The True Mechanism of Calcium Treatment for Hyperkalemia: Beyond Cell Membrane Stabilization

Daniel Sámano-Nieto[1], Ariel Eduardo Jiménez-Romo[1].

[1] Faculty of Medicine, Autonomous University of San Luis Potosi, San Luis Potosí, S.L.P., Mexico.

Corresponding author: Daniel Sámano-Nieto, pricemactavish@hotmail.com
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ABSTRACT

Hyperkalemia is a potentially lethal metabolic disorder characterized by an increase in serum potassium above 5.0 mEq/L (or 5.0 mmol/L). Severe hyperkalemia can trigger fatal arrhythmias by altering cardiac electrophysiology, specifically conduction and repolarization, manifesting as electrocardiographic changes such as QRS widening and a sinusoidal wave pattern.

In Mexico, its incidence and prevalence are closely linked to highly prevalent chronic diseases such as chronic kidney disease (CKD) and diabetes mellitus, as these conditions predispose to potassium accumulation in the blood due to decreased renal excretion and the use of medications that interfere with potassium metabolism.

While managing this condition is a common challenge in critically ill patients, calcium gluconate administration has traditionally been a key intervention in the acute management of hyperkalemia. However, recent studies suggest that, contrary to the prevailing view that its mechanism of action lies in "membrane stabilization," its primary effect is to restore electrical conduction through the activation of L-type calcium channels and ephaptic coupling.

The aim of this article is to provide the reader with context and disseminate these findings in order to highlight their importance in making informed clinical decisions in this clinical scenario.

Keywords: hyperkalemia, calcium, membrane stabilization.

INTRODUCTION

Potassium in its ionic form is a fundamental element in both excitable and non-excitable cells, as it regulates and maintains the resting membrane potential, cellular homeostasis, and other metabolic functions. Approximately 2% of the body's total potassium is found in the extracellular fluid, while 98% of exchangeable potassium is located in the intracellular compartment, establishing the resting plasma membrane potential of cells.

Hyperkalemia is the elevated concentration of serum potassium, typically above 5 mmol/L. If this alteration persists or worsens, it significantly affects cardiac electrical conduction, generating a risk of serious arrhythmias that could lead to death [1] (Figure 1). This condition is closely associated with pathologies of epidemiological relevance in Mexico, such as diabetes mellitus, systemic hypertension (and its management), and chronic kidney disease (CKD), making it essential to understand it.

The main clinical manifestations of hyperkalemia include neuromuscular symptoms such as paresthesia and fasciculations in the extremities, and ascending paralysis, which can eventually progress to flaccid quadriplegia. The trunk, head, and respiratory muscles usually remain unaffected, so respiratory failure is uncommon [2].

In addition, cardiac conduction abnormalities, detailed later, are observed.

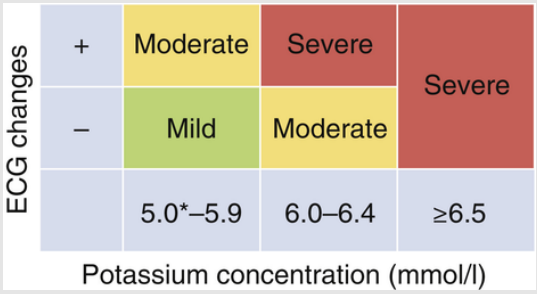


Figure 1. Classification of hyperkalemia. Consensus from the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. 2020. Adapted from: Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF, Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R; Conference Participants. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2020 Jan;97(1):42-61. doi: 10.1016/j.kint.2019.09.018. *5 or upper limit of normal.

HYPERKALEMIA AND CARDIAC ACTION POTENTIAL

The cardiac action potential (AP) differs from others (neuronal, skeletal muscle) due to the presence of a

plateau phase during repolarization and a longer overall duration, resulting from a precise interaction between ions, primarily sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) (Figure 2).

In normal cardiac muscle, the resting membrane potential (RMP) is close to -85 mV, while the depolarization threshold (DT) is close to -65 mV. Following nerve stimulation and during the so-called phase 0, the rapid influx of Na^+ promotes depolarization of the cell membrane. Repolarization then begins, divided into four phases. In phase 1, K^+ efflux begins, continuing throughout phase 2 (also called the plateau phase), during which L-type Ca^{2+} channels are activated, allowing the entry of this ion.

Its interaction with RyR receptors in the sarcoplasmic reticulum ultimately triggers the coupling of myosin and actin in muscle contraction. During phase 3, the influx of sodium and calcium ceases, and repolarization, driven by the late reentry of K^+, predominates. During phase 4, or the resting phase, the muscle returns to its resting state through the action of the Na^+/K^+ ATPase and the Na^+/Ca^{2+} type 1 exchanger (NCX1) [3, 4, 5].

