels: those with normal CO2 and pH; high CO2 and normal pH (compensated hypercapnia; and high CO2 and low pH during the first 24 hours of ICU stay.

The study concluded that hypercapnic acidosis in patients during the first 24 hours of ICU was associated with up to 30% increased risk of hospital mortality, compared to those with normal CO2 and pH. However, those with compensated hypercapnia did not have an increase in risk of death compared with those with normal CO2 and pH. Furthermore, in patients with hypercapnic acidosis the risk of hospital mortality increased with increasing PCO2 while in patients with compensated hypercapnia no increased risk of mortality was noted with increasing PCO2.

An editorial on the study, in the same issue of JAMA Neurology, noted that while clinical acute ventilation strategy recommendations specify a range for blood CO2 levels, they do not include a pH target. “In this context, the study by Tiruvoipati et al5 is interesting, specifically regarding the relative importance of hypercapnia with or without acidosis on outcomes after acute brain injury,” the editorial notes.

The editorial also says the finding that “patients with compensated hypercapnia did not have increased mortality risk, but rather the same likelihood of mortality as those with normocapnia and a normal pH” is “potentially important”. “(It) suggests that any impact of a single value of elevated blood CO2 early after acute brain injury needs to be considered in the context of the patient’s acid-base status (ie, pH value).”

It then discusses the implications of this for clinical ICU practitioners.

Professor Tiruvoipati said, “It is important to interpret PCO2 levels in conjunction with pH when treating patients with cerebral injury. Our study shows that hypercapnic acidosis (high PCO2 and low pH) was associated with increased hospital mortality and should be avoided or actively treated. However, when elevated CO2 is associated with a normal pH it may not be harmful.”

Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury. JAMA Neurol. 2018 Mar 19. doi: 10.1001/jamaneurol.2018.0123. [Epub ahead of print]

APPENDIX 11 Letter to the Editor

Letters

COMMENT & RESPONSE

What is the Association With Dissociation?

To the Editor We read with interest the article by Tiruvoipati et al.[1] We recognize and appreciate their data analysis of a large cohort that assessed the association of hypercapnic acidosis with cerebral injury. However, given the inherent limitations to retrospective data sets, we question whether hypercarbic acidosis yields deleterious outcomes and whether serum pH normalization improves neurological outcomes. In the article, the authors defined *compensated hypercapnia* as an elevated partial pressure of carbon dioxide (Pco_2 > 45 mm Hg) with a normal pH level (7.35-7.45) and *hypercapnic acidosis* (Pco_2 > 45 mm Hg) with a pH level of less than 7.35. They excluded patients with a metabolic acidosis or alkalosis from their analysis, but it is unclear how they defined these 2 acid-base states. Patients with compensated hypercapnia may represent a group of patients with competing acid-base disorders or a cohort of patients who experienced a less grievous initial physiological insult, whereas hypercapnic acidosis may actually reflect an increased severity of injury. As such, patients' pH levels and compensatory status likely represent dependent variables rather than causal agents.

This study provides an opportunity to highlight the importance of pH and the oxyhemoglobin dissociation curve within the context of microcirculatory resuscitation and cellular oxygen unloading.[2] According to the oxyhemoglobin dissociation curve, alkalemia discourages oxygen unloading at the cellular level, whereas acidemia encourages it.[3] Although acid-base abnormalities in cerebrospinal fluid alter cerebral blood flow,[4] to our knowledge, no studies have assessed the neurological association of serum pH, and alkalemia in particular, with oxygen unloading. Striving to normalize serological numbers as a surrogate for physiologic normality is a common force in critical care, especially when retrospective data like these support the attainment of "euboxia." While awaiting clinical data from a randomized prospective clinical trial that assesses the association of arterial pH with neurological outcomes in patients who have sustained a cerebral injury, we will continue to manage patients with postcerebral injuries using physiological principles that are associated with the hemoglobin dissociation curve along with other supporting measures.[5]

Shane B. Kappler, MD, MS
Rory J. Spiegel, MD
Michael T. McCurdy, MD

Author Affiliations: Division of Pulmonary and Critical Care, University of Maryland School of Medicine, Baltimore.

