Urinary System: Renal Physiology for Medical Students, L11-12

Chapter 30: Acid-Base Regulation in the Kidney

Reference: Guyton & Hall, Jordanian first edition

Dr. Ebaa M. Alzayadneh, PhD.

Email: e.zayadneh@ju.edu.jo

2023

Objectives

- Identify the mechanisms by which the kidney can maintain Acid-Base Balance
- Identify the most important buffers in different body fluids
- Identify the cellular mechanisms of for HCO_3^- reabsorption and Na^+ - H^+ exchange or H+ secretion in the nephron
- Understand the mechanism of renal compensations for

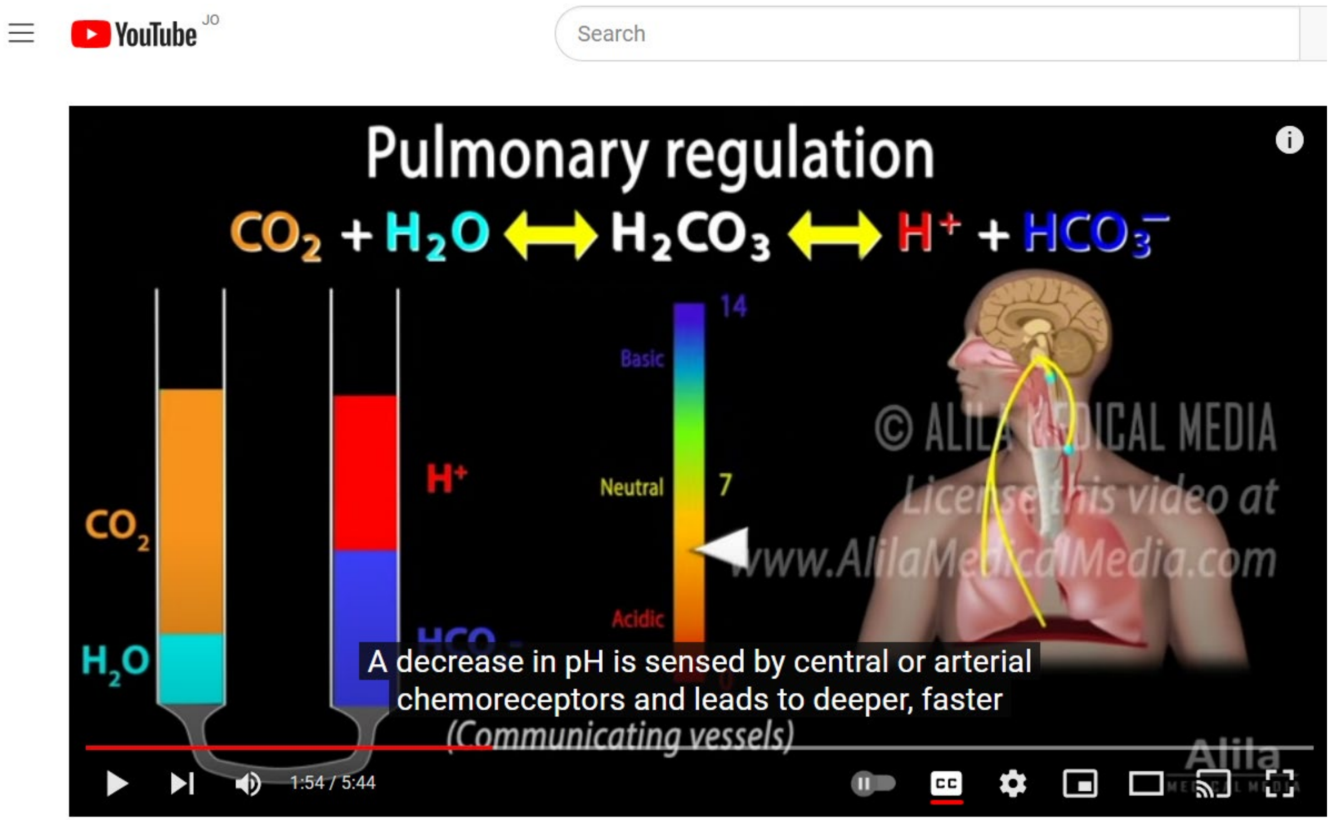
Acid-Base Disorders.

- To be able to determine the type of acid-base imbalance from given lab results and figure out the compensatory changes.
- To know how to use “Anion Gap” as a Diagnostic Tool for Metabolic Acidosis
- Identify main clinical conditions that are accompanied with acid-base imbalance

Audio-Visual Aid

- Please watch this video to help introducing you to the topic of this lecture

[Acid Base Balance, Animation. - YouTube]



A decrease in pH is sensed by central or arterial chemoreceptors and leads to deeper, faster

Acid Base Balance, Animation.

Mechanisms of Hydrogen Ion Regulation

$[H^+]$ is precisely regulated at 3-5 x 10 $^{-8}$ moles/L
(pH range 7.2 -7.4)

1. Body fluid chemical buffers (rapid but temporary)

- bicarbonate	- ammonia
- proteins	- phosphate

2. Lungs (rapid, eliminates CO_2)

$\uparrow [H^+] \longrightarrow \uparrow$ ventilation $\longrightarrow \uparrow CO_2$ loss

3. Kidneys (slow, powerful); eliminates non-volatile acids
   - secretes H^+
   - reabsorbs HCO_3^-
   - generates new HCO_3^-

Buffer Systems in the Body

Bicarbonate : most important ECF buffer

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

Phosphate : important renal tubular buffer

$$HPO_4^{--} + H^+ \longleftrightarrow H_2PO_4^-$$

Ammonia : important renal tubular buffer

$$NH_3 + H^+ \longleftrightarrow NH_4^+$$

Proteins : important intracellular buffers

$$H^+ + Hb \longleftrightarrow HHb$$

(60-70% of buffering is in the cells)

Importance of Buffer Systems

Normal H^+ concentration = 0.00004 mmol/L

Amount of non-volatile acid produced
~ 60-80 mmol/day

80 mmol /42 L = 1.9 mmol/L

= 47,500 times > normal H^+ concentration

PH ----6.8-8 lives for hours

Bicarbonate Buffer System

$$H_2O + CO_2 \xleftrightarrow{\text{carbonic anhydrase}} H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

$$pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

$\alpha = 0.03$

$pK = 6.1$

Effectiveness of buffer system depends on:

- concentration of reactants
- pK of system and pH of body fluids

Titration curve for bicarbonate buffer system.

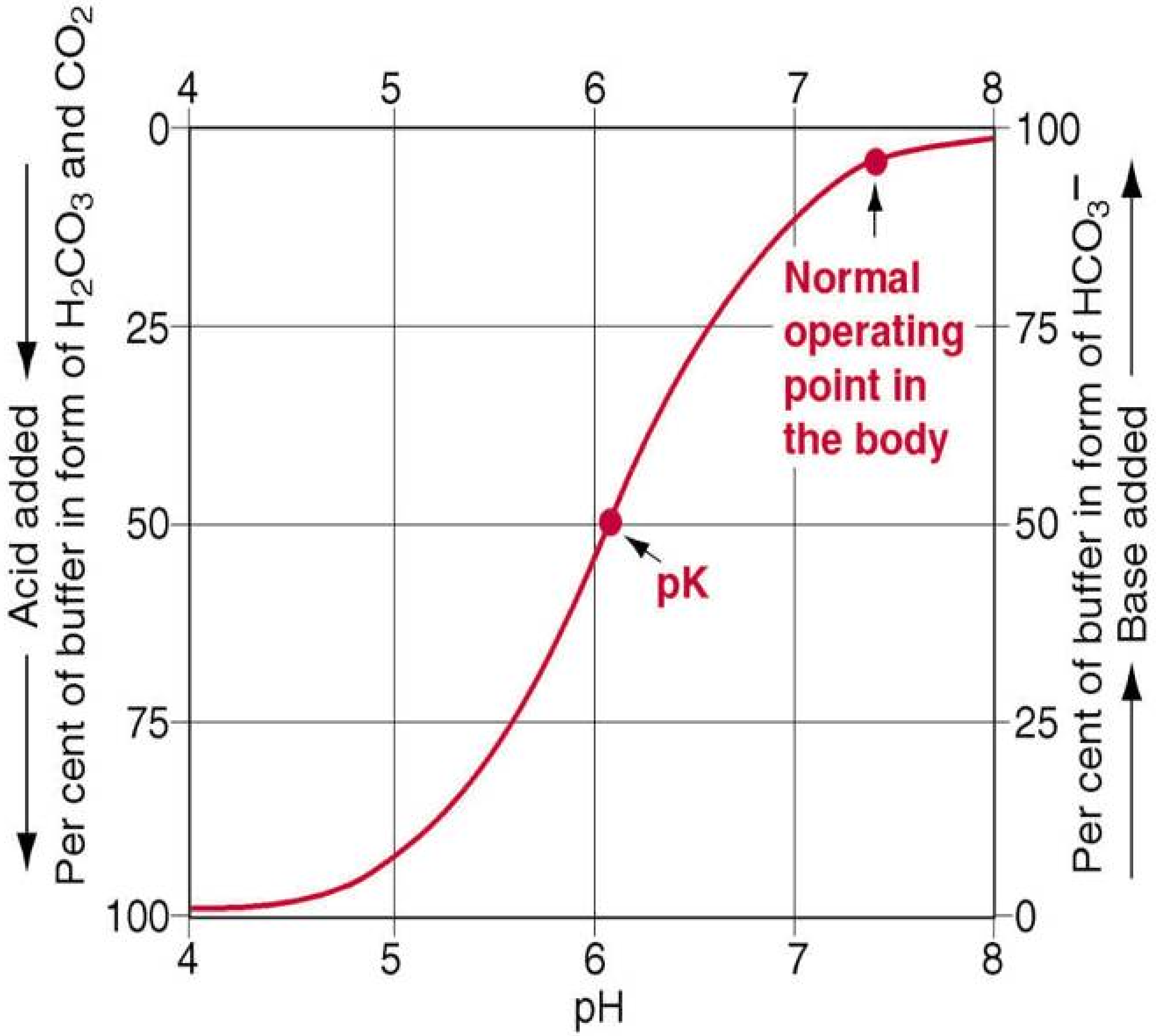


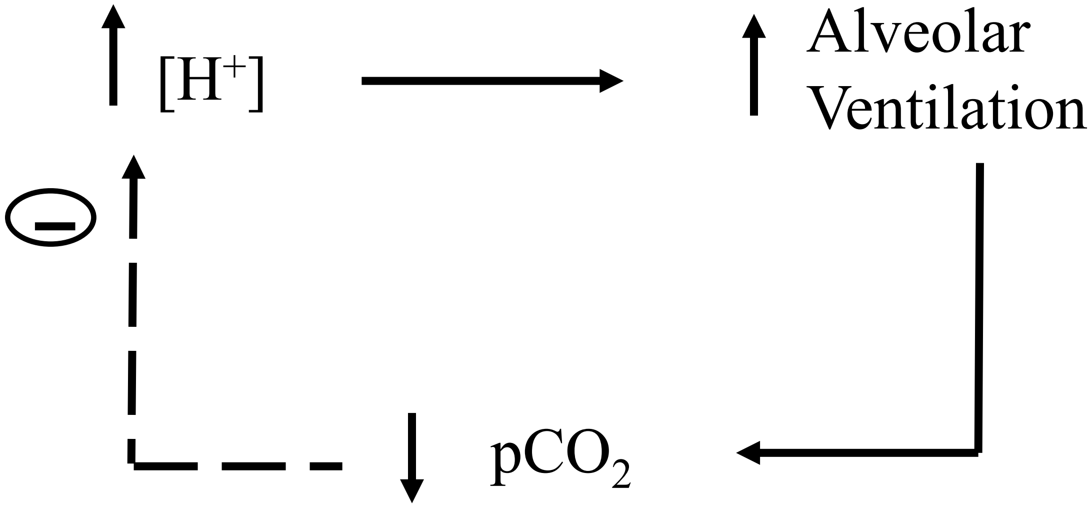
Figure 30-1.

