American Journal of Emergency Medicine 52 (2022) 85–91

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Dispelling myths and misconceptions about the treatment of acute hyperkalemia☆

Arnav A. Gupta, MD [a,*], Michael Self, MD [a,b], Matthew Mueller, DO, MPH [a,b], Gabriel Wardi, MD, MPH [a,c], Christopher Tainter, MD [a,b]

[a] Department of Emergency Medicine, University of California at San Diego, 200 W. Arbor Drive, San Diego, CA 92013, USA
[b] Division of Anesthesiology Critical Care Medicine, Department of Anesthesiology, University of California at San Diego, 200 W. Arbor Drive, San Diego, CA 92013, USA
[c] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, University of California at San Diego, 200 W. Arbor Drive, San Diego, CA 92013, USA

ARTICLE INFO

Article history:
Received 15 October 2021
Received in revised form 14 November 2021
Accepted 18 November 2021

Keywords:
Hyperkalemia
Myths
Misconceptions
Treatment
Lactated Ringer's
Calcium
EKG

ABSTRACT

Hyperkalemia represents a widespread and potentially lethal condition that affects millions of people across their lives. Despite the prevalence and severity of the condition, there are no consensus guidelines on the treatment of hyperkalemia or even a standard definition. Herein, we provide a succinct review of what we believe to be the most significant misconceptions encountered in the emergency care of hyperkalemia, examine current available literature, and discuss practical points on several modalities of hyperkalemia treatment. Additionally, we review the pathophysiology of the electrocardiographic effects of hyperkalemia and how intravenous calcium preparations can antagonize these effects. We conclude each section with recommendations to aid emergency physicians in making safe and efficacious choices for the treatment of acute hyperkalemia.

1. Introduction

Hyperkalemia is a potentially life-threatening electrolyte disturbance involved in over 800,000 Emergency Department (ED) visits each year [1]. It affects 2.6–2.7% of the population of the United States at some point in their life, and is associated with higher healthcare costs and increased mortality when correcting for other factors [2-4]. There are many misconceptions about treatment options for hyperkalemia, and as a consequence, there is significant variation in practice. A recent evaluation of ED practice patterns found that none of the 14 sites studied had defined treatment guidelines for the management of hyperkalemia, and there were 43 different combinations of treatments used overall [5]. The authors noted that a standard approach would likely improve outcomes, however, a single validated standard currently does not exist. Further complicating matters, there is not even a universal *definition* of hyperkalemia [6].

Historically, treatment approaches for acute hyperkalemia have centered around 3 concepts: "stabilizing" the cardiac depolarization threshold, shifting serum potassium intracellularly, and eliminating total body potassium. The urgency of these actions is often guided by EKG findings, since life-threatening dysrhythmias can occur across a wide range of serum potassium concentrations.

Due to the challenging nature of the prospective evaluation of a life-threatening condition, many of these well-intentioned ideas have perpetuated through generational learning, despite a paucity of evidence to support them. Here, we review some of the most significant myths and misconceptions regarding the treatment of acute hyperkalemia.

1.1. Myth #1: Kayexalate is safe and useful

Sodium polystyrene sulfonate (SPS), commonly known by the brand name Kayexalate, has long been taught as an essential part of the emergency management of hyperkalemia [7]. Sodium polystyrene sulfonate is a cation exchange resin administered orally or rectally, and works by binding potassium ions before the resin is passed from the body. On average, people consume 90 mEq of dietary potassium per day, while the colon excretes approximately 5 mEq of potassium per day. Theoretically, SPS can bind this potassium, however, there are no well-designed studies evaluating the precise location of action or quantity of potassium that is bound by SPS.

1.1.1. Efficacy

Sodium polystyrene sulfonate was approved by the Food and Drug Administration (FDA) in 1958 after the publication of a case series of

☆ This is a review article and has not previously been presented.

* Corresponding author at: Department of Emergency Medicine, University of California at San Diego, 200 W. Arbor Drive, San Diego, CA 92013, USA.
E-mail address: aagupta@health.ucsd.edu (A.A. Gupta).

https://doi.org/10.1016/j.ajem.2021.11.030

five patients that demonstrated a slight reduction in serum potassium levels in anuric patients with hyperkalemia after five days of therapy [8]. In 1961, two small trials including 42 patients were published which demonstrated lower serum potassium levels in patients receiving SPS in addition to a low- or no-potassium diet [9,10]. Importantly, these studies lacked a control group or statistical analysis, as the FDA did not require these components to bring a new drug to market until the Kefauver-Harris Drug Amendment of 1962 [11].

