# Investigating elevated potassium values

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One of the most frequently asked questions regarding phlebotomy is, why are the potassiums high? The answer involves a variety of factors, which can have a significant impact on the care of a patient. When an abnormally high value exists, it frequently sets off a train of investigations looking for such severe diseases as:

- renal failure;
- adrenocortical hypofunction; and
- diabetes.

A falsely elevated potassium value (pseudohyperkalemia) discovered in a pre-surgical work-up can unnecessarily delay surgery and result in additional time in the hospital. Conversely, pseudohyperkalemia can elevate an abnormally low potassium, masking a real illness such as:

- adrenocortical hyperfunction or tumor;
- renal failure (potassium-losing phase); and
- metabolic alkalosis secondary to obstructive lung disease.

*When potassium levels are falsely elevated by specimen-collection or -processing errors, patients can be subjected to medical mistakes with disastrous consequences.*

Some commonly used medications, such as those prescribed for congestive heart failure or hypertension, cause potassium loss with low potassium concentrations. Pseudohyperkalemia can mask these abnormalities by elevating the potassium value into the normal range. When elevated potassium results are not supported by other clinical findings, medical errors can be prevented by professional judgment. When pseudohyperkalemia elevates a patient with low potassium levels into the normal range, however, physicians may fail to act when action is necessary.

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Physicians question elevated potassium results when the numbers do not fit the clinical conditions. This is how we usually learn of elevated potassium problems. Pathologists, laboratory managers, and testing personnel are challenged to consider each of the known variables that can cause pseudohyperkalemia. No small task. Young's *Effects of Preanalytical Variables on Clinical Laboratory Tests* lists 59 variables that can falsely increase potassium results.[1]

## Mechanisms for pseudohyperkalemia

Several mechanisms or final pathways can cause pseudohyperkalemia:

- hemolysis;
- contribution of potassium from platelets, and red or white blood cells (RBC/WBC);
- specimen contamination;
- fist clenching;
- H+/K+ ion exchange; and
- inappropriate reference intervals.

Within each of these, however, there may be a number of pre-analytic causes that can be prevented by good laboratory technique. We discuss each mechanism with its preventable causes.

## Hemolysis

Hemolysis of red blood cells releases large amounts of potassium into the surrounding plasma. Erythrocytes contain 23 times as much potassium as the plasma. The most common causes for hemolysis are related to mechanical factors during the collection process:

***Use of a syringe with excessive suction applied to the plunger*** is by far the most common cause of hemolysis, with almost 80% of hemolyzed samples associated with use of a syringe rather than an evacuated tube for collection.[2] Nineteen percent of syringe-collected specimens were hemolyzed in one study, as compared to 3% of specimens that were collected in evacuated tubes.[3]

***Forcibly squirting the blood from a syringe into an evacuated tube*** causes shear forces on the red cell membrane, resulting in rupture of the cell.[4] Evacuated tubes should be allowed to fill slowly from the vacuum in the tube, without pressing on the syringe plunger.

***Drawing the blood through a small needle or catheter*** also ruptures red cells as they pass through either. The narrower the needle or catheter, the greater is the hemolysis.[5,6] Blood collected with a 23-gauge needle has higher potassium concentrations than blood from the same individual collected with a 19-gauge needle.[6] The hemolysis rate is inversely proportional to the diameter of the needle or catheter, with the highest hemolysis rates in 24- to 20-gauge catheters.[5]

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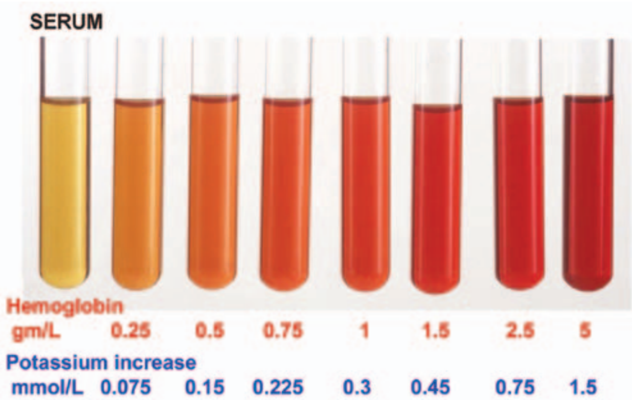
Figure 1. Hemolysis and its effect on potassium.