Bicarbonate Buffer System

Is the most important buffer in extracellular fluid even though the concentration of the components are low and pK of the system is 6.1, which is not very close to normal extracellular fluid pH (7.4).

Reason: the components of the system (CO_2 and HCO_3^-) are closely regulated by the lungs and the kidneys

Respiratory Regulation of Acid-Base Balance



↑ $[H^+]$

↑ Alveolar Ventilation

↓ pCO_2

⊖

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

Feedback Gain = 1.0 to 3.0
(corrects 50 to 75 %)

Renal Regulation of Acid-Base Balance

- Kidneys eliminate non-volatile acids (H_2SO_4, H_3PO_4) (~ 80 mmol/day)
- Filtration of HCO_3^- (~ 4320 mmol/day)
- Secretion of H^+ (~ 4400 mmol/day)
- Reabsorption of HCO_3^- (~ 4319 mmol/day)
- Production of new HCO_3^- (~ 80 mmol/day)
- Excretion of HCO_3^- (1 mmol/day)

Kidneys conserve HCO_3^- and excrete acidic
or basic urine depending on body needs

Reabsorption of bicarbonate (and H^+ secretion) in different segments of renal tubule.

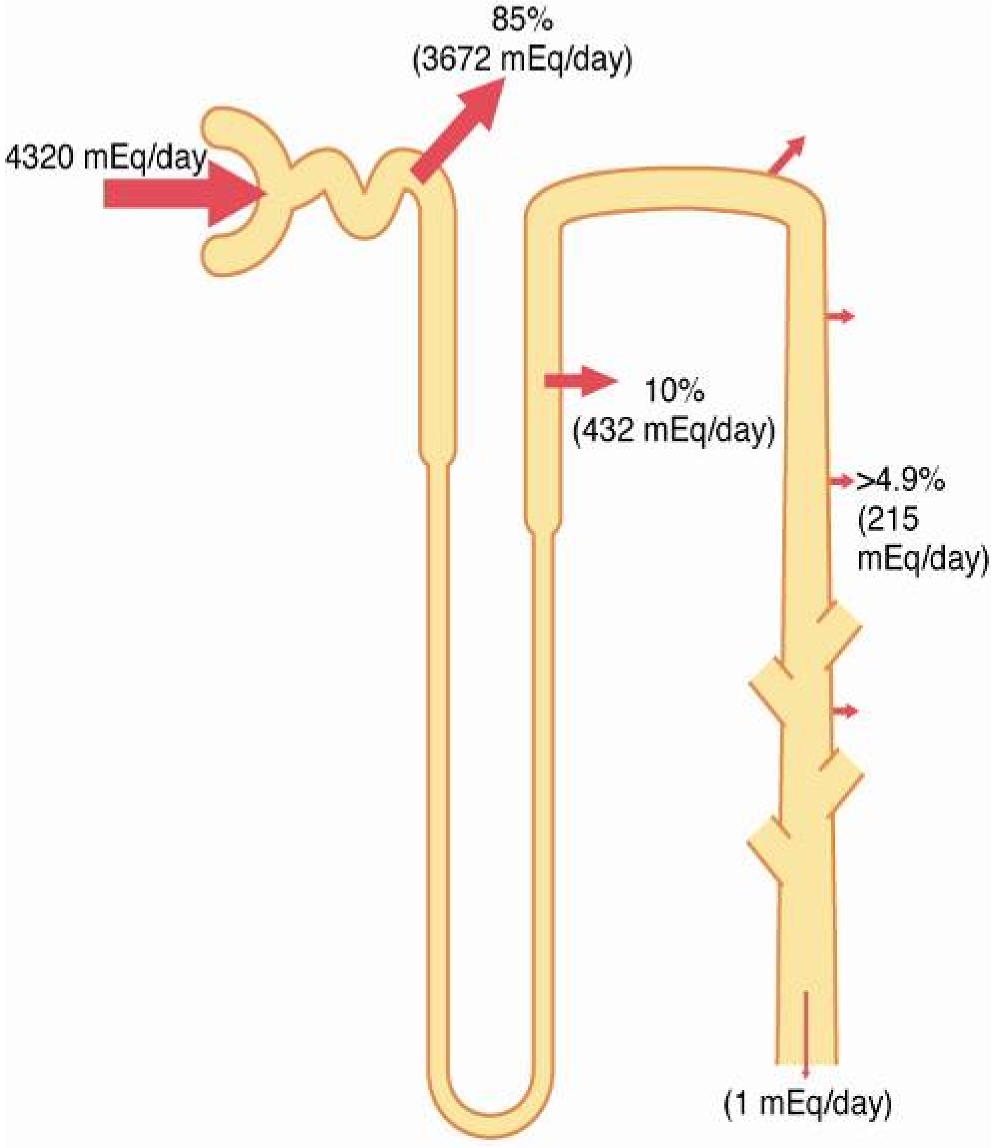
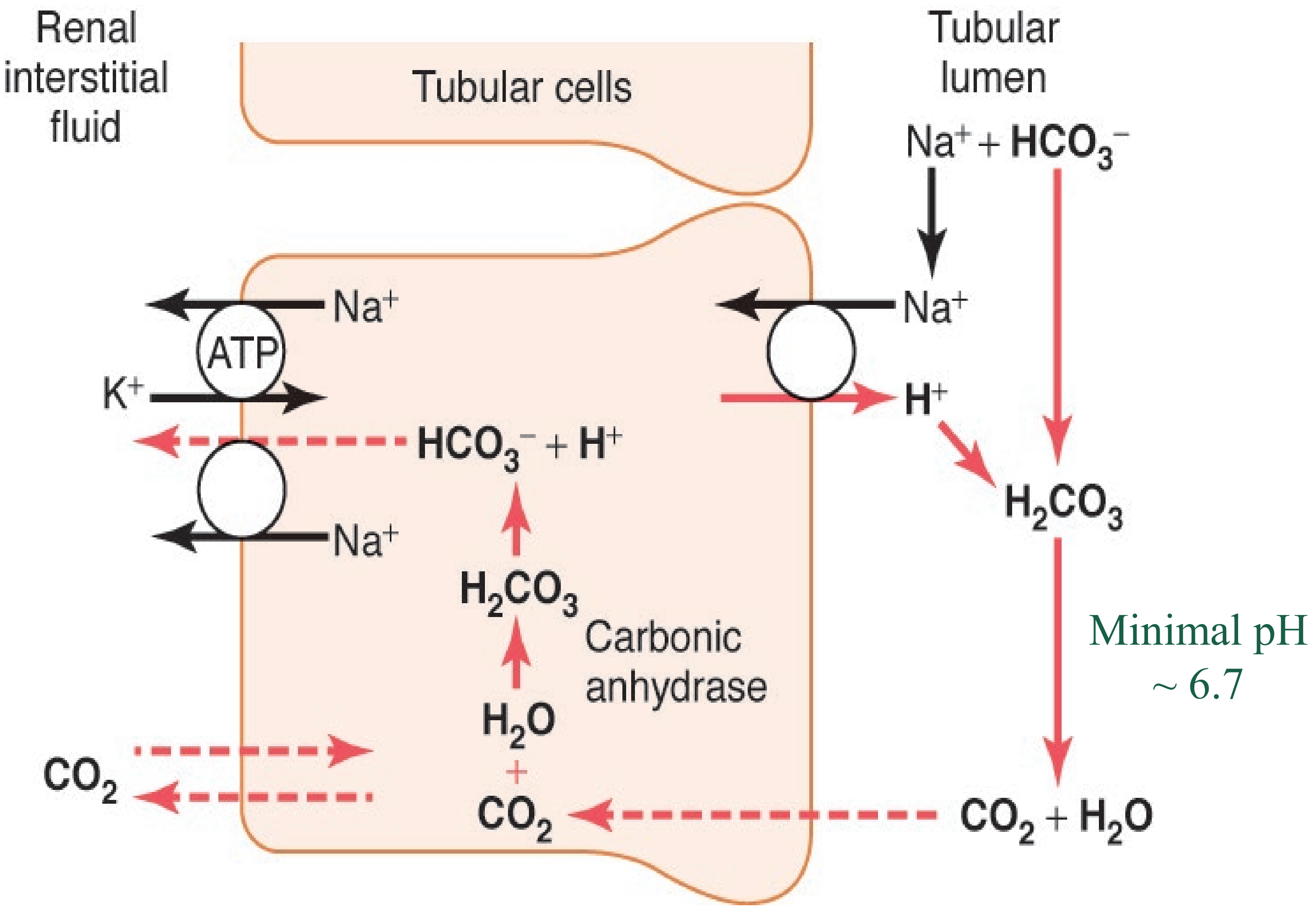


Figure 30-4.

Key point:
For each HCO_3^- reabsorbed, there must be a H^+ secreted

Mechanisms for HCO_3^- reabsorption and Na^+ - H^+ exchange in proximal tubule and thick loop of Henle



Minimal pH ~ 6.7

Figure 30-5.

