

Predicting Electrolyte Derangements in Heart Failure Patients

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Abstract

Acute Decompensated Heart Failure (ADHF) is one of the leading causes of hospitalization in the United States (US). It is also one of the leading causes of death in the US, contributing to 1 in 9 mortalities. One half of ADHF deaths are attributed to arrhythmia or SCD, with the primary driver of SCD being derangements in electrolytes. Here we describe the current literature regarding pathophysiology as well as clinical management of electrolytes with a focus on potassium homeostasis in ADHF.

Keywords: Heart failure; Diuresis; Electrolytes; Hyperkalemia; Hypokalemia; Potassium

Introduction

Physiology of electrolyte derangements

Multiple mechanisms drive the change in plasma potassium homeostasis in heart failure. Heart failure itself is defined as syndrome caused by cardiac dysfunction, generally resulting from myocardial muscle dysfunction or loss and is characterized by either LV dilation or hypertrophy or both [1,2]. Heart failure leads to neurohormonal and circulatory abnormalities which are a key driver of potassium dysregulation. A primary component of neurohormonal changes is hyperadrenergic tone which leads to potassium activation of beta-2 receptors and transport of plasma potassium intracellularly [3,4]. Additionally, hyperadrenergic tone is a direct activator of the renin-angiotensin-aldosterone system leading to increased reabsorption of sodium and increased excretion of potassium via sodium-potassium-chloride exchange in the loop of Henle. The aforementioned effects lead to total body potassium depletion unrelated to severity of heart failure, age, or renal function [5]. In addition to the natural physiologic mechanisms affecting plasma potassium and total body potassium homeostasis, iatrogenic etiologies are also a major contributor. The vast majority (90%) of heart failure hospitalizations are managed medically with diuretic therapy [6]. Adverse effects of diuretics are well established and include derangements in potassium as well as other electrolytes via potassium wasting [7]. Thus, further depleting total body potassium and plasma potassium stores.

Clinical management of hypokalemia

Despite Hypokalemia being a known risk factor for increased mortality in heart failure patients there is scant data on optimal levels or clinical risk factors for hypokalemia in ADHF [8,9]. Additionally, hyperkalemia is also associated with increased mortality in heart failure, especially when potassium elevations are acute [10]. Many small studies have evaluated risk factors for hyperkalemia and demonstrate an increased risk with the use of angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists. Larger studies evaluating risk factors for hyperkalemia have shown conflicting results [11,12]. Clinical guidelines for the management of heart failure do not make specific recommendations regarding the frequency of monitoring of electrolytes. Given the lack of data regarding clinical factors associated with hypokalemia and hyperkalemia in hospitalized ADHF patients we sought to evaluate factors contributing to potassium derangements and

to create predictive modelling to suggest optimal timing for monitoring electrolytes in hospitalized heart failure patients.

Hypothesis

In this study, we hypothesized that clinical factors including renal function, diuretic dosing, urine output, medication use, and potassium repletion would affect the risk of electrolyte derangements in hospitalized HF patients undergoing diuresis and could be modelled to predict the risk for hypo and hyperkalemia.

Methods and Materials

We retrospectively analysed 2,263 patients admitted for ADHF at a tertiary academic medical centre from January 2012 to December 2014. Electronic medical records identified by ICD-9 primary diagnosis was used to extract data regarding medication administration and dosing, fluid intake and output, laboratory values, and echocardiographic data. Patients were included in the study if they received oral or intravenous (IV) diuretic therapy and had measurements of creatinine, potassium and ejection fraction. Patients were excluded if they were treated with a continuous diuretic drip during their hospitalization(s) or if no echocardiogram was performed within 12 months of hospitalization. Estimated GFR was calculated using Chronic Kidney Disease Epidemiology Collaboration [13]. We defined hypokalemia and hyperkalemia using normal limits from our laboratory of <3.5 mEq/L and >5.1 mEq/L respectively. We used proportional odds logistic models for each outcome separately, with urine output, diuretic regimen, creatinine, ejection fraction, potassium supplementation, ACE-I/ARB use, mineralocorticoid receptor antagonist (MRA) use, and hypokalemia (<3.5 mEq/L) on prior lab draw (same admission) as the independent variables. Since each patient had multiple assessments included in the data, we used a cluster sandwich covariance estimator with the patient ID as a cluster in order to adjust the variance in our model to account for these repeated measurements. We allowed all continuous variables including urine output, effective diuretic dose,

