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СОВРЕМЕННЫЕ ПОДХОДЫ К ВЕДЕНИЮ БОЛЬНЫХ С ГИПЕРКАЛИЕМИЕЙ

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Modern Approaches to the Management of Patients with Hyperkaliemia

Резюме

Гиперкалиемия — наиболее часто встречающееся нарушение электролитного баланса в клинической практике. Гиперкалиемия может быть обусловлена повышенным поступлением калия в организм, выходом его из клеток и нарушением экскреции почками. Данное состояние ассоциировано с высоким риском смерти от аритмий, поэтому даже незначительное отклонение уровня калия в сыворотке крови от нормы нуждается в немедленной коррекции. Современные подходы к лечению гиперкалиемии включают устранение провоцирующих факторов и применение калийснижающих препаратов. Хотя ингибиторы ренин-ангиотензин-альдостероновой системы являются в настоящее время самыми лучшими препаратами с кардионефропротективным эффектом, их назначение также может приводить к гиперкалиемии, особенно при сердечной недостаточности, хронической болезни почек и сахарном диабете. В статье подробно рассмотрены вопросы физиологии калиевого обмена, возможные провоцирующие факторы гиперкалиемии, современные подходы к профилактике и лечению этого состояния.

Ключевые слова: *гиперкалиемия, калий, ЭКГ, острое почечное повреждение, хроническая болезнь почек, блокаторы ренин-ангиотензин-альдостероновой системы*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Hyperkalemia is the most common electrolyte imbalance in clinical practice. Hyperkalemia can be caused by an increased intake of potassium into the body, the shift of potassium out of cells or an abnormal renal potassium excretion. This condition is associated with a high risk of death from arrhythmias; therefore, even a slight deviation of the serum potassium level from the norm requires immediate correction. Modern approaches to the treatment of hyperkalemia include the elimination of predictors and the potassium-lowering drugs. Although inhibitors of the renin-angiotensin-aldosterone system are currently the best cardionephroprotective drugs, their administration can lead to hyperkalemia too, especially in heart failure, chronic kidney disease and diabetes mellitus. The article discusses in detail the physiology of potassium metabolism, possible predictors, prevention and treatment of hyperkalemia.

Key words: *hyperkalemia, potassium, ECG, acute kidney injury, chronic kidney disease, renin–angiotensin–aldosterone system inhibitors*

Conflict of interests

The authors declare no conflict of interests

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ACE—angiotensin-converting enzyme, ARA—angiotensin receptor antagonist, ARI—acute renal injury, ARNI—angiotensin receptor antagonist and neprilysin inhibitor, ATP—adenosine triphosphate, AV—atrioventricular, CBV—circulating blood volume, CKD—chronic kidney disease, CPS—calcium polystyrene sulfonate, CVD—cardiovascular disease, DM—diabetes mellitus, ECG—electrocardiogram, ESC—European Society of Cardiology, GFR—glomerular filtration rate, GIT—gastrointestinal tract, HF—heart failure, K^+—potassium, MCRA—mineralocorticoid receptor antagonist, NSAIDs—non-steroidal anti-inflammatory drugs, RAAS—renin-angiotensin-aldosterone system, SPS—sodium polystyrene sulfonate.

Introduction

Hyperkalemia is common in clinical practice, especially in patients with heart failure (HF), diabetes mellitus (DM), and chronic kidney disease (CKD). It significantly increases the risk of sudden death due to the development of fatal arrhythmias. It significantly worsens the quality of life and prognosis and is an indication for starting renal replacement therapy in patients with end-stage renal disease [1]. This article provides a detailed description of the physiology of potassium metabolism, causes of hyperkalemia, and methods of its prevention and correction.

Definition

Normal concentration of extracellular potassium (K^+) is in the range 3.5–5.0 mmol/L (for potassium, 1 mmol/L = 1 mEq/L). Hyperkalemia is defined as serum or plasma potassium > 5.0 mmol/L [2]. Laboratory potassium values may vary slightly depending on the population and accuracy of the potassium determination method.

Potassium is usually measured in clotted blood serum. However, it is now mostly measured in plasma of heparinized blood. Serum levels can be 0.5 mEq/l higher than plasma levels. Unfortunately, in many studies, it is unclear whether potassium was measured in serum or plasma [2].

Classification

Hyperkalemia can be divided into the following groups by severity:

- mild (> 5.0 < 5.5 mmol/L),
- moderate (5.5–6.0 mmol/L),
- severe (> 6.0–6.9 mmol/L), and
- extremely severe (> 7.0 mmol/L) [2, 3].

In recent decades, the clinical approach to assessing hyperkalemia and its classification into two groups of severity has become the leading approach:

- life-threatening hyperkalemia (> 6.5 mmol/L and/or the presence of ECG signs typical for hyperkalemia) and
- non-life-threatening hyperkalemia (< 6.5 mmol/L and the absence of ECG signs typical for hyperkalemia).

Fatal arrhythmias and sudden death in patients with hyperkalemia can develop at different potassium levels. Hyperkalemia < 6 mmol/L can often be asymptomatic, especially in patients with DM, CKD, and HF [2].

Hyperkalemia can be classified as acute or chronic (or recurrent) depending on the onset and number of past episodes of hyperkalemia. Chronic hyperkalemia means a high potassium level > 5.0 mmol/L detected periodically throughout the year [2].

Pseudohyperkalemia means a high potassium level in a test tube without a high potassium level in the blood [2]. It is caused by the mechanical release of potassium from cells during phlebotomy or sample processing [4]. Hemolysis is more common when blood is taken with a syringe than with a vacuum device. Fist clenching, using a tight tourniquet or a small-bore needle for phlebotomy can also cause pseudohyperkalemia [4]. Reverse pseudohyperkalemia is a phenomenon when plasma potassium level is falsely elevated, but its serum level is within normal. This is described in cases of hematological diseases with severe leukocytosis when malignant cells are prone to lysis with minimal mechanical stress due to increased fragility or changes in the activity of sodium-potassium ATPase [4].

Epidemiology

The exact incidence of hyperkalemia is unknown [5]. According to different authors, hyperkalemia develops in 2–4% of the population, 10–55% of hospitalized patients, 7.7–73% of patients with CKD, and 40% of patients with chronic HF [2, 5]. Men are more prone to hyperkalemia than women. Infants and the elderly are at high risk of hyperkalemia. In-hospital mortality among patients with hyperkalemia is approximately 14%, with K^+ level ≥ 7 mmol/L—28%, and with K^+ level ≤ 6.5 mmol/L—9%.

Physiology of Potassium Metabolism

Potassium is the most common cation in the human body (50–75 mEq/kg of body weight) [2]. Under physiological conditions, 98% of potassium is inside cells, and 2%—in extracellular space [4]. Intracellular potassium concentration is **higher** than extracellular concentration. A high transmembrane potassium concentration gradient is important for the function of excitable tissues. Therefore, abnormal potassium concentration leads to life-threatening disorders of the heart and nervous system [4]. The most important factors involved in potassium distribution between the intra- and extracellular space are insulin and catecholamines [4]. Insulin release after meals not only regulates blood glucose concentration, but also promotes the transportation of potassium into cells. During physical exertion, potassium is released from skeletal muscles and accumulates in intercellular space, leading to vasodilation. A simultaneous increase in the concentration of circulating catecholamines contributes to the uptake of potassium by cells via beta-adrenergic receptors. Kidneys excrete 90–95% of excessive potassium, and the gastrointestinal tract excretes a small amount [4].

Etiology

Hyperkalemia often develops in cases of CKD and urinary tract pathology, acute renal injury (ARI), cardiovascular diseases (CVD), DM, and oncological diseases (Fig. 1).

There are three main causes of hyperkalemia (Table 1):

1) hyperkalemia associated with increased intake (consumption/administration) of potassium into the body;
2) hyperkalemia associated with increased release of potassium from cells; and
3) hyperkalemia due to the impaired excretion of potassium by the kidneys.

