Acid- base disturbances

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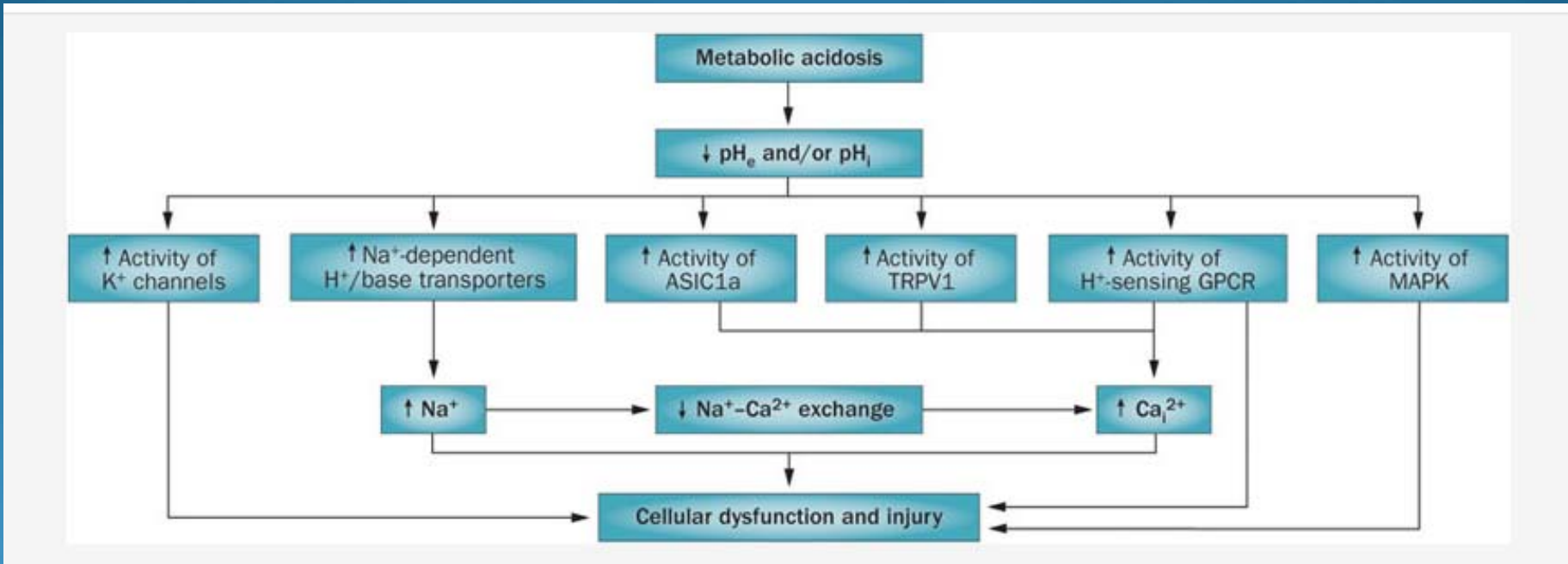
Woluwé 17 june 2014

Regulation of blood pH

- pH = 7.37 to 7.43
- (H+) = 37 to 43 nEq /l
- **Regulation** 1.000.000 times more precise than for Na+ !
- **Despite:**
- > 15.000 mmoles CO_2 produced daily
- > 50-100 mEq H + produced daily from the metabolism of sulfur aminoacids
- > 4150 mEq HCO_3 filtered daily

Consequences of metabolic acidosis

Kraut and Madias Nat Rev Nephrol 2012; 8:589-601



Henderson-Asselbach equation

- $(H+) = K (CO_2) / (HCO_3)$
- $pH = pK + \log (HCO_3)/(CO_2)$
- $pH = 6.10 + \log (HCO_3)/0.03\ p\ CO_2$

Power of the HCO3/CO2 buffer

- Not chemical (pK= 6.10 far from 7.4)
- Open system because CO2 is allowed to escape
- **Independent regulation of both components according to homeostatic need**

HCO_3/CO_2 buffer system regulation

Primary change	Homeostatic response
Decreased HCO_3	Hyperventilation
Increased HCO_3	Hypoventilation
Decreased pCO_2	Decreased urine acid excretion
Increased pCO_2	Increased urine acid excretion

Tissue type of respiratory acidosis

- Efficiency of the HCO_3/CO_2 buffer system requires that CO_2 generated by acid titration is readily eliminated by ventilation
- If blood flow is reduced more CO_2 is added by liter blood flow and pCO_2 rises
- Venous- arterial $pCO_2 > 10$ mmHg = compromission of buffer efficiency
-

Role of the kidney in the maintenance of acid-base balance

- **Reclaiming** filtered bicarbonate

- **Urinary acidification :**
- >Titratable acidity (1/3)
- > NH_4 + excretion (2/3)

Response to chronic acid load

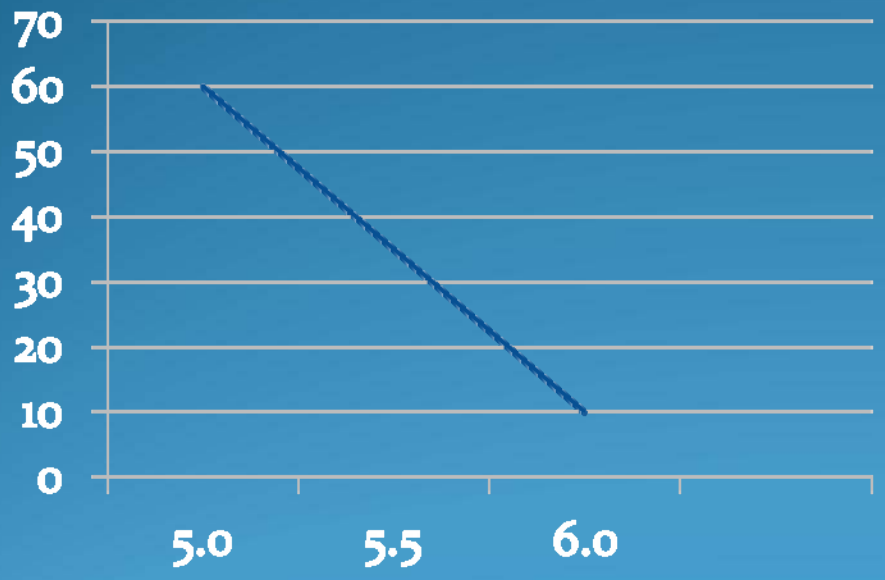
AB consequence of NH4 + excretion

- Glutamine → 2-oxoglutarate + 2 NH_4^+
- 2-oxoglutarate → 2 HCO_3

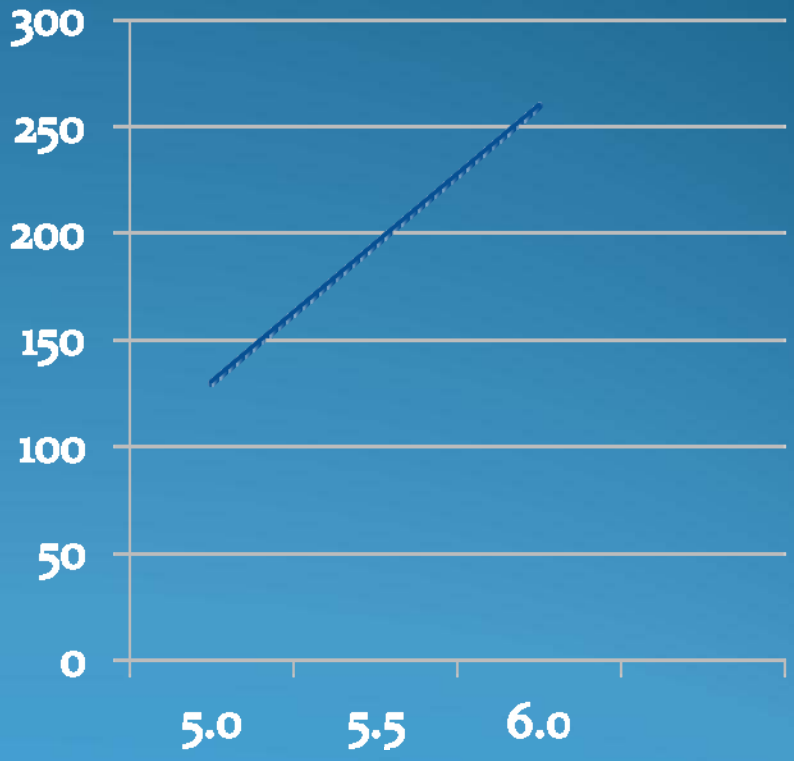
- **Renal excretion of NH_4^+** = gain of 2 HCO_3

- **w/o renal excretion** : (2 NH_4^+) + (2 HCO_3)→ urea in the liver→ AB neutral

Relationship between urine pH and NH4+ excretion



Acute acidosis



Chronic acidosis

Metabolic acidosis

- $(H^+ + A^-) + (Na^+ + HCO_3^-)$
  → $Na^+ + A^- + CO_2 + H_2O$
- If $A^- \neq Cl^-$ plasma anion gap increases (unless anion is quickly excreted)
- If $A^- = Cl^-$ plasma anion gap is normal (hyperchloremic acidosis)
- Renal response : excretion of $NH_4^+A^-$

Is the ventilatory response appropriate ?

