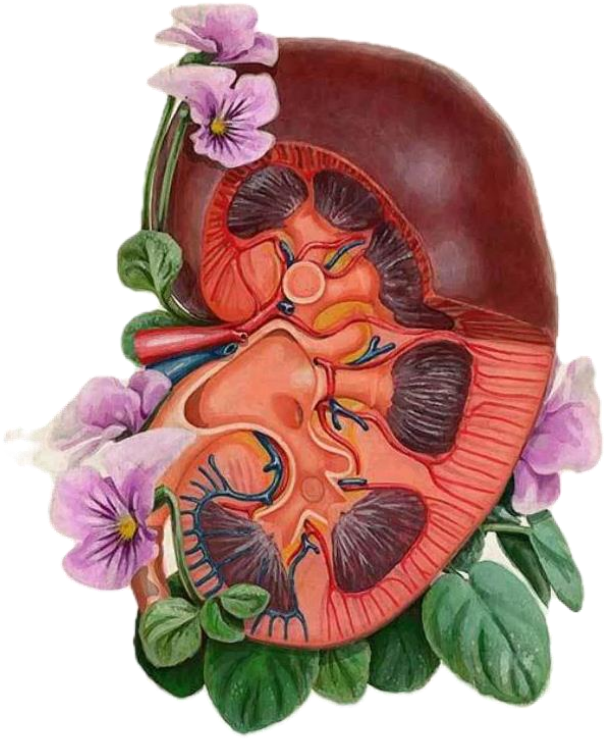
UGS Physiology Sheet 6 – V2



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In the previous lecture, we discussed how sodium is handled by the kidney. In this lecture, we will mainly discuss potassium and briefly touch on calcium. We will also link potassium homeostasis to other organ systems, particularly the heart, endocrine and adrenal glands.

Before we get into our lecture, here are a couple of questions based on the previous lecture:

1. In the presence of high aldosterone, most of the filtered water is reabsorbed in which segment of the nephron?

   The answer is the **proximal tubule**. Even though aldosterone acts on the distal segment, its contribution increases water reabsorption there to ≈10%, so the proximal tubule remains responsible for the majority (65%) of water reabsorption.

2. In the presence of high ADH, most of the filtered water is reabsorbed in which segment of the nephron?

   The same principle applies to ADH. When ADH levels are high, most water reabsorption still occurs in the **proximal tubule**, ADH only influences the reabsorption of about 9% of water in the collecting duct.

Recall: Absence of ADH causes **diabetes insipidus**, leading to polyuria and polydipsia. Note that glucose should **not** be present in the urine in diabetes insipidus. This condition can be **central** (no ADH is produced) or **peripheral** (the receptors do not respond) we also call it **nephrogenic** diabetes insipidus. In peripheral diabetes insipidus, patients do not respond to treatment with ADH because their plasma ADH levels are already high; instead, they require treatment to stimulate the receptor.

Potassium Homeostasis:

For proper potassium homeostasis, potassium intake must **equal** potassium output. This state is called **potassium balance**.

- **Positive balance** occurs when intake is **greater** than output.
- **Negative balance** occurs when intake is **less** than output.

The typical daily intake of potassium is about 100 mmol. Of this:

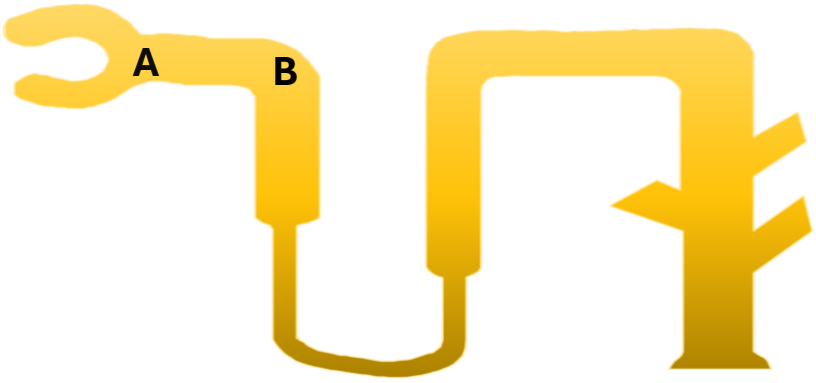
- 95 mmol is excreted through the kidneys. (major organ in eliminating K)
- 5 mmol is excreted through other routes, such as sweat and gastrointestinal secretions.