The release of potassium from cells results in a temporary increase in the potassium level, and decreased renal excretion—to persistent hyperkalemia.

Increased dietary potassium intake rarely leads to hyperkalemia in adults with normal renal function. However, it may result in hyperkalemia in patients with renal or adrenal disease. Dried fruits, seaweed, nuts, molasses, avocado, etc., contain large amounts of potassium. The following foods are also rich in potassium: spinach, jacket potatoes, tomatoes, broccoli, beets, carrots, kiwi, mangoes, oranges, bananas, melons, and red meat. These foods should be excluded from the diet of patients with severe renal impairment. Salt substitutes (sodium chloride replaced with potassium chloride) and dietary supplements can also be a source of potassium [2]. Drug products with high potassium level (especially when administered intravenously), herbs, parenteral nutrition, and massive blood transfusion can significantly increase serum potassium levels.

When cells are destroyed, potassium can move from cells into extracellular space. The release of 2% intracellular potassium can double the potassium concentration in blood serum. This happens in cases of hemolysis, trauma, and rhabdomyolysis. Tumor lysis syndrome can also cause acute hyperkalemia due to the mass death of cancer cells [4].

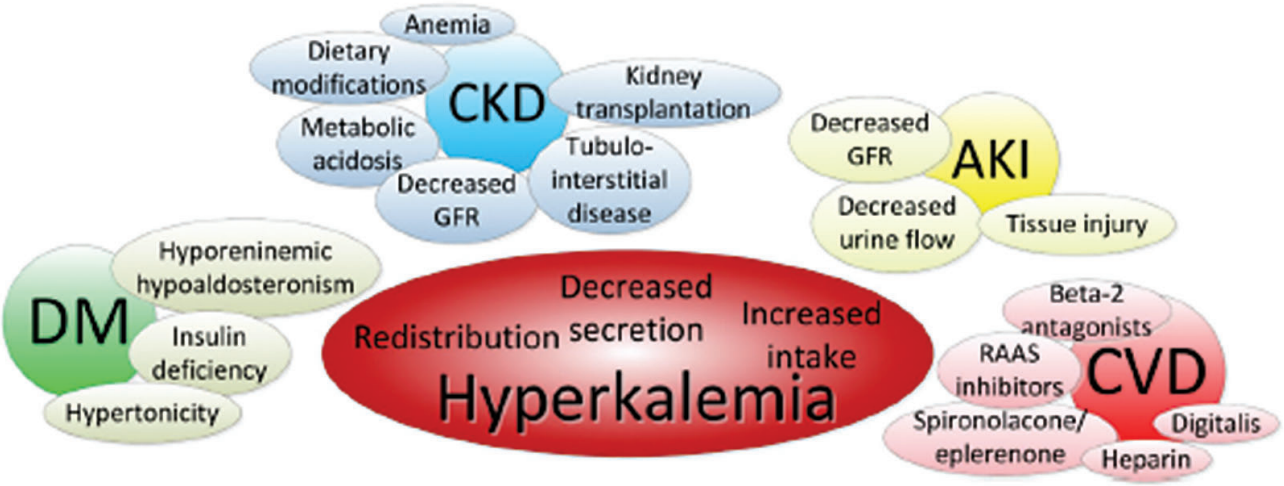

Figure 1. *Factors of the development of hyperkalemia in patients with different conditions[5].*
Note: AKI — acute kidney injury, RAAS — renin-angiotensin-aldosterone system, CVD — cardiovascular disease, DM — diabetes mellitus, CKD — chronic kidney disease, GFR — glomerular filtration rate

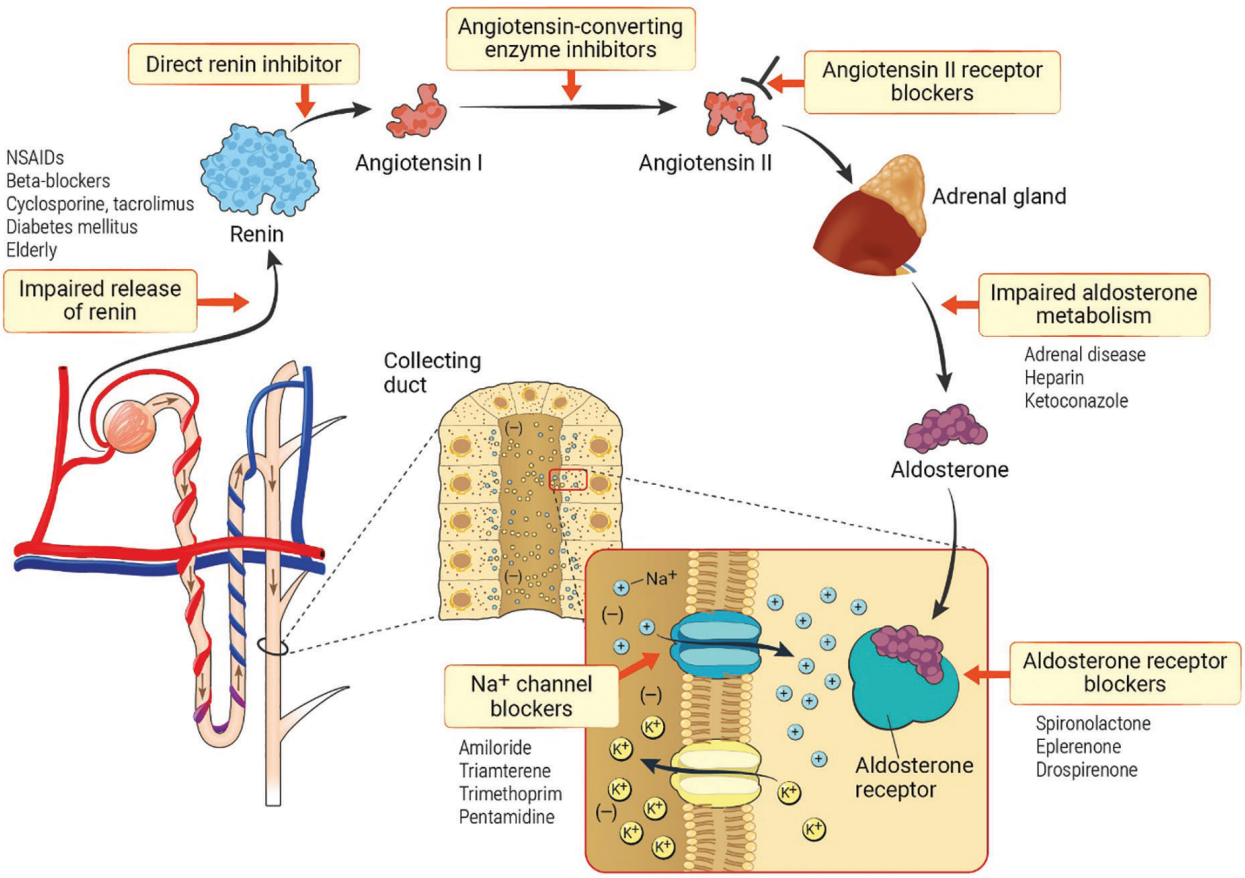

Figure 2. *A number of pharmocologic agents and conditions can interfere with the renin-angiotensin-aldosterone system, altering renal potassium excretion.*
Note: Reabsorbtion of sodium in the collecting duct increases the luminal electronegativity, providing a more favorable gradient for potassium secretion. In some patients, more than one distrurbance may be presents. NSAIDs=nonsteroidal anti- inflammatory drugs.
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Table 1. *Possible causes of hyperkalemia [2, 4]*