In the sixty years since SPS was introduced, only four randomized-controlled trials (RCTs) have been published evaluating the efficacy of SPS to reduce serum potassium levels, and only one of these showed statistically significant reduction after seven days [12-15]. During this same period, the majority of the more than twenty observational studies show a small reduction (<1 mEq/L) in serum potassium after 24 h [16]. Gruy-Kapral, et al. published an RCT in 1998 demonstrating that SPS did not significantly reduce potassium in six normokalemic patients with ESRD at twelve hours [12]. In 2014, Nasir, et al. randomized 97 adult ED patients with chronic kidney disease (CKD) and hyperkalemia to receive SPS or calcium polystyrene sulfonate (CPS), a calcium-based resin similar to SPS, and showed that these agents reduced serum potassium levels by 1.5 and 1 mEq/L, respectively, after three days [13]. However, there was no control group or statistical analysis performed. Lepage, et al. performed an RCT of 33 outpatients with CKD and mild hyperkalemia (5–5.9 mEq/L) and found that SPS reduced serum potassium by 1.04 mEq/L (95% CI -1.37 to −0.71), and was superior to placebo at seven days [14]. Finally, Nakayama, et al. randomized twenty outpatients with CKD to receive SPS or CPS and found that neither agent significantly reduced serum potassium at the end of four weeks of therapy [15].

In 2005, a Cochrane review specifically evaluated emergency management of hyperkalemia and concluded that SPS is not effective at lowering serum potassium in four hours and should not be used for acute hyperkalemia management [17]. In 2015, another Cochrane review evaluating pharmacologic agents used in acute hyperkalemia reported that high-quality studies are needed to provide a firm recommendation on the role of potassium-binding resins [18]. Finally, a third Cochrane review was performed in 2020 to assess the benefits of potassium binders for chronic hyperkalemia in patients with chronic kidney disease and again found a lack of high-quality studies to support their use in outpatients with chronic kidney disease [19]. However, the authors note that the newer potassium binders such as patiromer and sodium zirconium cyclosilicate may effectively lower serum potassium without the same risks as SPS.

1.1.2. Harm

Not only is the evidence lacking to support the use of SPS in the emergent management of hyperkalemia, but there is evidence suggesting that it can cause harm. In fact, the FDA added a warning to the package insert in 2011 highlighting the association between SPS and colonic necrosis, especially when used with sorbitol. Bowel injury has also been demonstrated in formulations without sorbitol. In a 2013 systematic review, Harel, et al. found a significant association between SPS use, with or without sorbitol, and gastrointestinal adverse events [20]. The authors identified 30 reports describing 58 cases of adverse events, most commonly intestinal necrosis, and found mortality to be 33% in these cases. A recent population-level cohort study of 20,020 individuals demonstrated a 1.9-fold higher risk of hospitalization for adverse gastrointestinal (GI) events within thirty days of initial prescription [21]. A recent observational study of SPS-naive patients with advanced CKD (CKD stage 4 or 5) in Sweden demonstrated a significant association with severe GI complications (HR 1.25, 95% CI 1.05–1.49), particularly those who received the recommended dose (HR 1.54, 95% CI 1.09–2.17), as opposed to those who were prescribed lower doses [22]. More recently, a systematic review assessing the rate of GI adverse events induced by SPS and CPS identified 135 adverse events among 41 unique articles demonstrating necrosis, ulceration, and perforation, and also showed mortality to be as high as 20.7% among patients experiencing complications [23].

Due to the lack of evidence demonstrating the utility of SPS in the acute management of hyperkalemia, a recent summary from the Kidney Disease: Improving Global Outcomes (KDIGO) conference could not provide a recommendation for using SPS in the emergent setting [24]. Furthermore, in the 2020 update to the American Heart Association guidelines for cardiopulmonary resuscitation, the use of SPS is now discouraged because of insufficient efficacy and the risk of bowel ischemia [25]. Additionally, every 15 g of SPS carries a sodium load of 1500 mg which may not be well tolerated in patients with heart failure or other conditions. In fact, in patients with volume overload, the use of SPS may be associated with further volume expansion and worsening of heart failure as it also works by exchanging potassium for sodium in the gut [26].

