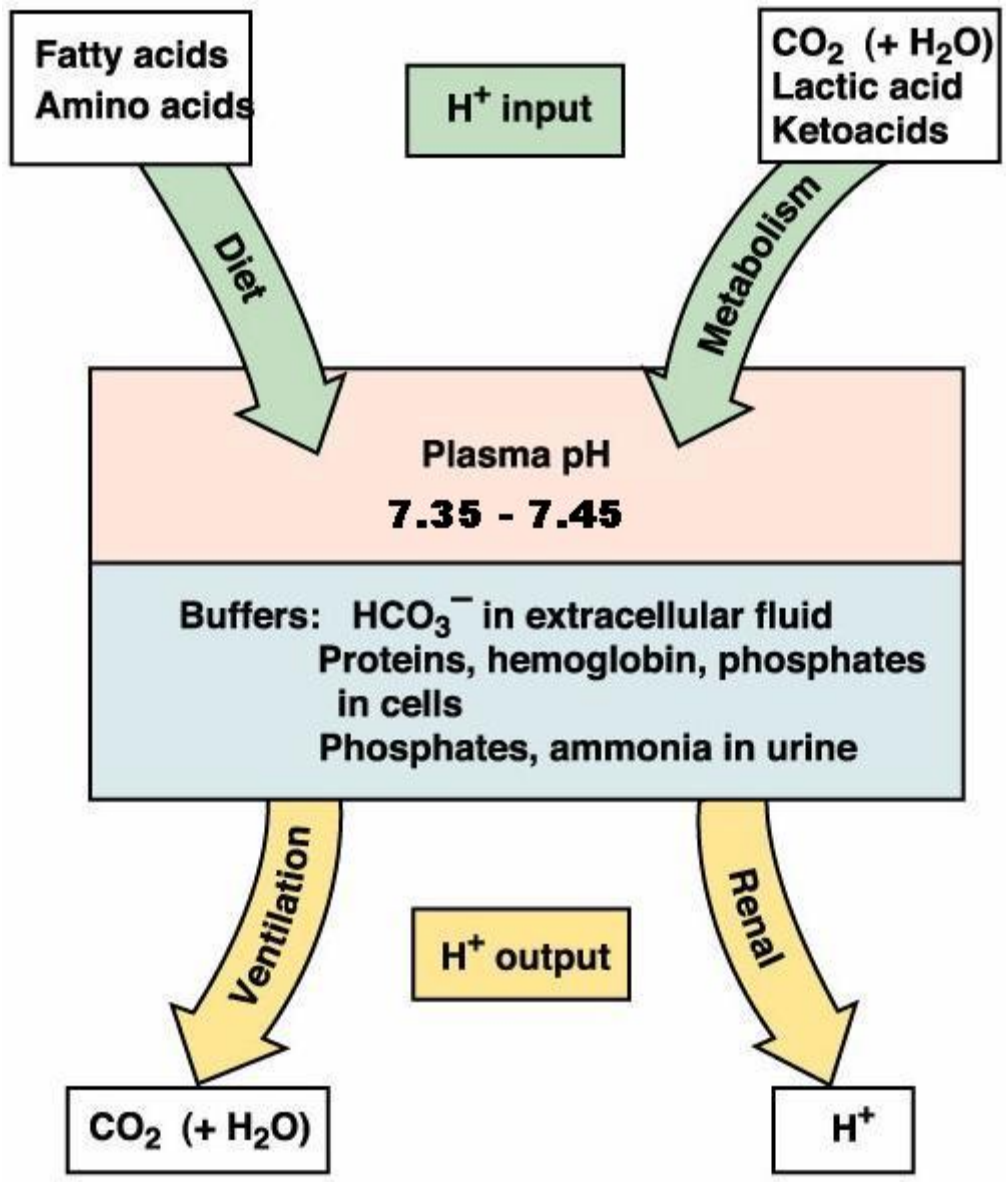
Regulation of Acid-base balance

Metabolism depends on the functioning of enzymes, and enzymes are very sensitive to pH. Slight deviations from the normal pH can shut down metabolic pathways as well as alter the structure and function of other macromolecules. Consequently, acidbase balance is one of the most important aspects of homeostasis.



Regulation acid-base balance means regulation of $[H^+]$ in the body fluid. Only slightly changes in $[H^+]$ from the normal value can cause marked alteration in the rates of chemical reactions in the cell. For this reason the regulation of $[H^+]$ is one of the most important aspects of homeostasis. The symbol pH is used for expressing the $[H^+]$.

$$pH = \log \frac{1}{[H^+]} = -\log [H^+] \qquad [1]$$

Note from the formula (1) that a low pH corresponds to a high $[H^+]$, which is called **acidosis**, and conversely, a high pH corresponds to a low $[H^+]$ which is called **alkalosis.** All acids are ionized to a

certain extent, and the percentage of ionization is called the degree of dissociation. For example the reversible relationship between undissociated carbonic acid and the two ions that it forms H^+ and HCO_3^-:

$$H_2CO_3 \rightleftarrows H^+ + HCO_3^- \quad [2]$$

Therefore;

$$\frac{[H^+] \text{ X } [HCO_3^-]}{[H_2CO_3]} = K1 \quad [3]$$

This formula state that in any given carbonic acid solution the concentration of H^+ times the concentration of HCO_3^- ions divided by the concentration of undissociated carbonic acid is equal to a constant, K1. However because it is almost impossible to measure the concentration of undissociated carbonic acid in a solution and because the concentration of undissociated carbonic acid is proportional to the amount of dissolved CO_2 , the formula can be written as follow:

$$\frac{[H^+] \text{ X } [HCO_3^-]}{[CO_2]} = K2 \quad [4]$$

The only real difference between the preceding two formulas is that the constant K1 is approximately 400 times the constant K2. The last formula can be written as follow:

$$[H^+] = K2 \text{ x } \frac{[CO_2]}{[HCO_3^-]} \quad [5]$$

If you take the logarithm of each sides of the last formula, it becomes the following:

$$\text{Log } [H^+] = \log K2 + \log \frac{[CO_2]}{[HCO_3^-]} \quad [6]$$

Therefore

$$-\log [H^+] = -\log K2 + \log \frac{[HCO_3^-]}{[CO_2]} \quad [7]$$

-log [H^+] is equal to the pH of the solution, and- log K is called the pK of a buffer. Therefore, this formula can be changed still further to the following:

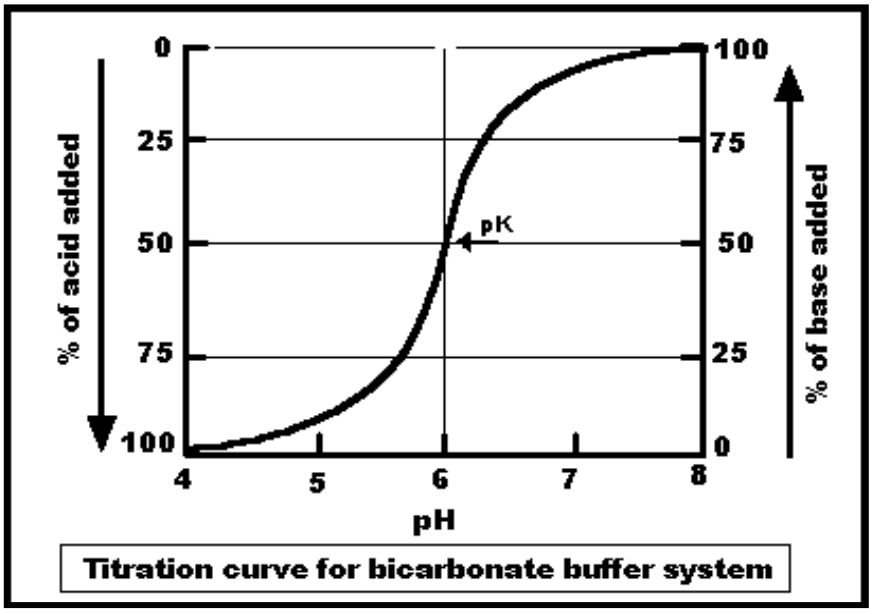
$$pH = pK2 + \log \frac{[HCO_3^-] \text{ in mmol/L}}{[CO_2] \text{ in mmol/L}} \quad [8]$$

For the bicarbonate buffer system the pK2 is 6.1, and last the formula may be expressed as Follow:

$$pH = 6.1 + \log \frac{[HCO_3^-] \text{ in mmol/l}}{[CO_2] \text{ in mmol/L}} \quad [9]$$

This is called the Henderson– Hasselbalch equation and by using it one can calculate the pH of a solution if the molar concentrations of bicarbonate ion and dissolved molar CO_2 are known. **$[CO_2]$ is equal to the PCO_2 (mmHg) X 0.03 (the solubility factor in mmol/L/mmHg at 37°C in plasma).** If the molar HCO_3^- concentration is equal to the dissolved molar CO_2 concentration, the equation will become; **pH = 6.1+ log 1 = 6.1 + 0 = 6.1**

Therefore for equal concentrations of the HCO_3^- and CO_2 the pH of the solution is equal to the pK2 (6.1) which represent the pH at which the buffer system can operate with its maximum buffering power. If we plot a titration curve for the bicarbonate buffer system in which the x-axis represents the pH of the solution and the y-axis represents the percentage of added HCO_3^- (as a base) or CO_2 (as an acid) to the solution we will see that at the central point of the curve the addition of a slight amount of acid or base causes minimal change in pH. However toward each end of the curve addition of a slight amount of acid or base causes the pH to change greatly. Thus buffering power of the buffer system is greatest when the pH is equal to the pK2, which is in the exact center of the curve. A second factor that determines the buffering power is the concentrations of the two elements of the buffer solution, the HCO_3^- and CO_2. Thus the buffering power of a buffer is also directly proportional to the concentrations of the buffer substances.



Titration curve for bicarbonate buffer system

Defense against change in $[H^+]$: To prevent acidosis or alkalosis, several control systems are available:

1. **Acid-base buffer system:** Which are present in all body fluids that immediately combine with any acid or alkali and thereby prevent excessive change in $[H^+]$ this system can act within a fraction of a second to prevent excessive changes in $[H^+]$.
2. **Respiratory center:** Upon the changes in $[H^+]$ the respiratory center is immediately stimulated to alter the rate of breathing .As a result, the rate of CO_2 removal from the body fluids is automatically changed and this causes the $[H^+]$ to return toward normal. This mechanism takes 1 to 15 minutes to readjust the $[H^+]$ after sudden changes have occurred .
3. **Kidneys:** when the $[H^+]$ changes from normal the kidneys excrete either an acid or alkaline urine thereby also helping readjust the $[H^+]$ of the body fluids back to normal. The kidneys provide the most powerful of all the acid-base regulatory systems but requires many minutes to several days to readjust the $[H^+]$.

The buffer system of the body fluids

The three major buffer systems of the body fluids are the bicarbonate buffer, the phosphate buffer, and the protein buffer .

[1] The bicarbonate buffer system: It consist of mixture of carbonic acid (H_2CO_3) and sodium bicarbonate ($NaHCO_3$) (K- or Mg- bicarbonate intracellularly). It constitutes about 53% of buffering capacity of whole blood (plasma. 35% and RBC 18%).

