Acid- Base Balance

Introduction

Normally the $[H^+]$ in the body fluids is kept at a low level, its concentration in the extracellular fluid is about 40nM/L (ranges from 4 times less (10 nM/L) to 4 times more than normal (160 nM/L) (16 times difference). The body can tolerate a greater increase of H^+ from 40 to 160nM/L (120 nM difference) than decrease from 40 to 10nM/L in the $[H^+]$ (30 nM difference). Our body is ready to deal with attacking acids more than with attacking alkali!!!!

(i.e our body can tolerate a greater change in the acidic direction than the alkaline direction).

Compare $[H^+]$ to $[Na^+]$: $[Na^+]$ = 145 mM/L

$[H^+]$ = 40 nM/L

$[Na^+]$: 3.5 million times more than $[H^+]$

$[H^+]$: the only ion that can vary widely from 10-160 nM

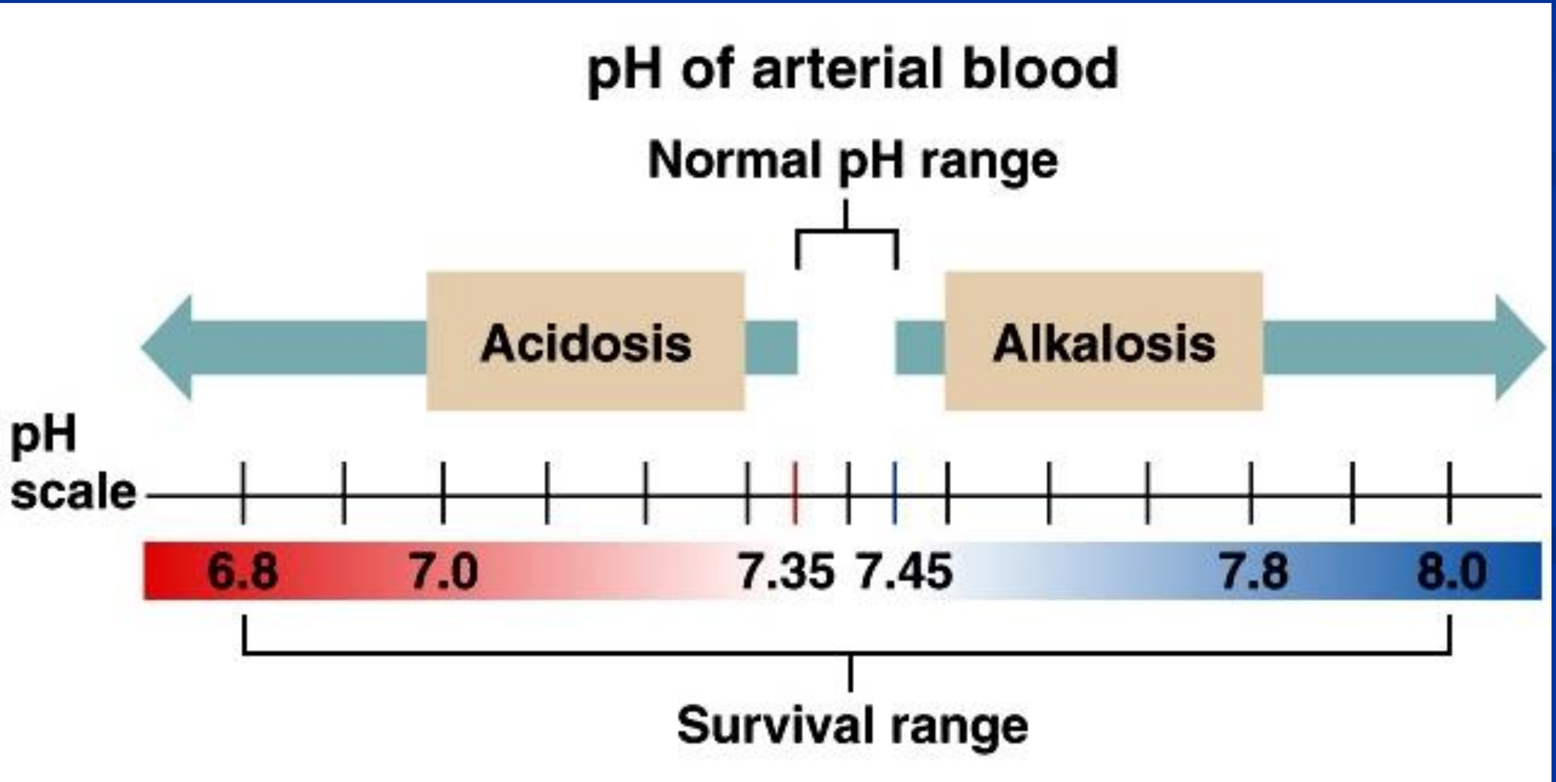
Normal Acid-Base Balance

Normal pH 7.35-7.45

- Below 7.35 acidosis Above 7.45 alkalosis

Narrow normal range

Compatible with life 6.8 - 8.0



- The pH = -log [H^+]…p stands for "-log"
- pCa^{++}=-log [Ca^{++}]
