CHAPTER 2

Disorders of potassium balance

The body in steady state is in potassium balance with potassium intake (normally 60–80 mmol/d) equal to potassium excretion (renal excretion 50–65 mmol/d and stool 10–15 mmol/d). The normal serum potassium concentration ranges from 3.5 to 5.0 mmol/L.

Learning point

Disturbances of plasma potassium (K) levels are commonly encountered in clinical practice. Both hyperkalaemia and hypokalaemia may be life-threatening medical emergencies.

Distribution

Some 98% of total body potassium is intracellular and this is maintained by the Na–K-ATPase pump (Fig. 2.1). Therefore, a significant shift in potassium to or from the intracellular fluid (ICF) can markedly affect the serum potassium concentration and exert profound effects on the resting membrane potential.

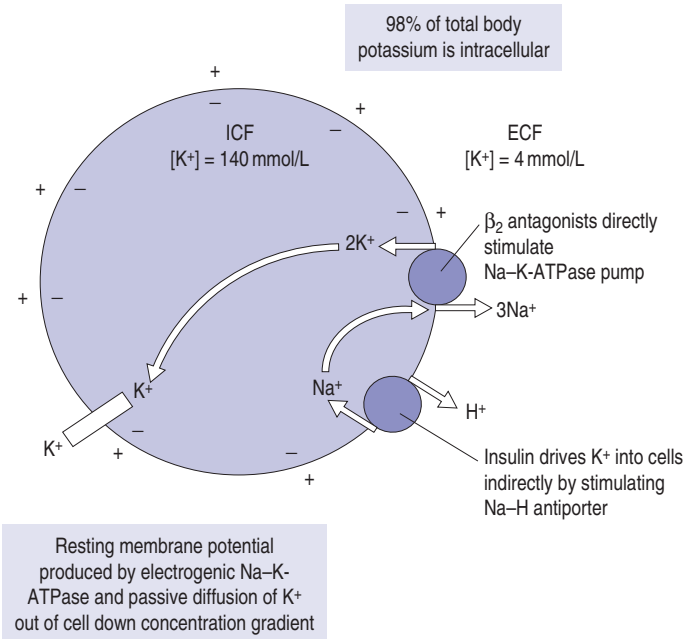

Figure 2.1 Potassium distribution and resting membrane potential. Some 98% of potassium is intracellular. The resting membrane potential is produced by the electrogenic Na–K-ATPase and passive diffusion of K^+ out of the cell down the concentration gradient. ICF, intracellular fluid; ECF, extracellular fluid.

Example:

A 70-kg man contains 42L total body water, 14L extracellular fluid and 28L intracellular fluid.

Total ECF potassium $= 14 \times 4.0 = 56$ mmol

Total ICF potassium $= 28 \times 140 = 3920$ mmol

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Potassium excretion

The kidney is primarily responsible for potassium regulation. In health, the kidney can lower renal excretion to 5–10 mmol per day or increase excretion to 450 mmol per day depending upon potassium intake.

Renal potassium excretion

Under normal circumstances, 180 L plasma are filtered per day, resulting in the entry of 720 mmol potassium into the lumen of the nephron. If the serum K concentration increases to 5.0 mmol/L, then an extra 180 mmol K will be filtered. The majority of the filtered K (around 500 mmol) is reabsorbed in the proximal tubule. The control of potassium secretion occurs primarily in the principal cells of the cortical collecting duct (CCD) (Fig. 2.2). Potassium secretion is dependent on the delivery of sodium and water to the CCD and on the action of the hormone aldosterone. Aldosterone increases sodium reabsorption from the lumen and promotes potassium secretion into the lumen, restoring electrical neutrality.

Gastrointestinal potassium excretion

Although gastrointestinal loss usually accounts for 10–15 mmol K excretion per day, this route can be increased in chronic renal failure, when it may account for up to 50% of potassium intake.

When should I check potassium level?

There are myriad potential reasons for requesting estimation of a serum potassium (K) level but the commonest and most important indications in clinical practice include the following.

Patients with cardiac disease

Both raised (hyperkalaemia) and subnormal (hypokalaemia) serum potassium levels may have significant effects upon cardiac conduction. It is therefore critically important to ensure that potassium levels are maintained in the normal range in patients with myocardial infarction, cardiac dysrhythmias or receiving digoxin therapy.