Sodium polystyrene sulfonate has traditionally been part of the dogma for hyperkalemia management despite the paucity of high-quality evidence. Observational trials suggest that SPS may reduce serum potassium after 24 h, but not without risk of bowel injury [27-29]. Newer resins, such as patiromer or sodium zirconium cyclosilicate, appear to be less likely to result in harm, and may be a more effective option if a potassium-binding resin is desired, although they have not been robustly studied in patients requiring emergent treatment for hyperkalemia and need further study for this indication [26].

Recommendation: Due to the potential harm and lack of efficacy, SPS should not be routinely included in the management of acute hyperkalemia.

1.2. Myth #2: Lactated Ringer's is contraindicated in hyperkalemia

Lactated Ringer's solution (LR) is a pH-balanced crystalloid solution that contains 130–131 mEq/L of sodium, 109–110 mEq/L of chloride, 4–5 mEq/L of potassium, 28–29 mEq/L lactate, and 2–3 mEq/L of calcium. In contrast, 0.9% sodium chloride, or “normal saline” (NS), a pH-unbalanced crystalloid solution, contains 154 mEq/L of both sodium and chloride. It has never definitively been shown that LR causes or worsens hyperkalemia, yet it is often avoided in patients with hyperkalemia for the concern that there is a small amount of potassium contained in LR, whereas 0.9% sodium chloride contains none. Importantly, two recent, large randomized control trials comparing pH-balanced crystalloids against NS in non-critically ill and critically ill patients showed no significant difference in serum potassium several days after admission [30,31]. Additionally, in hyperkalemic patients, the serum concentration of potassium is by definition higher than the potassium concentration of LR. Because the volume of distribution of potassium is greater than the extracellular fluid volume, the administration of LR, which has a near-normal potassium concentration, will have almost no effect on serum potassium level [32].

Furthermore, there are metabolic reasons why LR may be a superior resuscitation fluid when compared to NS in some hyperkalemic patients. Scheingraber, et al. demonstrated that NS administration is reliably associated with a hyperchloremic metabolic acidosis in operative procedures of even moderate length [33]. More recent studies by O'Malley, et al. and Modi, et al. reproduced this finding in renal transplant patients, and showed that NS was associated with greater incidence of increased potassium concentration compared to LR [34,35]. Theoretically, increased extracellular chloride forces bicarbonate intracellularly to maintain ionic balance. This reduces available bicarbonate for buffering the blood, leading to non-anion gap metabolic acidosis, which has been shown to exacerbate hyperkalemia [36]. It is also accepted that metabolic acidosis causes shifting of potassium from the intracellular space to the extracellular space. Therefore, LR appears to have lower risk of causing a clinically significant shift of potassium into the serum from within the intracellular space.

Recently, Toporek, et al. conducted a secondary analysis of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) to investigate

the effect of fluid composition on the incidence of hyperkalemia and renal replacement therapy (RRT) in critically ill patients. The analysis revealed that the use of balanced crystalloids was not associated with a significant increase in the incidence of severe hyperkalemia compared with saline. In fact, the balanced crystalloid group had a significantly lower incidence of RRT among patients with hyperkalemia and among patients with acute kidney Injury compared to those who received NS. The authors concluded that the acid-base altering effect of NS are more disruptive to potassium balance than the small quantity of potassium found in balanced crystalloids such as LR [37].

Recommendation: Lactated Ringer's solution is safe and appropriate for use in patients with hyperkalemia.

1.3. Hyperkalemia Myth #3: the EKG changes from hyperkalemia are predictable and reliable

1.3.1. EKG Changes Associated With Hyperkalemia

Early studies of hyperkalemia in canine experimental models showed a predictable progression in EKG changes with increasing potassium concentrations, however, in clinical practice, a wide range of effects may be observed [38,39]. Appendix 1 provides a brief review of the pathophysiology of hyperkalemia. Classically, the first evidence of hyperkalemia on EKG is a peaked, narrow-based T-wave, which occurs when the serum potassium concentration is approximately 5.5 mEq/L. This is likely caused by an increase in cardiac myocyte excitability and a shortening of the repolarization phase of the action potential [40]. At a serum potassium of approximately 6.5 mEq/L, the further decrease in the resting membrane potential causes a delay in the action potential, causing PR-segment prolongation, followed by QRS widening [41]. Bradycardia may occur as SA node automaticity is blunted. As the intraventricular conduction delay progresses, bundle-branch-block-like QRS morphologies may be seen. As potassium concentrations reach 8.0–9.0 mEq/L, the p-wave may be flattened or lost as the amplitude of the action potential further decreases [40]. At potassium concentrations greater than 10 mEq/L, SA node function is lost and a junctional rhythm occurs, with eventual progression to a sine wave-like morphology as the QRS and T- waves approach each other. This ultimately results in ventricular fibrillation, pulseless electrical activity (PEA), or asystole [40,42,43]. Other EKG abnormalities have been reported, including early PR and QT shortening, ST-segment elevation that may mimic myocardial infarction, and atrioventricular and fascicular conduction blocks [41]. Fig. 1 provides illustrative examples of the changes in the EKG due to hyperkalemia.

