Buffering a Permissive Hypercapnia - The Evidence

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Disclosures

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  – European Research Council [FP-7]
  – Health Research Board [Ireland]
Key Points

• Buffering a Hypercapnic Acidosis - the rationale

• Is Acidosis BAD or GOOD?

• Acidosis - insights from 'the bench'

• Bicarbonate – specific concerns

• Alternatives to Bicarbonate

• Conclusions
ARDS - 'The Baby Lung'
Why Buffer a Hypercapnic Acidosis?

- (Hypercapnic) Acidosis is *directly* ......... *HARMFUL*  

- Normalization of pH is ...... *BENEFICIAL*  

- Raising the pH minimizes the Hemodynamic depression induced by Acidosis  

- Normalizing Physiologic variables is ...... *GOOD*  

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Normal Parameters in the ICU

• Where is the evidence... ???

• "PO$_2$" - Premature Infants
  Retinopathy of Prematurity

• "MAP" - Penetrating Trauma
  Worse Mortality [Bickell 1994]

• "Hct." - ICU Anemia
  Worse Outcome [Hebert 1999]

• Normoglycemia - Tight Glucose Control
  Worse Outcome [NICE-SUGAR 2010]
Is Acidosis BAD……………….? 

• Acidosis indicates Disease / Dysfunction
  – Severity of Acidosis predicts Outcome
    • Post-Cardiac Arrest [Resuscitation 1999;42:173-82]
    • Sepsis [J Infect 2000;40:256-61]
    • Postpartum Neonate [Gynecol Obstet Invest 1991;32:220-3]
  – Association vs. Cause

It’s a marker of bad news, but is there a role for buffering it………….?
Hypercapnic acidosis and mortality in acute lung injury

David A. Kregenow, MD; Gordon D. Rubenfeld, MD; Leonard D. Hudson, MD; Erik R. Swenson, MD

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**Feature Articles**

Hypercapnia...association with Benefit in ARDS?
Hypercapnic Acidosis: Evidence for Benefit

- **Myocardial**

- **Brain**

- **Liver**
  - Gores et al, J Clin Invest 1989;83:386-96

- **Kidney**

- **Pulmonary**
  - Ischemic Reperfusion
  - Ventilation induced Lung Injury
  - Endotoxin induced Lung Injury
  - Hypoxia induced pulmonary Hypertension
Why might Buffering an Acidosis be BAD?

- 1. Abolition of a Protective Effect
- 2. Worsening of Intracellular Acidosis
- 3. Slow response to Treatment
- 4. Increased intracellular acid production
- 5. Specific deleterious effects
Buffering Hypercapnic Acidosis Worsens Acute Lung Injury

JOHN G. LAFFEY, DOREEN ENGELBERTS, and BRIAN P. KAVANAGH

Laffey, Kavanagh et al AJRCCM 2000
Hypercapnic Acidosis Impairs Plasma Membrane Wound Resealing in Ventilator-injured Lungs

Clinton H. Doerr, Ognjen Gajic, Jorge C. Berrios, Sean Caples, Matthew Abdel, James F. Lymp, and Rolf D. Hubmayr

Percent of injured ATII's with repaired plasma membranes

Hypocapnia

Normocapnia

Hypercapania

Doerr, Hubmayr et al AJRCCM 2005
Impact of buffering hypercapnic acidosis on cell wounding in ventilator-injured rat lungs

Sean M. Caples,1 Deborah L. Rasmussen,1 Won Y. Lee,1 Marla Z. Wolfert,1 and Rolf D. Hubmayr1,2

1Thoracic Diseases Research Unit, Division of Pulmonary and Critical Care Medicine, Department of Medicine, and 2Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota

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Fig. 1. Experimental protocol. PI, propidium iodide; THAM, tris-hydroxymethyl aminomethane.
<table>
<thead>
<tr>
<th></th>
<th>Bicarbonate</th>
<th></th>
<th>Krebs</th>
<th></th>
<th>THAM</th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Lung weight, measured, g</td>
<td>5.3 (1.2)</td>
<td>7.1 (2.1)</td>
<td>5.3 (1.2)</td>
<td>5.8 (1.0)</td>
<td>7.5 (2.4)</td>
<td>7.8 (2.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ Lung weight, g</td>
<td>4.5 (1.2)</td>
<td>6.2 (2.1)</td>
<td>4.4 (1.4)</td>
<td>5.0 (1.0)</td>
<td>6.8 (2.4)</td>
<td>7.0 (2.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ppa, cmH₂O</td>
<td>8.3 (3.9)</td>
<td>8.9 (2.1)</td>
<td>7.4 (2.5)</td>
<td>7.6 (2.8)</td>
<td>9.7 (2.9)</td>
<td>8.8 (2.5)</td>
<td>0.175</td>
</tr>
<tr>
<td>Paw, cmH₂O</td>
<td>40.3 (3.8)</td>
<td>44.1 (7.4)</td>
<td>40.5 (4.9)</td>
<td>40.4 (5.1)</td>
<td>50.8 (10.3)</td>
<td>46.7 (7.8)</td>
<td>0.017</td>
</tr>
<tr>
<td>Δ Paw, cmH₂O</td>
<td>10.0 (3.8)</td>
<td>10.3 (5.1)</td>
<td>10.3 (4.7)</td>
<td>13.7 (7.5)</td>
<td>20.6 (10.2)</td>
<td>16.2 (7.8)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Physiological responses are presented as means (SD). The P values correspond to overall comparisons between the groups: bicarbonate buffered, unbuffered, THAM buffered. Paw and Ppa were both measured at the conclusion of injurious ventilation. Δ Paw, mean change in peak airway pressures from beginning to end of injurious ventilation.
Percentage of cells with permanent plasma membrane wounds (PI-positive)

Unbuff Acidosis  Bicarb  THAM  Normocap

* * *
Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-κB dependent mechanism

D O’Toole,¹,² P Hassett,¹,² M Contreras,¹,² B D Higgins,¹,² S T W McKeown,³ D F McAuley,³ T O’Brien,⁴ J G Laffey¹,²,⁴

O’Toole D et al, Thorax 2009

Normocapnia

Hypercapnic Acidosis
Buffering does not restore Epithelial Wound Healing

O’Toole D et al, Thorax 2009
In vivo *E. Coli* induced ALI

Rats Randomised

- Room Air
  - n = 10

- E Coli Instillation
  - Ventilated 6 hours – 0% CO₂
    - Normocapnia
  - Ventilated 6 hours – 5% CO₂
    - Hypercapnic Acidosis

- Room Air
  - n = 10

- CO₂ = 8%
  - 72 hours
  - n = 10

- E Coli Instillation
  - Ventilated 6 hours – 5% CO₂
    - Buffered Hypercapnia
Pneumonia induced ALI

Nichol et al, Crit Care Med 2009
Buffering may worsen an Intracellular Acidosis
\[ \text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3 \]

\[ \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2 \]
## Bicarbonate worsens Intracellular Acidosis

<table>
<thead>
<tr>
<th>Source</th>
<th>Subject</th>
<th>Acidosis</th>
<th>Method of Measuring Intracellular pH</th>
<th>Serum pH</th>
<th>Intracellular pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beech et al. (^{55})</td>
<td>Rat</td>
<td>DKA, shock</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Rhee et al. (^{49})</td>
<td>Dog</td>
<td>Hypoxic lactic</td>
<td>( ^{31} )P NMR</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Beech et al. (^{53})</td>
<td>Rat</td>
<td>Hypotensive lactic</td>
<td>C2 NMR</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Bollaert et al. (^{60})</td>
<td>Rat</td>
<td>Septic (LPS)</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Shapiro (^{11})</td>
<td>Rat heart</td>
<td>Acidic perfusate</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Thompson et al. (^{61})</td>
<td>Rat</td>
<td>None</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Unchanged or Decreased</td>
</tr>
<tr>
<td>Kette et al. (^{34})</td>
<td>Pig</td>
<td>Cardiac arrest</td>
<td>Electrode</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Arieff et al. (^{46})</td>
<td>Dog</td>
<td>Phenformin lactic</td>
<td>( ^{14} )C DMO</td>
<td>Unchanged</td>
<td>Decreased</td>
</tr>
<tr>
<td>Graf et al. (^{47})</td>
<td>Dog</td>
<td>Hypoxic lactic</td>
<td>( ^{14} )C DMO</td>
<td>Unchanged</td>
<td>Decreased</td>
</tr>
<tr>
<td>Bersin and Arieff (^{62})</td>
<td>Dog</td>
<td>Hypoxic lactic</td>
<td>( ^{14} )C DMO</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Shapiro et al. (^{63})</td>
<td>Rat</td>
<td>( \text{NH}_4 \text{Cl, hypercapnic} )</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Shapiro et al. (^{64})</td>
<td>Rat</td>
<td>( \text{NH}_4 \text{Cl} )</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Arieff et al. (^{68})</td>
<td>Animal</td>
<td>Phenformin lactic</td>
<td>Not stated</td>
<td>Increased</td>
<td>Decreased</td>
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<tr>
<td>Nakashima et al. (^{65})</td>
<td>Human</td>
<td>None</td>
<td>( ^{31} )P NMR</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Bjerneroth et al. (^{66})</td>
<td>Lymphocytes</td>
<td>Acidic buffer</td>
<td>Fluorescent dye</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Ritter et al. (^{67})</td>
<td>Platelets</td>
<td>Acidic buffer</td>
<td>Fluorescent dye</td>
<td>Decreased</td>
<td></td>
</tr>
</tbody>
</table>