- $pCO_2 = HCO_3 + 15$
- pCO_2 equal to the decimal digits of the arterial pH
- $pCO_2 = 1.5 \times HCO_3 + 8 +/- 2$ (Winter's formula)
- pCO_2 decreased by 1.2 mmHG for each meq/l decrease in plasma HCO_3

Diagnostic toolbox in metabolic acidosis

- Plasma anion gap
- Plasma osmolal gap
- Urinary anion gap or urinary net charge
- Urinary osmolal gap
- Urinary pH

Plasma anion gap

- Na – (Cl + HCO_3) = 12 +/- 2 meq/l
- Greater by 4 meq/l if K is included
- Lower by 2.5 meq/l for each g/l albumin below 4 g/dl
- Higher by 2.5 meq/l for each g/dl albumin above 4 g/dl
- ! May be low in myeloma patients (cationic protein)
- ! May not be increased if acid anion quickly excreted
- ! Use patient reference value whenever possible
- ! Use your own lab reference values

Increased anion gap

- **K** etosis
- **U** remia
- **S** alicylates
- **S**
- **M** ethanol
- **A** ntifreeze = Ethylene glycol
- **U**
- **L** actate

Problems with the identification of acid anion

- Cetone tests detect acetoacetate and acetone but not βoH butyrate : may be (-) when NADH accumulates (hypoxia or alcohol ingestion)
- D- Lactate not measured as lactate (only L- Lactate)
- Unusual anions

D-Lactic acidosis

Kang et al Electrolyte & Blood Pressure 2006; 4: 53-5§

- D-Lactate formed by carbohydrates fermentation by bacteria
- D-Lactic acidosis when high carbohydrate load is given to colonic bacteria : short bowel syndrome or exocrine pancreatic failure + high carbohydraite oral load
- Encephalopathy + high anion gap acidosis
- ! D-Lactate not identified as lactate
- ! D-Lactate more readily excreted by the kidney than L-Lactate

Pyroglutamic acidosis

Fenves et al CJASN 2006;1:441-447

- **Genetic** (rare) deficiency in gluthatione-synthase
- **Acquired** : exposure to acetaminophen in women
- **Presentation**: High anion gap acidosis
- **Diagnosis** : 5-oxoproline in serum or urine
- **Treatment** : acetaminophen cessation +/- N-acetylcysteine

Pyroglutamic acidosis

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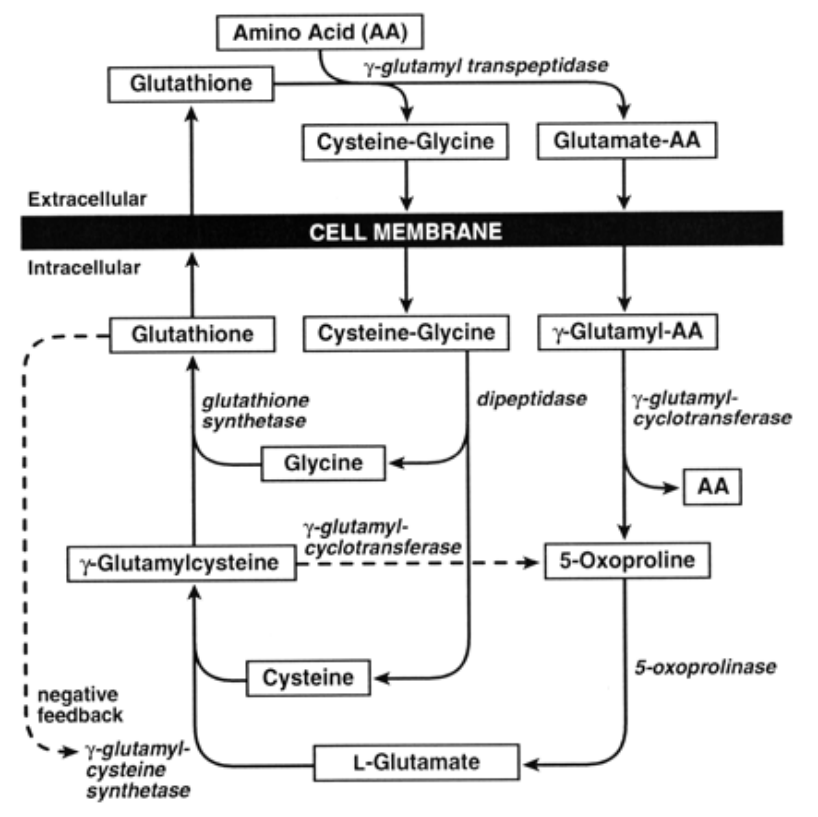

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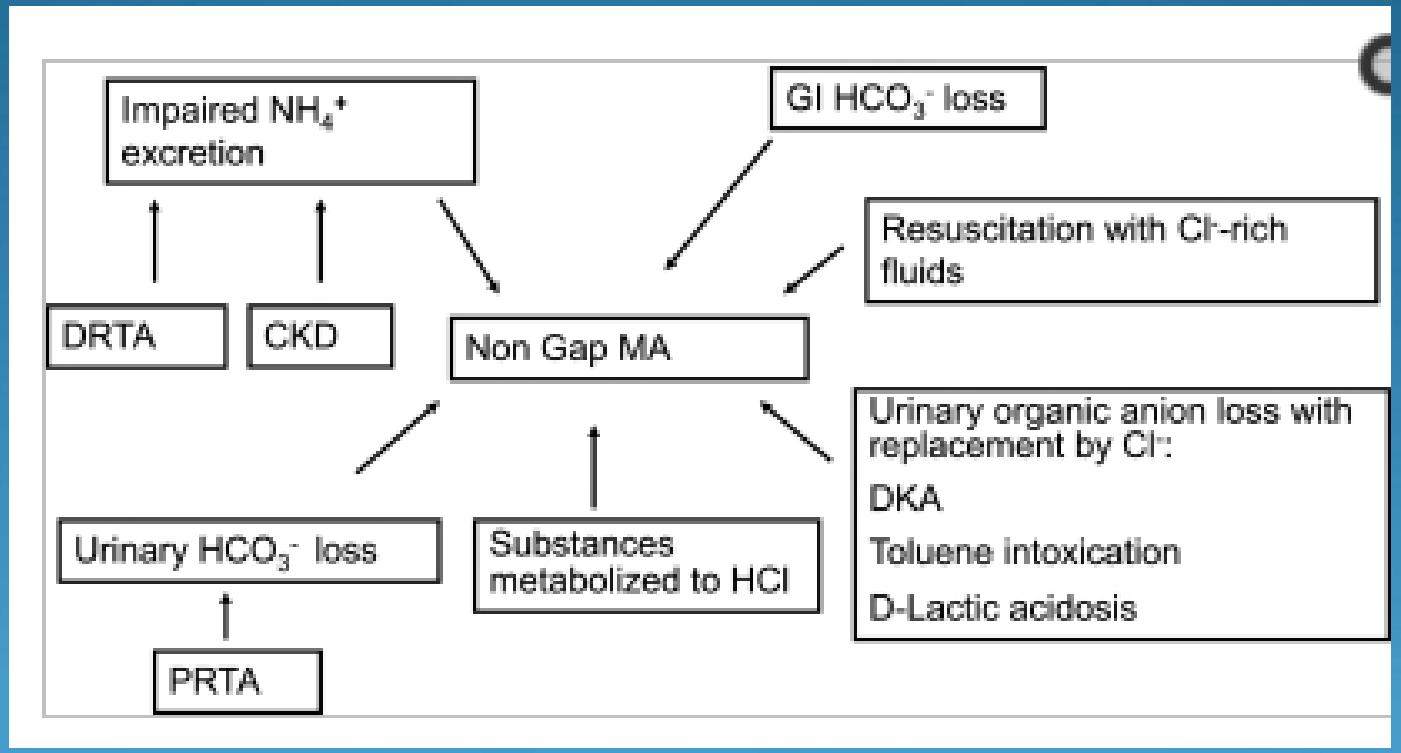
Plasma osmolal gap

- P osm – [(Na + K) x 2 + Glucose/18 + urea / 6]
- Gap > 10 mOsm/l → suspicion of alcohol ingestion
- Check methanol and ethyleneglycol
- Give ethanol (or fomepizole) to prevent aldehyde formation

