High-Goal 'Lytes: Repletion Gone Awry?

Ramzi Dudum, MD, MPH[1], Steven J Lahti, MD[1], Michael J Blaha, MD, MPH[1]*

[1]*Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Baltimore, Maryland.*

Electrolyte imbalances, *per se*, predispose to ventricular ectopy and, in extreme cases, sudden cardiac death.[1] As these outcomes are more common in the presence of intrinsic heart disease, serum electrolytes—particularly potassium and magnesium—are routinely monitored and made replete in patients with myocardial infarction (MI) or acute decompensated heart failure (ADHF).

Patients hospitalized with ADHF often present with metabolic derangements and varying degrees of chronic adaptations in their renin–angiotensin–aldosterone system.[1,2] In addition, during an ADHF hospitalization, they are subjected to guideline-directed medical therapy (GDMT), commonly in escalating doses, that exhibit well-established effects on serum potassium levels, including diuretics, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta blockers, and mineralocorticoid receptor antagonists. Thus, there are myriad ways patients hospitalized for ADHF might experience electrolyte abnormalities.

In this issue of the *Journal of Hospital Medicine*, O'Sullivan et al. explore the associations between mean 72-hour serum potassium and important clinical outcomes—in-hospital mortality, transfer to an intensive care unit (ICU), and length of stay (LOS)—among patients with normal admission serum potassium hospitalized for ADHF.[3] Through a retrospective review of electronic records from 116 hospitals, the authors identified 4,995 initially normokalemic heart failure (HF; identified by ICD-9 codes) patients and grouped them into low-normal (3.5-4.0 mEq/L), normal (4.0-4.5 mEq/L), and high-normal (4.5-5.0 mEq/L) potassium groups.[3] Adjustments were made for composite scores encapsulating other lab abnormalities and comorbidities.

Over the 72-hour exposure window, the authors observed no statistically significant difference in mortality, ICU transfer, or LOS between the low-normal and normal potassium groups.[3] Moreover, in a sensitivity analysis of patients who did not receive potassium supplementation, there remained statistically similar rates of mortality, ICU transfer, and LOS.[3] Together, these findings suggest that maintenance of potassium >4 mEq/L may not be efficacious for preventing in-hospital complications of ADHF.[3] In fact, they observed more frequent mortality and ICU transfer in patients who had high-normal potassium. This group, however, had a higher burden of chronic kidney disease and illness severity on presentation and was less likely to receive supplemental potassium.[3]

ADHF accounts for more than one million hospital admissions annually with one in four patients readmitted within 30 days; estimated costs surpass $30 billion.[2] Reducing unnecessary expenditures in the management of HF through evidence-based guidelines is paramount. Electrolyte repletion in the setting of ADHF may represent one such opportunity by reducing excess phlebotomy, laboratory services, and potassium supplementation. Patient experience may also improve from curbing these cumbersome practices. While society guidelines endorse potassium repletion in MI to reduce the risk of ventricular arrhythmia,[4] there is no uniform consensus in ADHF. As the authors cite, existing data regarding ideal potassium levels in patients with ADHF is lacking, with current evidence drawn from small observational studies. The present study, being much larger in size and being linked with observed rates of active potassium supplementation, provides some of the strongest evidence to date that a potassium goal of >4 mEq/L may not be efficacious at reducing ADHF-related complications in the generalized HF population.

While it remains uncertain if avoiding low-normal potassium levels in ADHF is beneficial, over the long term, intermediate-range potassium levels are clearly associated with the lowest HF-related mortality. In a study of over 2,000 HF patients who underwent longitudinal potassium monitoring, mortality was distributed along a U-shaped curve with highest mortality at the extremes of kalemia and a nadir at a level of 4.3 mEq/L.[5]

