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Review

Pseudohyperkalemia in Serum: A New Insight into an Old Phenomenon

Nikolaos Sevastos, MD; George Theodossiades, MD; Athanasios J. Archimandritis, MD, PhD

Pseudohyperkalemia, a rise in serum potassium concentration with concurrently normal plasma potassium concentration, is an *in vitro* phenomenon that was first described 50 years ago. It was originally attributed to the release of potassium from platelets during platelet aggregation and degranulation, and a significant correlation between pseudohyperkalemia and platelet count was established. During the last decade, new data were added to this phenomenon. In particular, pseudohyperkalemia was defined when serum potassium concentration exceeded that of plasma by more than 0.4 mmol/L provided that samples are collected under strict techniques, remain at room temperature and are tested within 1 hour from blood specimen collection. Moreover, it is positively correlated to (1) thrombocytosis due to the release of potassium from platelet granules during coagulation, (2) erythrocytosis due to the dilution of the released potassium in smaller volumes of serum, and (3) the presence of activated platelets, which have the capability of aggregation at a higher speed and release more potassium during degranulation. However, pseudohyperkalemia may be "masked" when in a state of hypokalemia because potassium moves back into the intracellular space *in vitro*, and the phenomenon is ameliorated or even not detected.

Keywords: Erythrocytosis; Leucocytosis; Plasma potassium; Pseudohyperkalemia; Serum potassium; Thrombocytosis

Hyperkalemia, as measured by the marked elevation of serum potassium levels, usually occurs in renal failure, adrenal insufficiency and massive tissue breakdown such as in trauma, rhabdomyolysis, marked hemolysis and in the tumor lysis syndrome. This condition may produce alterations in cardiac excitability with significant changes in the electrocardiogram, including the induction of cardiac arrhythmias, which can cause sudden death. In such cases, an aggressive therapeutic approach is necessary.

The phenomenon of pseudohyperkalemia was first reported by Hartmann and Mellinkoff[1] in 1955 as a marked elevation of serum potassium levels in the absence of clinical evidence of electrolyte imbalance. No toxic manifestation of hyperkalemia is present and no emergency therapy is required because the elevation of serum potassium concentration does not reflect the level of plasma potassium *in vivo*. Hartmann and his colleagues[1,2] concluded that the high potassium in serum is due to leakage from platelets *in vitro* during the clotting process, and was confirmed in many studies thereafter.[3-7] However, in 1960 Nilsson et al,[8] in order to explain some of the observed cases, suggested that potassium could be released from other cellular components and assumed that the red cells might be the source. Furthermore, in 1966, Bronson et al[9] described three cases of pseudohyperkalemia in chronic myelogenous leukemia in transformation and concluded that white blood cell breakdown could cause the release of potassium during coagulation as well. This observation resulted in confusion concerning which cellular component of blood is responsible and why it is not observed in every case where an increase of this component is present.

In the mid 1980s, new data were added to this phenomenon. In particular, the lag time between blood collection and potassium determination was confined to a maximum of 30 minutes,[10,11] and a positive correlation between platelet count and serum,[11,12] but not plasma potassium concentration, was found.[10]

Reprint Requests: Nikolaos Sevastos, MD, Second Department of Internal Medicine, Hippokration General Hospital, Vas. Sophias 114, 11527 Athens, Greece, Tel: +30 210 7774742, Fax: +30 210 7706871, E-mail: nsevast@med.uoa.gr

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Table 1. Indexes Dk and Dk100 (mean value and range) in patients with increased one or more of the cellular components of blood and controls.

Clinical settings	Dk (mmol/L)	Dk 100 (mmol/L)
Thrombocytosis (n=129)	0.82 (0.01-1.90)*	0.12 (0.00-0.28)
Leucocytosis (n=29)	0.22 (0.01-0.76)†	0.20 (0.01-1.80)
Erythrocytosis (n=95)	0.39 (0.02-0.73)‡	0.15 (0.01-0.37)
Mixed type disorders (n=182)	0.82 (0.00-2.61)δ	0.15 (0.00-9.14)
Controls (n=30)	0.27 (0.02-0.42)¶	0.11 (0.02-0.21)

Dk: serum potassium concentration-plasma potassium concentration, Dk100: Dk x 100,000 /platelet count.
* vs ¶, P<0.001, † vs ¶, P=0.74, ‡ vs ¶, P<0.001, δ vs ¶, P<0.001.
* vs ‡, P<0.001, δ vs ‡, P<0.001.
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Recent Advances

In 1997, Singh et al[13] suggested that pseudohyperkalemia should only be considered when the serum potassium level exceeds that of plasma by 0.4 mmol/L, and in 2002, Fukasawa et al[14] showed that normal counts of activated platelets might also be the cause. This finding was confirmed in later studies,[15,16] where pseudohyperkalemia was attributed to the presence of activated platelets and observed in a few patients admitted to intensive care units with normal platelet counts.

