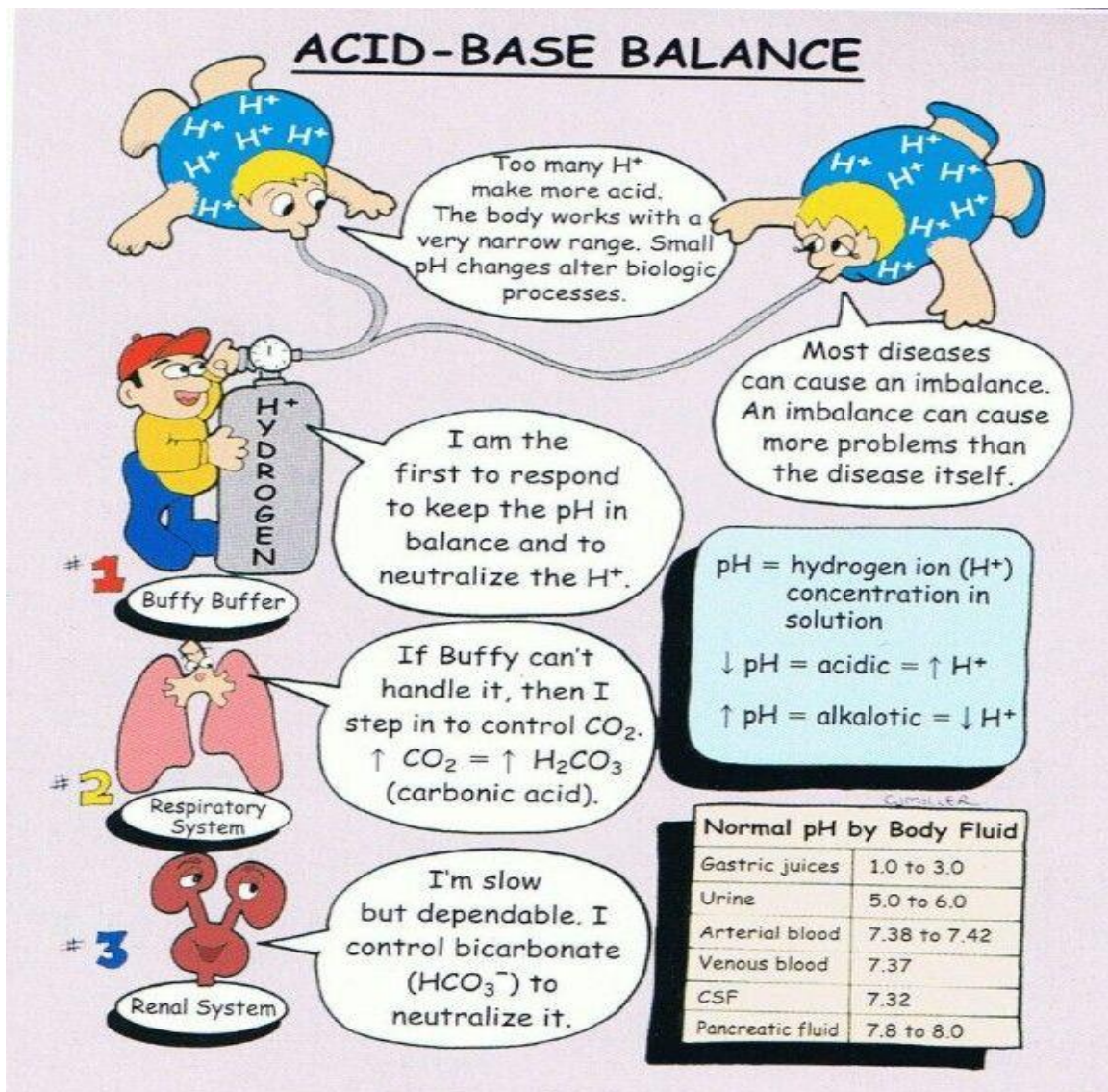


Physiology lecture (8): Acid – Base regulation



If we add hydrogen, we have three lines of defense against a mild change in pH:

- 1) Buffers, instantaneous, within a fraction of milliseconds.
- 2) The lung, takes minutes to start but hours to give a full response, its buffering capacity is twice as much as the total buffers in our body.
- 3) The kidney, slow, takes hours to start and days to give a full response, it can bring the pH back to normal totally, and it might not help in acute acidosis.

pH is determined by the following equation:

$$\text{pH} = -\log [\text{H}^+]$$

The hydrogen ion concentration is really small that it is measured in nanomolars rate, it can go as low as 10 nM/L or as high as 160 nM/L, so we can see there's a 16 times difference between the lowest and highest concentrations, but there's no way that the body can handle a 16 times difference.

For example: double the concentration of K^+ is enough to stop the heart, if Na^+ decreases by 20% it leads to serious abnormalities, same thing for Ca^{++} and hormones.

pH of lowest H^+ concentration $\text{pH} = -\log [10 \times 10^{-9}]$ $\text{pH} = 8$	pH of highest H^+ concentration $\text{pH} = -\log [160 \times 10^{-9}]$ $\text{pH} = 6.8$
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(pH < 6.8 OR > 8 is not compatible with life)

- The less the pH the more the hydrogen concentration, which causes acidosis. Acidosis affects enzymatic activity, because every enzyme has its own optimal pH.
- The more the pH the less the hydrogen concentration, which causes alkalosis.
- The normal arterial range of pH is **(7.35 – 7.45)**, and we will take **7.4** ($[\text{H}^+] = 40\text{nM}$) as an average.
- **CO_2** is masked **H^+** according to the equation :
$$(\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-)$$

and it is considered a volatile acid.

The body produces 300 liters of **CO_2** every day, which corresponds to 10 **molars**. This is way too much, but it gets removed by the lungs. the problem and threat resides in the non-volatile acids (fixed acids), such as

phosphoric acid and sulfuric acid which get produced daily.

80 mM of fixed acids is produced every day, and if we distribute them along the **14 liters** of extracellular fluid volume, we will get **>5 mmol/liter**, which corresponds to a **pH less than 3**, and this is not compatible with life.

If we try to solve the problem by buffering these 80mM of hydrogen by adding 80 mM of bicarbonate (HCO_3^-), converting the hydrogen to CO_2 and let the lung take care of it, the HCO_3^- reserve will supply us for only **4-5 days**.

$[\text{HCO}_3^-] = 24 \text{ mM/L}$ ECF vol. = 14 L $\text{HCO}_3^- \text{ reserve} = 24 \text{ mM/L} \times 14 \text{ L}$ $= 336 \text{ mM}$ $336 \text{ mM} / 80 \text{ mM} = 4.2 \text{ (enough for 4 -5 days)}$

So, still we have partially solved the problem!

We could've radically solved the problem if the kidney excreted these 80mM in the urine, but the minimum pH of the urine is **4.5**, and a pH of 4.5 corresponds to only **0.1 mM/ day** so that leaves us with **79.9 mM** of acids.

❖ Why is the kidney unable to further lower the pH?

The last stage of urine modification occurs in the cells of the collecting duct, these cells contain the hydrogen pump that is capable of secreting hydrogen 900 times against its concentration gradient. The environment inside these cells is slightly acidic with a pH of 7, and if we consider its capacity to be 1000 it will cause a drop in pH to 4.

Still we have not solved the problem!

$[\text{H}^+] = 10^{-7}$ $10^{-7} \times 1000 = 10^{-4}$ $\text{pH} = -\log [10^{-4}]$ $\text{pH} = 4$

Now that we are left with 80 mM of bicarbonate deficit, let's see how we can solve this problem.

What's a buffer?