Category	Examples of
Increased intake of K into the body	
Oral	Food products (dried fruits, seaweed, nuts, molasses, avocados, spinach, jacket potatoes, tomatoes, broccoli, beets, carrots, kiwi, mangoes, oranges, bananas, melons, red meat)
	Salt substitutes (KCl instead NaCl)
	Oral potassium supplements
	Amino acids (aminocaproic acid, arginine, lysine)
	Medicinal plants (alfalfa, dandelion, hawthorn berry, horsetail, lily of the valley, spurge, nettle, Siberian ginseng, noni juice)
	Potassium preparations
Parenteral	Blood transfusion
	Introduction of solutions with additives K
	K-containing drugs (for example, penicillin G)
	Full parenteral nutrition
Enhanced potassium exit from cells (potassium redistribution)	
Medicines	Succinilcholine
	Beta blockers
	Digoxin
Enhanced tissue catabolism	Tumor lysis syndrome
	Hemolysis
	Hemorrhage in soft tissue or bleeding from the gastrointestinal tract
	Burns
	Injury
	Rhabdomyolysis
Insulin deficiency	Diabetes mellitus
	Hunger
Genetic disease	Hyperkalemic family periodic paralysis
Other	Exercise
	Metabolic acidosis
Reducing potassium excretion	
Medicines	Angiotensin converting enzyme inhibitors
	Receptor blockers for angiotensin II
	Direct renin inhibitors (aliskiren)
	Sakubitril/Salsartan
	Cyclosporine or tacrolimus
	Heparin
	Glycosides
	K-saving diuretics (spironolacton, eplerenone, triamterene, amyloid)
	Nonsteroidal anti- inflammatory drugs
	Calcinevrine inhibitors
	Beta blockers
	Trimethoprim
	Pentamidine
	Mannitol
	Penicillin G
Hypoaldo-steronism	Adrenal insufficiency
Kidney pathology	Acute kidney damage
	Chronic kidney disease
	Renal tubal acidosis, type IV

Metabolic acidosis, which is often due to impaired blood supply to tissues (including sepsis or dehydration), can also facilitate potassium release from cells. The severity of hyperkalemia depends on the type of acidosis. Hyperchloremic acidosis (mineral acidosis) most often contributes to hyperkalemia due to the relative impermeability of the cell membrane to the chloride anion. Hydrogen ions move into cells due to the accumulation of hydrogen chloride or ammonium chloride; electroneutrality is maintained by potassium release from cells with the development of hyperkalemia [4]. Organic acidosis (associated with lactic, beta-hydroxybutyric, methylmalonic acid) does not usually lead to the release of potassium since most organic anions easily move into cells along with hydrogen ions. In lactic acidosis, potassium release from cells is often caused by the violation of membrane integrity due to ischemia. In diabetic ketoacidosis, hyperkalemia is often associated with insulin deficiency [4]. Hyperglycemia contributes to the movement of fluid from intracellular to extracellular space, which increases the concentration of potassium in cells and creates favorable conditions for its release through membrane channels. A similar picture can be observed in neurosurgical patients receiving large amounts of hypertensive mannitol. Repeated doses of immunoglobulin can result in extracellular accumulation of sorbitol, maltose or sucrose, which are added to the agent to prevent aggregation of immunoglobulins, with the development of hyperkalemia [4].

Certain agents, such as succinylcholine, can cause severe acute elevations of the potassium level, especially in cases of subacute neuromuscular diseases.

Hyperkalemic periodic paralysis is a rare autosomal dominant condition when potassium is transferred into extracellular space due to mutations in the SCN4 gene that encodes the alpha-subunit protein of the sodium channel, its dysfunction, prolongation of action potential, and abnormal muscle fiber membrane repolarization.

Decreased potassium excretion may be due to:

1) decreased sodium delivery;
2) lack of mineralocorticoids (hypoaldosteronism); and
3) dysfunction of collecting ducts.

Some cases include all three of these reasons.

Normally, potassium is freely filtered by glomeruli, then reabsorbed, mainly in proximal tubules and in the thick ascending limb of Henle's loop. Potassium secretion starts in the distal convoluted tubule and increases in the collecting ducts. Secretion is regulated according to physiological needs. Decreased GFR and decreased mass of active nephrons lead to a reduced number of collecting ducts and decreased potassium secretion. However, the increased capacity of the remaining nephrons to secrete potassium can work against it. Hyperkalemia often develops in cases of oliguria due to decreased distal sodium and water delivery. Also, the underlying pathology can contribute to increased catabolism and hyperkalemia in such patients [4]. Decreased renal function leads to the increased excretion of potassium by the colon. In patients with end-stage renal failure, potassium excretion with feces is three times higher than in patients with normal renal function [2]. This allows maintaining potassium concentration in plasma within the normal range until GFR drops below 10–15 mL/min/1.73 m^2 [4].

Decreased concentration or action of mineralocorticoids reduces renal potassium secretion and leads to hyperkalemia. Aldosterone deficiency can be isolated or accompanied by decreased cortisol levels. This is observed in cases of adrenal insufficiency. Heparin also leads to a reversible disorder of adrenal aldosterone synthesis. Blockers of renin-angiotensin-aldosterone system (RAAS: direct renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, sartans, mineralocorticoid receptor antagonists, angiotensin receptor antagonists and neprilysin inhibitors (ARNI), Figure 2, Table 2) reduce aldosterone levels and can lead to hyperkalemia.

Table 2. *Potential risk factors for hyperkalemia in patients taking renin-angiotensin-aldosterone system inhibitors [3]*

Risk factors	Mechanism
Age	Disruption of renin release followed by hypoaldosteronism (hyporenemic hypoaldosteronism)
Diabetes	Diabetic nephropathy Hyporenemic hypoaldosteronism Impaired ability of cortical collective tubes to secrete potassium Insulin deficiency
Kidney pathology	Impaired ability of cortical collective tubes to secrete potassium Hyporenemic hypoaldosteronism

The syndrome of hyporeninemic hypoaldosteronism is the most common cause of hyperkalemia in patients with GFR of 40–60 mL/min/1.73 m^2 [4].

Hyperkalemia can develop at underlying interstitial kidney diseases when the distal nephron is affected. In this case, GFR decreases slightly and the level of circulating aldosterone is within normal range. After kidney transplantation, with systemic lupus erythematosus, amyloidosis, urinary tract obstruction, or sickle cell anemia, impaired renin release may be combined with impaired tubular secretion [4].

Potassium-sparing diuretics impair the ability of collecting ducts to secrete potassium. In particular, amiloride and triamterene block sodium channels and inhibit sodium reabsorption. This reduces the negative charge in the lumen of tubules and potassium secretion [4]. Trimethoprim and pentamidine have similar effects [4].

Spironolactone and eplerenone compete with aldosterone at the mineralocorticoid receptor level and may cause hyperkalemia. Drospirenone, a non-testosterone progestin derivative found in several oral contraceptives, blocks the effects of mineralocorticoids similar to spironolactone [4].

Non-steroidal anti-inflammatory drugs can cause hyperkalemia by suppressing renin release and reducing sodium delivery to the distal nephron [4].

Calcineurin inhibitors reduce potassium secretion by suppressing renin release and directly affecting renal tubules [4].

Beta-1 and, to a lesser extent, beta-2 adrenergic blockers can also lead to a hyporeninemic state and hyperkalemia [4].

Special attention should be paid to plasma potassium level monitoring when these agents are administered, especially in polypharmacy [4].

Clinical Picture

Hyperkalemia has no specific symptoms; symptoms of the underlying disease may dominate in the clinical presentation. Patients may be asymptomatic or complain of weakness, fatigue, less often—paresthesia, fasciculations of the arms and legs, muscle cramps, rarely—ascending flaccid paralysis with quadriplegia. The most life-threatening symptoms of hyperkalemia are the signs of cardiac arrhythmias and conduction disorders—palpitations, irregular heart function, dizziness, and syncope. The severity of symptoms is determined not only by the concentration, but also by the rate of potassium level buildup in plasma. First clinical manifestations can appear only in fatal increase in potassium level [4]. In rare cases, hyperkalemia is accompanied by arterial hypotension, shortness of breath, mental changes, and confusion.