- So at normal extracellular H^+ concentration (40nM/L)
- -Log 40 nM= log $4X10^{-8}$ = log 4 + log 10^{-8} = 7.4
- our arterial blood pH is equal to 7.4 (7.35-7.45)
- Venous blood and interstitial fluid pH = 7.35 due to excess CO_2
- Intracellular pH ranges from 6.0 – 7.4 (In general 7.0 is the average).
- Urine pH ranges from 4.5 – 8. usually, it is acidic
- (<u>Note : Hypoxia decreases intracellular pH due to acid accumulation</u>)

- An acid is a proton donor, while a base is a proton acceptor.
- Strong acids or bases dissociate (ionize) completely in solution such as HCl and NaOH.
- Weak acids ionizes only partially in a solution: such as H_2CO_3.
- Weak bases also partially ionize such as $NaHCO_3^-$ or HPO_4^{-2} .

(Note : Hemoglobin and other body proteins are of the most important body bases).

Most of our body acids and bases are weak acids and weak bases

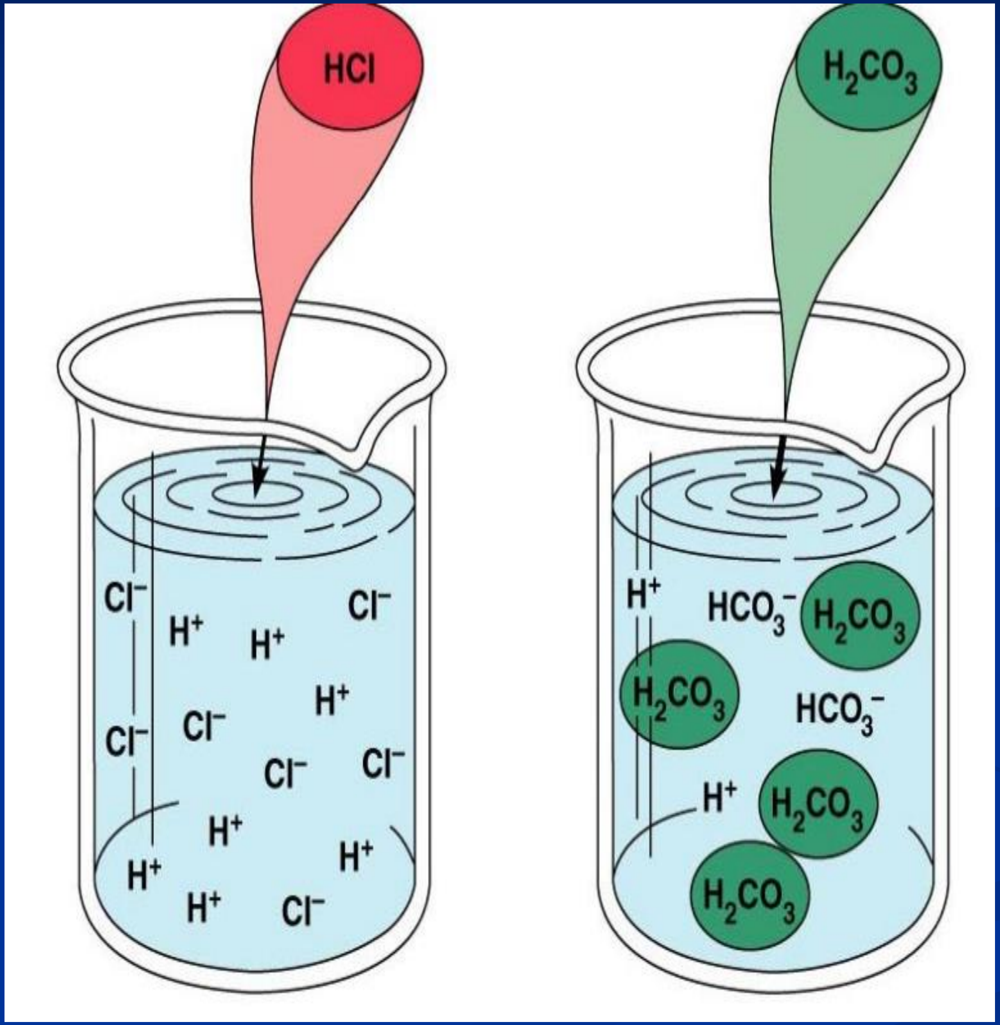
<u>Defense against changes in hydrogen ion concentration</u>:

Our body is at a constant threat of becoming acidic, so how does it deal with these acids?

