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# Consequences of K and Ca dysbalances on ❤️ and 💪

Jaromir Gumulec

- Depolarisation,
  - electrical activation of muscle cells
  - Movement of Na, K, Ca Cl across cardiac membranes
- Repolarisation
  - Electrical deactivation

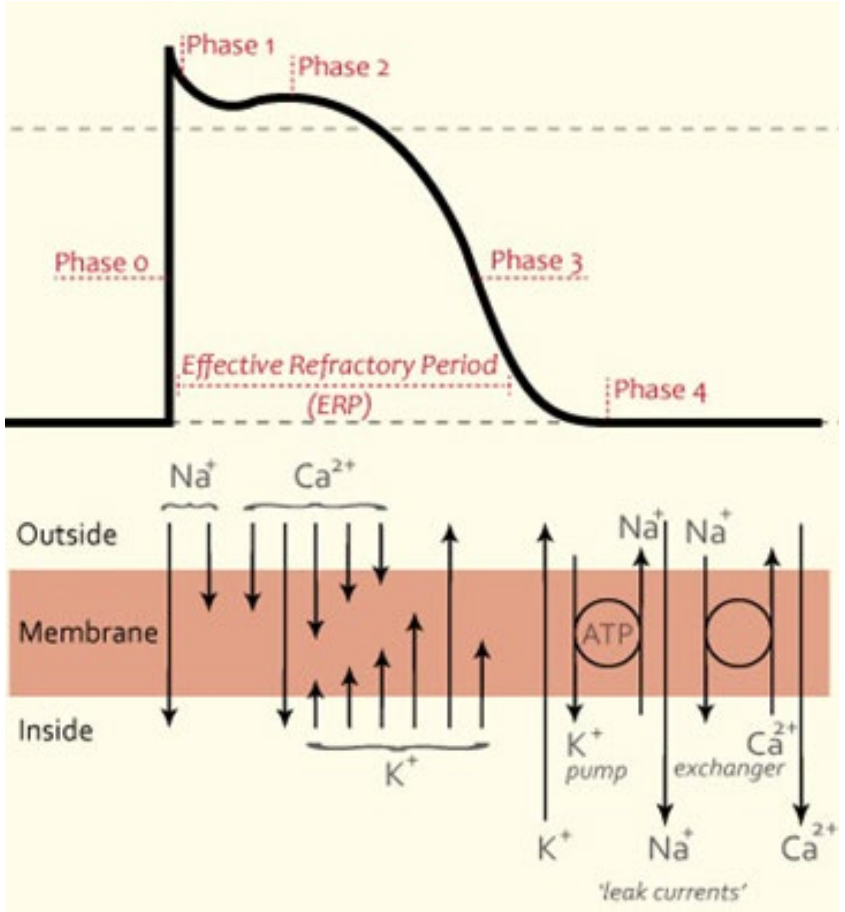

https://step1.medbullets.com/cardiovascular/108015/myocardial-action-potential

# Potential changes

- Movement of ions into and out of cells creates voltage difference across membrane – negative **resting membrane potential**
  - SA node -50 to -60 mV
  - AV node -60 to -70 mV
  - myocardial cells -80 to -90 mV
- Driven by
  - Na/K ATPase contributes to the negative resting potential
  - The **chemical gradient** driving $K^+$ out of the cell.
  - The **electrical gradient** pulling $K^+$ back into the cell as the inside becomes more negative.
  - At equilibrium, $K^+$ is the most permeable ion at rest (due to **$K^+$ leak channels**).
  - If more negative (by decrease of **extracel. K+) „hyperpolarisation“**

# Phases of action potential

- During depolarisation:
  - cell inside becames less negative *(more positively charged move to cell)*
  - When threshold potential is reached, cardiac action potential is fired.
  - Treshold = temoraly disrupted membrane selectivity
- Phases:
  - Phase 0: depolarisation: **rapid** Na+ entry to cell
  - Phase 1: early repolarisation: slow Ca enter to cell
  - Phase 2: plateau: **slow** Ca, Na enter to cell,
  - Phase 3: repolarisation: K out
  - Phase 4: return to resting membrane potential



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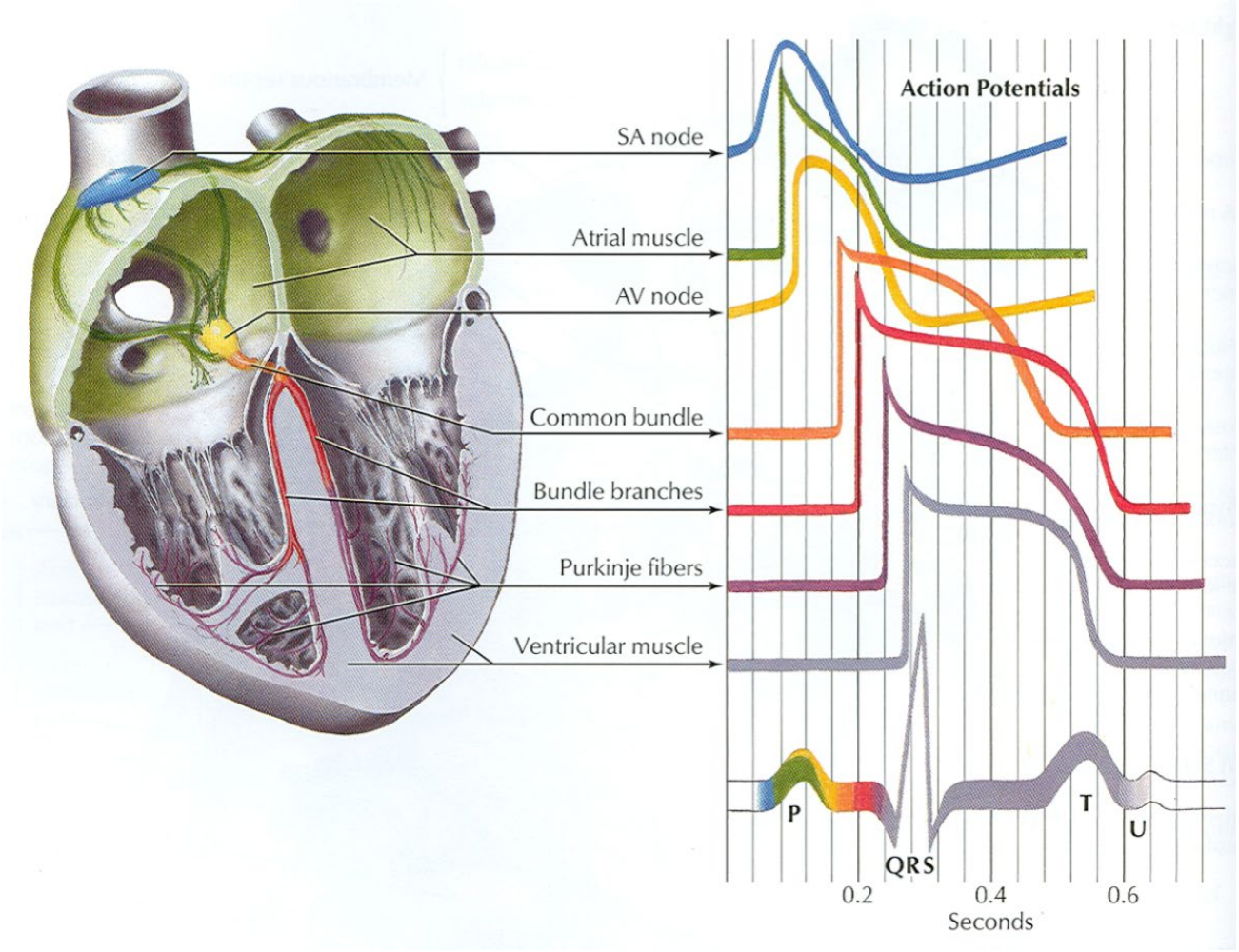


- In SA and AV:
- slow phase 0, lack of plateau
  - Slow inward current by slow Ca channels (block by verapamil slow heart rate

https://www.semanticscholar.org/paper/Mechanisms-of-Excitation-and-Remodeling-of-the-in-O%E2%80%99Connell/f5decafd0bebbaf2a80699c6a83de8ca389fd8e2/figure/0