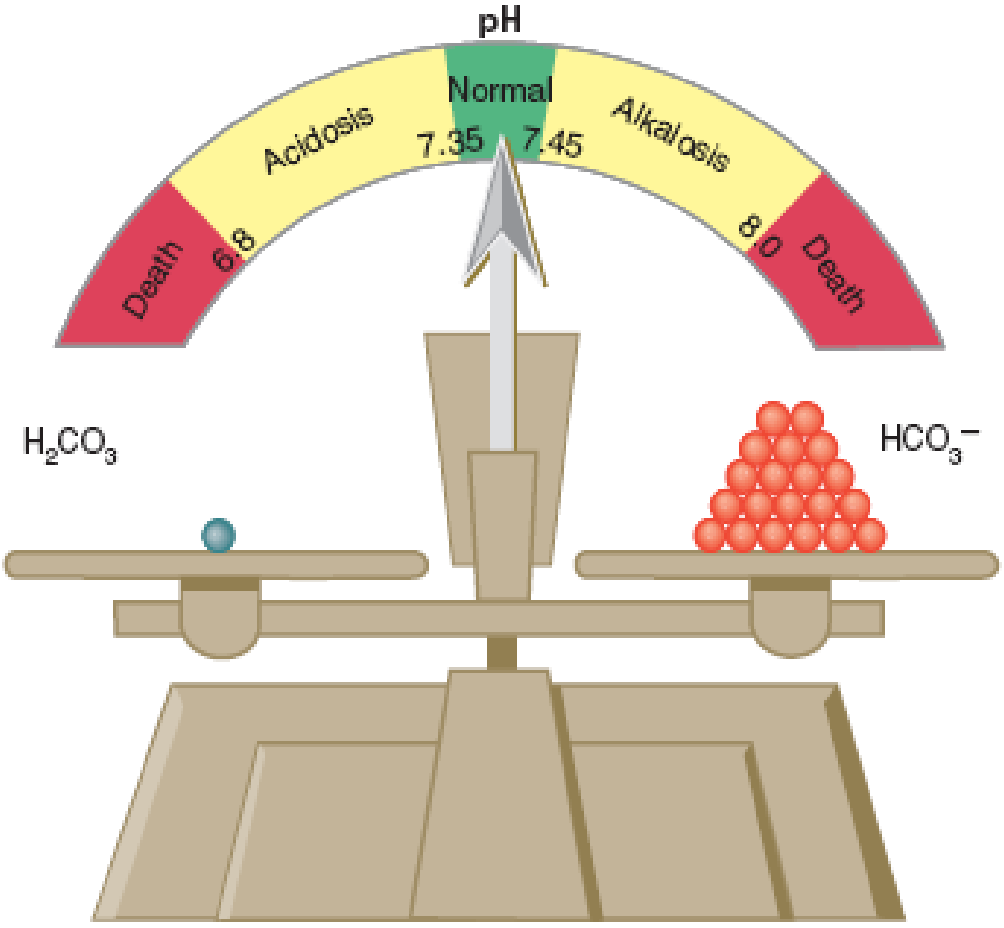


Figure 24.11 The Relationship of Carbonic Acid–Bicarbonate Ratio to pH. At a normal pH of 7.40, there is a 20:1 ratio of bicarbonate ions (HCO_3^-) to carbonic acid (H_2CO_3) in the blood plasma. An excess of HCO_3^- tips the balance toward alkalosis, whereas an excess of H_2CO_3 tips it toward acidosis.

When a strong acid such as HCI is added to a buffer solution containing bicarbonate salt, the following reaction takes place;

$HCI + NaHCO_3 \rightarrow H_2CO_3 + NaCl$

From this equation it can be seen that the strong HCl is converted into a very weak carbonic acid. Therefore, addition of HCl lowers the pH of the solution only slightly. On the other hand, if a strong base such as NaOH is added to this buffer, the following takes place;

$NaOH + H_2CO_3 \rightarrow NaHCO_3 + H_2O$

This equation shows that the hydroxyl ion of NaOH combines with the hydrogen ion from the carbonic acid to form water and that the other product formed is sodium bicarbonate. The net result is exchange of the strong base NaOH for the weak base $NaHCO_3$.

The bicarbonate buffer system is not powerful buffer for two reasons:

(a) The pH in the extracellular fluids is about 7.4, while the maximum buffering power of this system is around pH 6.1. (b) The concentrations of the two elements of the bicarbonate system, CO_2 and HCO_3^- are not great.

Yet, despite the fact that the bicarbonate buffer system is not especially powerful, it actually more important than all the others in the body because the concentration of each of the two elements of the bicarbonate system can be regulated, carbon dioxide by the respiratory system and bicarbonate ion by the kidneys. As a result, the pH of the blood can be shifted up or down by the respiratory and renal regulatory systems.

[2] Phosphate buffer system: It constitutes about 2% of buffering capacity of whole blood. It is composed of NaH_2PO_4 and Na_2HPO_4.

$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl$

The net result of this reaction is that the HCl is removed and in its place an additional quantity of NaH_2PO_4 is formed which is weak acid and the pH changes relatively slight.

$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$

Here sodium hydroxide is decomposed to form water and Na_2HPO_4 which is very weak base allowing only a slight shift in pH toward the alkaline side. The maximum buffering power of this system is around pH 6.8 (pk = 6.8) which is not far from the normal pH of 7.4 in the body fluids, this allows the phosphate buffer system to operate near its maximum buffering power. However, despite the fact that this buffer system operates in a reasonably good operating condition, its concentration in the extracellular fluid is only 1/12 those of the bicarbonate buffer. Therefore, its total buffering power in the extracellular fluid is even far less than that of the bicarbonate system. **On the other hand, the phosphate buffer is especially important in:**

[1] The tubular fluid of the kidneys for two reasons: (a) Phosphate usually becomes greatly concentrated in the tubules (because of their relative poor reabsorption and because of removal of water from the tubular fluid) thereby also greatly increasing the buffering power of the phosphate system. (b) The tubular fluid usually becomes more acidic than the extracellular fluid, bringing the operating range of the buffer closer to the pH for the maximum buffering power of this system.

[2] The intracellular fluids because the concentration of phosphate in these fluids is many times that in the extracellular fluids, and also because the pH at which this system operate at its maximum power is closer to the pH of intracellular fluid than the pH of the extracellular fluid.

[3] The protein buffer system: It constitutes about 42% of buffering capacity of whole blood (Hb 35% and plasma proteins 7%). The proteins of the body behave as weak acids and weak bases and therefore play an important part in buffering. Proteins and the amino acids of which they are formed, possess both acidic groups, usually the -COOH radical, and basic groups, usually the $-NH_2$ radical.

NH_2 –Protein-COOH → Undissociated protein.

NH_3^+ –Protein-COOH → In acid solution.

NH_2 –Protein-COO^- → In alkaline solution.