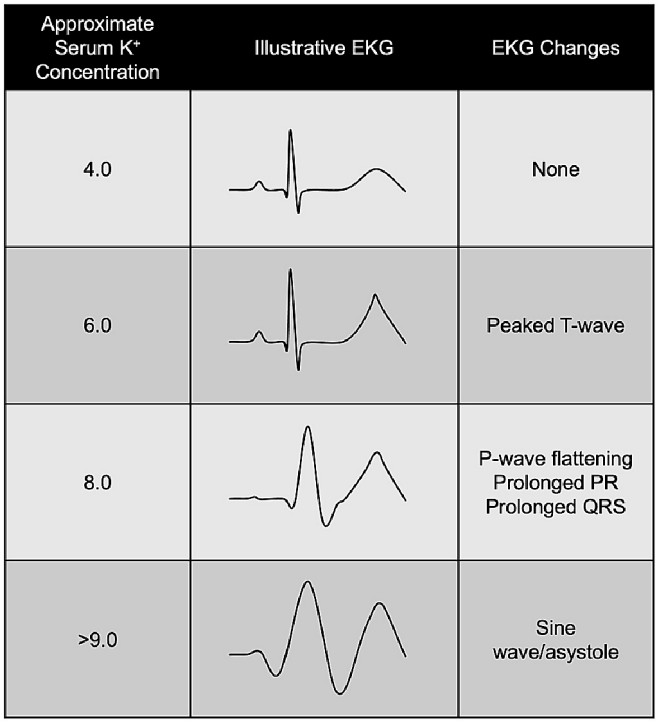


Fig. 1. EKG changes which may be observed with hyperkalemia.

1.3.2. A Normal EKG Does Not Exclude Hyperkalemia

Unfortunately, the orderly progression of hyperkalemic EKG changes described in experimental models does not equate to a predictable pattern in clinical practice. Multiple case series have illustrated patients with severe hyperkalemia (≥ 8.0 mEq/L) without any of the classic EKG findings. Szerlip, et al. described two patients with serum potassium concentration > 9.0 mEq/L with initial EKG's only notable for non-specific T-wave changes [44]. Two similar case reports noted T-wave inversions in the precordial leads as the only EKG abnormalities, despite serum potassium concentrations of greater than 10.0 mEq/L. In both cases, the T-wave inversions resolved after treatment of hyperkalemia [45,46]. Martinez-Vea, et al. expanded on this with a series of 7 cases, all with a potassium ≥8.0 mEq/L, with various non-specific EKG changes [47]. In addition, EKG abnormalities may vary dramatically over a very short period of time [48]. The majority of these cases occurred in critically ill patients with multiple co-morbidities and concomitant severe metabolic abnormalities, which may suggest that EKG manifestations of hyperkalemia are not only due to serum potassium level. It has been suggested that the rapidity of onset, serum pH, underlying electrocardiographic abnormalities, medications and other factors are critical in determining the clinical effect of hyperkalemia on cardiac conduction [43]. Unfortunately, these effects are exceedingly difficult to predict.

Larger studies have repeated the results of these case series. A retrospective cohort study of 220 episodes of hyperkalemia found “typical” EKG changes in only 43% of cases with potassium concentration ≥ 6 mEq/L, and in only 55% of cases with potassium concentrations >6.8 mEq/L. [49] Similarly, in a retrospective study of 90 inpatients with hyperkalemia, Montague, et al. observed EKG changes in 52% of cases and peaked T-waves in 32% of cases. Only 39% of patients with a potassium concentration ≥ 7.2 mEq/L were found to have EKG changes [50]. Fordjour, et al. prospectively evaluated 154 episodes of hyperkalemia in inpatients and found that only 50% of patients with K ≥6.5 mEq/L had EKG changes. Recorded abnormalities included peaked T-waves in 28% and conduction abnormalities including 1st degree AV block and prolonged QRS in 8 and 9% of patients, respectively. Interestingly, they reported patients with conduction abnormalities had a lower average potassium concentration than those with peaked T-waves, contrary to classic teaching [51].