1. First Line of defense: Chemical acid-base buffer system (Very Fast)
2. Second Line: The respiratory center (removes or retain CO_2: intermediate speed, few minutes to react and few hours to give the full response)
3. Third Line: The kidneys (the most powerful regulatory system), a slow system that takes a few hours to start working and 3-5 days to reach full response.

So, in acute acidosis, the kidney might not be able help.

Strong and weak acid



Normally it:

	10 nanoMol	←	40 nanoMol	→	160 nanoMol
	Tolerated	÷4	Normal	*4	tolerated
pH	(8)		(7.4)		(6.8)

Lethal ← 6.8 ← (7.35 – 7.45) → 8 → lethal

getting acidosis	Normal pH	getting alkalosis

pH < 6.8 OR > 8 : Deadly

Acid-Base Balance

Small changes in pH can produce major disturbances and have dramatic effects on normal cell function

1. **Influences enzyme activity.**

   Most enzymes function only with narrow pH ranges

Acidosis → suppression of CNS → coma → death.

alkalosis → convulsions of the respiratory muscle → death.

2. **Affects hormones.**

3. **Affects electrolytes (Na^+, K^+, Cl^-, Ca^{++}).**

4. **Changes in excitability of nerve and muscle cells.**

Example: Influences on K^+ levels

- When reabsorbing Na^+ from the filtrate of the renal tubules K^+ or H^+ is secreted (exchanged).
- Normally K^+ is secreted in much greater amounts than H^+.
- If H^+ concentrations are high (acidosis) then H^+ is secreted in greater amounts.
- This leaves less K^+ than usual excreted.
- The resultant **K^+ retention** can affect cardiac function and other systems.

Acids can be volatile or Non-volatile.

Volatile Acids:

The volatile acid are in the form of H_2CO_3. Normally we exhale 300 L of CO_2/D, which corresponds to daily production of 10 M H^+ **(huge amounts), but usually it does not cause problems because it is always getting engaged in this pathway:**

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

CA: carbonic anhydrase enzyme fits here.

- * If more H+ is produced in your body: reaction shift to left CO_2 will be eliminated by the lungs.

Therefore, acidosis is corrected.

*** If H+ is less, rxn shifts to right; respiration is depressed**

More CO_2, is retained → forming H^+

Note: "CO_2 is considered as masked H^+"

Our body has tendency towards acidosis rather than alkalosis.

- Acids taken with foods.
- Acids produced by metabolism of lipids, carbohydrates and proteins.
- Cellular metabolism produces CO_2.

$$CO_2 + H_20 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Non-volatile acids (Fixed Acids):

-Phosphoric acid from oxidation of phosphoproteins, phospholipids, and nucleic acid.

-Sulphoric acid → oxidation of methionine and cysteine

-Others: lactic, pyrovic, beta-OH butyric acid, acetoacetic acids, and Krebs cycle acids.

All these acids are not in the form of CO_2

Our body produces around 1 mmol/kg /day of these fixed acids

So, 80 mmol /day are being produced. *The body produces large amounts of acid but body fluids remain slightly alkaline*

80 mmol/day when distributed over the 14 L of ECF; each L gets 5 mmol (correspond tp pH less than 3): this is very low pH (incompatible with life)….we must get rid ot these 80 mM

- Why not secreting 80 mMole of H^+ in the urine in its free form???

Bcs: Minimum pH of urine = 4.5. this correspond to less than 0.1 mM

Other option: add 80 mMole of HCO_3^- from the ECF and convert it to CO2, and let the lung take care of it.

$CO2 + H2O \leftrightarrow H2CO3 \leftrightarrow 80\ mM\ H^+ + 80\ mM\ HCO_3^-$

The problem has been solved, and we get rid of these acids.

We need a Bicarbonate Bank (continuous formation)

$[HCO_3^-] = 24$ mmol /L

How much in 14L of ECF

24 * 14 = 336 mmol /L

→ those will be enough just for (4-5 days)

Each day you need 80 mmol.

- So, an important function of the kidney is to make new bicarbonate.