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Published Online: October 29, 2018. doi:10.1001/jamaneurol.2018.3220

Conflict of Interest Disclosures: None reported.

1. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury. *JAMA Neurol*. 2018;75(7):818-826. doi:10.1001/jamaneurol.2018.0123

2. Spiegel RJ, Winters ME, McCurdy MT. Cerebral resuscitation: shifting away from the basics. *Resuscitation*. 2017;121:e11. doi:10.1016/j.resuscitation.2017.09.028

3. Dash RK, Korman B, Bassingthwaighte JB. Simple accurate mathematical models of blood HbO2 and HbCO2 dissociation curves at varied physiological conditions: evaluation and comparison with other models. *Eur J Appl Physiol*. 2016;116(1):97-113. doi:10.1007/s00421-015-3228-3

4. Yoon S, Zuccarello M, Rapoport RM. pCO(2) and pH regulation of cerebral blood flow. *Front Physiol*. 2012;3:365. doi:10.3389/fphys.2012.00365

5. Wong GC, van Diepen S, Ainsworth C, et al; CCS Post Cardiac Arrest Guidelines Committee. Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology position statement on the optimal care of the postarrest patient. *Can J Cardiol*. 2017;33(1):1-16. doi:10.1016/j.cjca.2016.10.021

APPENDIX 12 Response to letter to editor

Letters

COMMENT & RESPONSE

In Reply We thank Kappler and colleagues for their interest in our article.[1] Our study showed an association of increased hospital mortality rates in patients with hypercapnic acidosis, and such an association with increased mortality rates was not seen in patients with compensated hypercapnia irrespective of increasing partial pressure of carbon dioxide (Pco_2).[1] The cohort of patients with hypercapnic acidosis had higher Acute Physiologic Assessment and Chronic Health Evaluation and Simplified Acute Physiology scores, suggesting that they had higher illness severity. While we have adjusted for several known confounders, including illness severity, the propensity to be hypercapnic, the propensity to be hypercapnic acidotic, baseline Glasgow Coma Scale, and the year of patient's admission, there could be other unknown confounders that may have accounted for the observed differences in the outcomes. We have highlighted this as a limitation of the study.[1] Nevertheless, to our knowledge, the study is the largest study published so far on evaluating the association of hypercapnia in conjunction with pH levels on important clinical outcomes.

The data support the view that in patients with acute cerebral injury, Pco_2 should not be treated in isolation, as the changes in Pco_2 are inextricably associated with changes in pH levels. Correcting compensated hypercapnia to the current recommended values (35-45 mm Hg)[2] will require hyperventilation that may need higher driving pressures and tidal volumes. This could cause or worsen lung injury.[3] Furthermore, the alkalemia that could develop when correcting compensated hypercapnia may lead to a reduction in cerebral oxygen delivery.

The oxyhemoglobin dissociation curve shift with changes in pH levels is integral to understanding the physiology of oxygen delivery. The shift of the oxygen dissociation curve to the right reduces the affinity of hemoglobin to oxygen. While this could facilitate oxygen unloading from blood to tissues, it is notable that this can also reduce the uptake of oxygen from pulmonary alveoli to pulmonary capillary blood.[4] The implication of this reduction in oxygen affinity with the right shift of the dissociation curve to clinical practice remains unknown. However, what is known from several clinical studies is that there is a strong association of adverse effects, including mortality with acidosis.[1,5,6] Given this strong association, it is inappropriate not to prevent or treat acidosis actively in treating patients with cerebral injury.

It is unlikely that there will be a randomized clinical trial that investigates the association of arterial pH with clinical outcomes in patients with cerebral injury. The current guidelines recommend Pco_2 management in isolation of pH levels and makes a conditional recommendation to target normal Pco_2 (35-45 mm Hg) based on low-quality evidence.[2] We hope that future guidelines on treating patients with acute cerebral injury may revise this recommendation and include a pH target when recommending Pco_2. These guidelines may guide clinicians not to rely on oxygen affinity based on the oxygen dissociation curve but rather by using the best available clinical data to guide the management of hypercapnia and acidosis in patients with acute cerebral injury.

