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Hyperkalaemia

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Hyperkalaemia is a common electrolyte abnormality that can result in life-threatening arrhythmias and is associated with an increased risk of mortality. The strongest risk factor for the development of hyperkalaemia is CKD, the effects of which are often exacerbated by concomitant comorbidities such as diabetes mellitus or CHF, and the use of medications such as RAAS inhibitors. Hyperkalaemia is managed by eliminating risk factors, and through interventions aimed at directly lowering serum K. Often the elimination of risk factors entails the cessation of potentially beneficial interventions, such as heart-healthy diets or the use of RAAS inhibitors, and hence represents an undesirable clinical compromise. Regular monitoring of serum K is strongly recommended for patients on RAAS inhibitors to optimize dosing and minimize the risk of hyperkalaemia. The emergence of new K-lowering medications has led to renewed interest in pursuing therapeutic strategies that enable the continued use of beneficial, but hyperkalaemia-inducing interventions, even in patients who are prone to hyperkalaemia.

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Aetiology and mechanisms

High K intake

Most K is absorbed in the small intestine and absorption increases in proportion to intake[1,2]. Increased K intake causes hyperkalaemia under conditions of impaired renal excretion and/or cellular redistribution. Sources of K include K-rich foods; K supplements (often prescribed with diuretics); salt substitutes; GI bleeding; and blood transfusions using outdated blood.

Abnormal cellular redistribution

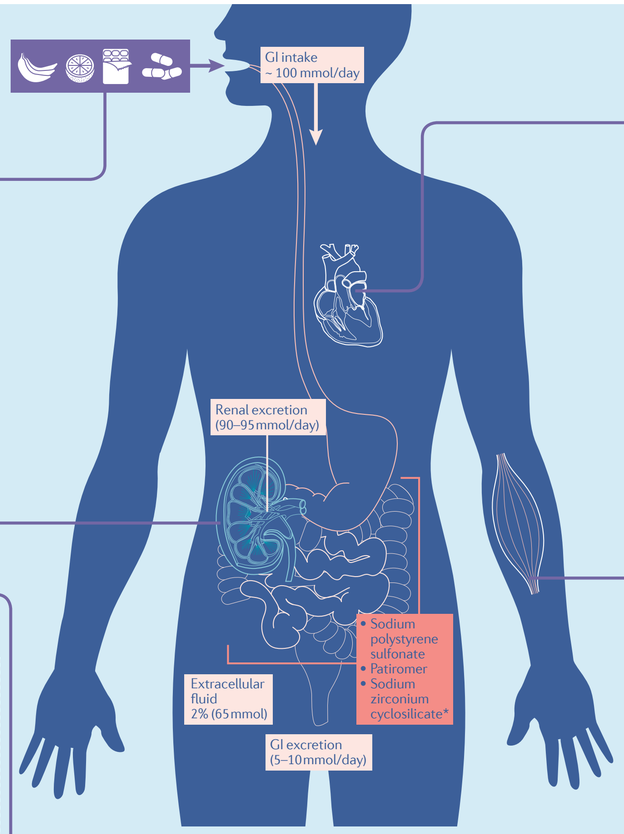
98% of K resides intracellularly. Hyperkalaemia can result from a decrease in the ability of a cell to shift K from the extracellular to the intracellular space, resulting in an insufficient response to K loading. Factors that can lead to K redistribution include insulin resistance, medications (e.g. β-blockers, α-stimulators) or hyperkalaemic periodic paralysis. Conversely, increased K leak (e.g. through cell destruction, hypertonicity or acidaemia) can also contribute to hyperkalaemia.