In AKI: Acidosis. Kidneys fail to produce new bicarbonate

Why not excreting H^+ in the urine in its free ..let form?...let us see

Minimum urine pH = 4.5 …this correspond to:

$[H^+] = 10^{-4.5}$ M/L = $3X\ 10^{-5}$ M/l = 0.03 mM/L

Yet, the kidneys must excrete, under normal conditions, at least 80 mmol non-volatile acids each day. To excrete this as free H^+ would require :

$$\frac{80 \text{ mmol}}{.03 \text{mmol/L}} > 2000 \text{ L per day !!!}$$

Mechanisms of Hydrogen Ion Regulation

Regulation maintained by:

1. Body fluid chemical buffers
   - bicarbonate
   - ammonia
   - proteins
   - phosphate

2. Lungs (eliminates CO_2)

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

3. Kidneys

   (powerful)

   - eliminates non-volatile acids
   - secretes H^+
   - reabsorbs HCO_3^-
   - generates new HCO_3^-

First line of defense against pH shift

- Chemical buffer system
  - Bicarbonate buffer system
  - Phosphate buffer system
  - Protein buffer system

Second line of defense against pH shift

- Physiological buffers
  - Respiratory mechanism (CO_2 excretion)
  - Renal mechanism (H^+ excretion)

Rates of correction

- Chemical buffers function almost immediately (fraction of a second to minutes).
- Respiratory mechanisms take minutes to hours.
- Renal mechanisms may take hours to days.

The Buffer System:

Buffers React within a fraction of a second.

A buffer prevents a change in pH when H^+ is added or removed from a solution within certain limits (All chemicals can buffer up to 1000 mM H^+ before there is any significant shift in pH).

- Buffer is a substance that releases or binds H^+ reversibly to resist marked pH changes and keep it compatible with life. Buffers don't eliminate or add H^+ but keep it tied up until balance can be reached.

- Principle body buffers:

a) Bicarbonate/carbonic acid buffer system (most important system in the ECF)

b) Phosphate buffer system (HPO_4^{-2}, $H_2PO_4^-$):most important intracelullar and intra-tubular

c) Proteins (important intracellular buffers, ex: Hemoglobin)

Buffer Systems in the Body

1. Bicarbonate: most important ECF buffer

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

2. Phosphate: important ICF and renal tubular buffer

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

3. Ammonia: important renal tubular buffer

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

4. Proteins: important ICF and ECF buffers

$H^+ + Hb$ HHb

Largest buffer store in the body

Albumins and globulins, such as Hb

Bicarbonate buffer system:

Consists of a weak acid (H_2CO_3) and a bicarbonate salt, predominantly $NaHCO_3$ which ionizes completely into Na^+ and HCO_3^-

Again to the same equation:

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

To calculate the pH of this buffer system, we use the ***Henderson-Hesselbalch Equation***:

$$pH = pK + \log [Salt/Acid]$$

The pK for the bicarbonate/carbonic acid is pK= 6.1

The salt is the bicarbonate ion, and the acid is CO_2

CO_2 is measured by its partial pressure (PCO_2)

To convert it to mMole :multiply by 0.03

Arterial PCO_2 = 40mm Hg correspond to 1.2 mMole (40 * 0.03)

Bicarbonate Buffer System

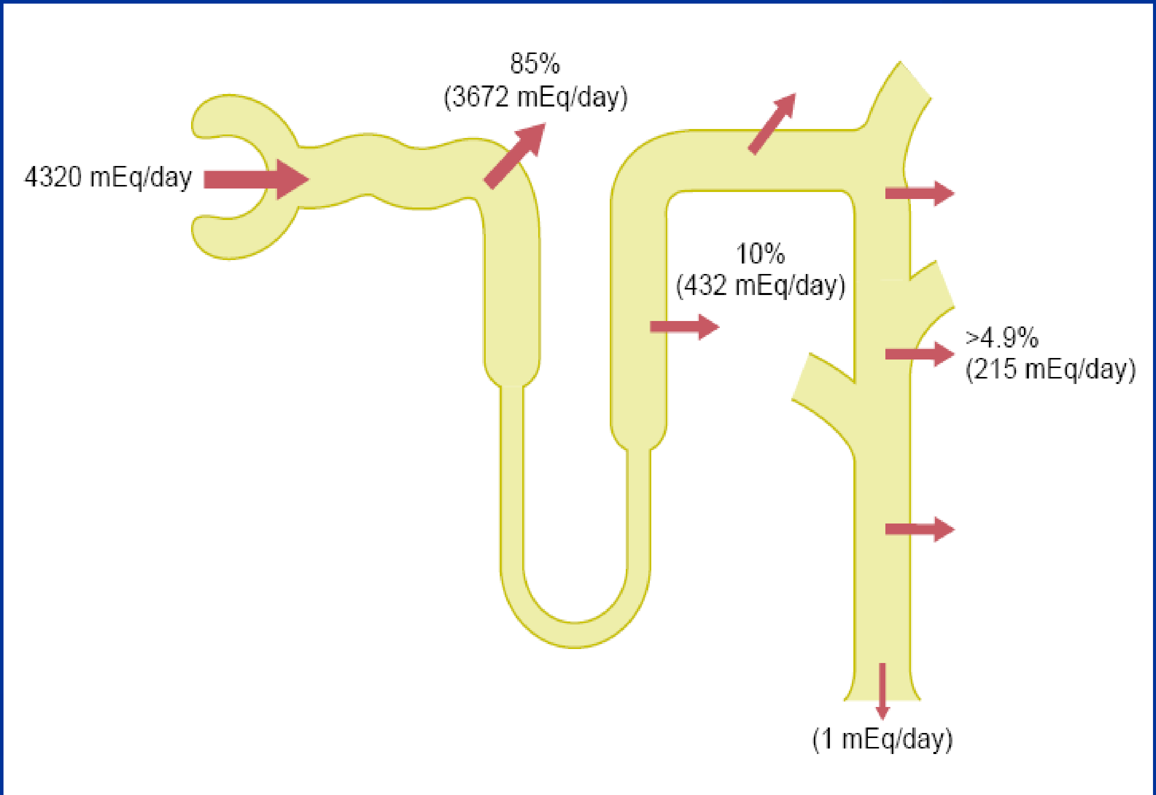
- Bicarbonate is the most important buffer in extracellular fluid.
- H_2CO_3 is formed in the body by the reaction of CO_2 with H_2O.