Normal anion gap acidosis

Kraut and Madias CJASN 2012; 7:671_679



Classification of normal acid gap acidosis according to plasma K

Kraut and Madias CJASN 2012. 7:671-679

High or Normal Serum K^+	Low Serum K^+
Administration of HCl	Diarrhea
TPN solutions	Intestinal fistulae
NH_4Cl[b]	Proximal RTA
Hyperkalemic distal RTA	Distal RTA
hyporeninemic hypoaldosteronism	Ureteroileostomy
tubular resistance to aldosterone	Ureterosigmoidostomy
aldosterone deficiency	Toluene intoxication
Chronic renal failure	Ketoacidosis[b]
Gordon's syndrome	D-Lactic acidosis
Decreased distal Na delivery	Administration of Cl-rich solutions[b]
Administration of Cl^--rich solutions[b]	
Drugs such as triamterene, amiloride, pentamidine, NSAIDs, CEIs, ARBs, trimethoprim, spironolactone, or heparin	

Urinary anion gap

- $NH_4 + Na + K + UC = Cl + UA$
- $NH_4 = Cl - Na - K - (UC-UA)$
- Since UA- UC = 80 meq/l
- $NH_4 = Cl - Na - K + 80$ meq/l
- Since UAG is Na + K – Cl
- $NH_4 = 80 - UAG$
- **If UAG < 0 → NH_4 > 80**
- **If urinary net charge is (-) → NH_4 is > 80**
- ! Detects only NH_4Cl excretion

Urinary osmolal gap

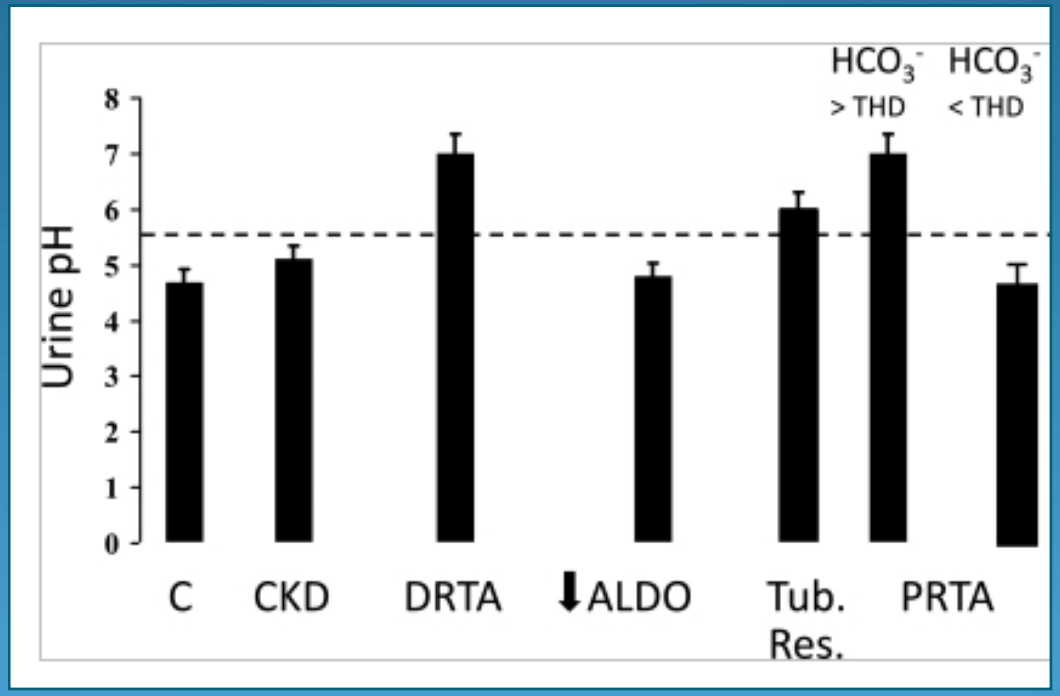
- UOG = Uosm – [2 (Na ur + K ur) + glu ur/18 + urea ur/6]
- NH_4 = UOG/2
- Factor by creatininuria to obtain meq/g creatinine
- Multiply by the expected 24h creatininuria (10-20 mg/kg BW) to obtain meq/24 h
- Detects NH_4 irrespective of the associated anion

Approach to hyperchloremic acidosis

- Estimate NH_4 excretion from UAG (or urinary net charge) or urinary osmolal gap
- If NH_4 is high → digestive loss of HCO_3
- If NH_4 is low → renal loss of HCO_3 or defective renal acidification
- If GFR is low : renal failure
- If GFR is normal : tubular acidosis
- Use urinary pH to explain why NH_4 ur is low

Urinary pH in distal acification defect

Kraut and Madias CJASN 2012; 7: 671-679



What do you think of this ?

Halperin et al Fluid ,Electrolyte, and Acid-Base Physiology Saunders-Elsevier 2010

Osmolality	units	Arterial Blood	Venous Blood	Urine
pH		7.20	7.00	6.0
pCO_2	mmHg	25	60	-
HCO_3^-	mmol/l	10	15	< 5
Na^+	mmol/l		120	50
K^+	mmol/l		2.3	30
Cl^-	mmol/l		90	0
Creatinine	mg/dl		1.7	34
Urea	mg/dl		14	420
Osmolality	mOsm/kgH_2O		250	500

What do you think of this ?

Halperin et al Fluid ,Electrolyte, and Acid-Base Physiology Saunders-Elsevier 2010

- Hyperchloremic acidosis with urinary pH of 6 = distal tubular acidosis ?
- In fact huge UOG = 500 – (160 + 70) = 270 mosm/kgH_2O
- Glue sniffing
- Toluène = Méthylbenzène → Hippuric acid
- Toluène acidosis ≠ tubular acidosis
- Toluène acidosis = overproduction acidosis

Hazards of acidosis correction

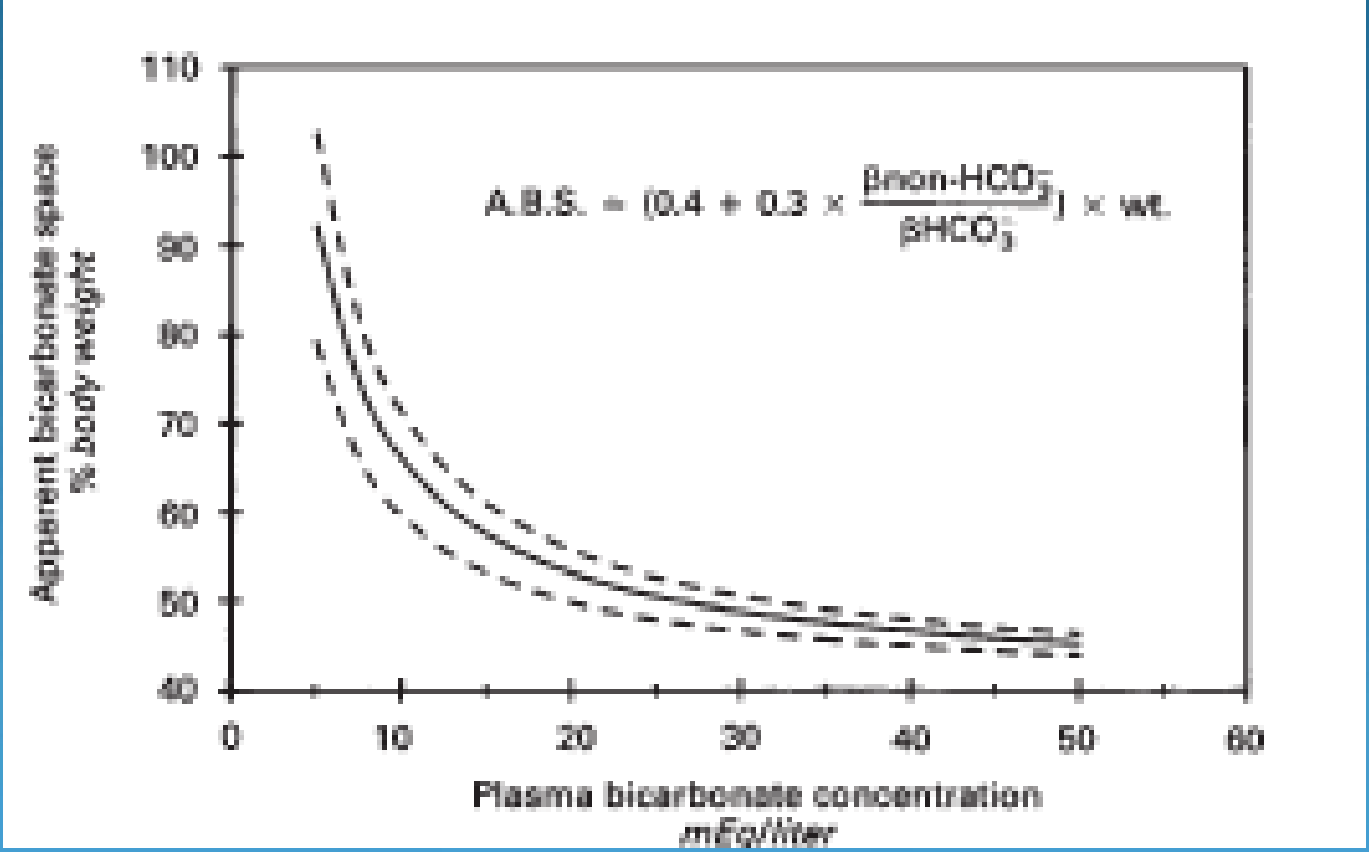
- Increased intracellular acidosis
- Volume overload
- Hyperosmolality
- Overshoot alkalosis
- Stimulation of organic acid production
- Reduced Ca i
- Cerebral oedema