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Received July 16, 2019; Accepted July 23, 2019; Published July 30, 2019

Citation: Brown CL, Fudim M, Harrell F, Wang L, McPherson JA, et al. (2019) Predicting Electrolyte Derangements in Heart Failure Patients. J Clin Case Rep 9: 1264.

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creatinine, potassium supplementation and ejection fraction to have a nonlinear relationship with the outcomes using restricted cubic spline with 3 knots. All analyses were performed using statistical software R version 3.1.2 [12-14].

Results

Characteristics

A total of 913 patients meeting the study criteria (13,739 measurements of potassium during hospitalization) were analysed (full characteristics can be found in Table 1); 718 (78.6%) were white, 173 (18.9%) were African American and 22 (2.5%) were other. The mean age of participants was 65.4 years and 593 (65%) patients were men.

Hypokalemia

Using multivariable proportional odds model, we identified three factors associated with future hypokalemia. Hypokalemia on prior lab (OR: 2.16; 95% CI: 1.70-2.74), higher diuretic dose [200 mg equivalents of furosemide] (OR:1.66; 95% CI: 1.43-1.93) and higher urine output (OR: 1.11; 95% CI: 1.00-1.24). Other factors, including mineralocorticoid use and ACE-inhibitor or ARB use were not associated with hypokalemia. Higher eGFR was associated with hypokalemia although it was not clinically significant (Table 1). Due to the strong effect of hypokalemia on prior lab we analysed the same

factors again limited to patients with normal potassium at baseline. This group resulted in 496 patients being included in analysis. Diuretic dose (OR: 1.92) was still associated with hypokalemia. Urine output was no longer clinically associated with hypokalemia (OR: 0.98). In the normokalemic patients a higher prior potassium (4.4 mEq/L vs. 3.7 mEq/L) was protective against hypokalemia (OR: 0.21; 95% CI: 0.18-0.26) (Table 2). There was a nearly linear and steep relationship with the likelihood of hypokalemia on the next blood draw as previous potassium fell below 4.1 mEq/L (Figure 1). The relationship between the likelihood of subsequent hypokalemia and diuretic dose and urine output are also linear, but the slopes are continuous (Figures 2 and 3).

Hyperkalemia

Using multivariable proportional odds model, higher eGFR (OR:0.33; 95% CI: 0.24-0.45) and higher urine output (OR:0.72; 95% CI: 0.56-0.93) were associated with decreased odds of hyperkalemia. Diuretic equivalents, mineralocorticoid use, and ACE-inhibitor or ARB use were not significantly associated with increased or decreased odds of hyperkalemia (Table 2). The risk for hyperkalemia on the next blood draw increased nearly linearly as baseline potassium increased above 4.0 mEq/L (Figure 4).

Potassium supplementation

In order to determine if predictive function could be constructed, we analysed factors associated with increased potassium supplementation.

Characteristics	All samples (n=913)
Age - Years	61.5+14
Male sex -- No (%)	593 (64.9)
White race -- No (%)	718 (78.6)
Ejection fraction	32+16
Serum Creatinine -- mg/dL	1.8+1.2
Ace-I or ARB -- no (%)	603 (66)
Mineralocorticoid receptor antagonist -- no (%)	675 (74)

Table 1: Baseline characteristics of study population.