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

Renal Regulation
Bicarbonate

H^+ Secretion and HCO_3^- reabsorption occur in all tubules (mainly proximal, 85%) except the descending and ascending thin limbs of the loop of Henle.

- Kidneys filtrate 4320 mEq/day bicarbonate.
- HCO_3^- completely reabsorbed under normal conditions.
- Equal amount of H^+ is secreted.



$pH = 6.1 + \log \{HCO_3^- / [0.03 * PCO_2]\}$

Substituting the actual concentrations would give us:

$pH = 6.1 + \log [24/1.2] = 6.1 + \log 20$

$= 6.1 + 1.3$

$= 7.4$

We can calculate the pH of any buffer by using the above equation if we know the pK and the concentration of the buffer in its salt and acid forms.

Ex: pK for phosphate buffer = 6.8

$pH = 6.8 + \log [1.0 mmol / 0.25]$

$= 6.8 + 0.6$

$= 7.4$

Ex: ammonia/ammonium ion system (pK = 9.2):

(Note: its not one of the buffer systems mentioned above)

$pH = 9.2 + \log [NH_3 / NH_4^+]$

the result is also 7.4

→ **Isohydric principle**:

States that all buffers in a common solution are in equilibrium with the same hydrogen ion concentration

Therefore, whenever there is a change in the ECF H^+ concentration, the balance of all other buffer systems changes at the same time.

→ Changing the balance of one buffer system changes the others because the systems actually buffer each other.

•To see how this buffer system works, if we add HCl (strong acid) to the solution, the following reaction takes place to change the strong acid (HCl) into a weak acid (H_2CO_3):

$$HCl + NaHCO_3 \longrightarrow NaCl + H_2CO_3$$

While if a strong base was added as NaOH, the buffer system changes it into a weak base ($NaHCO_3$) by the following reaction:

$$NaOH + H_2CO_3 \longrightarrow NaHCO_3 + H_2O$$

Back to Henderson-Hesselbalch Equation, to explain what pK is (taking the bicarbonate buffer as an example):

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

K' (Dissociation constant) = $[H^+]\ [HCO_3^-]\ /\ [H_2CO_3]$

From the equation, $[H^+] = K' * ([H_2CO_3]\ /\ [HCO_3^-])$

However, the CO_2 dissolved in the blood is directly proportional to the amount of undissociated H_2CO_3

So, the equation can be rewritten as:

$H^+ = K * (0.03 * PCO_2\ /\ HCO_3^-)$

Now, by taking – log of both sides, the equation will be:

$pH = pK + \log\ (HCO_3^-\ /\ 0.03 * Pco_2)$

Log (1) = zero, so when the concentration of the salt form (HCO_3^-), equals the concentration of the acid form (CO_2), then the pH = pK.