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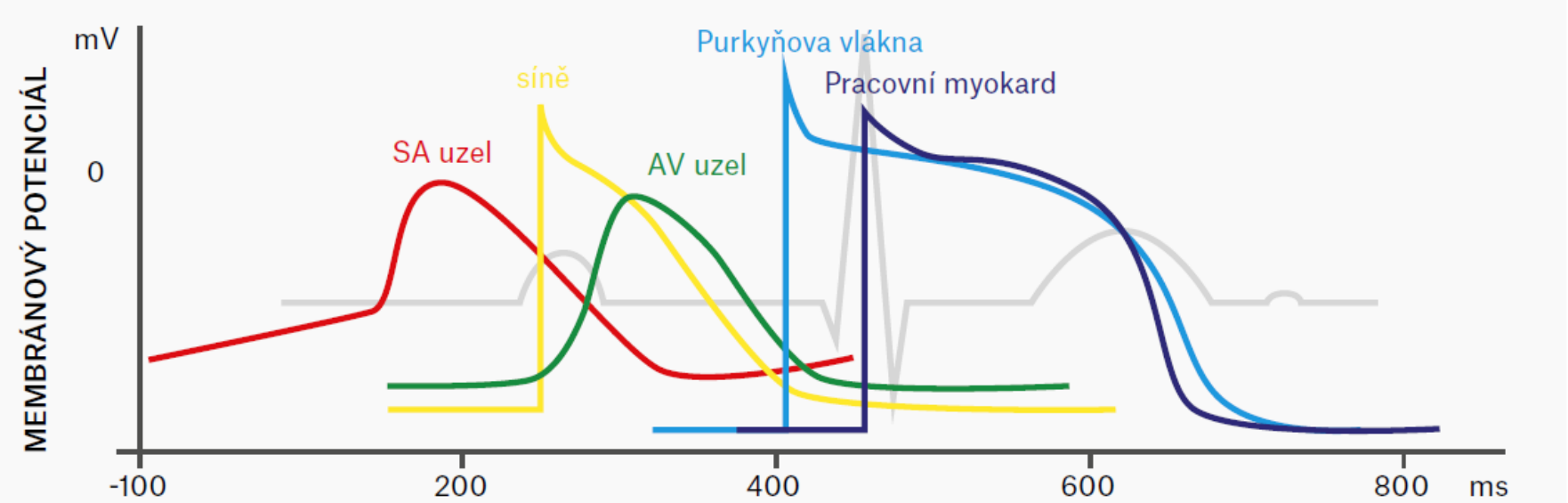
MEMBRÁNOVÝ POTENCIÁL
mV
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síně
Pracovní myokard
SA uzel
AV uzel
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200
400
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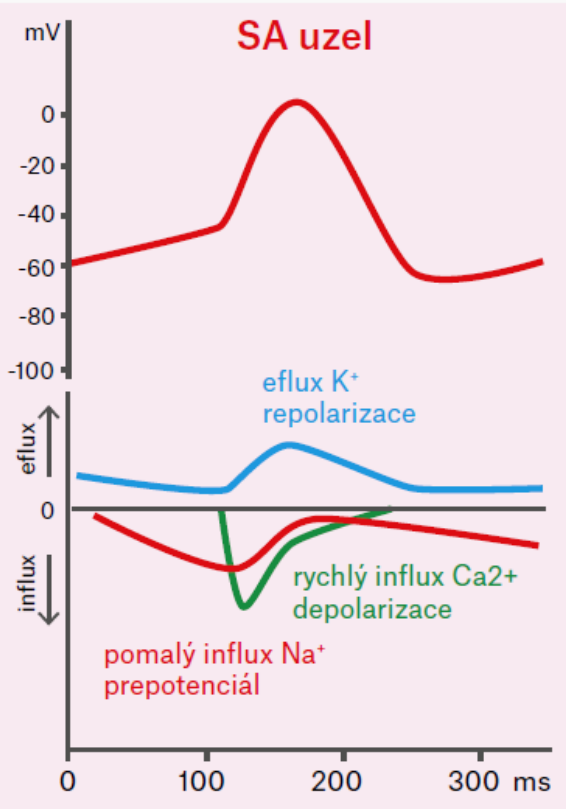
800
ms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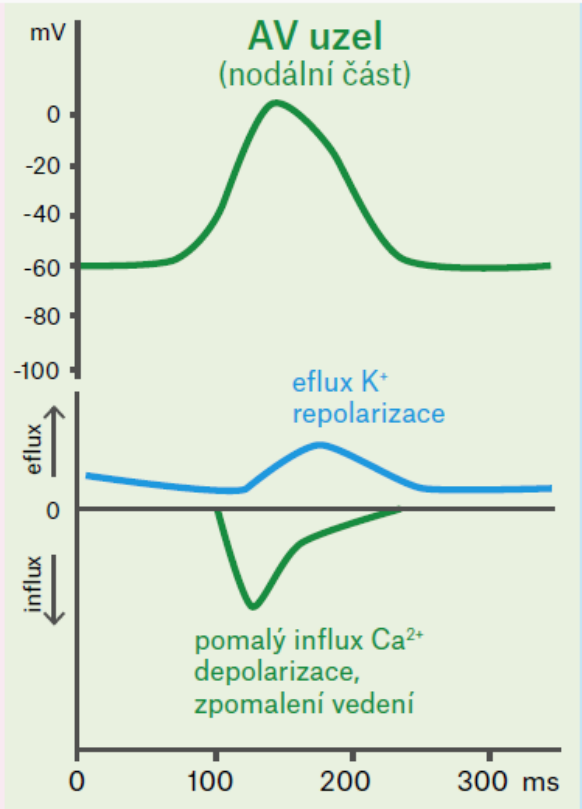
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(nodální část)
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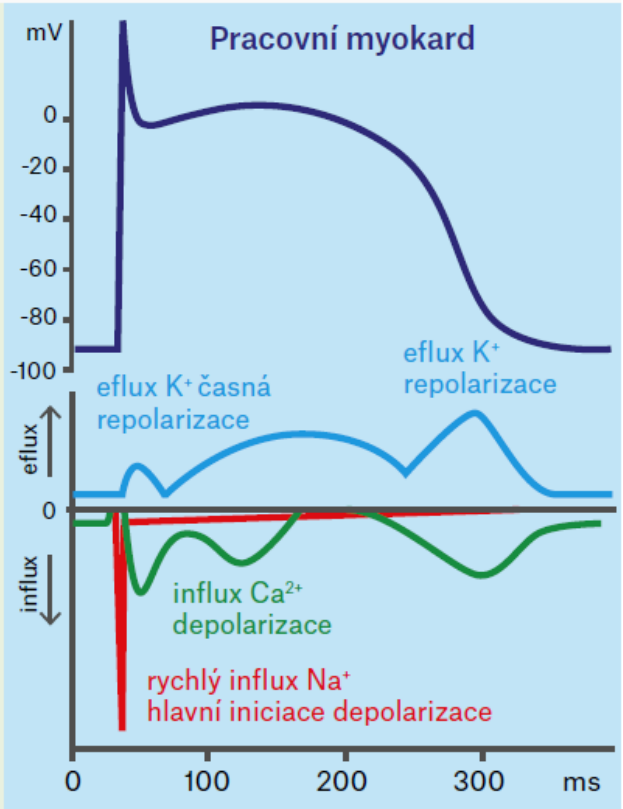
Pracovní myokard
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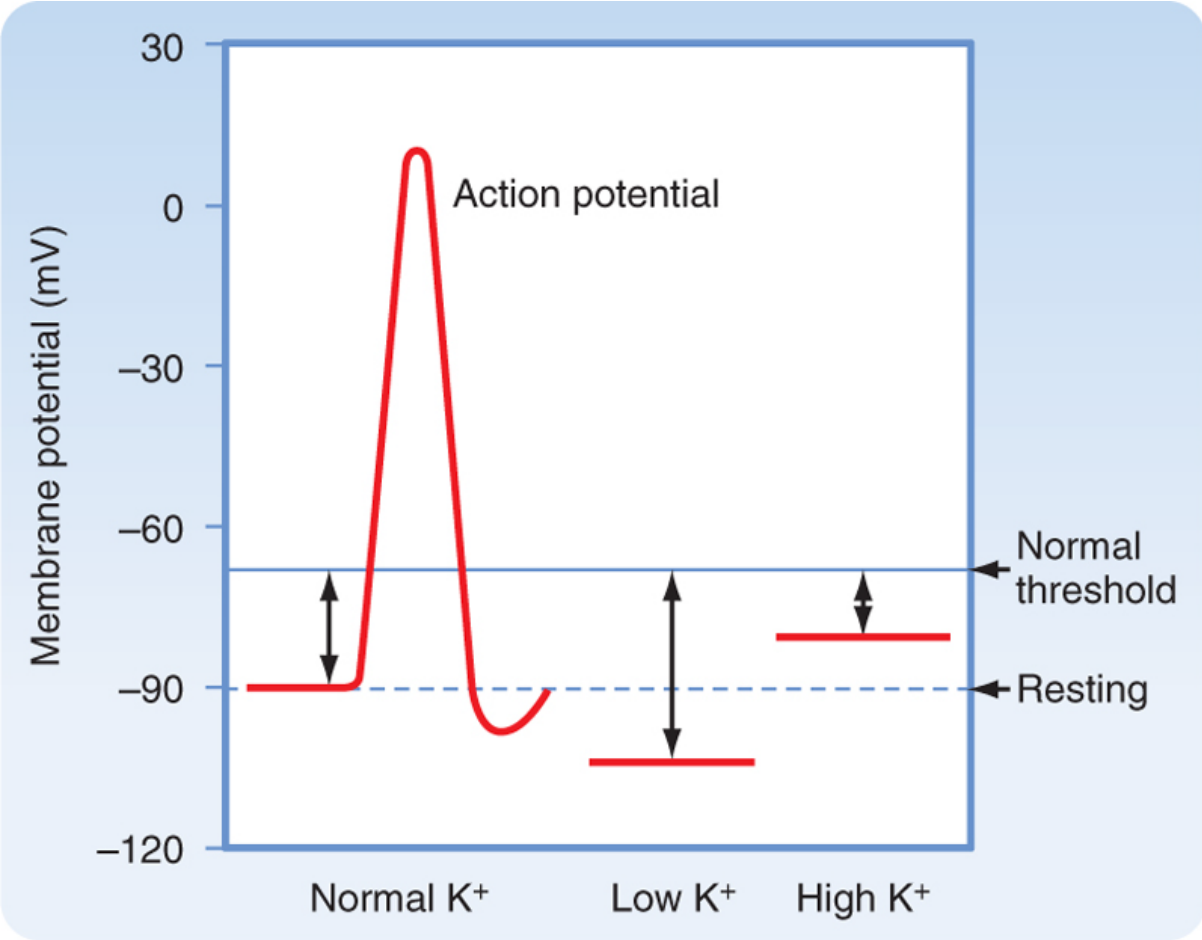
eflux
influx
influx Ca2+
depolarizace
rychlý influx Na+
hlavní iniciace depolarizace
0
100
200
300
ms