HCO_3^- reabsorption and H^+ secretion in intercalated cells of late distal and collecting tubules

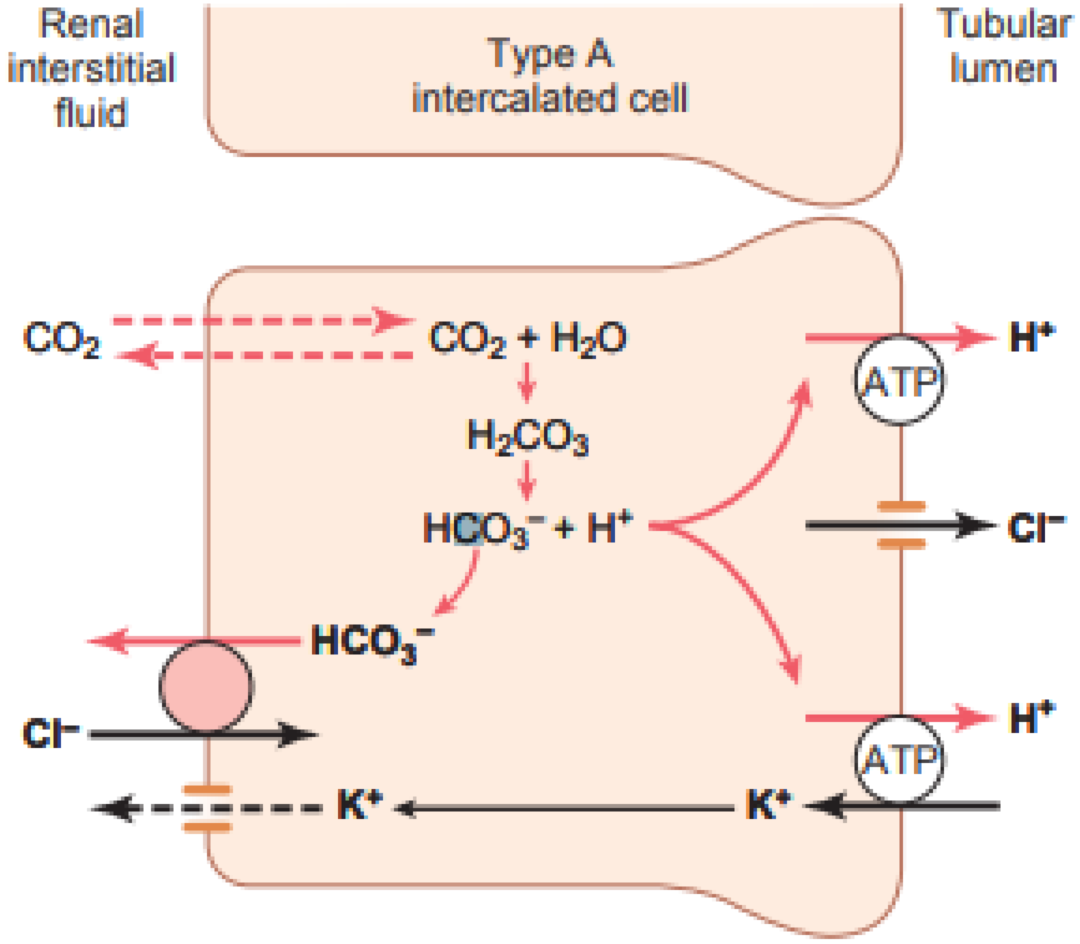


Figure 30-6.

Minimal pH ~4.5

Renal Regulation of Acid-Base Balance

- Kidneys eliminate non-volatile acids (H_2SO_4, H_3PO_4) (~ 80 mmol/day)
- Filtration of HCO_3^- (~ 4320 mmol/day)
- Secretion of H^+ (~ 4400 mmol/day)
- Reabsorption of HCO_3^- (~ 4319 mmol/day)
- Production of new HCO_3^- (~ 80 mmol/day)
- Excretion of HCO_3^- (1 mmol/day)

Kidneys conserve HCO_3^- and excrete acidic or basic urine depending on body needs

Regulation of H^+ secretion

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

$$pH = pK + \log \frac{HCO_3^-}{\alpha \quad pCO_2}$$

- Increased pCO_2 increases H^+ secretion

  i.e. respiratory acidosis

- Increased extracellular H^+ increases H^+ secretion

  i.e. metabolic or respiratory acidosis

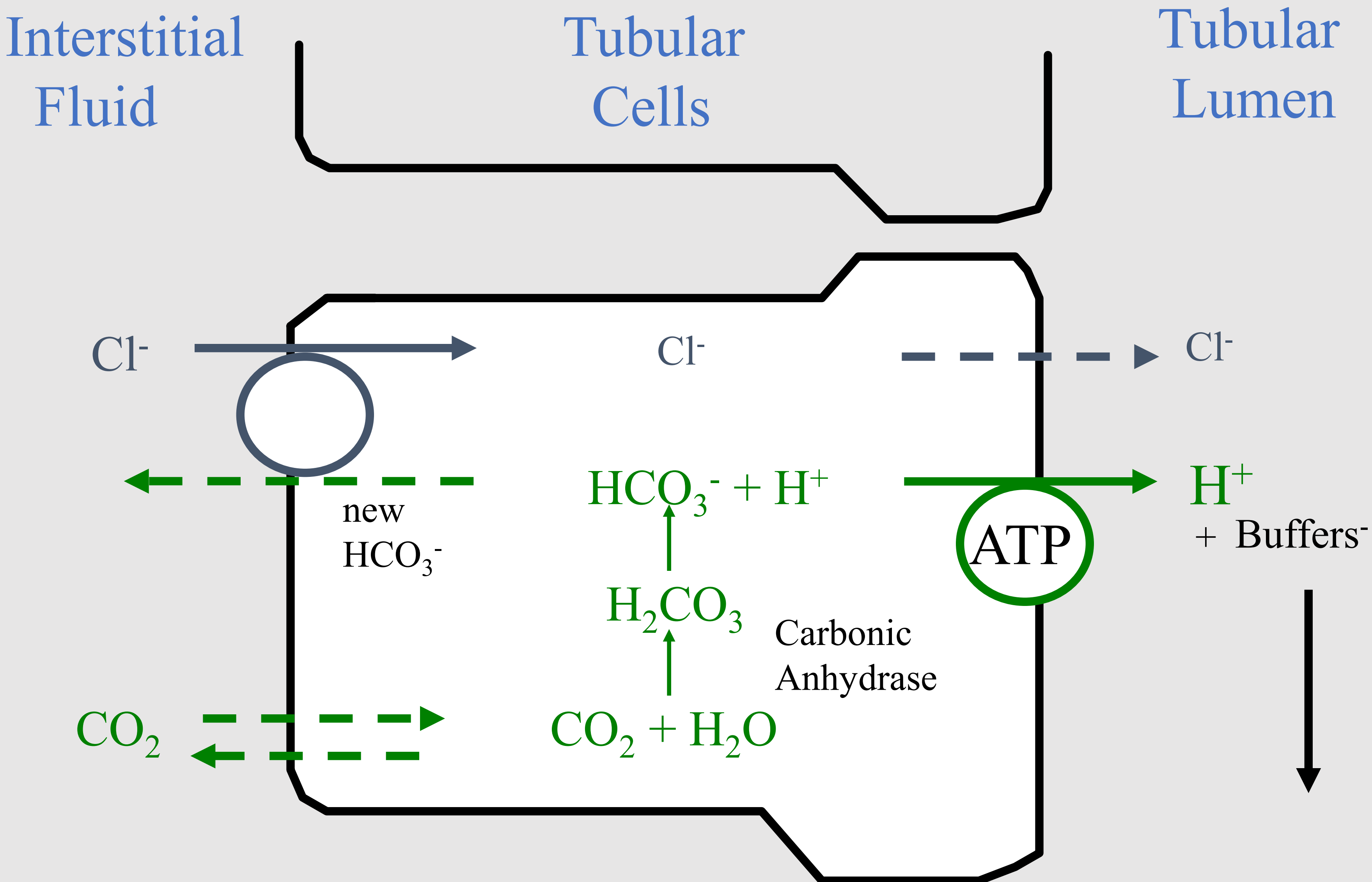
- Increased tubular fluid buffers increases H^+ secretion

  i.e. metabolic or respiratory acidosis

Renal Compensations for Acid-Base Disorders

- Acidosis:
  - increased H^+ secretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-
- Alkalosis:
  - decreased H^+ secretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine

In acidosis all HCO_3^- is titrated and excess H^+ in tubule is buffered



Importance of Renal Tubular Buffers

Minimum urine pH = 4.5

$= 10^{-4.5}$

$= 3 \text{ x } 10^{-5}$ moles/L

i.e. the maximal $[H^+]$ of urine is 0.03 mmol/L

Yet, the kidneys must excrete, under normal conditions, at least 60 mmol non-volatile acids each day. To excrete this as free H^+ would require :

$$\frac{60 \text{ mmol}}{.03\text{mmol/L}} = 2000 \text{ L per day !!!}$$

Buffering of secreted H^+ by filtered phosphate ($NaHPO_4^-$) and generation of "new" HCO_3^-

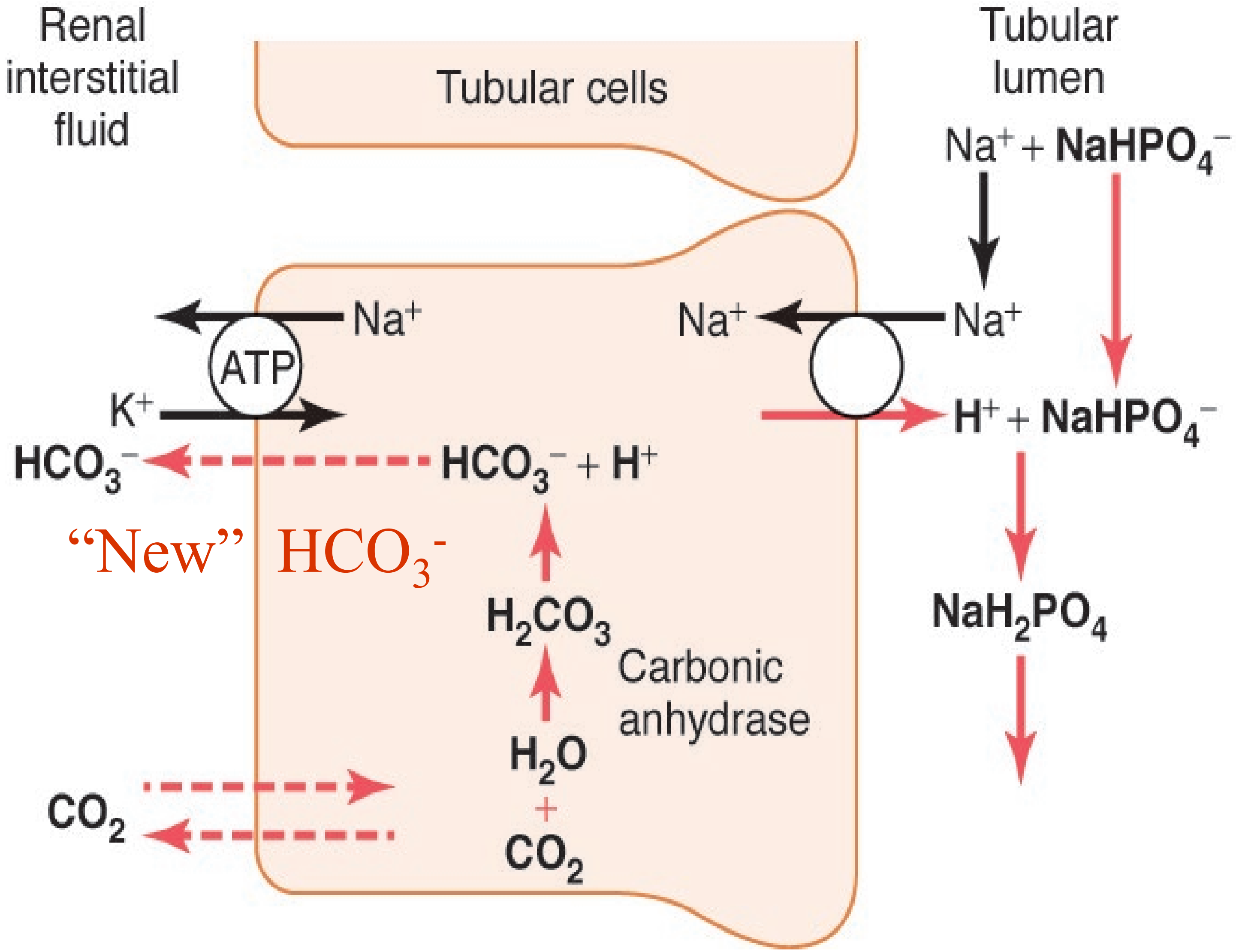


Figure 30-7.