Normal plasma concentration:
The normal concentration of potassium in plasma is between **3.5–5.5 mmol/L**.

- **Hypokalemia** refers to a plasma potassium level lower than 3.5 mmol/L.
- **Hyperkalemia** refers to a plasma potassium level higher than 5.5 mmol/L

Now we are going to discuss how each segment handles potassium:

Proximal Tubule:



To understand how the proximal tubule handles potassium, consider two points:

- **Point A**: where the tubular fluid composition is similar to plasma
- **Point B**: which represents the tubular fluid later along the segment

To see how this segment handles potassium we need to see first how it handles inulin, by using this equation which shows the clearance of inulin in this segment, we can determine the fraction of water reabsorbed.

$$\frac{[Inulin]_B}{[Inulin]_A} \times V = Clearance\ of\ Inulin$$

[ ]: Concentration in mEq/L

V: Represents the single nephron flow rate in this segment

Assume the [Inulin] at A = 1 and [Inulin] at B = 3, then: $\frac{3}{1} = 3$

Based on this example, **66%** of the filtered water is **reabsorbed** in the proximal tubule. (The [inulin] increased 3 times, for that to occur the volume of the tubular fluid must have decreased to 1/3 the original volume. Therefore 2/3 of the water have been reabsorbed). We then measure the potassium concentration at two points: point A and point B. We use micropipettes that take nanoliters of fluid to measure the concentration of inulin and K at both points.

We found that **potassium** concentration **remained the same** e.g., 4 mEq/L at both points A and B, so we can interpret that **66%** of the filtered potassium has also been **reabsorbed**, in parallel with water. This is why the potassium concentration remains unchanged along the segment.

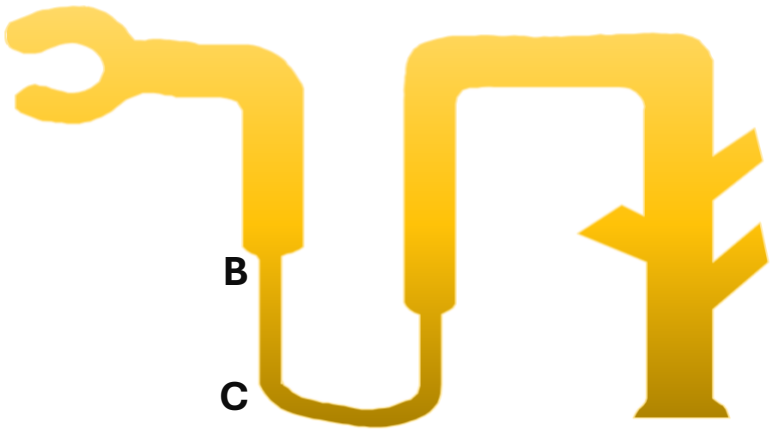
$$\frac{\frac{[K^+]_B}{[K^+]_A} \times V}{\frac{[Inulin]_B}{[Inulin]_A} \times V} = \frac{\frac{4}{4}}{\frac{3}{1}} = \frac{1}{3}$$

[ ]: Concentration in mEq/L

V: Represents the single nephron flow rate in this segment

Therefore, in this example, one-third of the filtered potassium has reached point B, and two-thirds have been reabsorbed.

Descending limb of Henle:



Consider points B and C along the descending loop of Henle. By measuring the concentrations of potassium and inulin at both points, we can interpret that, the increase in inulin concentration along the segment indicates that **water reabsorption has occurred** (if the [Inulin] remained the same this would mean that no water reabsorption has occurred). By interpreting potassium concentration as well, we can infer that **0% of potassium has been reabsorbed** in the descending loop.

