Acid Base

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CUMC

No Conflicts of Interest

Overview

- The extracellular [H^+] is tightly regulated
- Changes in [H^+] and thus pH result in altered protein charges and thus altered protein structure and function
- Cellular metabolism of fat and carbohydrates yields CO_2 which need to be excreted to prevent volatile acid accumulation (carbonic)
- Protein metabolism results in addition of non-volatile acid to the body

Major Players in Acid-Base Balance

- Kidneys-provide long term control of acid-base balance via modulation of acid/base excretion
- Lungs-respond to acute changes in pH by modulating ventilation (which changes CO2 levels)
- ECF HCO_3^-major ECF buffer
- Bone/cells-provide intracellular buffering

Henderson-Hasselbach

$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.03PCO_2}$$

$$pH \sim \log \frac{[HCO_3^-]}{PCO_2}$$

$[HCO_3^-]$ Regulated by renal H+ excretion

PCO_2 Regulated by alveolar ventilation

Body strives to keep pH constant, and thus the proportion of $HCO3/PCO_2$ must remain Constant.

Thus Compensation always occurs in the same ‘direction’; a decrease in the numerator Is compensated by an decrease in the denominator

Buffers

Buffers are weak acids that take up or release H^+ depending on the pH; they help to maintain pH constant in response to an acid load

HCO_3/CO_2 is the major buffering system in the body

$$CO_2 \leftrightarrow CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Gas phase — Aqueous phase

An ↑ H^+ leads to HCO3- consumption driving the reaction to the left leading to CO2 Exhalation and maintenance of a normal pH

A ↓ in H+ leads to breakdown of H2CO3 raising the HCO3 driving the reaction to The right leading to a decrease in ventilation and an increase in CO2

HCO3 buffering

- HCO_3 concentration is 24mmol/L or 24000000nmol/L
- H+ concentration is 40nmol/L
- There is $1x10^6$ more HCO_3^- than H^+
- The excess of hco3 makes it a great buffer

Buffers

HCO_3 is the major buffer to non-carbonic acids, but it cannot buffer carbonic acid

$\uparrow CO_2 \rightarrow CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$

HCO_3^- cannot buffer H_2CO_3 because $H^+ + HCO_3^-$ regenerates H_2CO_3

$\uparrow PCO_2 \rightarrow H_2CO_3 + HCO_3^- \rightarrow HCO_3^- + H_2CO_3$

H_2CO_3 is buffered by intracellular buffers

Buffering of HCl infused into nephrectomized dogs

Summary of data from the five experiments

EXP. No.	Wt.	HCl INFUSED			Δ TOTAL Cl	Δ $S^{35}O_4$ VOL.	FINAL PLASMA pH	Δ CONC. IN PLASMA WATER				Δ TOTAL EXTRACELLULAR				%HCl NEUTRALIZED BY			
		TOTAL	mM./Kg.	VOL.				Na	K	HCO_3	Cl	Na	K	HCO_3	Cl	TRANSF. TO E.C.F.		HCO_3 IN E.C.F.	TRANS. OF Cl
	Kg.	mM.		ml.	mM.	ml.		millimols per liter				millimols				Na	K		
1	18.1	190	10.5	650		+765	7.09	-6	+4	-16	+14	+87	+25	-78	+173	46	13	41	9
2	19.0	169	8.9	560		+565	7.15	-10	+5	-18	+14	+38	+27	-80	+142	23	16	47	16
3	20.6	189	9.2	650		+755	7.05	-6	+4	-19	+19	+80	+21	-87	+194	42	11	46	-3
4	16.8	161	9.6	550	158	+705	7.10	-11	+6	-18	+15	+55	+31	-67	+160	34	19	42	1
5	20.2	194	9.6	665	204	+785	6.96	-9	+6	-16	+15	+67	+35	-78	+182	35	18	40	6
Av.	18.9	180	9.5	615		+715		-8	+5	-17	+15	+65	+28	-78	+170	36	15	43	6

Expected pH if no buffering 1.8, observed average pH 7.07

~40% acid buffered by extracellular HCO_3 then exhaled by ventilation as CO2

~10% buffered by cellular hemoglobin

~50% buffered by intracellular Na/K exchange for extracellular H+

Swan RC JCI 1955 Feb; 34(2):205-212

Intracellular Buffers

Proteins
Organic/Inorganic Phosphates
Hb in erythrocytes

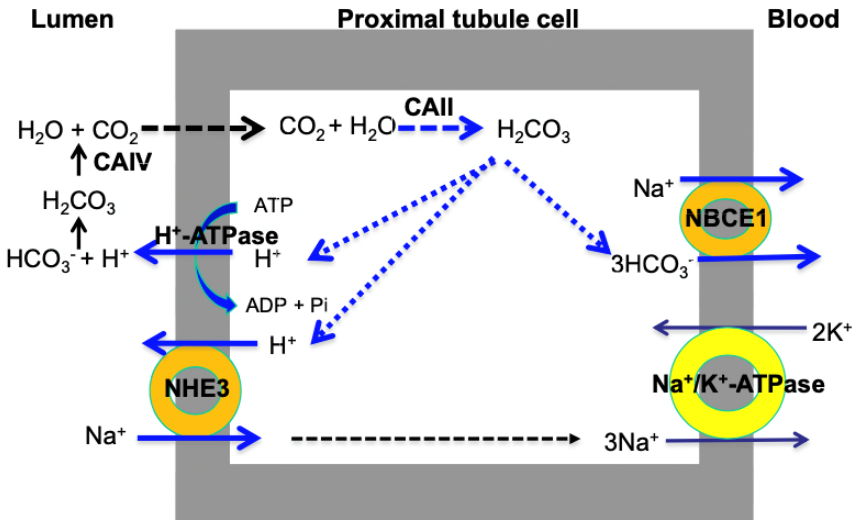
Bone Buffering

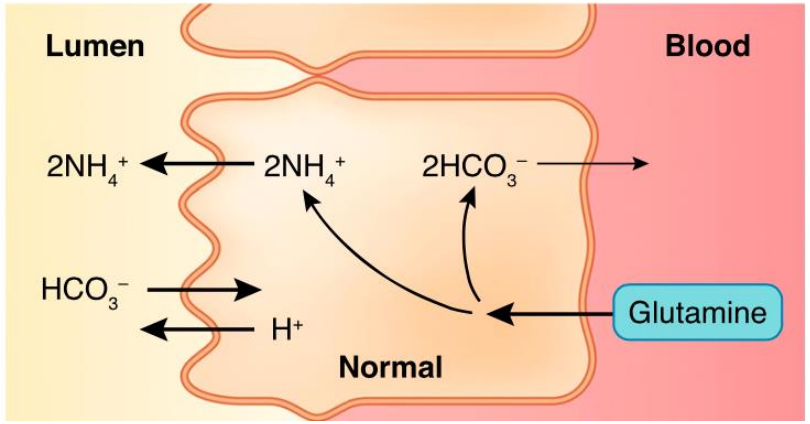
Up to 40% of a metabolic acidosis can be buffered by bone

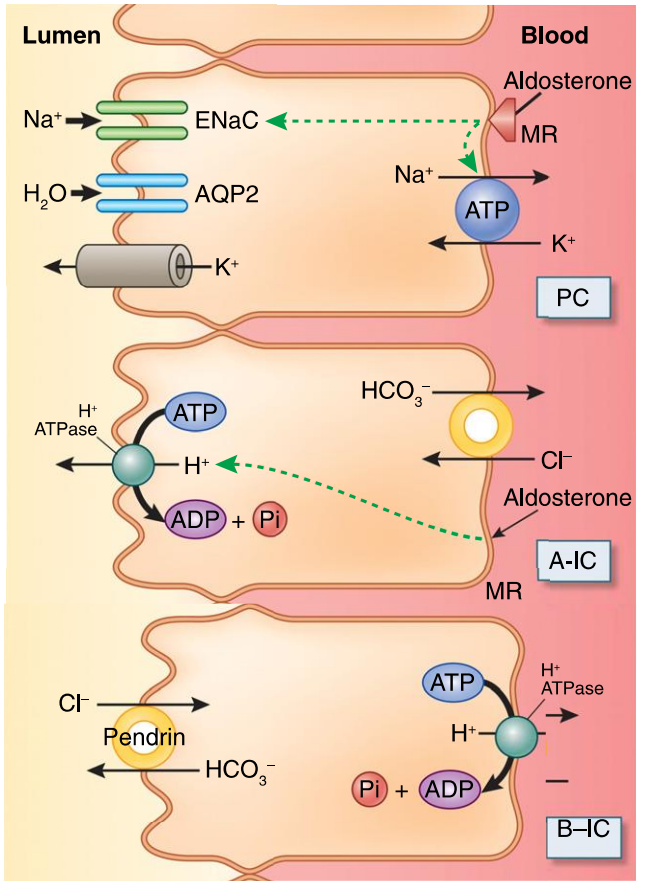
Bone Buffering can work in 2 ways-

1. exchange of intracellular Na, K for extracellular H+
2. bone dissolution w release of buffering compounds-$NaHCO_3$, $KHCO_3$, $CaCO_3$, $CaHPO_4$

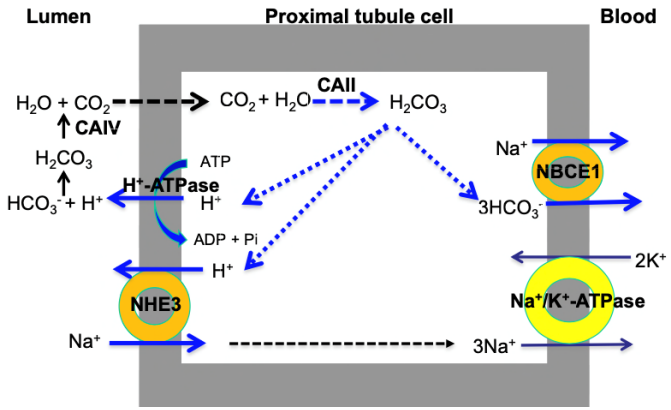
Important acid-base sites in the nephron

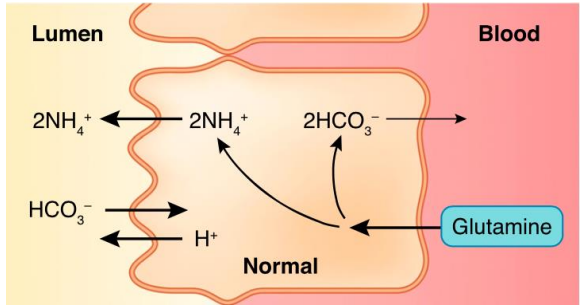


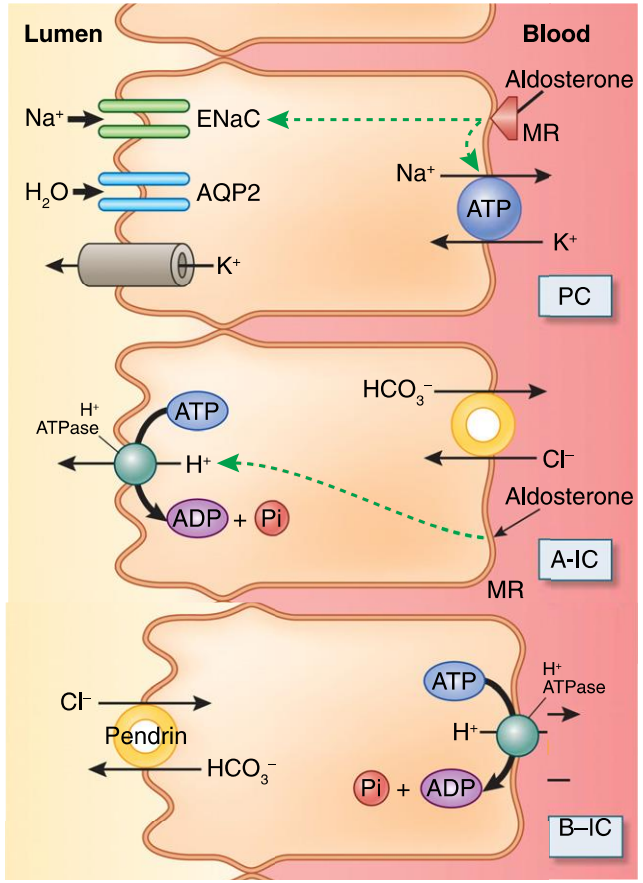




Renal Response to Metabolic Acidosis







↑Na/H transporter activity
(increases HCO3 reabsorption)

↑ammoniagenesis
*adds HCO_3
*adds NH_4 that can be used for proton excretion

↑H+ ATP-ase activity
*↑NH3→NH4
*↑free protons in urine
*↑titrateable acidity

Urine AG Na+K-Cl
↑NH4 in urine makes Urine AG more neg

NEPHSAP Fluid, Electrolytes, Acid Base 2015
Soleimani M AJKD 2016; 68(3):488

Causes of Metabolic Acidosis

- ↑ Anion Gap (GOLDMARRK)
  - Glycol (ethylene glycol, propylene glycol)
  - Oxoproline (pyroglutamic acid)
  - **Lactic acidosis (L-lactate)**
  - D lactic acidosis (D-lactate)
  - Methanol
  - Aspirin (salicylate)
  - **Renal failure*****
  - Rhabdomyolysis
  - **Ketoacidosis** (diabetic, alcoholic, starvation)
- Normal anion gap (gi vs kidney)
  - **Diarrhea**-hco3 loss
  - RTA 1, 2, 4
  - **High output intestinal fistula**
  - Tube feeds
  - **Renal failure*****
  - **Resuscitation acidosis** (saline administration)
  - ureterosigmoidostomy

Approach to metabolic acidosis

- Check AG
  - ↑-check lactate, blood sugar, ketones**, salicylate, osmolar gap (if above tests are normal), CK, ask about acetaminophen use
  - Check delta-delta (ΔAG, Δhco3)-limited utility-see later
- If AG normal-can check urinary AG (Na +K-Cl)
    - Expect ↑ammoniagenesis by kidney in response to metabolic acidosis, thus ↑NH_4 (unmeasured in urine) so urinary AG negative if a non-renal cause of acidosis or RTA 2
    - If renal cause of acidosis, cannot ↑NH_4 excretion so urinary AG will be 0 or positive
      - RTA1 decreased NH_4 because of impaired distal acidification (less NH3→NH4)
      - RTA4 impaired ammonium production (hyperkalemia) and decreased H+ secretion
      - Advanced renal failure-impaired NH_4 production

**The urine dipstick only reacts with acetoacetate, not with beta hydroxybutyrate (the ketoacid in highest concentration in DKA and AKA). Thus one could have low Level ketonuria, but not detect it with the urine dipstick

Anion Gap

- Na – (Cl +HCO_3)
- Normally 12
- Unmeasured anions are mostly plasma proteins (esp albumin)
- For every 1g/dl albumin ↓, add 2.5mg/dl to the AG
- ↓AG seen in hypoalbuminemia (most common) ,paraproteinemia, lithium intoxication
- Can rarely see negative AG in patients w bromism (excess bromide salt ingestion)-pyridostigmine, neostigmine, dextromethorphan. Bromine causes pseudohyperchloremia (bromine reacts more strongly than Cl w current Cl analyzers).

Anion Gap in Renal Failure

- Metabolism of aminoacids generates H_2SO_4→2H+ and 2 SO_4^{2-}
- H+ excretion mostly as NH_4 is a tubular function
- SO_4^{2-} excretion is a function of filtered load and reabsorption
- Progressive ↓GFR and ↓tubular function leads to retention of H+ and SO_4^{2-} leading to AG acidosis
- More severe tubular dysfunction (vs ↓GFR) leads to ↓↓H+ excretion as well as ↓SO_4^{2-} reabsorption which ↑SO_4^{2-} excretion leading to normal gap acidosis

Rose-Clinical Physiology of electrolyte and acid base disorders-5th Ed

ΔAG/ΔHCO3

- Expect the AG to ↑by the same amount the HCO3↓ in a pure AG acidosis
- However, since ~50% of an acid load is buffered intracellularly (ie does not consume hco3), the ΔAG is usually >ΔHCO3 which limits the utility of ΔΔgap
- If the ↓HCO3 is more than the ΔAG then there must be a superimposed non AG acidosis
- If the ↓HCO3 is less then the ↳AG then there must be a superimposed metabolic alkalosis

Osmolal Gap

- Calculated Posm= 2(Na) +(glucose/18) +BUN/2.8
- In the presence of a non–calculated osmole, the measured osm will be >calculated osm
- Can have ↑osmolal gap in DKA, AKA, lactic acidosis, chronic renal failure, ethanol intoxication
- In absence of lactic or ketoacidosis an osmolal gap ≥25 strongly suggests ethylene glycol or methanol intoxication

Ethanol, lactic acidosis, alcoholic ketoacidosis increase the osmolal gap

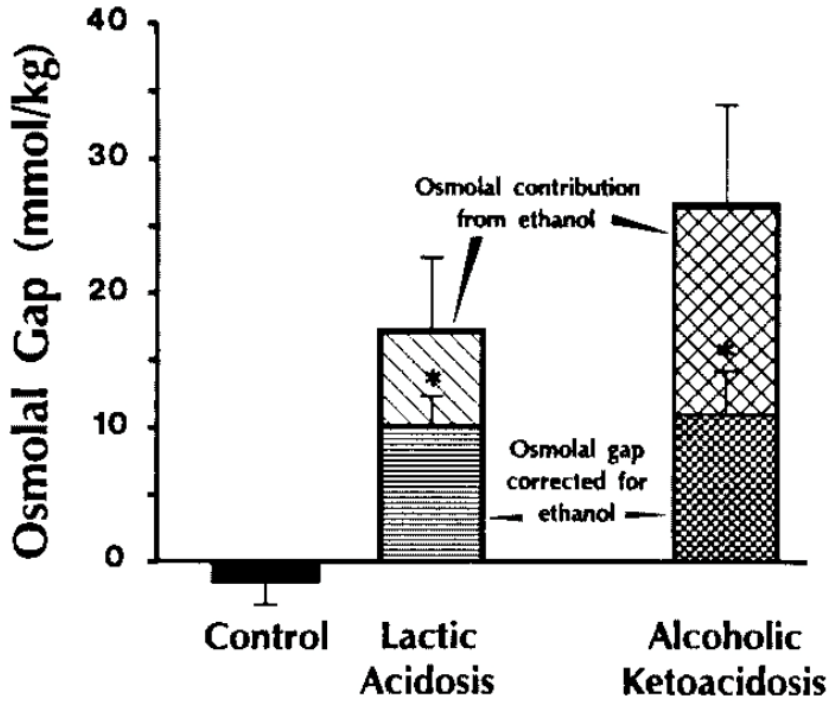


Figure 1. Total osmolal gap and the osmolal gap after correcting for the contribution of ethanol. An asterisk indicates $P < 0.05$ for total and corrected osmolal gap when compared with the control value.