Based on the above-mentioned background, we recently tried to extensively investigate the phenomenon of pseudohyperkalemia in the various conditions where it had been previously described.[17,18] The difference between serum and plasma potassium concentration (Dk) and a new index Dk100 (Dk x 100,000/platelets), which indicates what Dk corresponds to in 100,000/mm^3 of platelets, were estimated in patients with an increase in one or more of the cellular components of blood using standardized methods of blood collection, storage and testing. The index Dk100 was used because Dk values were substantially lower than expected in patients with extremely high platelet counts. Dk100 appears to be a relative estimate of the platelet contribution to pseudohyperkalemia and an attempt to normalize this contribution.

The median Dk was found to be significantly higher in the groups with platelet, erythrocyte or with mixed-type disorders than in controls. On the contrary, no significant difference was observed between controls and the group with white blood cell disorders (table 1), a finding that was in contrast to what had been previously described.[9,19-22] This may be due to the fact that in other studies no strict times-to-specimen processing were followed, and delays could have affected the results.

Moreover, a new finding that had not been previously described was the contribution of the red blood cells to the development of pseudohyperkalemia. In patients with isolated erythrocytosis, such as chronic obstructive pulmonary disease and congestive cyanotic heart disease, median Dk values were found to be higher than in controls, but lower than in those with thrombocytosis or mixed-type disorders (table 1) and, in addition, Dk was inversely correlated with hematocrit. Thus, it is reasonable to speculate that, in patients with erythrocytosis, the potassium load that exits platelets during the clotting process may be diluted in a significantly smaller volume of serum, which results in increased potassium concentration. However, in isolated erythrocytosis Dk never exceeded the value of 0.70 mmol/L that was identified as a significant independent predictor of polycythemia vera.[17]

Lastly and most importantly, Dk values were found to be significantly correlated to platelet count. In particular, among patients with isolated thrombocytosis or with mixed type disorders, Dk was usually high, ranging between 0.40 and 2.61 mmol/L, as had been previously reported (table 1).[10,23] However, there were some cases of thrombocytosis with Dk ≤0.40 mmol/L that were correlated to severe hypokalemia. In particular, in a study of serum-plasma differences in a patient with a myeloproliferative disease and

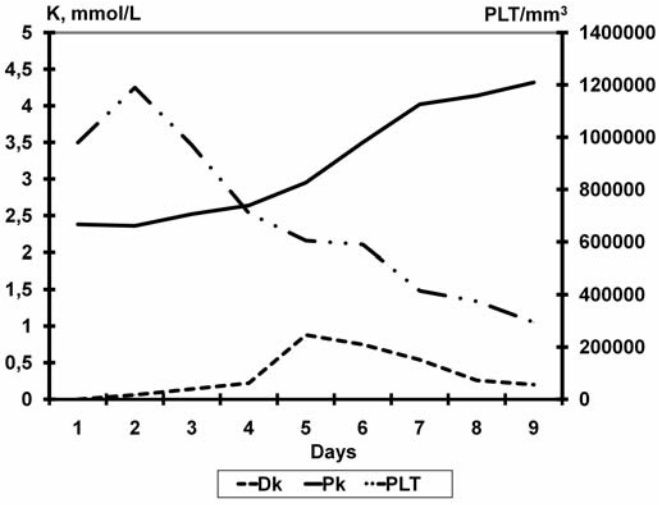

Figure 1. Changes in plasma potassium concentration (Pk) and serum potassium concentration minus plasma potassium concentration (Dk) in relation to platelet count (PLT) in a patient with thrombocytosis due to myeloproliferative disorder and severe hypokalemia due to excessive use of furosemide. The patient was treated with hydroxyurea and potassium supplements and a sudden increase of Dk was observed 5 days later, when Pk levels reached to 3 mmol/L, despite the decrease of platelet count to 500,000/mm3. Reprinted from Sevastos et al[18] (J Lab Clin Med 2006;147:139-144) with permission from Elsevier. Copyright 2006 Elsevier.

thrombocytosis, who had severe hypokalemia due to excessive use of furosemide, Dk was zero in repeated occasions. The patient was treated with hydroxyurea and potassium supplements and a sudden increase of Dk was observed 5 days later when normal potassium balance was restored despite the decrease of platelet count (figure 1).[18] This case study nicely demonstrates the value of using plasma rather than serum potassium concentration as a clinical measure.

In conclusion, pseudohyperkalemia in serum seems to be the result of two independent and sequential mechanisms: (1) degranulation of platelets, which offers a potassium load to the surrounding serum at the time of clot formation *in vitro*, and (2) transfer of a part of this potassium load back into blood cells in order to maintain electrolyte and osmotic homeostasis. The net result is that a significant amount of potassium remains in serum giving rise to the phenomenon of pseudohyperkalemia.

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Author Affiliations

Nikolaos Sevastos, MD
Second Department of Internal Medicine
National University of Athens Medical School
Athens, Greece

George Theodossiades, MD
First Regional Transfusion Center
Hippokration General Hospital
Athens, Greece

Athanasios J. Archimandritis, MD, PhD
Second Department of Internal Medicine
National University of Athens Medical School
Athens, Greece