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ORIGINAL ARTICLE
Heart Failure

Hyperkalemia in Patients With Left Ventricular Assist Devices

Teruhiko Imamura, MD, PhD; Nikhil Narang, MD; Pamela Combs, PhD; Umar Siddiqi; Corinne Stonebraker; Valluvan Jeevanandam, MD

Background: Both hypo- and hyperkalemia are associated with adverse events in heart failure patients. Their effects on patients with left ventricular assist devices (LVADs) remains unknown.

Methods and Results: The cohort included consecutive patients undergoing LVAD implantation between 2014 and 2018. In all, 170 patients (median age 56 years; 117 males) were stratified according to serum potassium levels 1 month after implantation into 3 groups: hypokalemia (<3.5 mEq/L; n=15), normokalemia (n=146), and hyperkalemia (>5.0 mEq/L; n=9). Compared with the normokalemia group, the adjusted hazard ratios for 1-year mortality were 0.91 (95% confidence interval [CI] 0.21–3.92) for hypokalemia and 4.14 (95% CI 1.47–11.65) for hyperkalemia. In the hyperkalemia group, the prevalence of renin-angiotensin-aldosterone system inhibitors decreased and serum potassium levels normalized following the first month.

Conclusions: Hyperkalemia was associated with increased mortality during LVAD support. Management of serum potassium needs further investigation.

Key Words: Chronic kidney disease; Heart failure; Mechanical circulatory support; Potassium

The prognostic impact of potassium homeostasis can best be represented as a "J-Curve" in various clinical situations, including chronic heart failure.[1] Hyperkalemia, defined as serum potassium levels >5.0 mEq/L,[2] and hypokalemia, defined as serum potassium levels <3.5 mEq/L,[2] are associated with increased all-cause mortality.

The most common causes of hyperkalemia in patients with heart failure are impaired renal function and the administration of renin-angiotensin-aldosterone system (RAS) inhibitors, including angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists.[3] Novel therapies allowing the continuation of heart failure-specific medical therapies are emerging as potential solutions to this common clinical dilemma.[4]

In contrast, there is little in the clinical literature regarding hyperkalemia in patients with left ventricular assist devices (LVAD).[5] Given that heart failure-specific therapies, which can often affect potassium levels, are recommended to be continued following LVAD implantation,[6–9] maintaining normokalemia is an important therapeutic target in LVAD patients. In this study we investigated the association between post-LVAD potassium levels and mortality.

Methods

Patient Selection

Consecutive patients who underwent LVAD implantation at our institution between 2014 and 2018 were retrospectively evaluated for inclusion in the study. All patients under LVAD support were medically treated by the heart failure team, including heart failure cardiologists, cardiac surgeons, and LVAD coordinators. Clinical decision making was made by this multidisciplinary team. Patients without data on serum potassium levels at 1 month after implantation, which was assumed to be the time of discharge, were excluded. In addition, patients who died within 1 month after implantation were excluded.

This study was approved by the Institutional Review Board of The University of Chicago (IRB16-0632). Written informed consent was obtained from all participants beforehand. The study was performed in accordance with the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

Primary Endpoint

Patients were stratified into 3 groups based on serum

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Second Department of Internal Medicine, University of Toyama, Toyama (T.I.), Japan; Department of Medicine (T.I., N.N.), Department of Surgery (P.C., U.S., C.S., V.J.), University of Chicago Medical Center, Chicago, IL; and Advocate Christ Medical Center, Oak Lawn, IL (N.N.), USA

Mailing address: Teruhiko Imamura, MD, PhD, FAHA, FACC, FESC, FHFSA, FAPSC, FACP, FICA, FASA, FJCC, Second Department of Internal Medicine, Toyama University, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: teimamu@med.u-toyama.ac.jp

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Table 1. Baseline Characteristics