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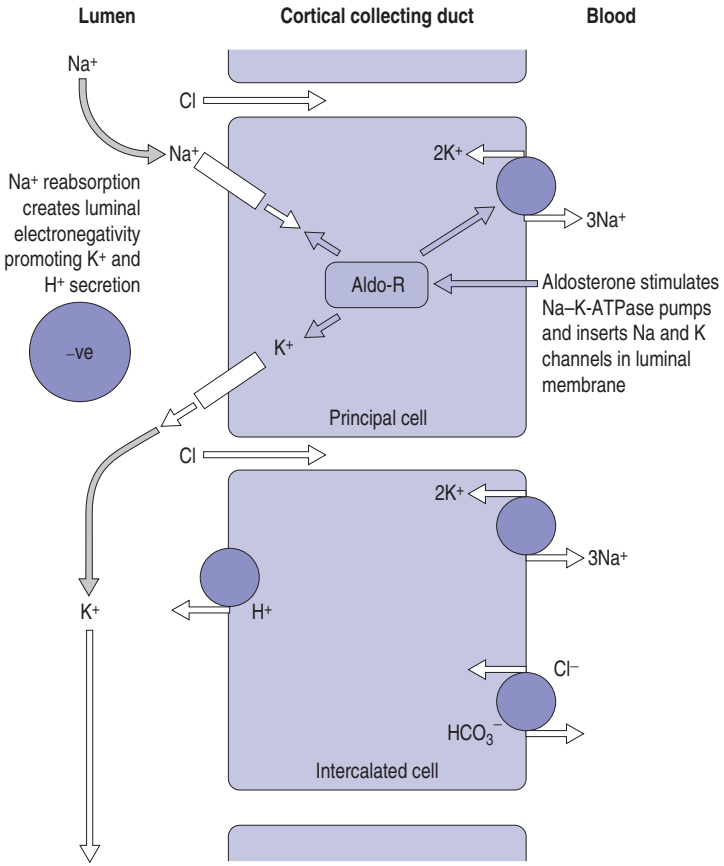

Figure 2.2 Renal excretion of potassium. Potassium secretion is controlled in the cortical collecting duct (CCD). Sodium reabsorption in this segment produces a negative voltage gradient, promoting K secretion under the actions of aldosterone. Aldo-R, aldosterone receptor.

Patients receiving drugs that may affect serum potassium level

Drugs such as loop diuretics may lower serum potassium levels, whereas drugs such as potassium-sparing diuretics, angiotensin

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converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) may increase serum potassium levels.

Patients with diabetes mellitus

Patients who present to hospital with acute diabetic ketoacidosis often have normal or slightly raised potassium levels as the systemic acidosis promotes the exit of potassium from cells into the extracellular fluid. Treatment with insulin drives potassium back into the intracellular compartment and the serum potassium level may rapidly fall such that hypokalaemia is a real risk. These dehydrated patients typically receive large volumes of intravenous fluid and are markedly polyuric. They therefore require very close monitoring of serum potassium level (2–4-hourly) combined with judicious potassium supplementation. Patients with long-standing diabetes mellitus may also develop a type IV renal tubular acidosis, which may lead to troublesome hyperkalaemia. This often results in an intolerance to ACE inhibitors and to renal replacement therapy being commenced slightly earlier in diabetic patients than in patients with other causes of renal failure.

Patients with major fluid and electrolyte fluxes

This may be seen in patients receiving large volume of intravenous fluids, e.g. postsurgical patients with major fluid losses from drains and wounds as well as patients receiving total parenteral nutrition. In addition, severe diarrhoea may cause significant fluid and electrolyte disturbance with hypokalaemia.

Patients with renal impairment

Patients with renal functional impairment have a reduced capacity to excrete potassium and are therefore more prone to hyperkalaemia. A low threshold for checking serum potassium is recommended in such patients, particularly if a potential cause for hyperkalaemia is present.

Patients with weakness of unknown aetiology

Potassium plays an important role in neuromuscular physiology, and paralysis and ventilatory respiratory failure may ensue from severe hypokalaemia.

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What do I do with the result?