- Stimulation of SA by sympathetic system
  - increases heart rate
  - Induce increased Ca2+ influx, which intreases contractile strength

# Potassium

- **Ratio of ICF to ECF K+ is major determinant of resting potential ➡️ excitability**
  - **Shift to cells**: Insulin *(stimulate Na/K pump)*, adrenaline, alkalosis
  - **Shift outa cells**: insulin deficiency, aldosteron deficiency, some types of acidosis, cell lysis, insensive excercise
  - **Block entry to cells**: glucagon
  - **Promote K excretion**: Glukocorticoids, aldosterone
- K is intracellular – difficult to measure





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# Potasium – hypokalemia (simple)

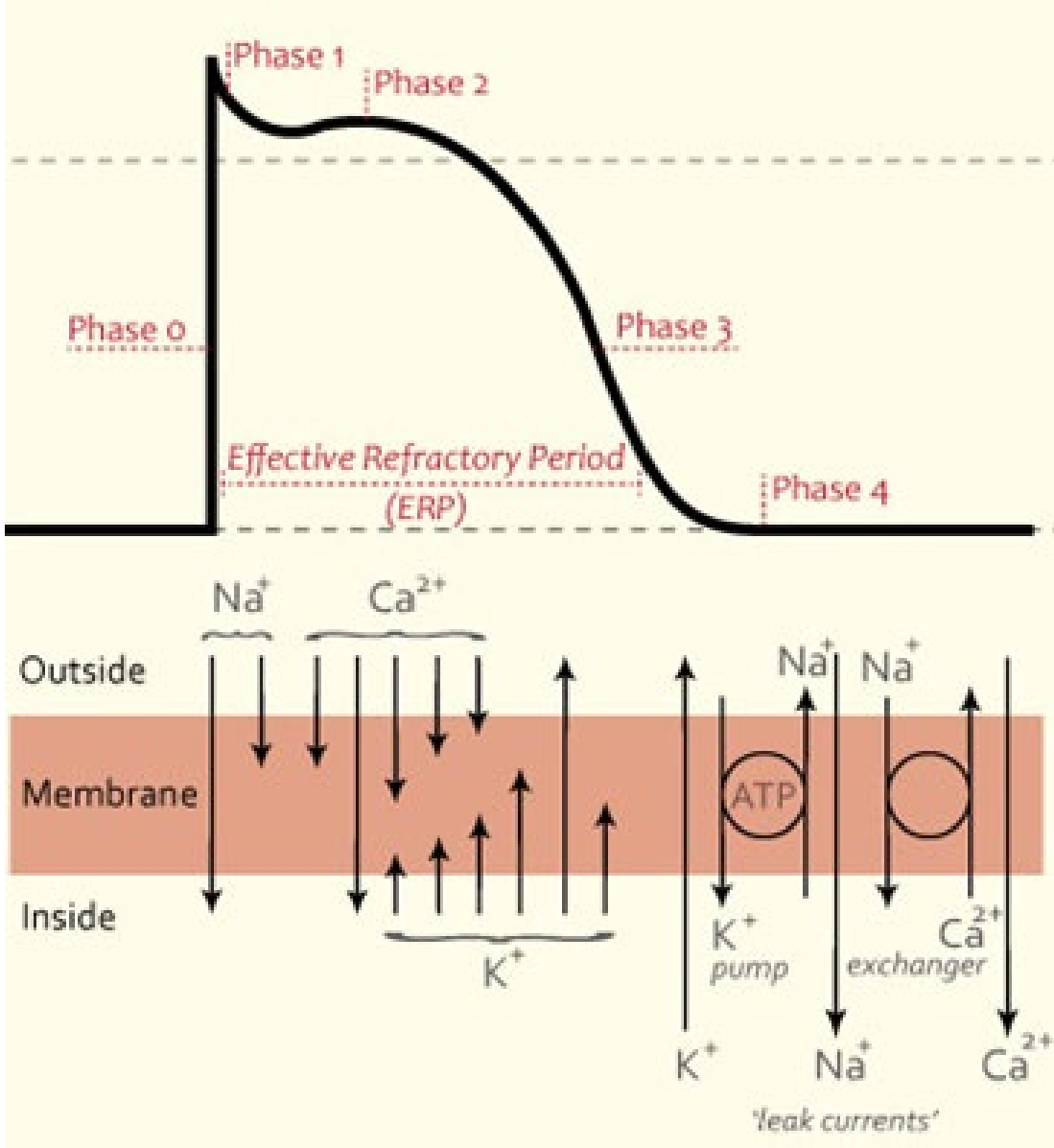
- more negative resting membrane potential (-90 to -100 mV):
- decrease of excitability: 💪 weakness, smooth muscle atony,
- delayed ❤️ **repolarisation** ➡️ **Risk of Dysrythmias**
- ➡️ **ECG** *decreased T, ST depression, U increase,*
- in severe hypokalemia *peaked P, prolonged QT*

# Potasium – hypokalemia (detailed)

- ECF hypokalemia can develop without losses of total body K+
- decrease of excitability:
  - 💪 skeletal muscle weakness, smooth muscle atony, cardiac dysrythmias,…
  - ❤️: more negative resting membrane potential (-90 to -100 mV): **hyperpolarised** membrane require greater stimulus to trigger AP
  - ❤️ hypoK also delays (ventricular) **repolarisation** ➡️ fail to conduct impulses efficiently ➡️ **Risk of Dysrythmias** *(sinus bradycardia, AV block)*
- Repolarisation relies on K efflux:
  - Reduced extracellular $K^+$ slows **$K^+$ efflux** during repolarization. ➡️ **prolongation of the action potential duration,** and delayed ❤️ repolarization. ➡️ **ECG** *decreased T, ST depression, U increase,* in severe *peaked P, prolonged QT.* ➡️ arrytmias Re-entry, EAD

# Na K ATPase X K efflux

- in **hypokalemia**, the decreased extracellular potassium does reduce the activity of the **$Na^+/K^+$ pump** ($Na^+/K^+$-ATPase). However, this **reduction in pump activity** does not fully counteract the effects of **slower $K^+$ efflux during repolarization**
  - **Delayed rectifier $K^+$ channels (I_Kr and I_Ks)** are the primary drivers of repolarization in cardiac myocytes during **Phase 3 of the action potential**.
  - The **$Na^+/K^+$ pump**, while affected by hypokalemia, plays a much smaller role in repolarization dynamics compared to these $K^+$ channels.



# Potassium - Hyperkalemia

- increased 💪 neuromuscular irritability
  - **Mild**: more rapid ❤️ repolarisation (smaller distance of Em and Et) ➡️ *narrow, taller T, short QT*
  - ***Severe****: delayed* ❤️ conduction ➡️ preventing repolarisation ➡️ ST depression, PR prolongation, QRS widening,
  - prolonged hypopolarization/partial depolarisation ➡️ **voltage-gated sodium channels ($Na^+$ channels)** become inactivated ➡️ cardiac arrest.

    For these channels to reset and become available for the next action potential, the membrane potential must be sufficiently **negative** during resting conditions
- Excitability determined by $K_{ECF}/K_{ICF}$ ➡️ manifestation in acute disorders,

  gradient normalises in chronical ones!
- Long-term increases in $K_{ECF}$ results in shift of K to ICF ➡️ $K_{ECF}/K_{ICF}$ normalised



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# Potassium and acidosis

- Acute acidosis:
  - H+ accumulate in ICF.*(unless anion portion of acid – acetoacetate, lactate – entered cells)*, **imbalance** occur. to maintain balance, **K leaves cells ➡️ hyperkalemia**
- Acute alkalosis

účinek na akční potenciál

účinek na EKG

klinický efekt

## TĚŽKÁ HYPOKALEMIE
< 2,5 mmol/L

↑ $E_m$ → ↓ $E_p - E_m$ → ↑ excitabilita

↓↓ $K^+$

snazší depolarizace
snazší repolarizace
vyšší excitabilita

deprese ST
prodloužení PQ
rozšíření QRS

fibrilace komor
arytmie (komorové extrasystoly)
junkční až idioventrikulární rytmus

## MÍRNÁ HYPOKALEMIE
< 3,5 mmol/L

↓ $E_m$ → ↑ $E_p - E_m$ → ↓ excitabilita

↓ $K^+$

obtížnější repolarizace
nižší excitabilita

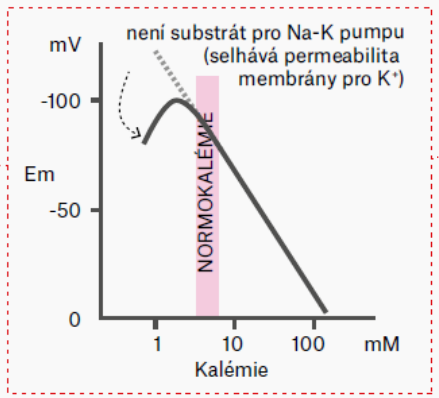
oploštění T
zvýraznění U

sinusová bradykardie
arytmie
↓ svalového tonu
zácpa
únava

## NORMOKALEMIE
3,5 – 5,1 mmol/L

$E_m = \frac{K^+_{ex}}{K^+_{in}}$

norma




## MÍRNÁ HYPERKALEMIE
5,5 – 6,5 mmol/L

↑ $E_m$ → ↓ $E_p - E_m$ → ↑ excitabilita

↑ $K^+$

snazší depolarizace
snazší repolarizace
vyšší excitabilita

úzké hrotnaté T
zkrácení QT

fibrilace komor
idioventrikulární rytmus
riziko re-entry tachy

## STŘEDNĚ TĚŽKÁ HYPERKALEMIE
6,5 – 7,5 mmol/L

obtížnější otevírání Na kanálů → prodloužení depolarizace → ↓ excitabilita

↑↑ $E_m$ → ↓↓ $E_p - E_m$ → !