Assume at B the [Inulin] and $[K^+]$=3, at point C the [inulin] and $[K^+]$=5

$$\frac{\frac{[K^+]_C}{[K^+]_B} \times V}{\frac{[Inulin]_C}{[Inulin]_B} \times V} = \frac{\frac{5}{3}}{\frac{5}{3}} = 1$$

[ ]: Concentration in mEq/L

V: Represents the single nephron flow rate in this segment

Only water is reabsorbed in the descending limb of Henle, this explains the increase in concentration of Potassium and Inulin from point B to C, and since the increase in concentration was due to **water reabsorption only** the concentration of K and Inulin increased by the same factor yielding a ratio of 1. (This note is added by the writer).

The doctor only presented the concept and the equation for the descending limb segment without giving all the numbers. I have added the numbers myself to help illustrate the idea more clearly.

Ascending limb of Henle:

Using the same approach, we can determine that another **25% of the filtered potassium** is reabsorbed in the ascending limb of Henle.

Summary of reabsorption so far:

- Proximal tubule: 66% reabsorbed
- Descending loop of Henle: 0% reabsorbed
- Ascending limb of Henle: 25% reabsorbed

Adding these together, approximately 90% of the filtered potassium has been reabsorbed by the end of the loop of Henle.

Filtration Load of Potassium:

Filtered load of potassium per day = GFR × plasma concentration of potassium.
Given: GFR = 180 L/day, plasma $[K^+]$ = 4 mEq/L
Filtered load = 180 × 4 = 720 mEq/day.

If 90% is reabsorbed, then 10% remains, which is 72mEq. However, we previously stated that daily potassium excretion is about 100 mEq (not 72mEq). This mismatch tells us that the remaining 28meq of **potassium must be secreted** and this secretion occurs in the distal segment under the control of **aldosterone**.

Effect of increased potassium intake:

If potassium intake increases to 200 mEq/day, plasma concentration increases slightly, from about 4 to 4.5 mEq/L. In this situation, the portion of excreted potassium coming from what is filtered and not reabsorbed, is **smaller** than the portion coming from secretion, recall that when potassium intake was 100mmol (72mmol filtered, 28mmol secreted).

Examples:

- **Intake 200 mEq/day:** ~70 mEq from filtered not reabsorbed, ~130 mEq from secretion.
- **Intake 300 mEq/day:** ~70 mEq from filtered not reabsorbed, ~230 mEq from secretion.

Thus, when potassium intake is high, most of the potassium excreted in the urine comes from **secretion**, not from the potassium that was filtered and not reabsorbed.

Clinical Cases:

Case 1: Hypertension with low potassium (hypokalemia):

If a patient has hypertension and their plasma potassium level is low, this suggests an adrenal tumor causing **Conn's disease** (it is usually unilateral microtumors -hard to detect on MRI or CT- in the zona glomerulosa that stimulate excess aldosterone production).

Case 2: Hypotension (low sodium) with hyperkalemia:

If a patient has hypotension (low sodium) along with hyperkalemia, this could be due to **Addison's disease**, which is the opposite condition caused by low or lacking aldosterone.

Potassium distribution after a meal – role of insulin:

Total body water is 60% of body weight. For a 70 kg person, total body water is 42 liters:

- 28 liters inside the cells
- 14 liters outside the cells (11L interstitial fluid, 3L in plasma)

Consider someone after a regular meal that contains about 50 mEq of potassium. If that 50 mEq were distributed into the extracellular fluid (14 liters), the increase in plasma concentration would be $50/14 \approx 3.5$ mEq/L. If the plasma potassium level was already 4 mEq/L, adding 3.5 would bring it to about 7.5 mEq/L.

This would mean that after each meal, the person would have an increase in potassium concentration, which is very dangerous to the heart.

However, this does not occur because of **insulin secretion**. Insulin plays a very important role **in pushing potassium into the cells**. With insulin's help, potassium enters the cells. Intracellular potassium increases slightly (from 150 to 153 mEq/L, for example), which is not a big deal inside the cells. What matters is that the plasma potassium level does not rise dangerously. Over the next few hours ($\approx 6hrs$), potassium slowly moves back out of the cells and is eventually excreted in the urine.