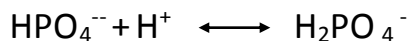
A buffer is a substance that releases/binds H^+ reversibly to resist marked pH changes and keep it compatible with life; Buffers don't eliminate H^+ or add it to our body, but keep them tied up until balance can be reestablished. It acts with a fraction of a second and is the first line of defense.

Buffer Systems in the Body

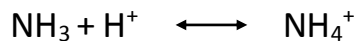
1) **Bicarbonate**: most important ECF buffer



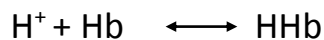
2) **Phosphate**: important renal tubular and intracellular buffer



3) **Ammonia**: important renal tubular buffer



4) **Proteins**: important intracellular buffers



$pH = pK + \log [\text{base}/\text{Acid}]$

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 acidic forms.

$$pH = pK_1 + \log [HCO_3^-/CO_2]$$

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

$$= 6.1 + \log 20$$

$$= 6.1 + 1.3$$

$$= 7.4$$

CO₂ is measured by its partial pressure (PCO₂)
To convert it to mMole we multiply by 0.03
Arterial PCO₂ = 40mm Hg correspond to 1.2 mMole (40 * 0.03)

$$\begin{aligned}
 \text{pH} &= \text{pK}_2 + \log [\text{HPO}_4^{2-} / \text{H}_2\text{PO}_4^-] \\
 &= 6.8 + \log [1.0 / 0.25] \\
 &= 6.8 + \log 4 \\
 &= 6.8 + 0.6 \\
 &= 7.4
 \end{aligned}$$

$$\begin{aligned}
 \text{pH} &= \text{pK}_3 + \log [\text{NH}_3 / \text{NH}_4^+] \\
 &= 9.2 + \log [\text{NH}_3 / \text{NH}_4^+] \\
 &\text{it also equals 7.4}
 \end{aligned}$$

⇒ If we have a solution which contains dibasic and monobasic phosphate, ammonia and ammonium and contains bicarbonate and CO_2 , when all of these buffers carry the same pH, this is called the isohydric principle (same pH for different buffers).

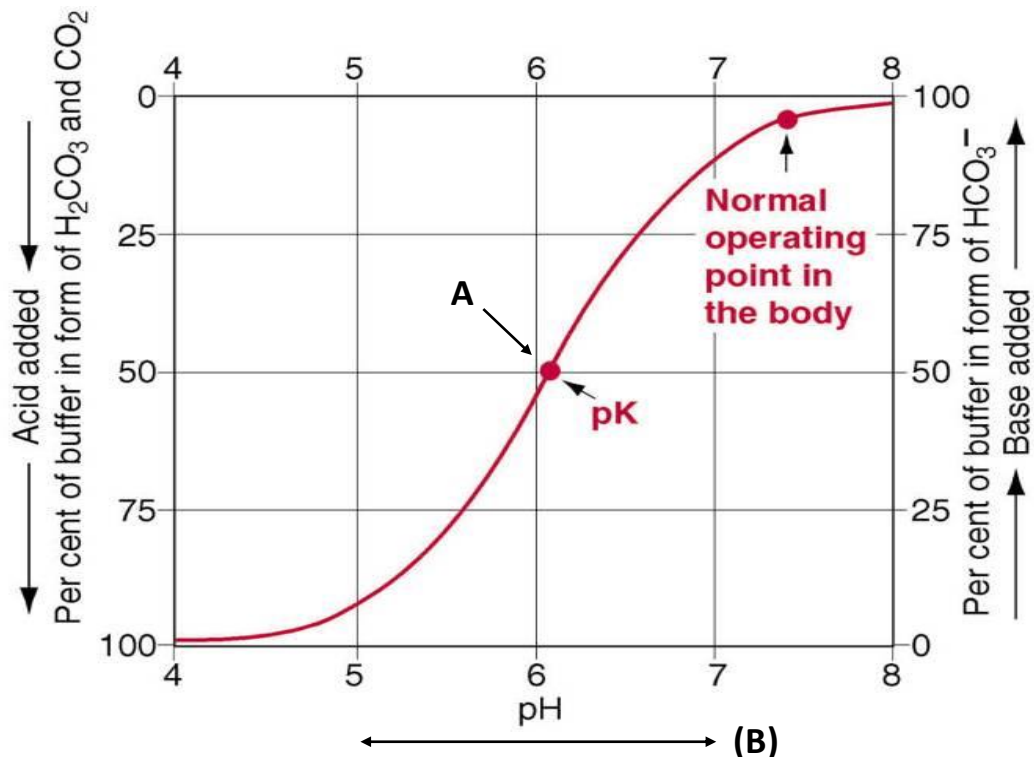
⇒ A buffer is a combination of a weak base with its weak acid.