Thus, an elevated osmolal gap does not automatically imply a toxic alcohol ingestion

Schelling Ann Intern Med 1990; 113:580

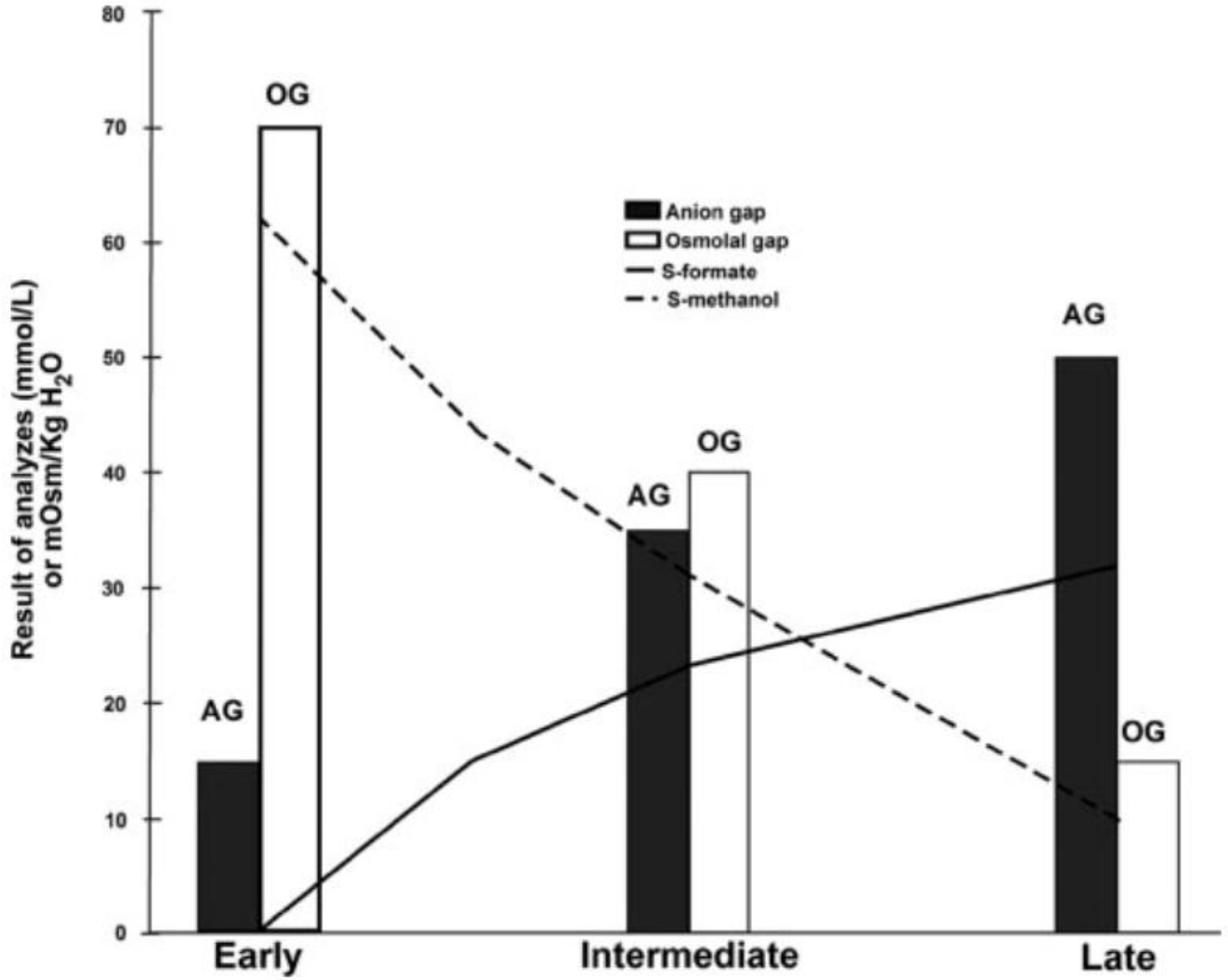
Osmolar Gap in Methanol and Ethylene Glycol

- Methanol-average osmolar gap in survivors 48 vs 90 in non-survivors
- Ethylene glycol-average osmolar gap in survivors 49 vs 79 in non-survivors

Coulter CV Clin Toxicol 2011; 49: 900

Changes in the osmolal gap and anion gap during the course of methanol intoxication

(Same phenomena is present in ethylene glycol intoxication)



Kraut CJASN 2008; 3:208

Mechanism of acidosis in toxic alcohol ingestions

- Methanol-acidosis mostly due to formic acid accumulation; can see mild lactic acidosis (impaired ox-phos). Ketoacidosis seen when there is co-ingestion with EtOH
- Ethylene glycol-mostly due to glycolic acid accumulation, can see minor lactic acidosis (impaired ox-phos)
- Propylene glycol-causes lactic acidosis
- Isopropanol-increases OSMOLAL GAP, but DOES NOT CAUSE AN ACIDOSIS (unless shock causes lactic acidosis)

Ethylene Glycol Poisoning-elevated lactate gap

54M presents w coma. BP 110/70, HR 90.

pH 6.8, lactate >30 (whole blood assay)
Lactate by chemistry 2.5

EG level 976.8

Whole blood assay uses lactate oxidase to convert lactate→pyruvate,
Pyruvate production is an indirect measure of lactate

EG metabolites glycolate and glyoxalate also react w lactate oxidase
Leading to false elevations in serum lactate.

Spectophotographic assays of plasma use lactate dehydrogenase to directly measure lactate and thus avoid false elevations

A lactate gap (high WB lactate, normal plasma lactate) can be
Used as an indirect EG detection method

CaOx dihydrate

Rothberger KI 2015; 88:419

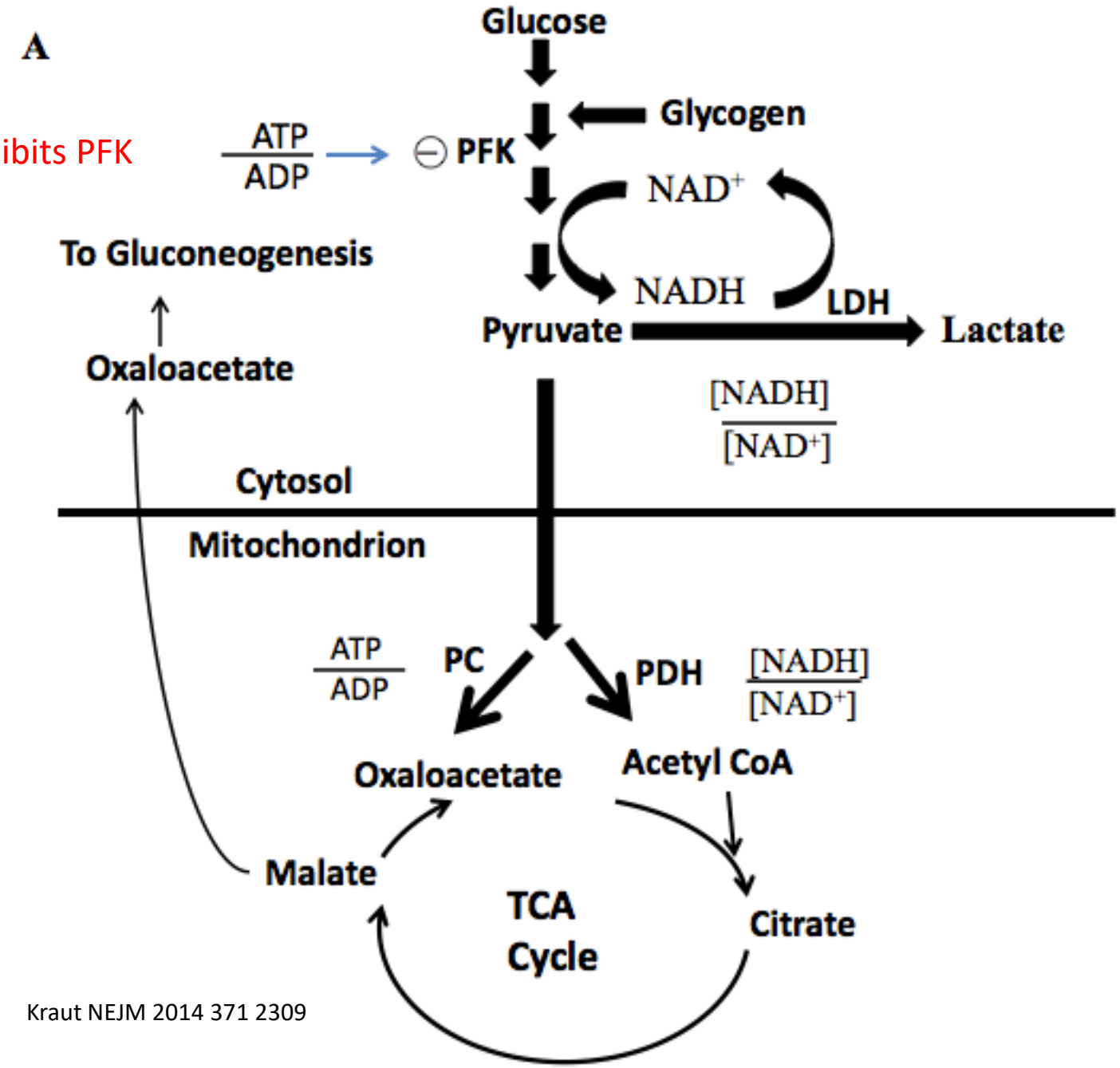
CaOx monohydrate

Nephsap fluid, electrolyte, acid base 2015

Riquier Annales Franc¸aises d'Anesthe´sie et de Re´animation 33 (2014) e79–e81

NORMAL LACTATE METABOLISM

ATP inhibits PFK

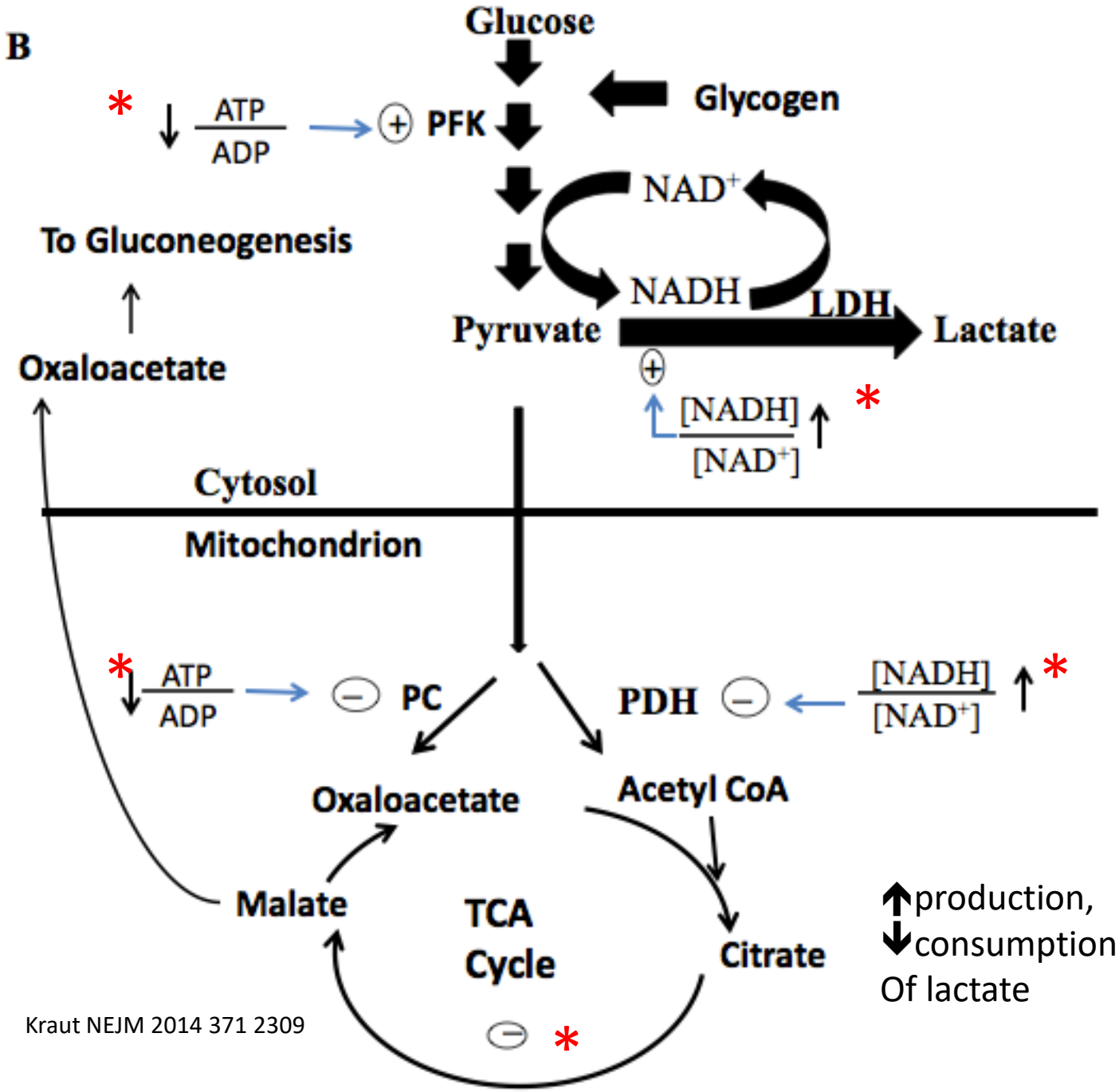


Kraut NEJM 2014 371 2309

Accumulation of Lactate in Tissue Hypoxia

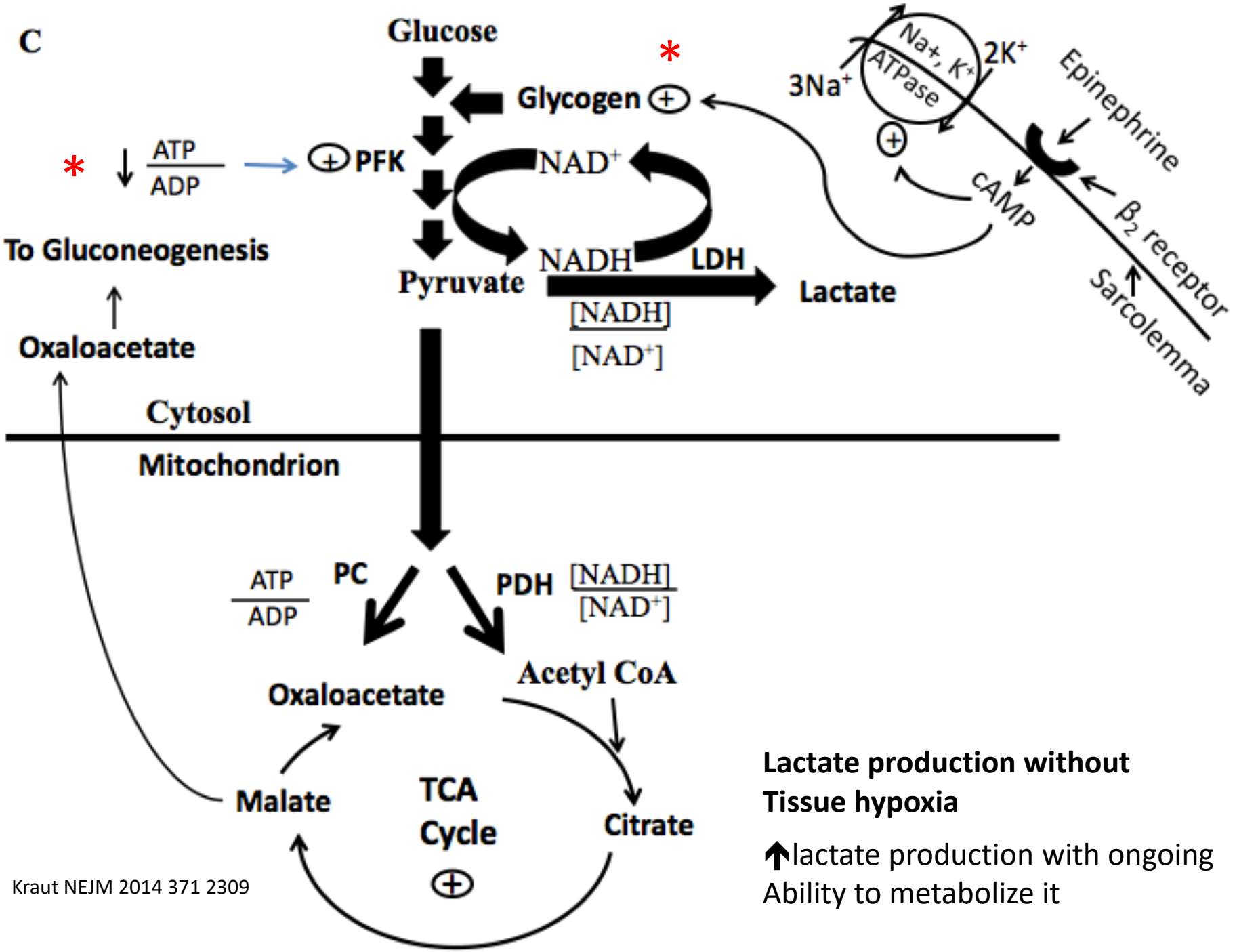
↑lactate production
Due to ↑anaerobic
glycolysis

↓lactate utilization
Due to inhibition of
Key pathway enzymes



↕production,
consumption
Of lactate

Kraut NEJM 2014 371 2309



Kraut NEJM 2014 371 2309

Lactate production without Tissue hypoxia

↑lactate production with ongoing Ability to metabolize it

Table 1. Causes of Lactic Acidosis.*

Cause	Presumed Mechanism or Mechanisms	Comments
Cardiogenic or hypovolemic shock, advanced heart failure, or severe trauma	Decreased O_2 delivery to tissues; epinephrine-induced β_2-adrenoceptor stimulation can be a contributory factor	With sepsis, these causes account for the majority of cases of lactic acidosis
Sepsis	Epinephrine-induced β_2-adrenoceptor stimulation with or without decreased O_2 delivery to tissues; reduced clearance of lactate even in hemodynamically stable patients	Evidence of decreased O_2 delivery can be subtle; even in the absence of macrocirculatory impairment, dysfunction of microcirculation can be present
Severe hypoxemia	Decreased O_2 delivery to tissues	Requires Pao_2 <30 mm Hg
Carbon monoxide poisoning	Decreased O_2 delivery to tissues, interference with oxidative phosphorylation	Hyperbaric O_2 therapy is recommended if pH <7.1
Severe anemia	Decreased O_2 delivery to tissues	Requires hemoglobin level <5 g/dl
Vigorous exercise, seizures, or shivering	Increased O_2 requirements	The decrease in pH and hyperlactatemia is transient; lactic acidosis can impair exercise performance
Diabetes mellitus	Mechanism unclear	The risk of death in patients with ketoacidosis can be increased by coexisting lactic acidosis
Cancer	Increased glycolytic activity of tumor (Warburg effect), tumor tissue hypoxia, decreased clearance of lactate with severe liver metastases	Lactic acidosis can be seen in association with lymphomas, leukemias, and solid tumors; HCO_3^- administration may increase lactic acid production; acidic microenvironment is critical for tumorigenesis, angiogenesis, and metastasis
Liver disease	Lactate clearance decreased	Fulminant liver disease can cause substantial hyperlactatemia; hyperlactatemia is usually mild with chronic liver disease alone; lactate clearance can also be decreased when liver function is normal, in association with sepsis
Pheochromocytoma	Decreased O_2 delivery to tissues and epinephrine-induced β_2-adrenoceptor stimulation	In rare cases, lactic acidosis is a presenting feature of pheochromocytoma
Metformin	Interference with oxidative phosphorylation, suppression of hepatic gluconeogenesis	This is usually seen in association with high plasma metformin levels; treatment with dialysis is beneficial
Nucleoside reverse-transcriptase inhibitors	Interference with oxidative phosphorylation	Marked hyperlactatemia is uncommon in the absence of other predisposing factors
Cocaine	Decreased O_2 delivery to tissues and epinephrine-induced β_2-adrenoceptor stimulation	Marked hyperlactatemia is seen in some patients having seizures or being restrained
Toxic alcohols, methanol, ethylene glycol, diethylene glycol	Interference with oxidative phosphorylation	The increase in lactate is small; a small increase in the osmolal gap (usually <20 mOsm/kg H_2O) can be seen in some cases of lactic acidosis without toxic alcohols
Propylene glycol	D-Lactate and L-lactate are normal products of metabolism	Lactic acidosis can occur in the absence of impaired oxidative phosphorylation
Salicylates	Interference with oxidative phosphorylation	Hyperlactatemia is usually minimal
Cyanide	Interference with oxidative phosphorylation	Lactic acidosis is an important manifestation of poisoning
β_2 agonists	Stimulation of aerobic glycolysis	This is most common with treatment of acute asthma; hypokalemia can result from enhanced cellular uptake of potassium
Propofol	Interference with oxidative phosphorylation	Lactic acidosis can be seen with prolonged high-dose infusion
Thiamine deficiency	Impairment of pyruvate dehydrogenase activity	This is most common in children or adults receiving parenteral nutrition or those with fulminant beriberi

Kraut JA, Madias NE.
N Engl J Med 2014;371:2309-2319

Causes of marked lactate elevation with stable hemodynamics

- Metformin poisoning
- Ethylene glycol poisoning (false lactate elevation)
- Tumor (w liver replacement by tumor)

Lactic Acidosis

- 50F w PUD, back pain on nsaids presents w severe abdominal pain. CT shows free air in the stomach, Ex-lap shows perforated gastric ulcer which is closed. Abd contents are otherwise intact.
- Post op-90/60, 120, 28, 95%. FiO2 40%, peep 5, VT 450
- Levo 20, vaso 2
- Cxr –bilateral pleural effusions, mild edema
- ABG 7.05-40-60
- Lactate 12
- BMP 138 5.2 100 12 46 1.9 gluc 130

Management

- Address mechanism of lactate (shock)
  - Optimize hemodynamics
  - Ensure perforation addressed
  - Antibiotics
- Optimize minute ventilation (resp compensation)
- ? Bicarbonate (IV bicarbonate vs dialysis)

Acidosis

- Severe acidemia (<7.1) causes myocardial depression, vasodilatation, catecholamine unresponsiveness
- Cells are freely permeable to co2, less so to H+ and HCO_3
- Respiratory acidosis results in a lower cellular pH than does metabolic acidosis due to the diffusability of co2

Carbonic anhydrase

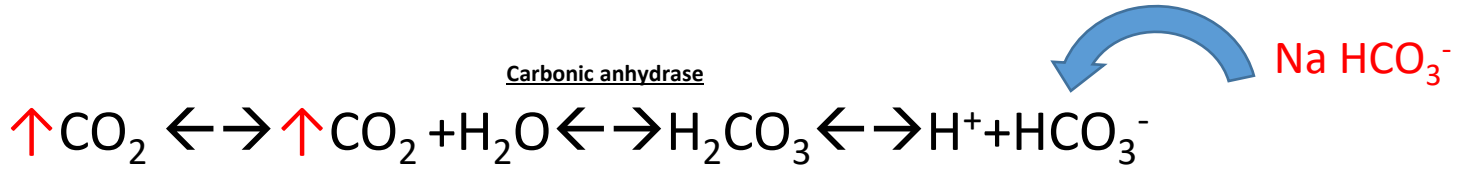
- $CO_2 \leftarrow\rightarrow CO_2 + H_2O \leftarrow\rightarrow H_2CO_3 \leftarrow\rightarrow H^+ + HCO_3^-$

$$pH \sim \log \frac{[HCO3^-]}{PCO_2}$$

$[HCO3^-]$ Regulated by renal H+ excretion

PCO_2 Regulated by alveolar ventilation

Effect of NaHCO3 in lactic acidosis



If CO_2 is not exhaled, the pH does not change in response to $NaHCO_3$ (since CO_2 will produce H_2CO_3)

An increase in extracellular CO_2 will lead to increased intracellular CO_2, which will acidify the cell. This can lead to decreased myocardial contractility and worsen shock.