Phosphate as a Tubular Fluid Buffer

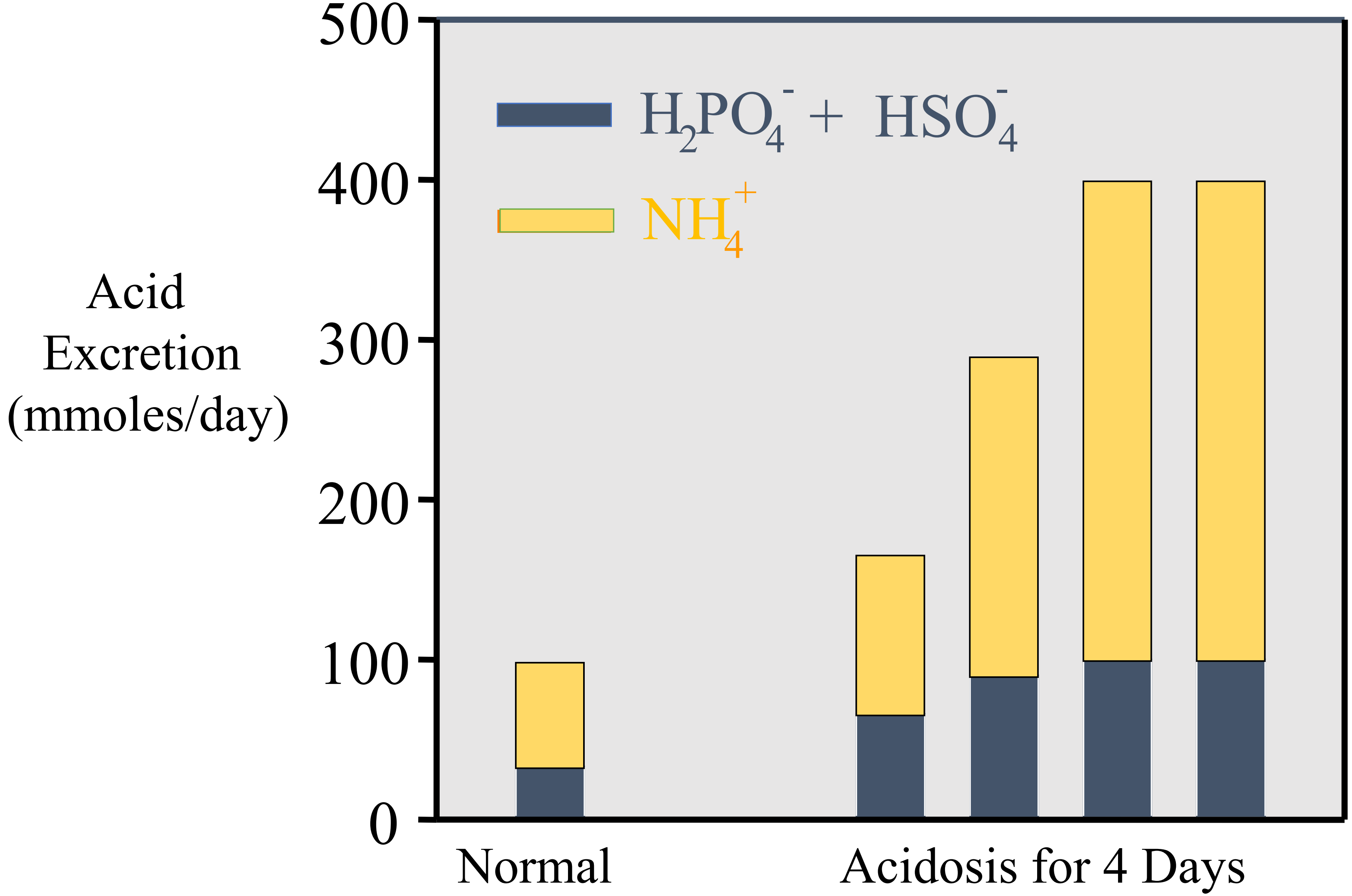
There is a high concentration of phosphate in the tubular fluid; pK = 6.8

Phosphate normally buffers about 30 mmol/day H^+ (about 100 mmol/day phosphate is filtered but 70 % is reabsorbed)

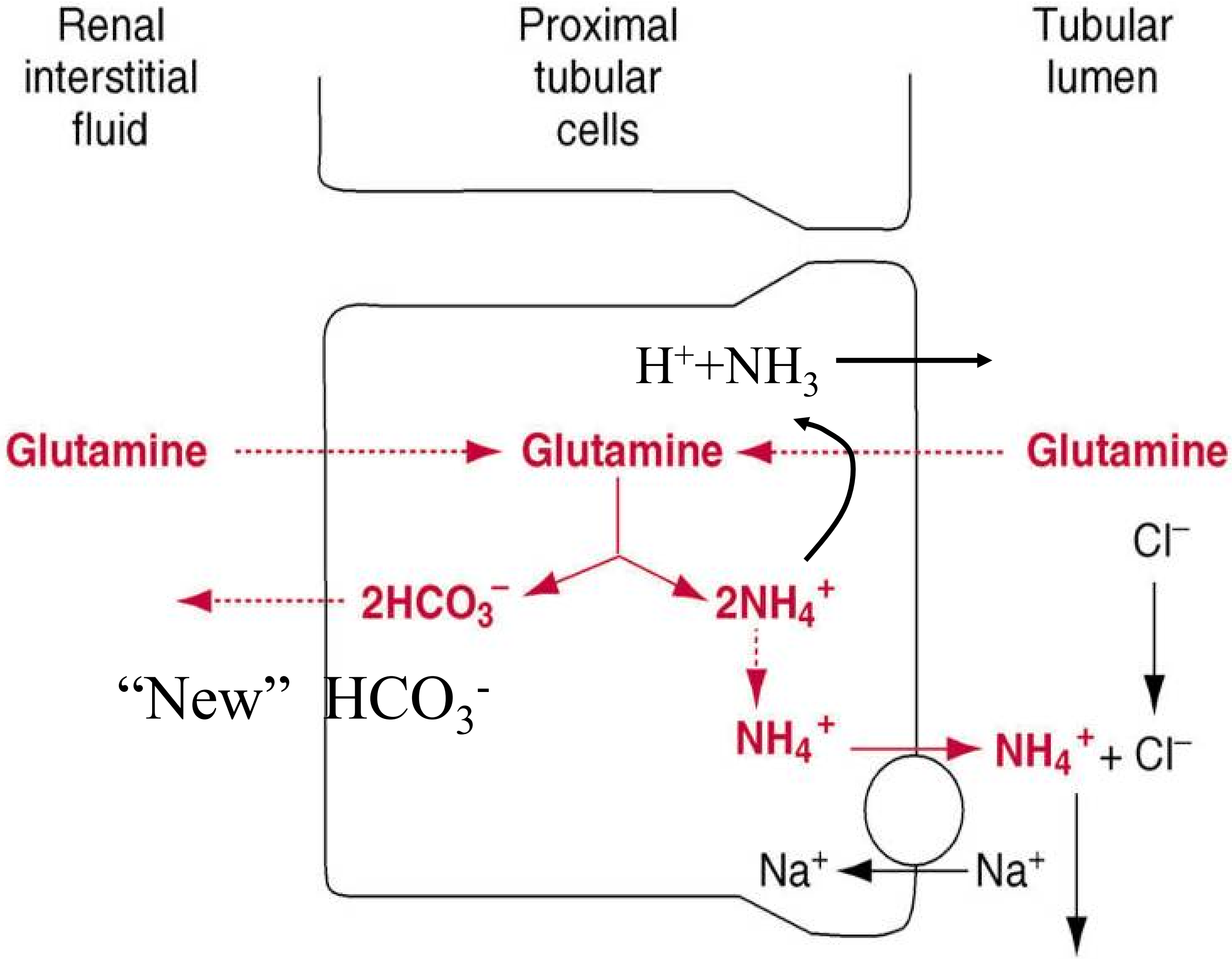
Phosphate buffering capacity does not change much with acid-base disturbances (phosphate is not the major tubular buffer in chronic acidosis

$$NaHPO_4^- + H^+ \longrightarrow NaH_2PO_4$$

Phosphate and Ammonium Buffering In Chronic Acidosis



Production and secretion of NH_4^+ and HCO_3^- by proximal, thick loop of Henle, and distal tubules



Renal interstitial fluid

Proximal tubular cells

Tubular lumen

$H^+ + NH_3$

Glutamine

Glutamine

Glutamine

Cl^-

$2HCO_3^-$

$2NH_4^+$

“New” HCO_3^-

NH_4^+

$NH_4^+ + Cl^-$

Na^+

Na^+

Figure 30-8.

Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules.

