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Clinical Case Study

A Brother and Sister with Fluctuating Potassium Concentrations

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CASE DESCRIPTION

A 61-year-old man was admitted to the emergency department (ED)[4] for increased potassium concentration of 6.3 mmol/L (reference interval, 3.5–5.0 mmol/L) that was ordered by the general practitioner as part of a yearly medical checkup. Physical examination did not reveal any symptoms associated with hyperkalemia. Reanalysis of potassium in a new blood sample drawn in the hospital resulted in a value of 3.7 mmol/L. Remarkably, his visit to the ED had been the third one in 3 years' time, all taking place after a yearly medical checkup during the winter season with increased potassium at each visit that was within the reference interval after reanalysis of a new blood sample drawn in the hospital. The patient was referred to an internist for further examination who ordered a potassium analysis 1 month after the last visit to the ED. Again, an increased concentration was noticed (6.6 mmol/L) followed by admission to the emergency room. Reanalysis of potassium in the hospital again showed a healthy potassium concentration (3.6 mmol/L). The patient did not use any medication. On his visit to the internist, he mentioned that 1 year ago his sister was also admitted to the ED for an increased potassium concentration (7.9 mmol/L) that could not be confirmed in a newly drawn blood sample.

QUESTIONS TO CONSIDER

1. What are possible causes of discrepant potassium results?
2. What is the differential diagnosis of hyperkalemia?
3. Which erythrocyte enzyme deficiencies can result in hemolysis?

DISCUSSION

LABORATORY INVESTIGATION

The hemolysis index (H-index) of the previously analyzed samples did not reveal hemolysis as an explanation for the potassium increase. The H-index ranged from 4–11 μmol/L, corresponding to a hemoglobin concentration of 6.4–17.7 mg/dL. We did notice that all samples with increased potassium concentrations were drawn in a phlebotomy service center operated by our laboratory between 8 and 9 a.m. and that samples arrived at the central laboratory at 12 p.m. The samples were collected in lithium heparin gel tubes and were centrifuged after arriving at the central laboratory. On these occasions, the minimum outside temperature varied between 1.1 °C and 6.1 °C (34–43 °F). Although an in vitro increase of >2 mmol/L of potassium is large, cold-induced potassium leakage from erythrocytes was suspected. To further investigate any role of low temperature and transport time, we asked the patient to visit the central laboratory for a new blood sample. Together with whole blood samples (collected in lithium heparin tubes) from 4 volunteers, the patient's blood was incubated at different temperatures. Control blood samples showed a steady increase in potassium concentration over time when incubated at ≤15 °C (59 °F) (Fig. 1A). However, the percentage increase in potassium concentration after 2 h was below the reference change value (RCV) of 12.9%. Surprisingly, blood samples from the patient showed an exaggerated increase in potassium concentration, with RCV being exceeded after 1-h incubation at 15 °C (59 °F; Fig. 1B). Incubation for 2 h at 6 °C (43 °F) led to an increase in potassium concentration >7 times RCV. No increase in the H-index or in lactate dehydrogenase activity was noted.

PREANALYTIC VARIABLES AND EFFECTS OF TEMPERATURE

Because a substantial false increase of potassium can result in unnecessary hospitalization and discomfort for the patient, both prevention and identification of samples with falsely increased potassium holds large benefits. Increase of potassium can be caused by specimen acquisition- or patient-related factors. Because erythrocytes contain a potassium concentration of approx-

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[4] Nonstandard abbreviations: ED, emergency department; H-index, hemolysis index; RCV, reference change value; FP, familial pseudohyperkalemia.

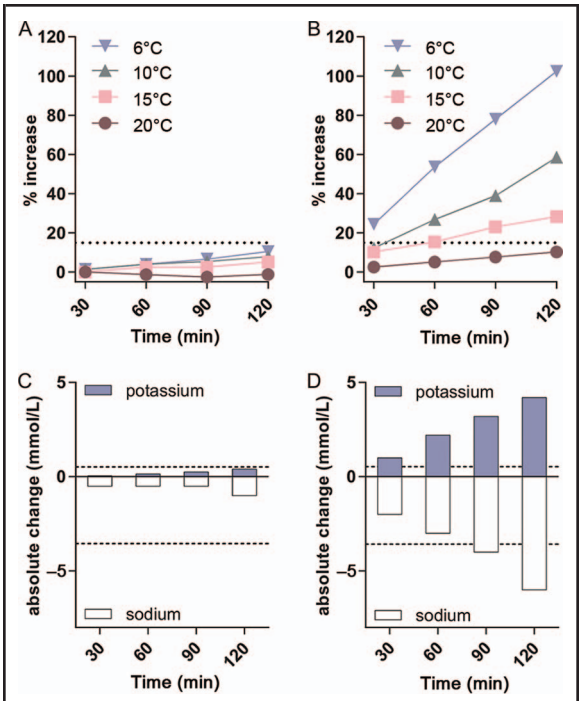

Fig. 1. Effect of temperature on plasma potassium and sodium concentration.