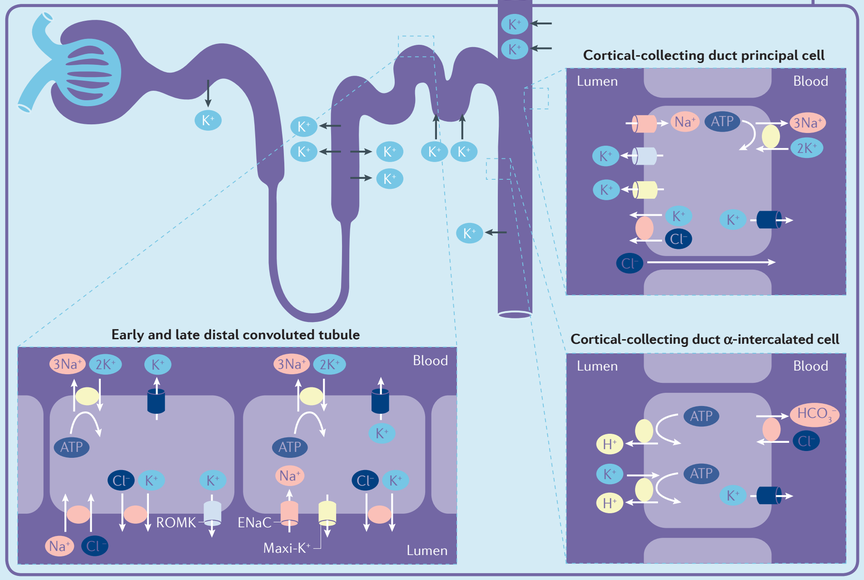
Decreased renal excretion

Abnormalities in renal K secretion and reabsorption can occur as a result of disorders affecting distal tubular flow rate and urine composition (e.g. Na, Cl and acid–base), the integrity or functionality of cells involved in K transport, and the function of hormonal systems that regulate K transport[3].

Structural anomalies:
- Decreased GFR (e.g. in AKI and CKD) leads to decreased filtration of Na and K. Tubular adaptation enables maintenance of mass balance even in patients with advanced CKD, but the ability of the kidney to adapt to rapid changes in K load is impaired[4].
- Tubulointerstitial dysfunction leads to decreased K secretion in distal tubular segments.

Functional anomalies:
- Decreased luminal flow and Na delivery (e.g. volume depletion, CHF).
- Metabolic acidosis or hypoaldosteronism (e.g. diabetes mellitus, kidney transplantation, pseudohypoaldosteronism type I and II, and various drug effects).





Urinary K excretion

The kidney has a crucial role in maintaining K homeostasis. Healthy kidneys possess a tremendous ability to dispose of excess K, maintaining normal serum K levels even with intakes as high as 400 mmol per day. Most of the filtered K is reabsorbed in the proximal convoluted tubule and the loop of Henle; therefore, renal K balance is largely determined by K secretion occurring in the distal nephron and collecting duct.

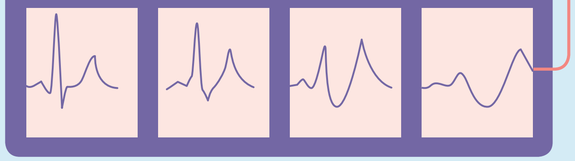
Drugs are a very common cause of hyperkalaemia

- RAAS inhibitors (decrease aldosterone)
- MRAs (block aldosterone)
- β-blockers (decrease renin, decrease K redistribution)
- Heparin (decreases aldosterone)
- Digitalis, trimethoprim, pentamidine, amiloride, triamterene (inhibit Na reabsorption)
- Calcineurin inhibitors (impair K secretion)[5]
- COX inhibitors (lower renin secretion, impair aldosterone release)
- Succinylcholine (affect K redistribution)

Cardiovascular consequences

Hyperkalaemia destabilizes myocardial conduction by decreasing the resting membrane potential, leading to increased cardiac depolarization, myocardial excitability, cardiac instability, conduction system abnormalities and arrhythmias, which can progress to ventricular fibrillation and asystole. It can be life threatening due to the increased risk of arrhythmias and sudden death.

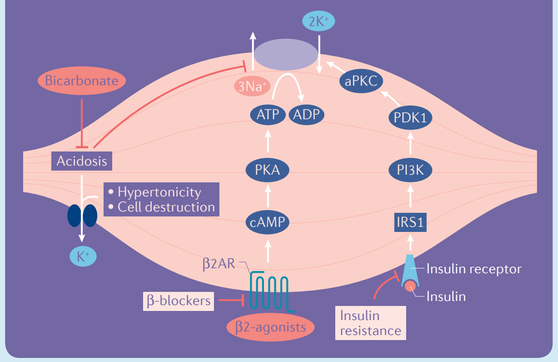
The specific serum K level and related kinetic pattern that predisposes patients to arrhythmias is uncertain. As arrhythmogenic potential depends on factors besides K level (e.g. Ca, Mg, acid–base, underlying LVH), and membrane potential also depends on factors that cannot be readily measured (e.g. intracellular K and other electrolyte levels), an ECG can indicate whether the observed hyperkalaemia is clinically significant (irrespective of the actual K level). ECG manifestations of hyperkalaemia are an indication for urgent treatment. However, patients can suffer sudden cardiac death and/or arrhythmias in the absence of typical ECG changes.



Cellular distribution

Most intracellular K is contained in muscle cells. The physiologic effects of K (e.g. on membrane potential) depend on a normal serum concentration. Serum K is minimally increased during dietary K intake due to increased K excretion by the kidney and to sequestration of K by muscle and liver cells. Conversely, serum K remains stable between meals due to K release primarily from skeletal muscle and liver cells.

The distribution of K between the intracellular and extracellular space is maintained by balancing the activity of the Na/K-ATPase with K leak. Effectors of K uptake and leak include insulin, catecholamines, mineralocorticoids, tonicity, exercise and acid–base status[3].