The most plentiful buffer of the body is the protein of the cells and plasma, mainly because of their very high concentrations. It has been shown that about 3/4 of all the chemical buffering power of the body fluids is inside the cells, and most of this results from the intracellular proteins. The majority of the $-NH_2$ and $-COOH$ groups of the amino acids forming a protein play no part in the buffering because they are forming the peptide links between the amino acid unit. The only intact $-NH_2$ and $-COOH$ groups are those at the ends of the peptide chains. However, certain amino acids contain additional $-NH_2$ and $-COOH$ groups in their molecules, and these groups are available for buffering as they do not form the peptide links.

Hb as a buffer system: Histidine is an amino acid which contains additional $-NH_2$ and -COOH groups. There are 38 histidine units in the Hb molecule and, as a result, Hb is a particular good buffer. The remarkable buffering capacity of Hb is due to the fact that this protein in the oxy forms (oxy-Hb-) is a stronger acid than in the reduced (deoxy) form (Hb-). At the lungs the formation of oxyHb from reduced Hb must therefore release hydrogen ions, which react with bicarbonate to form carbonic acid. Because of the low carbon dioxide tension in the lung, the equilibrium then shifts toward the production of carbon dioxide which continually eleminated in the expired air. However, in the tissue, where oxygen tension is reduced, oxyHb dissociates, delivering oxygen to the cells and reduced Hb is formed. At the same time, carbon dioxide produced in the course of metabolism enters the blood, where it is combined with water to form H_2CO_3, which ionizes to form H^+ and HCO_3^-. Reduced Hb acting as an anion, which accepts the H^+ ions, forming H-Hb, which is a very weak acid. Very little change in pH occurs because the newly arrived H^+ ions are buffered by formation of a very weak acid. When the blood returns to the lungs these H^+ ions will be released as a result of the formation of a stronger acid, oxyHb, and the newly released H^+ will immediately neutralized by HCO_3^-. This reaction is essential to the liberation of CO2 in the lungs.

Isohydric principle*:* Each of the buffer systems has been discussed as if it could operate individually in the body fluids. However, they all actually work together, for the H^+ is common to the chemical reactions of all the systems. Therefore, whenever any condition causes the H^+ concentration to change, it causes the balance of all the buffer systems to change at the same time. This phenomenon is called the isohydric principle. The important feature of this principle is that any condition that changes the balance of any one of the buffer systems also changes the balance of all the others, for the buffer systems actually buffer each other by shifting H^+ from one to the other.

Respiratory regulation of acid-base balance

Recalling the Henderson-Hasselbalch equation, it was noted that an increase in CO_2 concentration in the body fluids decreases the pH toward acidic side. Whereas a decrease in CO_2 raises the pH toward alkaline side.

[1] The CO_2 concentration in the extracellular fluid can be increased or decreased if the rate of metabolic formation of CO_2 becomes increased or decreased respectively.

[2] In addition, the CO_2 concentration in the extracellular fluid can be increased or decrease if the rate of pulmonary ventilation is decreased or increased respectively. Since alveolar ventilation can be reduced to zero ventilation or increased to about 15 times normal, one can readily understand how the pH of the body fluids can be changed by alterations in the activity of the respiratory system.

A change in blood CO_2 concentration or blood $[H^+]$ affects the rate of alveolar ventilation. These results from a direct action of H^+ on the respiratory center in the medulla oblongate that controls breathing. An increase in blood CO_2 concentration or a change in the arterial pH from 7.4 to the strongly acidic level can increase the rate of alveolar ventilation much higher than of a normal level, whereas a decrease in blood CO_2 concentration or an increase in pH into the alkaline range can decrease the rate of alveolar ventilation.

Because of the ability of the respiratory center to respond to blood CO_2 concentration and H^+ concentration, and because changes in alveolar ventilation in turn alter the blood CO_2 concentration and H^+ concentration in the fluids, the respiratory system acts as a typical feedback regulatory system for

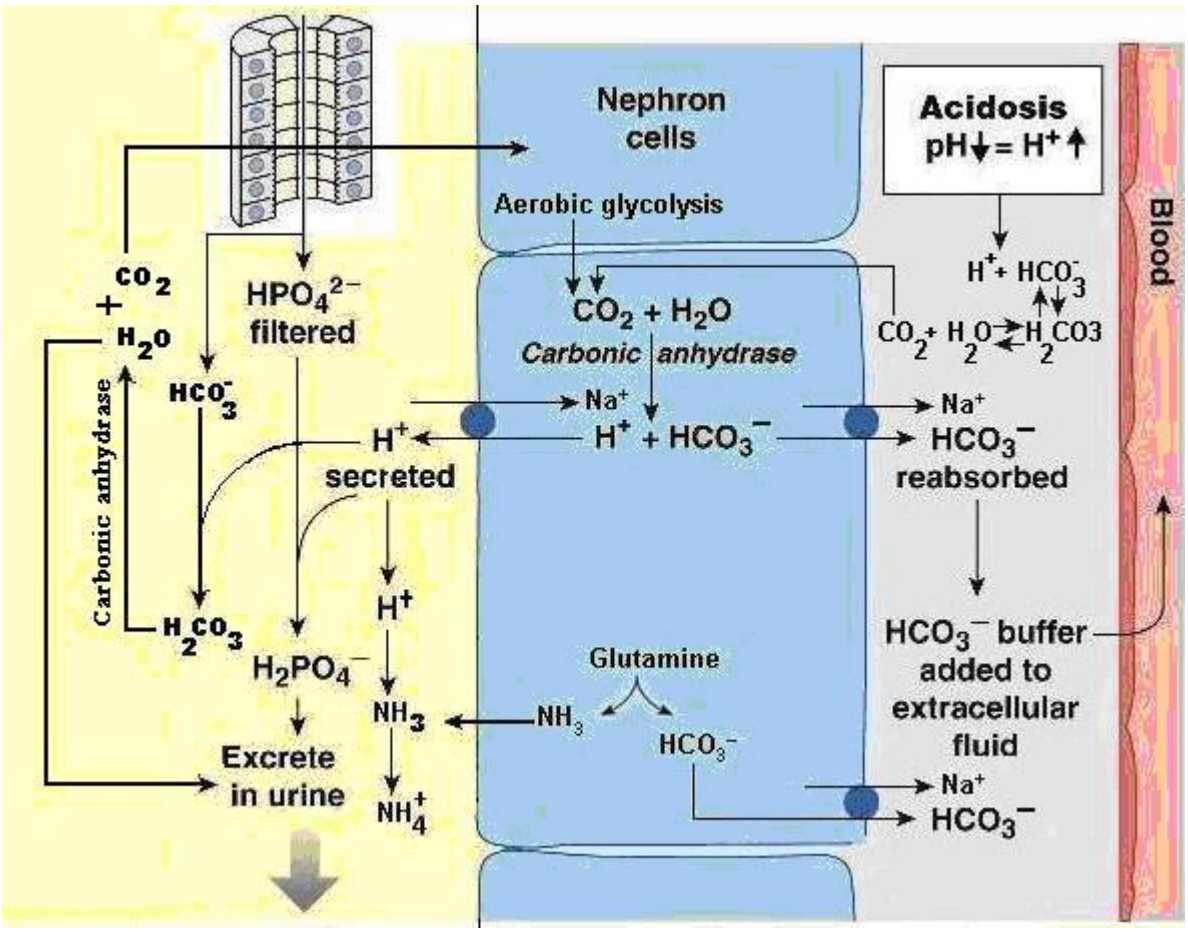
controlling H^+ concentration. That is, any time the H^+ concentration becomes high, the respiratory system becomes more active and alveolar ventilation increase. As a result, the CO_2 concentration in the extracellular fluids decreases, thus reducing the H^+ concentration back toward normal. Conversely, if the H^+ concentration falls too low, the respiratory center becomes depressed, alveolar ventilation also decreases, and the H^+ concentration rises back toward normal. The overall buffering power of the respiratory system is one to two times as great as that of all the chemical buffers combined.