prodloužení
rozšíření

↑↑ $K^+$

obtížnější repolarizace
snížená excitabilita

prodloužení PQ
... až vymizení P
rozšíření QRS
deprese ST

... až sinusové vlny

fibrilace komor
arytmie (komorové extrasystoly)
riziko re-entry tachy
junkční až idioventrikulární rytmus

## TĚŽKÁ HYPERKALEMIE
> 7 mmol/L

↑↑↑ $E_m$ → $E_p > E_m$ → žádná excitabilita

↓ neotevření Na kanálů

↑↑↑ $K^+$

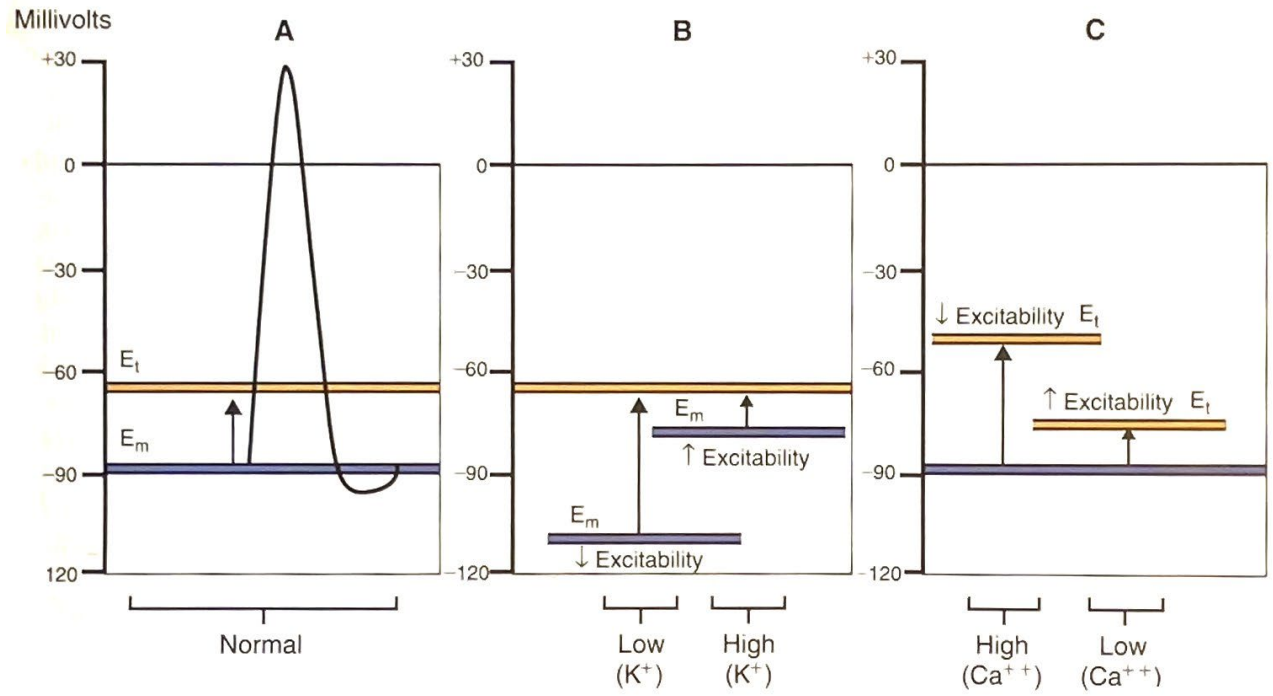
neschopnost depolarizace
žádná excitabilita

izoelektrická linie

zástava srdce v diastole

# Calcium

- $Ca^{2+}$ x $HPO_4^-$ = constant
- Serum free Ca pH-affected
  - **Acidosis:** ionized Ca increases ( $H^+$ binds to albumin ➡️Ca released (competition with albumin)
- Effect on 💪 initiation of action potential
  - *primarily in excitable membranes of neurons and* 💪
- *Effect on* ❤️
  - ❤️ *muscle contraction*
  - *Duration of action potential (repolarisation)*



# Calcium: Hypocalcemia (simple)

- Increase of 💪 neuromuscular excitablity
- weaker ❤️‍🩹 contraction
- prolonged QT



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# Calcium: Hypocalcemia (detailed)

- ➡️ Increase of 💪 neuromuscular excitablity, because
  - Ca+ stabilize the **voltage-gated sodium channels**
  - With fewer calcium ions stabilizing the sodium channels ➡️ Na ch destabilisatoin ➡️ Hypopolarisation ➡️ smaller stimulus needed ➡️ Partial depolarisation of nerves and muscles
  - Paresthesias, spasms, hyperreflexias
- **Lower** ECF Ca ➡️ **lower** Ca influx to ICF through L channels ➡️
  - ➡️ Weaker Ca efflux from sarcoplasmatic reticle ➡️ **weaker** ❤️ **contraction**
  - ➡️ **Prolonged repolarization** (less $Ca^{2+}$ is available to balance $K^{+}$ efflux during plateau ➡️ **longer** action potential ➡️ prolonged ❤️ depolarisation ➡️ **prolonged QT**
  - Specific to **cardiac muscle**, where calcium influx is directly responsible for **contraction strength** and the **plateau phase** of the action potential.

| Feature | Skeletal Muscle | Cardiac Muscle |
|---|---|---|
| **Source of calcium for contraction** | Mostly from the **sarcoplasmic reticulum (SR)** | From both **extracellular calcium** and **SR** |
| **Role of extracellular calcium** | Minimal, primarily stabilizes membrane potential | Essential for triggering **calcium-induced calcium release** (via ryanodine receptors (RyR2) |
| **Effect of hypocalcemia** | **No effect** on contraction strength, but increases excitability | **Weakens contraction** and prolongs repolarization (QT) |

In 💪 Hypocalcemia affects **membrane excitability**, not the intracellular calcium release machinery



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# Calcium: hypercalcemia (simple)

- stronger ❤️ contractility
- Shortening QT, depression of T
- In 💪 decreased excitability ➡️ Fatigue, 💪 weakness, letargy, anorexia, constipation, nausea

# Calcium: hypercalcemia (detailed)

- In ❤️ ECF Ca increased ➡️ greater influx of Ca ro cells (L channels)
  - Plato phase acceleration ➡️ increased calcium-induced calcium release (CICR) (from SR) ➡️ **stronger** ❤️ **contractility**
  - Hypercalcemia increases the rate of calcium reuptake by the **sarcoplasmic reticulum** *(via SERCA) and also enhances calcium extrusion via the $Na^+/Ca^{2+}$ exchanger.* ➡️ faster repolarisation + shorter plateau ➡️ Shortening QT, depression of T
- In 💪 contraction strength is not directly dependent on ECF Ca
  - (contraction relies on **intracellular calcium released from the SR)**
  - Elevated ECF Ca increases the **stabilization of voltage-gated sodium channels**, making them harder to activate ➡️ Treshold becomes more positive (**hyperpolarisation**) ➡️decreased excitability
  - Fatigue, 💪 weakness, letargy, anorexia, constipation, nausea



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| Effect | Cardiac Muscle | Skeletal Muscle |
|---|---|---|
| **Increased ECF $Ca^{2+}$ → CICR** | Enhanced CICR → **stronger contraction** (**positive inotropy**) | Little to no effect on CICR, as calcium entry plays a minimal role in skeletal muscle contraction. |
| **Effect on Plateau Phase** | Faster calcium uptake/release → **shortened QT interval** and faster repolarization. | N/A (no plateau phase in skeletal muscle action potentials). |
| **Reduced Excitability (Hyperpolarization)** | Stabilized $Na^+$ channels → reduced excitability, slower AP conduction (**arrhythmias possible**). | Stabilized $Na^+$ channels → **reduced excitability**, leading to **fatigue** and **weakness**. |
| **Overall Contractility** | **Increased strength of contraction (positive inotropy)**. | **No significant increase**; reduced excitability dominates, causing weakness. |