Hemolysis produced by adding increasing amounts of red cell hemolysate to a serum pool in a 19 X 75mm tube. The potassium increase is an average value expected. This cannot be used to correct the potassium value for hemolyzed specimens.

***Using a large-diameter needle that causes the blood to enter the evacuated tube with great force*** also can rupture red cells. Becton-Dickinson recommends using a special low-vacuum evacuated tube in this situation.

***Drawing the blood through an IV tube or catheter where the diameters of the catheter, tube adapter device, and cap-piercing needle are mismatched*** can cause turbulence of the blood, with cell rupture.

***Inverting the tube too vigorously to mix the blood with anticoagulant*** also causes turbulence.

Some authors have listed prolonged application of a tourniquet as a cause of hemolysis, or elevation of the potassium without hemolysis. Statland[7] studied the effect of tourniquet application for three minutes and found no significant change in potassium concentrations. Likewise, in Don's study of fist clenching,[8] tourniquet application for three minutes without fist clenching had no effect on the potassium.

Because the major cause for hemolysis is the use of a syringe rather than an evacuated tube system for blood drawing, it is mostly a problem in areas where blood is drawn by non-laboratory personnel, such as in emergency departments and ICUs. It tends, therefore, to be seen in clusters. It is reasonable to expect a hemolysis rate of less than 2%.[2,4]

But are we, unknowingly, likely to test a hemolyzed sample? And if it is hemolyzed, is it going to raise the potassium very much? Several studies have shown that hemolyzed serum or plasma containing 1 gram/Liter of hemoglobin will have an increase of .27 mmol/L to .33 mmol/L potassium.[9,10,11,12,13] In one study in which 100 patients were examined, the K:Hgb ratio was very variable, ranging from .20 to .35. It is not possible to correct the potassium of hemolyzed blood by applying a correction factor. Other cellular constituents, such as lactrate dehydrogenase, ALT, AST, and CK are also increased. Figure 1 relates the appearance of the hemolyzed serum to the resulting elevation of potassium.

## Contributions from platelets/WBCs/RBCs

All cells in the body contain a high concentration of potassium. During the blood-clotting and -spinning processes, platelets and WBCs can lyse or potassium can leak from cells.

***Prolonged clot-contact time***

There is a fine line between insufficient time for clotting of a serum specimen and excessive time. If the specimen is centrifuged before clotting is completed, a fibrin clot may occur that interferes with pipetting and analysis. If the serum sits on the clot too long, there can be changes in test results, including the potassium. The minimum time to form a good clot is usually 20 to 30 minutes. The maximum recommended time between collection and separation of clot and serum is two hours.[14] Clinically significant increases in potassium occur after three hours at room temperature. At elevated temperatures (32°C) the change is more complex, with a decrease due to glycolysis, followed by an increase because of potassium diffusion out of cells.[15,16,17] At refrigerated temperatures, the efflux of potassium out of the cells accelerates. Therefore, prior to centrifugation, specimens to be tested for potassium should be stored at ambient temperatures.

***Delayed processing***

Delayed processing for any reason can result in prolonged clot-contact time. One cause that is occurring with increased frequency is the use of anticoagulant drugs and aspirin that delays or prevents the formation of a good clot. Severe liver disease that results in a deficiency of clotting factors can do the same thing.

***Familial pseudohyperkalemia***

Also called the "leaky red cell syndrome," this is an inherited condition in which red blood cells, stored at room temperature, passively leak potassium through the red cell membrane. A significant increase in potassium is seen in two hours at room temperature, with a maximum increase in four hours. The condition causes no symptoms. The incidence of this condition is unknown, but it is rare.[18]

***Improper centrifugation***

This is a significant contributor to pseudohyperkalemia. When centrifuging tubes with gel barriers, follow the manufacturer's recommendation for obtaining the proper relative centrifugal force (rcf). Failure to properly calculate the speed and timing of centrifugation can result in gel failure and spurious potassium results. Fixed angle centrifuges are particularly vulnerable to inadequate rcf, and can result in the gel barrier not being uniform in thickness.

