Objectives

1. Understand the basic principles of acid-base physiology
2. Understand the characteristics of clinical acid-base disorders

Readings

Rose and Rennke, pages 123-140.
Rennke and Denker, pages 127-144.

I. Basic Principles of Acid-Base Physiology

A. Importance of intracellular acidity for cell function

Using arterial blood acidity as an index of intracellular acidity

B. Measurement of acidity

1. Logarithmic pH scale; pH = –log $[H^+]$, where $[H^+]$ is expressed in mol/liter.
2. Linear $[H^+]$ scale, usually in nEq/liter (nEq/liter = 10^{-9} Eq/liter)
3. Conversion of pH to $[H^+]$ in nEq/liter can be accomplished by solving the equation:

$[H^+]$ = antilog (9 – pH)

Relationship between pH and $[H^+]$

pH	$[H^+]$ nEq/liter	pH	$[H^+]$ nEq/liter
7.80	16	7.25	56
7.75	18	7.20	63
7.70	20	7.15	71
7.65	22	7.10	79
7.60	25	7.05	89
7.55	28	7.00	100
7.50	32	6.95	112
7.45	35	6.90	126
7.40	40	6.85	141
7.35	45	6.80	159
7.30	50		

C. The range of normal

Under physiologic conditions, arterial blood acidity is maintained within very narrow limits:

	Mean	Range
pH	7.40	7.37-7.43
$[H^+]$, nEq/liter	40	37-43

(Note that pH of 7.37 corresponds to $[H^+]$ of 43 nEq/liter and pH of 7.43 to 37 nEq/liter.)

D. Physiologic importance of the carbonic acid-bicarbonate system

Derivation of the Henderson and Henderson-Hasselbalch equations

$$PaCO_2 \downarrow \text{Dissolved } CO_2 + H_2O \xrightleftharpoons{\text{Carbonic Anhydrase}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$\frac{[H^+] \times [HCO_3^-]}{[H_2CO_3]} = K \quad (1)$$

$$[H^+] = K \times \frac{[H_2CO_3]}{[HCO_3^-]} \quad (2) \qquad pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]} \quad (3)$$

$$[H^+] = K \times \frac{a\,PaCO_2}{[HCO_3^-]} \quad (4) \qquad pH = pK + \log \frac{[HCO_3^-]}{a\,PaCO_2} \quad (5)$$

$$[H^+] = 24 \times \frac{PaCO_2}{[HCO_3^-]} \quad (6) \qquad pH = 6.1 + \log \frac{[HCO_3^-]}{.0301\,PaCO_2} \quad (7)$$

Figure 1

E. Determinants of arterial blood acidity

$$[H^+] = \frac{24 \text{ X } PaCO_2}{[HCO_3^-]}$$

Shown above is the Henderson equation. This equation stipulates the interrelationships among the acid-base parameters in blood when hydrogen ion concentration ($[H^+]$) is expressed in nEq/liter (10^{-9} Eq/liter), arterial carbon dioxide tension ($PaCO_2$) in mm Hg, and plasma bicarbonate concentration ($[HCO_3^-]$) in mEq/liter (10^{-3} Eq/liter). Under normal conditions, $PaCO_2$ averages 40 mm Hg and plasma $[HCO_3^-]$ 24 mEq/liter. Thus, arterial blood $[H^+]$ averages 40 nEq/liter (pH 7.40). From a physiologic perspective, arterial blood acidity can be viewed as a dependent variable, its value being a reflection of the prevailing levels of $PaCO_2$ (respiratory component) and plasma $[HCO_3^-]$ (metabolic component).

1. Determinants of $PaCO_2$

   The level of $PaCO_2$ is determined by the interaction of two factors, the rate of carbon dioxide production (V_{CO2}) and the rate of alveolar ventilation (V_A), as follows:

   $$PaCO_2 = K \text{ x } V_{CO2}/V_A \qquad \text{(where K is a constant)}$$

   Approximately 15,000 mmol of CO_2 are generated daily through the metabolism of carbohydrates and fats and are excreted quantitatively via alveolar ventilation. The normal range of $PaCO_2$ is 36-44 mm Hg.