In a retrospective study of 175 ED visits with a median potassium concentration of 6.5 mEq/L, Freeman, et al. found that the initial EKG was interpreted as abnormal in 83% of cases. Approximately one third of these abnormalities were peaked T-waves and one third were non-specific ST-abnormalities. In the authors retrospective EKG analysis 50% of EKGs were interpreted as having any abnormality consistent with hyperkalemia, 24% were noted to have nonspecific ST abnormalities, and 17% were found to be normal [52]. Wrenn, et al. reported that EKG has a sensitivity of 0.34–0.43 and a specificity of 0.85–0.85 for hyperkalemia. The sensitivity increased to 0.55–0.62 for patients with serum potassium greater than 6.5 mEq/L. [53] A more recent trial reported a sensitivity and specificity of 0.19 and 0.97, respectively, for EKGs read by emergency physicians in a cohort of patients with moderate to severe hyperkalemia, with a positive predictive value of 0.92 and negative predictive value of 0.46. When restricted to severe hyperkalemia, the sensitivity increased to 0.29 while the specificity decreased marginally to 0.94 [54].

1.3.3. EKG Changes may help predict adverse outcomes in hyperkalemia

While the EKG may not reliably predict hyperkalemia, the available evidence suggests that EKG changes may predict adverse outcomes from hyperkalemia, such as symptomatic bradycardia, ventricular dysrhythmia, cardiac arrest, or death. In the case series cited above, none of the patients with normal EKGs had severe adverse events [44-47].

In 2017, Durfey, et al. published a study evaluating the association between EKG findings and short-term adverse events in ED patients with hyperkalemia [55]. In 188 patients with a mean serum potassium concentration of 7.1 mEq/L, they found 71% of patients had any EKG abnormality suggestive of hyperkalemia, and 15% of patients had an adverse event, most commonly symptomatic bradycardia (12%). No patients with an adverse event had a normal EKG. The most frequent EKG findings in patients with adverse events were QRS prolongation (79%) and HR < 50 (61%), and multiple EKG abnormalities were found in 86%. Only 26% of patients with adverse events had peaked T-waves. Although well-performed, this relatively small, retrospective, single-center study is the only one to directly evaluate whether the EKG can predict adverse outcomes due to hyperkalemia.

Altogether, the available evidence indicates that while a normal EKG does not exclude hyperkalemia, it does confer a much lower risk of adverse events, and an EKG with conduction delays may help identify patients at high risk of life-threatening cardiac toxicity. However, given a lack of studies evaluating whether the EKG can predict adverse outcomes due to hyperkalemia, there may still be cases where a normal EKG rapidly progresses to life threatening conduction delays. Since the EKG is often available prior to laboratory values and adverse events frequently occur prior to laboratory identification of hyperkalemia, it remains an important tool in guiding empiric treatment of severe hyperkalemia in the critically ill patient [55]. Hyperkalemic patients with isolated T-wave abnormalities are overall at low risk of a serious adverse event, while patients with conduction abnormalities and other more severe electrocardiographic abnormalities deserve close monitoring and rapid treatment.

Recommendation: A normal EKG does not exclude hyperkalemia, however it is associated with a decreased likelihood of serious adverse events.

1.4. Myth #4: all patients with hyperkalemia should be treated with calcium

Intravenous calcium was first described as a treatment for hyperkalemia-related dysrhythmias in 1950 by Merrill, et al. This was later replicated in a small case series by Chamberlain, et al. in 1964, and since then, intravenous calcium has remained one of the cornerstones of acute hyperkalemia treatment [56,57]. It is suggested that increasing serum calcium concentration "stabilizes" the myocytes by increasing the depolarization threshold (making them less "excitable"). A more detailed review of the effect of calcium on antagonizing the electrochemical effects of hyperkalemia can be found in Appendix 2.

