Hyperkalemia in Patients With Left Ventricular Assist Devices

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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
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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.
Hyperkalemia in LVAD

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).
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.

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).

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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.
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. In the present study the prevalence of hyperkalemia was only 10%, although it is unclear how this compares to larger-scale registries or data from other centers. 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. 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. In the RALES trial, where spironolactone was added to RAS inhibitor therapy, the prevalence of therapy-related hyperkalemia was considerably higher, at 51%. 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 hyperkalemia cohorts in this study.

**Abnormal Serum Potassium Levels and Post-LVAD Mortality**

Hyokalemia may considerably increase the risk of ventricular tachyarrhythmias in patients with chronic heart failure. 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. 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. 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. 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, 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. Using the INTERMACS database, McCullough et al demonstrated that the neurohormonal blockade was associated with improved survival and quality of life.

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. Potassium-lowering agent-incorporating neurohormonal blockade therapy in LVAD patients is a strategy that requires further prospective investigation.

**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), 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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