2. Determinants of plasma $[HCO_3^-]$

   The normal range of arterial plasma $[HCO_3^-]$ is 22-26 mEq/liter. Regulation of plasma $[HCO_3^-]$ occurs as a by-product of the regulation of external hydrogen ion balance. This regulation largely involves three factors:

a. Hydrogen ion input

The metabolism of various dietary substances generates a number of acids and bases:

Endogenous acid load

Substrate	Endogenous Acids
Sulfur-containing amino acids (methionine and cystine)	H_2SO_4
Organophosphates (phosphoproteins and phospholipids)	H_3PO_4
Organic cations (arginine and lysine)	H^+
Neutral organic substances (carbohydrates, fats, nucleoproteins)	Organic acids (lactic acid, ketoacids, uric acid)

Endogenous alkali load

Substrate	Endogenous Alkali
Organic anions (glutamate and aspartate, lactate and acetoacetate)	HCO_3^-

The net effect of a usual diet of industrialized societies (i.e., rich in protein and relatively low in organic anions that are contained in fruits and vegetables) is production of endogenous acid on the order of 50-100 mEq/day in adults (about 1 mEq/kg/day).

b. Body buffering

If it were not for buffering, the addition of a large quantity of acid, such as that produced each day by cellular metabolism, would result in a lethal increase in hydrogen ion concentration of the body fluids. However, the presence of body buffers permits this large influx of acid to occur with only a limited rise in acidity. About 50% of the daily endogenous acid load is buffered by extracellular bicarbonate resulting in the generation of carbonic acid and then carbon dioxide and water. The remainder is buffered by other extracellular and intracellular buffers (HPO_4^{2-}, anionic sites on hemoglobin and other proteins) as well as bone buffers (e.g., CO_3^{2-}).

Body buffering

$H^+ + Buffer^- \rightarrow HBuffer$

$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$
$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$
$H^+ + Hgb^- \rightarrow HHgb$
$H^+ + Protein^- \rightarrow HProtein$
$H^+ + CO_3^{2-} \rightarrow HCO_3^-$

Although essential for survival, buffering does not contribute to *external* hydrogen ion balance. Unless the endogenous acid load is eventually excreted in the urine, the body buffers would be depleted and lethal acidemia develop. By excreting quantitatively the daily acid load in the urine (net acid excretion), the kidneys return an equal amount of new bicarbonate into the body fluids. This amount of new bicarbonate serves to replenish the bicarbonate stores and to back-titrate the other buffers to their base forms.

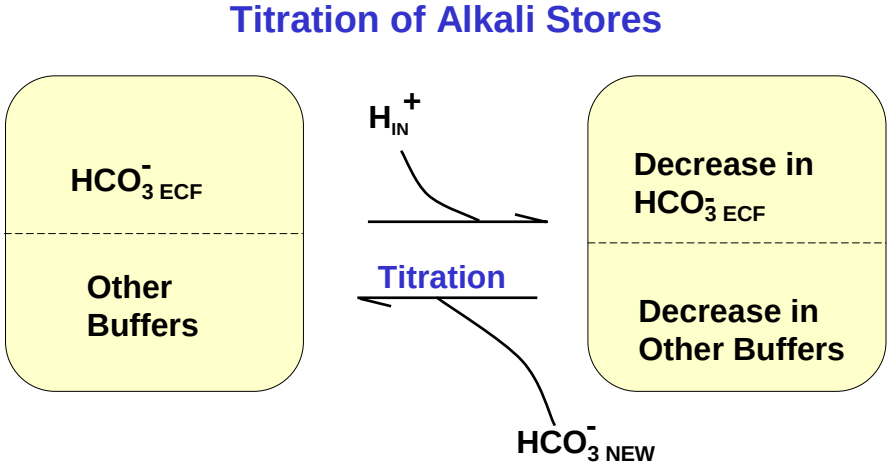

Figure 2

c. Acid excretion by the kidney

Dual role of the kidney in regulating hydrogen ion balance and, thus, plasma [HCO_3^-]:

i. Reclamation of filtered bicarbonate (HCO_3^- reabsorption)

ii. Net acid excretion (NAE) (new HCO_3^- generation)

Both tasks are accomplished by tubular secretion of hydrogen ions into the luminal fluid. In the proximal tubule, an apical Na^+/H^+-exchanger (antiporter) largely accomplishes hydrogen ion secretion with a lesser contribution from an apical H^+-ATPase pump. In the cortical and medullary collecting duct, hydrogen ion secretion is largely accomplished by an apical H^+-ATPase with a lesser contribution from an apical H^+/K^+-ATPase.

