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Potassium homoeostasis and pathophysiology of hyperkalaemia

Keld Per Kjeldsen1,2,3* and Thomas Andersen Schmidt2,4

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

KEYWORDS
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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...
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%). The occurrence varies a lot between studies, mainly due to different study settings. 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.

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 reduction during exercise and/or extremely rapid lowering of 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.

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 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.

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.

Pathophysiology of hyperkalaemia

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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. 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 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.

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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.
potassium level due to high affinity of the Na,K-pump for potassium cause an increase of potassium level and Na,K-pump mediated potassium uptake in skeletal muscle Na,K-pumps. Diabetes mellitus may be associated with hyperkalaemia due to lack of insulin-stimulated potassium excretion. Several cardiovascular drugs—ACE-inhibitors, AT2-inhibitors, β-blockers, 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. 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 homeostasis 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 homeostasis, 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

### Table 1: Important causes of increased potassium level

| Cause                                      |
|--------------------------------------------|
| Renal failure                              |
| Exercise                                   |
| Epilepsy                                   |
| Tissue breakdown—rhabdomyolysis, trauma, hyperthermia |
| 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.
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.

Conflict of interest: none declared.

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