Variables	Hypokalemia		Hypokalemia if normokalemic prior		Hyperkalemia on next lab		Total potassium supplementation received	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (70 vs. 53)	0.88 (0.72-1.08)	0.382	0.91 (0.71-1.17)	0.581	0.73 (0.49-1.11)	0.195	0.84 (0.65-1.08)	0.549
Female vs. Male	1.07 (0.92-1.26)	0.375	1.29 (1.06-1.57)	0.013	0.72 (0.52-0.99)	0.041	1.17 (0.96-1.43)	0.12
Black vs. White	0.82 (0.65-1.05)	0.16	0.75 (0.58-0.99)	0.117	0.74 (0.53-1.04)	0.214	0.72 (0.56-0.92)	0.029
Other vs. White	0.83 (0.63-1.10)		0.93 (0.59-1.46)		1.06 (0.46-2.44)		0.88 (0.52-1.50)	
Hypokalemia on prior lab (Yes vs. No)	2.16 (1.70-2.74)	<0.001	2.04 (1.60-2.60)	<0.001	0.63 (0.41-0.99)	0.044	2.25 (1.43- 3.54)	<0.001
Effective Diuretic Dose (mg IV furosemide equivalents, 200 vs. 40)	1.66 (1.43-1.93)	<0.001	1.92 (1.62-2.29)	<0.001	0.91 (0.67- 1.23)	0.818	1.62 (1.39- 1.88)	<0.001
ACE- Inhibitor or ARB use (0 vs. ≥1)	1.14 (0.98-1.32)	0.085	1.15 (0.96-1.38)	0.131	1.19 (0.92- 1.55)	0.188	1.10 (0.93- 1.30)	0.268
Urine output (mL/hr, 100 vs. 30)	1.11 (1.00-1.24)	0.018	0.98 (0.85-1.12)	<0.001	0.72 (0.56- 0.93)	<0.001	1.27 (1.14- 1.41)	<0.001
Ejection Fraction % (0.53 vs. 0.18)	0.98 (0.82-1.16)	0.423	0.93 (0.76-1.16)	0.542	1.30 (0.92 - 1.84)	0.09	0.91 (0.69-1.19)	0.615
Mineralocorticoid receptor antagonist use (0 vs. >0)	0.90 (0.75-1.09)	0.288	0.87 (0.69-1.08)	0.209	1.09 (0.80 - 1.49)	0.588	0.69 (0.57- 0.84)	<0.001
EGFR (60 vs. 15 mL/min)	0.82 (0.64-1.04)	0.017	0.93 (0.69-1.26)	0.405	0.33 (0.24 - 0.45)	<0.001	2.85 (2.24- 3.62)	<0.001
Potassium prior (4.4 vs. 3.7 mEq)	0.20 (0.17-0.24)	<0.001	0.21 (0.18-0.26)	<0.001	-	-	-	-

Table 2: Factors affecting hypokalemia and hyperkalemia in hospitalized heart failure patients.

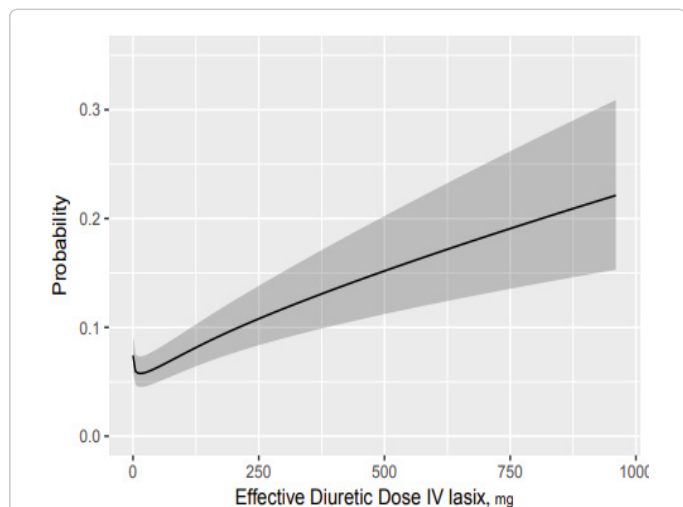


Figure 1: Probability of hypokalemia using continuous variable analysis of potassium on previous laboratory draw. (Solid line is mean and shaded are is 95% confidence intervals).