Ravindranath Tiruvoipati, FCICM
David Pilcher, FCICM
Michael Bailey, PhD

Author Affiliations: Department of Intensive Care medicine, Frankston Hospital, Frankston, Victoria, Australia (Tiruvoipati); Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia (Tiruvoipati); Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology & Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, Melbourne, Victoria, Australia (Tiruvoipati, Pilcher, Bailey); The Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation, Melbourne, Victoria, Australia (Pilcher, Bailey); Department of Intensive Care, The Alfred Hospital, Prahran, Victoria, Australia (Pilcher).

Corresponding Author: Ravindranath Tiruvoipati, FCICM, Department of Intensive Care Medicine, Frankston Hospital, Frankston, Victoria 3199, Australia, (travindranath@hotmail.com).

Published Online: October 29, 2018. doi:10.1001/jamaneurol.2018.3237

Conflict of Interest Disclosures: None reported.

1. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury. *JAMA Neurol*. 2018;75(7):818-826. doi:10.1001/jamaneurol.2018.0123

2. Wong GC, van Diepen S, Ainsworth C, et al; CCS Post Cardiac Arrest Guidelines Committee. Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology position statement on the optimal care of the postarrest patient. *Can J Cardiol*. 2017;33(1):1-16. doi:10.1016/j.cjca.2016.10.021

3. Amato MBP, 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. doi:10.1056/NEJMsa1410639

4. Morgan TJ. The oxyhaemoglobin dissociation curve in critical illness. *Crit Care Resusc*. 1999;1(1):93-100.

5. Gupta AK, Zygun DA, Johnston AJ, et al. Extracellular Brain pH and outcome following severe traumatic brain injury. *J Neurotrauma*. 2004;21(6):678-684. doi:10.1089/0897715041269722

6. Momiyama Y, Yamada W, Miyata K, et al. Prognostic values of blood pH and lactate levels in patients resuscitated from out-of-hospital cardiac arrest. *Acute Med Surg*. 2017;4(1):25-30. doi:10.1002/ams2.217

APPENDIX 13 Authorised prescriber approval from Therapeutic Goods Administration

Premier's Award Metropolitan Health Service of the Year 2007, 2009

RESEARCH PROGRAM

HUMAN RESEARCH ETHICS COMMITTEE

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Frankston Hospital

Rosebud Hospital

Mental Health Services

Aged Care, Rehabilitation & Palliative Care Services

Primary and Community Health

www.peninsulahealth.org.au

Peninsula Health

PO Box 52
Frankston Victoria 3199 Australia
Telephone 03 9784 7777

21 May 2014

Associate Professor Ravindranath Tiruvoipati
Intensive Care Unit
Peninsula Health
PO Box 52
FRANKSTON VIC 3199

Dear Associate Professor Tiruvoipati

Ethics committee endorsement for the purpose of becoming an Authorised Prescriber of an unapproved product under Section 41HC of the Therapeutic Goods Act

The Peninsula Health Human Research Ethics Committee hereby endorses you for the purpose of becoming an Authorised Prescriber under Section 41HC of the Therapeutic Goods Act.

This endorsement is restricted to the following circumstances imposed by the Peninsula Health New Technology and Clinical Practice Committee:

Unapproved device:	Hemolung Respiratory Assist System
Indication for use:	Patients with: • Hypercapnic respiratory failure who are non-responsive to non-invasive mechanical ventilation. • Invasive mechanical ventilation but lung protective ventilation cannot be instituted.
Site covered by endorsement:	Intensive Care Unit, Frankston Hospital
Conditions imposed by the HREC:	• Hemolung to be used as per the decision of the New Technology and Practice Committee (attached). • Reporting of adverse events to HREC and New Technology and Practice Committee. • Provision of usage reports to HREC and New Technology and Clinical Practice Committee.

Please present a copy of this endorsement letter to the TGA as part of your application to become an authorised prescriber.