Therapy

The physiologic effects of hyperkalaemia depend not only on serum K level but also on other factors such as the rapidity with which hyperkalaemia develops, and the presence of organic (e.g. LVH, CHF) or functional (e.g. hypocalcaemia, hypomagnesaemia) abnormalities that can predispose to arrhythmias[6]. The level of intervention should therefore be determined not only by serum K level, but also by the presence of electrophysiologic changes[7]. Severe hyperkalaemia represents a medical emergency requiring immediate electrophysiologic monitoring and interventions to stabilize membrane potential and lower serum K level.

Acute interventions
- Intravenous Ca or hypertonic saline[1] facilitate the restoration of normal cell membrane electrophysiology[8].
- Interventions that induce K uptake include insulin, β2-agonists and perhaps bicarbonate[9].
- Definitive treatment usually necessitates the removal of K (e.g. by haemodialysis)[1]. Approaches to facilitate K excretion can be initiated in the acute setting but are better suited as chronic interventions.

Chronic interventions

Long-term interventions involve eliminating risk factors and administrating therapies that facilitate K removal.
- Alkali normalizes cellular K redistribution and enhances tubular secretion in patients with metabolic acidosis.
- Diuretics enhance distal tubular Na flux and increase tubular K secretion, especially when combined with alkali therapy. This approach is feasible in patients with CHF, volume overload or hypertension, but might not be effective in patients with limited GFR.
- Mineralocorticoid stimulation enhances tubular K secretion but can cause Na retention and hypertension.
- Restriction of K intake through the removal of unnecessary sources of K (e.g. medicinal supplements). Dietary K restriction can also be implemented[10].
- Eliminating hyperkalaemia-inducing medications. Some medications (e.g. NSAIDs, trimethoprim) can be replaced. Several drug classes (e.g. RAAS inhibitors, CNIs), however, are clinically indicated in patients who are most prone to hyperkalaemia (e.g. those with CKD, CHF or kidney transplants), in whom their discontinuation is either not possible or undesirable[11]. RAAS inhibitor dose should be decreased in patients with serum K level ≥5.5 mmol/l and discontinued at >6 mmol/l[12].
- Increasing GI elimination with K-binding medications. Sodium polystyrene sulfonate is the most commonly used, but data on its long-term efficacy and safety are sparse. RCTs of the novel K-binding agents patiromer and sodium zirconium cyclosilicate* show that they effectively lower serum K levels[13–15]. Long term (52-week) data show that patiromer maintains normokalaemia and enables continued use of beneficial medications (e.g. RAAS inhibitors) in at-risk patients[16,17]; however, the effects of these novel agents on long-term clinical end points (i.e. renal and/or cardiac outcomes) are unknown.

Relypsa, Inc.

Relypsa, Inc. is a biopharmaceutical company focused on the discovery, development and commercialization of polymeric medicines for patients with conditions that are often overlooked and undertreated and can be addressed in the gastrointestinal tract. The Company's first medicine, Veltassa (patiromer) for oral suspension, was developed based on Relypsa's rich legacy in polymer science. Veltassa is approved in the USA for the treatment of hyperkalaemia. Veltassa has intellectual property protection until 2030 in the USA and 2029 in the European Union. More information is available at www.relypsa.com.

Veltassa

Veltassa is a potassium binder approved for the treatment of hyperkalaemia. Veltassa should not be used as an emergency treatment for life-threatening hyperkalaemia because of its delayed onset of action. Made in powder form consisting of smooth, spherical beads, Veltassa is mixed with water (90 ml or 3 ounces) and taken once-a-day with food. Veltassa is not absorbed and acts within the gastrointestinal tract. It binds to potassium in exchange for calcium, primarily in the colon. The potassium is then excreted from the body through the normal excretion process.

Abbreviations

*Not FDA approved. AKI, acute kidney injury; aPKC, atypical protein kinase C; β2AR, β2 adrenergic receptor; Ca, calcium; CHF, congestive heart failure; CKD, chronic kidney disease; Cl, chloride; CNIs, calcineurin inhibitors; COX, cyclo-oxygenase; ECG, electrocardiogram; ENaC, epithelial Na channel; GFR, glomerular filtration rate; GI, gastrointestinal; HCO_3^-, bicarbonate; IRS1, insulin receptor substrate 1; K, potassium; LVH, left ventricular hypertrophy; Mg, magnesium; MRA, mineralocorticoid receptor antagonist; Na, sodium; NSAIDs, nonsteroidal anti-inflammatory drugs; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial; ROMK, renal outer medullary K channel.

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Competing interests

C.P.K. has served as consultant for and received honoraria from Relypsa and ZS Pharma. F.Z. has received honoraria from Relypsa, ZS Pharma, Bayer, Pfizer and Novartis.

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