Even with adequate ventilation, severe shock will decrease tissue removal of CO_2 which can lead to co_2 retention and acidosis

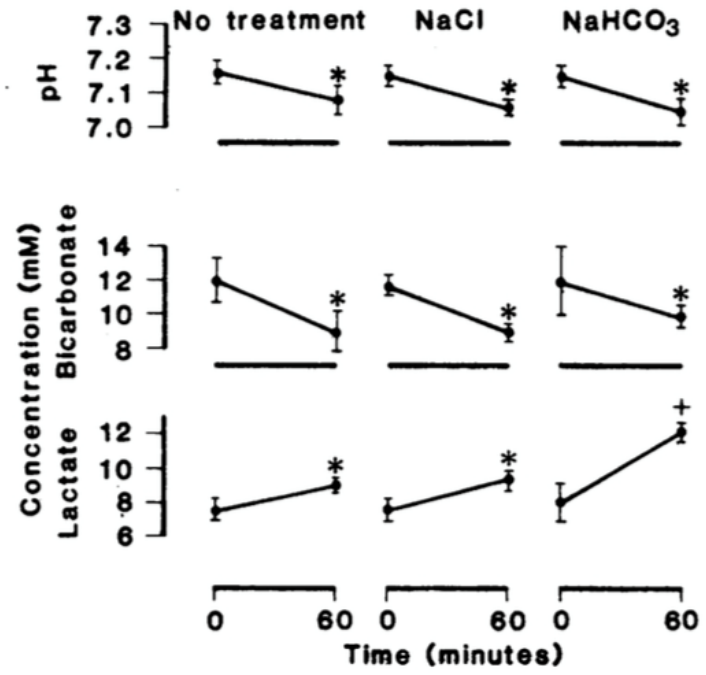
If CO_2 is exhaled, the pH might increase (depending on amount of HCO3 given vs amount/rate of acid production)

Case

- 44M w dm2, HTN, covid 19 ARDS requiring VV ECMO, AKI on CVVHD, shcok on pressors.
- VV ECMO 2.95L/min
- ABG 7.38-48-136 hco3 27
- Question of whether giving HCO3 will facilitate weaning of VVECMO without generating severe acidosis.
- Patient receives NaHCO3 infusion to increase serum HCO3
- ABG 7.38 57 129 HCO3 31
- Because the patient could not increase his minute ventilation, the increase in HCO3 was matched by an increase in CO2 such that the pH did not change.

Bicarbonate in Lactic Acidosis

**CO2 held constant in these experiments,
Thus, the generalizability to humans
who will increase minute ventilation
Is less clear



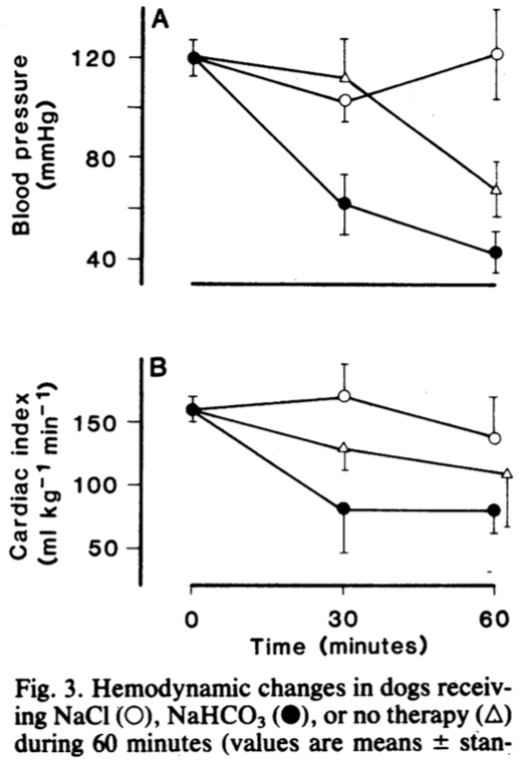


Fig. 3. Hemodynamic changes in dogs receiving NaCl (○), $NaHCO_3$ (●), or no therapy (△) during 60 minutes (values are means ± stan-

Model-dogs intubated, ventilated w 8%O2/92% Nitrogen
producing serum lactate >5mM and serum HCO3 <15mM
Dogs then followed for 1hr after 1 of 3 treatments

Group 1-no treatment
Group 2 rx 1M NaCl @2.5meq/kg/hr
Group 3 rx 1M NaHCO3 @2.5meq/kg/hr

Graf Science 1985; 227:754

Effects of HCO3 therapy in hypoxic lactic acidosis in dogs

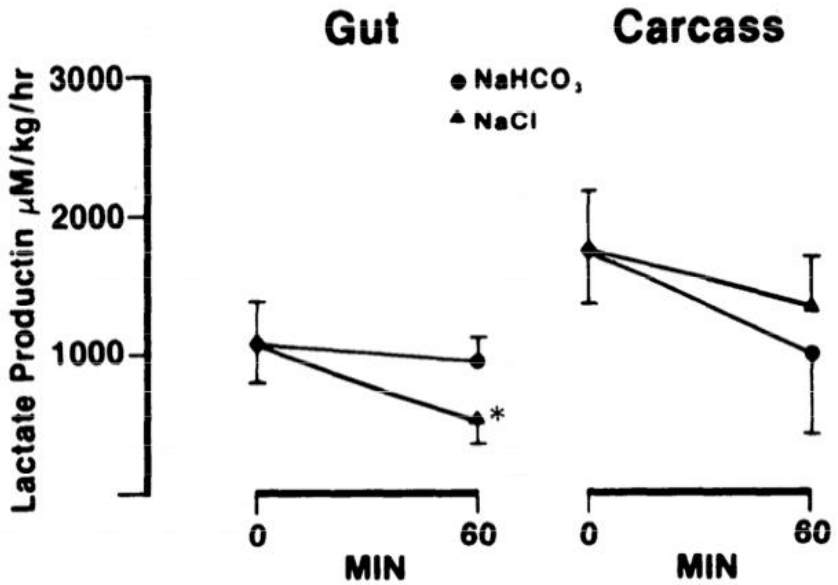


FIG. 2. Gut and carcass lactate production in dogs with hypoxic lactic acidosis treated for 60 min with $NaHCO_3$ or NaCl. *, $P < 0.05$ vs. control value at 0 min and <0.001 vs. $NaHCO_3$ at 60 min. Values are means ± SE; $n = 7$ in each group.

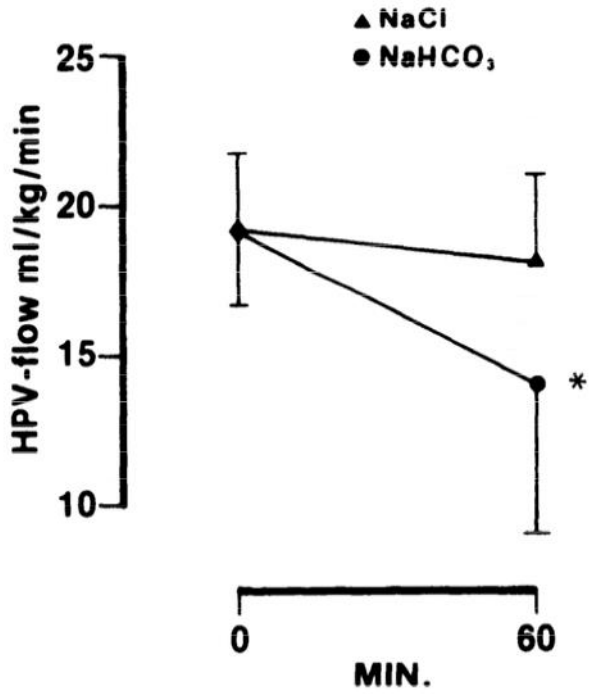
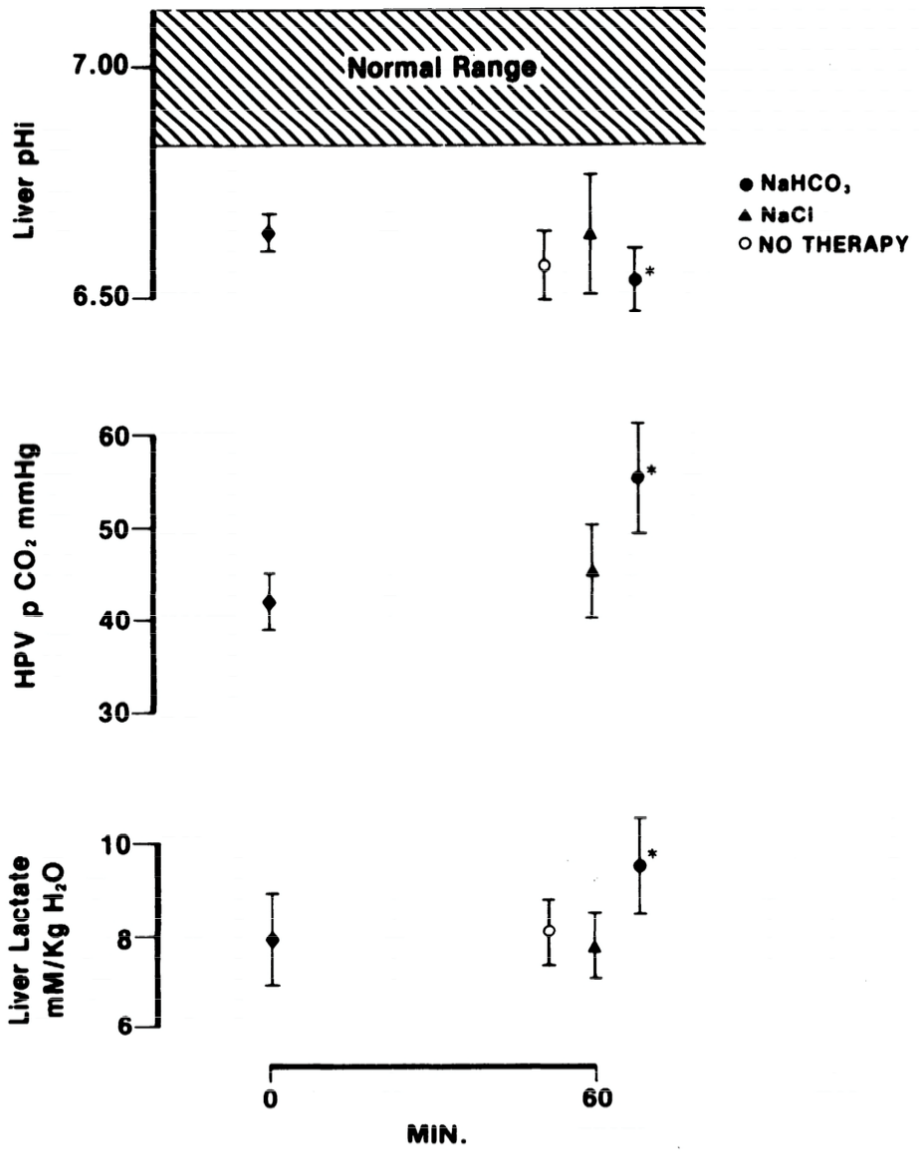


FIG. 3. Hepatic portal vein (HPV) blood flow in dogs with hypoxic lactic acidosis during 60 min of $NaHCO_3$ and NaCl treatment. *, $P < 0.05$ vs. control value at 0 min as well as NaCl at 60 min. Values are means ± SE; $n = 7$ in each group.

Graf Am J Physiol 1985; 249:F630

Hepatic pHi, HPV CO_2 and hepatic lactate in dogs with hypoxic lactic acidosis treated with HCO_3



As compared to dogs treated w NaCl, there is a significant decrease In pHi after 60min of HCO3 treatment

As compared to dogs treated w NaCl, Dogs treated w HCO3 have a significant Increase in portal venous CO2 after 60min of HCO3 treatment

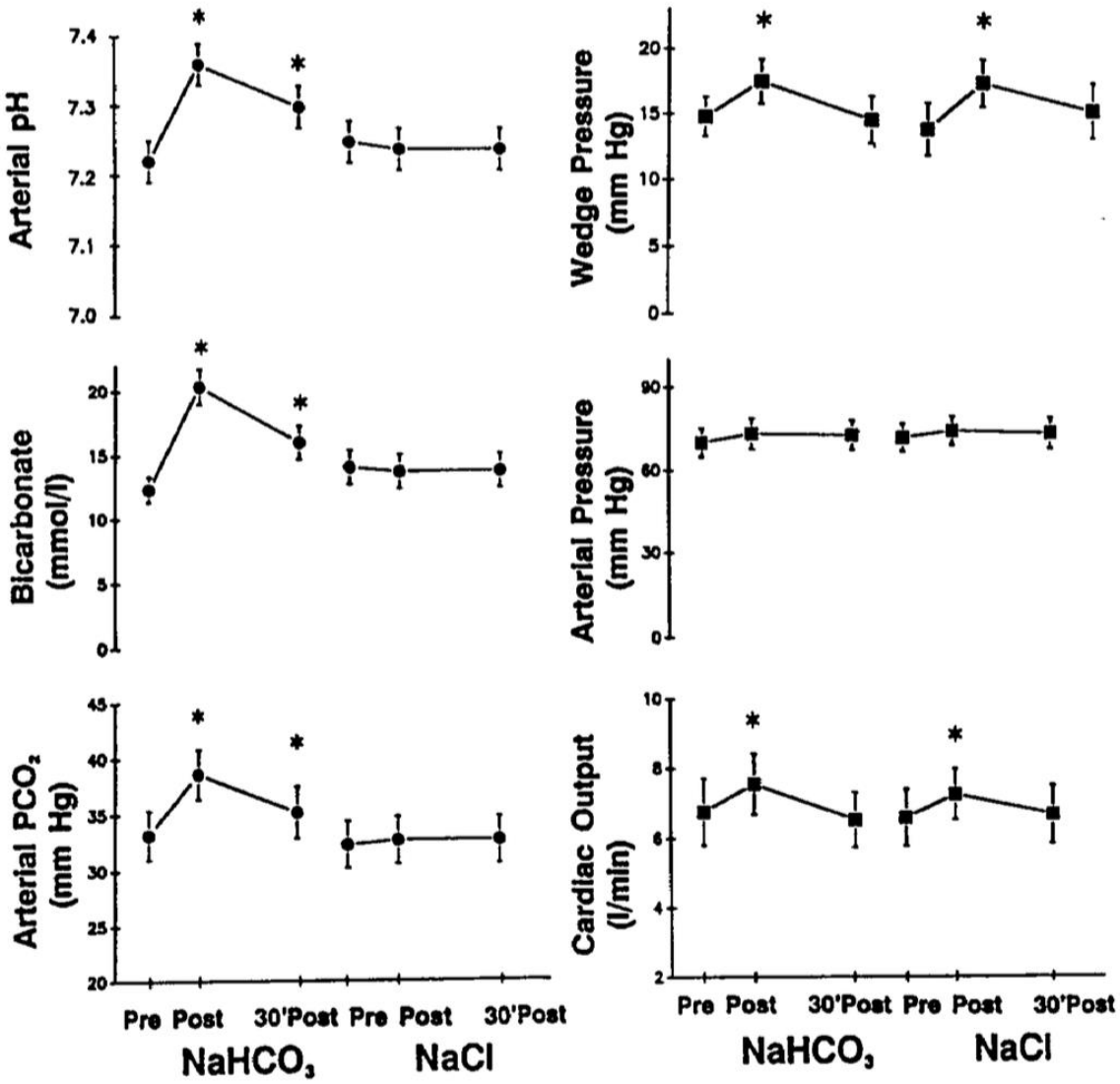
As compared to dogs treated w NaCl or No therapy, there is a significant increase In hepatic lactate in dogs treated w HCO3.

Graf Am J Physiol 1985; 249:F630

HCO3 vs NaCl therapy for lactic acidosis in humans

Mean pH 7.22
Mean lactate 7.8

Patients are not as sick
As those we would give
Hco3 to; unclear how
Much this translates to
Current practice



Cooper Ann Intern Med 1990; 112:492

Effect of HCO_3 in lactic acidosis

- HCO3 increases serum lactate
  - Releases acidemia effect to inhibit PFK-->↑glycolysis→lactate production
  - Increase in co_2 causes intracellular acidosis→decreased cardiac output→increased lactate
  - Hepatocyte acidification might affect lactate production or metabolism
- HCO_3 'pushes' (50meq/50cc) cause hypernatremia
- Studies show no survival benefit
- Some studies suggest that the time to death is delayed-this might be beneficial in a patient in whom a life saving therapy can be initiated

Lactate removal by CVVH (D)

- Lactate has a sieving coefficient of 1 (readily passes across hemofilter)
- Lactate clearance is ~ equivalent to urea clearance
- Lactate removal is proportional to its blood concentration
- Lactate concentration in dialysate effluent = to plasma concentration

Hemofilter lactate clearance in CVVH is negligible when compared to endogenous lactate clearance

Patient	TPLC (mL/min)	FLC (mL/min)	FLC/TPLC (%)
1	920.5	22.7	2.4
2	1410.0	32.9	2.3
3	1013.0	24.2	2.3
4	883.8	18.4	2.1
5	1492.5	35.6	2.4
6	1880.7	21.9	1.2
7	1552.0	7.1	0.5
8	1348.8	26.2	1.9
9	1417.3	34.4	2.4
10	753.7	24.2	3.2

TPLC, total plasma lactate clearance; FLC, filter lactate clearance.

Table 5 . Total plasma and continuous venovenous hemofiltration with dialysis lactate clearances for all patients

Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients.
Levraut, Jacques; Ciebiera, Jean-Pierre; Jambou, Patrick; Ichai, Carole; Labib, Yasser; Grimaud, Dominique

Critical Care Medicine. 25(1):58-62, January 1997.

Bicarbonate deficit

- HCO_3 deficit=HCO3 space x change in HCO3
- HCO_3 space=0.5-0.7x wt
- HCO_3 space increases w increasing severity of acidosis
- HCO_3 deficit= 0.7x wt x ΔHCO3

Bicarbonate Deficit in Severe Acidosis

- Consider-65M weights 100kg, has pH 7.10, serum HCO3 is 5
- Goal is to increase serum HCO3 by 5
- HCO3 deficit=0.7*100*5
- HCO3 deficit=350meq (7amps HCO_3)
- In an active acid generating condition most of the HCO3 will be consumed due to new acid production; thus need to give HCO3 bolus then maintenance infusion to maintain ↑pH
- Thus, could need 350meq or more (7amps) to acutely increase the pH, then several amps per hour to sustain the pH.