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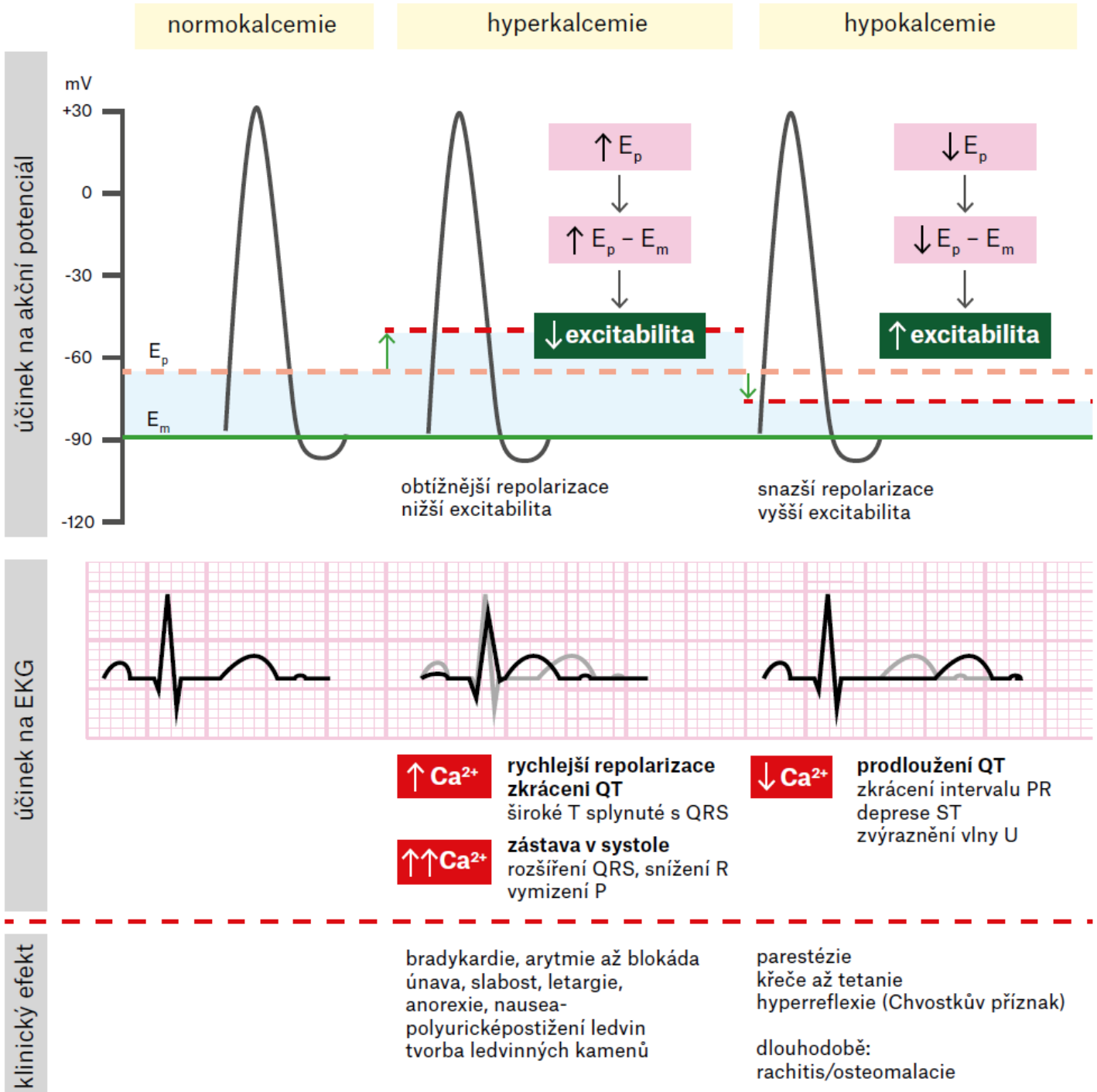

normokalcemie
hyperkalcemie
hypokalcemie
účinek na akční potenciál
mV
+30
0
-30
-60
-90
-120
$E_p$
$E_m$
$\uparrow E_p$
$\uparrow E_p - E_m$
↓excitabilita
$\downarrow E_p$
$\downarrow E_p - E_m$
↑excitabilita
obtížnější repolarizace
nižší excitabilita
snazší repolarizace
vyšší excitabilita
účinek na EKG
$\uparrow Ca^{2+}$
rychlejší repolarizace
zkrácení QT
široké T splynuté s QRS
$\uparrow\uparrow Ca^{2+}$
zástava v systole
rozšíření QRS, snížení R
vymizení P
$\downarrow Ca^{2+}$
prodloužení QT
zkrácení intervalu PR
deprese ST
zvýraznění vlny U
klinický efekt
bradykardie, arytmie až blokáda
únava, slabost, letargie,
anorexie, nausea-
polyuricképostižení ledvin
tvorba ledvinných kamenů
parestézie
křeče až tetanie
hyperreflexie (Chvostkův příznak)
dlouhodobě:
rachitis/osteomalacie

$K^+$ are difficult to measure, changes in $K^+$ balance are reflected by the plasma concentration, although not always accurately. In general, lowered serum $K^+$ level indicates a loss of total body $K^+$. When $K^+$ is lost from the ECF, the change in the concentration gradient favors the movement of $K^+$ from the cell into the ECF. The ICF/ECF concentration ratio is maintained, but the amount of total body $K^+$ is depleted.

Factors contributing to the development of hypokalemia include a reduced intake of potassium, an increased entry of $K^+$ into cells, and increased losses of $K^+$. A dietary deficiency of $K^+$ may occur in people who have inadequate intake of potassium-rich fruits and vegetables (influenced by fad diets, food insecurity, or lack of transportation to purchase fresh produce), and in individuals with alcoholism or eating disorders. A reduced $K^+$ intake generally becomes a problem when combined with other causes of $K^+$ depletion.

ECF hypokalemia can develop without losses of total body $K^+$. As discussed previously, with some types of acidosis, potassium shifts from the ECF to the ICF in exchange for hydrogen ions to maintain the plasma acid-base balance. In alkalosis, ECF hydrogen moves out of the cell to correct the alkalosis, and $K^+$ moves into the cell to maintain an ionic balance. Insulin promotes cellular uptake of $K^+$, and insulin administration can cause an ECF potassium deficit, particularly with the intake of high carbohydrate loads. For this reason, it is crucial to evaluate potassium status in emergency settings when treating a person with diabetes who presents with severe hyperglycemia and/or diabetic ketoacidosis (DKA). Failure to do so before administering IV insulin can result in life-threatening hypokalemia. Treating DKA typically requires administration of supplemental potassium simultaneously with IV insulin and rehydration therapy. With DKA, the overall insulin deficit results in potassium shifts from the ICF to the ECF, due to lack of insulin action on the $Na^+$-$K^+$ ATPase pump. A normal serum potassium level usually is maintained; however, potassium excretion through the kidney continues, resulting in a deficit of total body potassium. The deficit becomes clinically evident when insulin treatment and rehydration therapy are initiated. Accordingly, in the treatment of hyperglycemia with or without DKA, the standard of care is potassium supplementation with close monitoring.

Treatment of pernicious anemia with vitamin $B_{12}$ or folate also may precipitate hypokalemia if the formation of new red blood cells causes enough $K^+$ uptake to effect an extracellular decrease in $K^+$ concentration. **Familial hypokalemic periodic paralysis** is a rare genetically transmitted disease that causes $K^+$ to shift into the intracellular space with episodes of extreme muscle weakness.

Losses of $K^+$ from body stores are most commonly caused by gastrointestinal and renal disorders. Diarrhea, intestinal drainage tubes, fistulae, excessive ingestion of black licorice, and laxative overuse can all result in hypokalemia. Normally, only 5 to 10 mEq of potassium and approximately 100 mL of water are excreted in the stool each day. With diarrhea, fluid and electrolyte losses can be voluminous, with several liters of fluid and 100 to 200 mEq of $K^+$ lost per day. Vomiting or continuous nasogastric suction frequently is associated with $K^+$ depletion. The loss occurs in part because of the $K^+$ lost from the gastric fluid. However, the loss principally is caused by renal compensation for volume depletion and metabolic alkalosis, which occurs secondary to losses of sodium, chloride, and hydrogen ion. The loss of fluid and sodium stimulates the secretion of aldosterone, which in turn results in renal loss of $K^+$.

Renal losses of $K^+$ are related to increased secretion of $K^+$ by the distal tubule. Predisposing factors include the use of diuretics, excessive aldosterone secretion, an increased distal tubular flow rate, and a low plasma magnesium concentration. Many diuretics inhibit the reabsorption of sodium chloride, resulting in increased urine production. With enhanced fluid excretion, the increased flow through the distal tubule also promotes potassium excretion. If sodium loss is severe, the compensating aldosterone secretion (which causes secondary hyperaldosteronism) may further deplete $K^+$ stores. Primary hyperaldosteronism with excessive secretion of aldosterone from an adrenal adenoma also causes $K^+$ wasting. Many kidney diseases impair the kidney's ability to conserve sodium. The decreased sodium reabsorption produces a diuretic effect. As a result, the increased flow through the distal tubule promotes the secretion of $K^+$. Magnesium deficiency increases loop of Henle and distal potassium secretion, causing secondary hypokalemia.[11] Several medications, including amphotericin B, gentamicin, and nafcillin, cause hypokalemia by increasing the rate of potassium excretion. Rare hereditary defects in renal potassium transport (Bartter and Gitelman syndromes) also can result in hypokalemia (Table 3.9).

***Clinical Manifestations.*** Mild losses of $K^+$ are usually asymptomatic. With severe hypokalemia (<2.5 mEq/L), neuromuscular excitability decreases, causing skeletal muscle weakness, smooth muscle atony, cardiac dysrhythmias, glucose intolerance, and impaired urinary concentrating ability.

Symptoms occur in proportion to the rate of potassium depletion. The body can accommodate slow losses of potassium. Decreases in the ECF potassium concentration may facilitate a

**TABLE 3.9 Causes of Potassium Alterations**

| Hypokalemia <3.5 mEq/L | Causes |
|---|---|
| Decreased intake: starvation or eating disorders, inadequate replacement | Intake |
| Increased renal loss: renal concentrating defect, $K^+$-losing diuretics, hyperaldosteronism, vomiting, diarrhea, use of specific medications | Loss |
| Shift from ECF to ICF: metabolic alkalosis, insulin administration, gene mutations in $K^+$ transport | Cellular shifts |
| **Hyperkalemia >5.0 mEq/L** | **Causes** |
| Excess dietary or intravenous intake | Intake |
| Decreased renal loss: oliguric renal disease, $K^+$-sparing diuretics, hypoaldosteronism | Loss |
| Shift from ICF to ECF: some types of metabolic acidosis, massive cell injury or death | Cellular shifts |

*ECF*, Extracellular fluid; *ICF*, intracellular fluid; $K^+$, potassium.



shift in potassium away from the intracellular space and into the ICF. This dynamic promotes the return of the potassium concentration gradient toward a more normal status, reducing neuromuscular symptoms. With acute and severe potassium loss, the changes in neuromuscular excitability are more profound. Skeletal muscle weakness initially occurs in the larger muscles of the legs and arms and ultimately affects the diaphragm, compromising ventilation. With severe losses, paralysis and respiratory arrest may occur. Loss of smooth muscle tone may result in a variety of gastrointestinal manifestations, such as constipation, intestinal distention, anorexia, nausea, vomiting, and paralytic ileus (paralysis of the intestinal muscles). Table 3.10 contains a summary of $K^+$ alterations.