Potassium Clearance

Clearance of potassium can be calculated using the following equation:

$$Cl_K = \frac{U_K}{P_K} * V$$

Cl_k: potassium clearance, U_k: potassium concentration in urine, P_k: potassium concentration in plasma, V: volume of urine per minute

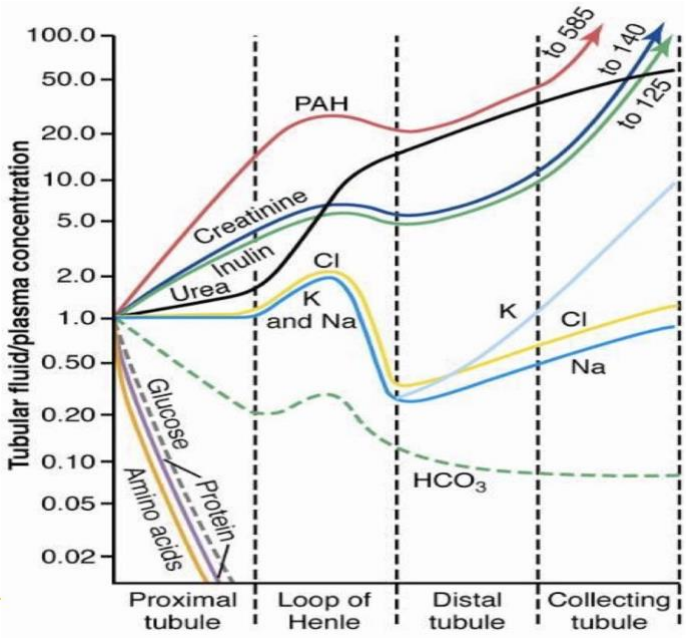
To calculate potassium concentration in urine:

$$U_K = \frac{amount\ of\ potassium\ excreted\ in\ urine\ per\ day}{volume\ of\ urine\ produced\ per\ day} = \frac{100\ mEq}{1.5\ L} \approx 66\ mEq/L$$

And as potassium concentration in the plasma is 4 mEq/L, and the urine output is 1 ml/min, clearance of potassium equals:

$$Cl_K = \frac{66\ mEq/L}{4\ mEq/L} * 1\frac{ml}{min} = \ 16.5\ ml/min$$

Figure Explanation



The figure above illustrates how the **ratio** of (The substance concentration in the tubular fluid **to** its concentration in the plasma) changes along the length of the nephron, as filtration, reabsorption, and secretion proceed.

Before studying the figure:

A. When the curve of any substance goes **up**; this indicates:

1. Either the substance has been secreted/added to the tubular fluid, **OR**
2. Water has been reabsorbed from the tubule while the substance has been trapped and concentrated there.

B. When the curve goes **down**; this indicates that the substance has been reabsorbed from the tubule, so its concentration there decreases.

C. When the curve remains a **horizontal** straight line; this indicates that:

1. The concentration of the substance is not changing as it moves through that segment of the nephron, **OR**
2. It has been reabsorbed in proportion to water reabsorption, so its concentration in the tubular fluid doesn't change.

The doctor did not clearly mention the earlier notes (a-c); we explained them more in details.

You can notice that **glucose**, **amino acids**, **small sized proteins** (not the large ones, as they are not filtered) and **bicarbonate** that have been filtered in the proximal tubule or beyond will eventually get reabsorbed to the circulation, and their levels in the tubular fluid reach zero. (Bicarbonate illustration in the figure is not correct, as it should drop in the tubular fluid to zero).

For Na+:

At the beginning of the proximal tubule (immediately after bowman's capsule), the ratio of tubular fluid concentration of sodium to the plasma concentration of sodium is **1**, (look at the Y-axis), and this is because sodium is freely filtered and its concentration in the filtrate equals that of the plasma, and equals 140 mEq.

As the filtrate moves through the proximal convoluted tubule, the ratio remains **1**, or very close to it, despite massive amounts of sodium being reabsorbed, and this is because sodium and water are reabsorbed in equal proportions, the concentration of sodium remaining in the tubule does not change, even though the total amount of sodium is decreasing.