Considerations in HCO3 therapy

- HCO3 pushes ↑ serum Na (the same amount as 100cc 3% saline)
- HCO3 therapy (serum alkalinization) ↓ serum K
- HCO3 therapy (serum alkalinization) ↓ionized Ca

Bicarbonate therapy in non-lactic acidosis

- Probably not beneficial in DKA unless pH is <7 despite therapy; concerns re hypokalemia w HCO3 therapy
- Beneficial in salicylate toxicity (re mobilizing salicylate from the tissues and trapping it in the ECF)
- Beneficial in acidosis of renal failure
- Beneficial in acidosis due to hco3 loss (diarrhea, fistulas)
- Beneficial in methanol/ethylene glycol (re acidosis)
- In RTA 1 and 2, K citrate preferred to $NaHCO_3$

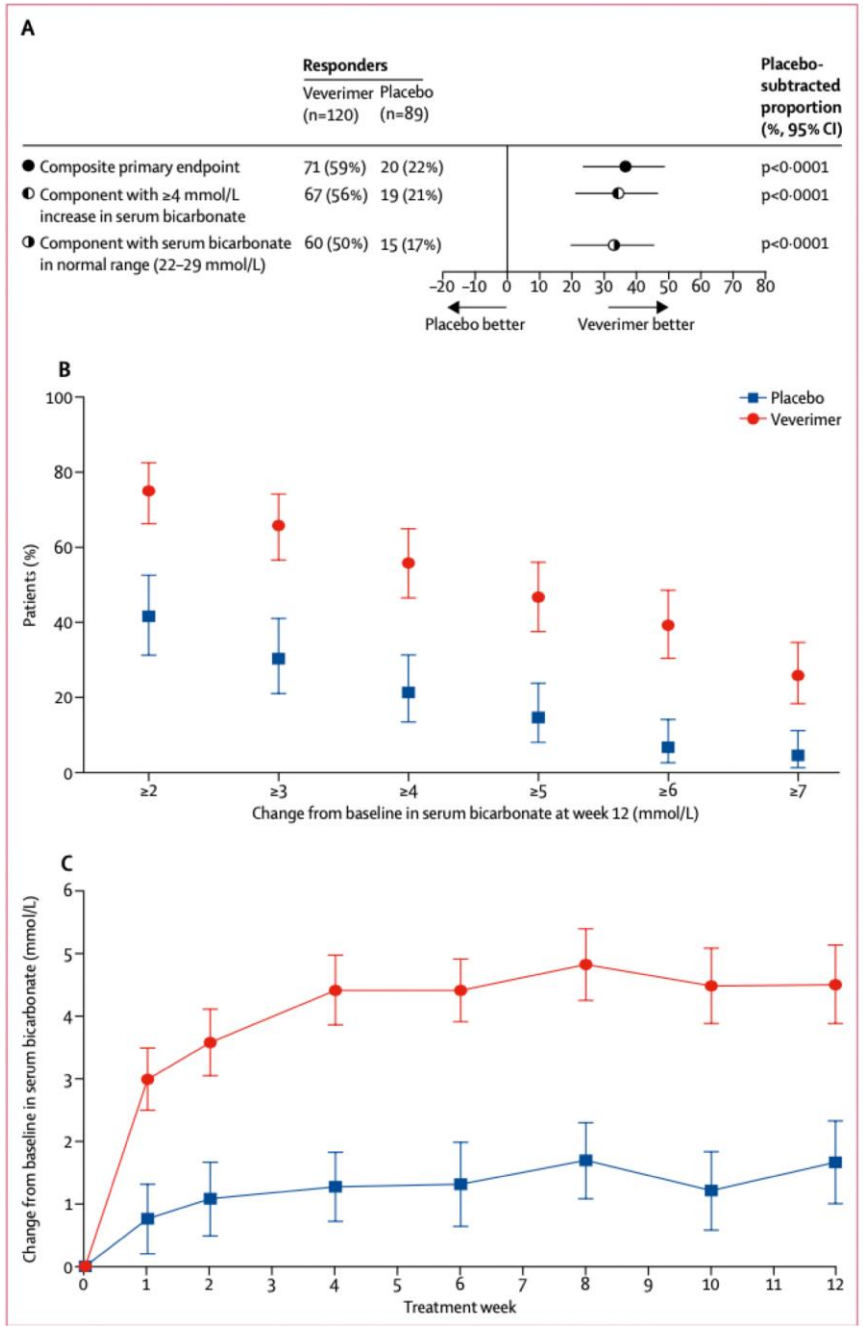
How to administer HCO3

- Life threatening acidosis-IV pushes (each push increases Na by ~2meq/L)
- Volume depleted w normal K-D5W w 150meq $NaHCO_3$
- Volume depleted w low K-D5W w 100meq $NaHCO_3$ + 20-40meq KCl
- Fluid overloaded, intact GFR-D5W w 150meq $NaHCO_3$ + lasix
- Fluid overloaded, impaired GFR-dialysis

Veverimer

- A non-absorbed polymer that binds HCl in the GI tract
- In a 12 week multicenter RCT of veverimer vs placebo for the treatment of metabolic acidosis due to CKD, more patients in the veverimer group (59%) vs placebo (22%) achieved the primary endpoint of ≧4meq/L increase in HCO3 or achieving a normal HCO3 (22-29meq/L) 95% CI 23-49, $p<0.0001$.
- Most common side effects diarrhea, flatulence, constipation, nausea (13% for veverimer vs 5% placebo)

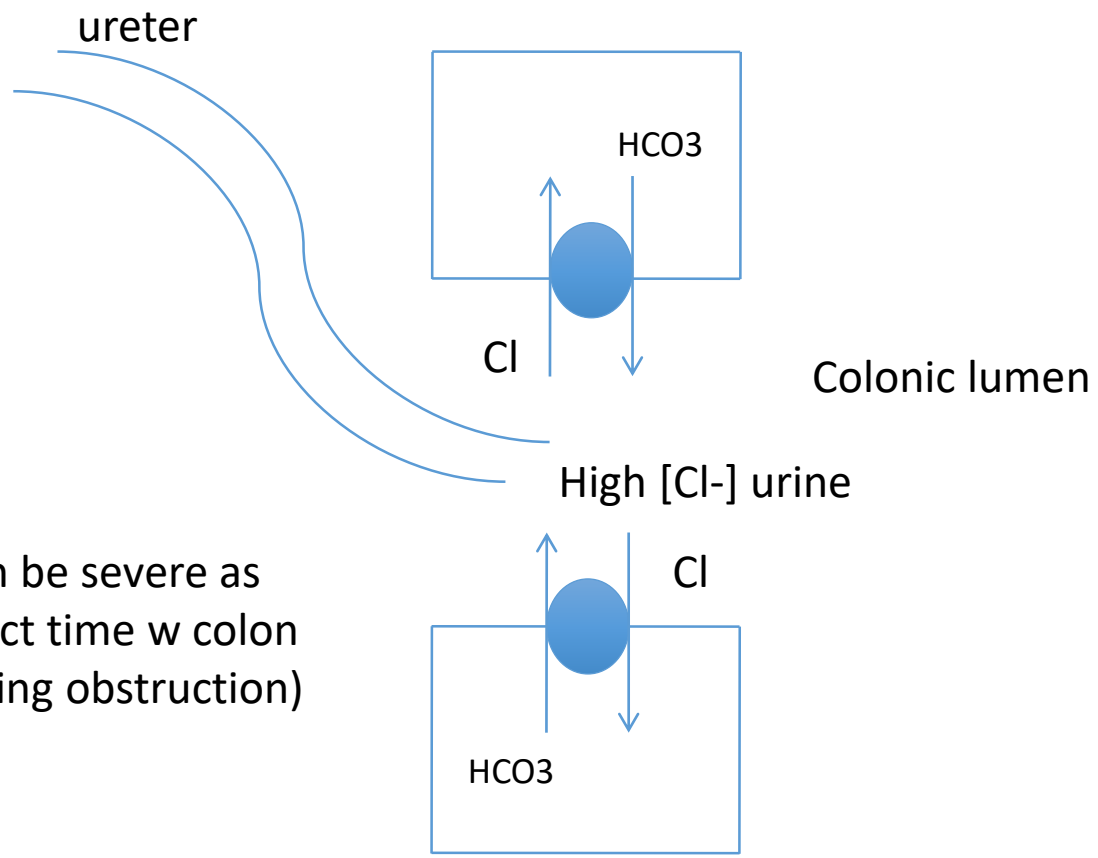
Wesson D. Lancet 2019; 393:1417



Wesson D. Lancet 2019; 393:1417

Part II

Normal Gap Acidosis w ureterosigmoidostomy (ileal conduit)



Acidosis can be severe as
Urine contact time w colon
Is ↑ (ie during obstruction)

D-Lactic acidosis

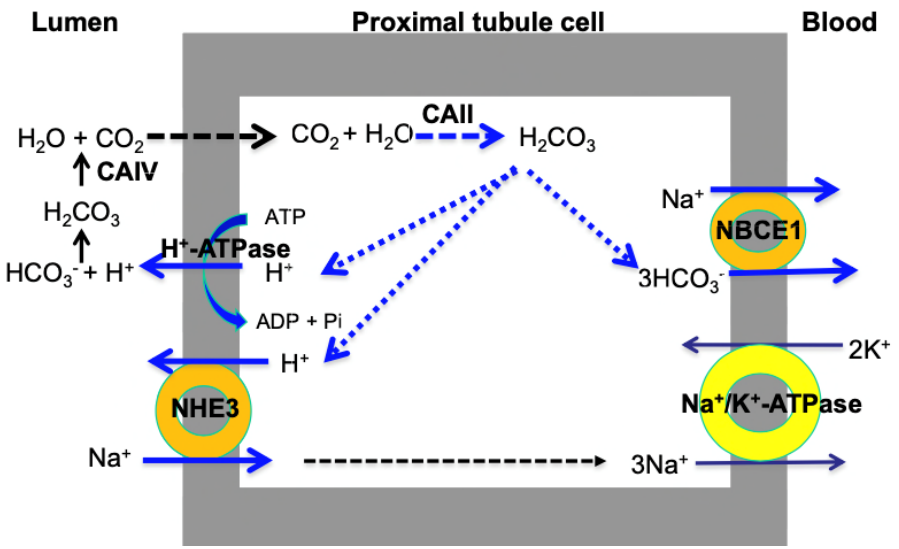
- Usual clinical lactic acidosis is L-lactic acidosis
- Patients w jejunoileal bypass or short-gut have delivery of glucose/starch (normally metabolized in small bowel) to colon where bacterial metabolize them to D-lactate
- D-lactate not recognized by LDH (so not converted to pyruvate)
- D-lactate not detected by L-lactate assay

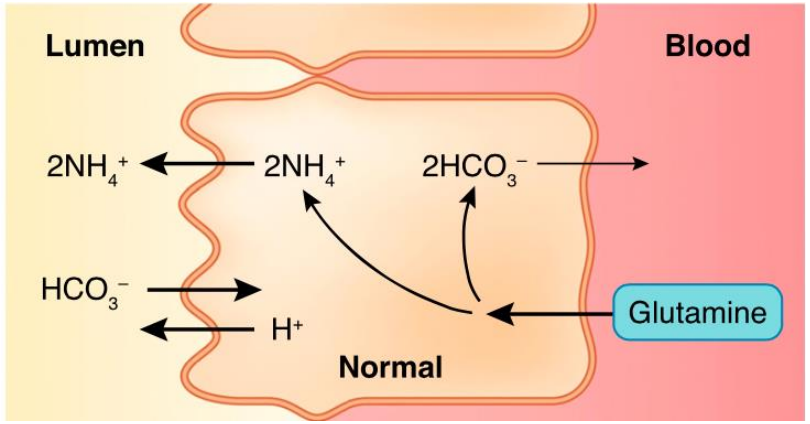
D-Lactic acidosis-clinical presentation

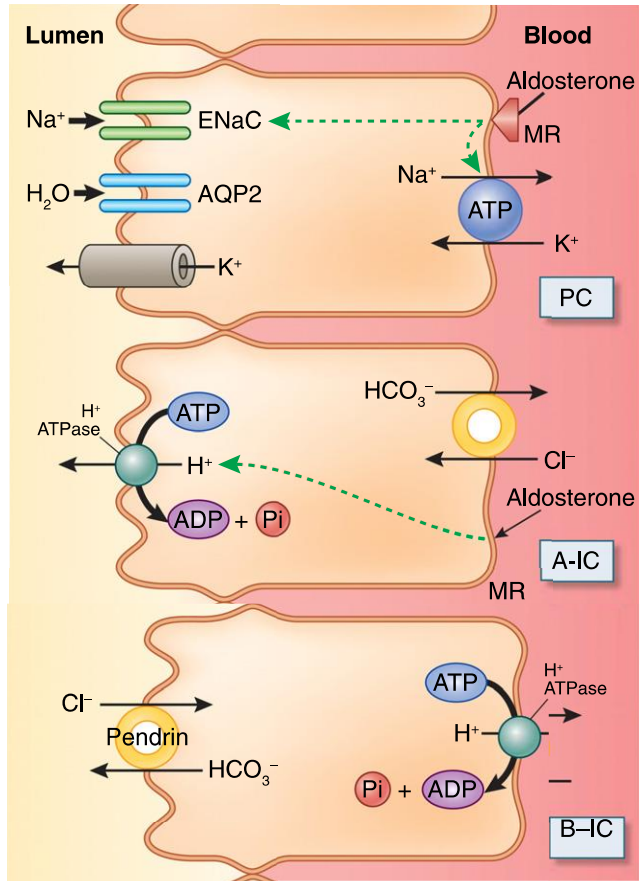
- Episodic metabolic acidosis after high carbohydrate meals
- Confusion, cerebellar ataxia, slurred speech, loss of memory (mimics EtOH intoxication, but negative EtOH levels)
- D-lactate rapidly excreted in urine so pt may have normal AG acidosis, or slightly elevated AG, but out of proportion decrease in HCO3-
- Must send off D-lactate soon after ED presentation (to mayo clinic)
- Therapy-HCO3 acutely, low carbohydrate diet, abx to reduce d-lactate producing organisms

Rose-Clinical Physiology of electrolyte and acid base disorders-5th Ed

Important acid-base sites in the nephron

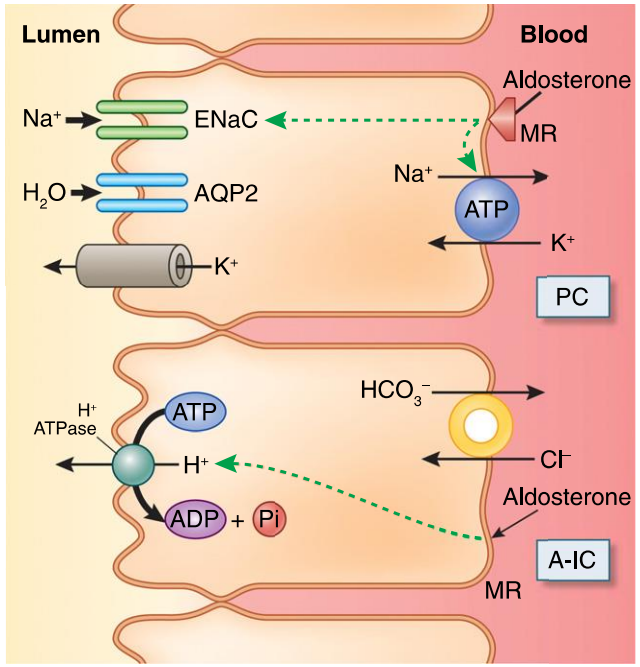






NEPHSAP Fluid, Electrolytes, Acid Base 2015
Soleimani M AJKD 2016; 68(3):488

Distal RTA-defect of CD H^+ ATPase pump



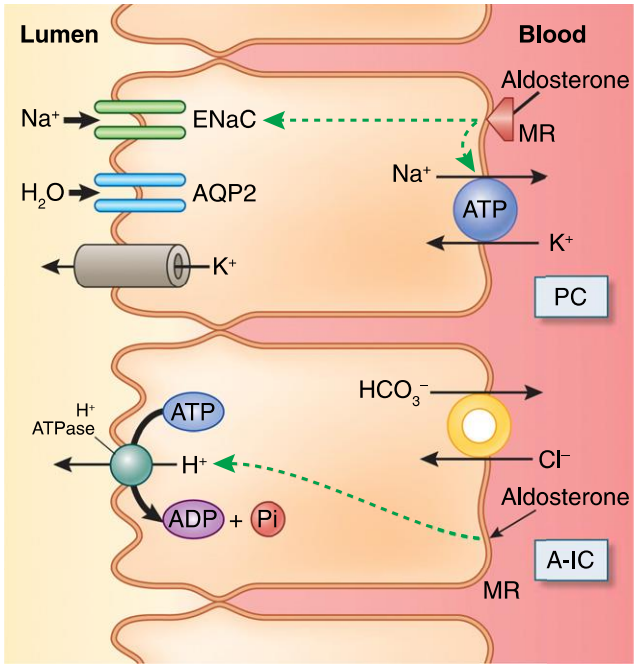
Inability to secrete protons in CD, so cannot acidify urine-urine pH >5.5

The negative charge of lumen (due to Na reabsorption) necessitates excretion of K to Balance charge causing hypokalemia

High urine pH (ca/P precip) w low citrate excretion→CaPhos stones and nephrocalcinosis

Need 1-2meq/kg hco3 to correct acidosis Rx w K citrate

Electronegative lumen
Due to Na reabsorbption
Via ENaC



In most RTA1, the defect is in the H+ ATP-ase. Since less H+ is secreted, more K needs to be secreted to maintain electroneutrality in the tubular fluid

In hyperkalemic distal RTA there can be tubular resistance to aldosterone or decreased Na reabsorption through ENaC resulting in a Smaller electrochemical gradient for K secretion

**(In type RTA 4, there is hyporenin, hypoaldosteronism. Urine pH would be <5.5)

Distal RTA-nephrocalcinosis

- Acidosis-bone buffering→↑phos, Ca release from bone→↑filtered load Ca, phos
- Acidosis-↑Ca excretion (inhibits TRPV5 in DT)
- Alkaline urine pH (bc inability to acidify urine)→CaPhos precipitation, ↓citrate excretion
- Nephrocalcinosis leads to tubulointerstitial inflammation and progressive renal failure

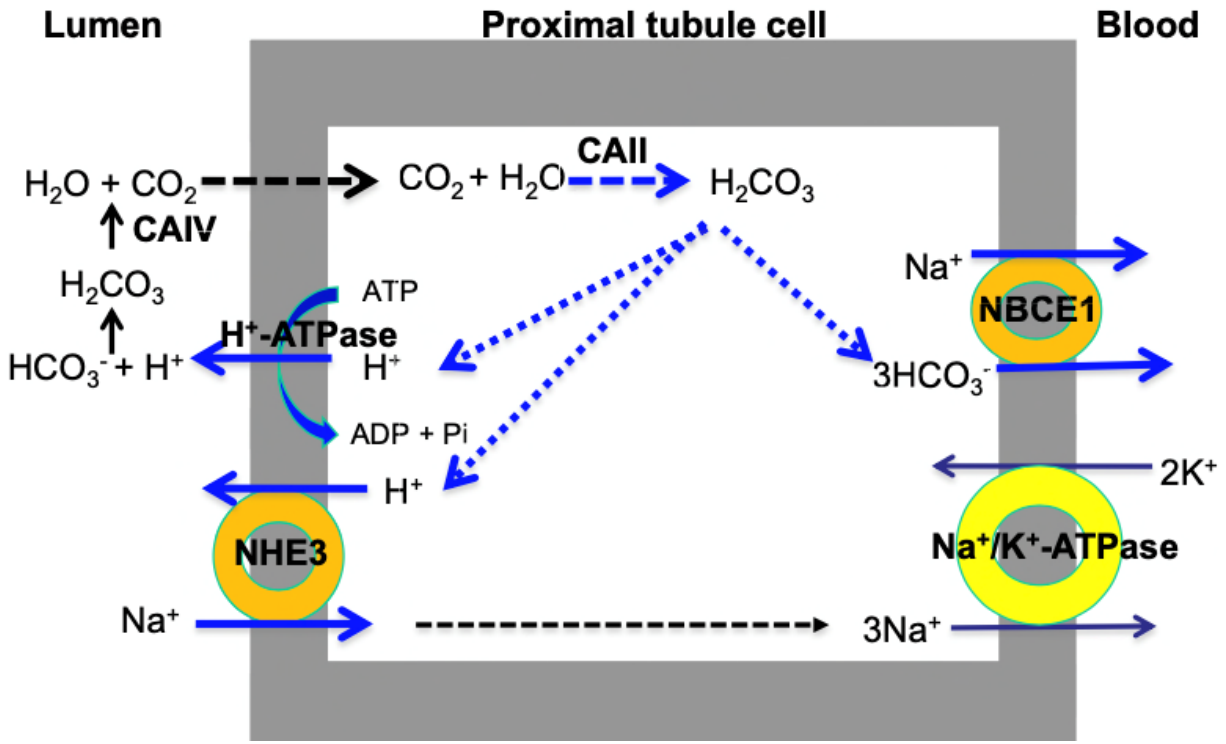
Voltage Dependent distal RTA

- ⬇principal cell Na reabsorption through ENaC→⬇lumen electonegativity→⬇drive for H+ secretion
- Seen in obstruction and HbSS disease
- Volume depletion leads to a reversible similar phenomenon
- In all cases of voltage dependent distal RTA see hyperkalemia (as opposed to usual hypokalemia)