Renal H^+ secretion = HCO_3^- reabsorption + NAE
HCO_3^- reabsorption = GFR x plasma [HCO_3^-] (if complete)
NAE = TA excretion + NH_4^+ excretion – residual HCO_3^- excretion
(where TA is titratable acid)

Under steady-state conditions,

NAE (new HCO_3^- generation) = Endogenous H^+ load

i. Bicarbonate reabsorption

The bulk of bicarbonate reabsorption (~ 90%) occurs in the proximal tubule resulting in a decrease of tubular fluid pH from 7.40 in the filtrate to 6.5-6.8 at the end of the proximal tubule. Of the bicarbonate delivered out of the proximal tubule, some is reabsorbed in the thick ascending limb of the loop of Henle (by an apical Na^+/H^+-exchanger) and the remainder in the cortical and medullary collecting duct. Under normal conditions, the urine is essentially bicarbonate free. Hydrogen ion secretion by the H^+-ATPase in the collecting duct generates a steep pH gradient that can attain a minimum tubular fluid pH of 4.5 after an acid load (~ 3 pH units difference from blood, i.e., a 1000:1 hydrogen ion gradient).

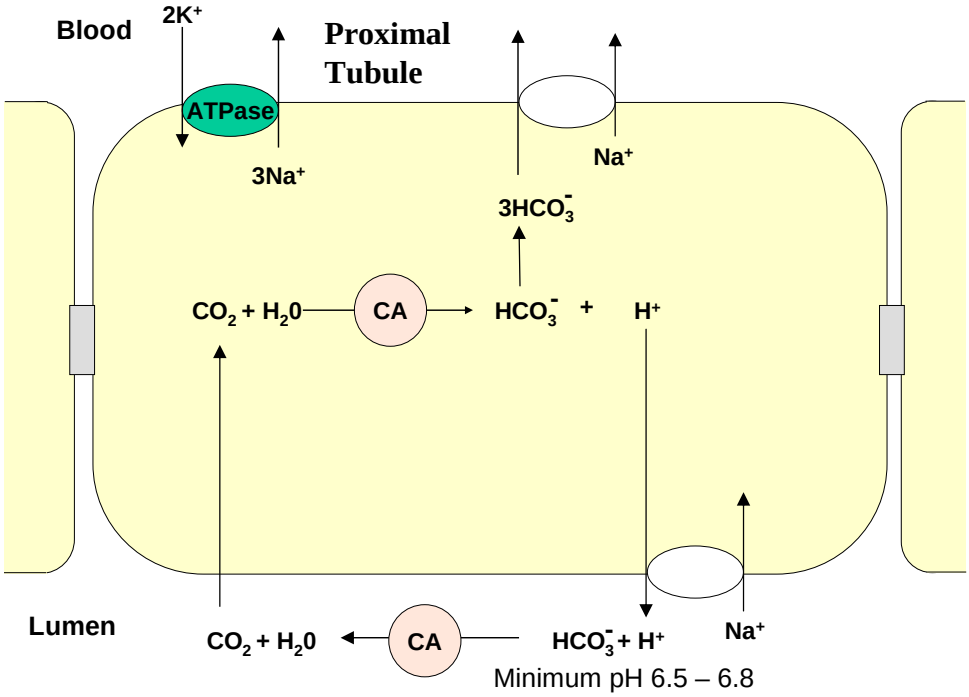

Figure 3(a)

