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Potassium homoeostasis and pathophysiology of hyperkalaemia

Keld Per Kjeldsen[1,2,3]* and Thomas Andersen Schmidt[2,4]

[1]*Department of Medicine, Copenhagen University Hospital (Holbæk Hospital), Smedelundsgade 60, DK-4300 Holbæk, Denmark;*
[2]*Institute of Clinical Medicine, Copenhagen University, Blegdamsvej 3B, 2100 Copenhagen, Denmark;*
[3]*The Faculty of Health Science and Technology, Aalborg University, Frederik Bayers Vej 7D 9100 Aalborg, Denmark; and*
[4]*Department of Emergency Medicine, Copenhagen University Hospital (Holbæk Hospital), Smedelundsgade 60, 4300 Holbæk, Denmark*

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Determination of potassium level is one of the most frequent laboratory tests in clinical medicine. Hyperkalaemia is defined as a potassium level >5.0 mmol/L and is one of the most clinically important electrolyte abnormalities, because it may cause dangerous cardiac arrhythmia and sudden cardiac death. Here, we review methodological challenges in the determination of potassium levels, important clinical aspects of the potassium homoeostasis as well as of the pathophysiology of hyperkalaemia.

Methodological challenges

Potassium level is usually determined in a venous blood sample. However, inappropriate blood sampling technique may affect the result. It may cause release of potassium from working skeletal muscle cells and/or release of potassium from cellular components of blood during or after sampling. Thus, potassium blood sampling should primarily be done following a few minutes of physical rest, because potassium level rises during physical activity and is not normalized before after a few minutes of rest. A large vein should be used, e.g. the cubital vein, without fist clenching and without prolonged application of a tourniquet. Only needles, tubes, and tube adapters approved for potassium measurements should be employed to minimize haemolysis. Moreover, samples for measurement of potassium should routinely be checked for haemolysis, and if an error is suspected, measurement should be repeated with blood sampled appropriately or eventually taken as an arterial sample. In case of haemolysis, the clinician should consider whether it occurred *in vitro* (in the test tube) or *in vivo* (in the body). Pseudohyperkalaemia refers to potassium >5 mmol/L in the test tube and normal potassium level in the body. It should be noted that in addition to causing pseudohyperkalaemia, errors of potassium determination may conceal hypokalaemia. Finally, potassium should not be measured in an arm that is also used for liquid infusion, because it may jeopardize the measurement. Thus, potassium levels should be determined using a standardized set-up ensuring high accuracy and precision.

Potassium levels were traditionally measured in serum from coagulated blood, but are now more frequently measured in plasma from heparinized blood. Serum levels may generally be 0.2–0.4 mmol/L higher than plasma levels, and up to 0.7 mmol/L higher levels have been reported in serum when compared with plasma. This is especially a problem with high values. Thus, when shifting from serum to plasma measurements the reference range for potassium level needs appropriate adjustment. This must be taken into consideration by the clinician when changing from

*Corresponding author. Tel: +4540253784, Email: kjeldsen@rh.dk

serum based to plasma based measurements. And in any scientific study on potassium levels it must be clarified, whether it is plasma or serum that has been used for potassium measurements. At present, it is confusing that 'plasma potassium' and 'serum potassium' are sometimes considered synonyms. Moreover, it is distracting that levels for normal potassium range, hyperkalaemia as well as hypokalaemia may differ. Thus, there is at present a need for international consensus on how to resolve and handle these flaws. First, then it will become possible to pool potassium levels from various hospitals, countries, and studies to clearly establish risks at various levels of hyper- and hypokalaemia. In this paper, we mostly use the expression 'potassium level', because it is at present unclear in many studies, what actually was measured.

The reference interval for potassium at our hospital is 3.5–4.6 mmol/L. Here, plasma potassium is measured. However, different reference intervals may apply in other settings. Hyperkalaemia may be defined as a potassium level >5 mmol/L and hypokalaemia as a potassium level <3.5 mmol/L, and indeed even other cut-off levels are sometimes applied. It should be noted that whereas hypokalaemia is defined as a potassium level below reference level, hyperkalaemia is defined as a potassium level 0.4 mmol/L above the reference level. Mild hyperkalaemia may be defined as a potassium level >5.0–5.5 mmol/L, moderate hyperkalaemia as a level >5.5–6.0 mmol/L, and severe hyperkalaemia as a level >6.0 mmol/L. For the clinician this is not so important, because physicians must react according to prevailing settings. However, for studies compiling potassium data from various hospitals, countries, and studies these variations are challenging and may blur the outcome significantly.[1–4] Thus, also here there is a need for international consensus.

Potassium homoeostasis

Potassium is the most abundant cation in the body. Daily potassium intake is around 100 mmol, and it mainly comes from fruits, vegetables, and meat.