Usually, the potassium level does not require overt action, although trends should be sought, i.e. if the potassium level is 'drifting up' then look for a cause and deal with it. Is the patient receiving potassium supplements? Is the patient's renal function normal? However, anything other than prompt action when potassium levels are below 3 mmol/L or greater than 6 mmol/L is perilous. The management of these important scenarios is outlined later in this chapter.

Hypokalaemia (<3.5 mmol/L)

Hypokalaemia may result from depletion of total body potassium secondary to excessive renal or gastrointestinal losses, but may also result from a shift of potassium into cells.

Symptoms and signs

> The primary symptoms of hypokalaemia are muscle weakness and paraesthesia. The primary risks are cardiac arrhythmias and ventilatory failure.

Hypokalaemia results in hyperpolarisation of the cell membrane, which impairs the ability of the cell to generate action potentials in excitable tissues such as muscles and nerves. Mild hypokalaemia (3–3.5 mmol/L) is often asymptomatic. Moderate hypokalaemia (2.5–3.0 mmol/L) may result in muscle weakness, fatigue and paraesthesia as well as ileus and constipation, because the smooth muscle of the gastrointestinal tract may be affected. In rare instances, severe hypokalaemia may precipitate rhabdomyolysis. Hypokalaemia may also interfere with the ability of the kidney to concentrate the urine, thereby resulting in nephrogenic diabetes insipidus with polyuria and polydipsia.

In patients with cardiac disease, hypokalaemia is associated with a greatly increased risk of ventricular arrhythmias. Although ECG changes (flattened T waves, inverted T waves, U waves) are typically present when the serum potassium level is less than 3.0 mmol/L, these changes do not correlate well with the risk of ventricular

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arrhythmias (Fig. 2.3). Severe hypokalaemia (< 2.5 mmol/L) can lead to weakness of respiratory muscles and ventilatory failure.

Differential diagnosis

Hypokalaemia may be considered to be due to insufficient potassium intake, a shift of potassium from the extracellular fluid to the intracellular compartment or excessive potassium excretion from the gut or kidneys.

Artefactual

This may occur if the blood was drawn from near the site of an intravenous infusion of fluid that does not contain potassium. In cases of doubt, take another sample to confirm or refute the diagnosis.

Low potassium intake

This may be due to insufficient potassium in the diet or intravenous fluids (e.g. postsurgery). It should be noted that, as the fall in potassium intake induces increased renal conservation of potassium, a low potassium intake alone does not cause hypokalaemia.

Shift of potassium into the intracellular compartment

Factors stimulating a shift of potassium into cells include insulin, β_2 agonists such as salbutamol, catecholamines or an alkalosis. Hypokalaemia may therefore occur in patients receiving treatment for diabetes mellitus or asthma. It should also be noted that concurrent hypophosphataemia is suggestive of an intracellular shift of potassium.

Gastrointestinal losses

Gastrointestinal losses such as vomiting, nasogastric aspiration or diarrhoea are a common cause of hypokalaemia. Interestingly, the potassium concentration of gastric juice is only 10 mmol/L, but the vomiting is often associated with extracellular volume contraction. This stimulates aldosterone release and, combined with the increased delivery of sodium bicarbonate to the distal nephron, results in renal potassium wasting. The potassium concentration in diarrhoea is often 30–35 mmol/L, and the hypokalaemia that may result is associated with a non-anion gap metabolic acidosis. Other causes of gastrointestinal potassium loss include villous adenomas, fistulae, laxative abuse and ureterosigmoidostomy.