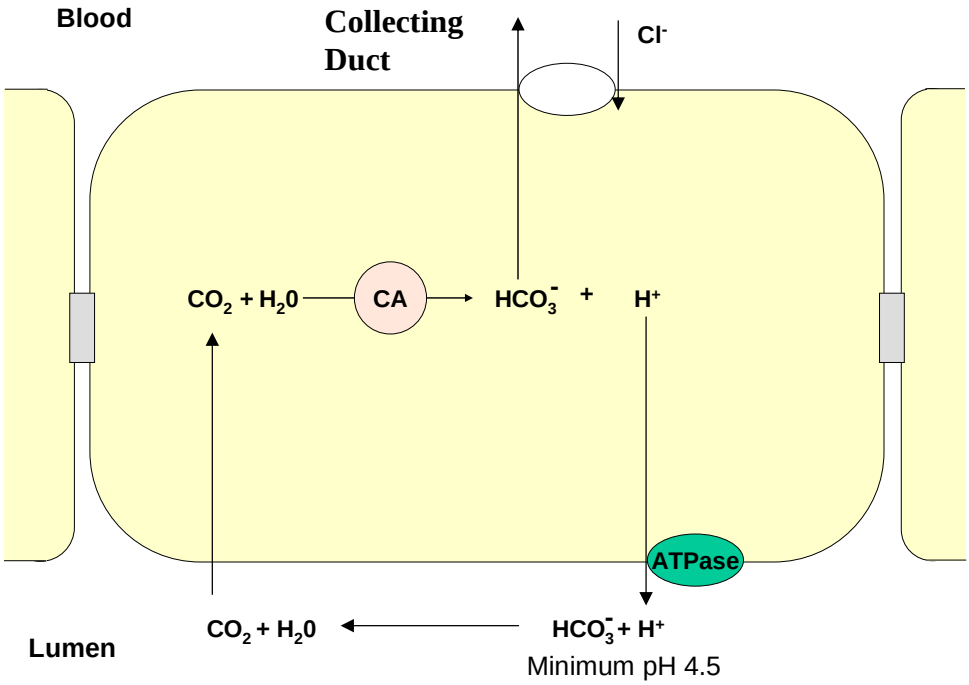

Figure 3(b)

ii. Titratable acid (TA) excretion

Note that even at the minimum urine pH of 4.5, substantive excretion of hydrogen ion in free form is precluded (pH 4.5 corresponds to a $[H^+]$ of about 0.03 mEq/liter). Therefore, urinary buffers must be relied on to excrete the relatively large quantity of hydrogen ions imposed by the daily endogenous acid production. Titratable acidity refers to weak acids of the filtrate that can act as buffers in the urine. By virtue of its substantial quantity in the filtrate and its pK (6.80), phosphate is the most effective such buffer in the urine. At the normal blood (and filtrate) pH of 7.40, 80% of phosphate is in the HPO_4^{2-} form. As tubular fluid pH falls along the nephron, increasing amounts of HPO_4^{2-} are converted into the $H_2PO_4^-$ form:

$$HPO_4^{2-} + H^+ \rightarrow H_2PO_4^-$$

At a tubular fluid pH of 5.3 (1.5 pH units below the pK), virtually all of the filtered HPO_4^{2-} will be converted to $H_2PO_4^-$. Note that for every hydrogen ion excreted in the urine with a titratable acid, one new bicarbonate ion is returned to the systemic circulation. Normally, titratable acidity accounts for the excretion of about 10-40 mEq of hydrogen ion per day.

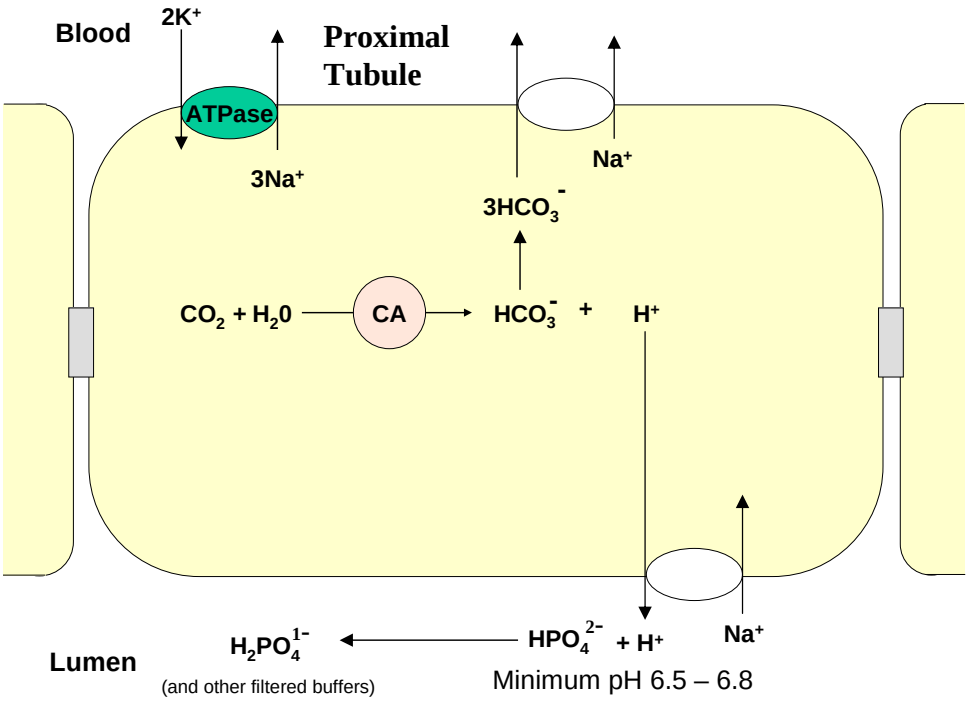

Figure 4(a)

