Acid-Base Physiology: II
Management of acid-base disorders

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Disclosures

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Outline of the lectures

- Part I (04/16/18):
  - An approach to the diagnosis of acid base disorders (with a particular focus on metabolic acidosis)
  - Practice exercises
  - A primer on lactic acidosis
  - A (very brief) look at the Stewart method
- Part II (04/23/18):
  - Treating acid-base disorders: when, how, and does it matter?
  - A brief overview of alpha stat and pH stat

Part II: Objectives

- Treating severe acid base abnormalities
  - Effect of acidemia/alkalemia on the body
  - When do we treat the pH?
  - Treatment modalities (bicarbonate and beyond)
  - Dealing with bicarbonate shortage
  - Does treatment improve outcomes?
- α stat and pH stat
  - A basic explanation
  - Clinical utility

MANAGEMENT OF SEVERE ACIDEMIA

Management of Severe Acidemia

- Treat the cause if you can
- While you are treating the cause, symptomatically treating severe acidemia MAY buy you time to improve outcomes
- In critically ill patients, it is the unmeasured anions and lactate that are correlated with worse outcomes
- Healthy patients can tolerate a lot of insult (acidosis *per se* is not the main problem)

Question:

- What is the highest recorded PaCO2 in a patient who survived the episode that lead to hypercapnea?

Management of Massive Grain Aspiration

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Table 1. Arterial Blood Gases

	Day 1 (time)		
	13:55	16:00	16:50
Place	ER 1	ER 2	OR
Ventilation	IPPV bag/mask	IPPV bag/ETT	IPPV bag/ETT
F_{IO_2}	1.0	1.0	1.0
Pa_{O_2} (mmHg)	86	76	300
pH	6.59	6.62	6.73
Pa_{CO_2} (mmHg)	146	501	344
Bicarbonate (mM)	14	51	46

TABLE 1. MAJOR ADVERSE CONSEQUENCES OF SEVERE ACIDEMIA.

Cardiovascular
- Impairment of cardiac contractility
- Arteriolar dilatation, venoconstriction, and centralization of blood volume
- Increased pulmonary vascular resistance
- Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow
- Sensitization to reentrant arrhythmias and reduction in threshold of ventricular fibrillation
- Attenuation of cardiovascular responsiveness to catecholamines

Respiratory
- Hyperventilation
- Decreased strength of respiratory muscles and promotion of muscle fatigue
- Dyspnea

Metabolic
- Increased metabolic demands
- Insulin resistance
- Inhibition of anaerobic glycolysis
- Reduction in ATP synthesis
- Hyperkalemia
- Increased protein degradation

Cerebral
- Inhibition of metabolism and cell-volume regulation
- Obtundation and coma

Adrogue and Madias, NEJM 1998

Question

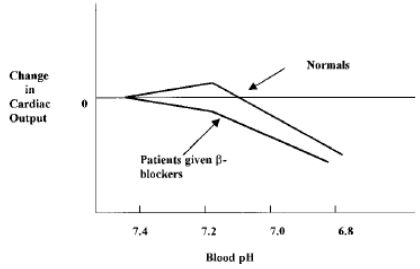
You are doing a multilevel spine case, and about 6 hours into the case, your patient starts to need escalating amounts of phenylephrine. An ABG shows: 7.24/42/140 on an FiO2 of 0.4. Looking at the pH a medical student observing the case wonders if you need to give bicarb, since the acidemia is depressing contractility and decreasing the effectiveness of pressors. Your response is:

A. Bicarb has no role in the management of acidosis
B. Great observation: I was about to hang the bicarb
C. The hypotension is the surgeon's fault
D. Let me call my attending
E. None of the above

Answer:

The hypotension and acidosis are likely due to hypovolemia from bleeding (expected in such a surgery, but not the 'surgeon's fault'). In the absence of severe acidemia (pH<7.15 or so) the sympathomimetic effects of acidemia predominate

Effect of pH on Cardiac Output



Kraut and Kurtz, AJKD 2001.