Note: * NH\(_4\)Cl = ammonium chloride; NMR = nuclear magnetic resonance; DMO = dimethyloxazolidine; IP = intraperitoneal; LPS = lipopolysaccharide
Buffering may slow the response to Treatment
Counterproductive Effects of Sodium Bicarbonate in Diabetic Ketoacidosis

YUKICHI OKUDA, HORACIO J. ADROGUE, JAMES B. FIELD, HIROYOSHI NOHARA, AND KAMEJIRO YAMASHITA

Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba (Y.O., K.Y.), Tsukuba, Japan; Department of Medicine, Renal Section, Department of Veterans Affairs Medical Center (H.J.A.), and Diabetes Research Laboratory, St. Lukes Episcopal Hospital, Division of Endocrinology and Metabolism (J.B.F.), Baylor College of Medicine, Houston, Texas 77211; and Department of Biochemistry, Niigata University School of Dentistry (H.N.), Niigata, Japan
Acid load

Systemic pH

Endogenous acid production (ketoacidosis, lactic acidosis)

Systemic pH

Alkali load

Systemic pH

Hood and Tannen NEJM 1998
Hemodynamic effects of Buffering
Osmotic Effects of Bicarbonate

- 100mls 8.4% Sodium Bicarbonate
  - Significant osmotic load

- Independent Beneficial effects of Osmotic Loads
  - improved hemodynamic profile in Haemorrhagic Shock
    [J Trauma 2000;49:580-3]
  - attenuates key aspects of the Immune Response
    [J Trauma 2000;49:580-3]
    [J Surg Res 1999;83:130-5].
  - prevents Lung Injury in experimental models
    [J Trauma 2003;54:121-30]
Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study.

Cooper DJ, Walley KR, Wiggs BR, Russell JA.

St. Paul's Hospital, University of British Columbia, Vancouver, Canada.
Hemodynamic effects in sepsis induced lactic acidosis

Buffering – Alternatives to Bicarbonate
• THAM penetrates into cells
  – Proton acceptor;
  – pKa 8.1 [effective pH range 7.1 – 9]

• Can buffer pH changes and reduce $\text{PCO}_2$
  – Binds H+, converts carbonic anhydrase to Bicarbonate

• Effective in a closed or semi-closed system.
  – Effective vs acidemia caused by hypercarbia
  – Given as 0.3M solution by infusion
Tromethamine Buffer Modifies the Depressant Effect of Permissive Hypercapnia on Myocardial Contractility in Patients with Acute Respiratory Distress Syndrome

THOMAS WEBER, HEINZ TSCHERNICH, CHRISTIAN SITZWOHL, ROMAN ULLRICH, PETER GERMANN, MICHAEL ZIMPFER, ROBERT N. SLADEN, and GÜNTER HUEMER

Department of Anesthesiology and General Intensive Care, University of Vienna, Austria; and Department of Anesthesiology, Division of Critical Care, College of Physicians and Surgeons of Columbia University, New York, New York

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Internet address: www.atsjournals.org
Methodology

• ARDS patients
  – Rapid induction of hypercapnic acidosis
  – THAM (n = 10) vs. Control (n = 10)
    [THAM infusion at 1 mmol · kg⁻¹ · h⁻¹ for 30 min and thereafter adjusted to achieve a pH > 7.3]

• Significant hemodynamic alterations seen
  – decreased systemic vascular resistance,
  – increased cardiac output,
  – decreased myocardial contractility,
  – decreased mean arterial pressure
  – increased mean pulmonary arterial pressure
Summary and Conclusions
Key Points

• (Hypercapnic) Acidosis is linked with adverse outcome
  – Link *Associative* rather than *Causative*

• Buffering a Hypercapnic Acidosis may
  – Abolish a Protective Effect
  – Worsening Intracellular Acidosis
  – Slow response to Treatment
  – Increase intracellular acid production
  – Exert specific deleterious effects

• No outcome data supporting efficacy of Buffering
  – Correct the primary problem if possible

• THAM holds promise in situations where hemodynamic consequences of acidosis of particular concern