The cardiac effects of hypokalemia are related to changes in membrane excitability. As the ECF potassium concentration decreases, the resting membrane potential becomes more negative (i.e., *hyperpolarized*; e.g., from −90 to −100 millivolts). A hyperpolarized membrane requires a greater stimulus to trigger an action potential (Fig. 3.8B). Potassium also contributes to the repolarization phase of the action potential; hypokalemia delays ventricular repolarization. Consequently, hypokalemia may result in various dysrhythmias, including sinus bradycardia, atrioventricular block, and paroxysmal atrial tachycardia. The characteristic changes in the electrocardiogram (ECG) reflect delayed ventricular repolarization with slowed conduction and pacemaker activity. The amplitude of the T wave decreases, the amplitude of the U wave increases, and the ST segment is depressed (Fig. 3.9). In severe states of hypokalemia, P waves peak, the QT interval is prolonged, and T-wave inversions may be seen. Hypokalemia enhances the therapeutic effect of digitalis by slowing the $Na^+$-$K^+$ pump and excessively increasing intracellular calcium and sodium concentrations. The risk of digitalis toxicity is increased.

Concurrent alterations in *plasma calcium concentration* also contribute to changes in neuromuscular excitability associated with hypokalemia. Increases in ECF calcium concentration tend to make the threshold potential ($E_t$) less negative. The result is decreased membrane excitability and potentiation of hyperpolarization, amplifying the neuromuscular effects of hypokalemia (see Fig. 3.8C).

A wide range of metabolic dysfunctions may result from potassium deficiency. Carbohydrate metabolism is affected. Hypokalemia depresses insulin secretion and alters hepatic and skeletal muscle glycogen synthesis. Renal function is impaired

**TABLE 3.10 Organ System Manifestations of Potassium Alterations**

| Organ System | Hypokalemia <3.5 mEq/L | Hyperkalemia >5.0 mEq/L |
|---|---|---|
| Cardiovascular | Postural hypotension<br>Dysrhythmias<br>ECG changes (flattened T waves, U waves, ST depression, peaked P wave, prolonged QT interval)<br>Weak, irregular pulse rate<br>Ventricular fibrillation | Dysrhythmias<br>ECG changes (peaked T waves, prolonged PR interval, absent P wave with widened QRS complex)<br>Bradycardia<br>Heart block<br>Cardiac arrest |
| Nervous | Lethargy<br>Fatigue<br>Confusion<br>Paresthesias<br>Decreased tendon reflexes | Anxiety<br>Tingling<br>Numbness |
| Gastrointestinal | Nausea and vomiting<br>Decreased motility<br>Distention<br>Decreased bowel sounds<br>Ileus | Nausea and vomiting<br>Early: Diarrhea<br>Early: Colicky pain |
| Kidney | Inability to concentrate urine<br>Water loss<br>Thirst<br>Kidney damage | Oliguria<br>Kidney damage |
| Skeletal and smooth muscle | Weakness<br>Flaccid paralysis<br>Respiratory arrest<br>Constipation<br>Bladder dysfunction | Early: hyperactive muscles and reflexes<br>SLate: weakness and flaccid paralysis |

ECG, Electrocardiogram.

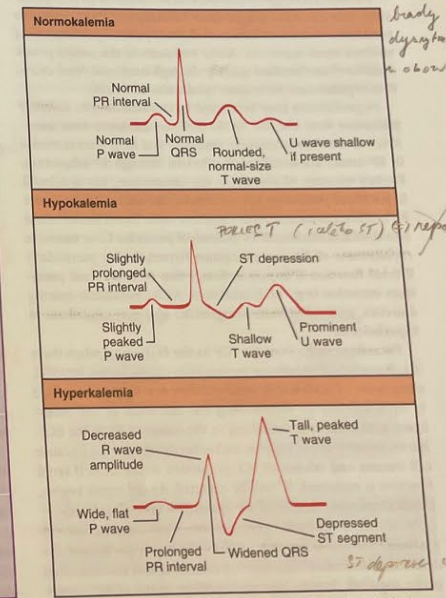
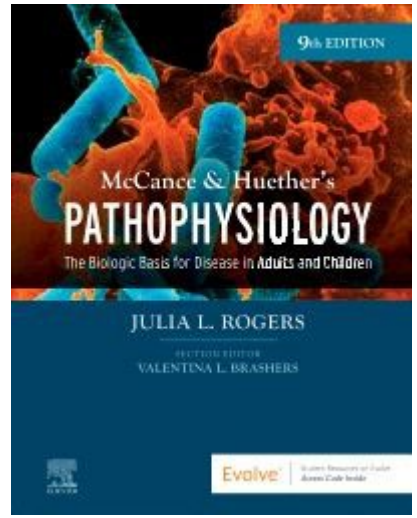



**Fig. 3.9** Electrocardiogram Changes With Potassium Imbalance.




Well, McCance is very concise in terms of channel mechanisms – **and this is totally enough!**

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by a decreased responsiveness to ADH, resulting in a decreased ability to concentrate urine, causing polyuria (increased urine). Polydipsia (increased thirst) may occur. Chronic potassium deficits lasting more than 1 month may damage renal tissue, with resulting interstitial fibrosis and tubular atrophy.

***Evaluation and Treatment.*** The diagnosis of hypokalemia is based on serum $K^+$ levels. Hypokalemia can result from disorders associated with potassium loss or from shifts of extracellular potassium into the intracellular space. Treatment involves replacing lost potassium to restore normal levels and correcting the associated fluid and acid-base imbalances. Once these have been corrected, further potassium loss should be prevented by correcting the underlying mechanism. In particular, individuals should be encouraged to eat potassium-rich foods. With normal renal function, the maximal rate of oral replacement is 40 to 80 mEq/day. A maximal safe rate of IV replacement is 20 mEq/h. Potassium is irritating to blood vessels and can result in considerable pain for the individual. Accordingly, IV infusions containing potassium should not exceed 40 mEq/L. Replacement therapy requires close monitoring of the plasma potassium concentration. Hypokalemia concurrent with hypomagnesemia is refractory to treatment until magnesium levels are corrected.

## Hyperkalemia

***Pathophysiology.*** **Hyperkalemia** is defined as an ECF potassium concentration greater than 5.5 mEq/L.[11a] Increases in the total body potassium level are relatively rare, largely because of efficient renal excretion. Acute increases in the serum potassium level are handled quickly through increased renal excretion of potassium, with some uptake also into cells.

Hyperkalemia may be caused by *excessive intake*, a *shift of potassium from the ICF to the ECF*, or *decreased renal excretion*.[12] If renal function is normal, slow and long-term increases in $K^+$ intake are usually well tolerated through $K^+$ adaptation. Dietary excesses of potassium are uncommon, but accidental ingestion of potassium salt substitutes can cause toxicity. Acute $K^+$ loading can exceed renal excretion rates. Use of stored whole blood, administration of IV boluses of penicillin G, or excessive replacement of $K^+$ can precipitate hyperkalemia, particularly if renal function is impaired. Drugs that decrease renal potassium excretion (e.g., ACE inhibitors, ARBs, potassium-sparing diuretics, and aldosterone antagonists) also may contribute to hyperkalemia.

Potassium shifts from the ICF to the ECF occur when there is a *change in cell membrane permeability* caused by cell hypoxia, some types of acidosis, or insulin deficiency. Hypoxia can lead to hyperkalemia by diminishing the efficiency of cell membrane active transport, resulting in the escape of $K^+$ to the ECF. Burns, massive crush injuries, and extensive surgeries can cause cell trauma and release of ICF potassium to the ECF. If renal function is sustained, $K^+$ will be excreted. As cell repair begins, hypokalemia may develop if the excreted $K^+$ is not replaced.

In states of *acidosis*, hydrogen ions shift into the cells in exchange for ICF potassium, unless the anion portion of the acid also enters cells; therefore hyperkalemia and acidosis often occur together. Insulin promotes cellular entry of $K^+$; consequently, *insulin deficits*, which occur with conditions such as DKA, are often accompanied by hyperkalemia. Hyperkalemia may result secondary to digitalis toxicity. High levels of digitalis inhibit the $Na^+$-$K^+$ ATPase transport pump, allowing potassium to remain outside the cell.

*Decreased renal function* is commonly associated with hyperkalemia. Oliguria (urine output <30 mL/h) secondary to acute kidney injury or end-stage renal disease typically presents with elevations of serum $K^+$ concentration. The severity of hyperkalemia is a function of the amount of $K^+$ intake, the degree of acidosis, and the rate of renal cell damage. *Hypoaldosteronism* can cause decreases in the urinary excretion of $K^+$. For example, Addison disease, characterized by adrenal cortical insufficiency, often presents with hyperkalemia secondary to decreased aldosterone secretion.