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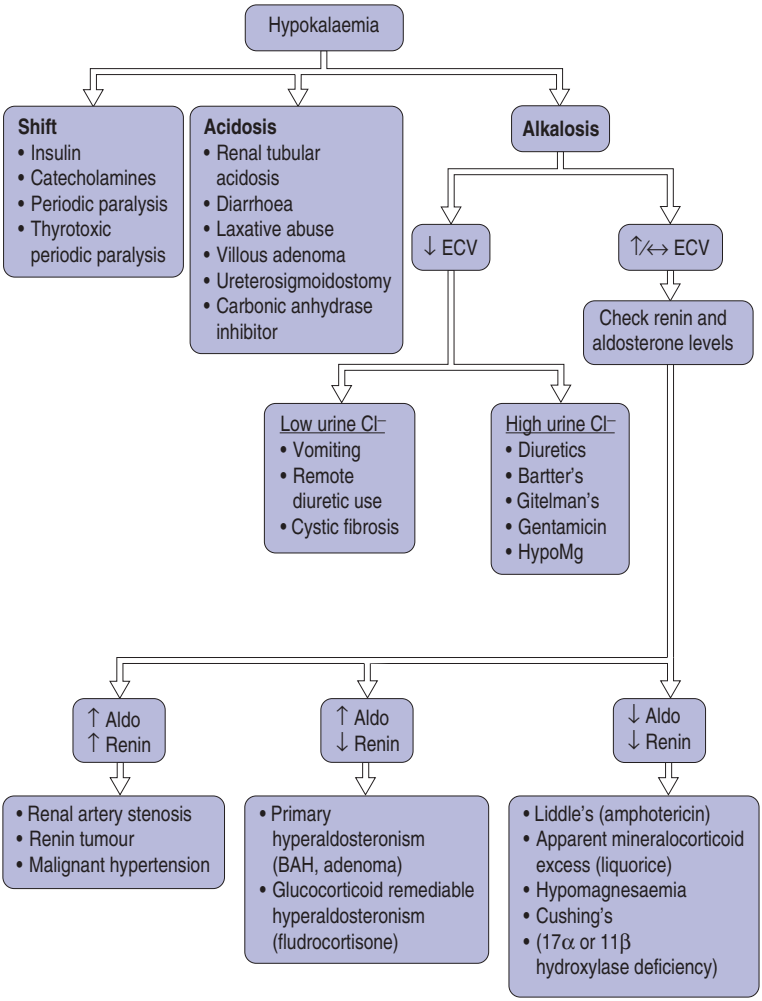

Figure 2.3 Differential diagnosis of hypokalaemia. Aldo, aldosterone; BAH, bilateral adrenal hyperplasia; ECV, extracellular fluid volume; hypoMg, hypomagnesaemia.

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Renal losses

Diuretics are the most common cause of hypokalaemia. They inhibit sodium reabsorption resulting in extracellular volume contraction with stimulation of aldosterone release, and increase the delivery of sodium and chloride to the CCD. Bartter's and Gitelman's syndromes are rare genetic conditions in which mutations in genes encoding sodium transporters in the loop of Henle and distal tubule respectively simulate chronic diuretic use.

Drugs associated with hypokalaemia:

Diuretics, gentamicin, amphotericin, carbenoxolone, laxatives, acetazolamide, fludrocortisone

Hyperaldosteronism secondary to a decreased extracellular volume promotes renal potassium loss. In primary hyperaldosteronism there is autonomous aldosterone production from an adrenal adenoma or bilateral adrenal hyperplasia resulting in expansion of extracellular volume and an increased delivery of sodium and chloride to the CCD. The sodium and water retention results in hypertension with a characteristic hypokalaemic metabolic alkalosis. Other causes of excess mineralocorticoid activity include Cushing's syndrome and exogenous corticosteroids or fludrocortisone.

Although renal diseases that result in renal failure are typically associated with hyperkalaemia due to a decreased glomerular filtration rate, some renal disorders are associated with hypokalaemia. For example, renal tubular acidosis (RTA) results in increased urinary potassium loss as well as causing a chronic systemic acidosis. The increased urinary potassium loss results from distal potassium secretion secondary to either increased sodium delivery to the distal tubule (proximal RTA) or defective distal hydrogen ion excretion (distal RTA).

Special situations

Heart disease

In patients with cardiac disease, e.g. postmyocardial infarction and cardiac failure (particularly if taking digoxin), hypokalaemia may induce ventricular arrhythmias and the serum potassium level should be maintained at the high end of normal.

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Liver failure

Hypokalaemia results in increased production of ammonia and can exacerbate hepatic encephalopathy.