Yours sincerely

Dr Laurie Warfe
Chair
21/5/14

(attach: New Technology and Clinical Practice Committee decision)

At Peninsula Health we value:
Service Integrity Compassion Respect Excellence

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Assoc Prof Ravindranath Tiruvoipati
Director of Intensive Care Medicine
Frankston Hospital
FRANKSTON VIC 3199

Dear Assoc Prof Tiruvoipati

Re: Hemolung Respiratory Assist System
Authorised Prescriber: 2013/123; Expiry Date: 23 May 2014

Thank you for your correspondence of **22 May 2013**, concerning authorisation to supply **Hemolung Respiratory Assist System** as an unapproved therapeutic good, under Section 41HC of the *Therapeutic Goods Act 1989* (the Act)

Your signed declaration of agreement to treatment directions and evidence of endorsement by the **Peninsula Health Human Research Ethics Committee** for the purpose of supply of this product is noted.

Pursuant to Section 41HC of the Act, an Instrument authorising you to supply **Hemolung Respiratory Assist System only in patients to treat hypercapnic respiratory failure who are non-responsive to non-invasive mechanical ventilation** has been signed. The authorisation is subject to the conditions outlined in **Attachment 1.**

This authorisation allows you to prescribe (supply) **Hemolung Respiratory Assist System for a period of up to one (1) year** for the specified indication without the need to obtain approval from the Therapeutic Goods Administration (TGA) for each individual patient.

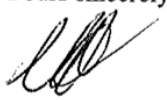
Regulation 47B of the Therapeutic Goods Regulations requires that an authorised prescriber provide the TGA with six monthly reports regarding the supply of an unapproved product. A suggested format for the report is at **Attachment 2.** Please note that the first report required will be for the period ending **30 June 2013.**

You are reminded that where an unapproved product is intended for use in a clinical trial, an appropriate notification of the trial under the Clinical Trial Notification (CTN) Scheme or approval of the proposed use of the product for experimental purposes under the Clinical Trial Exemption (CTX) Scheme is required.

PO Box 100 Woden ACT 2606 ABN 40 939 406 804
Phone: 02 6232 8679 Fax: 02 6232 8112 Email: info@tga.gov.au www.tga.gov.au

If you have any further enquiries regarding this authorisation, please contact Roxanne Prestridge on (02) 6232 8679.

Yours sincerely,



Dr Guy Hibbins
Clinical Adviser
Market Authorisation Group

23 May 2013

2013-123 Approval letter (doctor)

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AUTHORISATION OF SUPPLY UNDER s41HC
THERAPEUTIC GOODS ACT 1989
Consent to Treatment and Indemnity for Use of
Products Derived from Biological Tissue Including Human Blood or

I,……
(name of patient or parent/guardian)

understand that the Commonwealth can give no guarantee as to the quality, safety or efficacy
of……..……(name of product). Accordingly, the Commonwealth can accept no liability for its use.

I understand that this product is not approved for use in Australia but that use of the product has been approved under the provisions of section 41HC of the Therapeutic Goods Act 1989.

I confirm that the above statements have been explained to me and in this knowledge agree to administration of the product to me/my ward.

Patient's name:
……..

Signature of patient: …… **Date:**
……..
(or parent/guardian)

Signature of witness: …… **Date:**
……..

I have explained the above statements to the patient or the patient's parent/guardian.

Treating physician:
……...

Signature: …… **Date:**
……..

APPENDIX 14 Approval from New Technology Committee

Peninsula Health
New Technology and Clinical Practice Committee

Decisions re Application to Introduce
Hemolung Respiratory Assist System

The Committee recommended that Peninsula Health support the introduction of HemoLung RAS as a pilot for up to 6 patients on the following conditions:

- That the procedure be restricted to patients:
  - with hypercapnic respiratory failure who are non-responsive to non-invasive mechanical ventilation, , or on invasive mechanical ventilation but lung protective ventilation cannot be instituted and
  - who can provide consent or where consent can be gained from next of kin.

- Patient exclusions include:
  - Patients who have contra-indications to limited anti-coagulation
  - Patients with an allergy to heparin or have heparin induced thrombocytopenia
  - Patients with haemodynamic instability or uncontrolled arrhythmias
  - Patients with a platelet count of less than 75,000/mm3
  - Patients who are not for active management
  - Patients who are on concurrent hemofiltration
  - Patients who are inotrope dependant at the time of presentation.

- The determination to use the device should be made by two independent consultants, one of whom should be Associate Professor Ravindranath Tiruvoipati.

- Catheter insertion should only be undertaken by an ICU consultant.