***Clinical Manifestations.*** Symptoms vary with the severity of hyperkalemia. With a mild presentation, increased neuromuscular irritability may manifest as restlessness, intestinal cramping, and diarrhea. Severe hyperkalemia decreases the resting membrane potential from −90 to −70 millivolts, resulting in muscle weakness, loss of muscle tone, and paralysis. In mild states of hyperkalemia, myocardial cell repolarization is more rapid and reflected in the ECG as narrow and taller T waves with a shortened QT interval. Severe hyperkalemia (serum levels ≥6 mEq/L) causes delayed cardiac conduction, prevented repolarization of heart muscle. There is a decrease in conduction velocity, depressed ST segment, prolonged PR interval, and widening of the QRS complex (loss of atrial activity) (see Fig. 3.9). Brady dysrhythmias and delayed conduction are common in hyperkalemia; severe hyperkalemia can cause ventricular fibrillation or cardiac arrest.

Changes in the ratio of intracellular to extracellular $K^+$ concentration contribute to the clinical presentation of hyperkalemia (see Table 3.9). If extracellular $K^+$ concentration increases without a significant change in intracellular $K^+$ concentration, the resting membrane potential becomes more positive (e.g., changes from −90 to −80 millivolts) and the cell membrane is hypopolarized (the inside of the cell becomes less negative or partially depolarized [increased excitability]) (see Fig. 3.8B). With mild elevations in extracellular $K^+$ concentration, the cell more rapidly repolarizes and becomes more irritable (peaked T waves). An action potential then is initiated more rapidly because the distance between the resting membrane potential and the threshold potential has been decreased. With more severe hyperkalemia, the resting membrane potential approaches or exceeds the threshold potential (wide QRS merging with T wave). In this case the cell is not able to repolarize and therefore does not respond to excitation stimuli. The most serious consequence is cardiac arrest.

Like the effects of hypokalemia, the neuromuscular effects of hyperkalemia are related to the rate of increase in the ECF potassium concentration and the presence of other contributing factors, such as acidosis and calcium balance. Long-term increases in ECF potassium concentration result in shifts of $K^+$ into the cell because the tendency is to maintain a normal ratio of intracellular/extracellular potassium concentrations. Acute elevations of extracellular $K^+$ concentration affect neuromuscular irritability because this ratio is disrupted.



Because calcium influences the threshold potential, changes in ECF calcium concentration can augment or override the effects of hyperkalemia. With hypocalcemia the threshold potential becomes more negative, enhancing the neuromuscular effects of hyperkalemia. Hypercalcemia causes the threshold potential to become less negative, counteracting the effects of hyperkalemia on resting membrane potential (see Fig. 3.8C).

***Evaluation and Treatment.*** Hyperkalemia is a common finding in many clinical settings (e.g., renal disease, massive trauma, insulin deficiency, Addison disease, use of potassium salt substitutes, or some types of metabolic acidosis). How rapidly symptoms evolve often is a function of the underlying cause. An ECG will identify conduction abnormalities or dysrhythmias.

Management of hyperkalemia includes both treating the contributing causes and correcting excessive potassium concentration. Normalizing the extracellular potassium concentration can be achieved with a variety of methods; the treatment chosen is related to the cause and severity of the problem. Calcium gluconate can be administered to restore membrane excitability when serum potassium levels are dangerously high. Administration of glucose, which readily stimulates insulin secretion, or administration of glucose and insulin for those with diabetes, facilitates cellular entry of potassium. Renin-angiotensin-aldosterone system inhibitor therapy and use of the newer oral potassium binders optimize therapy. Buffered solutions correct metabolic acidosis and lower serum potassium level. Dialysis effectively removes potassium in cases of renal dysfunction.[13]

## Calcium and Phosphate

The total body content of calcium is approximately 1200 g. Most calcium (99%) is located in bone as hydroxyapatite (an inorganic compound that contributes to bone rigidity), and the remainder is in the plasma and body cells. The total fraction of calcium circulating in the blood is small (9.0 to 10.5 mg/dL), and approximately 50% is bound to plasma proteins, primarily albumin. Approximately 40% is in the free or ionized form (5.5 to 5.6 mg/dL). Ionized calcium has the most important physiologic functions. Approximately 20% of ingested calcium is absorbed in the small intestine, primarily in the duodenum.

**Calcium ($Ca^{2+}$)** is a necessary ion for many fundamental metabolic and cellular processes. In bound form, it is the major cation associated with the structure of bones and teeth. The ionized form serves as an enzymatic cofactor for blood clotting and is required for hormone secretion and the function of cell receptors. Plasma membrane stability, permeability, and repair are directly related to calcium ions, as is the transmission of nerve impulses and the contraction of muscles. Calcium metabolism is linked to phosphate and magnesium metabolism.

**Phosphate ($HPO_4^-$)** is found primarily in bone (85%), with smaller amounts found within the intracellular and extracellular spaces. In the plasma, phosphate exists in phospholipids and phosphate esters and as inorganic phosphate, which is the ionized form. The normal serum levels of inorganic phosphate range from 2.5 to 4.5 mg/dL and may be as high as 6.0 to 7.0 mg/dL in infants and young children. Intracellular phosphate has many metabolic forms, including the high-energy structures creatine phosphate and adenosine triphosphate (ATP). Phosphate acts as an intracellular and extracellular anion buffer in the regulation of acid-base balance; in the form of ATP, it provides energy for muscle contraction.

Calcium and phosphate concentrations are rigidly controlled. They are related by the product of calcium and phosphate ($HPO_4^-$) concentrations, which is a constant ($K$) [$Ca2+$) × $HPO_4^-$ = $K$]. Thus, if the concentration of one ion increases or decreases, that of the other normally increases or decreases.

Calcium and phosphate balance is regulated by three hormones: parathyroid hormone (PTH), vitamin D, and calcitonin. Acting together, these substances determine the amount of dietary calcium and phosphate absorbed from the intestine, the deposition and absorption of calcium and phosphate from bone, and the renal reabsorption and excretion of calcium and phosphate by the kidney.

The parathyroid glands secrete PTH in response to low levels of serum calcium. (The specific actions of PTH in relation to calcium and phosphate are described in Chapter 21.) **Parathyroid hormone (PTH)** controls levels of ionized calcium and phosphate in the blood and other ECFs. Renal regulation of calcium and phosphate balance requires PTH. PTH stimulates reabsorption of calcium along the distal tubule of the nephron and inhibits phosphate reabsorption by the proximal tubule of the nephron. The net result is an increase in serum calcium concentration and increased urinary excretion of phosphate. Fig. 3.10 summarizes hormonal regulation of calcium.

Another compound important to calcium and phosphate regulation is vitamin D. **Vitamin D** (cholecalciferol) is a fat-soluble steroid ingested in food or synthesized in the skin in the presence of ultraviolet light. Several steps of activation are required before vitamin D can act on target tissues. The first step occurs in the liver; final activation is in the kidney. The renal activation of vitamin D begins when the serum calcium level

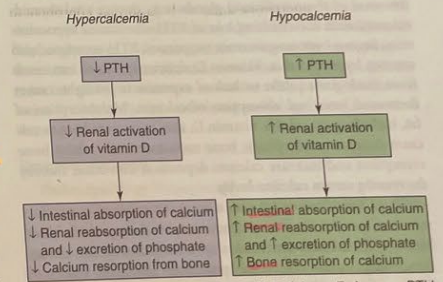


**Fig. 3.10 Hormonal Regulation of Calcium Balance.** *PTH*, Parathyroid hormone.

decreases and stimulates secretion of PTH. PTH then acts to increase calcium reabsorption and enhance renal excretion of phosphate, producing decreased phosphate levels. The combination of low calcium level and increased PTH secretion causes the renal activation of vitamin D. The activated vitamin D (vitamin $D_3$—calcitriol) then circulates as a hormone in the plasma and acts to increase absorption of calcium and phosphate in the small intestine, enhance bone calcification, increase renal tubular reabsorption of calcium, and increase excretion of phosphate. When end-stage renal disease occurs, vitamin D is not activated; serum calcium levels decrease; and phosphate levels increase.

As calcium levels increase, an opposite adaptation occurs, leading to suppression of PTH secretion, decreased renal vitamin D activation, decreased intestinal calcium absorption, and increased renal phosphate reabsorption. **Calcitonin** (produced by C cells of the thyroid gland) decreases calcium levels by inhibiting osteoclastic activity in bone and increasing renal calcium and phosphate excretion.

The fractions of serum calcium that are freely ionized or bound to plasma proteins are influenced by pH. In states of acidosis, levels of ionized calcium increase. When alkalosis develops, with an increase in pH, the amount of protein-bound calcium increases and the physiologically active, ionized calcium level decreases. The decreased concentration of ionized calcium may be great enough to cause symptoms of hypocalcemia, such as tetany.

## Hypocalcemia

***Pathophysiology.*** **Hypocalcemia** occurs when serum total calcium concentrations are less than 9.0 mg/dL and ionized levels are less than 5.5 mg/dL. In general, deficits in calcium are related to inadequate intestinal absorption, decreases in levels of PTH and vitamin D, or deposition of ionized calcium into bone or soft tissue.[14]

Nutritional deficiencies of calcium can occur in the instance of inadequate sources of dairy products or green, leafy vegetables, eating disorders, and malabsorption syndromes (celiac disease or short bowel syndrome). Excessive amounts of dietary phosphorus also bind with calcium in the gastrointestinal tract, so neither mineral is absorbed when such an excess occurs. Removal of the parathyroid glands (e.g., during total thyroidectomy) with the resulting loss of PTH also causes hypocalcemia. Severe hypomagnesemia suppresses PTH secretion, also causing hypocalcemia. Vitamin D deficiency, which can result from inadequate intake or lack of exposure to sunlight, causes decreased intestinal absorption of calcium. Malabsorption of fat, including fat-soluble vitamin D, also may contribute to calcium deficiency. Neoplastic bone metastases may inhibit bone resorption and increase calcium deposition into bone, thereby decreasing serum calcium levels.

