Review Article

Errors in Potassium Measurement: A Laboratory Perspective for the Clinician

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Abstract

Errors in potassium measurement can cause pseudohyperkalemia, where serum potassium is falsely elevated. Usually, these are recognized either by the laboratory or the clinician. However, the same factors that cause pseudohyperkalemia can mask hypokalemia by pushing measured values into the reference interval. These cases require a high-index of suspicion by the clinician as they cannot be easily identified in the laboratory. This article discusses the causes and mechanisms of spuriously elevated potassium, and current recommendations to minimize those factors. "Reverse" pseudohyperkalemia and the role of correction factors are also discussed. Relevant articles were identified by a literature search performed on PubMed using the terms "pseudohyperkalemia," "reverse pseudohyperkalemia," "factitious hyperkalemia," "spurious hyperkalemia," and "masked hypokalemia."

Keywords: Factitious hyperkalemia, Hemolysis, Potassium, Pseudohyperkalemia, Reverse pseudohyperkalemia, Spurious hyperkalemia

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Introduction

It has been estimated that 60-70% of clinical decisions are based on laboratory results and potassium is among the ten most commonly tested analytes.[1] About 4-32% of all laboratory errors occur during the analytical phase of testing the sample. The majority of errors (32-75%) occur before the sample is analyzed: During labeling, collection, transport or centrifugation.[2] The rest of the errors occur during report generation or interpretation. This article discusses the causes and mechanisms of spuriously elevated potassium, and current recommendations to minimize those factors. Masked hypokalemia, reverse pseudohyperkalemia and the role of correction factors are also discussed.

Measurement of Potassium

Potassium is usually measured using an Ion-selective electrode (ISE), which converts the activity (or effective concentration) of the ion dissolved in solution into an electric potential measured by a voltmeter. Both plasma and serum can be used to measure potassium. Samples can be collected in plain silicone coated glass/plastic tubes, gel separator tubes with or without clot activator for serum estimations (with thrombin-based clot activator for stat estimations) or in tubes containing lithium/sodium/ammonium heparin as an anticoagulant for plasma estimations with or without gel separator. Platelets release potassium during the clotting process, resulting in higher (0.36 ± 0.18 mmol/L) potassium concentrations in the serum as compared to plasma.[3] Pseudohyperkalemia is suspected when the laboratory value of the measured potassium is high but the patient does not manifest signs of hyperkalemia such as abnormal electrocardiogram. Some authors have tried to define pseudohyperkalemia as a difference between serum and plasma potassium concentrations of more than 0.4 mmol/L when samples remain at room temperature and are tested within an hour of collection.[4] The source of potassium is usually cells but can be contaminants. Since 98% of body potassium is intracellular, a small release of potassium can significantly affect the concentration of measured (extracellular) potassium. The ratio between intracellular and extracellular potassium is approximately 40:1 and a change in the ratio as small as 2.5% will increase the potassium concentration by 0.1 mEq/L.[5] Constituents of blood (red

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blood cells [RBC], white blood cells [WBC], platelets) and skeletal muscle release intracellular potassium either due to faulty collection techniques or disease states. The most common cause of cellular release is cell lysis, which can involve RBC (hemolysis), WBC (leukocytolysis), platelets (thrombocytolysis) or all the three (pancytolysis).

Causes of Pseudohyperkalemia

Mechanical factors

A tourniquet applied for prolonged periods of more than 1 min causes hemo concentration, altered water balance and hemolysis. Fist clenching is not recommended as it causes local release of potassium from the forearm muscle and increased blood flow.[6-8] In one study, the measured potassium in the pumping hand was 1.04 mmol/L higher compared to a simultaneously measured non-pumping hand.[6] Traumatic venipuncture or probing, inappropriate needle diameter, excessive force with syringe draws either during aspiration or transfer, increased turbulence due to diameter mismatch of catheter, tube adapter device and needle can all result in hemolysis and pseudohyperkalemia.[2,6] Cases of pseudohyperkalemia due to pneumatic tube transport/unpadded canisters have been reported, especially in disease states with fragile cell membranes such as leukemia.[9,10] Mechanical force during specimen processing such as vigorous mixing, excessive centrifugal force, prolonged fixed angle centrifugation or re-centrifugation of gel separator tubes also need to be considered.[2,6]