- Patient care should be provided nurses who are CNS and experienced critical care RNs.

Dr David Rankin
Executive Director - Medical Services
Chair

Peninsula Health

PO Box 52
Frankston Victoria 3199 Australia
Telephone 03 9784 7777

DR SUSANNAH AHERN

EXECUTIVE DIRECTOR

MEDICAL SERVICES & QUALITY AND CLINICAL GOVERNANCE

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Frankston Hospital

•

Rosebud Hospital

•

Mental Health Services

•

Rehabilitation, Aged & Palliative Care Service

•

Primary and Community Health

www.phcn.vic.gov.au

7 January 2015

Associate Professor Ravi Tiruvoipati,
Intensive Care Unit
PO Box 52
Frankston Victoria 3199 Australia

Dear Ravi,

Re: Hemolung

Thank you for your application to the Peninsula Health New Technology Committee regarding the above. Your application was reviewed and approved at the meeting of the New Technology Committee on December 8, 2014 for conditional use.
The approval is conditional on;

- Approved for limited number of patients (up to 5 patients /year).
- Hemolung patient physiological data/outcomes being monitored and recorded.
- Collaboration with other centres for prospective studies on the use of hemolung at the earliest opportunity.
- Ongoing TGA approval.

Thank you for your support of the New Technology process of Peninsula health, and I wish you well in the use of this technology.

Please do not hesitate to contact me if you have any further queries.

Yours sincerely

Dr Susannah Ahern
Chair of New Technology Committee

Cc Mr Brendon Gardner, Executive Director, Frankston Hospital
Dr John Botha, Clinical Director of ICU
Jenny Abernathy, Operations Director, Surgery & ICU

APPENDIX 15 Consent form to use Hemolung

PENINSULA HEALTH

PATIENT / RELATIVE INFORMATION SHEET AND CONSENT FORM FOR USE OF HEMOLUNG RAS

Frankston Hospital, Peninsula Health

We are considering to use Hemolung to treat you / your relative. This is because you/ your relative have severe respiratory failure and using a respirator to assist your / your relative's breathing. Hemolung is a new treatment device for severe respiratory failure which may help in management of your / your relative's respiratory failure.

This Information Sheet/Consent Form tells you about this device. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want this device to be used on you / your relative.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding, you might want to talk about it with a relative, friend or your local doctor. You /Your relative don't have to receive this treatment if you wish so. There are other treatements available to treat respiratory failure.

If you decide you / your relative to receive this treatment you have to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to use Hemolung for your / your relative's treatment
• Consent to have the tests and treatments that are described

You will be given a copy of this Information and Consent Form to keep.

1. What is the purpose of this treatment?

Acute respiratory failure is one of the common causes for admission to patients to intensive care unit. The management of such patients include identifying and treating the precipitating cause and providing supportive care till the lung function recovers. Supportive care in such patients includes provision of support to the lung function with ventilator (respirator). In some patients the respiratory failure may deteriorate and in these patients respiratory function may not be adequately supported

with ventilator. In such patients other treatments may have to be used to support the respiratory function. One of the new interventions is a minimally invasive blood gas exchanger called Hemolung (Hemolung® Respiratory Assist System, ALung Technologies, Pittsburgh, PA). This device was used with encouraging results in patients with severe respiratory failure in the Europe and India. This device is not yet used in Australia and therefore is an experimental treatment. This means that it is not an approved treatment for respiratory failure in Australia.

2. What does the use of Hemolung involve?

For using hemolung we have to insert a special catheter into one of your / your relative veins in the neck or groin. Insertion of such catheters is one of the commonly performed procedures in the intensive care. The insertion of such catheters is usually safe without any major complications. This procedure will be done under local anaesthesia by the doctors trained to do this procedure. The use of local anaesthesia should minimise pain or discomfort that may be associated with the insertion of catheter. After the catheter is inserted you/ your relative will be connected to Hemolung by this catheter. Hemolung will draw out blood from your/ your relative's body and remove excessive carbon dioxide and add oxygen to your / your relative's blood. This blood without excessive carbon dioxide will be reinfused into the body. This will support the lung function and allow lungs to rest and heal. While you / your relative are on Hemolung you will be given a drug called heparin to thin your blood and prevent your blood clotting in Hemolung circuit. This may be associated with an increased risk of bleeding. Hemolung will be used for up to 7 days depending upon the recovery of your / your relative's lung function. After the recovery of lung function Hemolung will be stopped and the catheter will be removed. After the removal of the catheter you will be treated as per the standard practice. There are no additional costs associated to you/ / your relative for the receiving this treatment. You will be asked to sign the consent form before you / your relative are treated with Hemolung.