Treatment options

You are doing a thoracic case (a lobar resection) in a woman with post cardiac transplant aspergilloma. Her lung compliance is poor, and you are barely managing to keep her oxygenated at a Vt of ~ 7 cc/kilo with a RR of 25. Her ABG is 7.18/74/74 on an FiO2 of 0.8, and your surgeon wants you to treat her acidemia. She is hemodynamically stable. Your choices are:

A. Bicarbonate
B. Nothing
C. THAM
D. Intraoperative CVVH
E. Zoniporide (What's that?)

Assumptions underlying the symptomatic management of acidemia

- Acidemia ***by itself*** is dangerous ➔Not really!
- Sodium bicarbonate (or it's alternatives) can increase the pH of blood when infused IV ➔Yes it can
- Increasing the pH of blood has a similar effect on intracellular pH ➔It's complicated…
- Symptomatic treatment of severe acidemia improves cardiovascular function (or some other relevant outcome) ➔It's complicated…
- The risk/benefit ratio favors the symptomatic treatment of acidemia ➔It's complicated…

HCO_3 and Acidemia

Which of the following is NOT an established indication for bicarbonate in the setting of cardiac arrest?

A. Hyperkalemic arrest
B. TCA overdose
C. Prolonged CPR
D. Pre-existing metabolic acidosis

Indications for HCO_3

- In the setting of cardiac arrest complicated by hyperkalemia, TCA overdose or known pre-existing metabolic acidosis
- In lactic acidosis/high AG acidosis with a pH ≤ 7.15 (No indication for bicarb in adult DKA)
- Bicarbonate losses (Diarrhea, RTA) -> Therapeutic (not sympmtomatic)
- Dose – BD X Weight (Kg) X 0.3; generally start with 1 mmol/kg and titrate to effect

Potential problems of giving HCO_3

- Respiratory status a significant limitation
- 'Paradoxical' intracellular acidosis
- Increased lactate generation
- Hypervolemia, hypernatremia, hyperosmolality
- Decreased ionized Ca^{++}
- Left shift of the ODC
- Evidence base is very poor

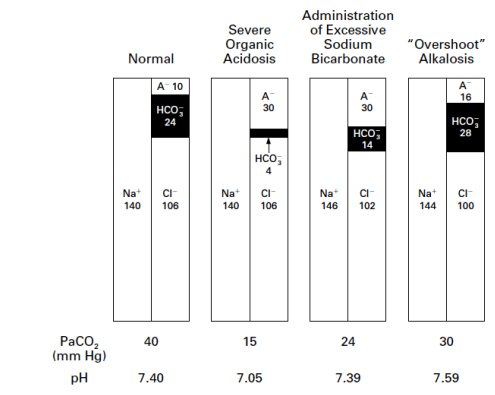


Figure 1. Schematic Illustration of "Overshoot" Alkalosis.

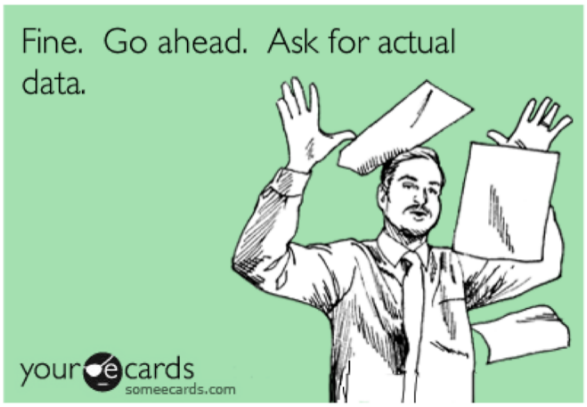
Adrogue and Madias, NEJM 1998

Table 5. Putative Factors Causing Decrease in Cardiac Output in Response to Bicarbonate Administration

Factor	Putative Mechanism	Comments
Decreased pH_i	Increased CO_2 generation and rapid entry into cells	Magnitude of decrease in pH_i dependent on quantity and rapidity of bicarbonate administered; pulmonary and tissue blood flow and alveolar ventilation affect the magnitude of increase in CO_2 tension; reduction in pH_i was transient in some studies
Decreased blood ionized calcium	Increased pH-related binding to albumin	Process occurs rapidly; good correlation between cardiac contractility and blood ionized calcium in some studies
Decrease ratio of phosphocreatinine and ATP to Pi	Mechanism unclear, but could be related to decrease in coronary blood flow	Found in absence of detectable change in myocardial pH
Increased myocardial calcium concentration	Augmented calcium entry through Na^+-Ca^{2+} exchanger	Observed during first few minutes of reperfusion of ischemic myocardium

Abbreviation: Pi, phosphate.