A major limitation of the present study is that it does not account for variability within the ADHF population. Firstly, knowledge regarding the use of GDMT, which not only affects serum potassium (all GDMTs) but also reduces the likelihood of arrhythmias (beta blockers), would have been informative. Moreover, the authors do not have access to data regarding incident arrhythmia and instead use ICU admission as a surrogate. In addition, ADHF patients in this study varied greatly in illness severity, ranging from those receiving initial therapy with loop diuretics alone to those requiring augmentation with thiazides and even the use of temporary mechanical circulatory support.[3] Escalating loop diuretic or metolazone use not only is associated with increased mortality[6] but often results in impressive natriuresis and, potentially dangerous, kaliuresis secondary to the sequential nephron blockade.[7] Those who underwent extensive potassium swings in the study may not be appropriately captured using 72-hour serum potassium averages. Additionally, this study did not assess for quantity of diuresis, which is known to affect serum potassium values. It is possible that those with low-normal potassium represent patients who underwent more

***Corresponding Author:** Michael J. Blaha, MD, MPH; E-mail: mblaha1@jhmi.edu; Telephone: 443-287-4960; Twitter: @MichaelJBlaha

Published online first July 24, 2019.

Received: June 25, 2019; **Accepted**: June 26, 2019

 DOI 10.12788/jhm.3274

effective diuresis and therefore were discharged sooner. Adding to the variability, ADHF in this study encompassed both systolic (HF with a reduced ejection fraction) and diastolic (HF with a preserved ejection fraction) HF although, perhaps not surprisingly, there were marked differences in the HF subtype by potassium group—the proportions with only diastolic dysfunction were 37.1%, 39.0%, and 45.8% in the low-normal, normal, and high-normal groups, respectively (P = .0174).[3] Given the known heterogeneity between these two HF subtypes,[8] particularly with respect to their response to mortality-reducing GDMT,[2,8] the results may be significantly confounded.

Relatedly, by excluding initially hypokalemic patients, the authors have lost considerable power and broad generalizability as these patients likely represent those at greatest risk of recurrent hypokalemia and its attendant complications during admission.

This study should be lauded for critically appraising the ubiquitous practice of electrolyte repletion. The authors present compelling preliminary data suggesting that maintenance of potassium >4 mEq/L in the general ADHF population is not efficacious at preventing ADHF complications and, as a corollary, is likely not cost-effective. However, we agree with the authors that a randomized controlled trial will be needed to change clinical practice. Ideally, such a study would account for HF subtype and GDMT use and could compare rates of arrhythmia, AHDF-related death, and all-cause mortality in patients maintained to goal normokalemia (>3.5 mEq/L) versus "high goal" (>4 mEq/L) with repletion. Only these types of studies will provide the strength of evidence needed to end a practice as well engrained in modern medicine as "high-goal 'lytes".

Disclosures: Dr. Blaha reports grants from NIH, grants from FDA, grants from AHA, grants and personal fees from Amgen Foundation, grants from Aetna Foundation, personal fees from Sanofi, personal fees from Regeneron, and personal fees from Novartis, from Novo Nordisk, and from Bayer, outside the submitted work. Dr. Dudum and Dr. Lahti have nothing to disclose.

References

1. Packer M, Gottlieb SS, Blum MA. Immediate and long-term pathophysiologic mechanisms underlying the genesis of sudden cardiac death in patients with congestive heart failure. *Am J Med*. 1987;82(3):4-10. https://doi.org/10.1016/0002-9343(87)90126-4.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239. https://doi.org/10.1016/j.jacc.2013.05.019.
3. O'Sullivan KF, Kashef MA, Knee AB, et al. Examining the "Repletion Reflex": the association between serum potassium and outcomes in hospitalized patients with HF. *J Hosp Med*. 14(12);729-736. https://doi.org/10.12788/jhm.3270.
4. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004;110(5):588-636. https://doi.org/10.1161/01.CIR.0000134791.68010.FA
5. Nunez J, Bayes-Genis A, Zannad F, et al. Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. *Circulation* 2018;137(13):1320-1330. https://doi.org/10.1161/CIRCULATIONAHA.117.030576.
6. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J*. 2002;144(1):31-38. https://doi.org/10.1067/mhj.2002.123144
7. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol*. 2010;56(19):1527-1534. https://doi.org/10.1016/j.jacc.2010.06.034.
8. Triposkiadis F, Butler J, Abboud FM, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J*. 40(26):2155-2163. https://doi.org/10.1093/eurheartj/ehz158.