	Total (n=170)	Hypokalemia (n=15)	Normokalemia (n=146)	Hyperkalemia (n=9)	P value
Demographics					
Age (years)	56 (48–66)	51 (45–58)	57 (48–66)	64 (54–70)	0.24
Male sex	117 (69)	10 (67)	99 (68)	8 (89)	0.42
BMI (kg/m^2)	29.5 [25.3–36.3]	36.9 [27.2–41.1]	29.6 [25.3–36.2]	25.3 [22.6–29.0]	0.019*
Ischemic etiology	49 (29)	3 (20)	45 (31)	1 (11)	0.33
Destination therapy	123 (72)	11 (73)	105 (72)	7 (78)	0.93
Comorbidity					
Atrial fibrillation	66 (39)	7 (47)	55 (38)	4 (44)	0.75
History of stroke	28 (16)	2 (13)	25 (17)	1 (11)	0.84
Diabetes	62 (36)	3 (20)	55 (38)	4 (44)	0.35
Device					
HeartMate II	44 (26)	3 (20)	37 (25)	4 (44)	0.13
HeartWare	84 (49)	10 (67)	73 (50)	1 (12)	–
HeartMate 3	42 (25)	2 (13)	36 (25)	4 (44)	–
Preoperative laboratory data					
Serum sodium (mEq/L)	137 [133–139]	138 [136–142]	137 [135–140]	134 [130–136]	0.59
Serum potassium (mEq/L)	4.1 [3.8–4.4]	3.8 [3.6–4.7]	4.1 [3.8–4.4]	4.2 [3.8–4.5]	0.54
eGFR (mL/min/1.73 m^2)	49 [37–61]	66 [47–86]	59 [43–75]	53 [32–74]	0.41
Preoperative echocardiography					
LVEDd (cm)	7.0 [6.3–7.7]	7.0 [6.4–8.0]	7.1 [6.4–7.7]	6.6 [6.0–7.3]	0.11
LVEF (%)	22 [16–30]	18 [15–20]	22 [16–29]	17 [16–30]	0.49
Moderate or greater MR	41 (24)	6 (40)	34 (23)	1 (11)	0.26
Moderate or greater TR	32 (19)	4 (27)	26 (18)	2 (22)	0.72
Moderate or greater RV size	68 (40)	6 (40)	57 (39)	5 (56)	0.42
Moderate or greater RV dysfunction	106 (62)	10 (67)	90 (62)	6 (67)	1.0
Preoperative hemodynamics					
RAP (mmHg)	12 [9–17]	12 [11–14]	12 [9–17]	14 [10–18]	0.88
PCWP (mmHg)	25 [20–31]	34 [25–34]	26 [20–31]	24 [21–25]	0.79
Cardiac output (L/min)	3.9 [3.2–4.9]	3.9 [3.3–4.6]	4.0 [3.5–4.8]	3.1 [2.9–3.9]	0.63
MAP (mmHg)	81 [72–89]	81 [74–89]	82 [75–89]	82 [81–83]	0.71
Preoperative medication					
β-blocker	115 (68)	8 (53)	101 (69)	6 (67)	0.60
RAS inhibitor	129 (76)	11 (73)	111 (76)	7 (78)	0.96
Diuretics	138 (81)	11 (73)	119 (82)	8 (89)	0.062
In-hospital duration (days)	21 [15–31]	18 [14–24]	25 [16–36]	19 [14–20]	0.12

Continuous variables are expressed as the median [interquartile range] and were compared using the Kruskal-Wallis test. Categorical variables are expressed as n (%) and were compared using Fisher's exact test. *P<0.05. eGFR, estimated glomerular filtration rate; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MR, mitral regurgitation; PWCP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RAS, renin-angiotensin-aldosterone system; RV, right ventricle; TR, tricuspid regurgitation.

potassium levels 1 month after LVAD implantation: (1) hypokalemia, serum potassium <3.5 mEq/L; (2) normokalemia, serum potassium between 3.5 and 5.0 mEq/L; and (3) hyperkalemia, serum potassium >5.0 mEq/L. The relative risk of abnormal serum potassium status (i.e., hypokalemia and hyperkalemia) on 1-year mortality was compared with normokalemia for the primary endpoint.

Data Collection

Data on serum potassium levels immediately before LVAD implantation and then 1 week and 1, 3, and 6 months after device implant were collected. Baseline characteristics, demographics, laboratory, echocardiography, hemodynamics, and medication data obtained just before LVAD implantation were also collected.

Following LVAD implantation, medication and laboratory data at 1, 3, and 6 months were retrieved. All-cause death during the 1-year observation period from the first month after LVAD implantation was considered the primary outcome.

Statistical Analysis

As a primary outcome, the effect of abnormal serum potassium status at 1 month after LVAD implantation (i.e., hypokalemia and hyperkalemia vs. normokalemia) on 1-year mortality was investigated. Continuous variables are presented as the median and interquartile range (IQR) and were compared among the 3 groups using the Kruskal-Wallis test (or Mann-Whitney U test for 2-group comparisons). Categorical variables are presented as numbers and percentages and were compared among 3 groups using Fisher's exact test.

