Sheet No.12

Physiology

Genitourinary system

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Quantification of Normal Renal Acid-Base Regulation

Total H+ secretion and net H+ excretion are two different measures of the kidneys' ability to regulate acid-base balance. Total H+ secretion refers to the total amount of H+ that is secreted into the tubular fluid by the kidneys. Net H+ excretion refers to the amount of H+ that is actually excreted in the urine.

Total H+ Secretion 4380 mEq/day = H+ secreted in exchange for the bicarbonate 4320 mEq/day + H+ of non-volatile acids produced in the body 60 mEq/day

=HCO3- reabsorption (4320 mmol/d) + titratable acid (NaHPO4-) (30 mmol/d) + NH4 + excretion (30 mmol/d)

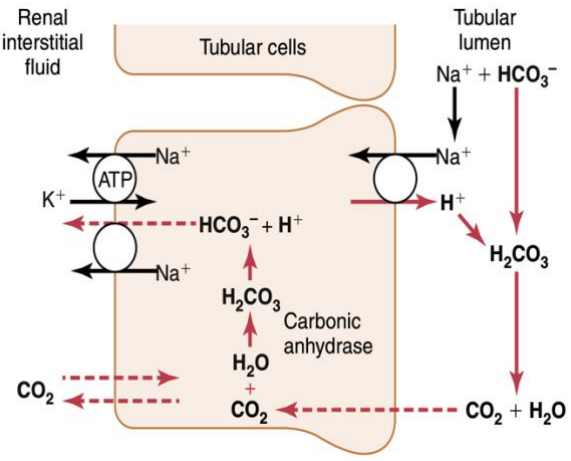
Net H+ excretion= H+ excreted by buffers not bicarbonate (=new bicarb) – new H+ added to blood (=HCO3- excreted)

Bicarbonate excretion is the same as adding an H+ to the blood. In alkalosis, the loss of HCO_3^- helps return the plasma pH toward normal.

the amount of new HCO_3^- contributed to the blood at any given time is equal to the amount of H+ secreted that ends up in the tubular lumen with **non-bicarbonate urinary buffers**. The primary sources of non-bicarbonate urinary buffers are NH4+ and phosphate. therefore, part of the HCO_3^- added to the blood (and H+ excreted by NH4+) is calculated by measuring NH4+ excretion.The rest of the non-bicarbonate, non-NH4+ buffer excreted in the urine is measured by determining a value known as titratable acid (mainly NaHPO4-).

The amount of titratable acid in the urine is measured by titrating the urine with a strong base to a pH of 7.4, the pH of normal plasma, and the pH of the glomerular filtrate. This titration reverses the events that occurred in the tubular lumen when the tubular fluid was titrated by secreted H+. Therefore, the number of milliequivalents of the strong base required to return the urinary pH to 7.4 equals the number of milliequivalents of H+ added to the tubular fluid that combined with phosphate and other organic buffers. The titratable acid measurement does not include H+ in association with NH4 + because the pK of the ammonia-ammonium reaction is 9.2, and titration with the strong base to a pH of 7.4 does not remove the H+ from NH4 +.

We don't use the H+ that is titrated by bicarbonate when we measure net H+ excretion because the H+ that is titrated by bicarbonate is not actually excreted in the urine. Because there is no net secretion of H+ via this mechanism. Each H+ secreted by the Na+-H+ exchanger in the luminal membrane combines with a filtered HCO_3^- to form CO2 and H2O, which enter the cell and are converted back to H+ and HCO_3^-. The H+ is recycled across the luminal membrane on the Na+-H+ exchanger to reabsorb more filtered HCO_3^-.



thus, the net acid excretion by the kidneys can be assessed as follows:

Net H+ excretion 59 mmol/day = titratable acid (30 mmol/d) + NH4+ excretion (30 mmol/d) - HCO3- excretion (1 mmol/d)(or new H to blood)

Normal Renal Acid-Base Regulation

To maintain acid–base balance, the net acid excretion must equal the nonvolatile acid production in the body.

for Acidosis

Titratable acid = 35 mmol/day (small increase)

NH4+ excretion = 165 mmol/day (increased)

HCO3– excretion = 0 mmol/day (decreased)

Net H+ excretion = 200 mmol/day

In acidosis, the **net acid excretion** increases markedly, the tubular H+ secretion is increased sufficiently to reabsorb all the filtered HCO3−, with enough H+ left over to excrete large amounts of NH4 +, thereby contributing large amounts of new HCO3 − to the extracellular fluid.