Renal regulation of acid-base balance

The kidneys regulate H^+ concentration principally by increasing or decreasing the HCO_3^- concentration in the body fluid.

[1] Increase H^+ secretion to the urine and HCO_3^- reabsorption to the interstitial fluids: the epithelial cells of the all renal tubules (except descending segment of the of the loop of Henle) secrete H^+ into the tubular fluid in an exchange with Na^+ ions and HCO_3^- into the extracellular fluids. The sodium ion and HCO_3^- then are transported together from the epithelial cell into the extracellular fluid. The mechanism by which this occurs is illustrated in the figure. Since the chemical reactions for secretion the H^+ begin with CO_2, the greater the CO_2 concentration, the more rapidly the reaction proceed, and the greater becomes the rate of H^+ secretion.

Therefore, any factors that increase the CO_2 concentration in the extracellular fluids, such as decreased respiration or increased metabolic rate, also, increase the rate of H^+ secretion. Conversely, any factor that decreases the CO_2, such as excess pulmonary ventilation or decreased metabolic rate, decreases the rate of H^+ secretion.



[2] Incomplete titration of secreted H+ against filtered $HCO3^-$: Under normal conditions, the rate of H^+ secretion is about the rate of filtration of HCO_3^- in the glomerular filtrate, thus, the

quantities of the two ions entering the tubules are almost equal, and they combine with each other and actually titrate each other in the tubules, the end – products being CO_2 and water (see the figure above). Thus, the basic mechanism by which the kidney corrects either acidosis or alkalosis is by incomplete titration of H^+ against HCO_3^-, leaving one or the other of these to pass into the urine and therefore to be removed from the extracellular fluid. From 85 to 98% of this titration process occurs in the proximal tubules, and the carbonic acid formed by the titration reaction is then split rapidly by the large amount of carbonic anhydrase attached to the luminal brush border surface of the proximal tubules (but not of the other tubules) into its end- products, carbon dioxid diffuses into the extracellular fluid.

In acidosis, the ratio of CO_2 to HCO_3^- in the extracellular fluid increases. Therefore, the rate of secreted and filtered H^+ rises to a level far greater than the rate of HCO^{3-} filtration into the tubules. As a result, a great excess of H^+ is passed into the tubules, which have far too few HCO_3^- to react with. These excess H^+ combine with the buffers in the tubular fluid and are excreted into the urine. The net effect of secreting excess H^+ into the tubules is to increase the quantity of HCO_3^- in the extracellular fluid. This increases the HCO_3^- portion of the HCO_3^- buffer system, which, in accordance with Henderson-Hasselbalch equation and the isohydric principle, shifts all the buffers to the alkaline direction, increasing the pH in the process, and thereby correcting the acidosis. When excess H^+ are secreted into the tubules, only a small portion of these can be carried in the free form by the tubular fluid into the urine. The majority of the excess H^+ is usually carried by combination with intratubular buffers which transport the excess H^+ into the urine and these are:

1. The phosphate buffer.

2. Ammonia buffer system: Which is composed of all ammonia (NH_3) and the ammonium ion (NH_4^+). The epithelial cells of the renal proximal tubules continually synthesize NH_3, and this diffuses into the tubules. This buffer system is especially important for two reasons:

[A] Each time an NH_3 molecule combines with a H^+ to form NH_4^+ the concentration of NH_3 in the tubular fluid becomes decreased, which causes still more NH_3 to diffuse from the epithelial cells into the tubular fluid. Thus, the rate of NH_3 secretion into the tubular fluid is actually controlled by the amount of excess H^+ to be transported.

[B] Most of the negative ions of the tubular fluid are chloride ions. Only a few H^+ could be transported into the urine in direct combination with chloride because HCI is very strong acid and the tubular pH would fall rapidly below the critical value of 4.5 below which further H^+ secretion is inhibited. However when H^+ combine with NH_3 and the resulting NH_4^+ then combine with chloride the pH does not fall significantly because NH_4CI is only very weak acidic. If the tubular fluids remain highly acidic for long periods of time the formation of NH_3 steadily increases during the first two or three days rising as much as tenfold illustrating that the NH_3 secreting mechanism can adapt readily to handle greatly increased loads of acid elimination. The principal cause of the increasing NH_3 formation is that local acidosis of the tubular cells induces the production of large amounts of the enzyme glutaminase that is responsible for releasing NH_3 from glutamine.