Common Causes RTA1

- Sjogrens
- Myeloma
- amphoB, ifosfamide
- Lithium
- Renal transplant rejection
- Voltage gated
  - Associated w hyperkalemia-sickle cell, urinary obstruction
  - Marked volume depletion of any cause

Proximal RTA-inability to completely reabsorb HCO3



Since NH4 production in prox tubule is intact
And since distal acidification is normal, will have
A normal urine AG

Inability to completely reabsorb HCO_3^- → bicarbonaturia→ causing alkaline urine pH during early phase.
Bicarbonaturia→increased lumen electronegativity→ ↑K secreation→ hypokalemia

Fanconi syndrome-pan proximal tubulopathy-phosphaturia, hypouricemia, glucosuria, 1αhydroxylase deficiency leading to bone disease

Need >3meq/kg (often 10-15) bicarb to correct acidosis

Soleimani M AJKD 2016; 68(3):488

RTA2

- HCO3 reabsorptive capacity is ↓, but not completely lost in RTA2 because proximal absorption is not completely lost and TALH, DCT, CD can increase HCO3 absorption.
- Thus serum HCO3 will decline until the filtered load of HCO3 is low enough to be completely reabsorbed (often 17 range).
- Thus have 2 phases of RTA2-
  - Active bicarbonaturia w obligate K losses, elevated urine pH (>5.5)
  - New steady state at ↓serum HCO3 w no bicarbonaturia, no K losses, acidic urine pH
  - Since CD H+ ATPase is functional, once there is no HCO3 in the urine, urine pH is appropriately <5.5
- Repletion of HCO3 again results in bicarobonaturia and large urinary K losses

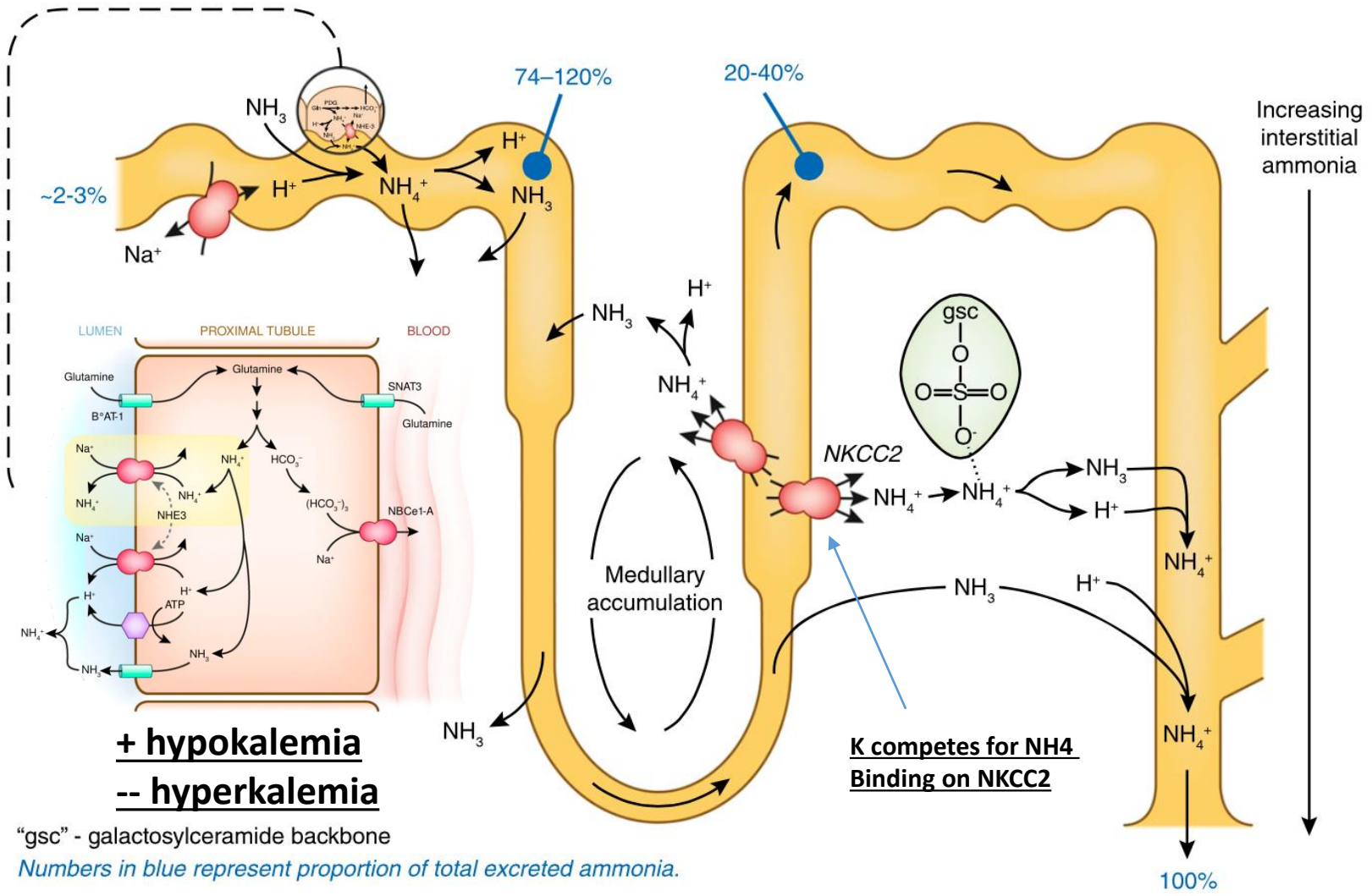
Causes of RTA2

- Myeloma (most common)
- Tenofovir
- Ifosfamide
- Acetazolamide
- Topiramate (carbonic anhydrase inhibition-also can impair distal H+ excretion)
- Lead
- Amyloid
- Renal transplant rejection
- Sjogren’s

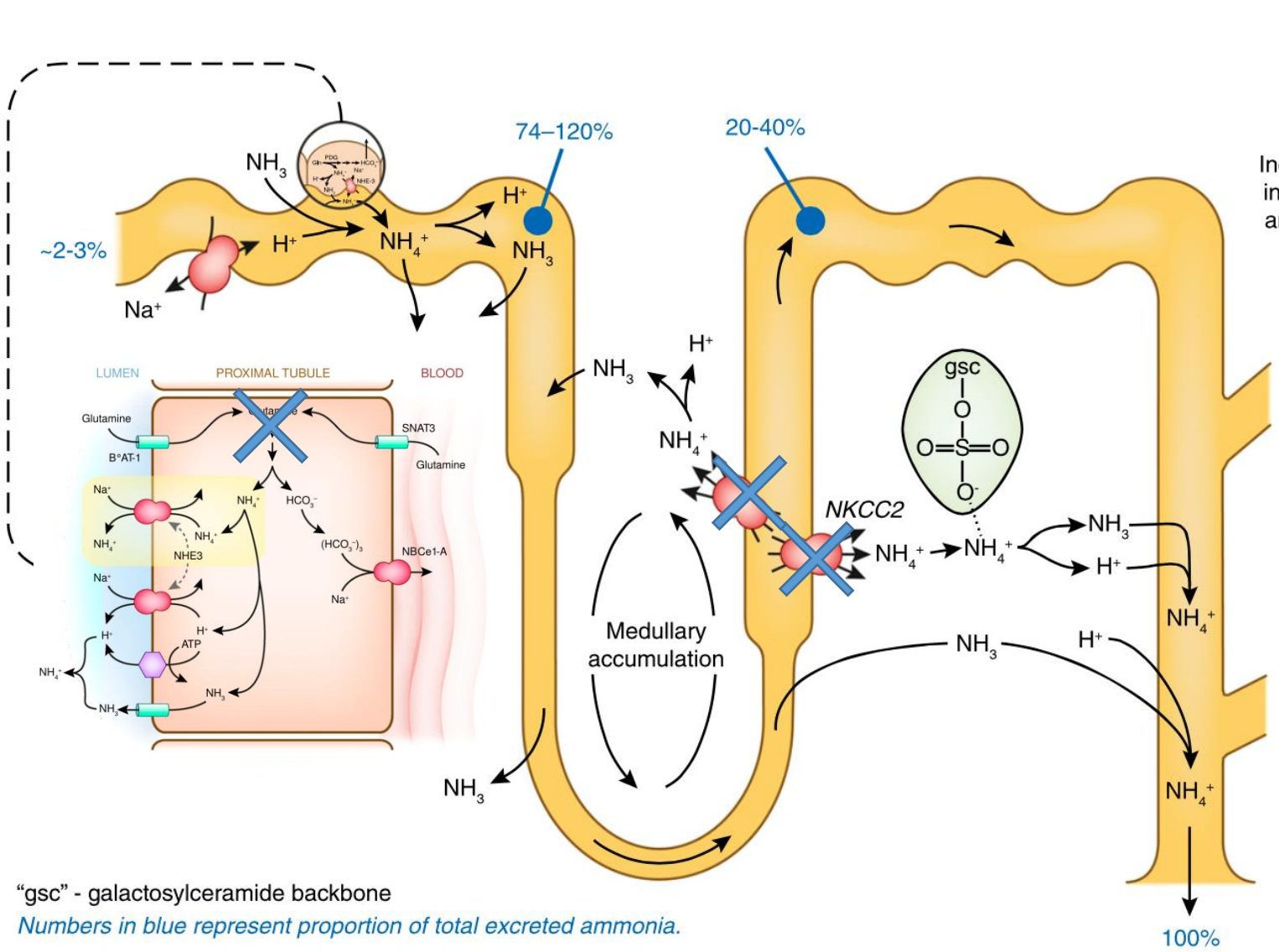
RTA 4 (hypoaldosteronism)

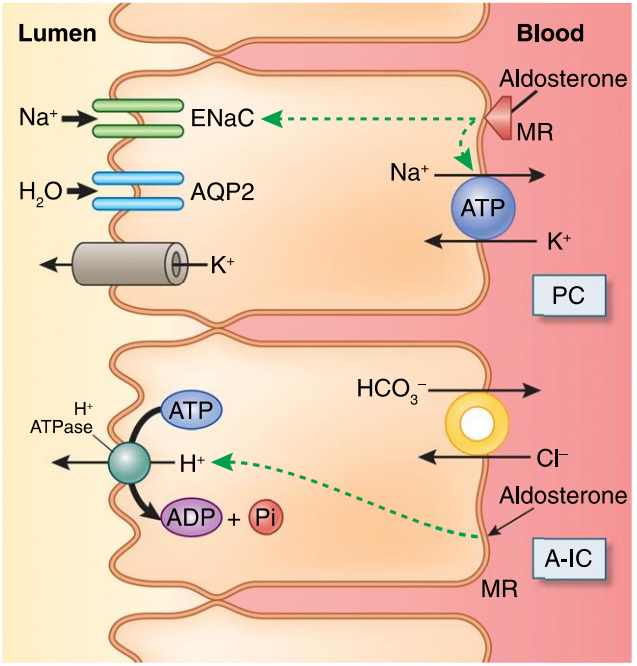
- Patients have hyporeninemic hypoaldosteronism
- Inability to increase H+ excretion in response to aldosterone
- Reduced ability to excrete K+
- Correcting K can normalize serum HCO3
- Rx w thiazide or loop diuretics

Ammonia production in the proximal tubule yields 2 HCO3-. In order to realize this yield, NH_3 must be excreted As NH_4^+ (if NH_3 is retained it is metabolized in the liver which consumes 2 HCO_3^-)



Hyperkalemia decreases proximal HCO3 generation and reduces NH4 TALH reabsorption





NEPHSAP Fluid, Electrolytes, Acid Base 2015

Since the H+ pump functions, the urine pH Will be <5.5. Since NH4 excretion is low (the major mechanism of acid secretion), There will be a systemic acidosis.

Hypoaldosteronism or lack of tubular response to aldosterone causes hyperkalemia and also contributes to the metabolic acidosis

Weiner CJASN 2014

	RTA 1	Hyperkalemic RTA 1	RTA2	RTA 4
Urine pH	>5.5	urine pH >5.5	generating phase >5.5 Maintenance phase <5.5	<5.5
K	low	high	generating phase low Maintenance phase normal/low	high
HCO3 required	1-2meq/kg/day	1-2meq/kg/day	10-15meq/kg/day	1-2meq/kg/day
Effect of HCO3 Infusion on urine pH	none	none	becomes alkaline	none
Urinary AG	0/+	0/+	neg	0/+
	Nephrocalcinosis, stones		osteomalacia, rickets	

Urinary anion gap

- Urine Na +K -Cl
- In a metabolic acidosis, the major mechanism of increased H^+ excretion is NH_4^+
- Since Cl is the major anion in the urine, an increase in unmeasured NH_4^+ should cause a negative urinary AG as the measured chloride increases relative to Na and K
- Thus, with some caveats, the urinary AG is a marker of NH_4^+ excretion

Urinary AG in non-gap metabolic acidosis

Negative (normal NH4 excretion)

- Diarrhea
- Proximal RTA

Positive (impaired NH4 excretion)

- Renal failure
- Type 1 (distal) RTA
- Type 4 RTA (hypoaldosteronism)

Berend NEJM 2014; 371:1434

Situations in which urinary AG is unreliable

- Polyuria
- Urine pH >6.5
- Urinary ammonium is excreted with an anion other than Cl-
  - Ketoacidosis
  - Acetylsalicylic acid
  - D lactic acid
  - High dose penicillin
- Urine Na <20 (need CD Na reabsorption to excrete acid)

Berend NEJM 2014; 371:1434

Urinary osmolal gap in non-gap metabolic acidosis

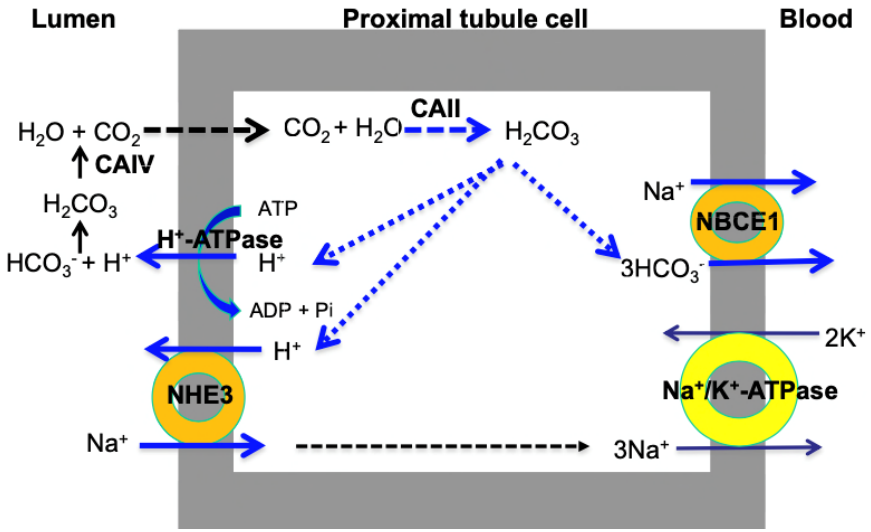
- 2(Na) + 2(K) + urinary BUN(2.8) + urinary glucose/18
- A urinary osmolal gap <40 indicates impaired urinary ammonium excretion
- A urinary osmolal gap reflects urinary ammonium excretion except in the presence of large quantities of non-dissociated acid as with beta hydroxybutyric acid in ketoacidosis
- The urinary osmolal gap has a better correlation with ammonia excretion than urinary anion gap

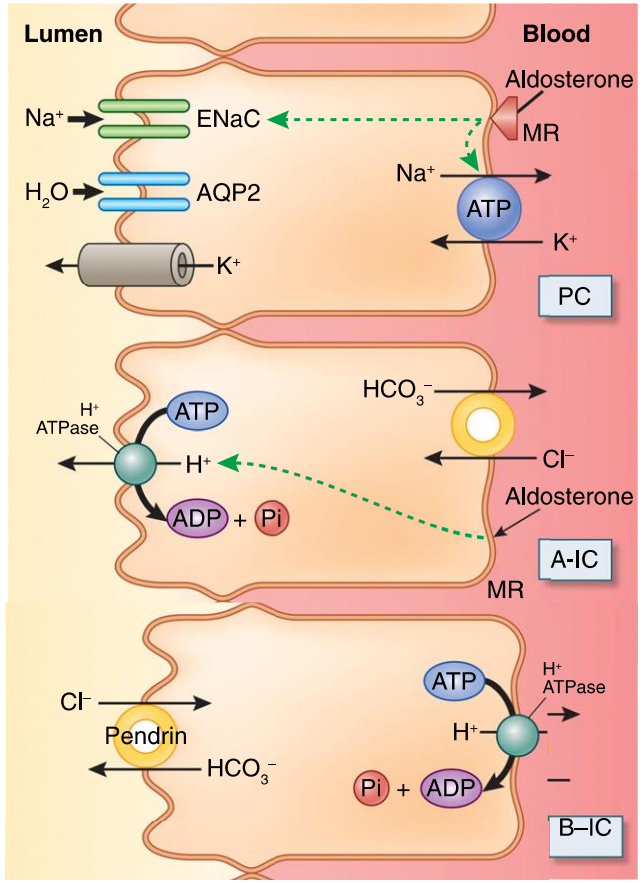
Berend NEJM 2014; 371:1434

Metabolic Alkalosis

- To develop a metabolic alkalosis-
  - Loss of acid by kidney or gi tract or Gain of bicarbonate (via oral therapy)
  - Decrease in hco3- excretion
- Causes of decreased HCO3- excretion
  - Chloride depletion
  - Hypokalemia
  - ECFV depletion

Urine Na and Cl in Metabolic Alkalosis





When there is a significant ↑in the HCO3 Filtered load, some HCO3 is not reabsorbed And appears in the urine. As a result, some Na will appear in the urine, even if there Is mild volume depletion. As a result, you Can see a high urine Na in early metabolic Alkalosis associated w volume depletion.

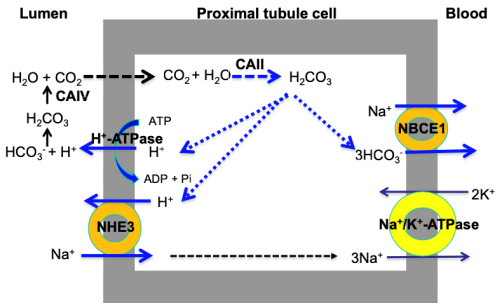
In this case the Urine Cl is <20 and is a better Marker of volume status.