3 What are the alternatives to treatment with Hemolung?

Hemolung is not the only treatment available for treating respiratory failure. Other options are available; these include standard management of your / your relative's respiratory failure with ventilator (respirator).

4 What are the possible benefits of Hemolung?

We cannot guarantee or promise that you will receive any benefits from the use of Hemolung; however, possible benefits may include improvement of respiratory function without the need for prolonged ventilator support or avoidance of invasive ventilator support and its associated complications.

5 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You / your relative may have none, some or all of the effects listed below, and they may be mild, moderate or severe. Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. The table below summarises some of the risks.

Side Effect	*How often is it likely to occur?*	*How severe might it be?*	*How long might it last?*
Injuries to surrounding structures at the time of catheter insertion	Less than 5%	Depends upon the structure injured. Usual structure involved includes arterial injury which is usually recognised at the time or soon after insertion	If recognised at the time of insertion, it is does not have any long lasting effects. However an unrecognised injury (which is very uncommon (<0.5%) may have lasting effects. This may include loss of limb/limb function or development of stroke.
Bleeding	Bleeding is one of the known complications	Bleeding into brain can be fatal	Bleeding into brain may cause permanent disability or death.

	(10%) of using such devices, but often this is minor. Rarely (<0.1%) this could be fatal		

6. Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information you can contact the following people:

Clinical contact person, for any clinical questions

Associate Professor Ravi Tiruvoipati
Intensivist
Frankston Hospital,
PO Box 52,
Frankston,
3199
VIC
Tel: 97707777
E mail: travindranath@hotmail.com; R.Tiruvoipati@phcn.vic.gov.au

Complaints contact person, for any complaints.
Customer Relations Manager
Quality and customers services department
Frankston Hospital,
PO Box 52,
Frankston,
3199
VIC
Tel: 9784 7298; 1800 858 727.

Consent Form

Declaration by Patient / Relative:

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Patient / Relative _____

Signature _____ **Date** _____

If relative: Relationship to the

Declaration by Clinician

I have given a verbal explanation on the treatment, its procedures and risks and I believe that the participant has understood that explanation.

Name of Clinician _____

Signature _____ **Date** _____

Consent Form

Declaration by Patient / Relative:

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Patient / Relative _____

Signature _____ Date _____

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Declaration by Clinician

I have given a verbal explanation on the treatment, its procedures and risks and I believe that the participant has understood that explanation.

Name of Clinician _____

Signature _____ Date _____

APPENDIX 16 Editorial on "Management of severe hypercapnia post cardiac arrest with extracorporeal carbon dioxide removal."

Anaesth Intensive Care 2014; **42: 175-177**

Editorial

Extracorporeal respiratory support: breaking conventions?

Hill et al[1] and Bartlett[2] reported the first successful use of extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) in adults and neonates in 1972 and 1975, respectively. This was soon followed by a randomised controlled trial[3] showing mortality rates around 90% with both ECMO and conventional treatment in ARDS patients, dampening any enthusiasm for ECMO. The complexity of using primitive ECMO technology and higher circuit blood-flows to completely support gas exchange was a significant limitation at that time. It was soon recognised that a significant proportion of gas exchange support can be provided by the use of less damaging mechanical ventilation strategies with adjunctive use of low-flow extracorporeal techniques that are directed at carbon dioxide (CO_2) removal rather than oxygenation support. Gattinoni et al and Kolobow et al[4] developed and explored the concept of extracorporeal carbon dioxide removal ($ECCO_2R$) and introduced the technique of low frequency positive pressure ventilation combined with low-flow veno-venous $ECCO_2R$ for ARDS. Despite some early success reported by Gattinoni et al[5], $ECCO_2R$ failed to demonstrate any survival benefit when compared to conventional ventilation in a subsequent randomised trial[6]. Extracorporeal respiratory support has received substantial attention again in recent years because of the increasing incidence of severe hypoxaemic respiratory failure, in part due to resurgence of influenza pandemics[7].