In the thick ascending limb, Na+ levels drop significantly in the tubular fluid because it is reabsorption there is not accompanied by water, (as the ascending limb is impermeable to water) so water remains in the lumen, causing the tubular fluid to become progressively dilute (hypotonic) relative to the plasma.

At the end of the collecting duct, Na+ levels in the tubular fluid become less that that of the plasma, and the ratio of the tubular/plasma concentration of Na+ becomes less than **1**.

For K+:

Notice how K+ levels in the distal tubule and the collecting duct increase relative to the plasma, because of its **secretion** there, and the ratio reaches up to 10, which means that TF concentration of K+ becomes 10 times more than that of the plasma.

For inulin:

In the ascending limb, inulin curve is a horizontal straight line, as the concentration of inulin remains constant throughout this segment. This is due to two factors: no water movement occurs at this segment, and inulin is neither reabsorbed nor secreted.

(Inulin illustration in the figure is not correct for this segment, as it should be a horizontal straight line).

If a substance has a clearance of zero, we can't say that it has not been filtered, (as you remember, while glucose clearance is zero, it is a freely filtered substance). However, we can at least be sure that this substance has not been excreted.

Potassium and the Resting Membrane Potential (RMP):

Potassium is highly related to the resting membrane potential in the cardiac muscle cells. Using the Nernst equation, with intracellular potassium concentration (K^+in) of 150 mEq/L and extracellular potassium concentration (K^+out) of 4 mEq/L, potassium equilibrium potential will be -90 mV. This is essentially the resting membrane potential, meaning the RMP is mainly under the effect of potassium.

$$\text{Nernst Equation: } RMP = -61 \times log \frac{[K^+]\ in}{[K^+]\ out}$$

If we **increase (K^+out)**- in plasma- to 8 mEq/L and **decrease (K^+in)**- intracellularly- to 17 mEq/L, then the RMP becomes **less negative**, around -70 mV. Therefore, the relationship between **extracellular** potassium concentration and RMP is **inverse**: as K^+out increases, the RMP becomes less negative.

A resting membrane potential of -70 mV instead of -90 mV will cancel the fast-acting sodium channels in phase 0 of the cardiac muscle' action potential. decreasing the excitability of the heart, potentially causing serious arrhythmias and cardiac arrest.

The underlined statement requires further discussion due to conflicting views; we wrote this based on what we understood from the doctor's explanation in the lecture, you can refer to these time stamps where he discussed this point. 7:58-9:01, 28:42-29:42

Here is what is mentioned in Guyton's Textbook (15th edition, Pg:125):
"Effect of Potassium Ions. Excess potassium in the extra- cellular fluids causes the heart to become dilated and flaccid and also slows the heart rate. Large quantities of potassium also can block conduction of the cardiac impulse from the atria to the ventricles through the AV bundle. Elevation of potassium concentration to only 8 to 12 mEq/L—two to three times the normal value—can cause severe weakness of the heart, abnormal rhythm, and death.
These effects result partially from the fact that a high potassium concentration in the extracellular fluids decreases the resting membrane potential in the cardiac muscle fibers, as explained in Chapter 5. That is, a high extracellular fluid potassium concentration partially depolarizes the cell membrane, causing the membrane potential to be less negative. **As the membrane potential decreases, the intensity of the action potential also decreases, which makes contraction of the heart progressively weaker**"

However, it seems that the doctor's slides mention something different, an image of the slide is inserted at the end of the file (refer to it). The info in the slide could be partially true because some external resources say that hyperkalemia is actually biphasic, where a mild elevation causes more excitability as the cells are closer to threshold, however moderate to severe elevation (which is clinically relevant) causes impaired conduction and reduced excitability as discussed earlier.

What happens in renal failure?

Renal failure is usually associated with hyperkalemia, as the kidney loses its ability to secrete (and excrete) potassium. However, it is not associated with hypernatremia,

because the trapped sodium will trap water along with it, thus Na+ remains constant or slightly decreases.

If a patient has renal failure and their potassium levels rise above 7 mEq/L, an ECG must be done immediately. ECG will show specific changes indicating whether the heart is affected and if hemodialysis or peritoneal dialysis is required to reduce potassium levels in the blood.