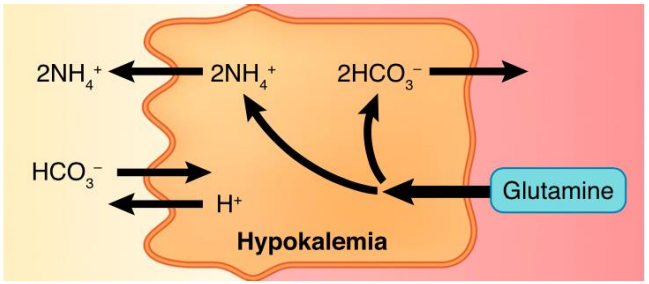
HCO3 is excreted in exchange for Cl reabsorption

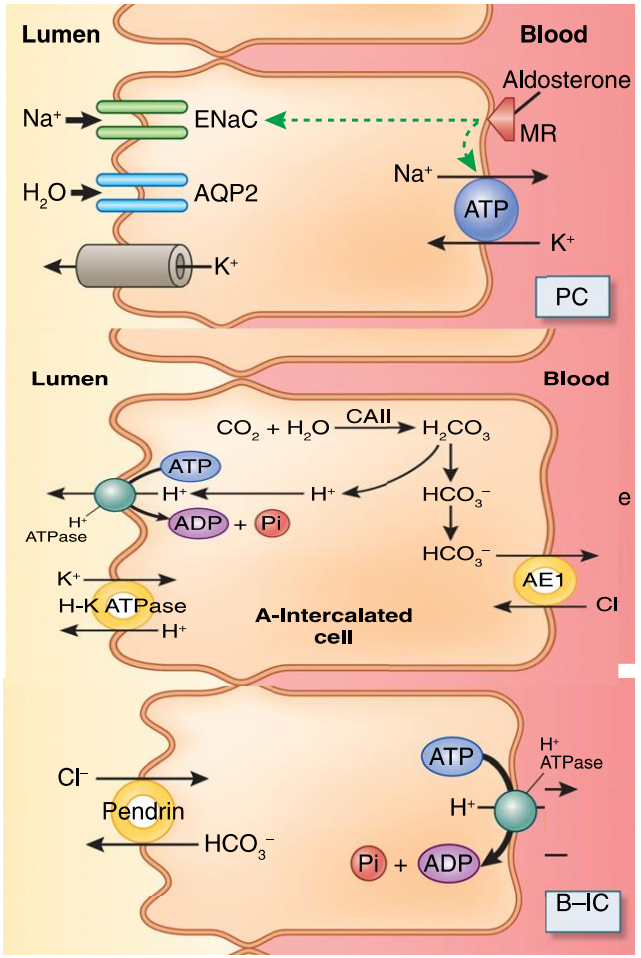
NEPHSAP Fluid, Electrolytes, Acid Base 2015
Soleimani M AJKD 2016; 68(3):488

Renal Response to Metabolic Alkalosis

Significance of Volume Depletion and hypokalemia







Hypovolemia→↑AT2→↑Na reabsorption via Na/H pump; this also ↑HCO3 reasorption

Hypokalemia stimulates ammoniagenesis→ ↑HCO3

In this setting both urine Na and urine Cl Will be low

2ndary hyperaldo causes H+ secretion, Which ↑HCO3

Hyperaldo causes K secretion→hypokalemia

Hypokalemia causes H+ secretion→which ↑HCO3

Cl depletion from hypovolemia leaves less Cl to Exchange for HCO3→ ↓HCO3 excretion

NEPHSAP Fluid, Electrolytes, Acid Base 2015
Soleimani M AJKD 2016; 68(3):488

Metabolic Alkalosis

- U_{Cl} <20
  - Vomiting/NG suction
  - Diuretics****
  - Significant sweating
  - Post hypercapnea
  - Calcium alkali

The U_{Cl} concentration depends on when the urine is taken in relation to the diuretics (must also take into account that old urine in the bladder may contain a high Cl content if the patient has not voided for many hours after the diuretic)

- U_{Cl} >20
  - Mineralocorticoid excess-HTN, high aldo
  - Diuretics****
  - Liddle Syndrome-HTN, low renin/aldo
  - Licorice ingestion-HTN, low renin/aldo
  - Bicarbonate administration
  - Bartter, Gitelman-hypotension, high renin, aldo
    - Gitelman-low serum Mag, low urine Ca/Cr
    - Bartter-normal serum mag, high urine Ca/Cr

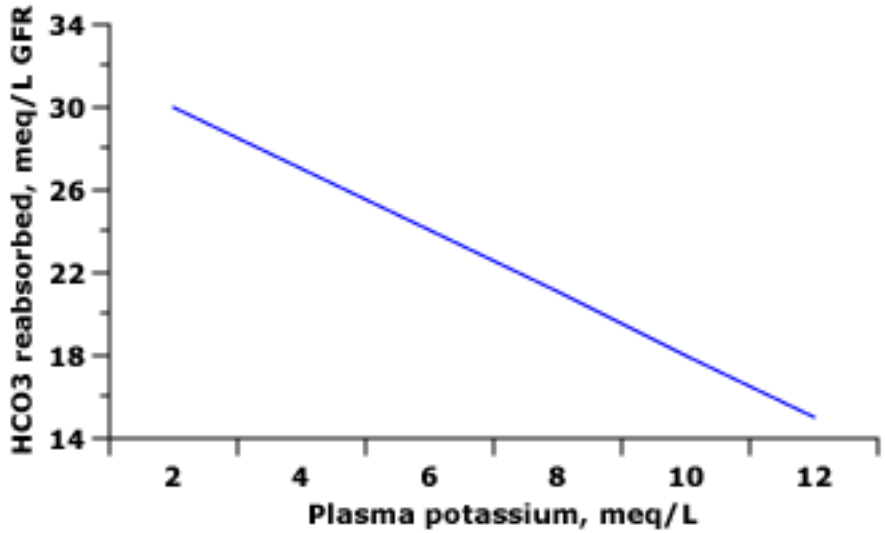
Gastric Alkalosis

- Secretion of acid from parietal cells will lead to the addition of hco3 to the blood
- This effect is only transient since entry of acidic gastric contents to the duodenum leads to hco3 secretion, which will reduce the blood hco3
- When there is vomiting or NG suction, there is loss of H+, but no secretion of hco3 in the duodenum (bc there is no acid load to stimulate this)
- In a patient with intractable vomiting or continuous ng suction, gastric acid blockade will be additive in treating the metabolic alkalosis
- Volume depletion leads to hyperaldo which causes H+ secretion
- Cl depletion limits HCO3 excretion
- Decreased GFR limits HCO3 excretion
- Hypokalemia furthers the metabolic alkalosis

Effect of hypokalemia

- In response to hypokalemia the α intercalated cell H+/K+ATPase activity increases causing H+ secretion for K+ reabsorption. This furthers alkalosis
- Hypokalemia tends to occur w hypovolemia and alkalosis because of
  - ↑H+/K+ ATPase activity
  - Hyperaldosteronism ↑ H+ ATPase activity and causes K+ excretion
  - Alkalemia causes transcellular exchange of H+ for K+
  - Hypokalemia stimulates proximal tubule ammoniagenesis

Relation between plasma potassium and bicarbonate reabsorption



Renal tubular reabsorption of HCO3 as a function of the plasma K concentration. There is an inverse relationship with HCO3 reabsorption rising with hypokalemia an falling with hyperkalemia.

Data from Fuller, GR, MacLeod, MB, Pitts, RF, Am J Physiol,182:111, 1956.

Calcium-Alkali Syndrome

Usually occurs with intake of ≥4g $CaCO_3$ for osteoporosis prevention or antacid
Or calcium based phos binders (w vitamin D) in CKD

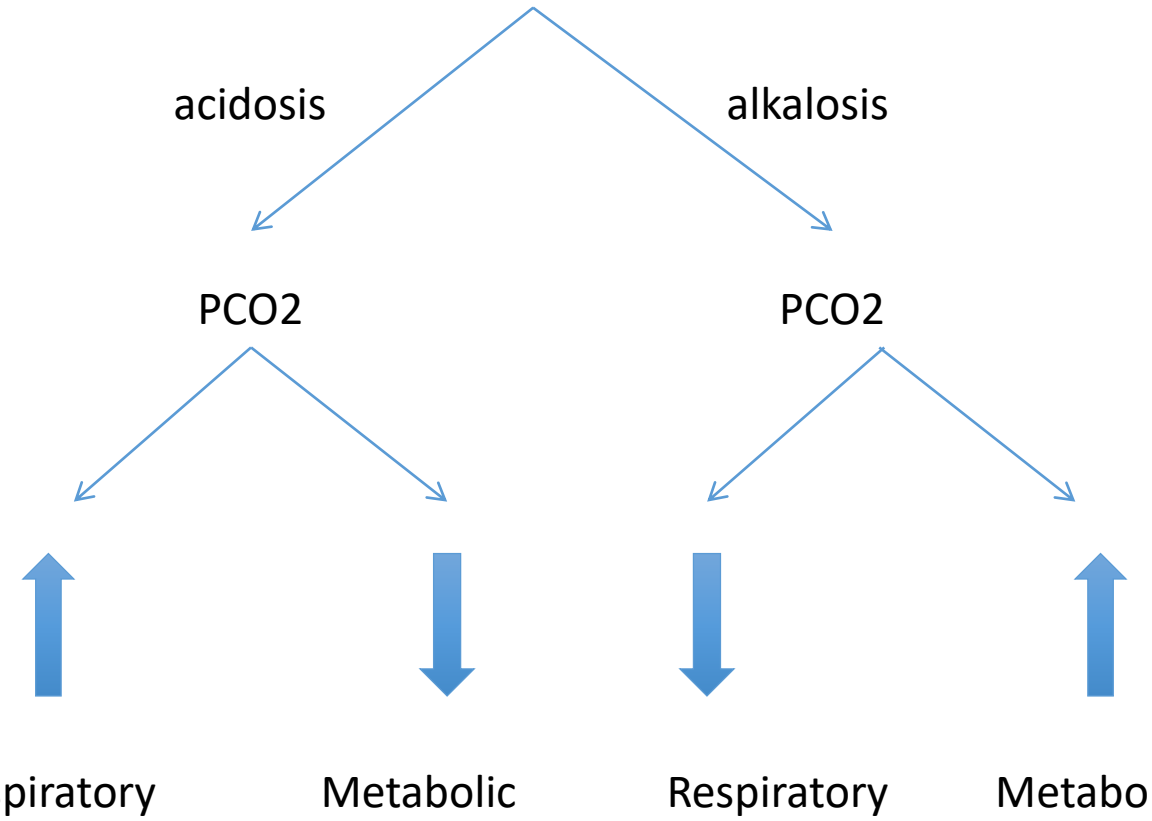
Pathophysiology
-initiating event is hypercalcemia (due to high Ca intake) and alkalemia (carbonate intake)
-hypercalcemia causes
    -renal arteriolar vasoconstriction→⬇GFR→⬇filtration of Ca→⬇Ca excretion
    -activates TALH CaSR→knocks out lasix sensitive transporter→volume depletion
    -inhibits collecting duct vasopressin receptors→DI→volume depletion
-Alkalemia-stimulates TRPV5 which causes calcium reabsorption despite hypercalcemia
-volume depletion causes ⬆prox tubule Na, Ca reabsorption. ↑proximal Na reabsorption
Increases proximal HCO3 reabsorption
-chloride depletion supports the alkalemia

Management of diuretic induced alkalemia

- If ‘over-diuresed’-hold diuretics vs give NaCl
- Correct hypokalemia w KCl
- K is low-Add spironolactone or amiloride
- K is high or unresponsive to ENaC blockade, can give acetazolamide

Approach to Acid Base

pH



If metabolic acidosis
-check AG
if AG elevated
-check lactate, ketones, salicylate
osmolal gap
if osmolal gap elevated and no other cause of acidosis obvious and clinical history compatible
-fomepizole
-hemodialysis
-non-gap acidosis
-if cause not obvious can check Urinary AG or osmolal gap

If metabolic alkalosis
-check urine Cl
-check BP

If pH is normal, but there is an anion gap, or abnormal PCO2, there must be an additional disorder

ABG vs VBG

- Venous pH normally ~0.5 less than arterial pH
- Venous pCO_2 is normally ~5-6 > arterial
- When assessing pH (or PCO_2) the a VBG is sufficient assuming the patient is not in shock

Case

- 66F w ESRD, recent enterocutaneous fistula surgery with ileus and high NG tube output
- AF, 146/72, 92, 18
- **7.66**-48-129
- BMP 156 2.8 84 >50 50 6.2 gluc 153
- Management?

Case

- HD with low HCO3 bath
- Replete K
- Gastric acid suppression

Case 1

- 67M w dm2, HTN, CKD Cr 1.3 presents w fatigue and emesis.
- Meds-hctz, lisinopril, metformin
- ED 35.9 141/67 113 24 98% room air.
- Exam-tachypneic, no distress, clear lungs, no edema, abd soft, nontender
- Na 131 K 6.6 Cl 97 HCO3 13 BUN 61 Cr 8.7 gluc 25
- AG 21

- ABG 7.35-24-117
- Urine ketones negative
- Salicylate, acetaminophen negative
- Lactate 7.7
- Dialysis→resolves

Case 3

- 81F w dm2, HTN presented 2 weeks ago with fatigue, dizziness, NS
- Hb 9.1, plt 81, Cr 1.4 (baseline 1.2), HCO3 20
- 2 weeks later-
  - BP 106/66-136/76, HR 80
  - BMP 129 5.7 102 12 30 1.5 gluc 41; AG 15
  - Hb 8.2, plts 60
  - Ast 942 alt 360 tbili 3.0
  - 7.12-30-134 NC O2
  - u/a neg ketones
  - Lactate 9.9
  - Ldh 4318
  - Uric acid 14.3
  - Imaging hepatosplenomegaly

Case 3

- Type B lactic acidosis due to lymphoma/lymphomatous liver infiltration with HLH

Case 4

- 39F w bipolar and schizoaffective disorder presented after being found down. She ran and walked 4 miles the day prior to presentation. She ran about 1mile on day 2 and syncopized. NO prodrome, chest pain, dyspnea.
- Meds-lithium, metformin, olanzapine
- Exam-temp 37.6, 132/69, 135, 22, 100% room air.
- Lethargic, supple neck, clear lungs, rrr, no edema, rigid muscles
- Na 133, K 4.8, Cl 100, HCO3 11, BUN 27, Cr 2.5, gluc 127, AG 22
- Ca 7.7, phos 6.6, alb 5.0

- ABG 7.36-22-154
- Lactate 1.6
- Lithium 0.6, salicylate <1, tylenol <1
- u/a trace ketones, 1+ prot, 3+ hb
- Umicro 2 wbc
- CK >400,000

Case 5

- A 69F w Sjogren's presents for the evaluation of electrolyte abnormalities. She has chronic dry eyes and dry mouth as well as a 3 year history of progressive body pain leading to a wheelchair bound state.
- Her meds-advil 400mg daily, hydroxychloroquine 200mg daily, alendronate 70mg weekly, cyclobenzaprine 10mg daily, baclofen 10mg tid
- Labs Na 136, K 2.9, Cl 110, HCO3 19, BUN 23, Cr 1.5, gluc 81, phos 1.7, uric acid 1.6. pH 7.34
- Urinalysis-pH 6.0, 2+ glucose, 2+ protein, 11 wbc, 0 rbc
- Which of the following diagnoses explains her acid-base and electrolyte abnormalities?
    A. Type 1 RTA
    B. Type 2 RTA
    C. Type 4 RTA
    D. Chronic renal failure
    E. Diarrhea

Case

- 34F w cocaine and alcohol abuse who presented with weakness.
- ED 161/113, 104
- BMP 143 1.7 109 13 12 0.8 132
- Phos 1.1
- AG 21
- 24hr urine K 133mmol
- Urine pH 7.0
- CT urogram-bilateral renal stones + medullary nephrocalcinosis

Case

- Rx k citrate
- Hypokalemia + elevated urine pH +nephrocalcinosis = distal RTA (1)

Case

- 40F 16 weeks pregnant presents w vomiting
- AF BP 90/50, HR 120s
- BMP 125 3.3 <60 34 38 2.6 141
- iCa 0.74
- 7.93-24-38(VBG)
- Lactate >16

Case

- Alkalemic
- AG acidosis due to lactate
- Expect pco2 is low despite a clear history of vomiting which should cause a metabolic alkalosis, thus there must be a superimposed primary resp alkalosis
- Triple acid base disorder
  - Metabolic alkalosis
  - Resp alkalosis
  - Lactic acidosis

Management

- NS with KCl
- Antiemetics
- More KCl
- Gastric acid suppression

END

Metabolic Acidosis Misc

- Metabolic acidosis leads to Na excretion and volume depletion (perhaps because less HCO3 to be reabsorbed via Na/H antiporter)
- Metabolic acidosis leads to hypercalciuria/hyperphosphaturia via bone dissolution
- Metabolic acidosis leads to hypercalciuria via inhibition of distal tubular TRPV5 channel

Diuretics and their sites of action in the nephron

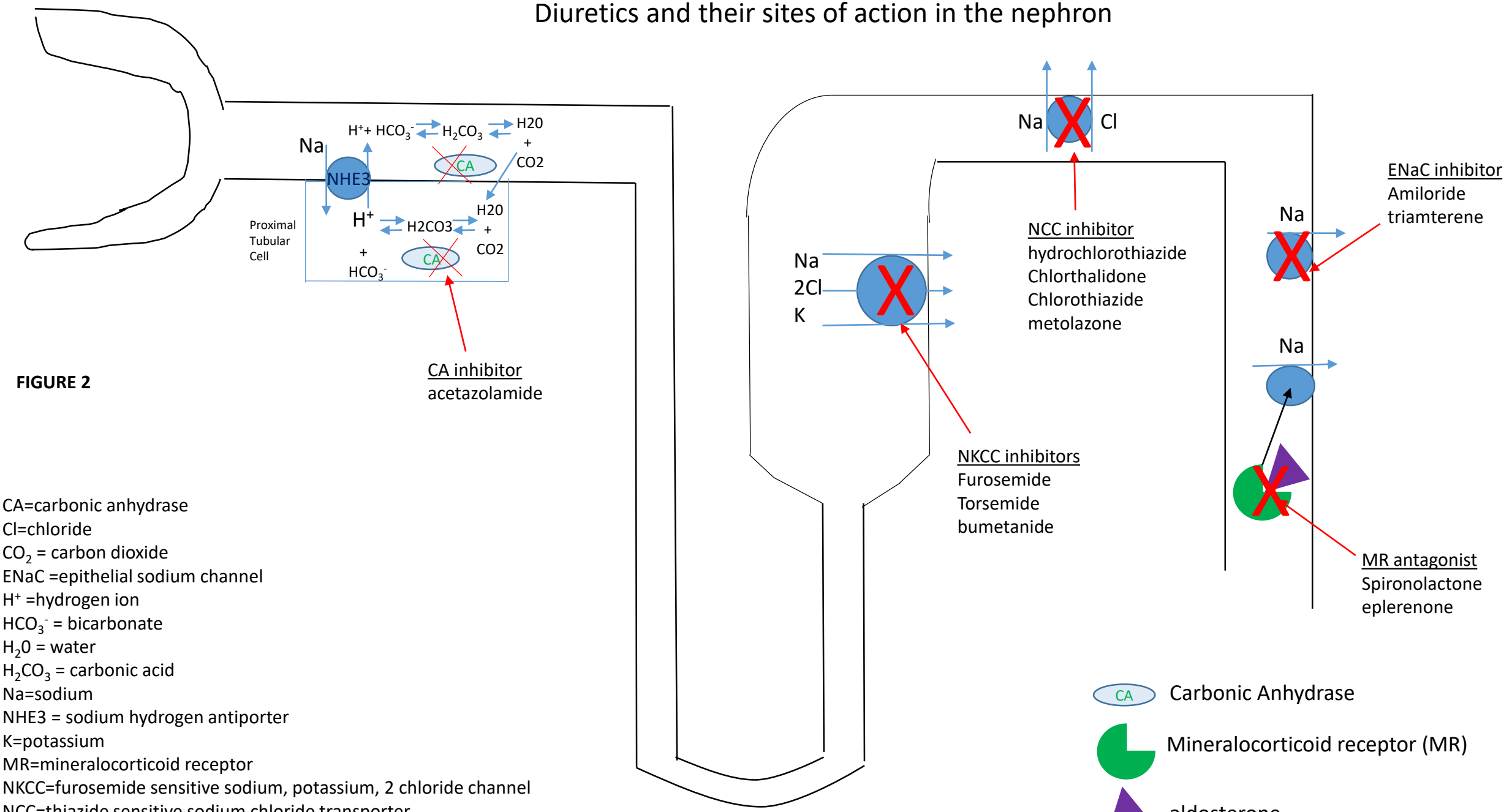
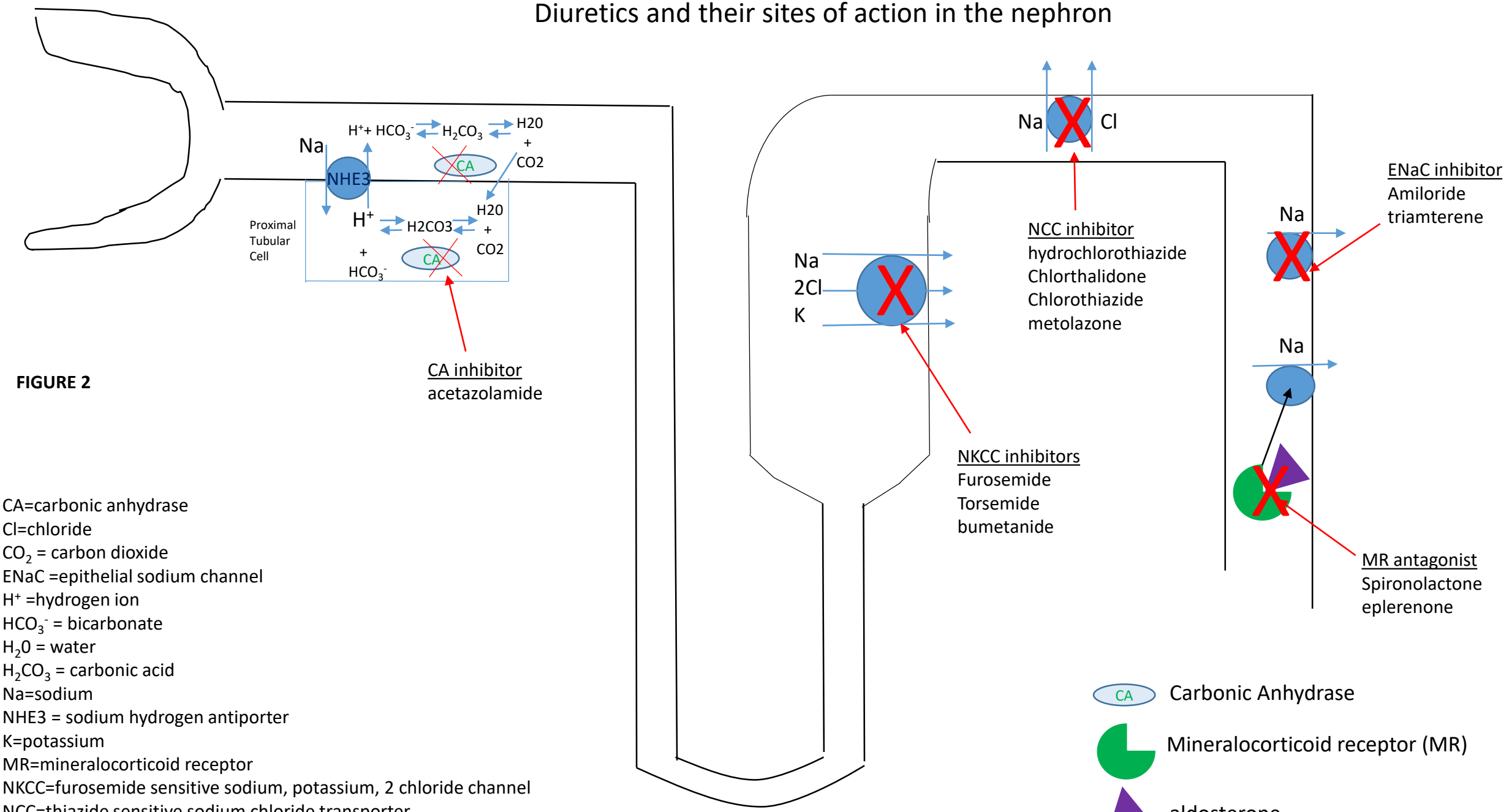