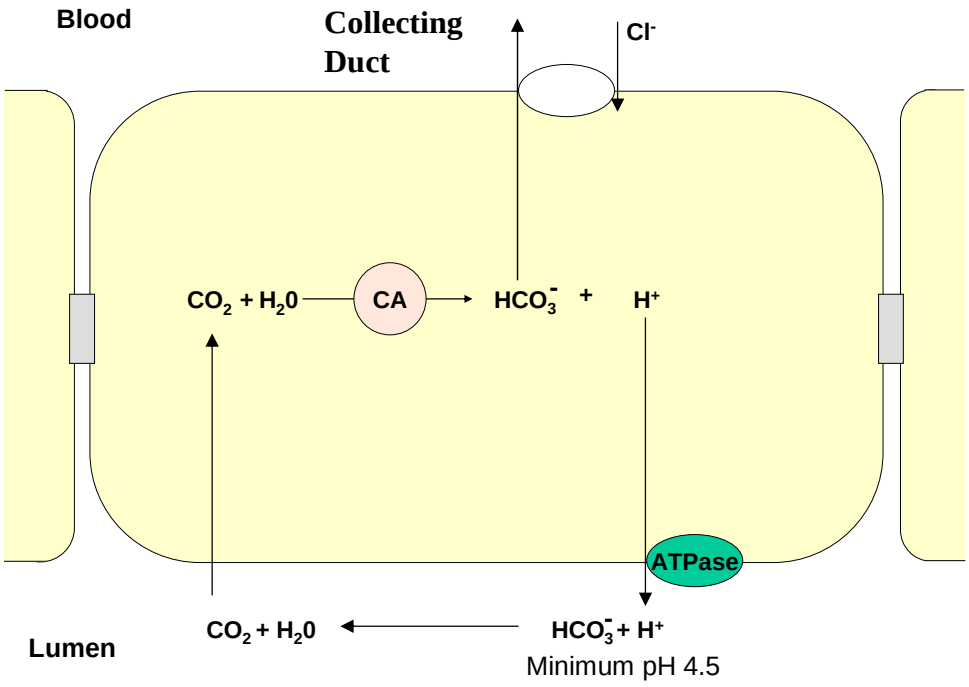

Figure 4(b)

iii. Ammonium (NH_4^+) excretion

Ammonium is the other major vehicle for hydrogen ion excretion in the urine. It is formed in the proximal tubule primarily from the metabolism of the amino acid glutamine as follows:

Glutamine ➔ NH_4^+ + glutamate$^-$ ➔ NH_4^+ + α-ketoglutarate^{2-}

Ammonium ions are secreted from the proximal tubule into the lumen by substituting for H^+ on the apical Na^+/H^+-exchanger. Also, lipid soluble NH_3 can passively diffuse from the medullary interstitium into the medullary collecting duct, where it combines with secreted H^+ and forms non-diffusible NH_4^+ ions, which are effectively "trapped" in the lumen and eliminated in the urine. The metabolism of α-ketoglutarate^{2-} (AKG^{2-}) within the tubular cell to either glucose or to $CO_2 + H_2O$ generates two new bicarbonate ions, which are returned to the systemic circulation. Therefore, each ammonium ion excreted in the urine is a marker for a new bicarbonate ion entering the systemic circulation. Normally, ammonium excretion amounts to 30-40 mEq per day, but it can increase by up to 10-fold in response to a maximal acid load, thus accounting in large part for the kidney's ability to regulate hydrogen ion balance.