In alkalosis the ratio of HCO_3^- to dissolved CO_2 molecules increases. This will result to an increase the ratio of HCO_3^- filtered into the tubules over the secreted and filtered H^+. Therefore far greater quantities of HCO_3^- than H^+ now enter the tubules. All the excess HCO_3^- pass into the urine and carry with them sodium ions or other positive ions thus in effect no bicarbonate is removed from the extracellular fluid. Loss of sodium bicarbonate from the extracellular fluid decreases the HCO_3^- portion of the bicarbonate buffer system which in accordance with Henderson –Hasselbalch equation and the isohydric principle shifts all the buffers to the acidic direction decreasing the pH in the process and thereby correcting the alkalosis.

In the process of adjusting the H^+ concentration of the extracellular fluid the kidneys often excrete urine at pHs as low as 4.5 or as high as 8.0. Even when the pH of the extracellular fluids is at the value of 7.4 a fraction of a millimole of acid is still lost each minute the reason for this is that about 50-80 millimoles more acid than alkali are formed in the body each day and this acid must be removed continually. Because of the presence of this excess acid in the urine the normal urine pH is about 6.0 instead of 7.4 the pH of the blood.

Clinical applications

This is guaranteed to keep coming up on every exam for the rest of your life, so you might as well learn it.

The normal physiological blood pH is between **7.35- 7.45**. **Acidosis** means that there is an excess of H^+ in the blood with pH of the arterial blood of 7.34 and less. **Alkalosis** means that there is less [H^+] than normal with pH of arterial blood of 7.46 or more.

Normal values:
pH = 7.35-7.45
Blood pCO_2 = 35-45 mmHg
Plasma HCO3- = 22-28 mEq/L

There are four types of disturbances: Respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis. These rarely occur clinically in isolation; there is usually a secondary change tending to restore [H^+] to normal and often a further complicating primary disorder which may tend either to restore or aggravates a change in [H^+].

1-Respiratory acidosis (CO_2 retention): This condition arises when the effective alveolar ventilation does not match with the rate of production of carbon dioxide. As a result the PCO_2 and carbonic concentration of the blood increases and the pH falls this condition frequently results from pathological condition and these are:

A. Any factor that interferes with the gaseous exchange between the blood and the alveolar air can cause respiratory acidosis such as airway obstruction, pneumonia, etc.
B. Any factor that causes a reduced breathing that may result from depression or damage to the respiratory center or skeletal deformities or paralysis of respiratory muscles that causes reduced breathing.

The primary laboratory findings in respiratory acidosis are the following:

[a] Arterial blood pH is below the normal value.

[b] Arterial blood [H^+] is above normal.

[c] Arterial blood PCO_2 is increased above the normal level. A number of biochemical reactions are initiated that minimize the rise in [H^+]. Weak acids, such as Hb and proteins, titrate [H^+], Cl^- moves into RBCs in exchange for HCO_3^- (chloride shift). Given time (hours or days) the kidney compensates for the rise in [H^+] by excreting more H^+ and retaining bicarbonate and producing a secondary responses in which;

[d] Arterial blood [HCO_3^-] is elevated because the kidney reacts to a raised PCO_2 by retaining bicarbonate ions and excreting hydrogen ions (thus excreting acidic urine). This process is significant during the first 24-48 hours and is usually maximal within 3-4 days. In compensatory respiratory acidosis, the pH is normal, arterial blood PCO_2 is increased above the normal level and arterial blood [HCO_3^-] is elevated. However renal compensation begins to fail when the PCO_2 rises above 9.5-10 kpa. Since the kidneys continue to excrete an acid urine for several days after the PCO_2 is lowered there is a great risk of causing an iatrognic metabolic alkalosis.

2-Respiratory alkalosis (CO2 washout or deficit): this condition arises when there is excessive loss of carbonic acid by overventilation of the lungs. It is usually due to over breathing from any cause such as:

[a] Hysteria.
[b] Overventilation in a mechanical respirator.
[c] Injury of respiratory center in the course of meningitis or encephalitis.
[d] In early stage of salicylate (aspirin) intoxication due to pharmacological stimulation of respiratory center but later a metabolic acidosis becomes the dominant change.
[e] In liver failure.
[f] At high altitude in which the low oxygen content of the air stimulates respiration that causes excess loss of carbon dioxide and development of mild respiratory alkalosis.

The primary laboratory findings are:
[a] Arterial blood pH is above the normal value,
[b] Arterial blood $[H^+]$ is below normal,
[c] Arterial blood PCO_2 is decreased below the normal level. The kidney reacts by excreting more bicarbonate ions and reabsorbing more H^+ ions (thus excreting an alkaline urine) causing a secondary response in which,
[d] Arterial blood $[HCO_3^-]$ is below normal level due to loss of bicarbonate in the urine. In compensatory respiratory alkalosis, the pH is normal, arterial blood PCO_2 is decreased below the normal level and arterial blood $[HCO_3^-]$ is decreased.

3-Metabolic acidosis: This condition arises as a result of the accumulation of acids other than carbonic acid in the body or as a consequence of body depletion of the base bicarbonate. The aetiologies of this condition are:

[A] Accumulation of lactic acid (vigorous exercise, shock from any cause, acute alcoholic intoxication.).
[B] Accumulation of ketone bodies in uncontrolled diabetes mellitus.
[C] Renal diseases: in which the kidneys are unable to excrete hydrogen ions at a normal rate as in renal failure, and renal tubular acidosis.
[D] Diuretics such as carbonic anhydrase inhibitor as acetazolamide (Diamox) which is used frequently to cause diuresis also cause a mild degree of acidosis. This occurs because inhibition of the carbonic anhydrase of the proximal tubular epithelium prevents adequate reabsorption of bicarbonate ions from the lumen of the nephrones of the kidney in the form of CO_2. Loss of these ions into the urine causes a decrease in bicarbonate ions in the extracellular fluid, thus leading to acidosis.
[E] Loss of intestinal contents: From fistulae or by intestinal aspiration or in severe diarrhoea that causes an excessive loss of bicarbonate ions present in the gastrointestinal secretion in the stool.
[F] Vomiting, if the vomitus contains the secretion of the intestinal tract (which is rich in bicarbonate), rather than the stomach contents only.
[G] Ingestion of toxins (salicylates, methanol, ethylene glycol).