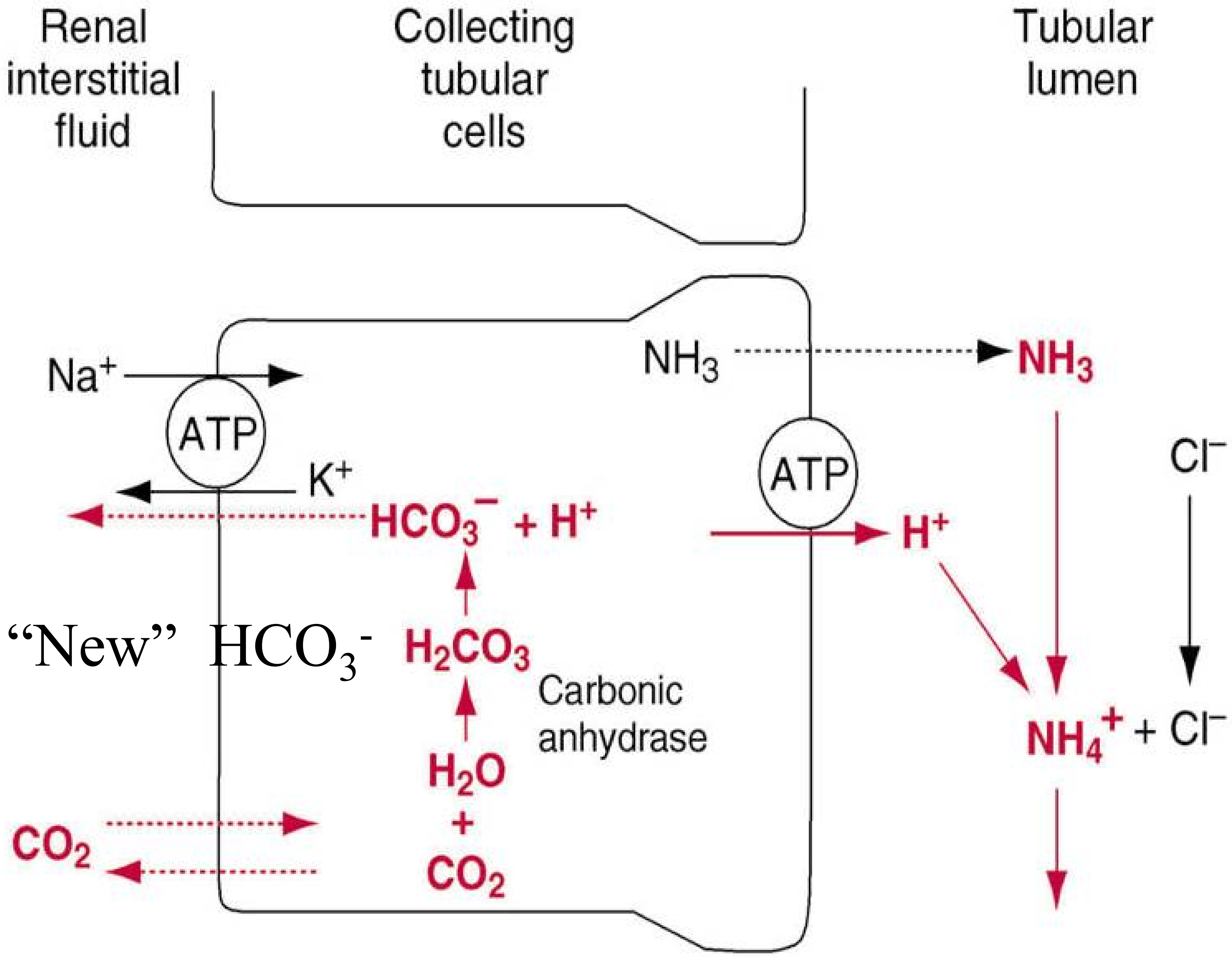


Figure 30-9.

Quantification of Normal Renal Acid-Base Regulation

Total H^+ secretion

= 4320 mEq of H+ secreted (HCO3)+ 60 mEq of H+ non-volatile= 4380

Total H^+ secretion = 4380 mmol/day

= HCO_3^- reabsorption (4320 mmol/d)

+ titratable acid ($NaHPO_4^-$) (30 mmol/d)

+ NH_4^+ excretion (30 mmol/d)

Net H+ excretion=

H+ excreted by buffers not bicarbonate(=new bicarb) - newH+ added to blood(=HCO3- excreted)

Net H^+ excretion = 59 mmol/day

= titratable acid (30 mmol/d)

+ NH_4^+ excretion (30 mmol/d)

- HCO_3^- excretion (1 mmol/d)(or new H to blood)

Normal Renal Acid-Base Regulation

Net addition of HCO_3^- to body
(i.e. net loss of H^+)

Titratable acid = 30 mmol/day
+ NH_4^+ excretion = 30 mmol/day
- HCO_3^- excretion = 1 mmol/day
Total = 59 mmol/day

Renal Compensation for Acidosis

Increased addition of HCO_3^- to body by kidneys
(increased H^+ loss by kidneys)

Titratable acid = 35 mmol/day (small increase)
NH_4^+ excretion = 165 mmol/day (increased)
HCO_3^- excretion = 0 mmol/day (decreased)
Total = 200 mmol/day

This can increase to as high as 500 mmol/day

Renal Compensation for Alkalosis

Net loss of HCO_3^- from body
(i.e. decreased H^+ loss by kidneys)

Titratable acid = 0 mmol/day (decreased)
NH_4^+ excretion = 0 mmol/day (decreased)
HCO_3^- excretion = 80 mmol/day (increased)
Total = 80 mmol/day

HCO_3^- excretion can increase markedly in alkalosis

Classification of Acid-Base Disorders from plasma pH, pCO_2, and HCO_3^-

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

$$pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

Acidosis : $pH < 7.4$

- metabolic : $\downarrow HCO_3^-$
- respiratory : $\uparrow pCO_2$

Alkalosis : $pH > 7.4$

- metabolic : $\uparrow HCO_3^-$
- respiratory : $\downarrow pCO_2$

Clinical
Perspective

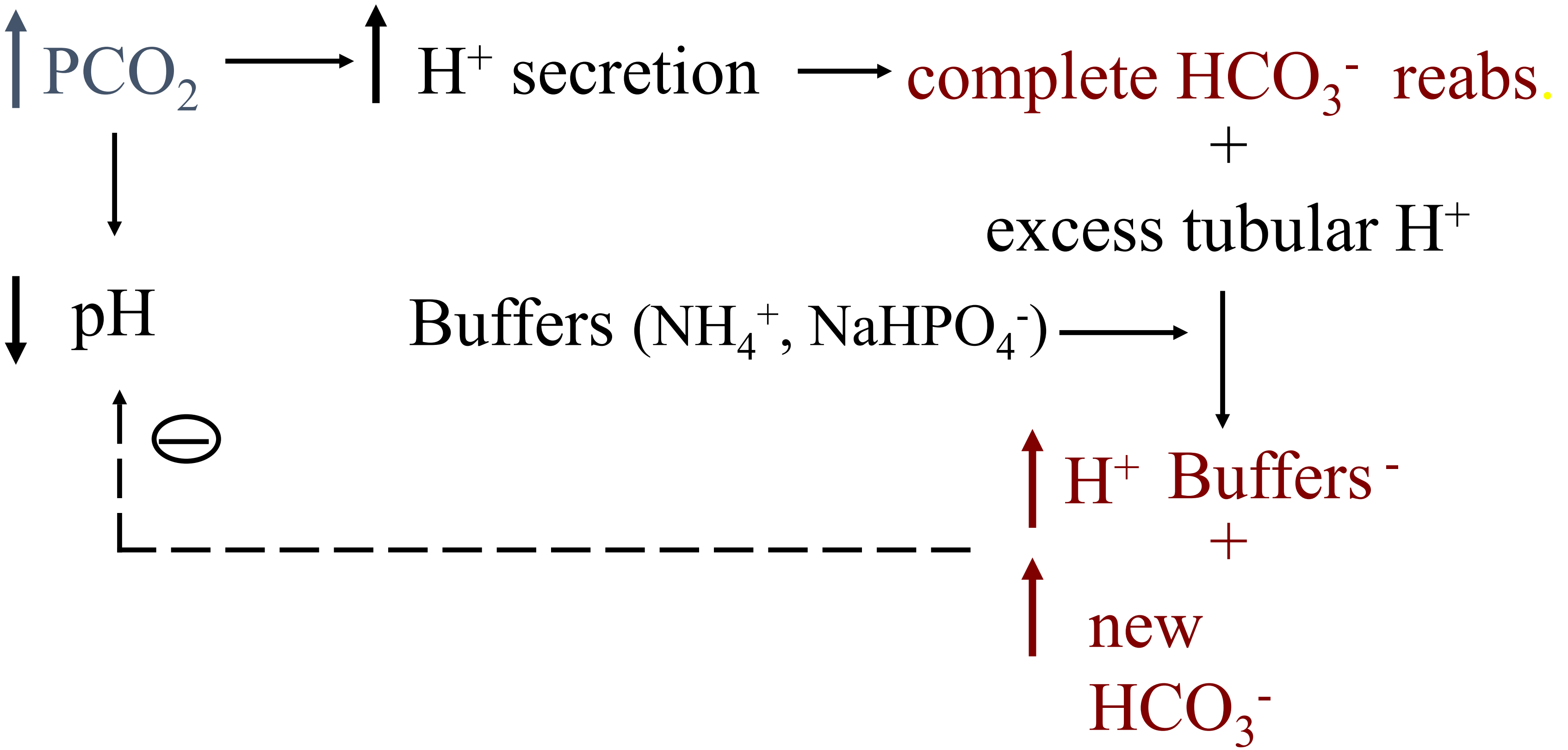
Renal Compensations for Acid-Base Disorders

- Acidosis:
  - increased H^+ excretion
  - increased HCO_3^- reabsorption
  - production of new HCO_3^-
- Alkalosis:
  - decreased H^+ excretion
  - decreased HCO_3^- reabsorption
  - loss of HCO_3^- in urine

Renal Responses to Respiratory Acidosis

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

Respiratory acidosis : ↓ pH ↑ pCO_2 ↑ HCO_3^-



↑ PCO_2 → ↑ H^+ secretion → complete HCO_3^- reabs.