Correction of acidosis

- **Low treshold** : pH <7.10 in organic acidosis and < 7.20 in hyperchloremic acidosis
- **Modest goal** : pH > 7.20 and HCO_3 > 10 meq/l
- Use **bicarbonate distribution space** of 50 % BW

Bicarbonate distribution space

Fernandez et al KI 1989;36:747-752



Base administration in acute metabolic acidosis

Kraut and Madias Nat Rev Nephrol 2012; 8: 589-601

Modality of base administration	Advantages	Disadvantages	Comments
Intravenous sodium bicarbonate	Inexpensive; simple to use	Might exacerbate intracellular acidosis; can provide large sodium load	Should be given slowly as isosmotic solution to avoid hyperosmolality and minimize extent of intracellular acidosis; estimate magnitude of bicarbonate deficit so as to administer minimum quantity necessary to achieve desired blood pH
Intravenous THAM	Buffers protons without generating CO_2; penetrates cells to buffer pH_i	Reports of hyperkalaemia, hypercapnia, and liver necrosis in newborns; requires intact renal function or dialysis	Given as 0.3 M solution (best via central vein); serum potassium and PCO_2 should be monitored carefully during therapy
Intravenous carbicarb	Buffers pH_e and pH_i without generating significant quantities of CO_2; preserves cardiac contractility in animal studies	None	Never introduced into practice but studies to re-examine its potential use are planned
Dialysis	Can provide large quantities of base while preventing volume overload or hyperosmolality; CRRT can deliver base over 24 h period at low rate	Requires use of dialysis equipment and personnel; risk of hypotension with procedure	Intermittent haemodialysis or CRRT modalities can be utilized; if available, CRRT is preferred

Abbreviations: CRRT, continuous renal replacement therapy; PCO_2, partial pressure of CO_2; pH_e, interstitial pH; pH_i, intracellular pH.

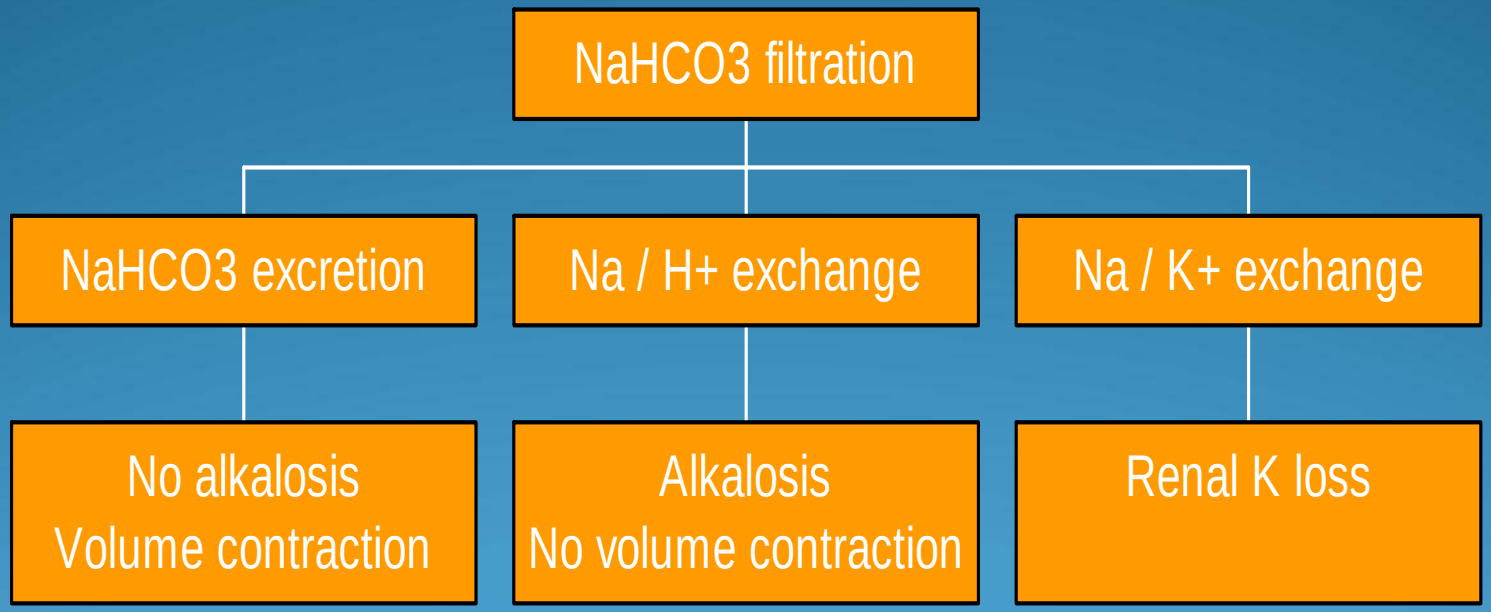
Exogenous base gain

- Administration of HCO_3 for cardiopulmonary ressuscitation
- Administration of HCO_3 for lactic acidosis or ketoacidosis
- Plasmapheresis or massive transfusion (500 ml blood = 17 mmoles citrate = 51 mmoles HCO_3
- Milk alkali syndrome

Digestive acid loss

- 1.Gastric fluid loss
- 2.Colon villous adenomas (10-20 %)
- 3.Congenital chloridorrhea
- 4.Gastrocystoplasty