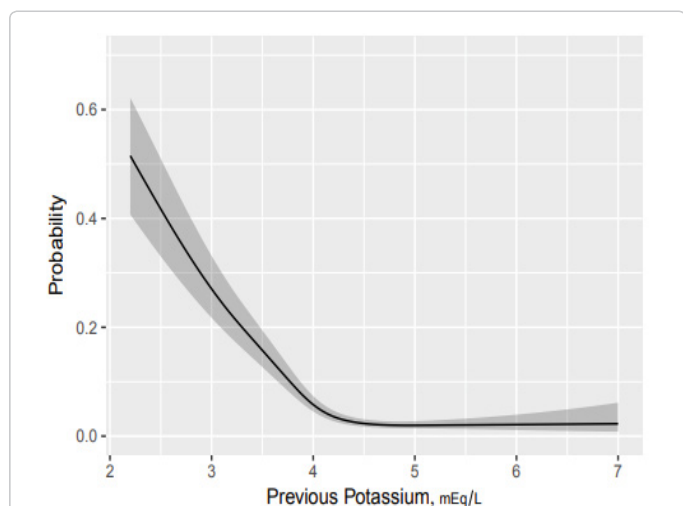


Figure 2: Probability of hypokalemia using continuous variable analysis of diuretic dose in mg equivalents of furosemide. (Solid line is mean and shaded are is 95% confidence intervals).

Higher urine output (OR:1.27; 95% CI: 1.14-1.41), higher effective diuretic dose (OR:1.61; 95% CI: 1.39-1.88), higher eGFR (OR:2.85; 95% CI: 2.24-3.62), and hypokalemia on prior lab (OR:2.25; 95% CI: 1.43-3.54) were all associated with increased potassium supplementation. Mineralocorticoid use was negatively associated with potassium supplementation (OR:0.69; 95% CI 0.57-0.84) (Table 2).

Predictive function for potassium

We constructed predictive modelling for hypokalemia using the clinical factors in our analysis. Due to the non-linear nature of the data and the lack of fit to the model, no significant function was able to predict changes in potassium or risk for hypokalemia.

Discussion

To our knowledge, this is the largest study assessing factors associated with electrolyte derangements in hospitalized ADHF patients. Previous studies have demonstrated the significant risks

associated with both hypokalemia and hyperkalemia including arrhythmias and death [8,10]. However, these studies did not evaluate causes of hypokalemia or hyperkalemia. We demonstrate multiple factors that are significantly associated with hypokalemia and hyperkalemia. Herein we provide the first set of parameters to inform electrolyte monitoring during a hospitalization for hyperkalemia.

The odds of hypokalemia during hospitalization were strongly related to the baseline presence and degree of hypokalemia (Table 1). There was a significant increase in odds of hypokalemia when the index potassium concentration was below 3.7 mEq/L. Diuretic dose and urine output also directly correlated with hypokalemia but the association was considerably less predictive. For example, an increase in hourly urine output from 30 to 100 mL only increased the odds ratio for hypokalemia by 11%. Similarly, the odds of hyperkalemia increased with increasing previous level of serum potassium (Figure 4). Odds of hyperkalemia also increased with decreasing renal function, and urine output.

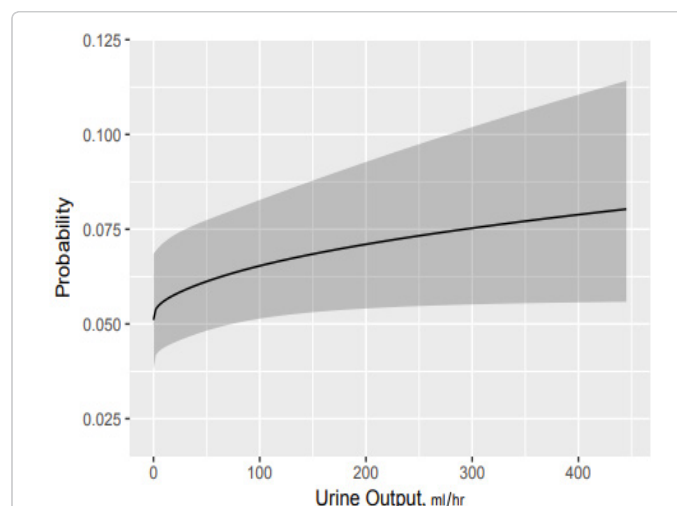


Figure 3: Probability of hypokalemia using continuous variable analysis of urine output in mL/hr. (Solid line is mean and shaded are is 95% confidence intervals).