\+

excess tubular H^+

↓ pH

Buffers (NH_4^+, $NaHPO_4^-$) →

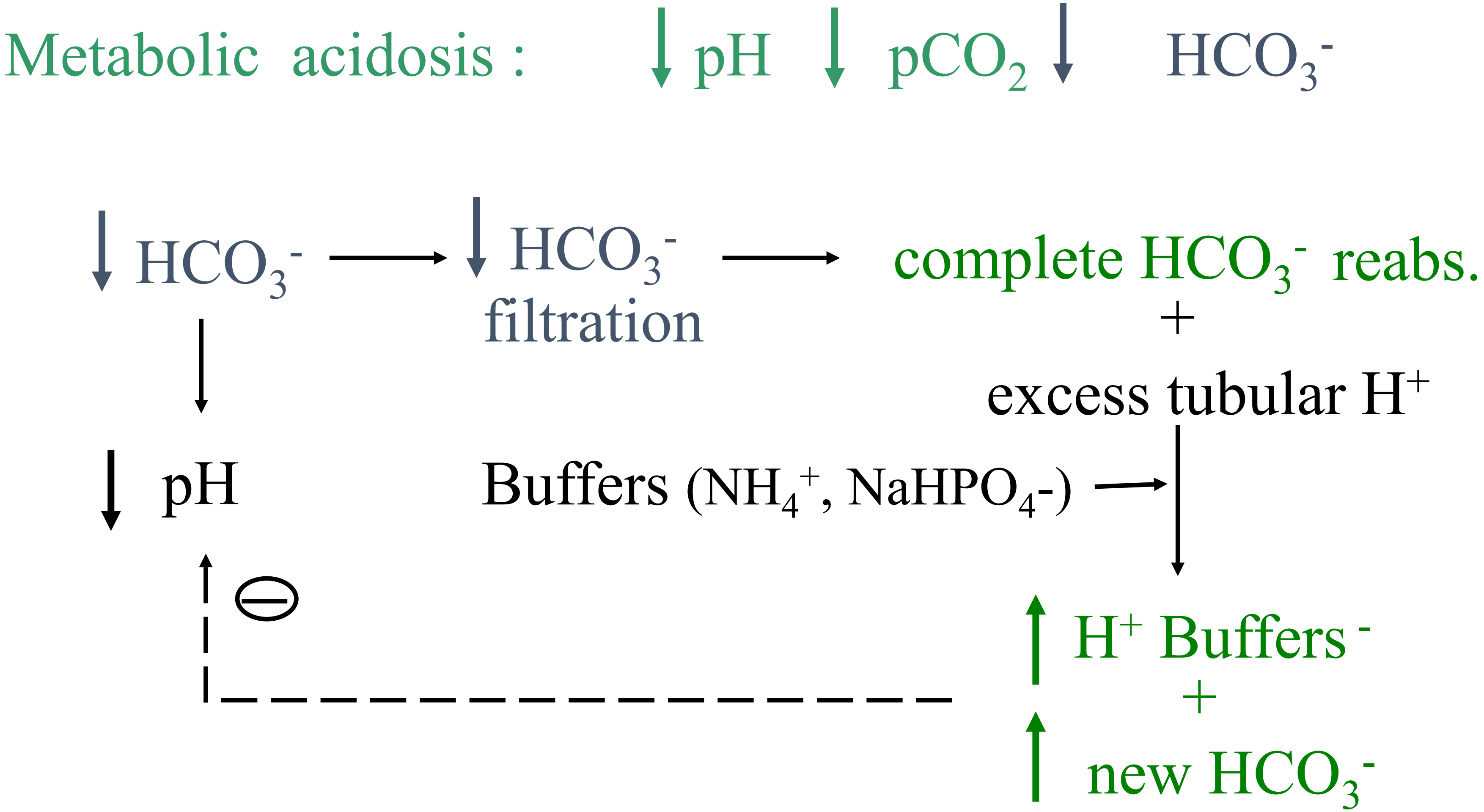
↑ H^+ Buffers $^-$

\+

↑ new HCO_3^-

⊖

Renal Responses to Metabolic Acidosis



Metabolic acidosis : ↓ pH ↓ pCO_2 ↓ HCO_3^-

↓ HCO_3^- → ↓ HCO_3^- filtration → complete HCO_3^- reabs.
+
excess tubular H^+

↓ pH

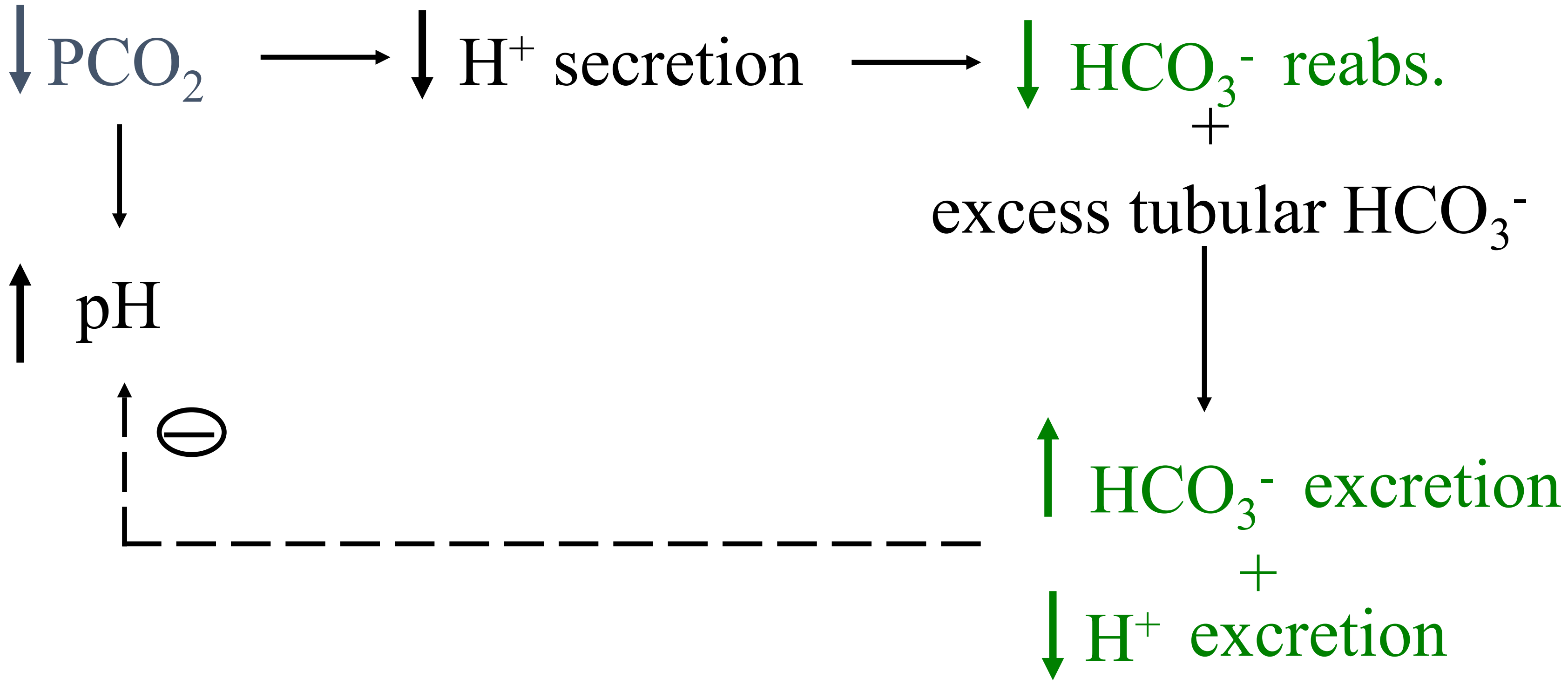
Buffers (NH_4^+, $NaHPO_4$-) →

⊖

↑ H^+ Buffers$^-$
+
↑ new HCO_3^-

Renal Responses to Respiratory Alkalosis

Respiratory alkalosis : ↑ pH ↓ pCO_2 ↓ HCO_3^-



↓ PCO_2 → ↓ H^+ secretion → ↓ HCO_3^- reabs.

+

excess tubular HCO_3^-

↓

↑ HCO_3^- excretion

+

↓ H^+ excretion

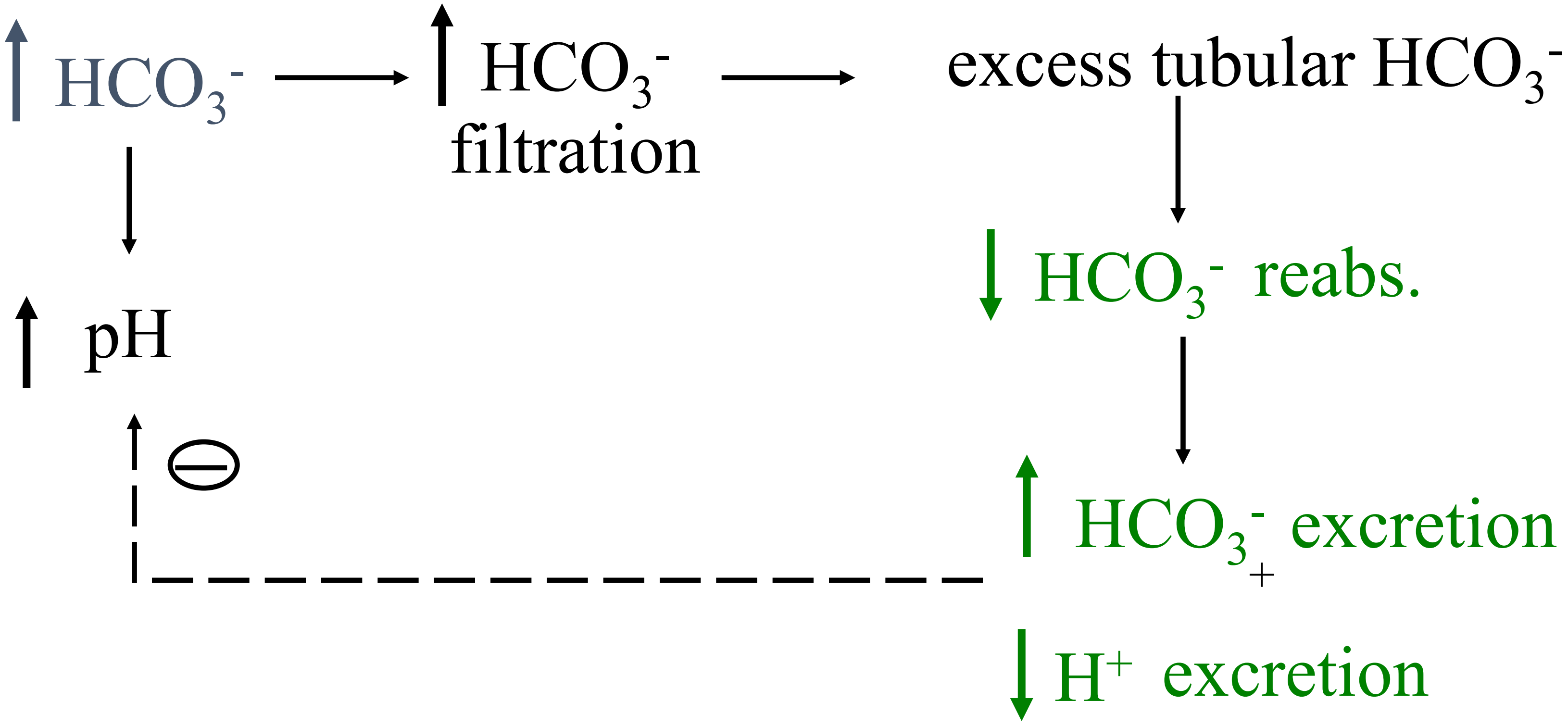
↓

↑ pH

⊖

Renal Responses to Metabolic Alkalosis

Metabolic alkalosis : ↑ pH ↑ pCO_2 ↑ HCO_3^-



↑ HCO_3^- → ↑ HCO_3^- filtration → excess tubular HCO_3^-

↑ pH

⊖

↓ HCO_3^- reabs.