With chronic acidosis, there is increased production of NH4 + and with severe chronic acidosis, as much as **500 mEq/day of H+ can be excreted in the urine, mainly in the form of NH4+.**

for Alkalosis

Titratable acid = 0 mmol/day (decreased)

NH4+ excretion = 0 mmol/day (decreased)

HCO3– excretion = 80 mmol/day (increased)

Net H+ excretion = 80 mmol/day (**negative**)

In alkalosis, the tubular secretion of H+ is reduced to a level that is too low to achieve complete HCO3 − reabsorption, enabling the kidneys to **increase HCO3− excretion**. Titratable acid and ammonia are not excreted in alkalosis because there is no excess H+ available to combine with non-bicarbonate buffers; therefore, no new HCO3− is added to the blood in alkalosis (**H+ is added to the blood**).

Classification & Renal Compensations of Acid-Base Disorders from plasma pH, pCO2, and HCO3-

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

Note: charts are on the last page

ACIDOSIS—

in respiratory acidosis, there is a reduction in pH, an increase in extracellular fluid H+ concentration, and an **increase in Pco2**, which is the initial cause of the acidosis. The excess H+ in the tubular fluid is due mainly to the rise in extracellular fluid Pco2, which stimulates H+ secretion.

The compensatory response is increase in plasma HCO3 −, caused by the addition of new HCO3 − to the extracellular fluid by the kidneys. the rise in HCO3 − helps offset the increase in Pco2, thereby returning the plasma pH toward normal.

In metabolic acidosis, there is also a decrease in pH and a rise in the extracellular fluid H+ concentration. However, in this case, the primary abnormality is a **decrease in plasma HCO3 −.** The excess of H+ occurs in the tubular fluid, primarily because of decreased extracellular fluid concentration of HCO3 − and therefore decreased glomerular filtration of HCO3 −. [H+ ions are buffered by bicarbonate ions. When the concentration of bicarbonate ions in the blood decreases, the kidneys are unable to buffer as much H+. This leads to an excess of H+ in the tubular fluid.]

The primary compensations include increased ventilation rate, which reduces Pco2, and renal compensation, which, by adding new HCO3 − to the extracellular fluid, helps minimize the initial fall in extracellular HCO3 − concentration.

ALKALOSIS—

In respiratory alkalosis, there is an increase in extracellular fluid pH and a decrease in H+ concentration. The cause of the alkalosis is **decreased plasma PCO2**, caused by hyperventilation. Reduction in PCO2 then leads to decreased renal tubular H+ secretion. Consequently, there is not enough H+ in the renal tubular fluid to react with all the HCO3 − that is filtered. therefore, the HCO3 − that cannot react with H+ is not reabsorbed and is excreted in the urine.

This results in a decreased plasma HCO3 − concentration and correction of the alkalosis. Therefore, ***the compensatory response*** to a primary reduction in PCO2in respiratory alkalosis is a reduction in plasma HCO3 − concentration, caused by increased renal excretion of HCO3 −.

In metabolic alkalosis, there is also decreased plasma H+ concentration and increased pH. the cause of metabolic alkalosis, however, is a **rise in the extracellular fluid HCO3 − concentration**. this rise is partly compensated for by a reduction in the respiration rate, which increases PCO2 and helps return the extracellular fluid pH toward normal. In addition, increased HCO3 − concentration in the extracellular fluid increases the filtered load of HCO3 −, which, in turn, causes excess HCO3

− secreted in the renal tubular fluid. the excess HCO3 − in the tubular fluid fails to be reabsorbed because there is no H+ with which it can react, and it is excreted in the urine.

In metabolic alkalosis, the primary compensations are decreased ventilation, which raises PCO2, and increases renal HCO3 − excretion, which helps compensate for the initial rise in extracellular fluid HCO3 − concentration.

	pH	H^+	P_{CO_2}	HCO_3^-
Normal	7.4	40 mEq/L	40 mm Hg	24 mEq/L
Respiratory acidosis	↓	↑	↑↑	↑
Respiratory alkalosis	↑	↓	↓↓	↓
Metabolic acidosis	↓	↑	↓	↓↓
Metabolic alkalosis	↑	↓	↑	↑↑