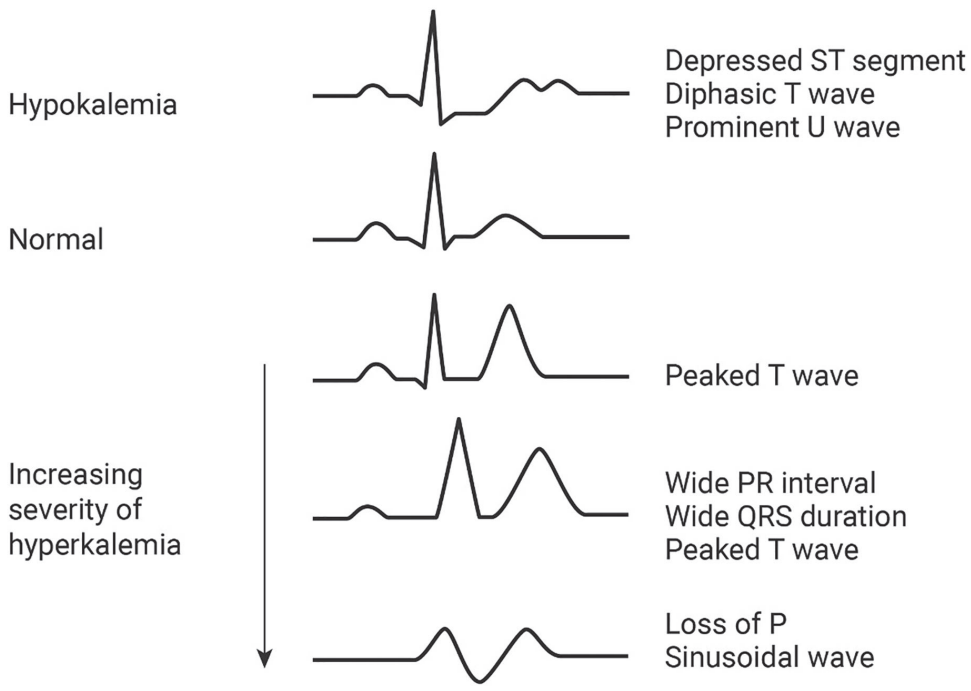

Figure 3. *Electrocardiographic signs of hyperkalemia.*
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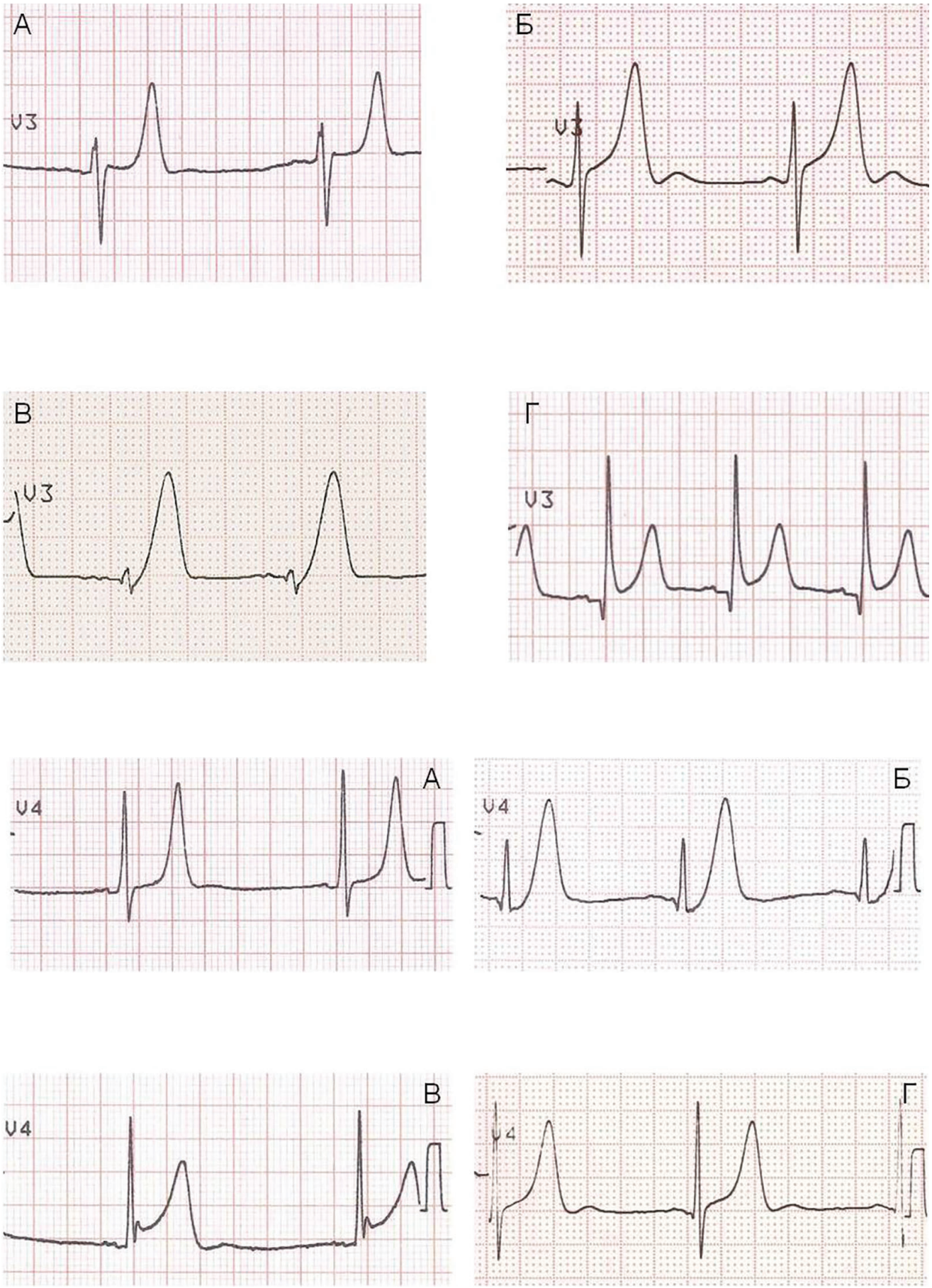