Digestive acid loss

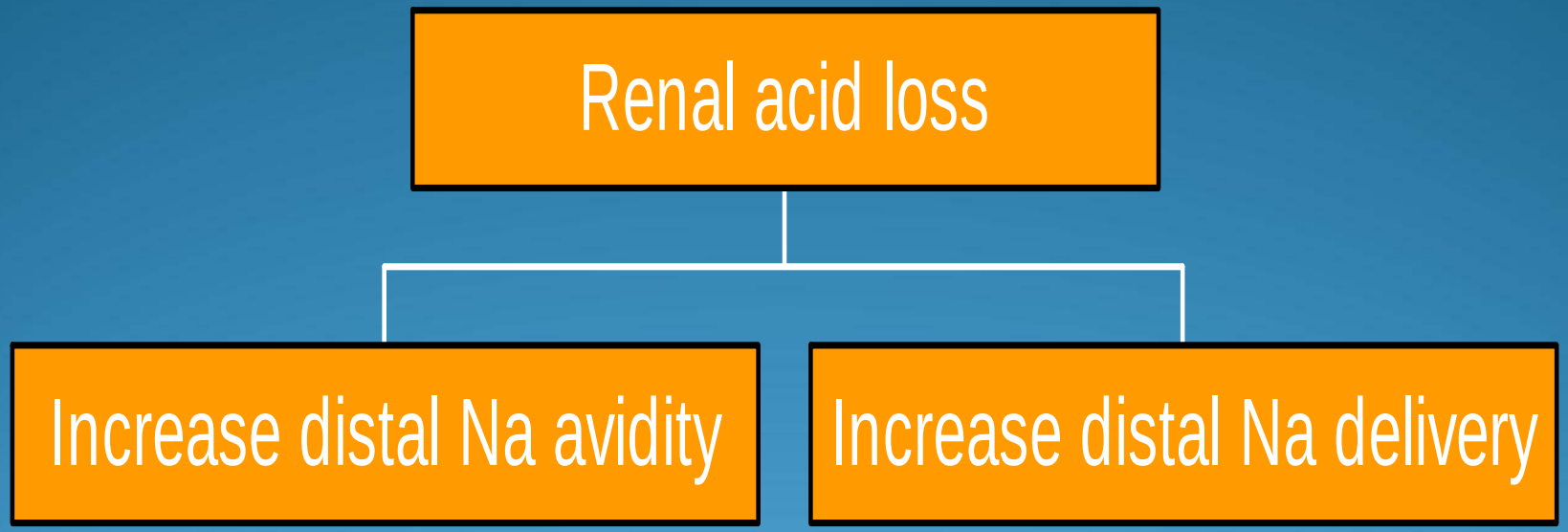


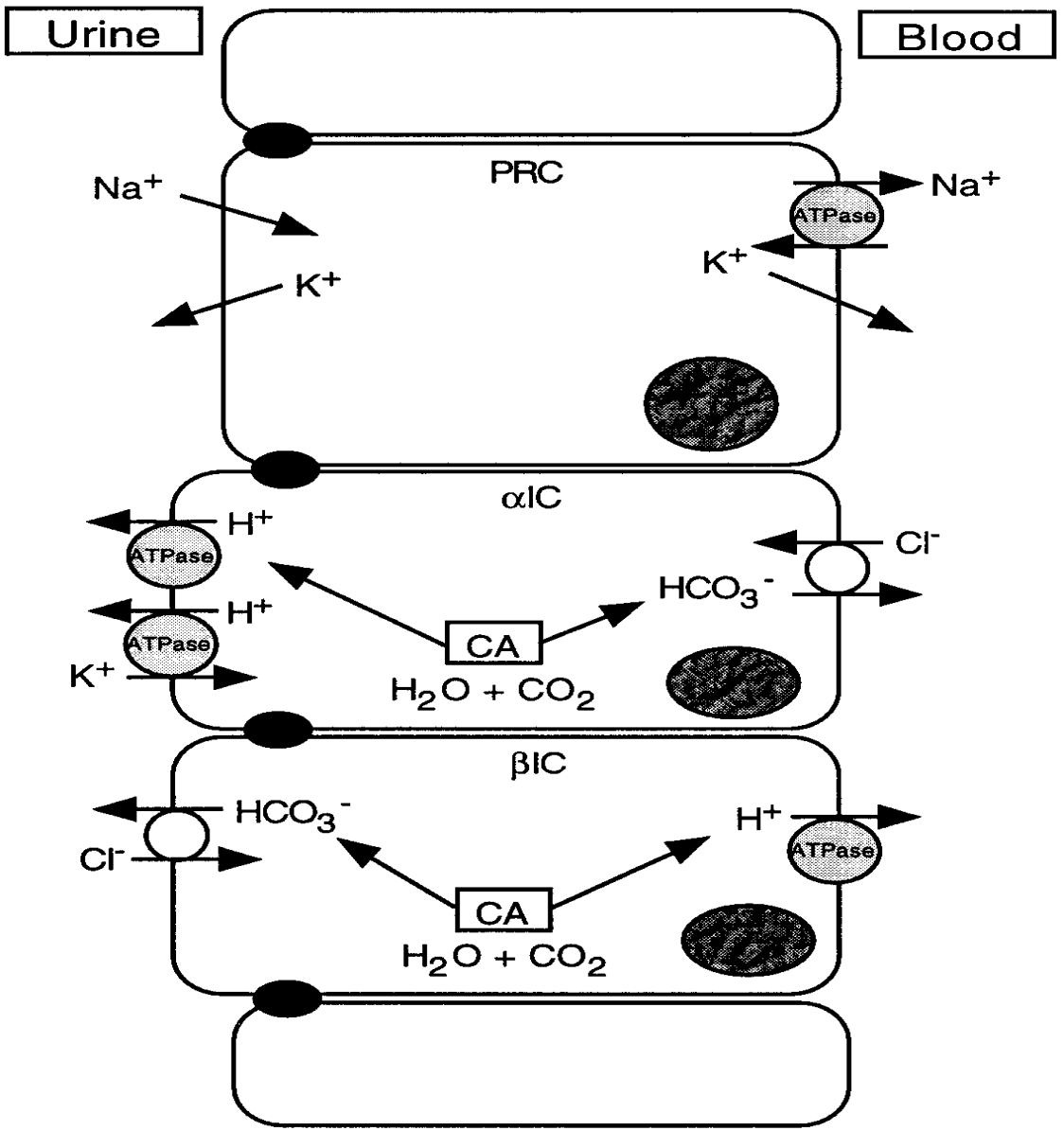
Skin Cl losses

- Normal sweat small amount of Cl

- Cystic fibrosis sweat Cl > 60 mmole/L
  risk of alkalosis in hot envirt
  risk greater with pancreatic failure

Renal acid loss




Urine
Blood
PRC
Na+
K+
Na+
ATPase
K+
αIC
H+
ATPase
H+
ATPase
K+
Cl-
HCO3-
CA
H2O + CO2
βIC
HCO3-
Cl-
H+
ATPase
CA
H2O + CO2

Increase in distal Na avidity

- **Primary increase in ENaC activity** (Liddle)
- **Increased stimulation of mineralocorticoid receptor**

  primary hyperaldosteronism

  hypercorticism

  defect in 11-betaOHsteroid desHase

  secondary hyperaldosteronism

Secondary hyperaldosteronism

- **1.With hypertension**

  malignant hypertension

  renal artery stenosis

  renin producing tumor

  renal infarction

- **2.Without hypertension**

  diuretics

  Bartter and Gitelman

  Mg deficiency

Increased distal Na delivery

Pressure natriuresis due to hypertension

Pressure independant defect in tubular Na reabsorption

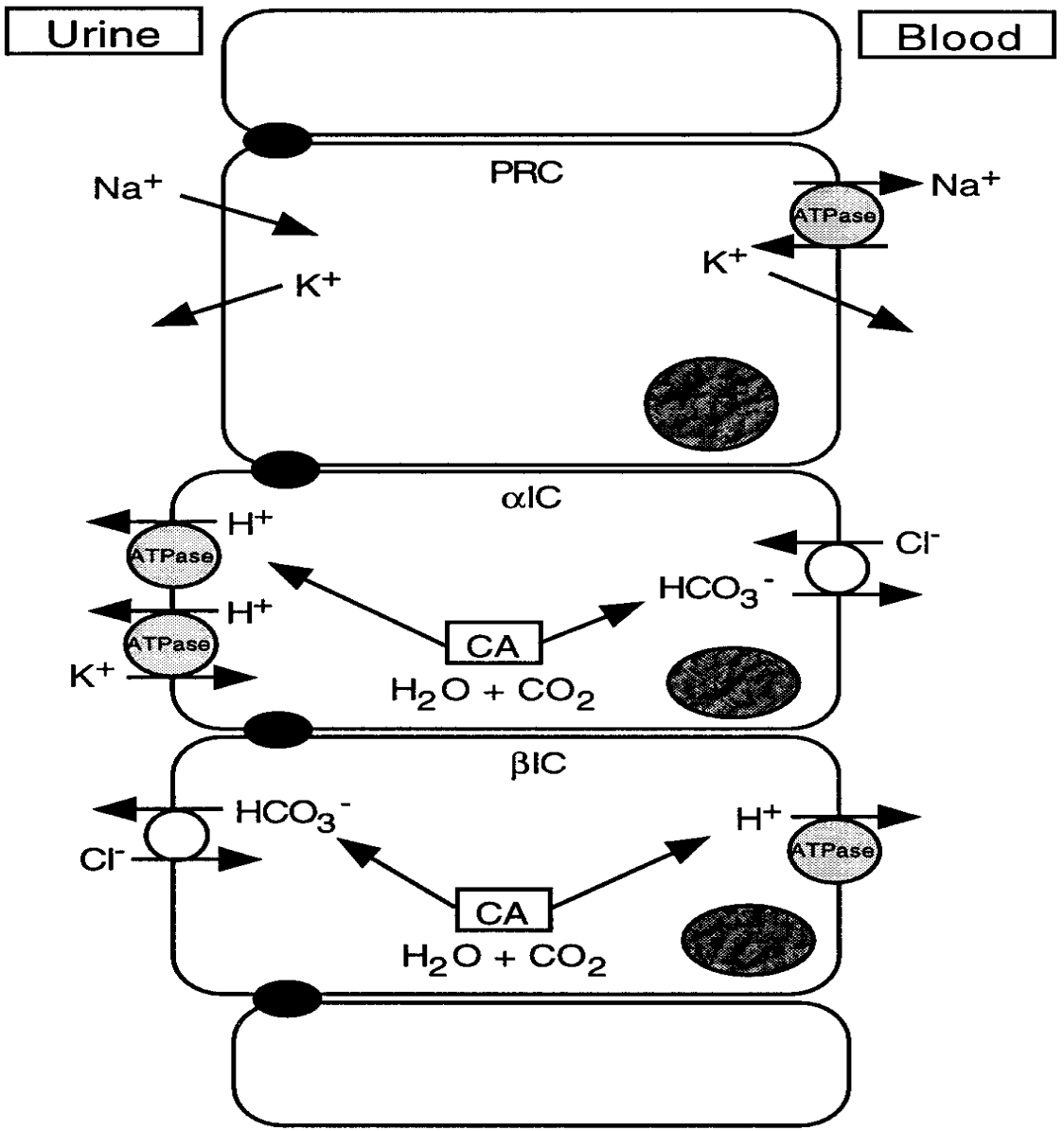
- Diuretics
- Bartter and Gitelman
- Mg deficiency

Importance of the association of distal Na avidity & availability

- **Na restriction** → no alkalosis
- **DOCA salt models** → no alkalosis unless high Na intake

Why is HCO3 not excreted by the kidney ?