The primary laboratory findings in metabolic acidosis are:
[a] Arterial blood pH is below the normal value.
[b] Arterial blood $[H^+]$ is above normal.
[c] Arterial blood $[HCO_3^-]$ is below normal value. The rise in $[H^+]$ causes an increase in pulmonary ventilation causing a secondary response in which,
[d] Arterial blood PCO_2 is decreased below the normal level due to stimulation of respiratory center by the high hydrogn ions concentration leading to an excessive washout of carbon dioxide from the body. In compensatory metabolic acidosis, the pH is normal, arterial blood PCO_2 is decreased below the normal level and arterial blood $[HCO_3^-]$ is decreased.

Anion gap: The accepted range for the normal anion gap is **5 to 11** mEq/L. Clinicians should consider their particular laboratory's reference range when assessing the anion gap. It is the difference between measured cations and measured anions. It is defined as:

The anion gap = [Na] - [Cl] - [HCO3]

Serum ion gap > 11 mmol/L can indicate metabolic acidosis
Serum ion gap > 20 mmol/L always indicates metabolic acidosis

The etiologies of metabolic acidosis are divided into:
[A] A **normal** anion gap acidosis (**hyperchloremic acidosis**). A normal anion gap acidosis occurs when Cl replaces the HCO3 lost in buffering H. Normal anion gap acidosis occures from loss of HCO3 through the kidneys or the gut, or from the addition of an acid with Cl as the accompaining anion. The most common cause is diarrhea; in its absence, a renal tubular acidosis is likely. The other causes are usually obvious from the history and medication list.

[B] Those that cause an **increase** in the anion gap (**normochloremic acidosis**).

An increased anion gap acidosis occurs when the anion replacing the HCO3 is albumin, phosphate, sulfates, or lactate. An increased anion gap does not always signify a metabolic acidosis. It increases in alkalemia, because of an increase in the net anionic charge on plasma proteins. Dehydration will also increase it because of an increased protein concentration. However, if it is greater than 20 mEq/l, a metabolic acidosis should be pursued.
The etioligies of increased anion gap acidosis are

- Accumulation of lactic acid
- Ingestion of toxins (salicylates, methanol, ethylene glycol)
- Accumulation of organic anions, phosphates, sulfates in renal failure

[4]- Metabolic alkalosis: This condition arises most commonly as a result of:

[A] Abnormal loss of HCl as in nasogastric suction or in the course of prolonged or severs vomiting. This type of alkalosis occurs in newborn children who have pyloric obstruction.
[B] Excessive ingestion of alkaline drugs such as sodium bicarbonate for the treatment of peptic ulcer.
[C] Diuretics in general cause increased flow of fluid along the tubules and this increase in the flow usually causes great excess amounts of sodium ions to flow into the distal and collecting tubules, leading also to a rapid reabsorption of sodium ions from these tubules. This rapid reabsorption is coupled with enhanced hydrogen ion secretion because of the Na^+- H^+ countertransport mechanism in the luminal membranes of the tubular cells that links hydrogen secretion to sodium reabsorption, hence excessive loss of hydrogen ions from the body and resultant extracellular fluid alkalosis.
[D] Excess aldosterone secretion by the adrenal glands. Aldosterone promotes extensive reabsorption of sodium ions and simultaneous excretion of potassium from the distal segments of the tubular system, but coupled with this reabsorption of sodium is increased secretion of hydrogen ions which promotes alkalosis.
[E] Chloride deficiency itself also leads to alkalosis because it stimulates the renal tubular reabsorption of bicarbonate. This is especially liable to occur with the use of high potency diuretics that block chloride reabsorption.
[F] Potassium depletion also gives rise to extracellular alkalosis. This is because extracellular K depletion encourages the transfer of hydrogen ions from plasma and extracellular fluid into the cells (intracellular acidosis) as well as their excretion in urine (acidic urine).

The primary laboratory findings are:
[a] Arterial blood pH is above the normal value.
[b] Arterial blood [H^+] is below normal.
[c] Arterial blood [HCO_3-] is above normal level. The fall in [H^+] causes a decrease in pulmonary ventilation causing a secondary response in which,
[d] Arterial blood PCO_2 is increased above the normal level due to loss of stimulation of respiratory center by the low hydrogen ion concentration leading to a less washout of carbon dioxide from the body, but this is often small and may not occur at all. The reason for this lack of respiratory response is not clear. The lack of respiratory response leads to the development of a significant alkalaemia in most cases of primary metabolic alkalosis.
[e] The urine pH in metabolic alkalosis is alkaline except in the presence of severe K depletion, when paradoxical aciduria can occur.

Summary of acid-base disturbances

The primary event is indicated by the double arrows (↑↑ or ↓↓). Note that respiratory acid-base disorders are initiated by an increase or a decrease in PCO_2, whereas metabolic disorders are initiated by an increase or decrease in HCO_3^-.

Condition	pH	PCO_2	[HCO_3^-]
Respiratory acidosis	↓	↑↑	↑ **compensation**
Respiratory alkalosis	↑	↓↓	↓ **compensation**
Metabolic acidosis	↓	↓ **compensation**	↓↓
Metabolic alkalosis	↑	↑ **compensation**	↑↑

Mixed disturbances: mixed disturbances are very common and may have opposing or additive effects on blood [H^+].

[A] Opposing disturbances:

[1] Respiratory alkalosis and metabolic acidosis: this combination occurs for example if heart failure with pulmonary congestion is combined with renal failure, and in salicylate poisoning. The latter condition is associated with initial respiratory alkalosis due to stimulation of the ventilation by the salicylate but later complicated by metabolic acidosis.