Management

Assessment

The presence of paralysis or arrhythmias indicates an emergency situation. Assess the cardiovascular status (pulse rate, rhythm, lying and standing blood pressure, jugular venous pressure, presence of oedema) and look for evidence of arrhythmias (check ECG) and hypo/hypervolaemia. Is the patient diabetic or asthmatic? Carefully scrutinise the fluid balance charts – is the patient oliguric and in renal failure? Examine the drug chart for drugs that can affect potassium levels, e.g. insulin, diuretics, steroids, gentamicin. Does the patient have an abnormal venous bicarbonate level indicating a metabolic acidosis or alkalosis? Consider the degree of potassium deficit and ongoing potassium losses from gastrointestinal tract or kidneys. Check the serum magnesium level in complicated patients or in those with severe hypokalaemia, as hypokalaemia will not respond to replacement therapy if the patient is hypomagnesaemic.

Emergency treatment

- If hypokalaemia is severe (<2.5 mmol/L) it may be associated with muscle weakness leading to ventilatory failure or cardiac arrhythmias. Intravenous replacement is appropriate in this setting.
- Potassium chloride should be diluted in normal saline to a concentration of $\leq$40–60 mmol/L. Note that dextrose solutions may stimulate insulin and shift potassium into cells and should not be used. Rarely 10–20 mmol potassium chloride (KCl) may be infused in 100 mL saline over 30 min in extreme situations. **Never give ampoules of KCl directly without diluting.** Potassium-containing intravenous solutions can be very irritant to peripheral veins and it may be preferable to give these through a central line.
- The initial rate of potassium replacement may be as high as 20–40 mmol/h, but this should be done only with continuous ECG monitoring. The replacement rate should be reduced to

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10 mmol/h when the patient is out of immediate danger. The serum potassium must be checked regularly (initially at least hourly) during emergency treatment.

Non-urgent treatment

- Any underlying conditions such as renal failure should be treated and causative drugs discontinued.
- Oral potassium replacement is the safest route for potassium replacement in most situations, although potassium supplements may cause gastrointestinal upset. Typical replacement in the short term may be 60–120 mmol potassium chloride per day in three or four divided doses. Attention should be paid to ongoing potassium losses, and treatment should be guided by serum potassium measurements.

Hyperkalaemia

Hyperkalaemia is often asymptomatic, but the primary risk is of cardiac arrhythmias and sudden death.

Symptoms and signs

Hyperkalaemia reduces the polarisation of the cell membrane so that it falls closer to the threshold for depolarisation, thereby making cells more excitable. Clinical symptoms are uncommon, although some patients may experience paraesthesia, cramps, severe muscle weakness or even paralysis.

The main danger is cardiac arrhythmia, particularly bradyarrhythmias or sudden death. The risk is related to the degree of hyperkalaemia (>6.0 mmol/L), the rate of rise of the serum potassium level and the degree of acidosis or hypoxia. ECG changes including tall peaked T waves are typically present, but more worrisome changes include bradycardia, prolongation of the PR interval, loss of P waves, broadening of the QRS complex and the development of a 'sine wave' pattern (Fig. 2.4).

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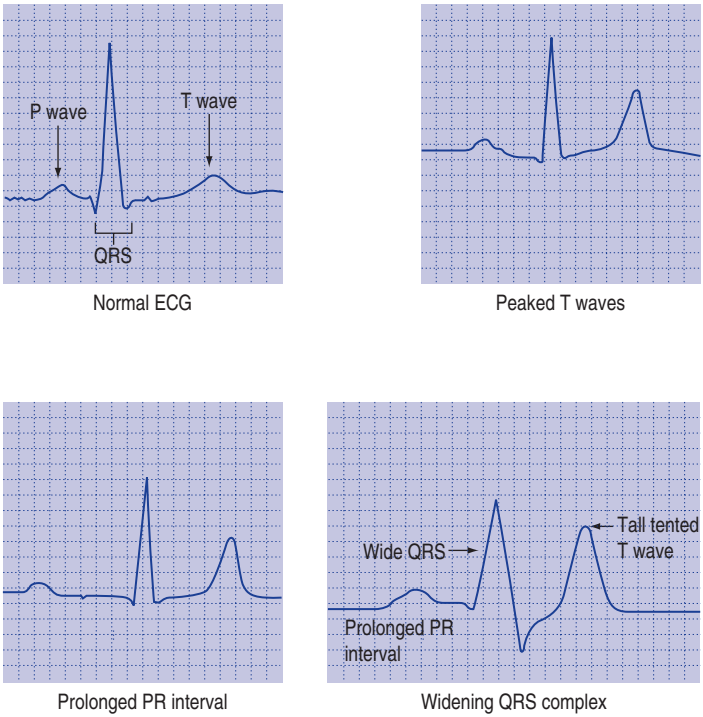

Figure 2.4 ECG changes of hyperkalaemia.