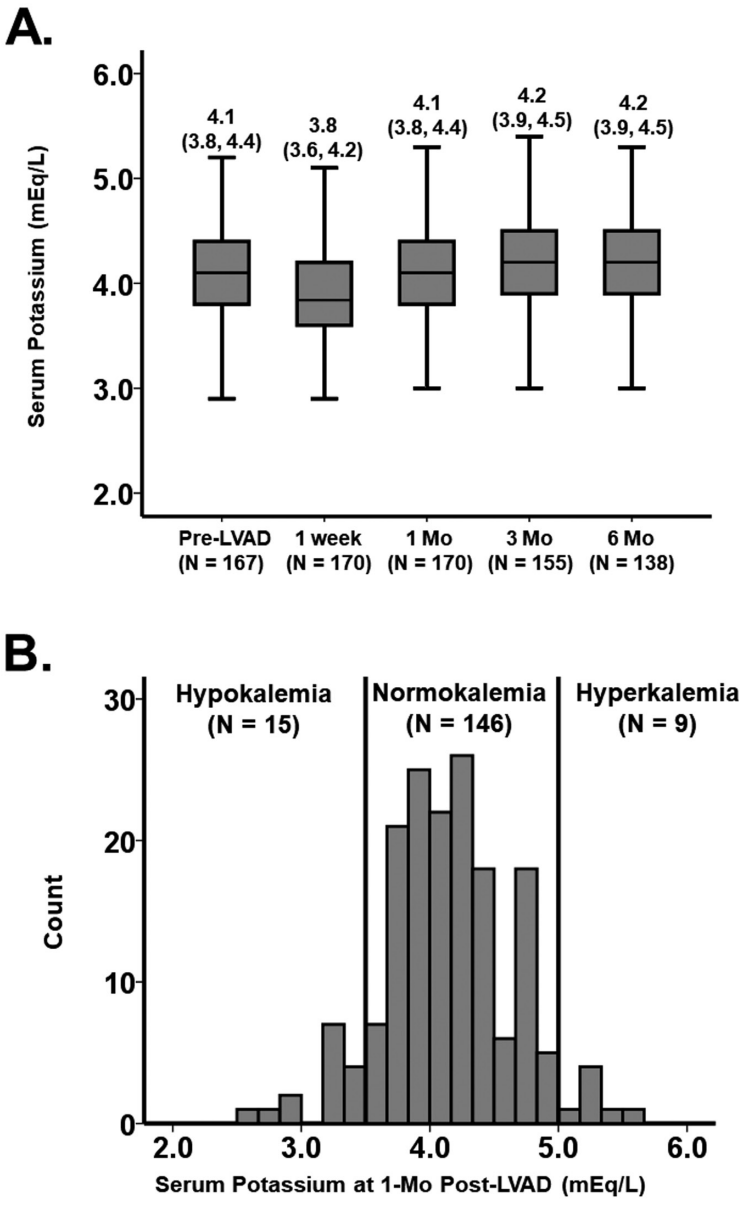

Figure 1. (**A**) Trends in serum potassium level before and after left ventricular assist device (LVAD) implantation and (**B**) distribution of serum potassium levels 1 month after LVAD implantation. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Values above boxes are the median (interquartile range).

One-year mortality was compared among the 3 groups using Kaplan-Meier analysis and log-rank tests. The effect of abnormal serum potassium status on 1-year mortality was assessed by Cox proportional hazard ratio regression analyses using normokalemia as a reference group. The effect was adjusted for clinically associated baseline characteristics, including age, body mass index, estimated glomerular filtration rate, and the use of an angiotensin-converting enzyme inhibitor.

Statistical analyses were performed using SPSS Statistics 22 (SPSS Inc., Armonk, IL, USA). Two-sided $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

In all, 204 consecutive LVAD patients were considered for inclusion in the study. Of these, 34 without data on potassium levels at 1 month after LVAD were excluded, leaving 170 LVAD patients (median age 56 years [IQR 48–66 years]; 117 [69%] males) in the study (**Table 1**). Most patients (72%) were indicated for destination therapy.

Trends in Serum Potassium Levels

The median overall serum potassium level just before LVAD implantation was 4.1 mEq/L (IQR 3.8–4.4 mEq/L). Serum potassium levels temporarily decreased 1-week after implantation and remained at a median level of 4.2 mEq/L during the 6-month follow-up (**Figure 1A**).