Figure 4. *T wave types in hyperkaliemia*

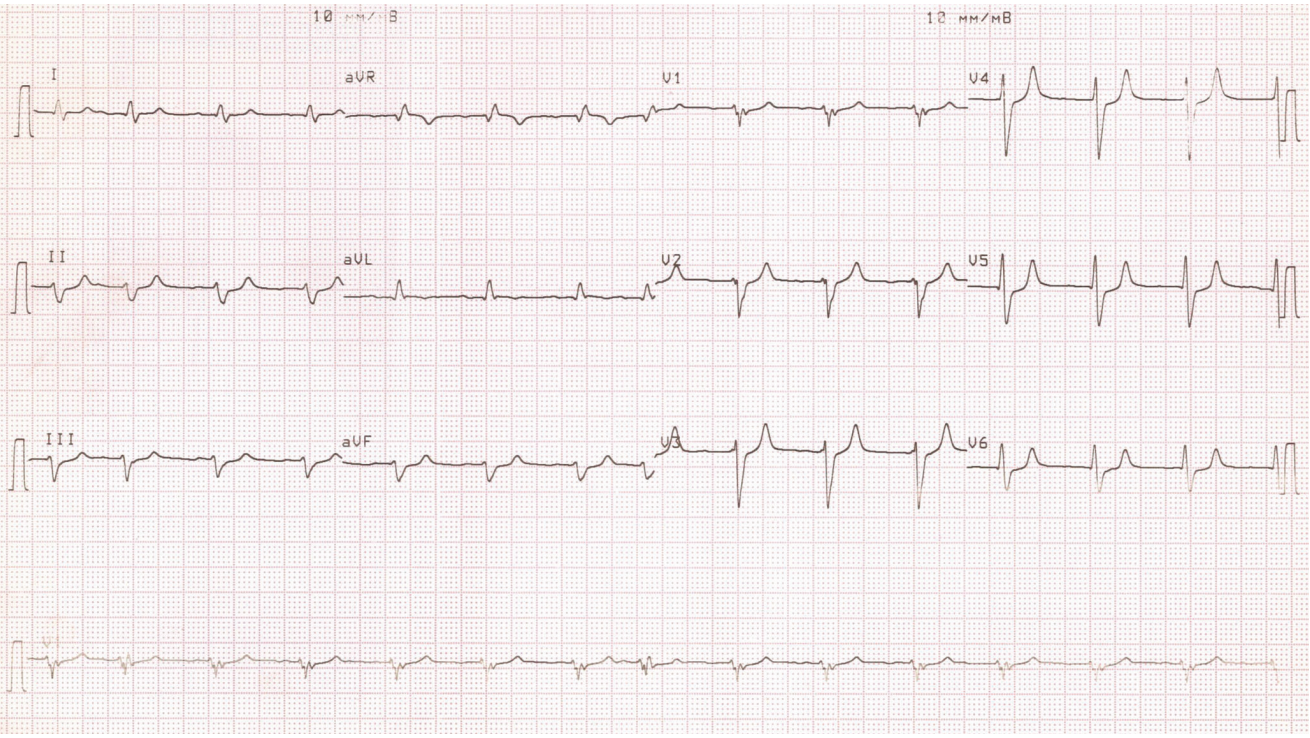

Figure 5. *ECG of 78-year old patient with acute renal injury and hyperkalemia 6,8 mmol/L. AV-block I, loss of P wave, QT 320 ms, QTc 363ms (Framingham), peaked T wave*

Diagnosis

The diagnosis of hyperkalemia requires the ongoing monitoring of blood potassium level, assessment of the renal excretion of potassium, and ECG.

Renal potassium excretion is best assessed by measuring the amount of potassium in daily urine or determining the potassium/creatinine ratio in urine. Daily potassium excretion of less than 15 mmol/L or potassium–creatinine ratio of less than 1 indicates an extrarenal cause of hypokalemia. A ratio of more than 20 corresponds to renal hyperkalemia [4].

Early ECG signs of hyperkalemia are often found in asymptomatic patients. Therefore, knowledge of the electrocardiographic manifestations of hyperkalemia becomes critical.

The severity of ECG changes depends on the potassium concentration in blood (Fig. 3). However, there is no linear dependence of electrocardiographic abnormalities on the potassium level. The ratio of cation content in the cell to extracellular fluid, the rate of transmembrane transportation of ions, not only potassium, changes in transmembrane potential due to ischemia, impaired acid-base balance, fluctuations in sympathetic tone and concentration of insulin, various medications, etc., largely determine the ECG presentation. This is also confirmed by our experience.

In case of hyperkalemia, P waves are flattened and widened, atrioventricular conduction slows down, the ventricular complex expands, and high peaked narrow T waves appear ("pinched T," Fig. 4 and 5). Such T waves are the most specific ECG changes in case of hyperkalemia and sometimes become its earliest manifestations. This form of T waves is associated with the reduction of the cardiomyocyte action potential, mainly of its second phase. This initially shortens the duration of the electrical ventricular systole, QT interval, as well as the effective refractory period, which contributes to arrhythmogenesis. With the progression of hyperkalemia, the ECG shape may resemble a sinusoid, which is a precursor of ventricular fibrillation and asystole (Fig. 6, 7, and 8).

Retrospective analysis revealed typical ECG changes only in 16 out of 90 cases of hyperkalemia. Thirteen patients demonstrated no changes in T wave. Only 1 of 14 patients with arrhythmia or asystole had ECG changes typical for hyperkalemia [4]. In cases of hyperkalemia, atrioventricular (AV) block of different degrees, paroxysmal ventricular tachycardia, ventricular fibrillation, bradycardia, and asystole can develop.

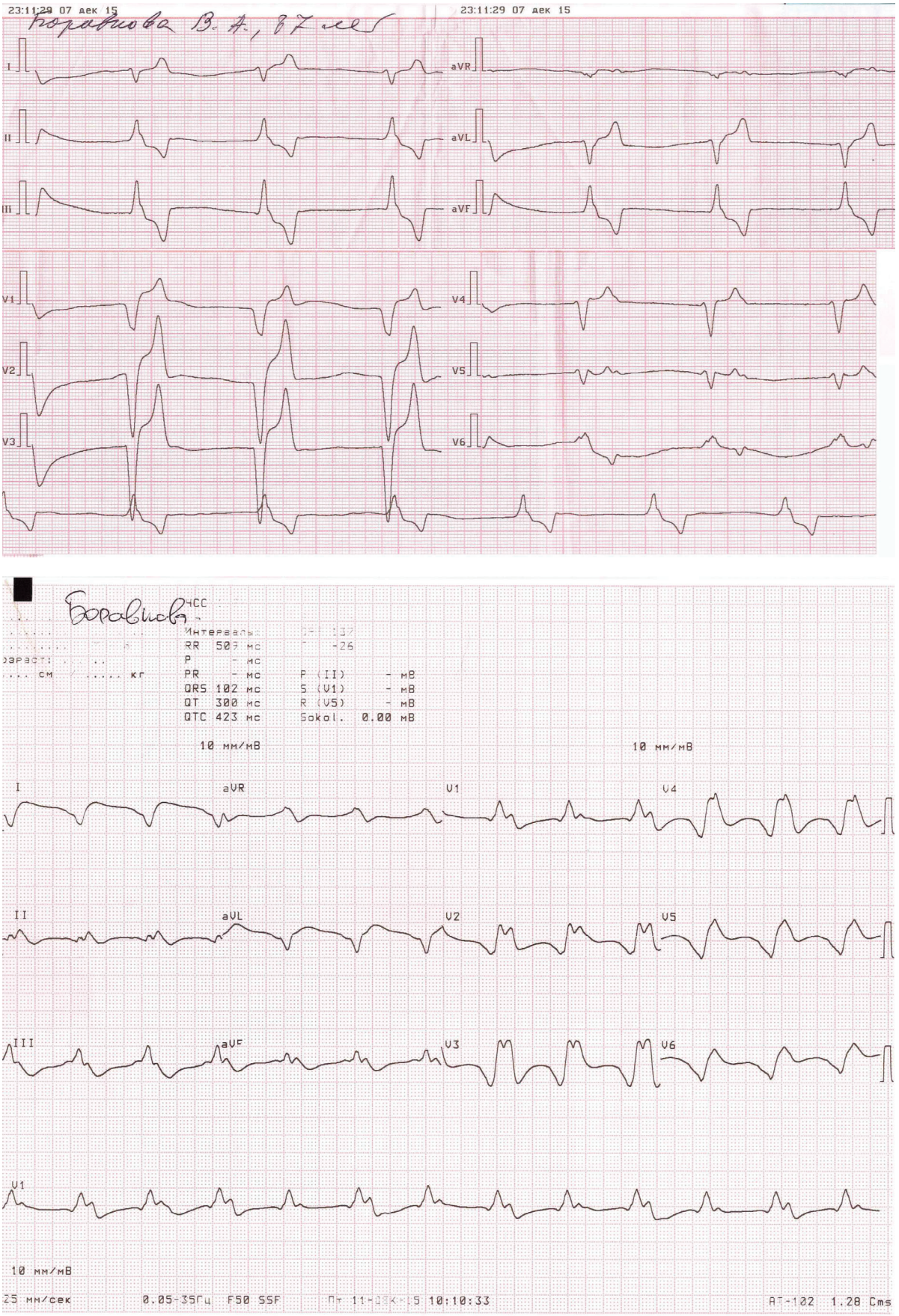

Figure 6. *ECG of 87-year old woman.*

A. *Wide QRS duration, junctional rhythm with abberant conduction and retrograde atrial excitation, hyperkalemia 8,6 mmol/L.*