Long-term regulation of potassium homoeostasis takes place over hours to days and in healthy subjects depends mainly on renal potassium excretion. Renal potassium handling has been intensively reviewed recently—see Kovesdy *et al*.[5] The colon is responsible for a remaining few percent of the potassium excretion, and the colon may in patients with end stage renal disease increase faecal potassium secretion. However, other tissues contribute to *short-term regulation* of potassium homoeostasis, which takes place over only seconds to minutes. Here, skeletal muscles play an important role primarily because skeletal muscles contain the largest single pool of potassium in the body. Thus, for an adult human subject it has been calculated that the potassium content of the total skeletal muscle pool is approximately 225 times larger than the potassium content in the extracellular phase. Moreover, due to the large number of Na,K-pumps (sodium, potassium-adenosinetriphosphatase) and potassium channels, the skeletal muscles possess a huge capacity for potassium exchange. Hence, for an adult human subject it has been calculated that if all potassium channels or all Na,K-pumps were activated to maximum capacity for potassium leakage or uptake, respectively, the entire extracellular potassium pool could be over flooded or cleared for potassium in a matter of seconds to minutes. Thus, a close regulation of skeletal muscle Na,K-pumps is essential, and takes place as an up- or down-regulation of the activity of prevailing Na,K-pumps or/and as an up- or down-regulation of the number of Na,K-pumps.[5,6]

Physical exertion or exercise is a major challenge to short-term potassium regulation. During exercise, skeletal muscle loses potassium during repetitive action potentials. Because skeletal muscles constitute the major reservoir for potassium in the body, potassium level may increase markedly and attain values up to around 8 mmol/L that may be sustained during exercise. Physical conditioning or training has been found to reduce the increase in potassium during exercise probably due to an increase in the number of Na,K-pumps in skeletal muscles. Upon cessation of exercise, recovering muscles regain lost potassium by Na,K-pump mediated potassium uptake. This leads to normalization of potassium level within minutes, which may be preceded by a temporary undershoot of potassium level and subsequent transient hypokalaemia (<3.5 mmol/L). In addition, volume changes occur during these potassium level changes. The important observation is however, that the heart may be exposed to high potassium levels during exercise and a major drop in potassium level at cessation of exercise. Also important is the observation that this drop seems to be associated with impaired cardiac repolarization, which could potentially trigger arrhythmia and sudden cardiac death in susceptible individuals with pre-existing hypokalaemia and/or heart disease such as ischaemic heart disease, heart failure, ventricular arrhythmia, and inherited or acquired long QT-syndrome.[7–9]

The knowledge of potassium homoeostasis during exercise and recovery has several implications: first, it emphasizes the importance of appropriate rest before blood sampling for determination of potassium level. Second, it shows that mild to moderate hyperkalaemia may be a normal phenomenon that should not always be feared. Third, to the normal range for resting potassium level a normal range for exercise potassium level could be of use. Fourth, in patients suspected to be prone to exercise induced arrhythmia, an exercise test could be considered during which monitoring of potassium level from rest, during exercise, and recovery might yield information of value. Fifth, exposure of the heart to extreme hyperkalaemia during exercise and/or extremely rapid lowering of potassium level after exercise may cause arrhythmia and sudden cardiac death in predisposed persons.

Pathophysiology of hyperkalaemia

Hyperkalaemia is one of the most clinically important electrolyte abnormalities, because it may cause dangerous cardiac arrhythmia and sudden cardiac death. The highest occurrence of hyperkalaemia has been found in patients with chronic kidney disease (73%).[10] The occurrence varies a lot between studies, mainly due to different study

Table 1 Important causes of increased potassium level

Renal failure
Exercise
Epilepsy
Tissue breakdown—rhabdomyolysis, trauma, hyperthermia
Hyperkalaemic periodic paralysis
Infusion of potassium. Oral potassium intake combined with reduced potassium excretion
ACE-inhibitors, AT2-inhibitors, β-blockers, aldosterone antagonists, and digoxin
Diabetes
Acidosis

ACE, angiotensin converting enzyme; AT2, angiotensin 2 receptor; β-blockers, β-adrenoceptor antagonists.

populations, but as discussed above also due to the methodological challenges associated with measurements of potassium levels and different limits for potassium level used in the diagnosis of hyperkalaemia.

