The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–14, 2018
Published by Elsevier Inc.
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2018.04.004

Clinical Reviews

CONTROVERSIES IN MANAGEMENT OF HYPERKALEMIA

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☐ **Abstract—Background: Hyperkalemia is a common electrolyte disorder that can result in morbidity and mortality if not managed appropriately. Objectives: This review evaluates the classic treatments of hyperkalemia and discusses controversies and new medications for management. Discussion: Potassium (K+) plays a key role in determining the transmembrane potentials of "excitable membranes" present in nerve and muscle cells. K+ is the predominant intracellular cation, and clinical deterioration typically ensues when patients develop sufficiently marked elevation in extracellular fluid concentrations of K+ (hyperkalemia). Hyperkalemia is usually detected via serum clinical laboratory measurement. The most severe effect of hyperkalemia includes various cardiac dysrhythmias, which may result in cardiac arrest and death. Treatment includes measures to "stabilize" cardiac membranes, to shift K+ from extracellular to intracellular stores, and to promote K+ excretion. Calcium gluconate 10% dosed 10 mL intravenously should be provided for membrane stabilization, unless the patient is in cardiac arrest, in which case 10 mL calcium chloride is warranted. Beta-agonists and intravenous insulin should be given, and some experts recommend the use of synthetic short-acting insulins rather than regular insulin. Dextrose should also be administered, as indicated by initial and serial serum glucose measurements. Dialysis is the most efficient means to enable removal of excess K+. Loop and thiazide diuretics can also be useful. Sodium polystyrene sulfonate is not efficacious. New medications to promote gastrointestinal K+ excretion, which include patiromer and sodium zirconium cyclosilicate, hold promise. Conclusions: Hyperkalemia can be deadly, and treatment requires specific measures including membrane stabilization, cellular shift, and excretion. Published by Elsevier Inc.**

☐ **Keywords—hyperkalemia; acidosis; electrocardiogram; calcium; beta-agonist; insulin; excretion; sodium polystyrene sulfonate; patiromer; sodium zirconium cyclosilicate; diuresis; dialysis; cardiac arrest**

INTRODUCTION

Potassium (K+) is an electrolyte required to enable normal transmembrane voltage gradients and physiology. A large concentration gradient for K+ exists between intracellular and extracellular environments (1–6). This gradient enables the establishment of useful transmembrane voltage gradients and the establishment of action potentials in "excitable membranes," such as those that exist in skeletal muscle, cardiac muscle, smooth muscle, and nerve cells (1–9).

K+ levels in the body are regulated primarily by the renal system. The kidneys perform 90% of the K+ excretion, with the remaining 10% excreted through the gastrointestinal system (6–10). Normal serum K+ level ranges from 3.5–5.0 mEq/L (9–13). Changes in these levels may affect transmembrane potentials and thus, excitable membrane function in all muscle and nerve cells. The sodium-potassium-adenosine triphosphatase (Na-K-ATPase) pump located in the cell membrane maintains

This review does not reflect the views or opinions of the U.S. government, Department of Defense, U.S. Army, U.S. Air Force, or SAUSHEC EM Residency Program.

Received: 24 June 2017; Final submission received: 7 February 2018;
Accepted: 10 April 2018

the transmembrane voltage gradient, and this pump actively transports sodium out and K+ into the cell (1–4,11–13).

Hyperkalemia is common among emergency department (ED) patients and can be associated with adverse outcomes. Hyperkalemia is defined by serum K+ level > 5.5 mEq/L. Hyperkalemia can be detected in approximately 10% of patients admitted from an ED (8,9,14,15). Mild hyperkalemia includes K+ levels of 5.5–6.5 mEq/L, moderate hyperkalemia includes K+ levels of 6.5–7.5 mEq/L, and severe hyperkalemia includes K+ levels ≥ 7.5 mEq/L. However, reliance on K+ levels alone to determine the potential need for treatment is not advised (6,8,9,12–14). Severe hyperkalemia can be fatal, and rapid diagnosis and management are essential. The rate at which hyperkalemia accrued is an important variable that impacts the severity of a hyperkalemic insult to the body's physiology (6,8,9).