FIGURE 2

CA=carbonic anhydrase
Cl=chloride
CO_2 = carbon dioxide
ENaC =epithelial sodium channel
H^+ =hydrogen ion
HCO_3^- = bicarbonate
H_20 = water
H_2CO_3 = carbonic acid
Na=sodium
NHE3 = sodium hydrogen antiporter
K=potassium
MR=mineralocorticoid receptor
NKCC=furosemide sensitive sodium, potassium, 2 chloride channel
NCC=thiazide sensitive sodium chloride transporter

Diuretics and their sites of action in the nephron



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Metabolic Alkalosis-importance of Cl- depletion

- Metabolic alkalosis can be corrected by Cl- repletion despite
  - Even or negative Na/K balance
  - Ongoing hco3 administration
  - Ongoing elevation in AT2/aldosterone
- Metabolic alkalosis is not corrected by
  - Na/K repletion without Cl- repletion
  - Cl repletion w GFR of 0
  - ECFV expansion by up to 25% or by restoring baseline GFR w/o Cl- repletion

Diuretic Induced Metabolic Alkalosis in Man

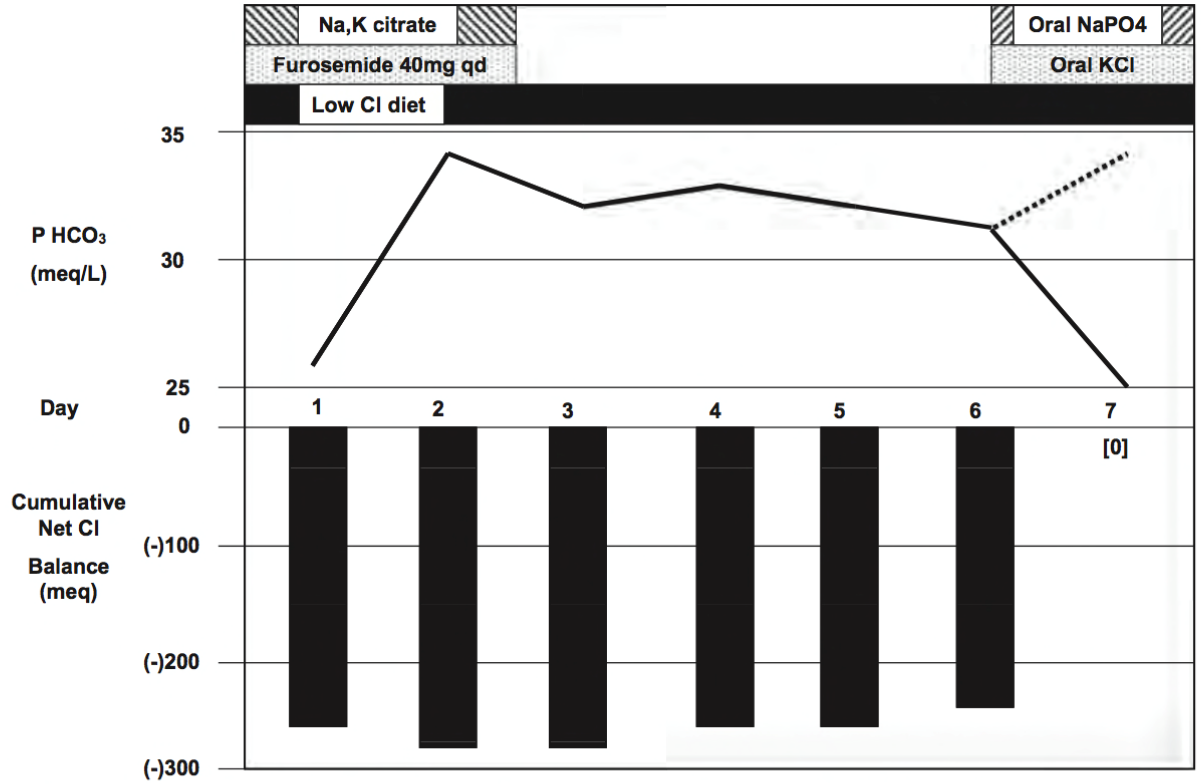


Figure 1. Diuretic-induced MA in men. Plasma HCO_3 and cumulative Cl balance are shown for each day of the study; K^+ balance was neutral (data not shown). Oral KCl started in the middle of day 6 for six men corrected alkalosis at the end of day 7 with quantitative Cl repletion, whereas oral $NaPO_4$ in two men worsened alkalosis. Reprinted from Galla JH: Chloride-depletion alkalosis. In: *Acid-Base Disorders and Their Treatment*, edited by Gennari FJ, Adrogue HJ, Galla JH, Madias NE, Boca Raton, Taylor & Francis, 2005, p 523, with permission.

Diuretics, Na, K, and low Cl given to cause metabolic alkalosis

KCl therapy resolved alkalosis whereas NaPO4 therapy resulted in persistent alkalosis

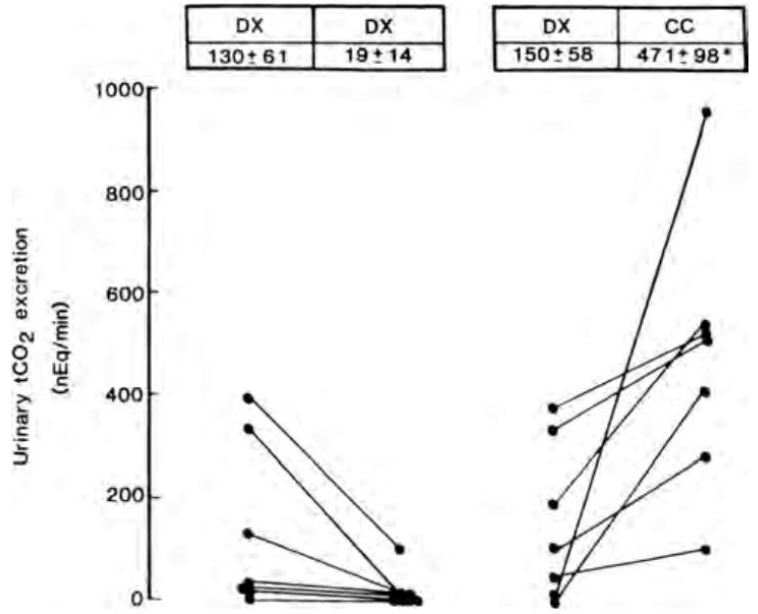


Figure 2. Urinary HCO_3 excretion in rats with persistent volume depletion, Na^+ depletion, and decreased GFR. Rats receiving Cl (CC) increased urinary HCO_3 excretion as alkalosis was corrected (data not shown), whereas those receiving only glucose (DX) had a further decrease while alkalosis was maintained (data not shown). Reprinted from Galla JH: Chloride-depletion alkalosis. In: *Acid-Base Disorders and Their Treatment*, edited by Gennari FJ, Adrogue, Galla JH, Madias NE, Boca Raton, Taylor & Francis, 2005, p 530, with permission.

Model-Cl- depletion and metabolic alkalosis induced in rats by performing PD w dialysate containing isotonic NaHCO3 and K w no Cl-

Therapy-in the intervention group an 80mM Cl- solution containing various cations But no Na caused ↑HCO3- excretion and correction of alkalosis whereas those Receiving only D5 infusion did not increase HCO3 excretion and alkalosis persisted

Loop diuretics inhibit NKCC in the thick ascending loop of henle, responsible for 25% of sodium reabsorption. Thiazide diuretics block NCC in the distal convoluted tubule, responsible for 5-10% of sodium reabsorption. The epithelial sodium channel (ENaC) in the collecting duct reabsorbs up to 5% of filtered sodium. Binding of aldosterone to the mineralocorticoid Receptor increases the number and open channel probability of ENaC, thus increasing sodium reabsorption. Direct ENaC antagonists include amiloride and triamterene, while mineralocorticoid receptor antagonists include spironolactone and eplerenone. Carbonic anhydrases present in the proximal tubule and collecting duct facilitate the conversion Of hyodrogen ions and bicarbonate to carbon dioxide and water. In this way carbonic anhydrase facilitate sodium and bicarbonate reabsorption, particularly in the proximal tubule. The carbonic anhydrase inhibitor acetazolamide, thus leads to sodium and bicarbonate excretion in the urine. Diuretic resistance is common in heart failure owing to neurohormonal changes And chronic diuretic use. Sequential blockade of sodium reabsorption with diuretics that act in different segments of the nephron produces greater sodium excretion and can overcome diuretic resistance in many patients. Hypokalemia is a common problem with combination loop and thiazide diuretic use. In addition to increasing sodium excretion, ENaC antagonists and mineralocorticoid receptor antagonists reduce potassium excretion. Mineralocorticoid receptor antagonists are favored over ENaC antagonists in Heart failure because they reduce mortality in heart failure with reduced ejection fraction. Sodium reabsorption that is blocked in the proximal tubule by acetazolamide is subsequently reabsorbed by more distal nephron segments which Limits the efficacy of acetazolamide as a diuretic. However, the ability of acetazolamide to inhibit bicarbonate reabsorption makes it effective for the management of metabolic alkalosis due to loop and thiazide diuretics.

Stewart Method

Principal-all anion and cation concentrations must balance to maintain electroneutrality
H+ and HCO3- concentrations are not independently determined, rather they are dependent variables
The gain or loss of cations or anions causes a necessary change in the serum HCO3 (via CO2 and H20)

SID = Na +K +Ca +Mg -Cl

A- = anionic forms of albumin, phosphate, other weak non-volatile acids

$SID - A^- = HCO_3^- + CO_3^{2-} + OH^- - H^+$

$SID - A^- \cong HCO_3^-$

$Na\text{-}Cl\text{-} A^- \cong HCO_3^-$

Na - Cl – HCO3 = AG

Na -Cl -AG =HCO3

Normal Na 140, normal Cl 100

SID - $A^- \cong HCO_3^-$

Na -Cl -AG =HCO3

50F w septic shock received 10L NS, has AKI, lactate 1

Na 142, Cl 115, AG 16, HCO3 11

Acidosis due to hyperchloremia

60M w HF EF 10% presents w pulmonary edema, systemic edema
Receives lasix 80mg IV bid and metolazone 5mg daily

Na 135, Cl 89, AG 12, HCO3 34

Alkalemia due to loss of Cl (loss of Na and Cl equal in urine (1:1)
Where as Na:Cl in serum is 1.4:1

Table 2. Acid–Base Disorders and Their Causes According to the Relationship between Gains and Losses of Circulating Cations or Anions.*

Metabolic alkalosis
- Decrease (loss) of anion
  - Hypochloremic
    - Gastrointestinal
      - Vomiting
      - Chloridorrhea (villous adenoma, some chloride secretory diarrheas)
    - Renal
      - Chloruretic agents (loop diuretics, thiazides)
      - Chloride channelopathies (e.g., the Bartter syndrome, the Gitelman syndrome)
      - Hypokalemia leading to loss of chloride
    - Sweat
      - Cystic fibrosis
  - Hypoalbuminemic state[13]: malnutrition
- Increase (gain) of cation
  - Sodium citrate, sodium lactate, sodium bicarbonate, sodium acetate
  - Hypernatremic
    - Hyperaldosteronism
  - Hypercalcemic
    - Milk alkali syndrome, calcium carbonate

Metabolic acidosis
- Increase (gain) of anion
  - Hyperchloremic (potassium chloride, calcium chloride, hydrogen chloride, sodium chloride, arginine hydrochloride, lysine hydrochloride, ammonium chloride)
  - Anion-gap acidosis
    - Lactic acidosis
    - Diabetic ketoacidosis
    - Other unmeasured anions
    - Thiosulfate
  - Hyperphosphatemic
- Decrease (loss) of cation (sodium and potassium)
  - Renal
    - Renal tubular acidosis
    - Natriuretic agents (e.g., amiloride, triamterene)
    - Sodium with anions in urine: ketoacids, D-lactate, hippurate
    - Hypoaldosteronism
  - Gastrointestinal
    - Diarrhea with bicarbonate or bacterial organic anions in stool
    - Vomiting pancreatic secretions

Seifter NEJM 2014;371:1821

HCO3 therapy in lactic acidosis results in an increased serum lactate as compared to NaCl or no treatment

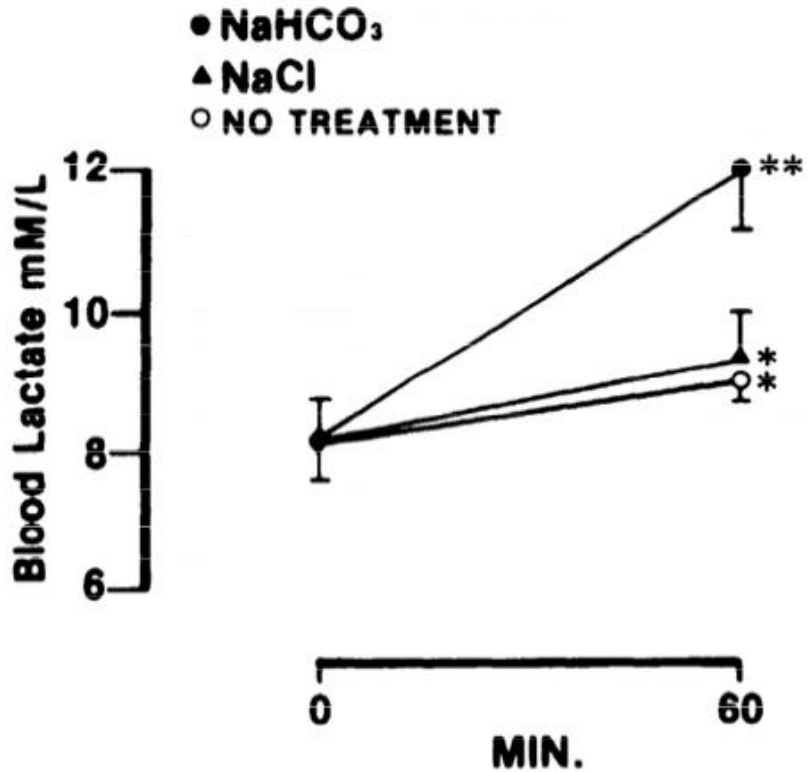
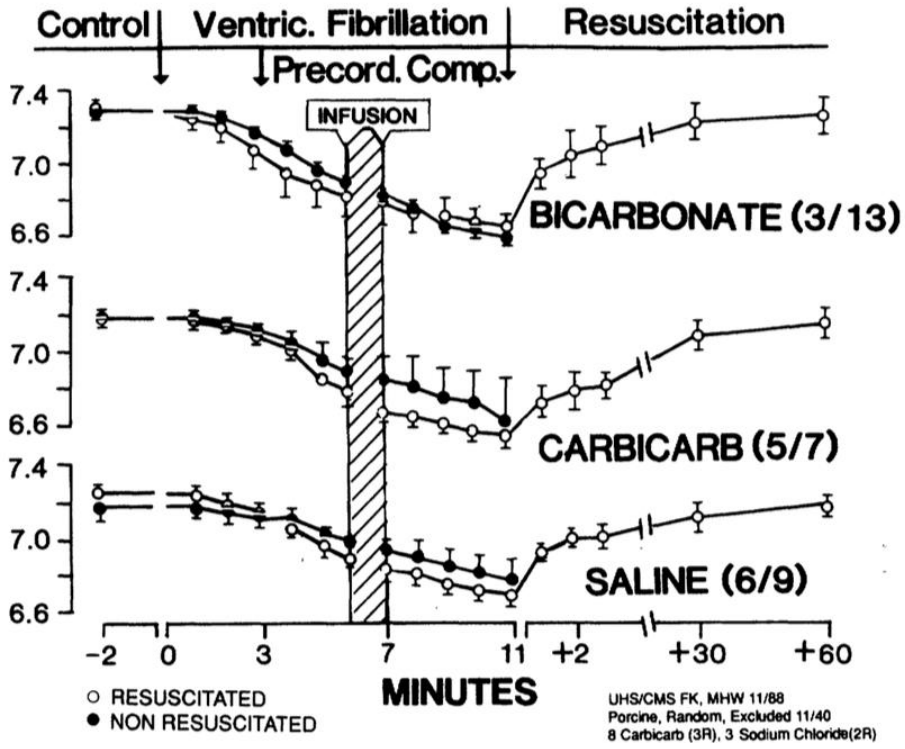


FIG. 1. Blood lactate values in dogs with hypoxic lactic acidosis treated for 60 min with $NaHCO_3$ or NaCl or had no treatment. Values are means ± SE; $n = 7$ in each group. *, $P < 0.05$ vs. paired control value at 0 min; **, $P < 0.01$ vs. NaCl and no treatment at 60 min.