The median serum potassium level 1 month after LVAD was 4.1 mEq/L (IQR 3.8–4.4 mEq/L). At 1 month after LVAD, 15 patients were classified as hypokalemic, 146 were classified as normokalemic, and 9 were classified as hyperkalemic (**Figure 1B**).

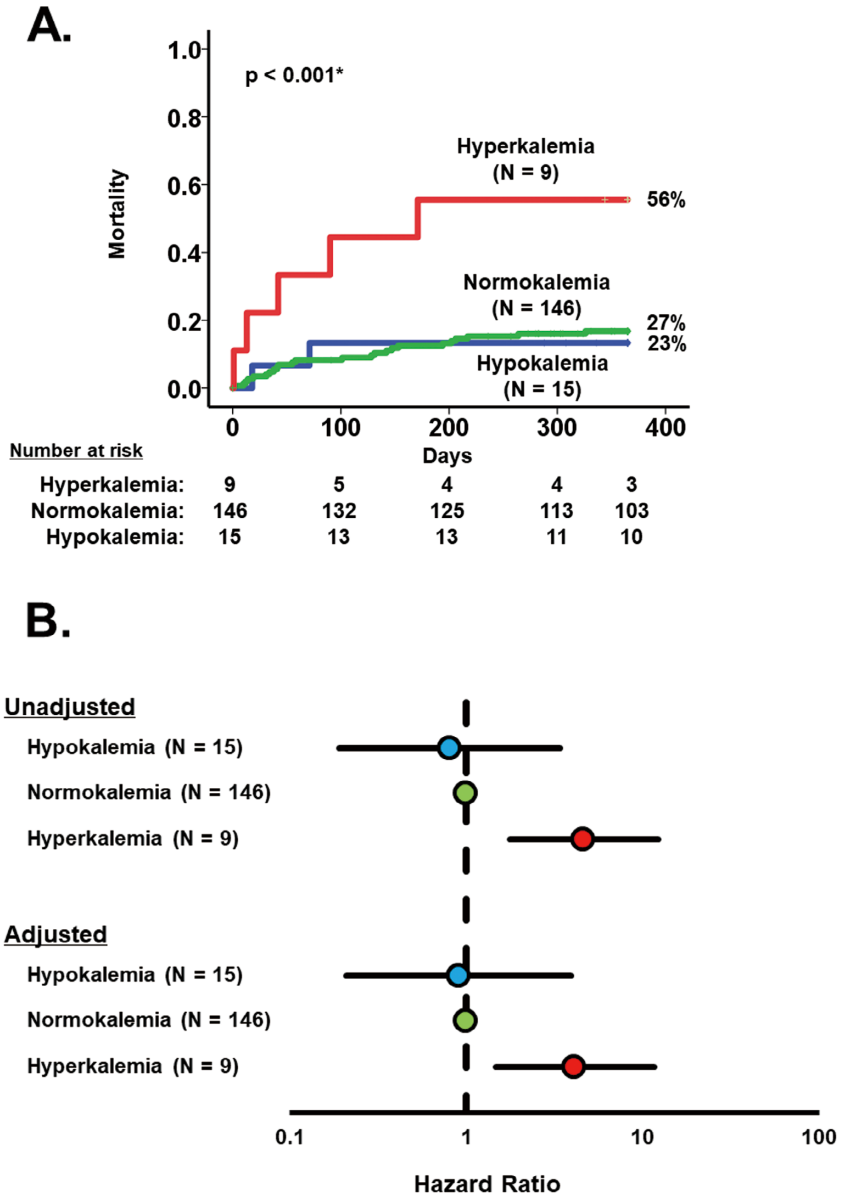

Figure 2. (**A**) One-year cumulative mortality from the first month following left ventricular assist device (LVAD) implantation stratified by serum potassium status. Day 0 was defined as the 1-month time point after LVAD implantation. Patients were stratified according to serum potassium levels in the first month after implantation. (**B**) Forest plot showing hazard ratios for serum potassium status on 1-year mortality. Hazard ratios were adjusted for age, body mass index, estimated glomerular filtration rate, and the use of angiotensin-converting enzyme inhibitors, with normokalemia used as the reference group.

Baseline Characteristics Stratified by Serum Potassium

There were no statistically significant differences in demographics, comorbidity burden, and laboratory, echocardiographic, hemodynamic, and medication data obtained just before LVAD implantation among the 3 groups, except for a lower body mass index in the hyperkalemia group (**Table 1**). This group also tended to be older and possess more impaired renal function.