Important causes of increased potassium levels are given in *Table 1*. The physiological increase in potassium level during exercise has already been mentioned. A similar increase in potassium level has been described as a result of generalised muscle cramps such as in epilepsy. It may also be seen in generalized skeletal muscle breakdown such as rhabdomyolysis, trauma against skeletal muscles, burns, and hyperthermia. Hyperkalaemic periodic paralysis is a rare genetic anomaly in skeletal muscle ion channels causing depolarization of muscle cells and hyperkalaemia. In these patients, exercise or ingestion of potassium rich nutrients may provoke attacks of paralysis and hyperkalaemia that may be abated by inhalation of a β2-adrenoceptor agonist at the beginning of the attack. Intravenous administration of potassium may increase potassium level, cause hyperkalaemia, cardiac arrest, and sudden death. Thus, intravenous potassium should always be given with utmost precaution. Oral potassium intake combined with reduced potassium excretion may cause hyperkalaemia. Several cardiovascular drugs—ACE-inhibitors, AT2-inhibitors, β-adrenoceptor antagonists, aldosterone antagonists, and digoxin—may increase potassium level. Interestingly all of these drugs have a positive or neutral effect on life expectancy in heart failure patients that may be due to a decreased risk of hypokalaemia. Digoxin intoxication may be associated with hyperkalaemia due to inhibition of skeletal muscle Na,K-pumps. Diabetes mellitus may be associated with hyperkalaemia due to lack of insulin-stimulated Na,K-pump mediated potassium uptake in skeletal muscles. Also, acidosis may due to reduced kidney excretion of potassium cause an increase of potassium level and hyperkalaemia. It should be noted that reduced oxidation arising from hypoxia only induces a modest increase in potassium level due to high affinity of the Na,K-pump for oxygen.[4,11-17]

Symptoms may be relatively weak. However, hyperkalaemia may induce arrhythmia that may cause palpitations, dizziness, syncope, and sudden cardiac death. Skeletal muscle function may become impaired causing muscle fatigue and muscle paralysis. Nevertheless, hyperkalaemia is often detected in a routine blood sample. It may also be detected in a routine ECG. Progressive hyperkalaemia is typically characterized by tented or peaked T waves, widened QRS complexes, flattened P waves, and when extreme by sinus-wave appearance. Hyperkalaemia may also cause ventricular fibrillation and cardiac arrest. The ECG changes may erroneously mislead ECG interpretation software to determine a two-fold increase in heart rate, and hyperkalaemia should be considered if this phenomenon occurs. On the other hand, if ECG is normal although potassium level is high pseudohyperkalaemia should be considered. The risk of severe arrhythmia varies among various studies in part due to the methodological challenges associated with measurements as discussed earlier. Interestingly however, in a study on potassium levels in patients with acute myocardial infarction it was found that in patients with a potassium level 1 mmol/L above the reference interval 10% developed ventricular fibrillation or cardiac arrest corresponding to a two-fold increase of potential fatality as compared to patients with potassium levels in the normal range. Even more interestingly it was found that in patients with a potassium level 1 mmol/L below the reference interval 25% developed ventricular fibrillation or cardiac arrest corresponding to a five-fold increase in potential fatality when compared with patients with potassium in the normal range. Similar observations have been found in patients with heart failure indicating that hyperkalaemia should of course be feared, but hypokalaemia should probably be feared even more. Thus, whenever initiating prophylaxis against or treatment of hyperkalaemia precautions should be taken to avoid subsequent development of hypokalaemia and a subsequent even higher cardiovascular risk.[18-20]

Conclusions

Since determination of potassium levels may be afflicted with various errors, potassium levels should be determined using a standardized set-up ensuring high accuracy and precision of measurements. Potassium levels may be measured as 'plasma potassium' or 'serum potassium', but these values should not be considered synonyms because serum values may be higher than plasma values. Hyperkalaemia may be defined as a potassium level >5 mmol/L, but other cut-off levels are sometimes applied. Thus, there is a need for establishing an international consensus in this area. *Long-term regulation* of potassium homoeostasis takes place over hours to days and depends mainly on renal potassium excretion. Other tissues, mainly skeletal muscles, contribute to *short-term regulation* of potassium homoeostasis, which takes place over seconds to minutes. Major causes of hyperkalaemia are renal failure, exercise, epilepsy, tissue breakdown, diabetes, and acidosis, treatment with ACE-inhibitors, AT2-inhibitors, β-blockers, aldosterone antagonists, and digoxin intoxication. Hyperkalaemia may induce impaired muscle function, ECG changes and arrhythmias that may cause palpitations, dizziness, syncope, and sudden cardiac death. A decrease in potassium level by

1 mmol/L below the reference interval causes a 2.5-fold higher risk of ventricular fibrillation or cardiac arrest than an increase in potassium level by 1 mmol/L above the reference interval. This indicates that of course hyperkalaemia should be feared, but hypokalaemia should probably be feared even more. Thus, whenever initiating prophylaxis against or treatment of hyperkalaemia, precautions should be taken to avoid subsequent development of hypokalaemia and an even higher cardiovascular risk.

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