Graf Am J Physiol 1985; 249:F630

Effect of Buffering Agents on Intramyocardial pH During Cardiac Resuscitation



Model-
VF was induced for 3 minutes in pigs via alternating current applied to epicardium
Minute 3-11 open cardiac massage was performed
During resuscitation 1 of 3 solutions infused
Pigs then cardioverted
Intramyocardial pH monitored

Kette Circulation 1990; 81:1660-1666

Coronary Perfusion Pressure, but not Myocardial pH Predicts Successful Resuscitation

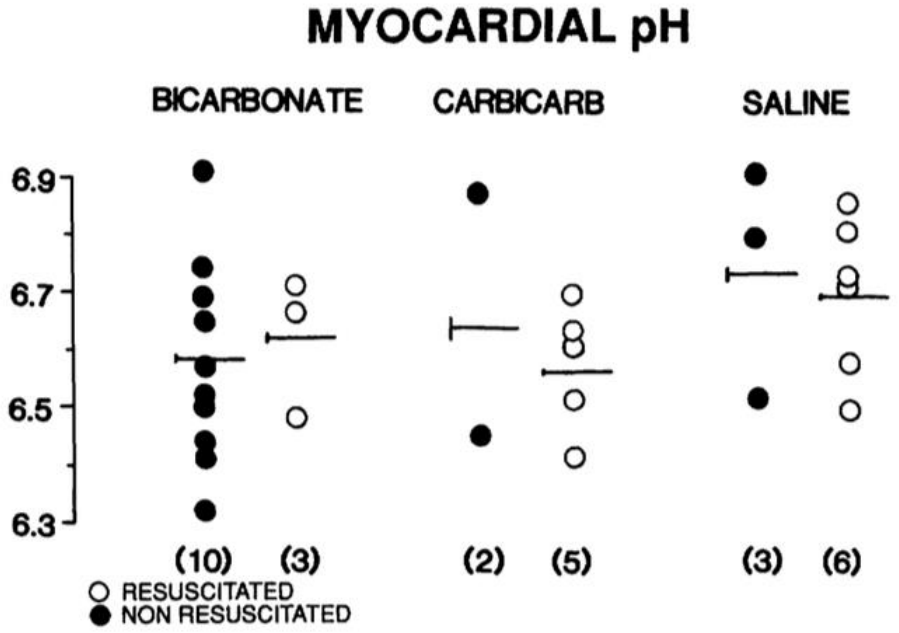


FIGURE 4. *Plot of myocardial pH before defibrillation. Myocardial pH predicted neither successful defibrillation nor resuscitability.*

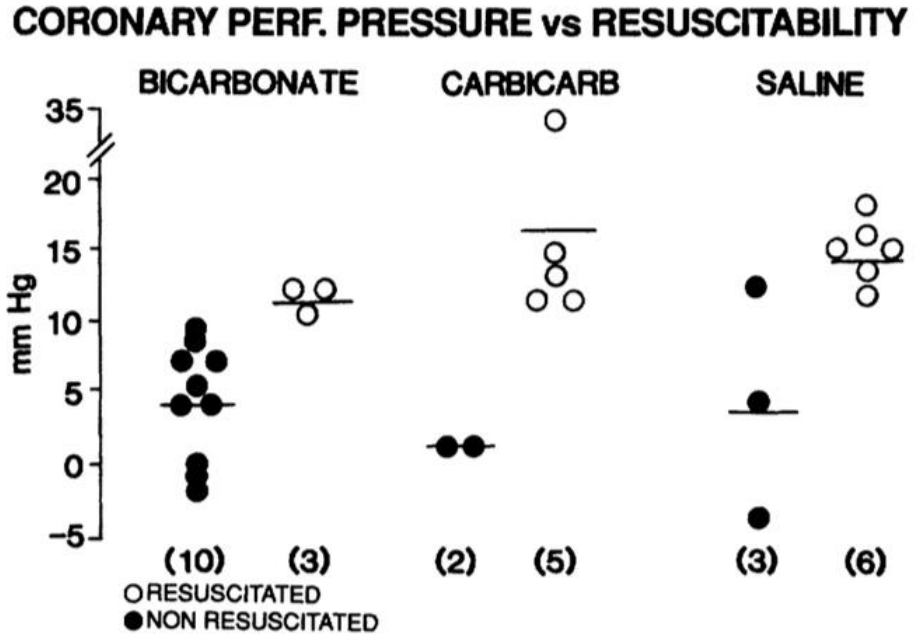
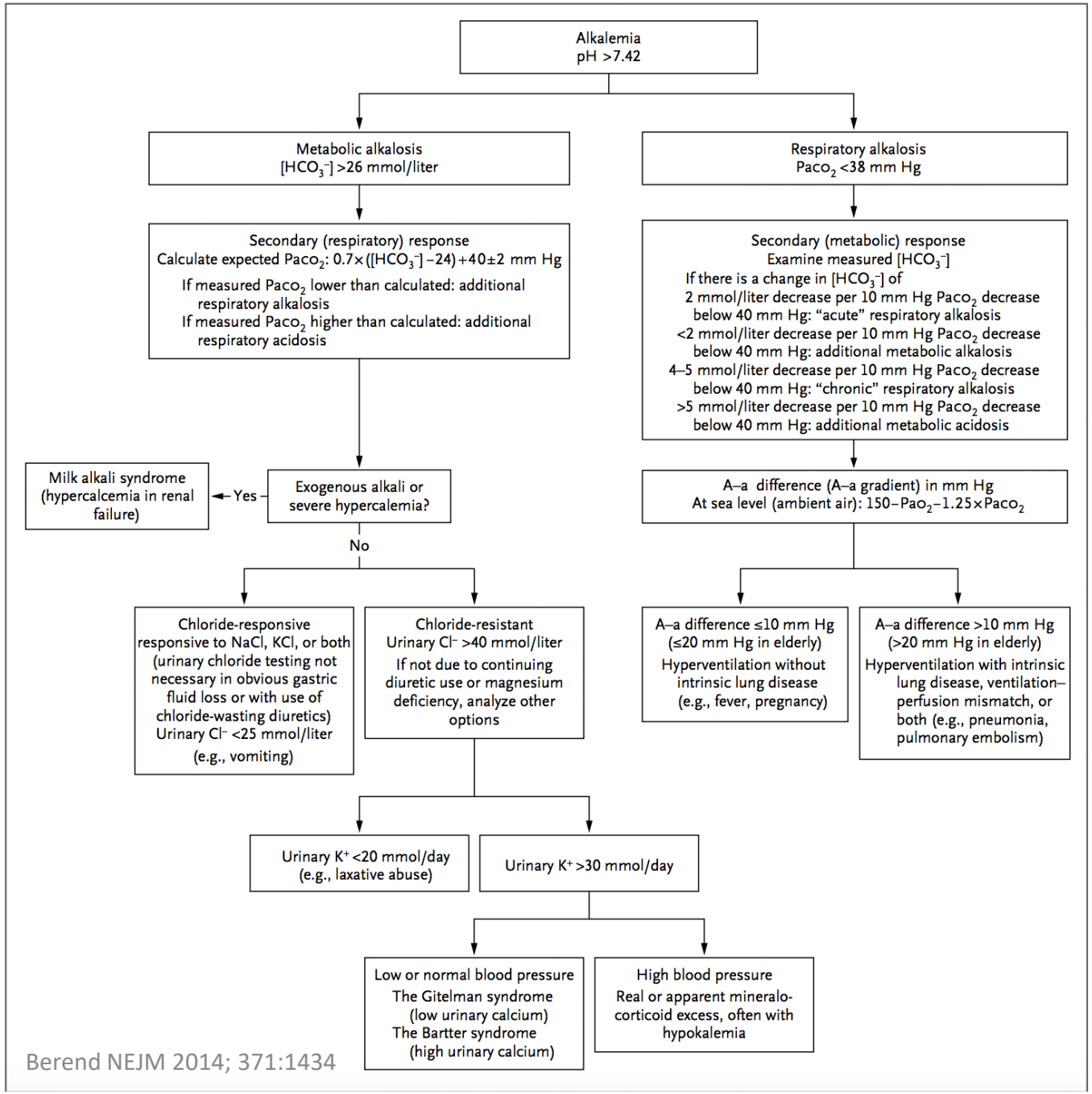


FIGURE 5. *Plot of coronary perfusion pressure before defibrillation. The coronary perfusion pressure immediately before defibrillation was highly predictive of successful resuscitability.*

Kette Circulation 1990; 81:1600-1660



Berend NEJM 2014; 371:1434

Furosemide acidifies the urine

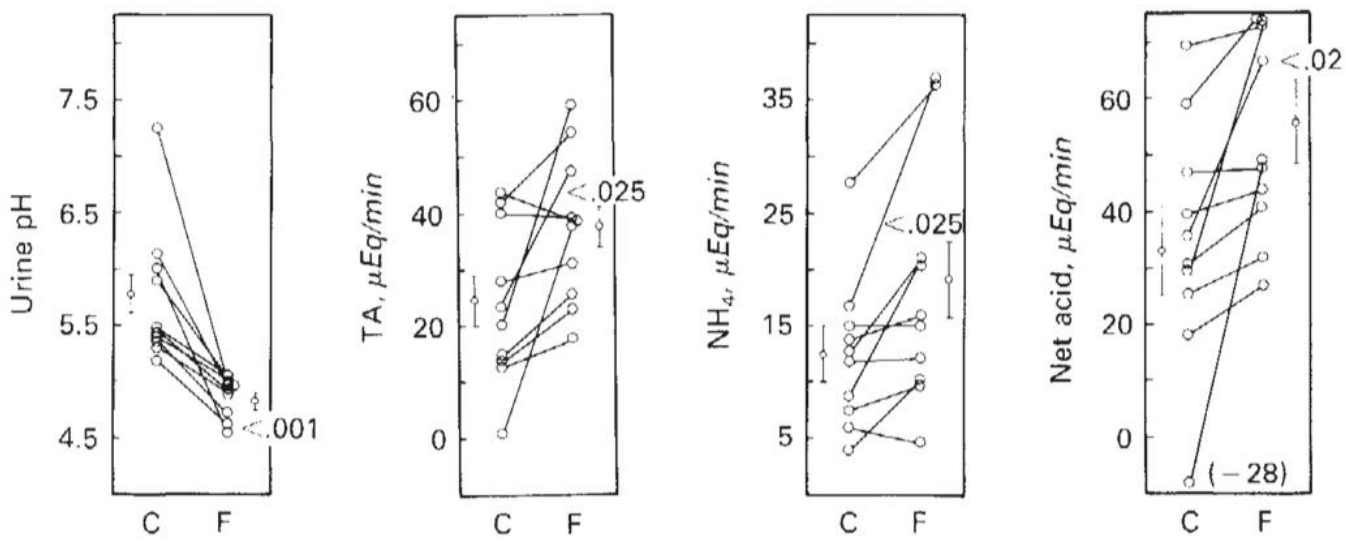


Fig. 1. *The effect of furosemide (F) on urine pH, titratable acid (TA), ammonium (NH_4), and net acid excretion in ten normal subjects.* The data shown in this figure were obtained when urine pH after furosemide was the lowest. C denotes data obtained immediately before furosemide administration.

Mechanism-increased CD Na delivery leads to increased Na reasborption→↑lumen electronegativity →↑driving force for H+ secretion

Same effect with thiazides

Batlle KI 1986; 30:546

Urinary acidification due to furosemide is inhibited by amiloride

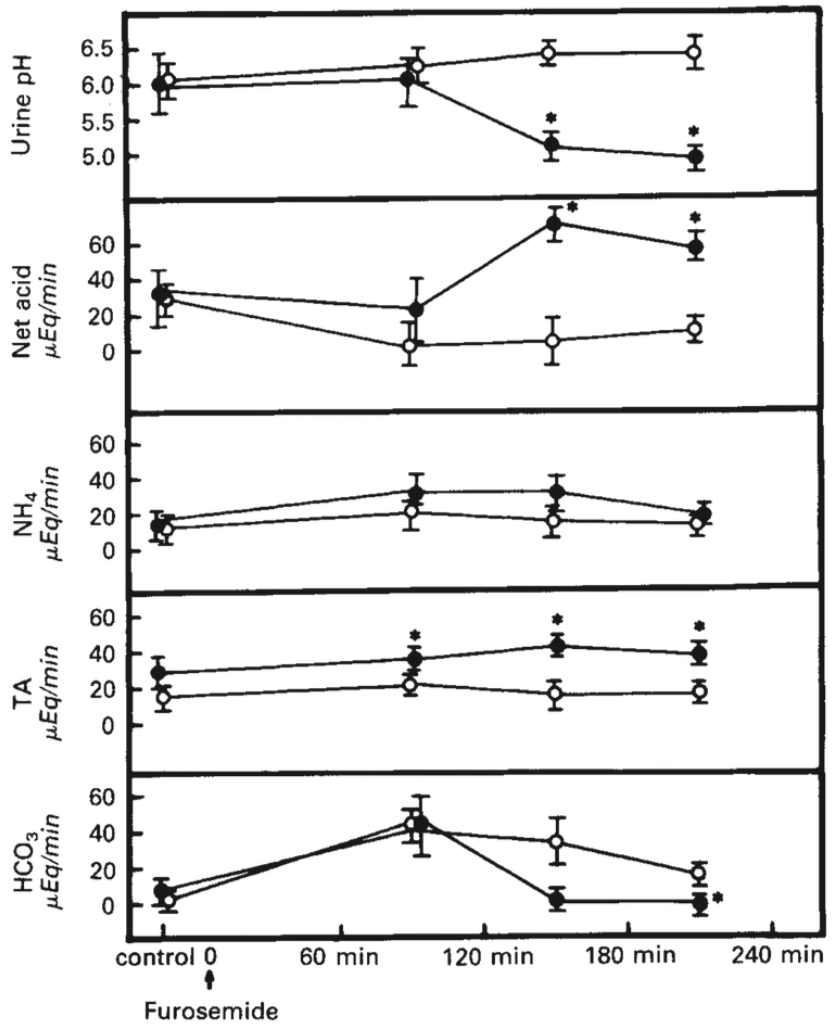
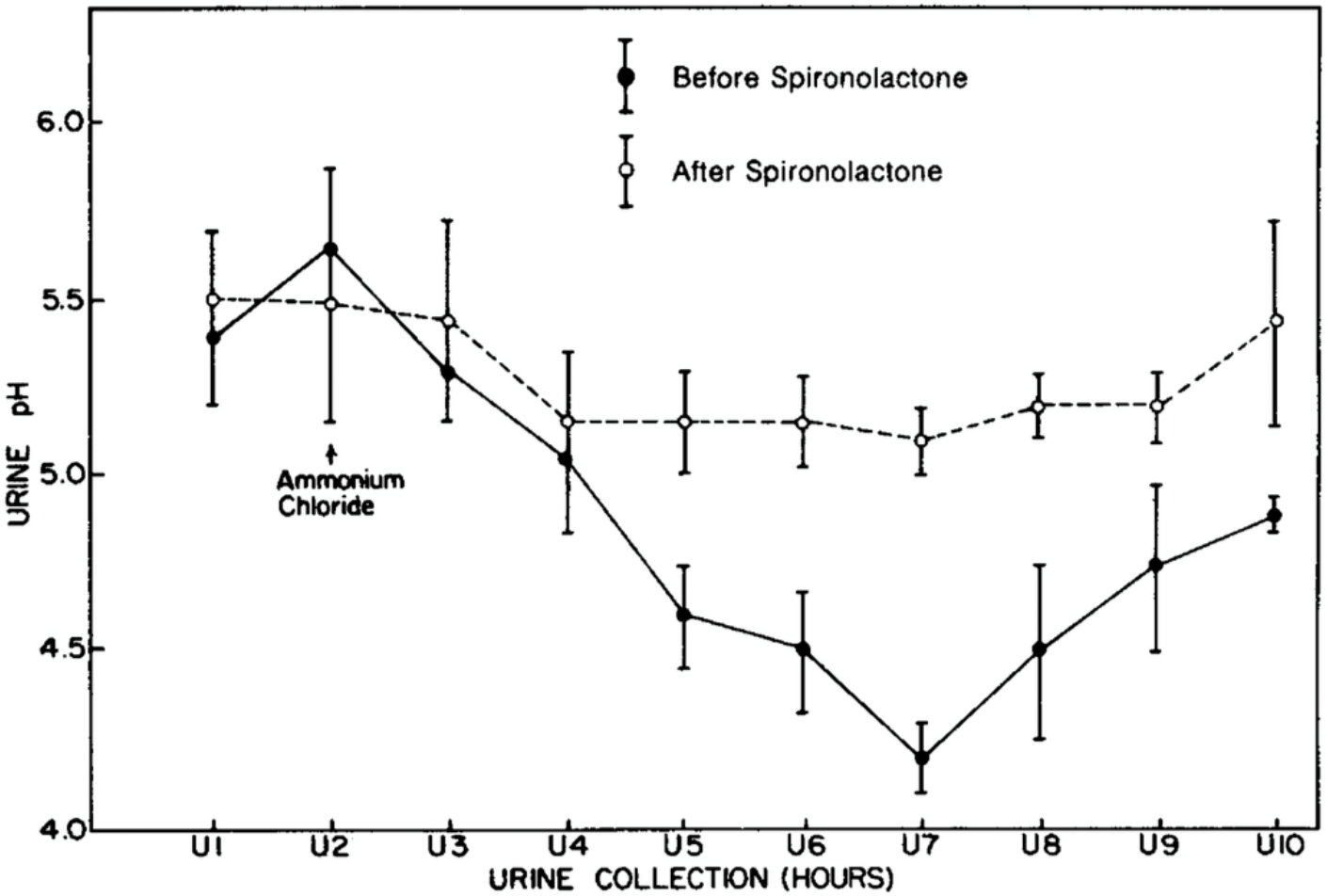


Fig. 3. *The effect of furosemide* (●) *and furosemide + amiloride* (○) *on urinary acidification in four normal subjects.* The asterisk denotes a significant difference between the two experimental conditions.

Batlle KI 1986; 30:546

Spironolactone impairs urinary acidification in response to NH_4Cl



Mean pH ± SEM of each collection period (U_1 to U_{10}) during ammonium chloride loading before and after spironolactone administration.

Manuel Arch Intern Med 1974; 134:472

Acetazolamide effectively treats metabolic alkalosis in the critically ill

Table I. Acid-base parameters at baseline and 24 hours

Parameters	*Baseline*	*24 hours*
pH	7.49 (7.43 – 7.58)	7.42 (7.37 – 7.44)
BE (mEq/L)	+7.8 (+3.5 – +13.6)	0.80 (−6 – +6.6)
BIC (mEq/L)	31.8 (26.8 – 39.0)	25.4 (17.1 – 30.2)
$Paco_2$ (mm Hg)	39.7 (33.6 – 45.7)	34.2 (31.2 – 39.6)

BIC, Bicarbonate.

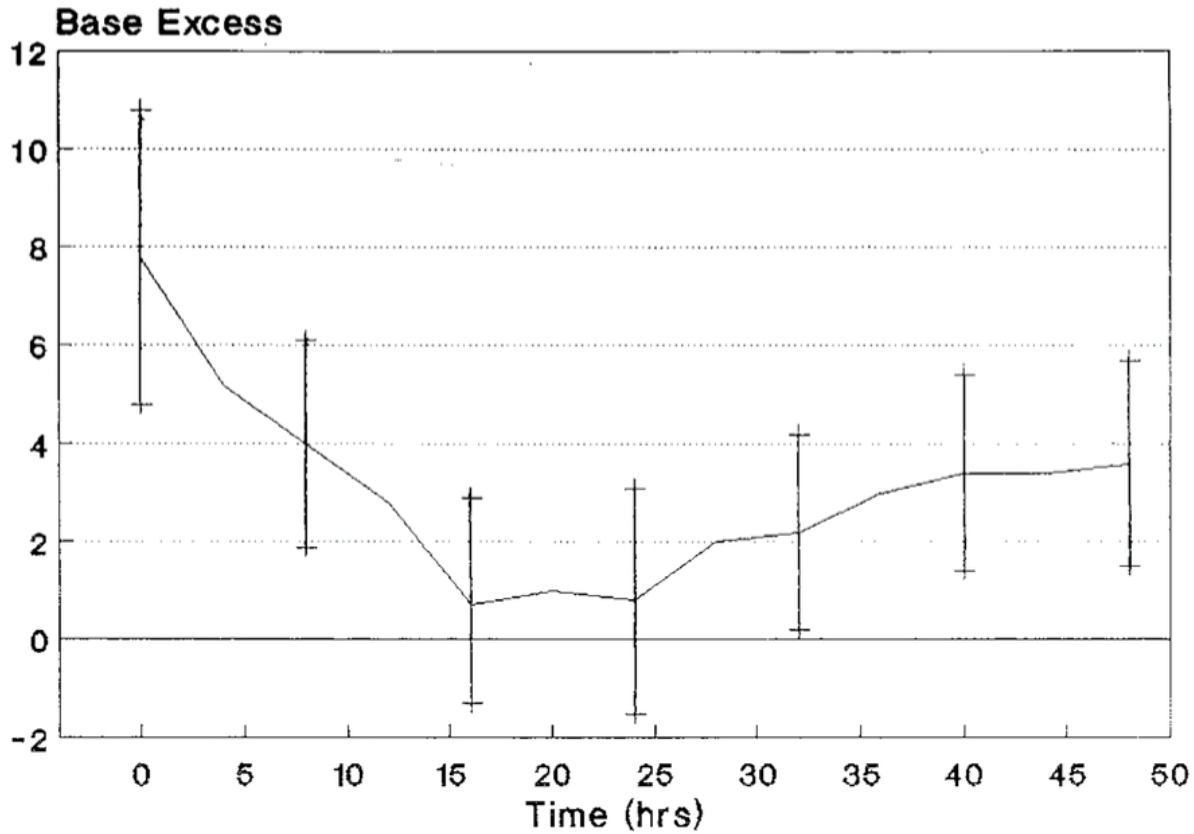


Fig. 1. Change in base excess (±2 SD) with time.

Marik Heart Lung 1991; 20:455

U_{Na} in metabolic alkalosis

- Early metabolic alkalosis→bicarbonaturia→requires some Na loss due to excess negative charge in CD lumen
- Progressive volume depletion and Cl depletion→↑HCO3 reabsorption→no bicarbonaturia→low urine Na
- Thus, urine Na may be high in early metabolic alkalosis due to bicarbonaturia
- However, Cl will always be low in Cl depletion alkalosis
- U_{Cl} is more reliable than urine U_{Na} to estimate volume status in metabolic alkalosis