↑ HCO_3^- excretion

+

↓ H^+ excretion

Question

The following data were taken from a patient:

urine volume = 1.0 liter/day
urine HCO_3^- concentration = 2 mmol/liter
urine NH_4^+ concentration = 15 mmol/liter
urine titratable acid = 10 mmol/liter

- What is the daily net acid excretion in this patient ?
- What is the daily net rate of HCO_3^- addition to the extracellular fluids ?

Question

The following data were taken from a patient:

urine volume = 1.0 liter/day
urine HCO_3^- concentration = 2 mmol/liter
urine NH_4^+ concentration = 15 mmol/liter
urine titratable acid = 10 mmol/liter

net acid excretion = Titr. Acid + NH_4^+ excret - HCO_3^-
= (10 x 1) + (15 x 1) - (1 x 2)
= 23 mmol/day

net rate of HCO_3^- addition to body = 23 mmol/day

Classification of Acid-Base Disorders from plasma pH, pCO_2, and HCO_3^-

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

$$pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

Acidosis : $pH < 7.4$

- metabolic: $\downarrow HCO_3^-$
- respiratory: $\uparrow pCO_2$

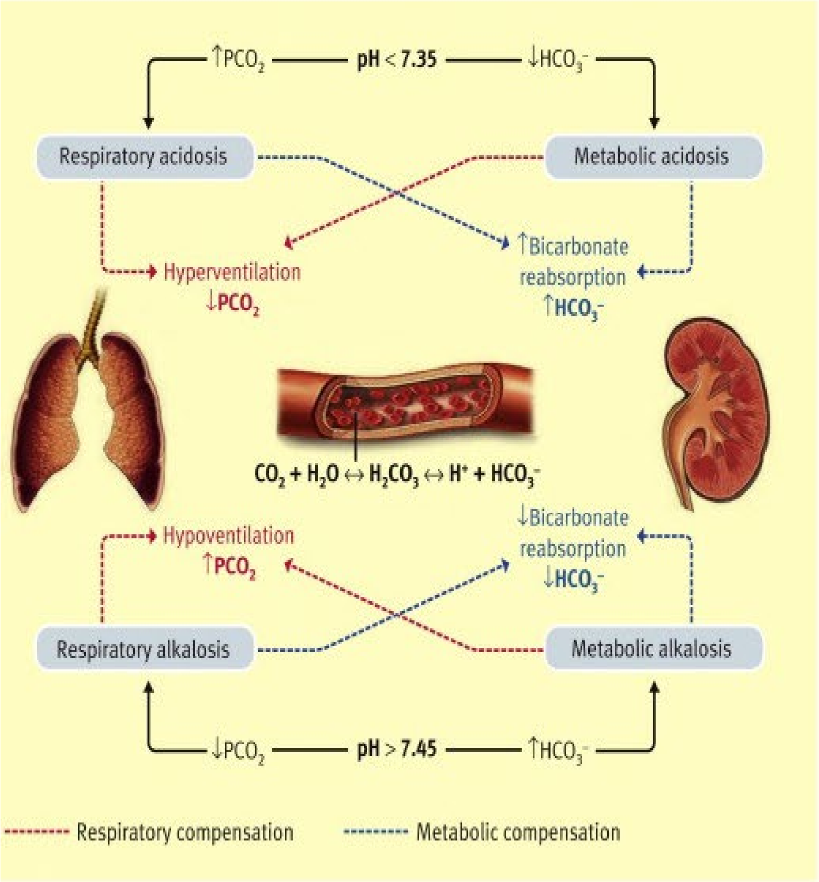
Alkalosis : $pH > 7.4$

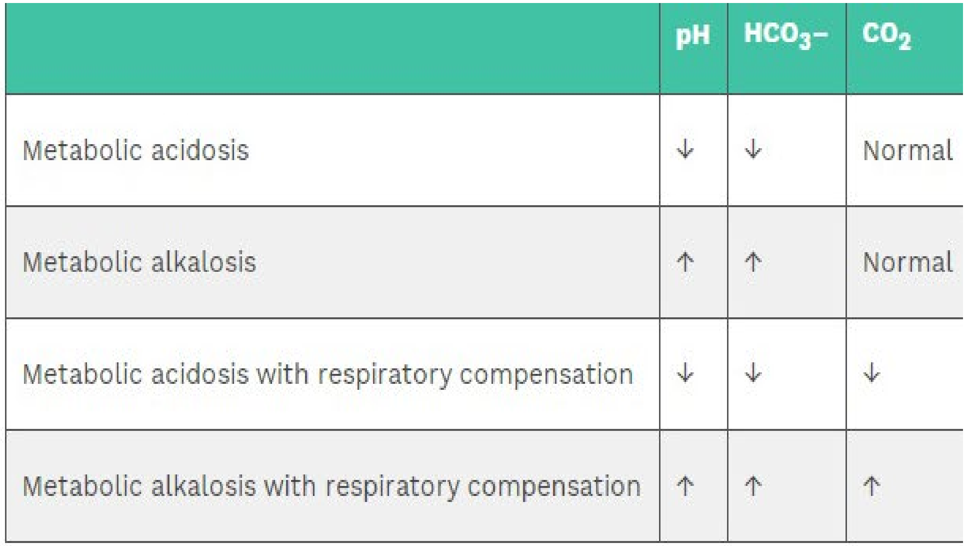
- metabolic: $\uparrow HCO_3^-$
- respiratory: $\downarrow pCO_2$

Clinical
Perspective

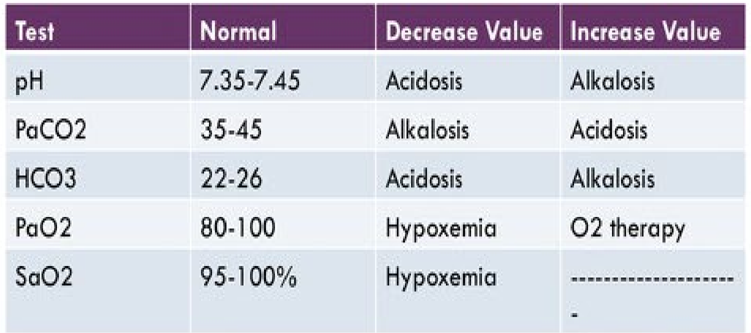
Classification of Acid-Base Disturbances

	Plasma			
Disturbance	pH	HCO_3^-	pCO_2	Compensation
metabolic acidosis	↓	↓	↓	↑ ventilation ↑ renal HCO_3 production
respiratory acidosis	↓	↑	↑	↑ renal HCO_3 production
metabolic alkalosis	↑	↑	↑	↓ ventilation ↑ renal HCO_3 excretion
respiratory alkalosis	↑	↓	↓	↑ renal HCO_3 excretion

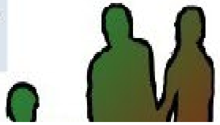




	pH	HCO_3-	CO_2
Metabolic acidosis	↓	↓	Normal
Metabolic alkalosis	↑	↑	Normal
Metabolic acidosis with respiratory compensation	↓	↓	↓
Metabolic alkalosis with respiratory compensation	↑	↑	↑



Test	Normal	Decrease Value	Increase Value
pH	7.35-7.45	Acidosis	Alkalosis
PaCO2	35-45	Alkalosis	Acidosis
HCO3	22-26	Acidosis	Alkalosis
PaO2	80-100	Hypoxemia	O2 therapy
SaO2	95-100%	Hypoxemia	------------------- -



Question

A plasma sample revealed the following values in a patient: norm for PCO2 35-45, HCO3 22-26

$pH = 7.12$

$PCO_2 = 50$

$HCO_3^- = 18$

diagnose this patient's acid-base status :

acidotic or alkalotic ? Acidotic

respiratory, metabolic, or both ? Both

Mixed acidosis: metabolic and respiratory acidosis

Mixed Acid-Base Disturbances

Two or more underlying causes of acid-base disorder.

pH= 7.60
pCO_2 = 30 mmHg
plasma HCO_3^- = 29 mmol/L

What is the diagnosis?

Mixed Alkalosis

- Metabolic alkalosis : increased HCO_3^-
- Respiratory alkalosis : decreased pCO_2

Question

A patient presents in the emergency room and the following data are obtained from the clinical labs:

plasma pH= 7.15, HCO_3^- = 8 mmol/L, pCO_2= 24 mmHg

This patient is in a state of:

1. metabolic alkalosis with partial respiratory compensation
2. respiratory alkalosis with partial renal compensation

[✓ 3. metabolic acidosis with partial respiratory compensation]

4. respiratory acidosis with partial renal compensation

Acid-Base Disturbances

- Metabolic Acidosis : ↓ HCO_3^- / pCO2 in plasma

  ↓ (↓ pH, HCO_3^-)

- aspirin poisoning (↑ H^+ intake)
- diabetes mellitus (↑ H^+ production)
- diarrhea (HCO_3^- loss)
- renal tubular acidosis (↓ H^+ secretion, ↓ HCO_3^- reabs.)
- carbonic anhydrase inhibitors (↓ H^+ secretion)

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

$$\downarrow \ pH = pK + \log \frac{HCO_3^-}{\alpha \ pCO_2}$$

Anion Gap as a Diagnostic Tool

In body fluids: total cations = total anions

Cations (mEq/L)	Anions (mEq/L)
Na^+ (142)	Cl^- (108)
	HCO_3^- (24)
Unmeasured	
K^+ (4)	Proteins (17)
Ca^{++} (5)	Phosphate,
Mg^{++} (2)	Sulfate,
	lactate, etc (4)
Total (153)	(153)

Clinical
Perspective

Anion Gap as a Diagnostic Tool

In body fluids: total cations = total anions

$Na^+ = Cl^- + HCO_3^- +$ unmeasured anions

unmeasured anions $= Na^+ - Cl^- - HCO_3^- =$ anion gap

$= 142 - 108 - 24 \qquad = 10$ mEq/L

Normal anion gap = 8 - 16 mEq / L

Clinical
Perspective

Anion Gap in Metabolic Acidosis

- loss of HCO_3^- = normal anion gap

↔ anion gap = Na^+ ↑ - Cl^- ↓ - HCO_3^-

hyperchloremic metabolic acidosis

- ↑ unmeasured anions = ↑ anion gap

↑ anion gap = Na^+ ↔ - Cl^- ↓ - HCO_3-

normochloremic metabolic acidosis

i.e. diabetic ketoacidosis, lactic acidosis, salicylic acid, etc.

Clinical
Perspective

Use of "Anion Gap" as a Diagnostic Tool for Metabolic Acidosis

Increased Anion Gap (normal Cl^-)

- diabetes mellitus (ketoacidosis)
- lactic acidosis
- aspirin (acetysalicylic acid) poisoning
- methanol poisoning
- starvation

Normal Anion Gap (increased Cl^-, hyperchloremia)

- diarrhea
- renal tubular acidosis
- Addison' disease
- carbonic anhydrase inhibitors

Question

Laboratory values for an uncontrolled diabetic patient include the following:

arterial pH = 7.25
Plasma HCO_3^- = 12
Plasma P_{CO_2} = 28
Plasma Cl^- = 102
Plasma Na^+ = 142

Metabolic Acidosis
Respiratory Compensation

What type of acid-base disorder does this patient have?