Б. *Sinusoidal curve before death, potassium not determined.*

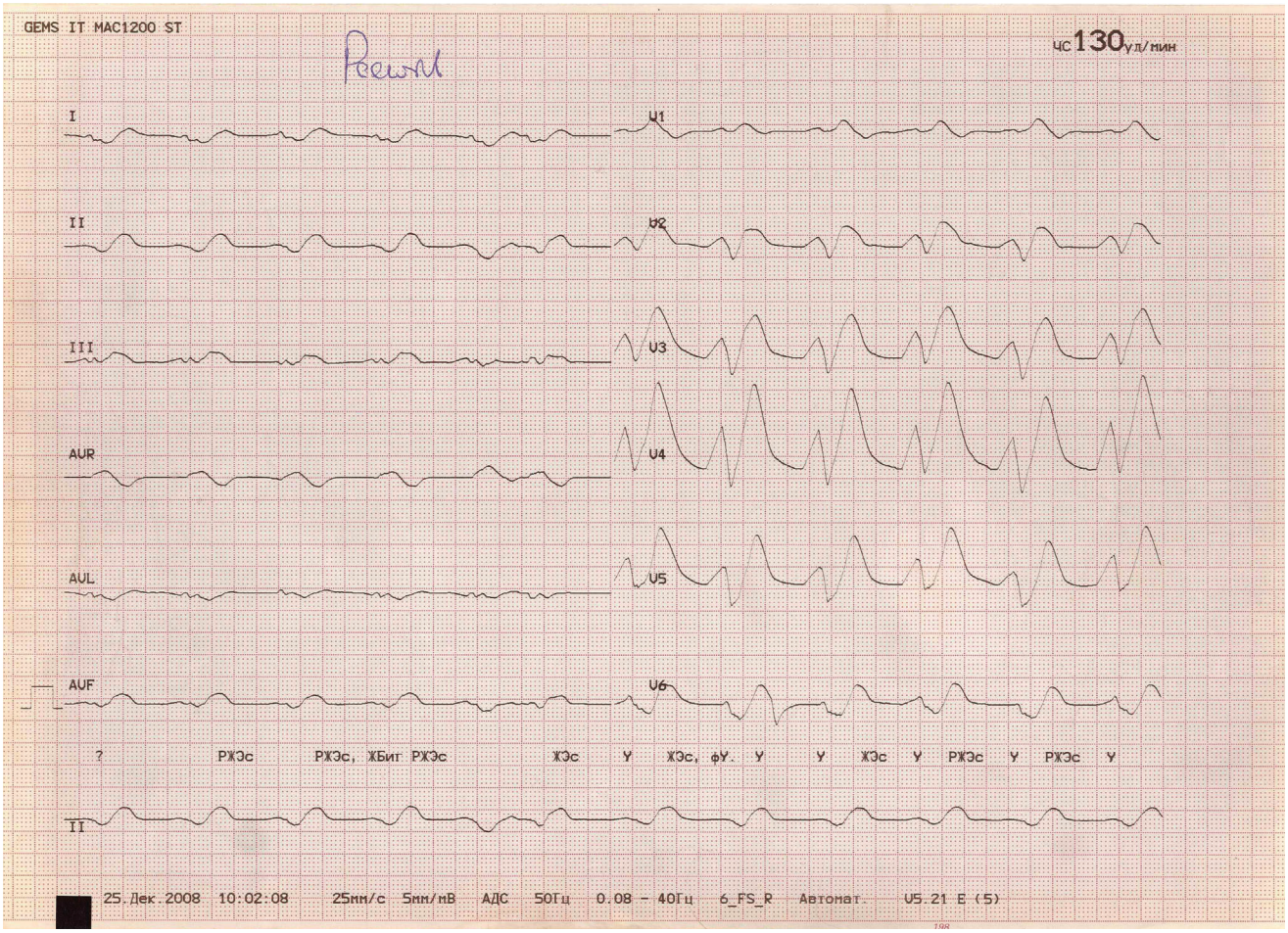

Figure 7. *ECG of a patient who died from terminal CHF (decompensation of aortic stenosis), potassium — 7.0. Sinusoidal curve*

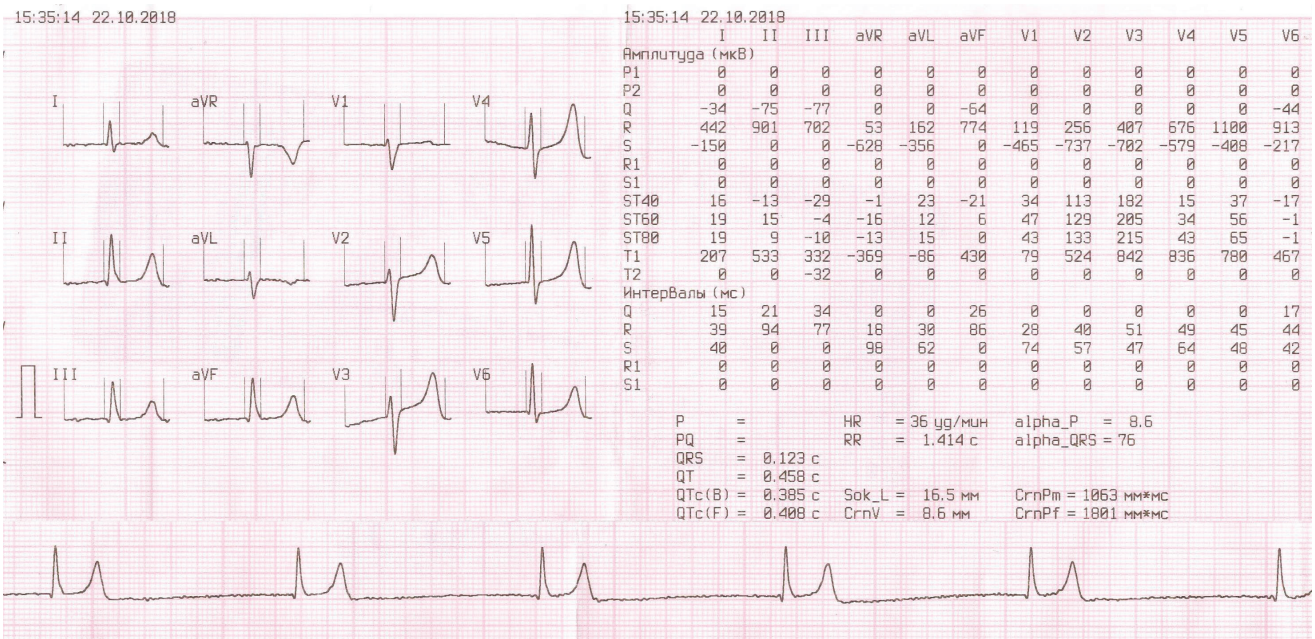

Figure 8. *ECG of a patient with hyperkalemia 7.7 mmol/L. Nodular bradycardia, tall, peacked T waves*

Table 3. *Treatment of acute and chronic hyperkalemia [2]*

Mechanism	Therapeutic approach
Promoting the transition of potassium into intracellular pro-day	Stimulation of Na/K-ATFase: Beta2 agonists (intravenously, via nebulizer) Insulin (intra-glucose) Sodium bicarbonate (in metabolic acidosis)
Heart membrane stabilizers	Calcium chloride or gluconate (intravenous) Hypertensive saline solution (3-5%)
Increased potassium withdrawal	Loop diuretics (intravenous, oral) to increase renal potassium excretion Hemodialysis Cationexchange resins (sodium polystyrolosulfonate — oral, rectal) Sodium bicarbonate alkalizes urine and increases potassium excretion with urine Patiromer Ciklosilicate sodium zirconium
Other	Fludrocortisone (oral) in aldosterone deficiency

Management of Acute Hyperkalemia

The management of hyperkalemia (Table 3) depends on the degree to which plasma potassium concentration increases, the presence or absence of ECG changes, or neuromuscular symptoms. Emergency treatment is indicated for severe ECG changes or severe muscle weakness [4].