Despite being a mainstay in acute hyperkalemia treatment, intravenous calcium administration is not without risk. Calcium salts may cause soft tissue injuries if extravasation occurs. Although injury can occur with either preparation, the severity of soft tissue injury appears to be correlated with the concentration of calcium [58-60]. Historical case series suggest that calcium administration may exacerbate digoxin toxicity. Although more recent evidence has cast doubt on this association, extra care should be taken when treating patients with suspected digoxin toxicity with infusion rates decreased [61,62]. Given that administration of IV calcium is not without risk, care should be taken to reserve its use for patients who are at high risk for cardiac complications of hyperkalemia.

No RCTs have compared the efficacy or safety of calcium chloride to calcium gluconate for treatment of hyperkalemia. Several sources cite decreased risk for soft tissue injury as justification to use calcium gluconate as a first line agent, with calcium chloride reserved for patients in cardiac arrest [26]. However, as calcium gluconate typically comes in 10 mL doses of 10% solution, 2 to 3 sequential doses are needed to reach an equivalent dosing of 1 g calcium chloride. The ideal infusion times of calcium preparations have not been studied. In cases of hemodynamic instability, severe conduction delays or cardiac arrest, rapid intravenous push of calcium chloride is indicated as it is generally more readily available and may be more rapidly administered than calcium gluconate. However, over-zealous administration of calcium preparations may cause flushing, bradycardia, nausea or vomiting, or transient changes in blood pressure. Thus, it is reasonable to infuse calcium over 5 min in the absence of hemodynamic instability or cardiac arrest [63]. In the absence of hemodynamic instability or cardiac arrest, it is reasonable to use calcium gluconate as there is less risk of tissue necrosis should the medication extravasate compared to calcium chloride. Additionally, studies have found no difference in the rate or value of serum ionized calcium concentration rise when administering equivalent doses of either formulation [64,65].

1.4.1. Clinical use

Despite many professional guidelines, reviews and recommendations, there is no high-quality evidence about which hyperkalemic patients benefit from the administration of intravenous calcium [26,61,63]. There is general consensus that calcium is indicated for patients with evidence of conduction delays or dysrhythmias typical of hyperkalemia on EKG, even if the potassium concentration is unknown [26,61-63,66]. Significant EKG changes place patients at much higher risk for serious adverse events and these events often occur prior to laboratory reporting of potassium concentration [55]. There is also consensus that calcium is indicated for patients in cardiac arrest with electrocardiographic evidence of hyperkalemia, even in the absence of laboratory evidence [26,61-63,66,67]. Similarly, there is consensus that patients with mild hyperkalemia (<6.0–6.5 mEq/L) without EKG changes should *not* be treated with calcium [26,61-63,65,66].

However, there is no consensus on whether calcium is indicated in severe hyperkalemia (>6.0–6.5 mEq/L) *without* EKG changes or with isolated peaked T-waves [26,61-63,66]. Patients without conduction delays are at lower risk for hyperkalemia-induced adverse events, and because calcium infusion has some potential for harm, it is reasonable to withhold calcium in the absence of EKG changes [50,55,58-60,68]. Although peaked T-waves alone are not associated with significant adverse events, the rapidity of decompensation to conduction delays is unknown, likely multifactorial, and highly variable from patient to patient [48,50,52,65]. Without high quality evidence, it is up to the clinician to use their best judgement on a case-by-case basis. In either of these scenarios, the decision to treat with calcium should not delay initiation of other treatments to lower the serum potassium concentration. Table 1 summarizes current guidelines for the use of calcium in hyperkalemia.

Recommendation: Treatment with intravenous calcium is indicated only for patients with hyperkalemia manifesting EKG changes.

2. Conclusion

Hyperkalemia is a common and potentially life-threatening electrolyte abnormality. Misconceptions and controversies about its management have led to conflicting management strategies. Here, we have addressed four of the most prevalent - and we believe the most significant - of these myths, and provided recommendations based upon the interpretation of available evidence. We recommend that clinicians continue to evaluate the available evidence and make management decisions based on the balance between the potential benefit and harm of each of these interventions.