***Respinning gel-separator tubes***

Those who process specimens to be tested for potassium should avoid respinning gel-separator tubes a second time to obtain more serum or plasma if more than two hours have passed since collection. Recentrifugation combines the serum or plasma separated in a timely manner with that which has had prolonged contact with the potassium-rich red blood cells. As a result, the specimen will likely render an elevated potassium result.[19]

## Specimen contamination

Contamination of specimens can come from two sources:

- potassium introduced into the specimen; and
- a material that reacts with the ISE (ion-selective electrode) to produce a signal that is measured as potassium.

Both mechanism have been reported to erroneously increase potassium assay values.

***Order of draw***

Potassium can become falsely elevated if the individual performing the collection fills the tubes without regard for the proper order of draw.[20] If the blood from an EDTA tube, which contains

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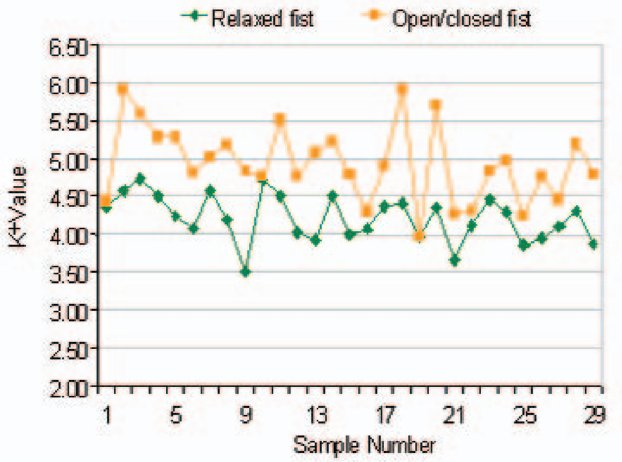
Figure 2. Relaxed fist vs. pumping (open/closed) fist study.




potassium, carries over into a tube to be tested for potassium, the carryover may spike the reported result and lead to inappropriate physician intervention or the lack of intervention when it is necessary. All specimen-collection personnel should fill tubes according to the proper order of draw as recommended by the Clinical and Laboratory Standards Institute[14], which is as follows:

- First: blood culture tubes or vials;
- Second: sodium citrate tube (e.g., blue stopper);
- Third: serum tube with or without clot activator or gel separator (e.g., red, gold, speckled stopper);
- Fourth: heparin tube (e.g., green stopper);
- Fifth: EDTA tube (e.g., lavender stopper); and
- Sixth: glycolytic inhibitor tube (e.g., gray stopper).

(***Note:*** Some facilities alter this order reflecting internal studies that support a modification. Follow your facility's policy.)

***Povidone-iodine (Betadine)*** disinfectants on the skin can sometimes cause an erroneous result. Investigators have reported a 1 mmol/L increase in potassium when a skin-puncture specimen was measured for potassium.[21] No reason for the interference has been proposed. Because of the very small likelihood of similar contamination during a venipuncture, this is probably not a problem when that technique is used.

***Benzalkonium-heparin bonded catheters*** are commonly used as intravascular-access devices in critical-care areas. This coating on the interior of a vascular catheter prevents thrombi from forming and decreases the incidence of infections. It also interacts with some — but not all — potassium and sodium ion specific electrodes. The problem appears to be related to the surfactant properties of benzalkonium chloride. Those electrodes that measure potassium in a diluted sample are affected.[22,23]

The interfering coating is eluted from the catheter surface early in its use. After 10 mL of blood has washed the surface, there is no interference with potassium assays. If the laboratory uses an ISE system that measures potassium from undiluted plasma or whole blood, there is no interference. With other ISE systems that require pre-dilution of the sample before measurement, interference can be avoided by flushing the catheter with 10 mL of blood before drawing the specimen for potassium.

## Fist clenching

One of the most common causes for elevated potassium is fist clenching or pumping before or during the venipuncture. Fist pumping has been taught to generations of medical students and phlebotomists as a means to make the veins more visible for venipuncture; however, it adversely affects the potassium.