- In other words,

  <u>pK is the pH of a solution when the salt form is equal to the acid form. (Here pK=6.1)</u>

Bicarbonate Buffer System

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

$$pH = pK + \log \frac{HCO_3^-}{\alpha * PCO_2}$$

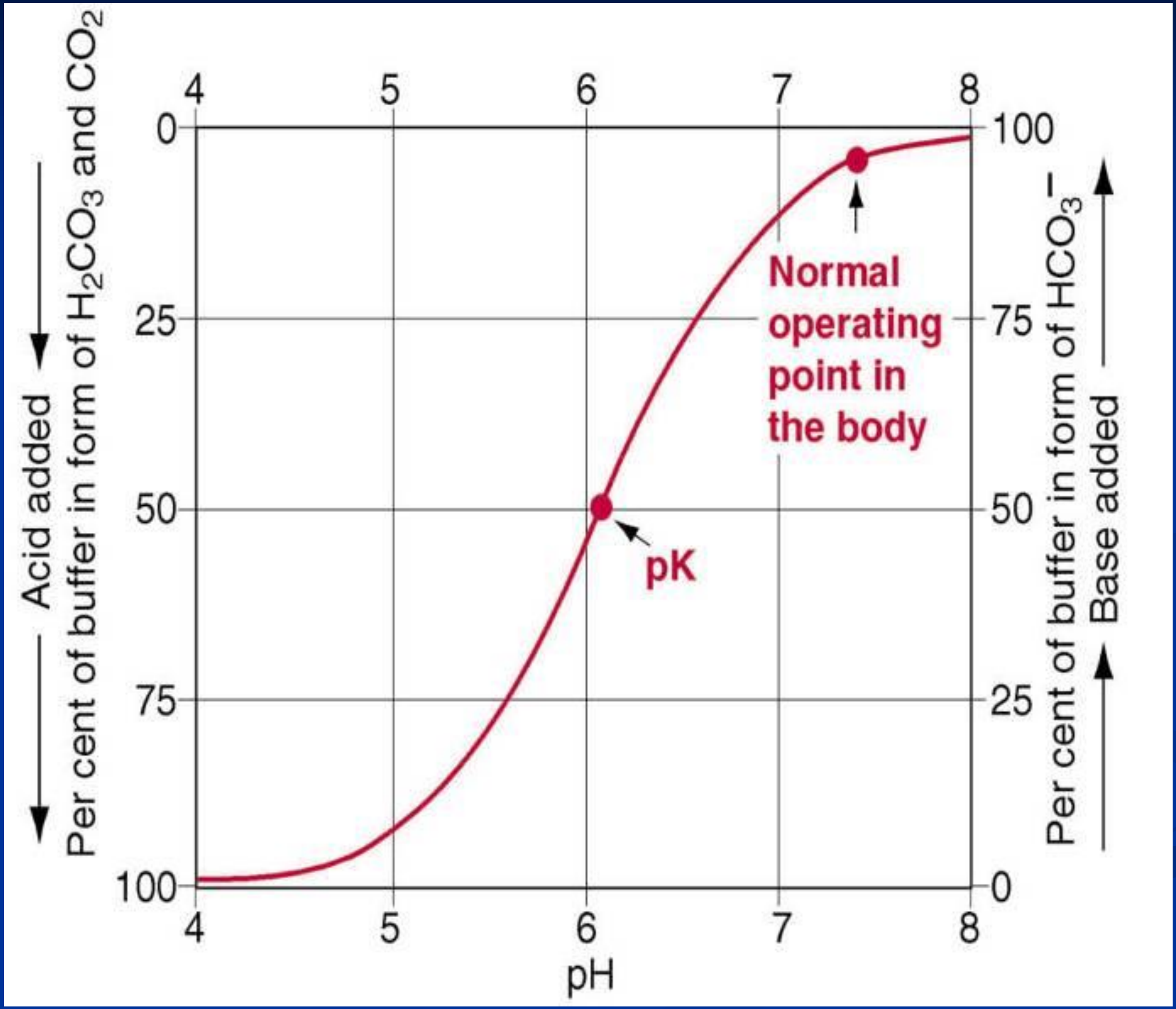
$\alpha = 0.03$

$pK = 6.1$

Effectiveness of buffer system depends on:

- absolute concentration of reactants
- pK of system and pH of body fluids
- Renewal ability

The figure below shows the titration curve for the bicarbonate buffer system:



- when the CO_2 percentage = 50% and the HCO_3^- =50% in solution we get a pH=pK = 6.1.

- The buffer is most effective within 1.0 pH unit of the pK of the buffer (i.e the linear portion of the curve above).

So, the bicarbonate buffer is most effective at pH range 5.1 – 7.1

- At normal body pH (7.4), the ratio of the basic form is 20 times more than the acid form.

We worry about acids in our body, and increasing H^+ will shift the curve closer to the linear portion (5.1 – 7.1), so it can work effectively.

- <u>Criteria to determine the buffering power and capacity of a system:</u>

1. The absolute / total concentration.
2. The relative concentration (pK of the system relative to pH of the surrounding).
3. The renewal tendency of the buffer.
   → which is considered asthe most important factor

- By applying these criteria to the bicarbonate buffer system (the most important extracellular buffer), we find that:

- It is a weak buffer in terms of pK (because plasma pH is 7.4, which is outside its most effective area) and in terms of concentration, it is an intermediate buffer having a concentration of 24mEq/L.