Table 1
Recommendations for calcium treatment in hyperkalemia

Serum K+ Concentration	Clinical Scenario	EKG Findings	Recommendation
> 5.4 mEq/L	Any	Conduction abnormality or dysrhythmia concerning for hyperkalemia	Calcium chloride—10% 5 to 10 mL IV over 2 to 5 minutes
> 5.4 mEq/L	Unstable	Any / None	Calcium chloride—10% 5 to 10 mL IV over 2 to 5 minutes
> 5.4 mEq/L OR unknown	Cardiac arrest with risk factors for hyperkalemia	Any / ECG Unavailable	Calcium chloride—10% 5 to 10 mL IV over 2 to 5 minutes
Severe (>6.0 ~ 6.5 mEq/L)	Stable	None	Variable
> 5.4 mEq/L	Stable	Isolated peaked T-wave	Variable
Mild (< 6.0 ~ 6.5 mEq/L)	Stable	None	Do NOT treat with calcium

The Renal Association, European Resuscitation Council, American Heart Association [61,63,66].

Author contributions

Dr. Wardi and Dr. Tainter conceived the idea. Dr. Gupta, Dr. Self, Dr. Mueller, Dr. Wardi, and Dr. Tainter all contributed to drafting the manuscript and critical revisions. Dr. Gupta assumes responsibility of the article as a whole.

Declaration of Competing Interest

Dr. Wardi has received funding from the National Institute of Health and the Gordon and Betty Moore Foundation, although unrelated to this work. The remaining authors have no conflicts of interest to disclose.

Acknowledgements

No grant or other financial support was used in the creation of this manuscript.

Appendix A. Appendix 1

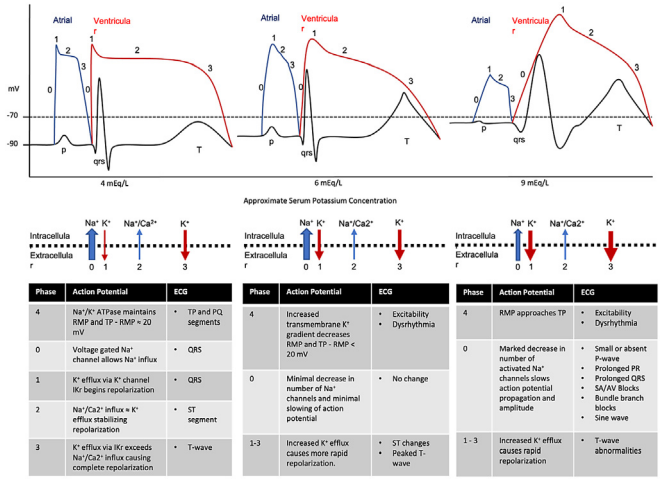
A.1. A brief review of potassium physiology and the effect of hyperkalemia on the EKG tracing

Potassium (K^+) is an essential monovalent cation in human physiology. It is the primary intracellular cation, with 98% of total body potassium content maintained within the cell and only 2% in the extracellular space. Total body potassium stores are approximately 3500 milliequivalents (mEq) in a healthy adult, with a normal serum concentration of 3.5–5.0 milliequivalents per liter (mEq/L) and an intracellular concentration of around 150 mEq/L. [7]

Potassium homeostasis is tightly regulated by both extracellular and intracellular systems. Despite the fact that the total daily intake of potassium may exceed the total extracellular content, the daily change in serum potassium content is typically no more than 10% [69]. Such careful control is maintained through both extracellular and intracellular mechanisms. Potassium is primarily (80–90%) excreted through the kidneys, with small amounts stored in the liver and skeletal muscle [69]. Within the nephron, potassium passes freely through the glomerulus and is then reabsorbed, first in the proximal convoluted tubule and then again in the ascending limb of the loop of Henle. In the distal convoluted tubule, potassium is then secreted into the urine in exchange for the reabsorption of sodium. An intricate balance of negative and positive feedback loops involving the renin-angiotensin-aldosterone system, hypothalamic-pituitary-adrenal axis, and other systems rapidly manipulates renal and gastrointestinal potassium excretion and resorption as well as the release of potassium storage from hepatic and skeletal muscle storage sites to maintain extracellular homeostasis [69,70].

On a cellular level, a large concentration gradient exists between intracellular and extracellular potassium. The significant electrochemical potential of this gradient is maintained by the sodium-potassium adenosine triphosphatase pump (Na/K ATPase), which expends the potential energy within adenosine triphosphate to move potassium into the cell against the electrochemical potential in exchange for sodium (Na^+). The Na^+/K^+ ATPase works in conjunction with potassium leak channels, which allows for potassium to move out of the cell down its concentration gradient. The electrochemical potential created by this gradient is crucial in maintaining the resting membrane potential (RMP) of approximately −90 mV in cardiac myocytes [69,70]. Fig. 2 provides an overview of how hyperkalemia influences various ion channels and the EKG tracing.