Chemical factors

If ethanol containing antiseptics are not allowed to dry completely before venipuncture, the solution can enter the blood stream and disrupt cell membranes.[2]

Temperature

Cold temperature inhibits the sodium potassium pump resulting in leakage of potassium. Higher temperatures initially decrease and then increase potassium concentrations, probably related to increased usage and exhaustion of glucose that generates adenosine triphosphate (ATP) for the sodium-potassium pump. Recommended temperature for specimen storage prior to testing is 15-25°C.[2] Specimens should not be stored between 2°C and 8°C, or above room temperature for more than 24 h.[2] Elevations in potassium more commonly observed in samples from doctors' offices compared to inpatient or laboratory collections, attributed to changes in temperature that the sample is exposed to during transport in winter, have been dubbed "Seasonal Pseudohyperkalemia."[11,12]

Time

Delayed processing, results in exhaustion of available glucose to generate ATP. Since ATP fuels the sodium potassium pump and maintains the gradient across the cell membrane, failure of the pump results in leakage of potassium out of the cell, resulting in pseudohyperkalemia.

Patient factors

Fear of imminent venipuncture or crying associated with hyperventilation (even for 3-6 min) is associated with acute respiratory alkalosis, which results in a significant hyperkalemic response mediated by enhanced alpha-adrenergic activity. Though the exact cellular mechanism is not known, animal models suggest a role for alpha receptor mediated activation of hepatic calcium dependent potassium channels.[13]

Thrombocytosis results in increased release of potassium during the clotting process. Sevatos, *et al*. examined platelet count and release of potassium during the clotting process and found an average increase of 0.82 mmol/L (range of platelet count: 400-1500 $\times 10^3/mm^3$). However, the increase was not proportional: There was an initial linear increase at higher levels of platelets followed by a drop, presumably caused by re-entry of potassium into RBC to maintain homeostasis.[14] The increase was more profound in thrombocytosis and mixed RBC disorders compared to pure erythrocytosis. Factitious hyperkalemia may be seen in WBC neoplasms due to increased membrane fragility and little reserve capacity for withstanding mechanical agitation or by leakage into the serum.[10] It is suspected that neoplastic WBC membranes (e.g., chronic lymphocytic leukemia) are more likely to be leaky or to be disrupted during pneumatic chute transport. Another factor is that at high-levels of leukocytosis, there is increased consumption (and thereby exhaustion) of metabolites that fuel the ATP pump.

As the spleen is a major reserve for platelets, post-splenectomy status has also been reported to be associated with pseudohyperkalemia.[15,16] In patients with chronic renal failure, pseudohyperkalemia due to co-existing myeloproliferative neoplasm was identified only when therapy failed to reduce potassium concentration.[17,18]

Familial pseudohyperkalemia is an autosomal dominant disorder characterized by abnormal passive outward leakage of potassium across the RBC membrane. It is an *in-vitro* phenomenon, occurring when blood is stored at room temperature.[19,20]

Contaminants

Potassium containing IV fluids are common contaminants as are potassium salts of tube additives.

If the recommended order of draw during phlebotomy is not maintained, carryover and back flow of potassium salts of tube additives such as ethylenediamine tetra-acetic acid (EDTA) or oxalate can elevate measured potassium. The recommended (simplified) order of draw is: Culture tubes followed by sodium citrate tubes, serum tubes (with or without clot activator/gel separator), heparin tubes, EDTA tubes, and sodium fluoride tubes.

Povidone iodine in one study has been associated with increase in measured potassium up to 1 mmol/L, the mechanism of which is unknown.[21] Contaminants can also interfere with the ion-selective electrode that measures potassium. For example, *Benzalkonium heparin,* a chemical used to coat catheters in IV-access devices to decrease thrombus formation and infections, interfered with electrodes in an older generation of instruments that measured potassium indirectly using a diluted sample.[22,23]

Miscellaneous causes

Using plasma reference ranges to interpret serum values could result in pseudohyperkalemia. Mislabeling of patient samples should be excluded.