[2]. Respiratory acidosis and metabolic alkalosis: this combination occurs in patients with ventilatory failure and edema (as in corpulmonale) that is overtreated with diuretics is causing K and / or Cl ions depletion. This combination is commonly associated with intracellular acidosis.

[B] Additive disturbances:

[1] Respiratory acidosis and metabolic acidosis: this combination occurs in respiratory failure associated with circulatory failure.

[2] Respiratory alkalosis and metabolic alkalosis: this combination can occur as a complication of respiratory failure if excessive artificial ventilation is given and K and/or Cl ions depletion is induced by excessive diuretic therapy.

Base Deficit:

The base deficit (or excess) is the number of mEq/L of base (or acid) needed to titrate a serum pH back to normal when the contribution of respiratory factors is taken out of the equation. That is, how much acid or base would be required to correct the patient's arterial pH to 7.4 as if the pCO_2 were 40, at 37C.

The BD/BE is a quick indication of the metabolic component of the patient's condition. If there is a large base deficit it indicates that even if the patient's respiratory problems were resolved, there is a significant metabolic acidosis.

The BD can be used to calculate the whole body base deficit in the same way you would calculate the amount of sodium to replete in hyponatremia:

BD * 0.5 * kg = mEq of bicarbonate

However, it is recommended that replacement consist of only 0.3 * BD * kg per dose or trials of 1 mEq/kg/dose. These doses should be infused slowly (over 30 to 60 minutes). Bicarbonate should only be administered when adequate ventilation is assured. Generally, it is used to correct the pH up to 7.1.

The BD/BE can be used in conjunction with the other data provided on a blood gas to assess the patient's acid-base status.

Helps in interpretation of acid-base disturbances:

The results of arterial blood gases can lead to one of the following conclusions

Respiratory acidosis

- Uncompensated – pH decreased, HCO3 normal, and PCO2 increased
- Partially compensated – pH decreased, HCO3 increased, and PCO2 increased
- Fully compensated – pH normal, HCO3 increased, and PCO2 increased

Respiratory alkalosis

- Uncompensated – pH increased, HCO3 normal, and PCO2 decreased
- Partially compensated – pH increased, HCO3 decreased, and PCO2 decreased
- Fully compensated – pH normal, HCO3 decreased, and PCO2 decreased

Metabolic acidosis

- Uncompensated – pH decreased, HCO3 decreased, and PCO2 normal
- Partially compensated – pH decreased, HCO3 decreased, and PCO2 decreased
- Fully compensated – pH normal, HCO3 decreased, and PCO2 decreased

Metabolic alkalosis

- Uncompensated – pH increased, HCO3 increased, and PCO2 normal
- Partially compensated – pH increased, HCO3 increased, and PCO2 increased

- Fully compensated – pH normal, HCO3 increased and PCO2 increased

In fully compensated acidosis the pH will be below 7.40, and in fully compensated alkalosis it will be above 7.40.

You can figure out if a patient is in Respiratory or Metabolic Acidosis/Alkalosis depending on the values of the arterial blood gases (ABGs). The easiest way to decide whether or not it is Respiratory or Metabolic is by using the **ROME** technique.

Respiratory **O**pposite, **M**etabolic **E**qual. If the pH is opposite the PCO2 (either high or low), then it is a respiratory problem. If the pH is equal to the HCO3, it is metabolic.

Here are examples:

pH 7.30, PCO2 50, HCO3 26
Uncompensated respiratory Acidosis.

pH 7.50, PCO2 43, HCO3 45
Uncompensated metabolic Alkalosis.

pH 7.31, PCO2 33 mmHg, HCO3 16, Na+ 134, Cl- 108
Partially compensated metabolic acidosis
The anion gap is Na - (Cl + HCO3-) = 134 - (108 + 16) = 10
since gap is within normal range.

pH 7.05, PCO2 12, HCO3 5
Partially compensated metabolic acidosis

pH 7.38, PCO2 76, HCO3 42
Fully compensated respiratory acidosis

pH = 7.08, PCO2 = 14, HCO3 = 4, Na = 140, Cl = 104
Partially compensated metabolic acidosis
The anion gap is 140 - (104 + 4) = 32, thus elevated

pH 7.37, PCO2 = 18, HCO3 = 10, Na = 140, Cl = 114
Fully compensated metabolic acidosis
The anion gap is 140 - (114 + 10) = 16, thus elevated

pH = 7.34, PCO2 = 68, HCO3 = 32.4
Partially compensated respiratory acidosis

pH = 7.35, PCO2 = 30 mm Hg, HCO3 = 16 mmol/L
Fully compensated metabolic acidosis

pH = 7.45, PCO2 = 30 mm Hg, HCO3- = 20 mmol/L
Fully compensated respiratory alkalosis

pH = 7.55, PCO2 = 27 mm Hg, HCO3 = 23 mmol/L
Uncompensated respiratory alkalosis ("get the bag out!")

pH = 7.30, PCO2 = 34 mm Hg, HCO3 = 24 mmol/L
Data incompatibility ("get the technician out?)

pH = 7.5, PCO2 = 29, HCO3 = 25
Uncompensated respiratory alkalosis

pH = 7.2, PCO2 = 64, HCO3 = 25
Uncompensated respiratory acidosis

pH = 7.31, PCO2 = 72, HCO3 = 35
Partially compensated respiratory acidosis

Calculations:
A: Calculate the pH of an arterial blood at arterial PCO_2 = 40 mmHg, and $[HCO_3^-]$ = 24 mmol/L.
Answer:

$$pH = 6.1 + \log \frac{[HCO_3^-] \text{ in mmol/l}}{[CO_2] \text{ in mmol/L}} = 6.1 + \log \frac{[HCO_3^-] \text{ in mmol/L}}{PCO_2 \text{ X } 0.03}$$

:

$$pH = 6.1 + \log \frac{24 \text{ mmol/L}}{40 \text{ mmHg X } 0.03} = 6.1 + \log 20 = 7.4$$

B: Conversion of $[H^+]$ to pH: Calculate the pH of a solution with $[H^+]$ = 40 nmol/L

$$pH = 9 - \log [H^+]$$
$$= 9 - \log 40$$
$$= 9 - 1.6$$
$$= 7.4$$