Special situations

Diabetic ketoacidosis

Hyperkalaemia may occur at presentation due to a shift of potassium out of cells (due to insulin lack and hyperglycaemia). However, total body potassium is depleted due to prior urinary loss of K (osmotic diuresis and loss with keto-anions) and serum potassium levels can fall precipitously when insulin and IV fluids are commenced.

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Differential diagnosis (Fig. 2.5)

The most common causes of hyperkalaemia are

- Acute or chronic renal impairment with consequent reduced potassium excretion
- Drug related
- Acute shifts of potassium out of cells into the extracellular fluid.

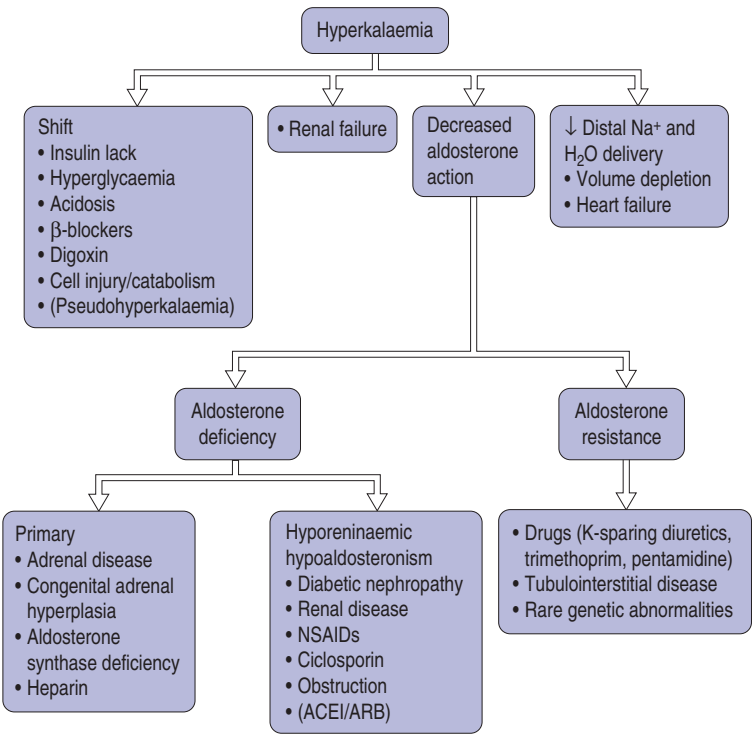

Figure 2.5 Differential diagnosis of hyperkalaemia. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs.

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Artefactual and pseudohyperkalaemia

This may occur if the venesection was traumatic or there was a long delay (>3 h) between venesection and separation of the plasma, as potassium may leak slowly from cells. Consider pseudohyperkalaemia in situations where there is a marked leukocytosis ($>11 \times 10^6$/mL) or thrombocytosis ($>400 \times 10^6$/mL). In this case the serum K concentration will be raised but the plasma K level will be normal.

High potassium intake

Increased potassium intake *per se* is not a cause of hyperkalaemia as the kidneys can excrete a large potassium load. A high potassium intake, however, may be a significant contributing factor especially in patients with impaired renal function. High intake may be dietary (fruits, certain vegetables) or iatrogenic (secondary to excessive K replacement).

Shift of potassium from the intracellular compartment

Factors promoting a shift of potassium out of cells include hyperglycaemia, a lack of insulin, β_2 antagonists and acidosis. Note that the combination of hyperphosphataemia and hyperkalaemia is found in conditions associated with cell damage such as rhabdomyolysis, severe burns, tumour lysis syndrome or following severe blood transfusion reactions.

Reduced renal potassium excretion

This is most commonly due to renal failure or to drugs that interfere with potassium excretion.

Drugs associated with hyperkalaemia

ACE inhibitors, angiotensin II receptor blockers, potassium-sparing diuretics, NSAIDs, digoxin, β_2 antagonists, ciclosporin.