For emergency correction of hyperkalemia, calcium chloride (3–5 mL 10% for 2 minutes) or calcium gluconate (10 mL 10% for 2 minutes) should be administered. The effect of calcium gluconate starts 1–2 minutes after administration and lasts for 30–60 minutes; if changes in ECG persist 5 minutes after administering calcium gluconate, the agent is re-administered at the same dose. Intravenous calcium quickly normalizes membrane excitability. However, it has no effect on potassium concentration in blood.

A more prolonged antihyperkalemic effect is achieved by infusing glucose solution with insulin, which should be started after calcium gluconate administration. For this purpose, 40-% glucose solution is commonly used in an amount of up to 300 mL adding 8–12 U of insulin for every 100 mL of 40-% glucose solution. The administration of glucose with insulin ensures the transfer of potassium from blood plasma into cells; its antihyperkalemic effect starts 5–10 minutes after the infusion and lasts up to 4–6 hours. Potassium concentration in blood decreases by 0.5–1.5 mmol/L within 15–30 minutes; a decrease in potassium concentration, although not so fast, is also observed with the administration of glucose only (due to the secretion of endogenous insulin).

Beta-2 adrenergic receptor agonists have a similar effect. Potassium moves into cells due to insulin and beta-2 agonists by increasing the activity of sodium-potassium ATPase, primarily of skeletal muscles [4]. For this purpose, salbutamol 10 mg through a nebulizer can be prescribed for 15 minutes every 60 minutes; its effect starts in 15–30 minutes and lasts for 2–4 hours; K^+ concentration in plasma decreases by 0.5–1.5 mmol/L. The procedure can be repeated until 20 mg of salbutamol is administered during 120 minutes. Alternatively, salbutamol 0.5–2.5 mg can be administered intravenously (except for patients with coronary heart disease) [6].

Sodium bicarbonate (NaHCO3) 1.4% or 8.4% infusion, 10–20 mEq/h with no acidosis in the patient, only slightly reduces potassium concentration in plasma. It should be prescribed to patients with severe metabolic acidosis after administration of glucose with insulin, adrenergic agents and calcium [4, 6]. Sodium bicarbonate 50 mmol IV during 15 minutes contributes to the movement of potassium into cells; it should be administered with an isotonic solution. It increases potassium excretion by the kidneys by increasing sodium delivery to collecting ducts [4].

These emergency hyperkalemia correction methods should be accompanied by treatment aimed at reducing the amount of potassium in the body, including the administration of diuretics and potassium-binding agents [4]. For patients with hypervolemia, it is recommended to administer furosemide (1 mg/kg of body weight as an IV push (up to 80 mg), then 10–20 mg/h as a continuous infusion) and thiazides or thiazide-like diuretics (for example, metolazone 5–10 mg orally) [6].

Hemodialysis is the fastest and most effective way to reduce K^+ concentration in plasma; it is indicated when other procedures have no effect.

Management of Chronic Hyperkalemia

If hyperkalemia is detected, treatment should be revised first, and agents that may contribute to hyperkalemia should be excluded [4].

Diet (Table 4). Patients should be advised to reduce their dietary potassium intake and avoid potassium-containing salt substitutes and herbs that might increase potassium levels. In the early stages of CKD, potassium restriction to 4.7 g/day is required to prevent hyperkalemia. In serum potassium level > 5.3 mmol/L, potassium intake should be limited to 2–3 g/day [1].

Diuretic therapy is efficient in minimizing the risk of hyperkalemia in patients with CKD. Thiazide and loop diuretics increase potassium excretion by increasing sodium delivery to collecting ducts. Thiazide diuretics should only be given for GFR > 30 mL/min/1.73 m^2 [4].

Sodium polystyrene sulfonate (SPS) is a cation-exchange resin that binds potassium in the gastrointestinal tract in exchange for sodium (1 g of the agent binds 1 mmol K^+) and is used to manage hyperkalemia. This agent is most often prescribed with sorbitol for the management of acute hyperkalemia. Despite that this agent is widely used, its potassium-lowering effect in most cases is due to the increased stool volume caused by sorbitol [4]. Long-term use of the agent is poorly tolerated due to the development of constipation, diarrhea, hypernatremia, hypokalemia, hypocalcemia, or hypomagnesemia. Long-term use should be avoided due to possible gastrointestinal (GI) adverse effects such as colon necrosis [1]. No rigorous placebo-controlled studies of this agent were performed. Since sodium is an anti-exchange ion when administering SPS, this agent should be prescribed with caution in case of HF, arterial hypertension, edemas [2].

Calcium polystyrene sulfonate (CPS, Veltassa VR) has a number of advantages over SPS because it binds potassium in the distal colon in exchange for calcium and does not cause sodium retention. Like for SPS, long-term efficacy and safety data for this agent are scarce [1].

Patiromer and sodium zirconium cyclosilicate are two new potassium-binding agents that have proved effective in lowering plasma potassium concentrations along with the continued use of RAAS blockers (Table 5).

Patiromer is a non-absorbable polymer approved for clinical use in the management of hyperkalemia.

Table 4. *Approaches to the treatment of chronic hyperkalemia*

Approach to treatment	Diet	Sodium (SPS) and calcium polystyrene sulfonate (CPS)-non-selective cation — exchange resins	Increased urinary K excretion	Increased urinary K excretion
Mechanism of sK decreas	Restricted intake of K-rich foods	Increased fecal K excretion	Increased urinary K excretion	Increased potassium levels in urine
Efficiency	Variable, depending on prescription and patient compliance	Can decrease sK concentration by 0.7–1.1 mEq/L	Variable, depending on dose and state of effective arterial blood volume	Withdrawal can decrease sK concentra-tion by 0.2–0.5 mEq/L
Side effects/ tolerability	Poor patient compliance in the long term, due to difficult preparation and poor palatability	Bind calcium and magnesium May cause hypomagnesemia, hypocalcemia and sodium overload GI side effects (constipation, nausea) FDA warning for the risk of colonic necrosis (SPS)	May cause further deterioration of kidney function due to volume depletion May cause/worsen electrolyte and acid–base disorders (e.g. hyponatremia, hypomagnesemia, metabolic alkalosis)	-
Limitations	Need for skilled health professionals (renal dietician) May interfere with the prescription of protein-restricted diet in advanced CKD	Poor tolerability and adhernce due to GI side effects Slow effect onset	Inappropriate in the absence of fluid overload May be poorly effective in advanced stage of CKD	Dose reduction or withdrawal reduce renal and cardiovascular benefits of treatment

Table 5. *Characterization of K-binding agents for the treatment of hyperkalemia [8]*

Drug	SPS	Patiromer	Sodium zirconium cyclosilicate
Type of molecule	Non-specific cation binding, sodium-containing organic resin	Selective, calcium-containing sodium-free, organic polymer	Highly selective, sodium- and zirconium-containing, inorganic crystalline silicate
Mechanism of action	Non-specific binding of K in exchange for sodium	Non-specific binding of K in exchange for calcium	Selective K binding in exchange for Sodium or Hydrogen
Linked cations	Potassium, magnesium, calcium	Potassium, magnesium	Potassium
Route of administration/ formulation	Oral or rectal suspension	Oral suspension	Oral suspension
Site of action	Colon	Dystal colon	Entire intestinal tract
Onset of effect	1–6 h	4-7 h	1–6 h
Duration	Variable, 4-6-24 hours	12-24 hours	Unclear
Dosing	15–60 g/day orally in 100 ml 20% sorbitol solution — to prevent constipation); 30-50 g/day rectally (50 ml 70% sorbitol solution, 150 ml water); Up to 4 receptions per day	8.4-25.2 g/day once	Initial dose: 10 grams 3 times a day for 48 hours, supportive — 5-15 g/day
Destination features	Separate from the appointment of other oral drugs: 3 hours before or 3 hours after; gastroparares — 6 hours	Separate from the prescribing of other oral drugs: 3 hours before or 3 hours after	Separate from the prescribing of other oral drugs with clinically significant pH-dependent bioavailability: 2 hours before or 2 hours after
Most common adverse events	Gastrointestinal intolerance Hypokalemia Hypernatremia Hypocalcemia Volume overload Colonic necrosis	Gastrointestinal intolerance Hypokalemia Hypomagnesemia	Gastrointestinal intolerance Hypokalemia Oedema
Serious adverse events	Colon necrosis	None	None

This medication binds potassium in exchange for calcium in the gastrointestinal tract, mainly in the distal colon, and increases potassium excretion with feces [1]. It reduces plasma potassium concentration in a dose-dependent manner, with maximum decrease observed in patients with higher baseline values. Patiromer demonstrated effective control of plasma potassium concentrations in a one-year randomized study in high-risk patients taking RAAS blockers. Common adverse events observed during clinical trials were constipation and hypomagnesemia, which required correction of magnesium levels in several patients. However, this medication was well tolerated overall [4, 7].