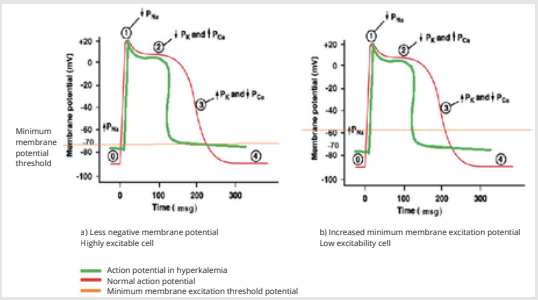


Figure 2. Effects of hyperkalemia on the cardiac action potential. Left: Initially, the cell becomes hyperexcitable as the resting membrane potential becomes more positive due to the increase in extracellular potassium, while repolarization is achieved in a shorter time. Right: As hyperkalemia becomes established, the depolarization threshold becomes less negative; this, combined with the shortening of phase 3 of repolarization, makes it more difficult for a stimulus to achieve sufficient magnitude to induce depolarization. Adapted from: Clinical Fundamentals. Potassium [Internet]. [cited January 31, 2025]. Available from: https://fundamentosclinicos.com/content/potasio

The characteristics of the cardiac action potential vary along the myocardial wall, from the endocardium, through the mid-myocardium, to the epicardium. Epicardial cells exhibit a prominent phase 1 and a shorter action potential [5].

In hyperkalemia, there is increased permeability to K^+, which makes the action potential less negative, bringing it closer to the diastolic threshold (DT) and initially facilitating conduction. However, if this persists, the DT also becomes less negative, requiring stronger stimuli to open Na+ channels in phase 0. This progressively hinders the excitability of the cardiac conduction system (Figure 2), which in turn results in arrhythmias [6].

On the ECG, this manifests as peaked T waves, flattened P waves, prolonged PR interval, widened QRS complex, and a sinusoidal wave pattern [7] (Table 1).

Approximate Serum K^+ Concentration	Illustrative EKG	EKG Changes
4.0		None
6.0		Peaked T-wave
8.0		P-wave flattening Prolonged PR Prolonged QRS
>9.0		Sine wave/asystole

Table 1. Effects of hyperkalemia on the electrocardiogram (ECG). Approximate values. Adapted from: Gupta AA, Self M, Mueller M, Wardi G, Tainter C. Dispelling myths and misconceptions about the treatment of acute hyperkalemia. Am J Emerg Med. 2022;52:85-91. Available from: https://doi.org/10.1016/j.ajem.2021.11.030.

BEYOND MEMBRANE STABILIZATION

Calcium administration in the form of calcium gluconate is one of the main measures for controlling electrophysiological alterations in cardiac muscle. However, when its mechanism of action was questioned, the answer was limited to a deduction: considering that calcium gluconate does not directly reduce serum potassium levels, its action must be related to the cell membrane, specifically the restoration of the resting membrane potential (RMP) (i.e., membrane stabilization) [7,8]. Until recently, the details of this mechanism eluded general knowledge.

Piktel *et al.* [9] suggest that the restoration of conduction velocity after calcium administration under hyperkalemic conditions is achieved without modifications to the RMP and propose some theories about its mechanism of action:

1. ***L-type calcium channels:*** The activation of these voltage-gated channels during the plateau phase and the consequent influx of calcium into the cell, facilitated by the increase in extracellular calcium levels, appears to be achieved even when the resting potential is elevated.
2. ***Ephaptic coupling:*** This physiological phenomenon, described primarily in nervous tissue (Figure 3), occurs when voltage changes during an axon's action potential induce a new action potential in a neighboring axon via local extracellular electric fields. Studies suggest that this mechanism plays an important role in facilitating and propagating the electrical impulse in cardiac tissue during rapid heart rhythms, even in tissues with poorly coupled gap junctions (poor connexin expression), acting as a "lifeline" for conduction blocks [10, 11, 12]. Calcium can reduce the space between intercellular gap junctions,

optimizing conduction and compensating for the decrease in sodium channel function, thus contributing to the restoration of cardiac conduction.

These findings challenge the conventional view that calcium stabilizes cell membranes by restoring the resting potential. Instead, its main effect lies in maintaining the efficient propagation of electrical impulses.

CLINICAL RELEVANCE

Understanding these mechanisms allows the physician in training to understand the reasoning behind the intravenous administration of calcium when electrocardiographic alterations consistent with hyperkalemia are observed, and therefore will allow them to make informed and accurate decisions in their future practice.