-1 * RMP

[K+] out

Diabetic Ketoacidosis

Diabetic Ketoacidosis (DKA) is a serious, life-threatening complication of diabetes (mostly Type 1, but it can occur in Type 2). It happens when the body doesn't have enough insulin to move blood sugar into cells for energy, even though the sugar levels are very high.

In order to get energy, the body shifts toward fat metabolism, which produces toxic acids, known as ketones. As these ketones accumulate, they drop the blood's pH, leading to severe acidosis that can cause a patient to lose consciousness.
H+ ions will increase the respiratory rate, so the patient starts hyperventilating to get rid of CO_2, a major source of hydrogen ions (you will learn this in lecture 8).

How cells deal with DKA?

To deal with the high acidity of the blood, hydrogen ions start getting to the inside of the cells, while K+ ions start moving to the outside of the cells, accumulating in the blood, and causing hyperkalemia.

When doctors administer insulin to treat the DKA, two things happen simultaneously:

- Insulin drives glucose into the cells.

-Insulin also activates the Na+/K+ ATPase pump, which forcefully pushes potassium back into the cells.

Because insulin moves potassium from the blood into the cells so rapidly, the blood levels of potassium drop and lead to hypokalemia, which can cause fatal heart arrhythmias. Because of that, **K+ is given to the patient along with insulin** to prevent this insulin-induced hypokalemia.

Aldosterone and K+

Aldosterone is a hormone released rom the outermost layer of the adrenal cortex **zona glomerulosa**. (Recall that the adrenal cortex consists of three layers glomerulosa → aldosterone, fasciculata → cortisol, reticulata → DHEAS).

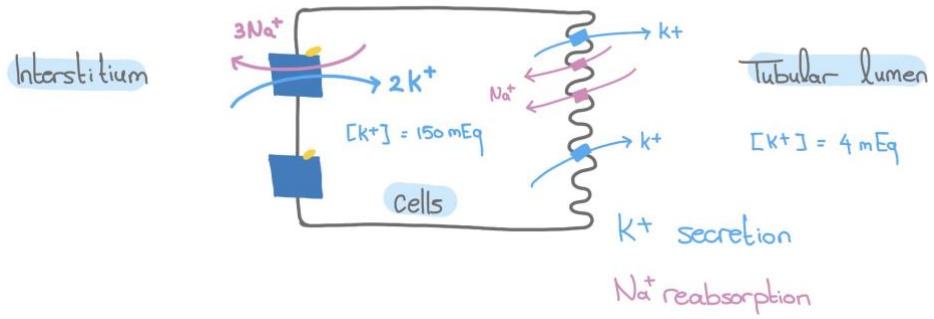
Its release is triggered directly by hyperkalemia, hyponatremia, Angiotensin II as a part of RAAS, and ACTH from the anterior pituitary (plays a minor role).

Aldosterone causes reabsorption of sodium, which is followed by water reabsorption - so the osmolarity and sodium concentration in the tubule remain relatively the same- it also causes **secretion** of potassium, which can lead to hypokalemia.

Aldosterone exerts a part of its action on the genetic level, by **increasing the expression** of K+ channel genes, which are responsible for moving K+ from the tubular epithelial cells to the tubular lumen, thus, **secreting** K+.

It also aids in the genetic expression of Na+/K+ ATPase pumps that are located on the basolateral membrane of the tubular epithelial cells.
Those pumps get activated when Na+ moves from the tubular fluid to the intracellular compartment.

They move 3 Na+ ions from the intracellular compartment to the interstitial fluid, in exchange for 2 K+ ions from the interstitium to the intracellular compartment, concentrating K+ within cells by an active process that consumes ATP, in order to create a driving force for K+ secretion.



TO SUM UP, how can we increase the K+ secretion?

1. Activate Na+/K+ ATPase pumps
2. Make more K+ channels at the luminal side
3. Keep the gradient by removing the luminal K+ through increasing tubular fluid (TF) flow rate, which is how diuretics work, they increase the flow.

These are the three mechanisms by which K+ secretion is affected.

1 and 2 are by the effect of aldosterone.