- The bicarbonate buffer has a good renewal capacity which makes it the most important extracellular buffer.

- Bicarbonate concentration is regulated by the kidney. And PCO_2 is controlled by the rate of respiration.

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

The Phosphate buffer system

In our body we have 700 g of phosphorus. 85% in the bone and teeth, 15% in soft tissue, and 0.1% in ECF.

Filtered load/D= 7000 mg ≈ 200-250 mM/D

- Proximal Tubule reabsorbs 80% of the filtered phosphate.
- Distal tubule reabsorbs 10%
- The remaining 10% are execrated.
- In mM concentration: The filtered load = 1.2mM/l * 180L/D= 216 mM/D
- 90% reabsorbed , and only 10% (22 mM) excreted.
- Its concentration in ECF ≅ 1.2-1.4 mM/L (only 8% of the HCO_3 concentration).
- The free PO_4 which can be filtered is around 1.2-1.4 mmol/l (90% of the total ECF PO4). The rest is bound to protein and lipids and is not filterable (10%).
- Forms: NaH_2PO_4 (monosodium phosphate) and $Na_2HPO4^=$ (disodium phosphate).
- pK = 6.8 close to 7.4. **Its salt/acid ratio ($HPO_4^=$: $H_2PO_4^=$) is only 4,** then it is not proper to protect the body against acids as in **HCO3-** (20 times more).
- Its level in the blood rises in ARF.
- \- Its total buffering power is less than for HCO3- in ECF.
- \- However, it is important in tubular fluid (also inside the cells) of the kidneys because:
- 1. pH of tubular fluids is closer to phosphate pK.
- 2. Their concentration ↑ because of H2O reabsorption (>99% of H_2O is reabsorbed but only 90% of phosphate. Thus, 10-times concentrated).
- The average diet contains 1000-1600 mg PO_4 per day. PO4 is excreted from the kidney under the control of PTH. Normally serum Ca^{++} X PO4 is maintained around 30-40 (mg/dl).

The Phosphate Buffer System:

Note: PTH inhibits phosphate reabsorption by affecting T max.

- Its concentration in plasma is low but its pK is equal to 6.8, which is close to intracellular pH (7.0) .

- We get the phosphate mostly from food and its plasma concentration is under the control of the kidney.

- There is a Tmax for phosphate reabsorption. **Phosphate is 90% reabsorbed and 10% excreted.**

- Its filtration load is equal to 180L/day * (1-1.5mmol/L) = 200-250 mmol/day

- The phosphate is more concentrated intracellular and its pK is closer to intracellular pH (7.0). → phosphate is a good buffer intracellular and intratubular, but not an important extracellular buffer.

The protein Buffer System:

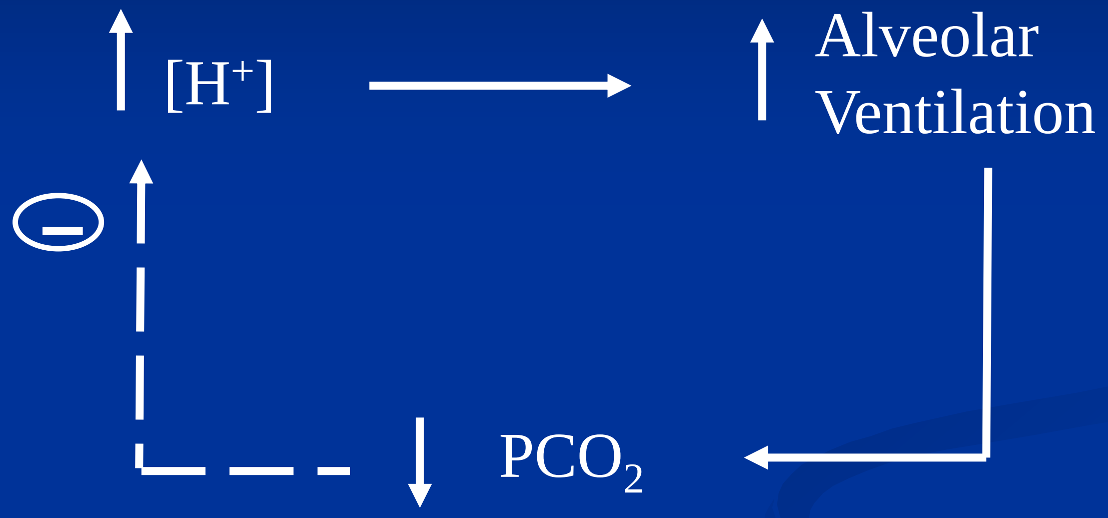
- An important intracellular buffer
- Its plasma concentration is negligible.
- Proteins have an imidazole group that binds to H^+ reversibly. The pK is around 7, (close to 7.4), so almost the same as intracellular pH.
- Intracellular proteins as hemoglobin have other functions but they work secondarily as buffers.
- Their concentrations cannot be controlled and they are not renewed.