Anecdotal but well-documented success during the 2009 H1N1 pandemic[7] and lack of any obvious harm in the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure study[8] was considered by many as sufficient evidence for the use of ECMO as a rescue therapy in ARDS for selected patients who fail conventional ventilation with lung-protective ventilation (LPV)[9]. One of the consequences of LPV is hypercapnic acidosis that may lead to patient–ventilator dyssynchrony and some unfavourable haemodynamic changes, including pulmonary hypertension, raised intracranial pressure and compromised renal blood-flow. Although many risks and benefits of hypercapnia are identified in basic science research, there is no clarity regarding what is an acceptable level of arterial CO_2[10].

With further refinements in $ECCO_2R$ technology[11], CO_2 can now be removed with relative ease using minimally invasive techniques. In this issue of *Anaesthesia and Intensive Care*, Tiruvoipati et al[12] report partially correcting $PaCO_2$ using a veno-venous $ECCO_2R$ device (Hemolung®, ALung Technologies Inc., Pittsburgh, PA, USA) as part of a post-resuscitation neuroprotective measure in a patient with advanced chronic obstructive pulmonary disease, difficult ventilation and hypercapnia. The use of $ECCO_2R$ in this patient, who had suffered an

Table 1
Available or emerging techniques for extracorporeal carbon dioxide removal

Complete respiratory support	Partial respiratory support	
CO_2 removal + oxygenation	CO_2 removal + some oxygenation	CO_2 removal only
Veno-venous ECMO	Arterio-venous CO_2 removal	Veno-venous CO_2 removal
Veno-arterial ECMO	•Interventional lung assist (iLA Novalung®) •Affinity® NT	Multiple console devices: •Decap®/Decap Smart®, •Novalung®
	Gas exchange catheters •Intravascular oxygenator (IVOX) •Dynamic intravascular lung assist device (D-ILAD) •Hattler catheter	Single console devices: •Hemolung® • iLA Activve® Respiratory dialysis

ECMO=extracorporeal membrane oxygenation.

unwitnessed out-of-hospital cardiac arrest, may be considered extraordinary by many, is not supported as a strategy by any high level of evidence and ultimately did not prove of benefit. However, this case does highlight the possible expanding use of extracorporeal therapies in intensive care practice in achieving a short-term physiological target. Nevertheless, critical care physicians should also be mindful of the associated costs, the risks and benefits of using invasive therapies to achieve a physiological target and the potential ethical dilemma of offering aggressive therapy to patients who have little chance of recovery.

So, is there any hope that these newer, low-flow partial $ECCO_2R$ devices will be used to improve patient outcomes? A recent study[13] in patients with moderate ARDS that used arterio-venous pumpless $ECCO_2R$ (Interventional Lung Assist, Novalung® GmbH, Hechingen, Germany) to facilitate ultra-protective lung ventilation did not show any difference in the number of ventilator-free days at 28 and 60 days. However, there was a significant reduction in duration of mechanical ventilation in patients with more severe ARDS (PaO_2/FiO_2 <150) and future studies may explore this further. Veno-venous $ECCO_2R$ is obviously more appealing because of its ease of use and possibly has less mechanical complications due to the avoidance of arterial cannulation. Despite the claim that the newer veno-venous $ECCO_2R$ devices require less intense anticoagulation, the risk of cannula and/or membrane thrombosis cannot be underestimated[14].