Sodium zirconium cyclosilicate (SZC, ZS-9, Lokelma) is a non-absorbable microporous inorganic compound that does not adsorb and binds potassium in exchange for sodium throughout the gastrointestinal tract. It was shown to be effective in lowering plasma potassium concentration in a dose-dependent manner in high-risk patients, most of whom received RAAS blockers. Adverse events observed during clinical trials were generally comparable to the placebo; however, edema developed more frequently with higher doses. This is because the agent contains a large amount of sodium—800 mg in a 10 g dose [1, 4].

Prevention of Hyperkalemia in Patients Receiving RAAS Blockers

In patients with arterial hypertension with no risk factors, the incidence of hyperkalemia along with monotherapy with a RAAS blocker is ≤ 2%; it increases to 5% along with a two-component RAAS blockade, and up to 5–10% with a two-component RAAS blockade prescribed in patients with HF or CKD. In the RALES study, hyperkalemia developed in 13.5% and 40% of patients receiving 25 mg and 50 mg of spironolactone, respectively. This suggests that limiting the dose to 25 mg per day may reduce the risk of hyperkalemia. In actual clinical practice, the incidence of hyperkalemia during

treatment with mineralocorticoid receptor antagonists (MCRA) is 6–12% in cases of chronic HF with reduced left ventricular ejection fraction; sometimes, it reaches 50% [2]. Interestingly, during treatment with RAAS blockers, hyperkalemia develops even in patients with anuria who are on long-term hemodialysis, probably due to decreased gastrointestinal excretion [5]. Hyperkalemia was the reason why ACE/ARA and MCRA inhibitors were not administered in 8.5% and 35.1%, respectively [2].

In the PARADIGM-HF study in patients receiving MCRA, the incidence of hyperkalemia demonstrated no differences between the enalapril group and the sacubitril/valsartan group. However, severe hyperkalemia was more common in the enalapril group (3.1–3.3 vs 2.2 per 100 patient-years) [9].

To reduce the risk of hyperkalemia with underlying intake of agents blocking RAAS, treatment should be started with low doses and potassium level should be monitored after 1–2 weeks from the start / dose titration. If potassium concentration in the blood is higher than 5.5 mmol/L, despite the above precautions, the use of a potassium binder can be considered before discontinuing agents that block RAAS [4]. Some guidelines recommend prescribing a K-lowering agent for potassium levels > 5.0 mmol/L (Table 6). If it is ineffective, the dose of the RAAS inhibitor should be reduced or withdrawn [1]. Mortality in patients with CKD, HF, and type 2 DM is minimal at serum potassium values of 4.0–4.5 mmol/L and significantly increases at values > 5.0 mmol/L and < 4.0 mmol/L [1]. In accordance with the European Society of Cardiology (ESC) guidelines for the management of patients with HF, low-dose MCRA followed by titration should be started in patients with serum potassium level < 5.0 mmol/L. If potassium level increases > 5.5 mmol/L, the MCRA dose should be halved; if it is > 6.0 mmol/L, MCRA should be immediately withdrawn [10]. Serum potassium and creatinine levels should be monitored 1 and 4 weeks after treatment start/ dose increase, then after 8 and 12 weeks, 6, 9, and 12 months, then once every 4 months. The recommended potassium level during treatment with ACE inhibitors and sartans, when the patient should consult a specialist, is > 5.0 mmol/L; drug withdrawal is recommended when serum potassium increases > 5.5 mmol/L [1, 10].

A recent consensus published by the ESC Working Group on Cardiovascular Pharmacotherapy recommends a diet with reduced potassium intake and a higher dose of non-potassium-sparing diuretics for the prevention and management of hyperkalemia. Treatment with approved potassium binders is recommended when the potassium level rises above 5.0 mmol/L in patients taking targeted doses of RAAS blockers to continue this life-saving treatment. Potassium binders can be started earlier, at potassium level < 5.0 mmol/L, to allow titration of doses of RAAS blockers to target or maximum tolerated doses. Preference should be given to patiromer and sodium zirconium cyclosilicate, although there are no data on their efficacy and safety in administration for more than 12 months [2]. A secondary analysis performed

Table 6. *Existing recommendations on renin-angiotensin-aldosterone system inhibitors use according to K+ levels*

K^+ level, mmol/L	Recommendation
>6	Stop RAASi (ESC HF, ESC CVPT, NICE)
>5,5	Reducing the dose of/stop ACE/ARA inhibitors (K/DOQI)
5,0-5,5	K/DOQI :take measures to lower K+ when initiating RAASi
>5	Do not start RAASi if >5,0 (K/DOQI, HFSA HF, NICE) Reduce dose of/stop RAASi>5,0 (ACCF/AHA HF, ESC HF, K/DOQI) MRA not recommended if >5,0 (HFSA HF) Maintain MRA between 4,0-5,0 (ACA/AHA) Do not routinely offer a RAASi to people with CKD in their pre-treatment K+ levels are >5,0 mmol/L A K+ lowering agent should be started
4,5-5,0	In patients not on maximal guideline-recommended target dose of RAASI therapy, it is recommended to up-titrate/start RAASi therapy and closely monitor Kю levels.

Note: ACA — American College of Cardiology, AHA — American Heart Association, ESC — European Society of Cardiology, CKD — chronic kidney disease, ESC CVPH — the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology, ESC HF — Heart Failure Association of the European Society of Cardiology, HF — Heart Failure, HFSA HF — heart failure Society of America, K/DOQI — Kidney Disease Outcomes Quality Initiative, NICE — National Institute for Health and Care Excellence, RAASi — renin angiotensin aldosterone system inhibitor; ARB — angiotensin II receptor blocker; K^+ — potassium; MRA — mineralocorticoid receptor antagonists

in the Randomized Aldactone Evaluation Study and EMPHASIS-HF study demonstrated a beneficial effect of MCRA on cardiovascular outcomes in HF patients with serum potassium level 5.0–5.5 and > 5.5 mmol/L [11–13]. However, the main clinical trials of MCRA in cases of HF did not include patients with serum potassium level > 5.0 mmol/L and creatinine level > 2.5 mg/dL or GFR < 30 mL/min/1.73 m^2 [1]. According to the Italian Society of Nephrology, serum potassium level > 5.0 mmol/L with underlying CKD is considered abnormal and requires careful monitoring and preventive and therapeutic approaches aimed at maintaining potassium levels in the range of 4.0–4.5 mmol/L [6].

Conclusion

Hyperkalemia is a common and serious disease, especially in the management of patients with CKD, DM, HF, and cardiorenal syndrome of different types [14, 15]. Previously, withdrawal of RAAS blockers was the main strategy for preventing/correcting hyperkalemia. Other approaches to preventing or managing chronic hyperkalemia are associated with low adherence (diet), unfavorable efficacy and safety profile (SPS), and potential adverse effects (intensive treatment with diuretics). Patiromer and sodium zirconium cyclosilicate are the new effective and well-tolerated agents for the long-term treatment of patients with hyperkalemia or at risk of its development. They may allow wider use of RAAS blockers at recommended doses in patients with CKD, DM, and HF and may delay the start of renal replacement therapy required due to the development of hyperkalemia in patients with end-stage renal disease.

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