- Cl depletion
- K depletion
- Hyperactive cationic exchange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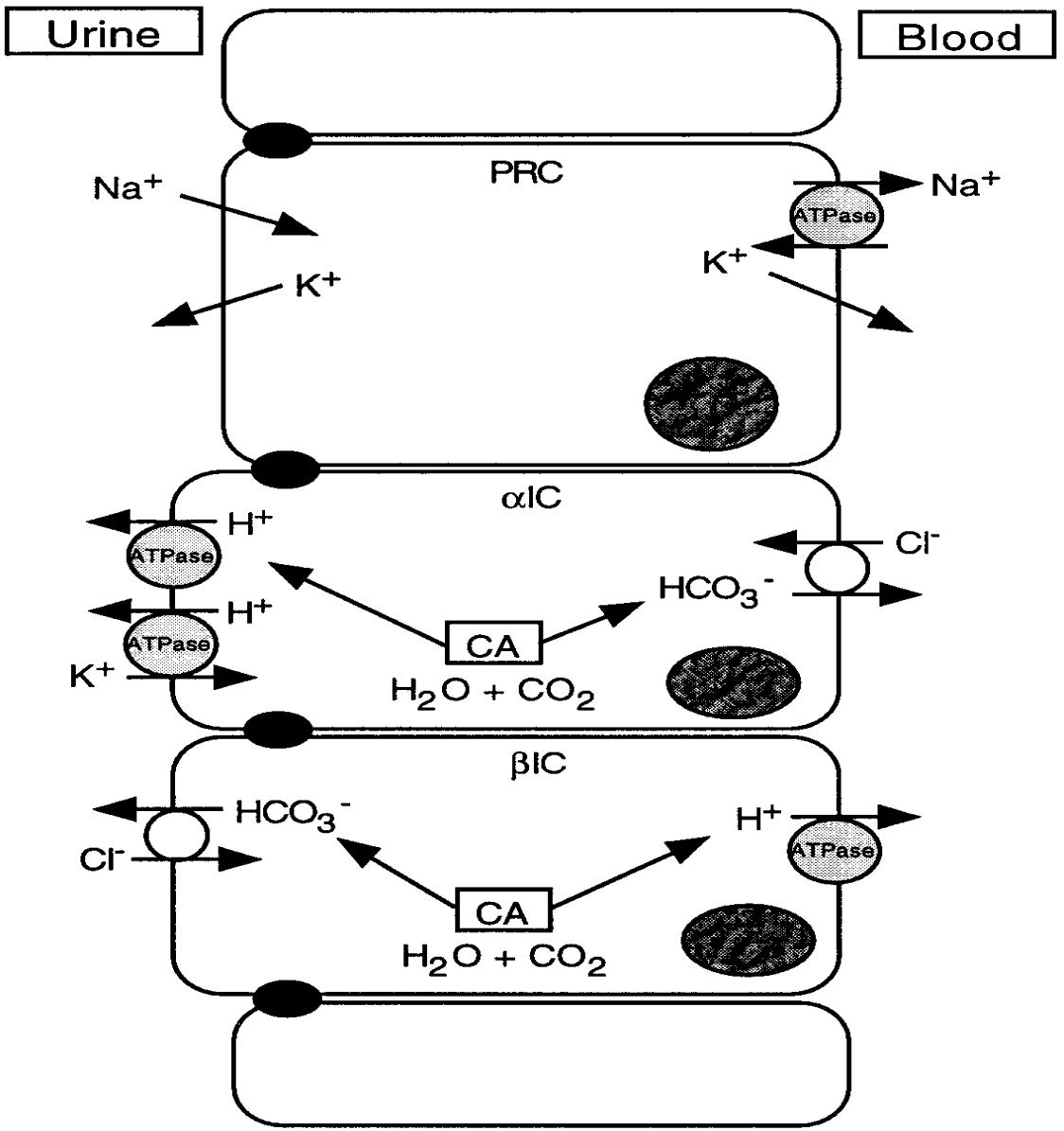
H+
ATPase
K+
Cl-
HCO3-
CA
H2O + CO2
βIC
HCO3-
Cl-
H+
ATPase
CA
H2O + CO2

Potential role of K depletion

- Intracellular H+ shift
- Renal vasoconstriction and decrease in GFR impairing HCO_3 filtration
- Stimulation of tubular H+ secretion (proximal and distal)

The interplay between K depletion and aldosterone

- ENaC and Na/K ATPase stimulated by aldosterone
- H+ATPase stimulated by aldosterone
- H/K ATPase stimulated by K depletion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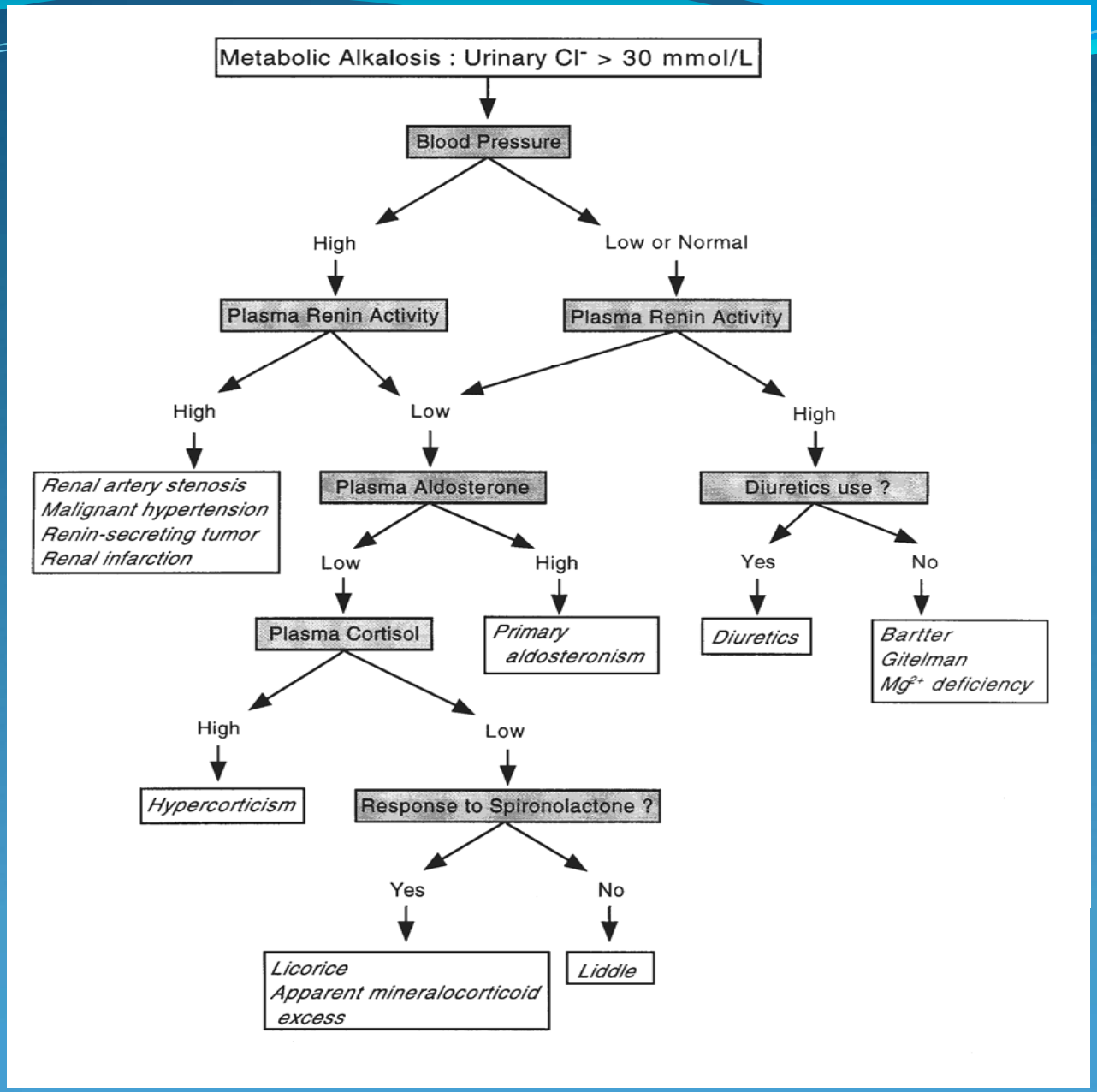
H+
ATPase
H+
ATPase
K+
Cl-
HCO3-
CA
H2O + CO2
βIC
HCO3-
Cl-
H+
ATPase
CA
H2O + CO2

Diagnosis of metabolic alkalosis

- **CLUE 1** *BLOOD GAS ANALYSIS* : pH > 7.43 and plasma HCO_3 > 26 mmole/l
- **CLUE 2** *URINARY Cl* : < 20 mmole/l = Cl depletion alkalosis and > 30 mmole/l = Cl resistant alkalosis
- **CLUE 3** *PRA AND ALDOSTERONE*
- **CLUE 4** *URINARY K* no information!