The left panel illustrates the baseline EKG tracing and ion flow during the various phases of the action potential in a normokalemic patient. It also describes ion flow during each phase of the action potential and what segments of the EKG tracing correspond with each phase. The middle and right panels illustrate how rising levels of serum potassium concentration influence the EKG tracing and action potential ion flow. They also describe the subsequent effects on the action potential phases and the EKG tracing derangements associated with increasing levels of serum potassium. Moderate hyperkalemia decreases the magnitude of the transmembrane potassium concentration gradient,



Phase	Action Potential	ECG
4	Na^+/K^+ ATPase maintains RMP and TP - RMP ≈ 20 mV	• TP and PQ segments
0	Voltage gated Na^+ channel allows Na^+ influx	• QRS
1	K^+ efflux via K^+ channel IKr begins repolarization	• QRS
2	Na^+/Ca^{2+} influx ≈ K^+ efflux stabilizing repolarization	• ST segment
3	K^+ efflux via IKr exceeds Na^+/Ca^{2+} influx causing complete repolarization	• T-wave

Phase	Action Potential	ECG
4	Increased transmembrane K^+ gradient decreases RMP and TP - RMP < 20 mV	• Excitability • Dysrhythmia
0	Minimal decrease in number of Na^+ channels and minimal slowing of action potential	• No change
1-3	Increased K^+ efflux causes more rapid repolarization.	• ST changes • Peaked T-wave

Phase	Action Potential	ECG
4	RMP approaches TP	• Excitability • Dysrhythmia
0	Marked decrease in number of activated Na^+ channels slows action potential propagation and amplitude	• Small or absent P-wave • Prolonged PR • Prolonged QRS • SA/AV Blocks • Bundle branch blocks • Sine wave
1 - 3	Increased K^+ efflux causes rapid repolarization	• T-wave abnormalities

Fig. 2. Effect of hyperkalemia on the cardiac action potential and the EKG tracing.

slowing potassium efflux, and raising the resting membrane potential (RMP) of cardiac myocytes, causing them to be less electronegative [40,41]. Initially, the decreased resting membrane potential moves closer to the threshold potential (TP), causing increased myocyte excitability [41]. However, as the extracellular potassium concentration continues to rise, the increased resting membrane potential reduces the number of voltage-gated sodium channels activated during phase 0 of the cardiac action potential, leading to a slower action potential and prolonged membrane depolarization [41]. On the EKG, these abnormalities manifest as a prolonged PR interval and QRS complex [40]. Hyperkalemia also affects phase 2 and 3 of the cardiac action potential by intensifying the outward potassium current, leading to a more rapid repolarization [41]. The shortened repolarization and previously mentioned early increase of myocyte excitability cause the characteristic peaked T- waves and ST-segment changes of hyperkalemia [40]. As serum potassium continues to climb, there is a marked decrease in the number of activated sodium channels which slows action potential propagation. Further increase of potassium reflux causes repolarization to become even more rapid. EKG findings associated with these effects are the appearance of a sine wave, prolonged PR segment, prolonged QRS, and other conduction abnormalities [37,38].

Appendix B. Appendix 2

B.1. Calcium antagonizes the electrochemical consequences of hyperkalemia

Increased extracellular calcium concentration counteracts the cardiac effects of hyperkalemia by three mechanisms [41]. 1) Increased extracellular calcium concentration shifts the threshold potential of the cardiac myocyte to a less electronegative value. As described above, hyperkalemia makes the resting membrane potential of the cardiac myocyte less electronegative [38-40]. By making the threshold potential less electronegative, calcium increases the difference between the resting and threshold potentials, decreasing cardiac myocyte excitability [41]. 2) Increased extracellular calcium concentration changes the relationship between the voltage-gated sodium channels (responsible for phase 0 of the cardiac action potential) and the membrane potential, causing a greater number of sodium channels to be active at any given potential. Recruiting more voltage-gated sodium channels increases the rate of depolarization during the cardiac action potential, returning impulse propagation back to physiologic rates [41]. 3) Increased extracellular calcium concentration increases the inward calcium current and calcium gradient across the cardiac myocyte, increasing the speed of impulse propagation during phase 2 and 3 of the cardiac action potential [41]. These mechanisms combine to cause rapid, often dramatic normalization of hyperkalemia-induced conduction delays on EKG or cardiac monitoring.

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