Renal potassium excretion requires an adequate glomerular filtration rate, delivery of sodium to the distal nephron and the action of aldosterone (see Fig. 2.2).

- A decreased glomerular filtration rate is found in acute and chronic renal failure.

- Reduced sodium delivery to the distal nephron may be seen with severe volume depletion or heart failure – the urine sodium concentration is low (<20 mmol/L).
- Impaired aldosterone action may be due to adrenal disease (e.g. Addison's disease, hyporeninaemic hypoaldosteronism) or aldosterone resistance (e.g. potassium-sparing diuretics, tubulointerstitial disease, obstructive nephropathy). It should be noted that diabetic patients with diabetic nephropathy may develop hyporeninaemic hypoaldosteronism and troublesome hyperkalaemia at an earlier stage than non-diabetic patients with chronic renal impairment, often necessitating the institution of renal replacement therapy at an earlier stage.

Management

Assessment

If the serum potassium is >6.5 mmol/L then emergency treatment is merited. Check the ECG trace for signs of cardiac instability and proceed to emergency treatment if ECG changes are present. Assess the patient's cardiovascular status (pulse rate and rhythm, lying and sitting/standing blood pressure, jugular venous pressure, presence of oedema) for evidence of arrhythmias and hypo/hypervolaemia. Is the patient diabetic? What is the blood glucose level? Is the patient hypoxic or acidotic? Check the urine output and the drug chart carefully for drugs that may be implicated in raising the potassium level.

Emergency treatment (Table 2.1)

If ECG reveals changes of hyperkalaemia, continue ECG monitoring and obtain intravenous access.

1. Give intravenous calcium gluconate (10%, 10 mL administered over 5 min) to antagonise the effects of hyperkalaemia on the heart and stabilise the myocardium. This drug is short acting and may need to be repeated.
2. Shift potassium into cells by giving insulin and dextrose (6 units fast-acting insulin and 50 mL 50% dextrose) over 10 min. Commence an insulin and dextrose infusion (6 units fast-acting insulin, 50 mL 50% dextrose in 500 mL 5% dextrose) with monitoring of blood glucose levels. If the patient is acidotic and not in pulmonary oedema, consider giving sodium bicarbonate (500 mL 1.4% $NaHCO_3$

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Table 2.1 Emergency therapy of hyperkalaemia

Therapy	Dose	Mechanism of action	Onset	Duration of action	Risks
Calcium gluconate	10 mL of 10%	Stabilise myocardium	1 min	10–20 min	Vein irritation
Insulin and dextrose	50 mL 50% + 6 units insulin	Shifts K^+ into cells	20–30 min	2 h	Hypoglycaemia
Sodium bicarbonate	500 mL of 1.4%	Shifts K^+ into cells	2–4 h	Up to 24 h	Volume overload
Salbutamol	20 mg in 4 mL saline nebulised	Shifts K^+ into cells	15–30 min	2 h	Tachycardia
Calcium resonium	15 g t.i.d. (with 30 mL lactulose)	Binds K^+ in bowel	2–4 h	Removes K^+	Intestinal obstruction
Haemodialysis	–	Removes K^+	30 min	Removes K^+	

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over 1–2 h). Note that 8.4% $NaHCO_3$ is hypertonic and should not be given peripherally. If central venous access is available, consider giving aliquots of 25–50 mL 8.4% $NaHCO_3$ but monitor carefully for volume overload. β_2 agonists such as salbutamol will also shift potassium into cells, but may exacerbate cardiac instability and are usually used in children.

3. Increase potassium elimination by giving cation exchange resin (15 g calcium resonium with 30 mL lactulose three times per day). This is a slow-acting treatment and not appropriate in an emergency setting.
4. Dialysis may be required in patients with renal failure and refractory hyperkalaemia.

Non-urgent treatment

Any underlying causes should be treated, offending drugs discontinued and a low potassium diet considered. Long-term therapy with cation exchange resins should be avoided as there is a risk of forming concretions in the bowel. Increased renal potassium elimination may be achieved by volume expansion with normal saline and judicious use of loop diuretics to improve the distal delivery of sodium and water. Fludrocortisone may be useful in the setting of hypoaldosteronism.

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