Kraut and Kurtz, AJKD 2001.



Data

- In general, low quality, non-randomized studies, often with very low numbers of patients
- Two blinded, crossover RCTs comparing bicarbonate vs saline in lactic acidosis did not reveal any hemodynamic advantage[1,2]
- A prospective, uncontrolled study of 177 patients with bicarb based hemofilteration showed resolution of acidosis in 45% of patients with better than *expected* mortality[3]
- A randomized, double-blinded study in patients with cardiac arrest found a trend to improved survival with HCO_3 in patients with prolonged (>15 min) arrest time[4]

Treating acidemia 2/2 permissive hypercapnea

- The original ARDSNet trial protocolized bicarbonate use for pH<7.2 (not ideal!)
- There may be some indications for the treatment acidemia associated with lung protective ventilation (e.g. concomitant head injury)
- The data seems to suggest that respiratory acidosis may actually be protective, although mechanisms are unclear

Alternatives to HCO_3

- **Dichloroacetate** – stimulates PDH and increases Acetyl CoA (Stacpoole PW, et al. NEJM, 1992) effective in decreasing lactate and improving pH, but no effect on survival
- **Carbicarb**: $NaHCO_3$+Na_2CO_3. Similar to bicarbonate, but generates less CO_2. Lot of animal data, but only one human study (Leung et al. Crit Care Med 1994). Not for clinical use
- **NHE1 Inhibitors**: Na-H Exchange Inhibitors may be used to prevent complications of intracellular acidosis. However, two randomized trials for the treatment of ischemia-reperfusion injury in the heart (GUARDIAN (Circulation, 2000) and EXPEDITION (Ann Thorac Surg, 2008)) failed
- **THAM**
- **Sodium Acetate**

THAM

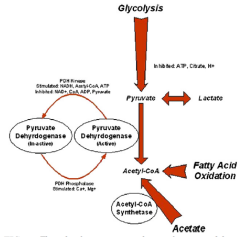
- Tris-hydroxy-amino-methane
- $R\text{-}NH_2$+ H Lac -> $R\text{-}NH_3$+ Lac^-
- pK 7.8, so more effective than bicarb (pK 6.3)
- No CO_2 generation, but needs adequate renal function
- Effective at treating intracellular acidosis, no sodium load
- Experimental and limited clinical evidence of efficacy (head injury, ARDS, in cardioplegia)
- Has been used in neonatal RDS
- We will sometimes use it in liver transplantation or in the ICU
- Dosing: Volume in ml of 0.3M THAM solution = lean body wt (kg) X base deficit (Max dose = 15 mmol/kg, or 3.5 L in a 70 kg adult)

Complications with THAM

- Hypoglycemia
- Hyperkalemia (especially in the setting of renal failure)
- Respiratory depression
- Venous irritation
- Osmolar gap with pseudohyponatremia

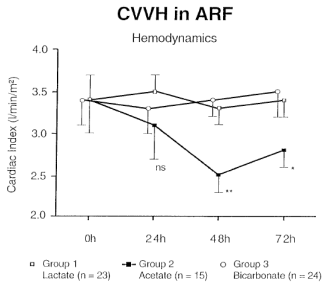
Sodium Acetate

- Acetate is converted to Acetyl CoA, after which it enters the Kreb's cycle, generating CO_2 and water



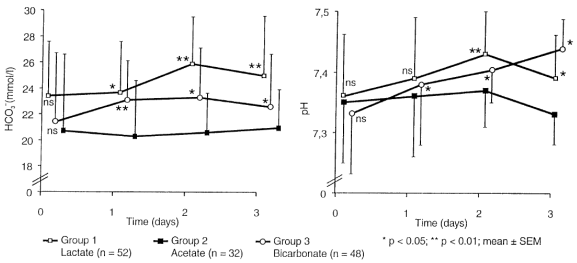
McCauge A et al. *J Surg Res* 2012

- Acetate buffered HD/CVVH solutions were found to cause depressed cardiac contractility and hypotension