Metabolic Alkalosis : Urinary Cl⁻ > 30 mmol/L
Blood Pressure
High
Low or Normal
Plasma Renin Activity
Plasma Renin Activity
High
Low
High
Renal artery stenosis
Malignant hypertension
Renin-secreting tumor
Renal infarction
Plasma Aldosterone
Diuretics use ?
Low
High
Yes
No
Plasma Cortisol
Primary aldosteronism
Diuretics
Bartter
Gitelman
Mg2+ deficiency
High
Low
Hypercorticism
Response to Spironolactone ?
Yes
No
Licorice
Apparent mineralocorticoid excess
Liddle

Treatment of Cl depletion alkalosis

- Stop nasogastric succion, antacids, antiemetics
- NaCl (normal saline) and KCl (40-60 mmole/l)
- Cardiorespiratory failure : acetazolamide 500 mg/day

Cl resistant alkalosis

- Withdrawal of the cause (adrenalectomy, tumour resection…)
- Spironolactones
- Amiloride (Liddle)
- NSAID (Bartter)
- **Correct K and Mg depletion !**

Severe CDA (pH > 7.54 and/or HCO3 > 40 mmole/l)

- HCl 0.1 to 0.2 N = 100-200 mmoles/l in normal saline or 5 % dextrose
- Infusion through central venous catheter (0.2 mmoles/kg/h)
- Peripheral infusion if mixed with aminoacids and lipid emulsion
- Better than NaCl *(no volume overload)*
  KCl *(no risk of hyperkaliemia)*
  NH_4Cl *(possible with hepatic failure)*

Mixed acid base disturbances

- Except respiratory acidosis and respiratory alkalosis all acid-base disturbances may coexist
- Metabolic acidosis and metabolic alkalosis
- Same direction and different origin : metabolic acidosis and respiratory acidosis, metabolic alkalosis and respiratory alkalosis
- Opposite direction and different origin : metabolic acidosis and respiratory alkalosis, metabolic alkalosis and respiratory acidosis
- Triple acid –base disturbances

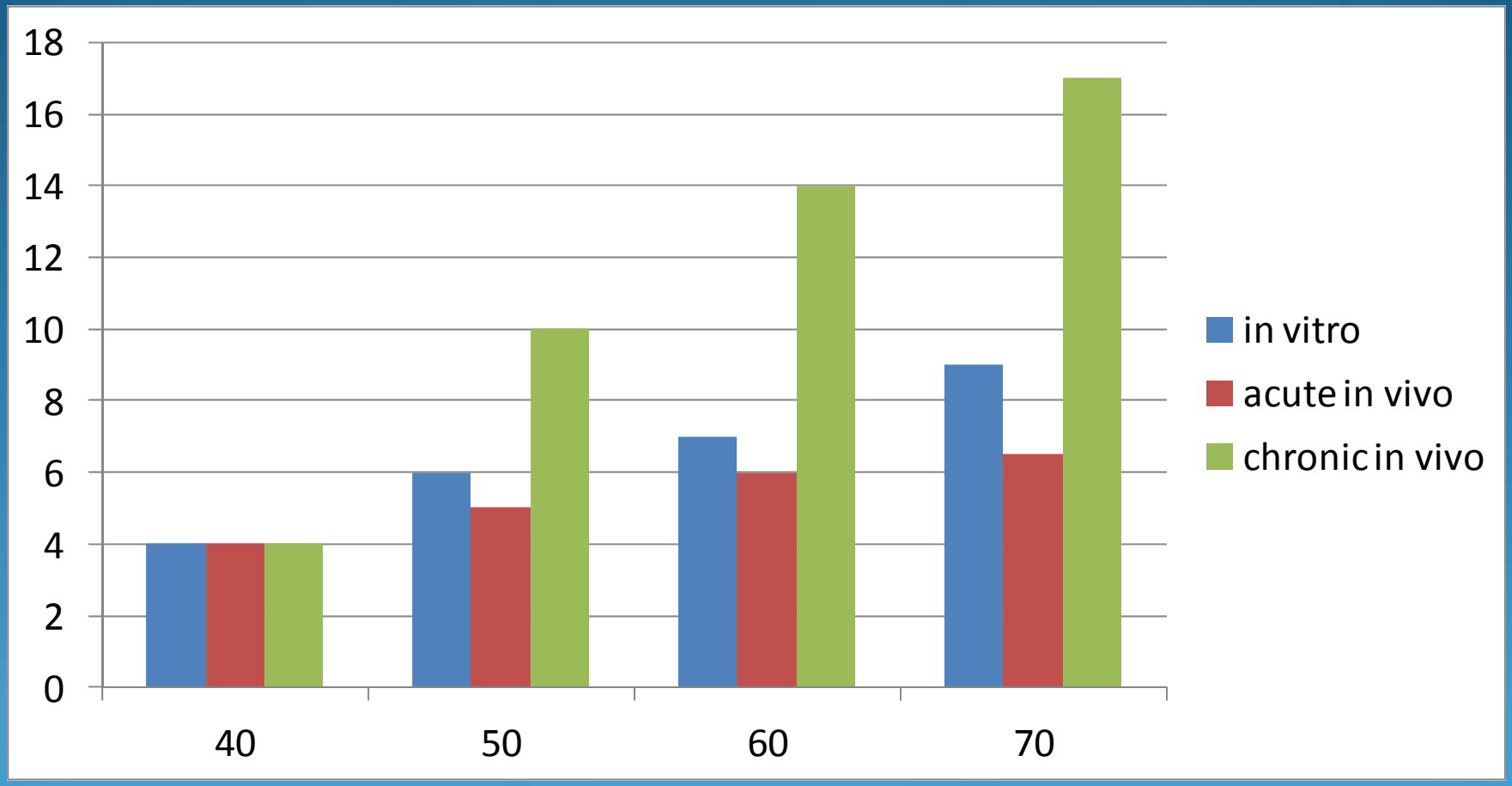
Mixed acid-base disturbances

	Metabolic acidosis	Metabolic alkalosis
Respiratory acidosis	HCO_3 = pH decreased ++ Circulatory arrest, septic shock with ARDS, cardiogenic shock with pulmonary oedema, pulmonary lesions with methanol or ethylene glycol poisoning	HCO_3 increased ++ pH = Respiratory failure and vomiting, post hypercapnia alkalosis
Respiratory alkalosis	HCO_3 decreased ++ pH = Septic shock, hepatic failure with lactic acidosis or with hepatorenal syndrome or with distal tubular acidification defect, salycilate poisoning	HCO_3 = pH increased ++ Hyperventilation (pain, fever, hepatic failure) with vomiting, diuretics or massive alkali administration (perfusions or transfusions)

Base-excess

- Standard HCO_3 = HCO_3 of the sample is pCO_2 is brought back to 40 mmHg
- Base excess = Standard HCO_3- Actual HCO_3
- **Base excess introduced to express the metabolic component of a mixed acid-base disturbance**
- Hidden assumption : titration curve of the blood identical in vitro and in vivo

Blood titration curve



The base-excess paradox

- Where it is accurate, it is not needed
- Where it is needed, it is not accurate

Renal and repiratory compensation to primary AB disturbances in humans

BD Rose and TW Post Clinical Physiology of Acid-Base and Electrolyte Disorders McGraw-Hill 2001