What is his anion gap ?

Anion gap = 142 - 102 -12 = 28

Question

Which of the following are the most likely causes of his acid-base disorder?

a. diarrhea
[✓ b. diabetes mellitus]
c. Renal tubular acidosis
d. primary aldosteronism

Acid-Base Disturbances

- Respiratory Acidosis : ↓ $HCO_3^- / pCO2$ in plasma

↓ (↑ pH, pCO_2)

- brain damage
- pneumonia
- emphysema
- other lung disorders

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

$$\downarrow \; pH = pK + \log \frac{HCO_3^-}{\alpha \; pCO_2}$$

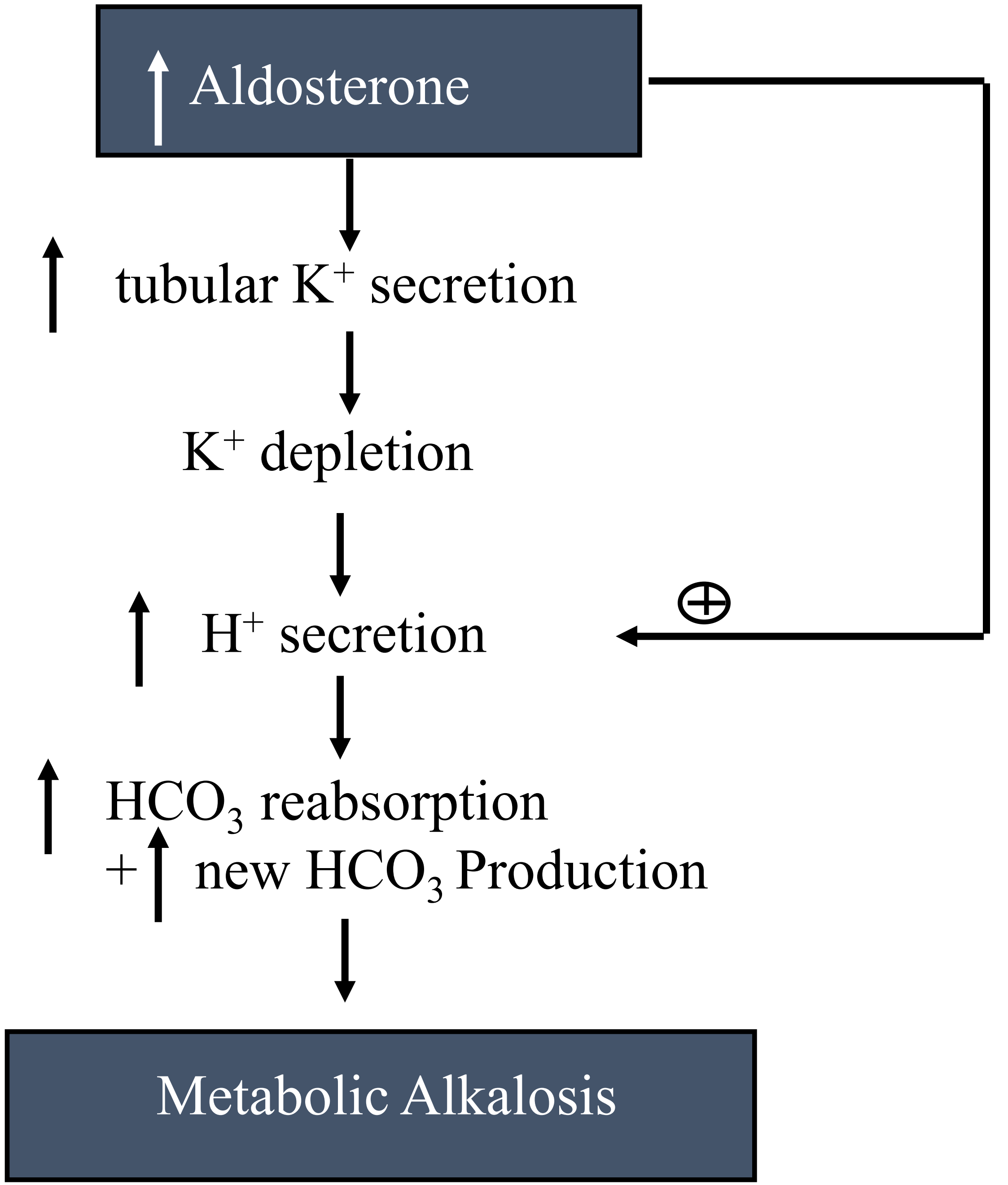
Acid-Base Disturbances

- Metabolic Alkalosis : ↑ HCO_3^- / pCO_2 in plasma
  ↑ (↑pH, HCO_3^-)

  - increased base intake (e.g. $NaHCO_3$)
  - vomiting gastric acid
  - mineralocorticoid excess
  - overuse of diuretics (except carbonic anhydrase inhibitors)

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

$$\uparrow pH = pK + \log \frac{HCO_3^-}{\alpha \ pCO_2}$$



↑ Aldosterone

↑ tubular K^+ secretion

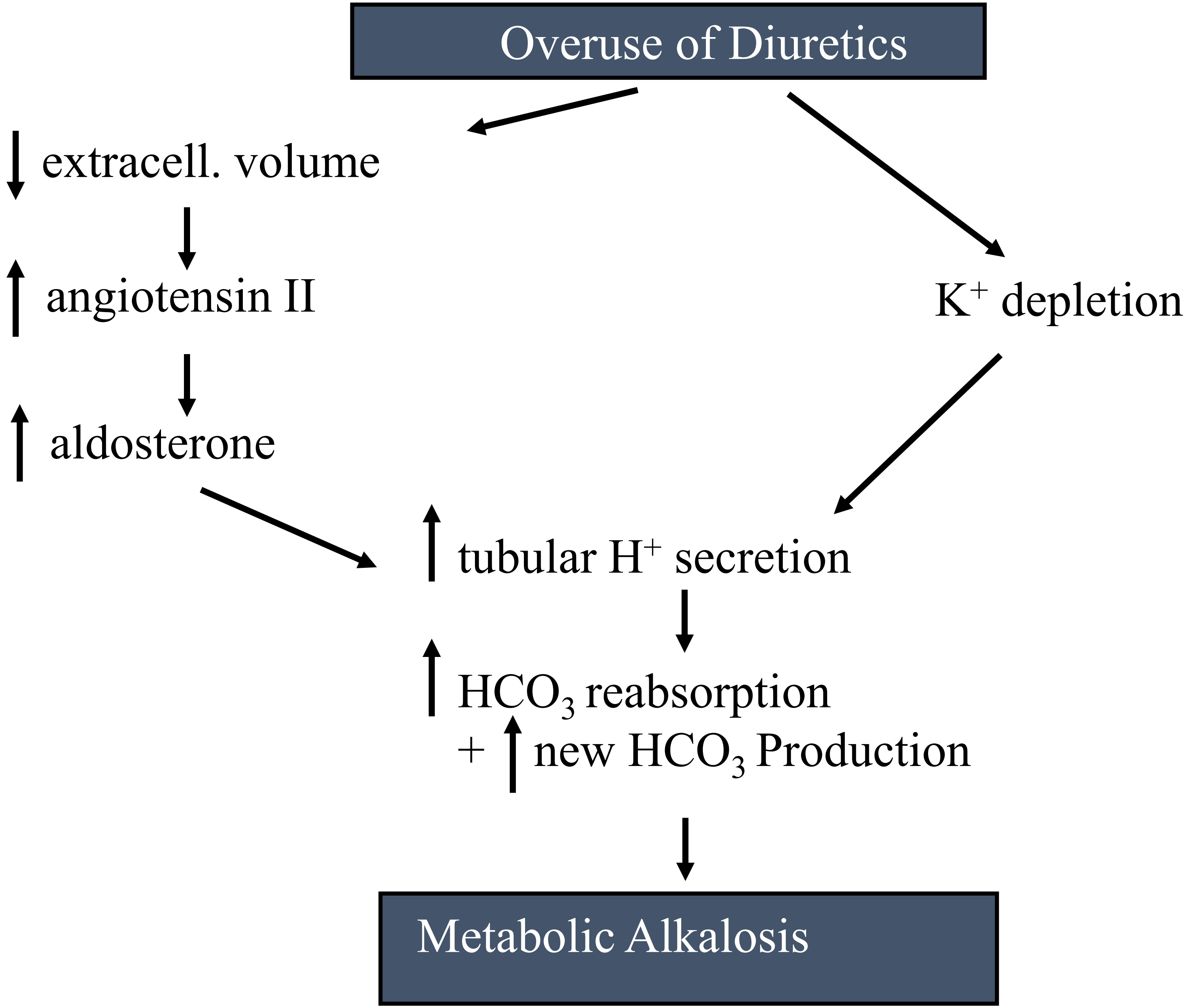
K^+ depletion

↑ H^+ secretion

⊕

↑ HCO_3 reabsorption
+ ↑ new HCO_3 Production

Metabolic Alkalosis



Overuse of Diuretics

↓ extracell. volume

↑ angiotensin II

↑ aldosterone

K$^+$ depletion

↑ tubular H$^+$ secretion

↑ HCO$_3$ reabsorption
+ ↑ new HCO$_3$ Production

Metabolic Alkalosis

Acid-Base Disturbances

- Respiratory Alkalosis : ↑ HCO_3^- / pCO2 in plasma
  ↑ (↓ pH, pCO_2)

  - high altitude
  - psychic (fear, pain, etc)

$$H_2O + CO_2 \longleftrightarrow H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

$$\uparrow pH = pK + \log \frac{HCO_3^-}{\alpha \ pCO_2}$$

Question

Laboratory values for a patient include the following:

arterial pH = 7.34
Plasma HCO_3^- = 15
Plasma P_{CO_2} = 29
Plasma Cl^- = 118
Plasma Na^+ = 142

Metabolic Acidosis
Respiratory Compensation

What type of acid-base disorder does this patient have?
What is his anion gap ?

Anion gap = 142 - 118 - 15 = 9 (normal)

Question

Which of the following are the most likely causes of his acid-base disorder?

[✓ a. diarrhea]
b. diabetes mellitus
c. aspirin poisoning
d. primary aldosteronism

Question

Indicate the Acid -Base Disorders in Each of the Following Patients

pH	HCO_3^-	PCO_2	Acid-Base Disorder ?
7.34	15	29	Metabolic acidosis
7.49	35	48	Metabolic alkalosis
7.34	31	60	Respiratory acidosis
7.62	20	20	Respiratory alkalosis
7.09	15	50	Acidosis: respiratory + metabolic

Audio-Visual Aid
Links to recorded lectures

UGS physiology lecture 11 - YouTube

UGS physiology - lecture 12 - YouTube