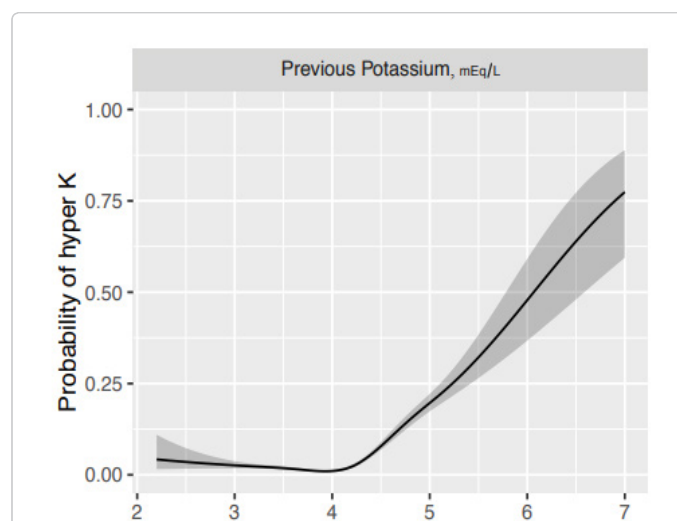


Figure 4: Probability of hyperkalemia based on previous potassium. (Solid line is mean and shaded are is 95% confidence intervals).

The fact that hypokalemia begets hypokalemia and hyperkalemia begets hyperkalemia should not be surprising. When considering 98% of total body potassium is intracellular, even a mild deficit of 0.5 mEq/L (serum potassium of 3.0 mEq/L) in an average size individual is a total body deficit of over 150 mEq/L, which is unlikely to be fully replenished with standard dosing of 10 mEq of potassium for every 0.1 mEq derangement. The same logic also holds true for hyperkalemia where a significant amount of potassium must be excreted by the kidney in order to achieve normokalemia.

Practical application of the aforementioned findings would suggest, using 10% probability of electrolyte derangement (either hypo or hyperkalemia) as a threshold for increased monitoring, that diuretic dose above 160 mg furosemide equivalent, eGFR less than 15 mL/hr and baseline potassium below 3.7 mEq/L or above 4.5 mEq/L warrant more frequent monitoring (i.e., twice daily).

We also demonstrate that the use of MRA or ACE-I/ARB were not protective against hypokalemia nor were they associated with increased odds of hyperkalemia (Table 1). This finding was a surprise given the longitudinal data suggesting that medications affecting the renin-angiotensin-aldosterone system (RAAS) cause hyperkalemia [15-18]. However, these studies were performed on outpatients who are receiving lower doses of diuretics. Additionally, patients in the inpatient setting have medications transiently held for many reasons. Thus, neither continued administration nor discontinuation of drugs interfering with the RAAS can be relied on to prevent derangements in potassium in hospitalized ADHF patients. Additionally, all of our findings also hold true for both heart failure with reduced and preserved ejection fraction; thus, our findings can be applied widely to all patients admitted for ADHF.

We were unable to determine a predictive function for changes in potassium or risk of future hypokalemia. The lack of fit to predictive function is important as it demonstrates that each single factor must be taken into consideration when evaluating patient's serum potassium when determining monitoring frequency. Our study has several important limitations. This is a single centre retrospective analysis using billing codes to identify potential patients for evaluation raising concern for selection bias. Also, non-significant associations may be true associations but result from study power not being sufficient to detect the differences.

Conclusion

In conclusion, baseline potassium is highly useful in predicting the odds of hypokalemia or hyperkalemia on next the next laboratory draw. Increase in UOP and diuretic dose also increase the odds of hypokalemia in hospitalized ADHF patients. Higher urine output and

higher eGFR were protective against hyperkalemia. No single factor or set of factors could model the risk of hypo or hyperkalemia.

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