Serum Potassium Status 1 Month After LVAD and 1-Year Mortality

During the 1-year observation period, 2 of 15 patients died in the hypokalemia group (pump thrombosis and stroke), 24 of 146 patients died in the normokalemia group (8 stroke, 6 heart failure, 3 sepsis, 2 pump thrombosis, 2 gastrointestinal bleeding, 1 ventricular tachyarrhythmia, and 3 unknown causes), and 5 of 9 patients died in the hyperkalemia group. Of note, the causes of death in the hyperkalemia group were sepsis (n=2), stroke (n=2), and ventricular tachyarrhythmia (n=1).

One-year mortality in the hypokalemia group was 23%, which did not differ significantly from that in the normokalemia group (27%; P=0.76; **Figure 2A**). Proportionally, the hyperkalemia group had a significantly higher mortality rate than the normokalemia group (56% vs. 27%; P<0.001).

In both unadjusted and adjusted models, the hypokalemia group had a statistically comparable risk of mortality compared with the normokalemia group (P>0.05 for both; **Figure 2B**). Mortality risk in the hyperkalemia group was significantly greater than in the normokalemia group in both unadjusted (hazard ratio [HR] 4.66; 95% confidence interval [CI] 1.77–12.23) and adjusted (HR 4.14; 95% CI 1.47–11.65) models.

Table 2. Medication and Laboratory Data Following Left Ventricular Assist Device Implantation

	Hyperkalemia (n=9)	Normokalemia (n=170)	P value
Medication (% use)			
ACEI or ARB			
1 month	67	52	0.40
3 months	13	56	0.016*
6 months	20	64	0.048*
Mineralocorticoid receptor antagonist			
1 month	44	39	0.77
3 months	13	42	0.099
6 months	0	48	0.035*
Diuretics			
1 month	44	74	0.087
3 months	38	71	0.097
6 months	33	69	0.073
β-blockers			
1 month	50	66	0.41
3 months	60	65	0.79
6 months	60	66	0.77
Laboratory data			
Serum potassium (mEq/L)			
1 month	5.3 [5.2–5.4]	4.1 [3.9–4.4]	<0.001*
3 months	4.4 [4.0–4.9]	4.2 [4.0–4.5]	0.71
6 months	4.2 [3.5–4.8]	4.2 [4.0–4.5]	0.86
Serum sodium (mEq/L)			
1 month	137 [135–140]	135 [132–138]	0.076
3 months	139 [137–141]	138 [135–141]	0.69
6 months	139 [136–141]	138 [137–140]	0.89
Serum chloride (mEq/L)			
1 month	98 [96–101]	97 [94–99]	0.078
3 months	100 [97–103]	101 [96–104]	0.52
6 months	101 [98–103]	104 [99–106]	0.37
eGFR (mL/min/1.73 m^2)			
1 month	53 [38–81]	57 [43–73]	0.52
3 months	67 [61–92]	59 [45–72]	0.46
6 months	66 [44–76]	52 [40–64]	0.33
Serum BUN (mg/dL)			
1 month	22 [15–30]	30 [18–44]	0.031*
3 months	20 [13–28]	18 [16–23]	0.78
6 months	22 [17–31]	17 [15–19]	0.32

Continuous variables are expressed as the median [interquartile range] and were compared using the Mann-Whitney U test. Categorical variables are expressed as percentages and were compared using Fisher's exact test. *P<0.05. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor II blocker; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

Other Post-LVAD Data

Medication and laboratory data following LVAD implantation were compared between the hyperkalemia and normokalemia groups (**Table 2**). The prevalence of the use of RAS inhibitors did not differ significantly between the 2 groups at 1-month after implantation.

After the first month (i.e., at 3 and 6 months), the prevalence of the use of RAS inhibitors decreased considerably in the hyperkalemia group, whereas usage increased in patients with normokalemia. Serum potassium levels normalized following the first month in the hyperkalemia group and remained within normal range in the normokalemia group.

Renal function did not significantly differ between the groups during the observation period.

Discussion

In this study we investigated the effect of postoperative potassium levels on mortality in LVAD patients. Our major findings are that: (1) most patients had normokalemia in the first month following LVAD implantation (~10% had hypokalemia and 5% had hyperkalemia); (2) postoperative hyperkalemia was independently associated with 1-year mortality; and (3) the prevalence of the use of RAS inhibitors decreased after 1 month post-LVAD implantation in

the hyperkalemia group.