→ ALL chemical buffers can buffer up to 1000 mmol of H^+.
→ 70% of this buffering is due to proteins.

Since H^+ ion can't penetrate the cell membrane easily, the proteins can't really work acutely, but in chronic conditions they help.

(The blood buffering capacity is due to: 55% HCO_3^-, 35% Hb and 5% HPO_4^-)

Respiratory Regulation of Acid-Base Balance



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

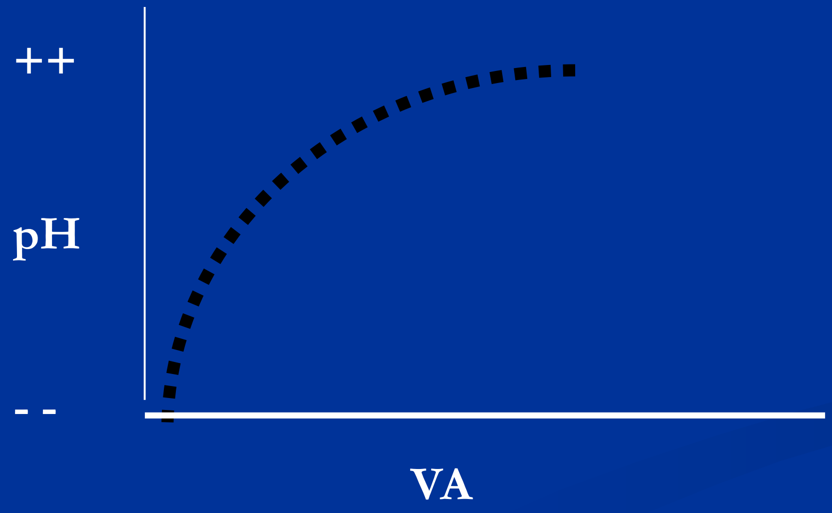
Feedback Gain = 1.0 to 3.0
(corrects 50 to 75 %)

Respiratory System:

As you remember from your respiratory lectures; the effect of increasing alveolar ventilation → alkalosis by reducing P_aCO_2 as seen in the curve below.

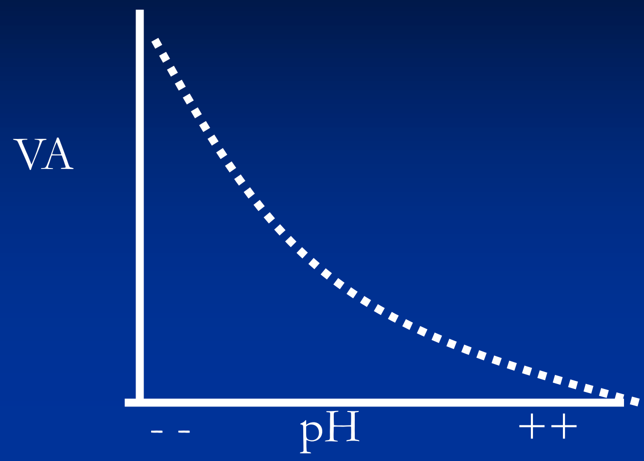
Respiratory compensation can return pH back to normal up to 50-75% normal only. The response start within 3-12 min. For full compensation, you need 6-12 hrs.

The buffering capacity of the respiratory system is 1-2 times the total buffering power of the chemicals of ECF.



$$pH = pK + \log\left[\frac{HCO_3}{0.03 * PCO_2}\right]$$

This next figure shows us the effect of blood pH on the rate of alveolar ventilation:



Respiratory Regulation

Respiratory System controls the pH by the rate and depth of respiration to increase or decrease the release of CO_2.

- Hyperventilation -- blow off CO_2
- Hypoventilation -- retain CO_2

- If this pH is decreased to 7.3 (acidosis), the ventilation rate will increase (hyperventilation), but it doesn't add any O_2 to the blood because of the shape of the O_2-Hb dissociation curve. Therefore, there is no increase in O_2 to counterbalance acidosis → This hyperventilation isn't opposed by any other factor.

- If we increased the pH to 7.5 (alkalosis), this will depress ventilation but not to the extent that is expected because in alkalosis, hypoxia (Low PO_2 will stimulate ventilation and thus opposes the effect of alkalosis on ventilation).

-