A buffer keeps the change in pH very small when an acid or a base is added. For example if I have a strong acid as HCl and I add to it NaHCO_3 , it will produce HCO_3^- and NaCl, so the strong acid is thus converted into a weaker acid.

If I add NaOH which is a strong base to H_2CO_3 it will produce NaHCO_3 and H_2O , so we've converted the strong base into a weaker one.

A strong acid or a strong base is that which completely dissociates, for example 1 mole of HCl will give 1 mole of H^+ , and 1 mole of NaOH will give 1 mole of OH^- .

The buffering capacity curve (Ex. For Bicarbonate) looks like this:



- If we add more acids we shift the pH to a lower value.
- If we add more bases we shift the pH to a higher value.
- At point (A), the pH of the solution is equal to the pK

$$[\text{acid}] = [\text{base}]$$

$$\text{pH} = \text{pK} + \log [\text{base}/\text{acid}]$$

$$= \text{pK} + 0$$

(the pK of a buffer is its pH when the acidic form is equal to the basic form)
- The area (B) which is one unit less of the pK and one unit more is steep, this indicates that adding too much acid or too much base corresponds to little change in pH. So we conclude that **the buffering capacity of a solution depends on its pK relative to the pH of the surrounding solution.**

- The pK of the bicarbonate buffer is 6.1 which is far away from our normal range (7.4), in cases of acidosis we approach the buffering strength of bicarbonate, but this does not usually happen, why?

$$\text{pH} = \text{pK} + \log [\text{HCO}_3^- / \text{CO}_2]$$

$$\text{pH} = 6.1 + \log [24/1.2]$$

$$= 6.1 + \log 20$$

$$= 6.1 + 1.3$$

$$= 7.4$$

From this equation we notice that the basic form is 20 times higher than the acidic form, and what really happens is that when there's a drop in HCO_3^- the CO_2 will drop as well keeping the ratio (20) constant and the pH as 7.4, (ex. If HCO_3^- becomes 12, the CO_2 will become 0.6), so normally there's a shift in the same direction as a compensatory mechanism.

The equation can be written this way:

$$\text{pH} = \text{pK} + \log [\text{Kidney/Lung}]$$

so if for example we had too much bicarbonate, there will be CO_2 retention.

Usually in acid- base disturbance, both acid and base concentrations are shifted in the same direction, if that doesn't occur it means one of two things, either we don't have compensation or we have a mixed disturbance (problem in both lungs and kidneys).

⇒ The buffering capacity depends on three things:

- 1) The absolute concentration.
- 2) The pK of the buffer, the closer it is to our normal pH the stronger is the buffer.
- 3) If the buffer can be regulated (increased or decreased), and its renewal capacity.

Now let's compare the buffering systems:

- In terms of concentration.