Literature Search Methods

Authors searched PubMed and Google Scholar for articles using the keywords "potassium," "hyperkalemia," "treatment," "acidosis," "electrocardiogram," "calcium," "beta-agonist," "insulin," "glucose," "excretion," "sodium polystyrene sulfonate," "patiromer," "sodium zirconium cyclosilicate," "diuresis," "dialysis," and "cardiac arrest." Authors decided which studies to include for this narrative review by consensus. A total of 167 articles were selected for inclusion in this review.

Etiology

Three primary classes of elevated or apparently elevated K+ levels exist. These include: 1) laboratory error or factitious hyperkalemia; 2) hyperkalemia due to transmembrane shifts, as occurs when there has been increased K+ release from cells or when there has been lysis of cells (such as occurs with conditions such as rhabdomyolysis); or 3) decreased K+ excretion (5,7–9). Hyperkalemia due to increased intake of K+ is rare and is unlikely if renal function is intact (5–9).

Factitious hyperkalemia is the most common reason that a laboratory reports an elevated K+ level and must be a consideration when assessing a patient for whom hyperkalemia seems unlikely, or in whom hyperkalemia is unexpected on clinical grounds (8,9). Factitious hyperkalemia occurs due to red cell lysis before the sample has been analyzed. Cell lysis can occur during the obtaining of blood or due to delays of processing that blood. Cell lysis during obtaining of blood can result from poor phlebotomy technique, prolonged tourniquet use, or repeated fist clenching by the patient. Fist clenching alone can increase the reported K+ concentration by 1 mmol/L (8,9,16–19). Leukocytosis, thrombocytosis, and polycythemia increase cell fragility and may also result in factitious hyperkalemia (8,16–20). Accuracy of measurement should be verified when laboratory-reported hyperkalemia is unexpected by analyzing blood obtained from a second withdrawal (21–23). However, if the patient appears to be clinically unstable and hyperkalemia has been reported by the laboratory, immediate patient assessment, with a focus on the cardiac rhythm, is indicated, even though factitious hyperkalemia remains suspected.

Increased release of K+ from cells occurs with conditions that affect the acid-base status of the body or Na-K-ATPase pump (8,9,11–13). These include alpha-adrenergic agents, beta-adrenergic blockade, toxins (digitalis, fluoride), and acidemia, which shifts hydrogen ions into cells. With acidemia, K+ fluxes from intracellular to extracellular locations to counteract the hydrogen ion cellular influx that accompanies the acidemia. This exchange allows cells to maintain a neutral pH (5–12).

Causes of decreased excretion of K+ include renal failure, effects of certain medications (angiotensin-converting enzyme inhibitors, spironolactone, nonsteroidal anti-inflammatory drugs, and succinylcholine), reduced aldosterone production as occurs in primary adrenal disease (Addison's disease), renal tubular disease, and impaired responsiveness of the distal renal tubule to aldosterone (12–14,24,25).

Decreased K+ excretion and increased K+ intake often occur concomitantly to cause an increased serum K+. However, prolonged or recurrent hyperkalemia is most commonly related to decreased excretion (12–14,24,25).

Clinical Manifestations of Hyperkalemia

A change in K+ plasma concentration can cause a variety of clinical effects including cardiac, neuromuscular, and metabolic effects. Hyperkalemia decreases the transmembrane K+ gradient. This results in cell membrane depolarization, slowing of ventricular conduction, and a decrease of the action potential duration. These changes result in electrocardiogram (ECG) manifestations including peaked T waves, widening of the QRS complex, loss of the P wave, and eventually, ventricular fibrillation, which leads ultimately to asystole (8–10,26–29). Classic changes are demonstrated in Table 1 (26–29). Peaked T waves are a result of resting membrane potential changes, which lead to early excitatory reaction. These T waves are most commonly found in the precordial leads.

These changes may not appear in step-wise fashion. For instance, Dodge et al. in 1953 found that patients may progress from normal sinus rhythm directly to ventricular fibrillation (30). The ECG in hyperkalemia may be modified by many different factors. These include the serum pH and the serum levels of catecholamines, insulin, calcium,