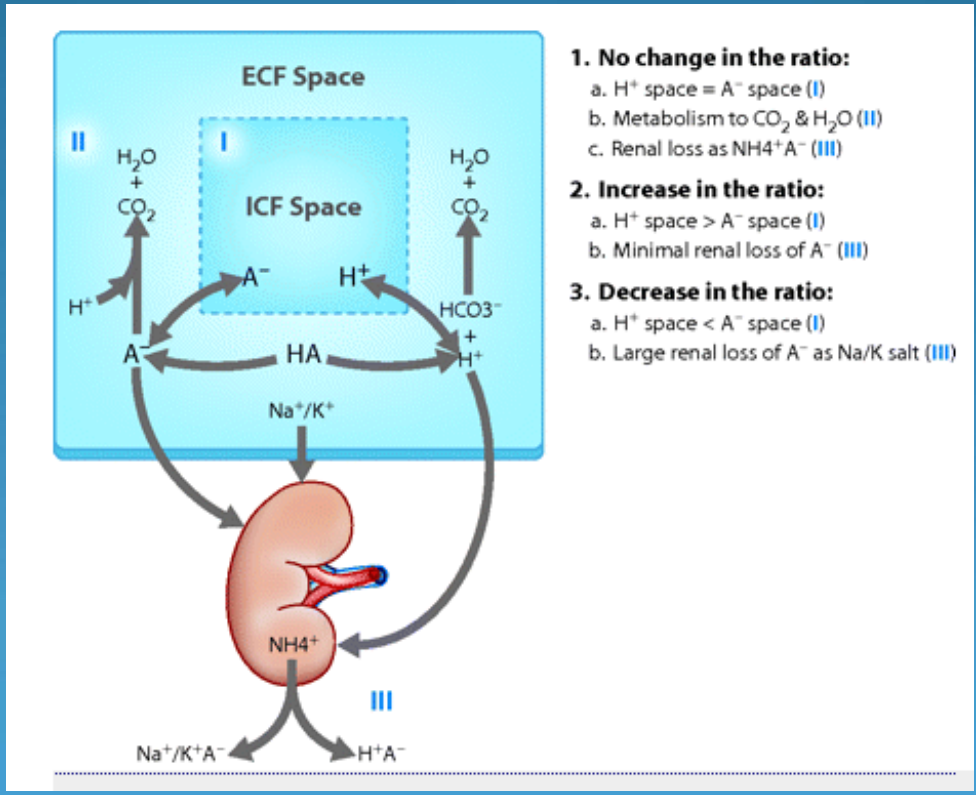
Disorder	Primary change	Compensatory reponse
Metabolic acidosis	Decreased HCO_3	- 1.2 mmHg pCO_2/meq HCO_3
Metabolic alkalosis	Increased HCO_3	+ 0.7 mmHg pCO_2/meq HCO_3
Acute respiratory acidosis	Increased pCO_2	+ 1 meq/l HCO_3 / 10 mmHg pCO_2
Chronic respiratory acidosis	Increased pCO_2	+ 3.5 meq/l HCO_3 / 10 mmHg pCO_2
Acute respiratory alkalosis	Decreased pCO_2	- 2 meq/l HCO_3/ 10 mmHg pCO_2
Chronic respratory alkalosis	Decreased pCO_2	- 4 meq/l HCO_3/ 10 mmHg pCO_2

Δ AG / Δ HCO3

- $HA + NaHCO_3 \rightarrow NaA + H_2CO_3 \rightarrow NaA + CO_2 + H_2O$
- A- appearance and HCO_3- disparition stoechiometrically related
- Δ AG / Δ HCO_3 expected to be 1
- If >1 : hidden metabolic alkalosis or respiratory acidosis
- If < 1 : hidden hyperchloremic metabolic acidosis or respiratory alkalosis

Factors affecting Δ AG / Δ HCO3

Rastegar CJASN 2007;18:2429-2431



What is the normal value of Δ AG / Δ HCO3 ?

Lactic acidosis = 1.6

Ketoacidosis = 1.1

D-Lactic acidosis or Toluene poisoning < 1

Δ AG / Δ HCO_3 should be between 1 and 2

Δ AG / Δ HCO3 > 2

- Hidden metabolic alkalosis (vomiting)
- Hidden respiratory acidosis

Δ AG / Δ HCO3 < 1

- Rapid renal excretion of the acid anion (KA, D-lactic acidosis, toluene)
- Tubular dysfunction in early stage CKD
- Superimposed hyperchloremic acidosis (diarrhea with lactic acidosis)
- Superimposed respiratory alkalosis

Approach to mixed acid base disturbances

- Use pH to define the dominant trouble
- Assess whether respiratory or metabolic compensation are appropriate
- Use the Δ AG /Δ HCO_3 to detect triple acid base disturbances

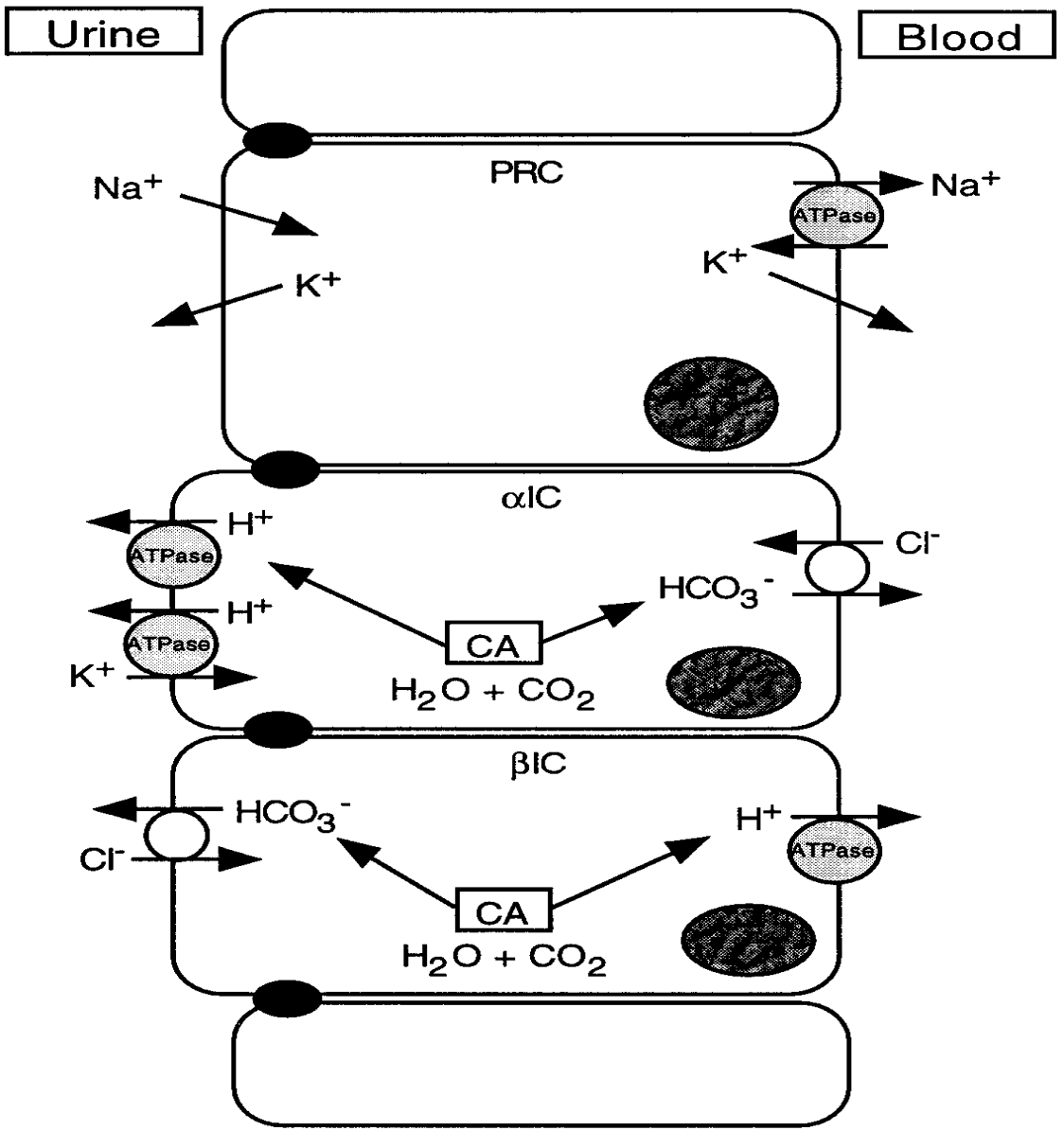
Adverse effects of severe acidemia

Adrogue and Madias NEJM 1998;338:26-34

- 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

(U-B)pCO_2 in alkaline urine

- To test the ability to secrete H + with a favorable pH gradient
- Secreted H+ titrates HCO_3- and produces H_2CO_3
- No carbonic anhydrase → slow dehydration of H_2CO_3
- Thickness of urothelium prevents CO_2 backdiffusion
- Gradient of pCO_2 between urine and blood proportional to acid secretion
- U pCO_2 > 70 mmHg in alkaline urine and (U-B) pCOé > 30 mmHg


Urine
Blood
PRC
Na+
K+
Na+
ATPase
K+
αIC
H+
ATPase
H+
ATPase
K+
Cl-
HCO3-
CA
H2O + CO2
βIC
HCO3-
Cl-
H+
ATPase
CA
H2O + CO2

dRTA with normal (U-B) pCO2

- **Amphotericine B** induced acidosis : « leaky » collecting duct unable to maintain ph gradient

- **Mistargeting** of Anion Exchanger 1

Adverse effects of severe alkalemia

Adrogue and Madias NEJM 1998; 338: 107-111

- 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

The crucial role of Cl depletion

- Cl repletion corrects alkalosis whether Cl is given as NaCl or KCl
- Potential mechanism:

1.volume contraction

2. Stimulation of RAA system

3. Direct tubular effect of chloride

Evidence for the direct role of Cl

- Volume expansion with albumin, no effect
- PD with high HCO_3 solutions : Cl corrects alkalosis despite persistent volume contraction
- Micropuncture experiments : correction in the collecting duct