The devices currently available or being developed for $ECCO_2R$[15] are usually classified by their ability to provide partial or complete respiratory support and are summarised in Table 1. Unlike oxygen, which displays sigmoidal saturation kinetics to the carrier haemoglobin, most CO_2 is transported as dissolved bicarbonate and exhibits linear kinetics without saturation[11]. CO_2 also diffuses rapidly across extracorporeal membranes, allowing efficient removal even at blood-flows <1 l/minute. In contrast, blood-flows in the order of 60 to 70% of patients' cardiac output may be required for complete respiratory support during veno-venous ECMO. Newer $ECCO_2R$ devices allow much lower blood-flows (400 to 600 ml/minute), enabling the use of a single dual-lumen catheter that can combine continuous renal replacement therapy with CO_2 removal[11]. The current clinical experience with these veno-venous $ECCO_2R$ devices is, however, limited to individual case reports, case series and animal studies. Other potential applications for $ECCO_2R$ that merit further investigation include partial respiratory support for acute exacerbations of chronic airways disease and bridging selected patients with chronic lung disease to lung transplantation.

Even though definitive evidence for their routine use is lacking, we may be on the cusp of a paradigm shift in using ECMO and $ECCO_2R$ in the management of severe respiratory failure. While measurable short-term and long-term outcome benefit need to be demonstrated to justify wider uptake of extracorporeal respiratory support, appropriately powered, randomised controlled trials may take years to complete. Standardisation of technology and its clinical application, global collaboration and minimisation of diversity in other aspects of intensive care unit care are necessary prerequisites to the design of a clinical trial that intends to rigorously test extracorporeal respiratory support in the new era.

Future studies should identify subgroups of patients with severe respiratory failure who are most likely to benefit from extracorporeal support. Qualitative outcomes and parallel economic assessment should be of high priority and investigators should ensure long-term follow-up of survivors. Apart from evidence and science, areas such as cost-effectiveness, ethics, governance, quality control and benchmarking, education, prompt and accurate reporting, creation of databases that reflect the changing demography and technology, accreditation and credentialling all need to be simultaneously addressed at a global and local level. The recently formed Asia-Pacific Chapter of the Extracorporeal Life Support Organization in collaboration with the global Extracorporeal Life Support Organization and other regional organisations will play a key role in ensuring many of these facets of extracorporeal support are addressed in the region. With time, we may eventually witness some meaningful comparisons made between conventional and extracorporeal respiratory support techniques. Until then, $ECCO_2R$ should remain used only as a rescue therapy for highly selected patients.

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REFERENCES

1. Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med 1972; 286:629-634.
2. Bartlett RH, Gazzaniga AB, Jeffries MR, Huxtable RF, Haiduc NJ, Fong SW. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. Trans Am Soc Artif Intern Organs 1976; 22:80-93.

3. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979; 242:2193-2196.
4. Kolobow T, Gattinoni L, Tomlinson T, White D, Pierce J, Iapichino G. The carbon dioxide membrane lung (CDML): a new concept. Trans Am Soc Artif Intern Organs 1977; 23:17-21.
5. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F et al. Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986; 256:881-886.
6. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Weaver LK et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; 149:295-305.
7. Pham T, Combes A, Roze H, Chevret S, Mercat A, Roch A et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2013; 187:276-285.
8. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009; 374:1351-1363.
9. Shekar K, Davies AR, Mullany DV, Tiruvoipati R, Fraser JF. To ventilate, oscillate, or cannulate? J Crit Care 2013; 28:655-662.
10. Tiruvoipati R, Botha JA, Pilcher D, Bailey M. Carbon dioxide clearance in critical care. Anaesth Intensive Care 2013; 41:157-162.
11. Cove ME, Maclaren G, Federspiel WJ, Kellum JA. Bench to bedside review: Extracorporeal carbon dioxide removal, past present and future. Crit Care 2012; 16:232.
12. Tiruvoipati R, Gupta S, Haji K, Braun G, Carney I, Botha JA. Management of severe hypercapnia post cardiac arrest with extracorporal carbon dioxide removal. Anaesth Intensive Care 2014; 42:248-252.
13. Bein T, Weber-Carstens S, Goldmann A, Muller T, Staudinger T, Brederlau J et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO_2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 2013; 39:847-856.
14. Baker A, Craig G. Extracorporeal carbon dioxide removal (ECCO2R) in respiratory failure: an overview, and where next? JICS 2012;13.
15. Kaushik M, Wojewodzka-Zelezniakowicz M, Cruz DN, Ferrer-Nadal A, Teixeira C, Iglesias E et al. Extracorporeal carbon dioxide removal: the future of lung support lies in the history. Blood Purif 2012; 34:94-106.