In 1990 Don, et al,[8] presented a case that clearly demonstrated the harm that can occur if the potassium is falsely elevated. The patient was a university professor whose elevated potassium led to hospitalization with many investigations that led nowhere, because the potassium was, in fact, *not* elevated. A series of experiments were conducted that showed fist clenching was the cause for the elevated potassium. The source of the potassium is local release of muscle-cell potassium from the forearm muscles.[8] Increased potassium in the interstitial fluid of the muscles of the forearm may increase the blood flow to those muscles.

Authors Gambino and Willeford undertook some experiments to study this problem. In a pilot study, Gambino put a tourniquet on his right and left arms. The right hand was relaxed while the left hand pumped by opening and closing the hand for 15 seconds, continuing as the blood was drawn from both arms. They analyzed the heparinized plasma and found that the left (pumping) arm potassium was 1.04 mmol/L higher than the right arm blood drawn at the same time.

In the main study, to validate the effect of fist pumping on potassium values, Willeford drew specimens from 29 normal volunteers at two separate times — first, keeping their hands relaxed during phlebotomy and, second, pumping the fist during the phlebotomy procedure (see Figure 2).

*One of the most common causes for elevated potassium is fist clenching or pumping before or during the venipuncture.*

Using a paired t-test at the 99% level of significance, sufficient evidence ($p < 0.01$) showed that fist pumping generated higher potassium values versus non-fist pumping. Opening and closing the fist during collection resulted in an average increase of 17% (0.7 mmol/L) in potassium results, with a range of from 0.0 mmol/L to 1.5 mmol/L.

Armed with this information, the procedure was changed for drawing patients, eliminating any instruction to patients to clench or pump their fist during the procedure. Prior to the changes, the daily percentage of elevated (>5.3 mmol/L) potassiums was 3.68%. Since the changes have been in place, the daily percentage has held steady over the past two years at around 2.38%.

## H+/K+ exchange

***Crying and hyperventilation*** will either increase or decrease the plasma potassium, depending on its duration. Hyperventilation (including crying) for three to six minutes causes an acute alkalosis and a rapid shift of potassium ions into the plasma. It is postulated that the source of the potassium is the intestines and liver.[24] The increase in potassium during this phase averaged 1.2 mmol/L.[25] After about 30 minutes of hyperventilation, however, there is a drop in potassium, with a shift of potassium from the intracellular to extracellular space as the body attempts to buffer the respiratory alkalosis with K+ ions replacing H+ ions.

## Inappropriate reference intervals

***Use of the plasma reference intervals with a serum specimen*** will give an apparent hyperkalemia when one does not exist. Serum potassium concentration is, on the average, 0.4 mmol/L higher than that of the plasma. The difference is quite variable among individuals and is not proportional to either the platelet or white blood cell count, although these cells are probably the source of the extra potassium.[26,27,28] Because of the variability, it is not possible to apply a correction factor when converting from plasma to serum specimens. Heparinized plasma is the specimen of choice for electrolyte assays. If serum is used, the appropriate reference intervals need to be given.

*Potassium can become falsely elevated if the individual performing the collection fills the tubes without regard for the proper order of draw.*

## Best practices

Although the list of factors that can elevate the plasma potassium concentration is large, a relatively small number of them have a major effect. These are:

- fist clenching;
- migration of potassium across a thin or compromised gel barrier in the barrier tube; and
- recentrifugation of barrier tubes.

Hemolysis is often given as a cause for elevation of potassium — and it is a cause — but *in vitro* hemolysis sufficient to raise the potassium is obvious. Such tubes would be rejected. Policies and procedures that minimize problems are:

- no fist clenching;
- using double gel transport tube if tubes are transported from outside of the hospital;
- using a swing-arm centrifuge;
- holding and transporting blood specimens at room temperature;
- using 21-gauge needles or catheters;
- drawing directly into evacuated tubes;
- once blood is collected into a plastic vacuum tube, mix nine times to ensure that the clot-activator material coating the tube enters the blood sample uniformly;
- do not centrifuge before clotting is complete — usually when retraction starts; and
- centrifuge and aliquot specimens promptly.

Educate lab and non-lab personnel about reasons for K+ increases and procedures to reduce the problems. Monitor the rate of hyperkalemia. You should be able to keep the rate below 2.5%. Keep and inspect monitoring data for trends. Investigate elevated values for patterns. Following these procedures and policies should help reduce the number of false potassium readings and improve patient care. ☐

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