Reverse Pseudohyperkalemia

Reverse pseudohyperkalemia is when plasma potassium is falsely high but the serum potassium is normal.[24-26] This phenomenon has been reported in samples of patients with leukemia/lymphoma. In one study, the plasma potassium concentration of a sample collected in a lithium heparin tube was 6.0 mmol/L higher than simultaneously measured serum potassium concentration.[26] The degree of increase in potassium was directly related to the amount of heparin. Potassium measured using a heparin coated syringe which contains about one-third the amount of heparin in a tube, did not cause an increase in plasma potassium. There was no evidence of hemolysis, suggesting a non-RBC source of potassium. It is postulated that neoplastic WBC membranes are especially sensitive to disruption by heparin, the anticoagulant used for plasma estimations. High values of potassium and lactate dehydrogenase (LDH) in the absence of hemolysis might indicate *in-vitro* lysis of WBC.

Masked Hypokalemia

The same factors that cause pseudohyperkalemia can mask hypokalemia by pushing the measured potassium of a hypokalemic patient into the reference interval. These cases are not easily identified as they require a high index of suspicion by the clinician.[4,27] In one study, more than a third of hypokalemic cases were missed due to hemolysis when using whole blood to estimate potassium.[28] Re-evaluation of cases of suspected hypokalemia with serum/plasma concentrations of potassium within the reference range might be indicated especially, in the setting of a high Hemolysis Index (HI). The HI is a semi-quantitative measurement of the concentration of free hemoglobin in mg/dL.

Correction Factors

Several researchers have attempted to quantify potassium release during hemolysis using indices such as the serum or plasma free hemoglobin concentration, -I), Mean Corpuscular Hemoglobin Concentration (MCHC) or HI multiplied by a constant (e.g., Corrected K^+ = Measured K^+-(HI × 0.004). Though some have found a linear relationship between potassium elevation and degree of hemolysis, others have not.[29-36] Correction factors for platelet counts have also been proposed.[37] A quantitative corrected potassium result may be unreliable as pseudohyperkalemia can be caused by the interplay of several factors that may not be measurable. However, these correction factors might have a role in estimating the likelihood of potassium being low, high or within the reference interval, in the interest of patient care, where a repeat sample would be difficult, if not impossible to obtain.[28]

Whole Blood Testing

The need for rapid accurate assessment of potassium in critically ill patients where the expected turnaround time is in the order of a few minutes has led to the use of blood gas analyzers and point of care testing using whole blood. Investigators have analyzed the interchangeability of electrolytes measured with point of care, blood gas, and central laboratory analyzers. Some have found stat measurements using whole blood to be comparable to laboratory analyzers using serum/plasma.[38,39]

Interestingly Chacko, *et al*.[40] found that while agreement between whole blood and serum was good, differences were large and clinically significant at concentrations below 3 mmol/L (whole blood measurements were up to 1 mmol/L lower compared to serum). The authors had used plastic lithium coated ABG syringes (DRIHEP A-LINE arterial blood gas collection syringe, 3.0 mL volume, 1.6 mL recommended draw Becton Dickinson Diagnostics®, Plymouth, UK) for blood gas analysis to minimize the effect of heparin flushes and also determined that their pneumatic system did not significantly alter the electrolyte values. The authors proposed electrode differences as one of the probable causes for the difference: Direct ISE (GEM 3000® ABG analyzer) for on-site assessment compared to indirect ISE in central laboratory analyzers (Olympus

AU2700 discrete chemistry analyzer, Olympus Optical Company, Ltd., Japan) which can be affected by dissolved solids such as proteins. The authors caution against over/underestimating therapeutic effect when comparing potassium concentrations from two different sample types/analyzers.

In another study, Hawkins, *et al*.[28] demonstrated that over 33% of hypokalemic cases were missed when using whole blood to determine potassium concentration. Moreover, hand disinfectants have been shown to significantly elevate potassium concentration especially when direct ion selective electrodes were used in point of care testing of whole blood samples.[41]

Conclusion

There are several factors which singly or in combination can contribute to a spurious elevation of measured potassium or mask hypokalemia by pushing the measured potassium into the reference interval. Potassium is predominantly intracellular; hence small shifts can cause large changes in the measured value. Efforts must be made to minimize these factors. In addition, clinicians must have a high-index of suspicion when the measured potassium is sharply discordant from prior readings, or when the laboratory values are not concordant with the clinical picture. If pseudohyperkalemia is suspected, the laboratory should be consulted, so that appropriate samples can be submitted and investigations performed.

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