Blood samples were analyzed on an ABL90 FLEX (Radiometer) blood gas analyzer. (A), Whole blood samples from 4 healthy volunteers were incubated for the indicated timepoints at different temperatures. The mean % increase in potassium in 4 volunteers is plotted. (B), A blood sample from our patient was incubated for the indicated time points at different temperatures. (C), Absolute change in plasma sodium and potassium concentration measured in whole blood incubated at 6 °C (43 °F). Bars indicate the mean change measured in samples from 4 volunteers. (D), Absolute change in plasma sodium and potassium concentration measured in whole blood from our patient incubated at 6 °C (43 °F). Dashed lines indicate the RCV in either percentage (A,B) or mmol/L (C,D). The RCV (potassium 12.9%; sodium 2.6%) was calculated using laboratory imprecision data and the following values for biological variation: potassium 4.6%; sodium 0.6%.

imately 95 mmol/L *(1)*, a low degree of hemolysis will result in an increase in the plasma potassium concentration. The extended use of a tourniquet during the phlebotomy procedure can result in hemolysis and increased muscle tension during the procedure can result in an increase of plasma potassium in a hemolysis-independent manner *(2, 3)*. Patient-related factors that contribute to an in vitro increase in potassium are thrombocytosis and leukocytosis. Temperature can also affect the potassium concentration in whole blood samples. Low temperature increases the plasma potassium concentration and thereby the chance of pseudohyperkalemia *(4)*. However, not all whole blood samples seem equally susceptible to low temperature, suggesting an underlying genetic cause that could affect ion transport or passive ion leakage from the erythrocyte.

THE Na+/K+-ATPASE PUMP, LOW TEMPERATURE AND ION LEAKAGE

Ion pumps requiring ATP (Na^+/K^+-ATPase, Ca^{2+}-ATPase) maintain electrochemical gradients necessary for secondary transport processes, cellular homeostasis, and the generation of action potentials along nerves. The Na^+/K^+-ATPase, also present in erythrocytes, cycles between 2 conformations: one conformation binds 3 Na^+ ions on the inside of the plasma membrane, whereas the other conformation binds 2 K^+ ions outside the cell per molecule of ATP hydrolyzed. In this way the antiporter generates a Na^+/K^+-gradient *(5)*. The main cause for cold-reduced activity of the human Na^+/K^+-ATPase in erythrocytes seems to be a reduced affinity for ATP *(6)*, disrupting the normal Na^+/K^+-gradient by sustained ion flux through cation channels. Equilibration of the Na^+/K^+-gradient was also evident in our patient. Although 3 control samples did not exceed the RCV for sodium (2.6%) and potassium (12.9%) at 6 °C (43 °F; Fig. 1C), samples from our patient showed an extracellular increase of potassium and a concomitant decrease of extracellular sodium both exceeding the RCV over time (Fig. 1D).

GENETIC FACTORS AND PSEUDOHYPERKALEMIA

A genetically inherited condition that results in increased loss of potassium from red blood cells at reduced temperature is known as familial pseudohyperkalemia (FP). Depending on time and temperature, the potassium concentration in blood samples from patients with FP will steadily increase to concentrations above 7 mmol/L *(7)*. These red blood cells do not show hemolysis and the red blood cell trait is asymptomatic. A small number of cases of FP have been described with their own characteristic temperature-dependent profile of potassium loss *(8)*. Severe potassium leakage at low temperature, as described here, coincides with FP, for which mutations in the *ABCB6* [ATP binding cassette subfamily B member 6 (Langereis blood group)] gene, encoding an ATP-binding cassette transporter, have been identified *(9)*. The frequency of 1 specific dominant missense mutation in the *ABCB6* gene (c.2168G>A; p.Arg723Gln) in the European population has been estimated at 1:500 *(10)*. However, the exact role of mutations in *ABCB6* in relation to cation leakage is currently unknown.

POINTS TO REMEMBER

- Temperature and transport time can considerably influence the plasma potassium concentration in whole blood samples.
- A mutation in the *ABCB6* gene is relatively common in Europe and is associated with increased in vitro potassium leakage from erythrocytes at low temperature.
- Transport of unprocessed blood samples from patients with FP should ideally be performed at 20 °C (68 °F) for no longer than 2 h to prevent a substantial increase in plasma potassium concentration.

PREVENTION OF PSEUDOHYPERKALEMIA

To prevent pseudohypo- or hyperkalemia, blood samples collected in heparin gel tubes should be centrifuged within a reasonable amount of time or, alternatively, room temperature should be sustained during transport to the central laboratory. A study by Esther et al. showed that storage and transport of unprocessed blood samples is safe for prolonged periods of time when the ambient temperature lies between 20 °C and 25 °C (68 °F–77 °F) and samples are centrifuged and analyzed within 5 h *(11)*. Considering our patient with FP, whole blood stored at 20 °C (68 °F) for 2 h showed a small clinically nonsignificant increase in potassium concentration, suggesting that transport times up to 2 h should be safe for blood samples from patients with FP.

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Commentary

Mitchell G. Scott*

Drs. Vos, Bouwhuis, and Dikkeschei describe a very interesting patient with "bouncing" plasma potassium (K) concentrations. It is unfortunate for the patient, as well as his sister, that the spuriously increased K results led to multiple emergency department visits during which the high K values could not be replicated. The authors speculate that these variably high K values are because of a genetically inherited condition known as familial pseudohyperkalemia. Their

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