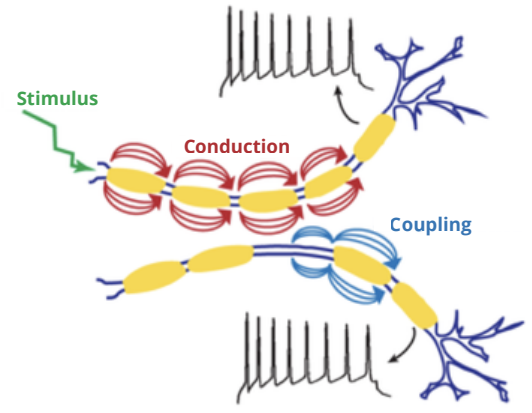


Figure 3. Ephaptic coupling (illustrative). This occurs when voltage changes during the action potential of an excitable membrane induce the firing of a new action potential in a neighboring excitable membrane. Calcium acts by reducing the physical space between membranes, facilitating this alternative mechanism of impulse propagation. *Translated from Spanish to English.* Taken from: Treviño-Frenk I. Transient symptoms in multiple sclerosis. Rev Mex Neurociencia [Internet]. 2015 [cited 2025 Jan 6];16(3):32-33. Available from: https://previous.revmexneurociencia.com/wp-content/uploads/2016/03/RevMexNeuroci-No-3-May-Jun-2015-26-38R.pdf

CONCLUSION

Intravenous calcium improves electrical conduction in severe hyperkalemia through novel mechanisms such as L-type channel activation and ephaptic coupling. This knowledge updates clinical practice by strengthening the theoretical basis for physicians' actions in managing and preventing the cardiac complications of hyperkalemia. The main limitations of the article are related to the nature of the experimental (animal) model, which could call into question the extrapolation of the results to human conditions, and to the possible interaction of calcium with other common therapies for the conditions with which it is associated, such as insulin, ion exchange resins, and others.

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Conflict of interest

The authors declare no conflicts of interest.

Ethical considerations

This work did not involve the participation of human subjects or animals, nor the collection of primary data; therefore, it did not require approval from a research ethics committee. All data used came from previously published and publicly accessible secondary sources.

REFERENCES

1. Clase, CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, Kovesdy CP, Kline GA, Lindner G, Obrador GT, Palmer BF, Cheung M, Wheeler DC, Winkelmayer WC, Pecoits-Filho R; Conference Participants. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidnet Int. 2020 Jan;97(1):42-61. doi:10.1016j.kint.2019.09.018.
2. Palmer BF, Clegg DJ. Diagnosis and treatment of hyperkalemia. Cleve Clin J Med. 2017 Dec;84(12):934-942. doi: 10.3949/ccjm.84a.17056. PMID: 29244647.
3. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009 Apr;2(2):185-194. doi:10.1161/CIRCEP.108.789081.
4. Aziz Q, Li Y, Tinker A. Potassium channels in the sinoatrial node and their role in heart rate control. Channels (Austin). 2018;12(1):356-366. doi:10.1080/19336950.2018.1532255.
5. Kléber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev. 2004 Apr;84:431-88. doi: 10.1152/physrev.00025.2003
6. Fundamentos Clínicos. Potasio [Internet]. [citado 31 de enero de 2025]. Disponible en: https://fundamentosclinicos.com/content/potasio
7. Gupta AA, Self M, Mueller M, Wardi G, Tainter C. Dispelling myths and misconceptions about the treatment of acute hyperkalemia. Am J Emerg Med. 2022 Feb;52:85-91. doi: 10.1016/j.ajem.2021.11.030. Epub 2021 Nov 27. PMID: 34890894.
8. De Sequera P, Alcázar Arroyo R, Albalate Ramón M. Trastornos del potasio: Hipopotasemia e hiperpotasemia. Nefrología al Día [Internet]. Disponible en: https://www.nefrologiaaldia.org/es-articulo-trastornos-del-potasio-hipopotasemia-hiperpotasemia-383

9. Piktel JS, et al. Beneficial Effect of Calcium Treatment for Hyperkalemia Is Not Due to “Membrane Stabilization.” Critical Care Medicine. 2024;52(10):1499-1507. DOI:10.1097/CCM.0000000000006376.
10. Weinberg, SH. Ephaptic coupling rescues conduction failure in weakly coupled cardiac tissue with voltage-gated gap junctions. Chaos. 2017 Sep;27 (9):093908. doi: 10.1063/1.4999602
11. Lin J, Keener JP. Ephaptic Coupling in Cardiac Myocytes. IEEE Trans Biomed Eng. 2013 Feb;60 (2):576-82. doi:10.1109/TBME.2012.2226720
12. Wei N, Mori Y, Tolkacheva, EG. The dual effect of ephaptic coupling on cardiac conduction with heterogeneous expression of connexin 43. Journal of Theoretical Biology. 2016 Mar 8;397:103-14. doi: 10.1016/j.jtbi.2016.02.029