↑ renal HCO3 production

↑ renal HCO3 excretion

↑ ventilation

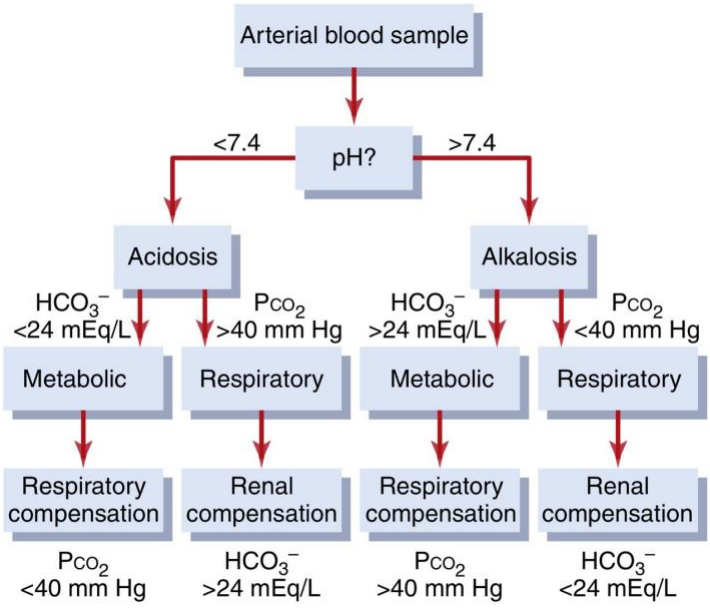
↑ renal HCO3 production

↓ ventilation

↑ renal HCO3 excretion

Diagnosis of Acid-Base Disorders

1. By plasma pH, pCO2, and HCO3-/ + Classification



If the compensatory responses are markedly different from those shown at the bottom of the figure, one should suspect a mixed acid-base disorder.

In simple respiratory acidosis would be reduced plasma pH, increased PCO2, and increased plasma HCO3 − concentration after partial renal compensation.

In simple metabolic acidosis, one would expect to find a low pH, a low plasma HCO3 − concentration, and a reduction in PCO2 after partial respiratory compensation.

In simple respiratory alkalosis, one would expect to find increased pH, decreased PCO2, and decreased HCO3 − concentration in the plasma.

In simple metabolic alkalosis, one would expect to find increased pH, increased plasma HCO3 −, and increased PCO2.

In some cases, acid–base disorders are not accompanied by appropriate compensatory responses. When this situation occurs, the abnormality is referred to as a mixed acid–base disorder, which means that there are two or more underlying causes for the acid–base disturbance.

2. Use of Anion Gap to Diagnose Acid-Base Disorders

The concentrations of anions and cations in plasma **must be equal to maintain electrical neutrality**. Therefore, there is no real anion gap in the plasma. However, only certain cations and anions are routinely measured in the clinical laboratory. The cation normally measured is Na+, and the anions are usually Cl− and HCO3 −. The anion gap—which is only a diagnostic concept— is the **difference between unmeasured anions and unmeasured cations** and is estimated as follows:

$$\text{Anion gap} = [Na^+] - [Cl^-] - [HCO3^-] \qquad \text{E.g.,= } 142 - 108 - 24 = 10 \text{ mEq/L}$$

the anion gap will increase if unmeasured anions rise or if unmeasured cations fall. The most important unmeasured **cations** include calcium, magnesium, and potassium, and the major unmeasured **anions** are albumin, phosphate, sulfate, and other organic anions. Usually, the unmeasured anions exceed the unmeasured cations, and the **anion gap ranges between 8 and 16 mEq/L**

The plasma anion gap is used mainly in **diagnosing different causes of metabolic acidosis**. In metabolic acidosis, plasma HCO3 − concentration is reduced.

1) If plasma sodium concentration is unchanged, the concentration of anions (Cl− or an unmeasured anion) increases to maintain electro-neutrality. If plasma Cl− increases in proportion to the fall in plasma HCO3 −, the anion gap will remain normal. This is often referred to as hyperchloremic metabolic acidosis.
2) If the decrease in plasma HCO3 − is not accompanied by increased Cl−, there must be increased levels of unmeasured anions and therefore an increase in the calculated anion gap. Metabolic acidosis caused by excess nonvolatile acids, such as lactic acid or ketoacids, is associated with an increased plasma anion gap because the fall in HCO3 − is not matched by an equal increase in Cl−.

Table 31-4 Metabolic Acidosis Associated With Normal or Increased Plasma Anion Gap

Increased Anion Gap (Normochloremia)	Normal Anion Gap (Hyperchloremia)
Diabetes mellitus (ketoacidosis)	Diarrhea
Lactic acidosis	Renal tubular acidosis
[redacted]	Carbonic anhydrase inhibitors
Aspirin (acetylsalicylic acid) poisoning	Addison disease
Methanol poisoning	
[redacted]	
Starvation	

Acid-Base Disturbances

Respiratory Acidosis:

1. Brain damage (pathological conditions that damage the respiratory centers)
2. pneumonia
3. emphysema
4. other lung disorders → obstruction of the passageways of the respiratory tract

Metabolic Acidosis:

1. aspirin poisoning (H+ intake)
2. diabetes mellitus (H+ production)
3. diarrhea (HCO3 - loss)
4. renal tubular acidosis (H+ secretion, HCO3 - reabs.)
5. carbonic anhydrase inhibitors (H+ secretion)