Bicarbonate	20 millimolar
Phosphate	1.2 millimolar
Proteins	Good intracellular buffers (hydrogen is charged and it's difficult for it to enter the cell, hydrogen pump is present)

- In terms of pK

bicarbonate	6.1 (away from normal 7.4)
Phosphate (dibasic)	6.8
proteins	7.0 (same as the inside of the cells)

- In terms of regulation

Phosphate	Can't be regulated
Bicarbonate	can be regulated
proteins	Can't be regulated

- In blood phosphate is not a good buffer due to its low concentration, even though its pK is closer to the normal 7.4, while inside the cells the phosphate is more concentrated making it a good intracellular buffer.

Phosphate is a good intratubular buffer, why?

Because its pK is close to the pH of the proximal tubule and because it gets more concentrated distally.

In the renal tubules, phosphate is freely filtered, its filtered load ($1.2 \times 180 = 200 \text{ mM}$), 90% of the phosphate is reabsorbed leaving 10%, and 99% of water is reabsorbed, leaving 1%, so the phosphate in the tubular fluid gets concentrated 10 times more.

In addition, the pH inside the cells of the proximal tubule is 7, where

hydrogen is secreted against its concentration gradient with the help of sodium (secondary active transport/ counter transport) so the hydrogen concentration is 5-6 times more in the tubular fluid than inside the cells of the proximal tubule, and it reaches 6.5 making it closer to the pK of the phosphate.

****note:** most of the hydrogen secretion (net secretion) occurs in the proximal tubule even if the pH has dropped to only 6.5, while in the collecting duct a small amount of hydrogen is capable of producing a change in pH to 4.5

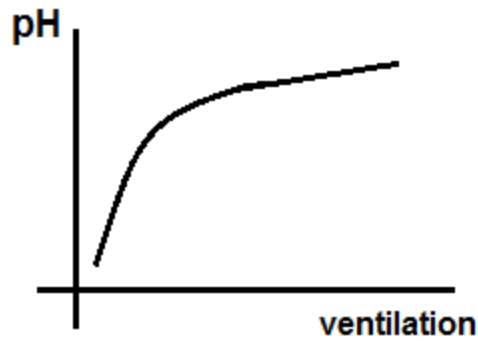
- bicarbonate system regulation:



- We can suppress ventilation and shift the equation to the right, making more hydrogen.
 - We can hyperventilate, removing CO_2 , shifting the equation to the left and washing out more hydrogen.
 - CO_2 is regulated by the lung while bicarbonate is regulated by the kidney, the kidney can make around 500-600mM of new bicarbonate each day maximum, so whatever you eat and whatever exercise you do you shouldn't get acidosis because the kidney is providing sufficient bicarbonate, but it requires time to make it, so it doesn't help in acute acidosis, for ex. Taking a very high dose of aspirin it's unlikely the kidney can help, while ascending to high altitudes or in cases of COPD the kidney is able to help because it's a slow process.
- 70% of the buffering capacity of total buffers comes from proteins, their pK is similar to the intracellular environment, but they cannot be regulated and acid-base balance is not their primary function.
 - So far, the most important buffer is the bicarbonate, mainly due to its good renewal capacity.

The lung as a second line defense

How does the pH affect the respiratory system?



Acidosis induces hyperventilation, and hyperventilation produces an increase in oxygen and a decrease in CO_2 . But adding oxygen will not suppress ventilation, for example if PO_2 becomes 120 that doesn't indicate an increase of PO_2 by 20% due to the oxygen-hemoglobin dissociation curve, so high oxygen levels have no effect on the respiratory center, it's half tailed (has an effect when it's below 60). Thus, high Oxygen levels will not oppose the effect on ventilation produced by **acidosis**.

While if a patient had alkalosis, ventilation will be suppressed to increase the PCO_2 , but here suppressing the ventilation will produce a decrease in PO_2 , so the low oxygen here will oppose the effect of **alkalosis**.

So, one unit decrease in pH has more effect on ventilation compared to the same unit increase in pH, because of the opposing effect of oxygen.

Remember that the respiratory system has twice the strength of buffering capacity than the entire buffering systems.