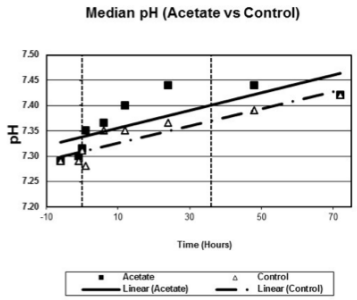
Heering P, et al. *Intensive Care Med* 1999

Acetate based CVVH was not as effective at correcting acidemia as HCO_3 or lactate based fluids



Heering P, et al. *Intensive Care Med* 1999

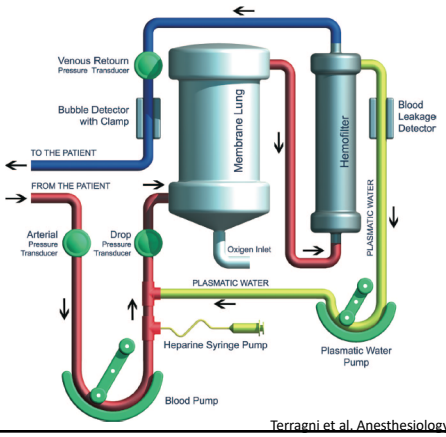
Acetate based IV fluids have been shown to improve pH in trauma patients compared to NS



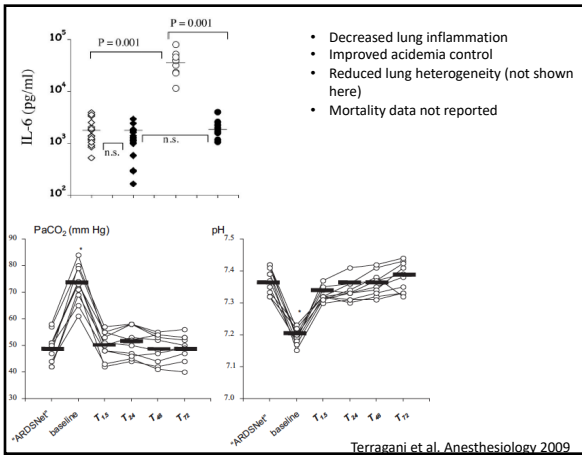
McCauge A et al. *Scand J Trauma Resusc Emerg Med* 2011

Renal Replacement Therapy (RRT) for Acidemia

- Conventional CVVH (Bicarbonate or Citrate Buffer)
  - Effective at treating acidemia
  - Citrate used for regional anticoagulation
- High volume Ultrafiltration
- Extracorporeal CO_2 removal as an adjunct to reduce V_t below 6 ml/kg



Terragni et al. Anesthesiology 2009



- Decreased lung inflammation
- Improved acidemia control
- Reduced lung heterogeneity (not shown here)
- Mortality data not reported

Terragani et al. Anesthesiology 2009

In a hospital without bicarbonate…

- Diagnose the cause of acidemia and attempt to correct it. While doing that…
- Tolerate acidemic states based on clinical condition – not everyone with a pH of 7.2 needs treatment!
- Use the lungs if you can - reduce $PaCO_2$ to low normal (sometimes lower) levels o give yourself pH room. Avoid severe hypocapnea in patients with focal or global CNS injury
- If possible, consider cooling your febrile patient to normothermia to reduce CO_2 generation
- Treat acidemia symptomatically (HCO_3, Acetate, THAM) if possible
- Depending on the trajectory of your patient, consider early CVVH

Management of Severe Alkalemia

TABLE 2. MAJOR ADVERSE CONSEQUENCES OF SEVERE ALKALEMIA.

Cardiovascular
Arteriolar constriction
Reduction in coronary blood flow
Reduction in anginal threshold
Predisposition to refractory supraventricular and ventricular arrhythmias
Respiratory
Hypoventilation with attendant hypercapnia and hypoxemia
Metabolic
Stimulation of anaerobic glycolysis and organic acid production
Hypokalemia
Decreased plasma ionized calcium concentration
Hypomagnesemia and hypophosphatemia
Cerebral
Reduction in cerebral blood flow
Tetany, seizures, lethargy, delirium, and stupor

Adrogue and Madias, NEJM 1998

Treat underlying cause…

- Metabolic Alkalosis (>7.55)
  - Chloride responsive vs resistant (Check urinary $[Cl^-]$: > 20 mmol/L – chloride resistant; < 10 mmol/L chloride sensitive)
  - Fluid expansion, modification of diuretics (chloride responsive)
  - K^+ sparing diuretics, sodium restriction (chloride resistant)
  - IV HCl (0.1 – 0.2N infused into a central vein)
- Respiratory alkalosis
  - Narcotics (remifentanyl)
  - Add dead space to breathing circuit