Serum Potassium Abnormalities in LVAD Patients

Clinical data on the impact of potassium homeostasis following LVAD implantation are lacking.[5] In the present study the prevalence of hypokalemia was only 10%, although it is unclear how this compares to larger-scale registries or data from other centers.[10] The prevalence of hyperkalemia in the present study was only 5%. Hyperkalemia was associated with greater age, lower body mass index, and renal impairment, which is compatible with previous reports of patients with chronic heart failure.[3] In the PARADIGM-HF trial, the incidence of hyperkalemia (serum potassium ≥5.5 mEq/L) was approximately 15% in both the sacubitril/valsartan and enalapril arms.[11] In the RALES trial, where spironolactone was added to RAS inhibitor therapy, the prevalence of therapy-related hyperkalemia was considerably higher, at 51%.[12] The relatively low prevalence of hyperkalemia in the present study may be due, in part, to a relatively younger patient population with preserved renal function, as seen in both the normokalemia and hypokalemia cohorts in this study.

Abnormal Serum Potassium Levels and Post-LVAD Mortality

Hypokalemia may considerably increase the risk of ventricular tachyarrhythmias in patients with chronic heart failure.[13] However, in the present study, post-LVAD hypokalemia was not associated with worsening mortality. It is plausible that hemodynamic deterioration due to ventricular tachyarrhythmia may be mitigated following LVAD implantation.[14] Of note, 6 of 15 patients with hypokalemia experienced ventricular tachyarrhythmia events without hemodynamic deterioration. Hyperkalemia was observed to have a 4-fold risk of mortality. Several mechanisms underlying the increased risks of mortality are discussed below.

Hyperkalemia and Mortality Ventricular tachyarrhythmia events are considered to be among the most common causes of mortality in patients with hyperkalemia.[4] In our selected cohort, of the 5 total mortalities in the hyperkalemia group, only 1 patient died due to ventricular tachyarrhythmia. The maximum serum potassium level in this specific case was 6.4 mEq/L. We observed a relative normalization of serum potassium levels in the hyperkalemia group in the months following LVAD implantation. Hyperkalemia itself may not singularly increase the risk of mortality.

Chronic Kidney Disease and Mortality Chronic kidney disease is another common cause of hyperkalemia.[3] In our selected cohort, we observed comparable glomerular filtration rates among the hypokalemic, hyperkalemic, and normokalemic subgroups during LVAD support.

Termination of RAS Inhibitor and Mortality In the hyperkalemia group, the prevalence of the use of RAS inhibitors decreased considerably following the first month, likely due to elevations in serum potassium. Diuretic use overall was less prevalent in the hyperkalemia group. This may further explain the relative normalization of potassium levels following index implantation. Despite the observed eventual normalization of hyperkalemia, mortality was proportionally significant within this subgroup.

Although the clinical implications of RAS inhibitors in LVAD patients are controversial,[15] prior observational studies have suggested potential benefits. For example, Grupper et al demonstrated that the neurohormonal blockade in LVAD patients was associated with cardiac reverse remodeling and improvements in mortality and morbidity.[7] Using the INTERMACS database, McCullough et al demonstrated that the neurohormonal blockade was associated with improved survival and quality of life.[9]

Termination of RAS inhibitors in the present study may have increased the risk of mortality, rather than the hyperkalemia itself, although the low number of clinical endpoints makes it difficult to ascertain definitive associations. More recently, the emergence of potassium-lowering agents presents a new path to continue therapies with clear mortality benefits in heart failure patients.[4] Potassium-lowering agent-incorporating neurohormonal blockade therapy in LVAD patients is a strategy that requires further prospective investigation.[16]

Study Limitations

This study is not without limitations. Despite a moderately sized overall study cohort, the unequal distribution of those with abnormal serum potassium levels and low event numbers are clear limitations. We attempted to adjust for 4 additional clinical potential confounders, although there may have been other uninvestigated confounders that we did not account for. A larger-scale study is needed to better understand the clinical risk associated with these given subgroups. We also lacked comprehensive echocardiography and invasive hemodynamic data during the treatment period. We used conventional cut-offs to define abnormalities in serum potassium (i.e., 3.5 and 5.0 mEq/L),[2] which may not apply to patients with durable mechanical circulatory support.

Conclusions

Post-LVAD hyperkalemia was associated with increased mortality. Management of serum potassium levels using RAS inhibitors and potassium-lowering agents may reduce the risk of clinical events in LVAD populations, but remains a topic requiring further investigation.

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IRB Information

This study was approved by the Institutional Review Board of The University of Chicago.

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