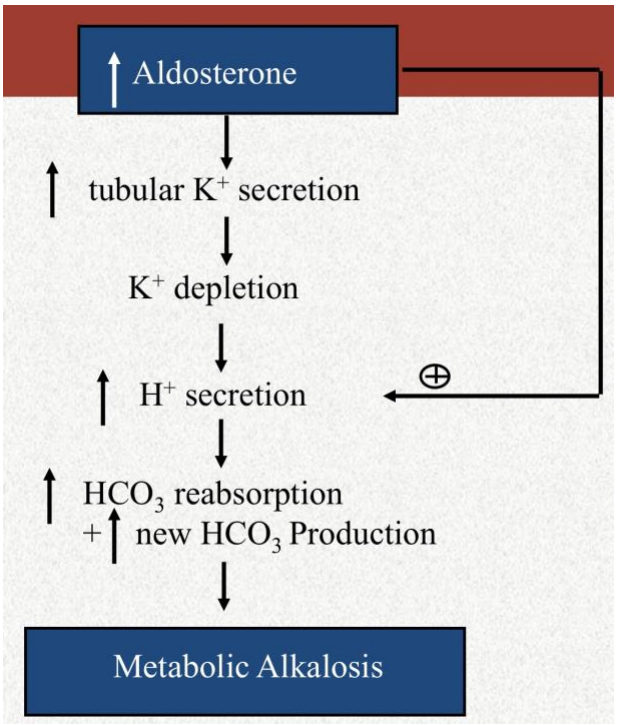
Metabolic Alkalosis:

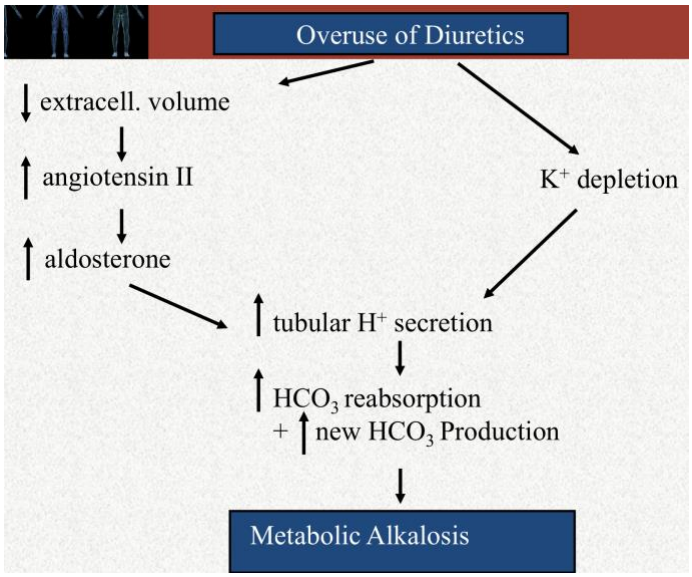
1. increased base intake (e.g., NaHCO3)
2. vomiting gastric acid
3. mineralocorticoid excess
4. overuse of diuretics (except carbonic anhydrase inhibitors)

A special factor that can increase H+ secretion under some pathophysiological conditions is excessive aldosterone secretion. and increased angiotensin II (Ang II), may also secondarily increase H+ secretion and HCO3 − reabsorption.

Changes in plasma potassium concentration can also influence H+ secretion, with hypokalemia stimulating and hyperkalemia inhibiting H+ secretion. (Excessive Aldosterone causes K+ depletion)

Overuse of Diuretics cause increased angiotensin II / aldosterone secretion & K+ depletion, which increase H+ secretion and HCO3− reabsorption and cause metabolic alkalosis





Respiratory Alkalosis: (excessive ventilation by the lungs)

1. high altitude
2. psychic (fear, pain, etc.)

Continue to the Questions page …

Questions

1. 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 ?

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

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

2. A plasma sample revealed the following values in a patient:

norm for PCO_2 35-45,

HCO_3 22-26

pH = 7.12

PCO_2 = 50

HCO_3^- = 18

diagnose this patient's acid-base status: acidotic or alkalotic ? respiratory, metabolic, or both ?

Acidotic, Both

Mixed acidosis: metabolic and respiratory acidosis

3. 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

4. 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

5. Laboratory values for an uncontrolled diabetic patient include the following:

arterial pH = 7.25

Plasma HCO_3^- = 12

Plasma PCO_2 = 28

Plasma Cl^- = 102

Plasma Na^+ = 142

What type of acid-base disorder does this patient have? Metabolic Acidosis Respiratory Compensation

What is his anion gap ? Anion gap = 142 - 102 -12 = 28

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

6. Laboratory values for a patient include the following:

arterial pH = 7.34

Plasma HCO3 - = 15

Plasma PCO2 = 29

Plasma Cl- = 118 Plasma

Na+ = 142

What type of acid-base disorder does this patient have? Metabolic Acidosis Respiratory Compensation

What is his anion gap ? Anion gap = 142 - 118 - 15 = 9 (normal)

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

7. ***

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

Charts