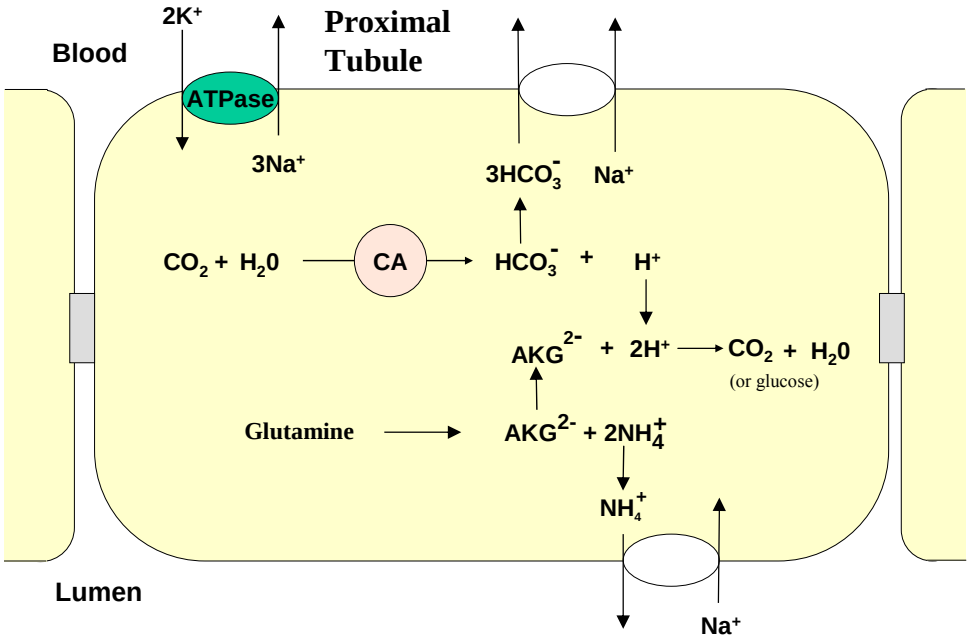

Figure 5

II. Clinical Acid-Base Disorders

A. Definition of terms

Acidemia:	Increased blood [H^+] or decreased blood pH
Alkalemia:	Decreased blood [H^+] or increased blood pH
Hypercapnia:	Increased $PaCO_2$
Hypocapnia:	Decreased $PaCO_2$
Hyperbicarbonatemia:	Increased plasma [HCO_3^-]
Hypobicarbonatemia:	Decreased plasma [HCO_3^-]
Acidosis:	A pathophysiologic process tending to acidify body fluids
Alkalosis:	A pathophysiologic process tending to alkalinize body fluids
Respiratory acid-base disorders:	Those acid-base disorders initiated by a change in $PaCO_2$ (respiratory component)

Respiratory acidosis: The acid-base disorder initiated by an increase in $PaCO_2$

Respiratory alkalosis: The acid-base disorder initiated by a decrease in $PaCO_2$

Metabolic acid-base disorders: Those acid-base disorders initiated by a change in plasma $[HCO_3^-]$ (metabolic component)

Metabolic acidosis: The acid-base disorder initiated by a decrease in plasma $[HCO_3^-]$

Metabolic alkalosis: The acid-base disorder initiated by an increase in plasma $[HCO_3^-]$

Simple acid-base disorder: The presence of a primary (initiating) abnormality in $PaCO_2$ (respiratory component) or plasma $[HCO_3^-]$ (metabolic component) coupled with the appropriate secondary response in the other component

Mixed acid-base disorder: The simultaneous presence of two or more simple acid-base disorders (the appropriate secondary response to the primary abnormality of a simple acid-base disorder should not be taken as one of the components of a mixed acid-base disorder)

B. The four simple acid-base disorders

Note that the secondary response is directional to the primary change thereby lessening its impact on acidity (for this reason the secondary responses are also known as "compensatory").

Table 1

Type of Disturbance	Primary Alteration	Secondary Response	Mechanism of Secondary Response
Metabolic acidosis	Decrease in plasma HCO_3^-	Decrease in $PaCO_2$	Hyperventilation
Metabolic alkalosis	Increase in plasma HCO_3^-	Increase in $PaCO_2$	Hypoventilation
Respiratory acidosis	Increase in $PaCO_2$	Increase in plasma HCO_3^-	Acid titration of tissue buffers; transient increase in acid excretion and sustained enhancement of HCO_3^- reabsorption by kidney
Respiratory alkalosis	Decrease in $PaCO_2$	Decrease in plasma HCO_3^-	Alkaline titration of tissue buffers; transient suppression of acid excretion and sustained reduction of HCO_3^- reabsorption by kidney

References

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