α-stat and pH stat

A quick question

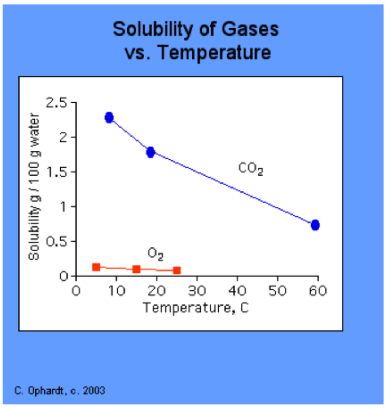
When you send out a blood gas in the regular ORs, what system of acid-base management do you use?

- pH stat
- α stat
- Neither: they only apply to cardiac anesthesia

α-stat and pH-stat

Hypothermia and cerebral physiology

- Decreased $CMRO_2$ – the 'gold standard' method of cerebral protection during cardiac surgery
- Hypothermia ➔left shift of the oxygen dissociation curve
- Increased CO_2 solubility (with a consequent decrease in $PaCO_2$)
- A relative alkalemia (which further left shifts the ODC, potentially impairing oxygen delivery to cells)
- Cerebral vasoconstriction from the alkalemia
- Increased viscosity of blood



Question

The following is true for a pH stat based management strategy EXCEPT:

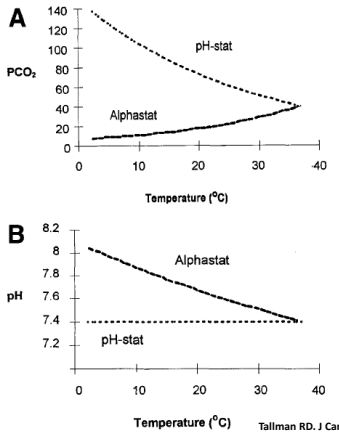
A. ABGs need to be temperature corrected
B. Cerebral autoregulation is preserved
C. Increases cerebral blood flow
D. CO_2 added to circuit

Alpha Stat

- Vertebrates regulate their acid-base status to preserve the ratio (α) between the dissociated to undissociated forms of the imidazole ring of the AA histidine (think of poikilotherms)
- ABG is measured at 37C – do NOT correct for temperature
- Causes relative alkalosis
- Maintains cerebral autoregulation

pH Stat

- pH kept constant as temperature decreases
- Requires addition of CO_2 or decreased ventilation to make up for increasing solubility of CO_2 in plasma (think hibernation)
- Increases cerebral blood flow, but autoregulation is lost
- Difference with α-stat probably significant only at very low temperatures



Tallman RD. J Cardiothorac Vasc Anesth 1997

Advantages of each approach

- α-stat
  - Used in adults undergoing CBP
  - The longer the pump run, the safer an alpha stat strategy is
  - Advantage thought to be due to preserved autoregulation and less microemboli
- pH-stat
  - Children undergoing DHCA less neurocognitive impairment
  - May be due to improved brain cooling and rewarming efficiency at higher CBF, improved O_2 supply to brain

Does alpha-stat vs. pH stat matter outside the cardiac OR?

- ABG management in post-cardiac arrest cooling:
  - In a study of 1013 ABGs from 120 CA patients authors compared differences in pH in alpha stat vs. pH stat blood gases[4]
  - Alpha stat: 7.33 (7.25-7.41) and pH stat: 7.37 (7.29-7.44)
- Does this matter?
- For TH s/p cardiac arrest I think a '$PaCO_2$-stat' technique may be most reasonable!

Take home points

- Develop a systematic method for thinking about acid-base issues
- The specific method does not matter as much as a consistent approach
- Some memorization is essential
- Acidosis caused by lactate/unmeasured anions is associated with worse outcomes
- Treat the cause – but the sicker the patient, the more the need for symptomatic therapy
- Symptomatic Rx (pH<7.15) – Bicarbonate or THAM
- Treating the pH may not make an outcome difference, but is worth trying if done carefully
- Alpha stat better for adults; pH stat better for pediatrics (DHCA)!

Questions?

References:

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