Blood transfusions are also a common cause of hypocalcemia because the citrate solution used in storing whole blood binds with calcium and makes it unavailable to the tissues. Pancreatitis causes release of lipases into soft tissue spaces, so the free fatty acids that are formed bind calcium, causing a decrease in the concentration of ionized calcium. Metabolic or respiratory alkalosis causes symptoms of hypocalcemia because the change in pH enhances protein binding of ionized calcium. Hypoalbuminemia lowers total serum calcium levels by decreasing the amount of bound calcium in the plasma.

***Clinical Manifestations.*** Many individuals with chronic hypocalcemia are asymptomatic. The clinical manifestations are a function of severity and rapidity of onset. Severe manifestations are caused by an increase in neuromuscular excitability with partial depolarization of nerves and muscles. As the threshold potential becomes more negative and approaches the resting membrane potential (hypopolarization) (see Fig. 3.8C), a smaller stimulus is required for initiating an action potential. The symptoms include paresthesias around the mouth and in the digits, carpopedal spasm (muscle spasms in the hands and feet), hyperreflexia, seizures, laryngospasm, and anxiety.

Two clinical signs of increased neuromuscular excitability are Chvostek sign and Trousseau sign. *Chvostek sign* is elicited by tapping on the facial nerve over the zygomatic arch. A positive sign is a strong twitch of the nose or lip. *Trousseau sign* is contraction of the hand and fingers when the arterial blood flow in the arm is occluded for 3 to 5 minutes with the use of a blood pressure cuff.

The characteristic ECG change is a prolonged QT interval, indicating prolonged ventricular depolarization and decreased cardiac contractility. Intestinal cramping and hyperactive bowel sounds also may be present because hypocalcemia affects the smooth muscles of the gastrointestinal tract. Table 3.11 contains a summary of the manifestations of calcium level alterations.

***Evaluation and Treatment.*** Serum and ionized calcium, albumin, phosphate, and magnesium levels are evaluated. Further evaluation includes renal function and measurement of PTH and vitamin D. Severe symptoms of hypocalcemia require emergency treatment with IV 10% calcium gluconate, volume repletion, and ECG monitoring. The underlying cause must be identified. Oral calcium replacement should be initiated, and serum calcium levels should be monitored. Decreasing phosphate intake facilitates long-term management of hypocalcemia.

## Hypercalcemia

***Pathophysiology.*** **Hypercalcemia** with total serum calcium concentrations exceeding 10.5 mg/dL (5.2 mEq/L) can be caused by a number of diseases. The most common among these are hyperparathyroidism (which can be associated with thyrotoxicosis); many different types of cancer; sarcoidosis; and vitamin D toxicity. Many malignant tumors produce PTH or PTH-related protein, which causes bone resorption, thus elevating the serum calcium levels. Mild hypomagnesemia also stimulates PTH secretion and increases serum calcium. Sarcoidosis appears to increase vitamin D levels. Prolonged immobilization can also lead to hypercalcemia from enhanced bone resorption and decreased calcium deposition into bone. Acidosis decreases serum binding of calcium to albumin, increasing ionized calcium levels.

***Clinical Manifestations.*** Many symptoms of hypercalcemia are nonspecific and related to severity and rapidity of onset.



**TABLE 3.11 Alterations in Calcium, Phosphate, and Magnesium Levels**

| Causes | Manifestations |
|---|---|
| **Hypocalcemia (<8.5 mg/dL)**<br>Inadequate intestinal absorption, deposition of ionized calcium into bone or soft tissue, blood administration, or decreases in PTH and vitamin D levels; nutritional deficiencies occur with inadequate sources of dairy products or green, leafy vegetables; alkalosis, elevated calcitonin level | Increased neuromuscular excitability; tingling, muscle spasms (particularly in hands, feet, and facial muscles), intestinal cramping, hyperactive bowel sounds; osteoporosis and fractures; severe cases show seizures and tetany; prolonged QT interval, cardiac arrest |
| **Hypercalcemia (>10.5 mg/dL)**<br>Hyperparathyroidism; secretion of PTH and PTH-related protein from cancer cells; sarcoidosis; excess vitamin D; overuse of calcium-containing antacids | Many nonspecific; fatigue, weakness, lethargy, anorexia, nausea, constipation; impaired renal function, kidney stones; dysrhythmias, bradycardia, cardiac arrest; bone pain, osteoporosis, fractures |
| **Hypophosphatemia (<2.0 mg/dL)**<br>Intestinal malabsorption related to vitamin D deficiency, overuse of magnesium- and aluminum-containing antacids, long-term alcohol abuse, and malabsorption syndromes; respiratory alkalosis; increased renal excretion of phosphate associated with hyperparathyroidism | Conditions related to reduced capacity for oxygen transport by red blood cells and disturbed energy metabolism; leukocyte and platelet dysfunction; deranged nerve and muscle function; in severe cases, irritability, confusion, numbness, coma, seizures; possibly respiratory failure (because of muscle weakness), cardiomyopathies, bone resorption (leading to rickets or osteomalacia) |
| **Hyperphosphatemia (>4.7 mg/dL)**<br>Acute or chronic oliguric renal disease with significant loss of glomerular filtration; treatment of metastatic tumors with chemotherapy that releases large amounts of phosphate into serum; long-term use of laxatives or enemas containing phosphates; hypoparathyroidism | Symptoms primarily related to low serum calcium levels (caused by high phosphate levels) similar to symptoms of hypocalcemia; when prolonged, calcification of soft tissues in lungs, kidneys, joints |
| **Hypomagnesemia (<1.5 mEq/L)**<br>Malnutrition, malabsorption syndromes, alcoholism, urinary losses (renal tubular dysfunction, loop diuretics) | Behavioral changes, irritability, increased reflexes, muscle cramps, ataxia, nystagmus, tetany, seizures, tachycardia, hypotension |
| **Hypermagnesemia (>3.0 mEq/L)**<br>Usually oliguric renal disease; also excessive intake of magnesium-containing antacids, adrenal insufficiency | Lethargy, drowsiness; loss of deep tendon reflexes; nausea and vomiting; muscle weakness; hypotension; bradycardia; respiratory depression or arrest; heart block, cardiac arrest |

*PTH,* Parathyroid hormone.

Because serum calcium levels are increased, a greater amount of calcium is also contained inside the cells. The threshold potential becomes more positive (hyperpolarized) (e.g., moves from −60 to −50 millivolts) and the cell membrane becomes refractory to depolarization (decreased excitability) and results in a greater difference between threshold potential and resting membrane potential (see Fig. 3.8C). Thus, many of the symptoms are related to loss of cell membrane excitability. Fatigue, weakness, lethargy, anorexia, nausea, and constipation are common.

Mental status changes and confusion may occur. Impaired renal function frequently develops with polyuria or formation of kidney stones from precipitates of calcium salts. A shortened QT segment and depressed widened T waves also may be observed on the ECG, with bradycardia and varying degrees of heart block. Table 3.11 contains a summary of the manifestations of alterations in calcium levels.

***Evaluation and Treatment.*** With elevated serum calcium levels, often a reciprocal decrease in serum phosphate values occurs. Specific diagnostic procedures to identify the contributing pathologic condition are required.

Treatment is related to the severity of symptoms and the underlying disease. When renal function is normal, oral phosphate administration is effective. When acute illness and high calcium levels are present, treatment options include IV administration of large amounts of normal saline to enhance renal excretion of calcium, administration of bisphosphonates in the absence of renal dysfunction, and administration of calcitonin. Bisphosphonates and denosumab are used for malignancy-associated hypercalcemia, and cinacalcet is approved for the reduction of **hypercalcemia** associated with parathyroid carcinoma.[15] Ultimately, the underlying pathologic condition must be treated.

## Hypophosphatemia

***Pathophysiology.*** **Hypophosphatemia** is a serum phosphate level less than 2.0 mg/dL and is usually an indication of phosphate deficiency. In some conditions, total body phosphate concentration is normal, but serum concentrations are low. The most common causes are intestinal malabsorption and increased renal excretion of phosphate. Inadequate absorption is associated with vitamin D deficiency, use of magnesium- and

# Excitation-Contraction Coupling

E-C coupling refers to the entire process by which an **electrical signal** (excitation) is translated into a **mechanical contraction** of the muscle.

**1.Excitation**: An action potential travels along the muscle cell membrane (sarcolemma) and into the **T-tubules**.

**3.Calcium Release**:

- Cardiac muscle: CICR occurs—calcium entry via DHPR triggers calcium release from the sarcoplasmic reticulum (SR) through **ryanodine receptors (RyR2)**.
- Skeletal muscle: Calcium release is **directly triggered by mechanical coupling** between DHPR and **RyR1** on the SR membrane, **independent of extracellular calcium influx**.

**2.Trigger Signal**:

- In cardiac and skeletal muscle, this signal opens **L-type calcium channels** in the T-tubule membrane.

**4.Contraction**: The released calcium binds to **troponin C**, initiating the interaction of actin and myosin, leading to muscle contraction.

# Calcium-Induced Calcium Release

CICR is a specific mechanism where **calcium influx** through **L-type calcium channels** acts as a trigger to release more calcium from the sarcoplasmic reticulum via **ryanodine receptors**.

- **Occurs in**:
  - **Cardiac muscle**: CICR is the main mechanism by which calcium is released from the SR. The calcium entering the cell during the action potential (via L-type channels) amplifies calcium release from the SR.
  - **Smooth muscle**: CICR also plays a role in smooth muscle contraction, depending on the specific tissue.

- **Does not occur in skeletal muscle**: In skeletal muscle, calcium release from the SR is **mechanically coupled** to L type Ca channels, without requiring calcium entry from the extracellular space.