Chronic acidosis can poison and impair the function of Na+/K+ ATPase pumps. This inhibition prevents potassium from being actively transported into cells, eliminating the necessary concentration gradient (driving force) for its secretion, trapping it in the blood and causing hyperkalemia (Keep in mind that DKA is an acute acidosis state).

At the same time, chronic acidosis inhibits sodium and chloride reabsorbtion, and thus, water reabsorbtion, which will increase the tubular flow and washout (similar to diuretics), This fast-moving washout creates a powerful gradient for K+ to be passively pulled out of the blood, regardless of the broken pumps. Ultimately, the volume of potassium lost to this washout exceeds what is being trapped, resulting in hypokalemia.

Beta blockers, Exercise, and Potassium level

During exercise, skeletal muscles release K^+ into the extracellular space, which can cause transient hyperkalemia.

Epinephrine acts on β2 receptors on the skeletal muscles to stimulate Na^+/K^+-ATPase pumbs and drive K^+ into cells.

Beta-blockers for hypertension treatment (propranolol or atenolol) act by blocking β2 receptors, preventing the activation of Na^+/K^+-ATPase pumbs and impair potassium cellular uptake.

So, patients on beta-blockers experience impaired cellular potassium uptake in the usual conditions, and this becomes more significant during exercise where K+ in the blood increases. Additionally, alpha-1 receptors in some organs are activated during exercise to slightly decrease potassium sequestration, and increase its release from the liver, exposing patients on beta-blockers to the risk of severe hyperkalemia during intense exercise.
Note that selective β1 blockers like atenolol will affect K+ levels less significantly compared to non-selective ones like propranolol.

Calcium

Calcium homeostasis is regulated by three main organs (skin, GI tract, and kidneys) and three primary hormones (Vitamin D, Calcitonin, and PTH).
While 98% of the body's calcium is stored in the bone, the remaining 2% is found extracellularly, split into 50% protein-bound and 50% free (ionized) forms.

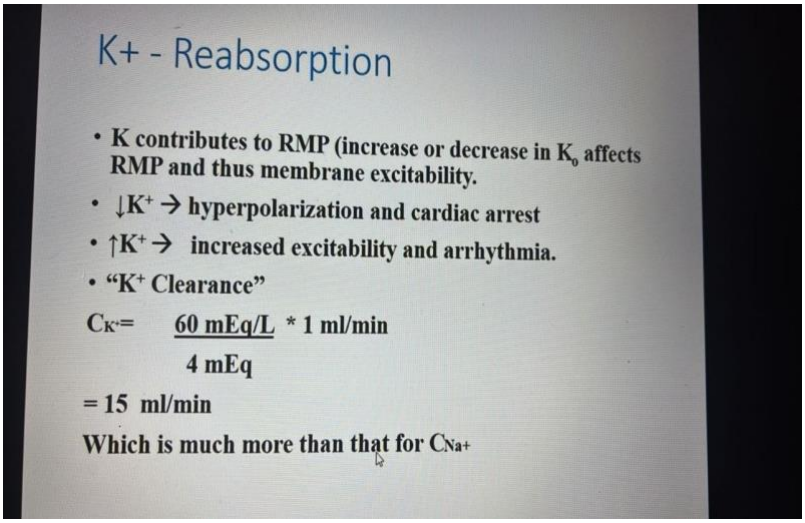
Hyperventilation washes out CO_2, which as we said, a major source of H+, resulting in alkalosis.
Alkalosis increases the bound fraction of calcium, leading to a **drop** in the **free** ionized calcium.
Although the **total** amount of calcium remains the same in alkalosis, the condition is still called hypocalcemia, as the decreased fraction is the free fraction that the body can utilize and deal with.

When free calcium decreases, motor neurons that go to the peripheral muscles will be stimulated, leading to spasms in the hands, face, and diaphragm, and causing death.
On the other hand, acidosis increases free calcium levels.

V1: page 10

Instead of (hyperkalemia decreases the excitability of the heart)—> (hyperkalemia increases the excitability of the heart).

While hypokalemia causes hyperpolarization and cardiac arrest.



V2: Rediscussed and explained the different views on the hyperkalemia effect on the excitability of the heart on page 10.