Impact of AKI in Patients with Out-of-Hospital Cardiac Arrest Managed with VA ECMO

Prasanth Ravipati,1 Sean Murray,1 Demetris Yannopoulos,1 Paul E. Drawz,1 and Jason A. Bartos1

Key Points
- AKI is associated with a high rate of mortality in patients managed with VA ECMO after out-of-hospital cardiac arrest.
- Therapeutic hypothermia is associated with hypokalemia and hypophosphatemia.
- During rewarming after hypothermia, hyperphosphatemia and hyperkalemia can develop. Electrolyte replacement should be carefully monitored.

Introduction
Venoarterial extracorporeal membrane oxygenation (VA ECMO) has emerged as an option for cardiogenic shock and cardiac arrest because it improves hemodynamics and serves as a bridge until alternative management strategies can be implemented (1,2). Since 2015, VA ECMO has been used at the University of Minnesota as part of the Minnesota Resuscitation Consortium’s (MRC’s) treatment strategy to improve outcomes for patients who suffer out-of-hospital cardiac arrest due to refractory ventricular fibrillation/ventricular tachycardia.

In this patient population, the incidence and clinical effect of AKI and AKI requiring RRT is not known. The goal of this study was to describe the effect of AKI and AKI requiring RRT on mortality for patients who suffer out-of-hospital cardiac arrest due to refractory ventricular fibrillation/ventricular tachycardia.

Methods
We conducted a retrospective chart review of patients treated in the MRC’s Advanced Perfusion and Reperfusion Cardiac Life Support Strategy for Out-of-Hospital Refractory Ventricular Fibrillation. Briefly, the protocol included patients aged >18 years suffering cardiac arrest with a shockable presenting rhythm refractory to standard advanced cardiovascular life support. They were transported directly to the University of Minnesota cardiac catheterization laboratory with ongoing mechanical cardiopulmonary resuscitation (CPR) via the automated Lund University cardiac arrest system. On arrival to the cardiac catheterization laboratory, patients were cannulated for VA ECMO, coronary angiography was performed, and revascularization by percutaneous coronary intervention completed when appropriate. All patients received therapeutic hypothermia with a goal temperature of 34°C, unless limited by life-threatening bleeding (3).

Patient data were obtained via an electronic database created as part of the resuscitation program’s quality improvement process, in conjunction with the health system’s electronic health record. The database provided baseline patient characteristics and clinical trends while inpatient. Review of the electronic health record identified those patients who required RRT (and follow-up of relevant outcomes at discharge, 90 days, 6 months, and 1 year). The Institutional Review Board at the University of Minnesota approved this study (Institutional Review Board 1703M11301).

Comorbidities were defined by chart review and through diagnosis codes. AKI was defined as Kidney Disease Improving Global Outcomes Stage 2 (serum creatinine 2.0–2.9 times baseline) or Stage 3 (serum creatinine 3.0 times baseline, serum creatinine ≥4.0 mg/dl, or initiation of RRT) AKI. Initiation of RRT was determined by the consulting nephrologist. Continuous venovenous hemodiafiltration was the initial modality for all patients with exception of one, who was initiated on conventional hemodialysis. Continuous venovenous hemodiafiltration was conducted through integration into the ECMO circuit via a Luer lock connection to the oxygenator. Anticoagulation was directed by the cardiology service per ECMO protocol (regional anticoagulation with citrate is not available at our institution). Mortality was ascertained by chart review and linkage with the Minnesota Death Index.

Analyses
We restricted analyses to participants without ESKD on admission and those who survived ≥24
hours to allow for development of AKI. Patients were categorized as no-AKI, AKI, and AKI requiring RRT. Descriptive statistics were utilized to describe baseline characteristics. Cox proportional hazards models were utilized to evaluate the association between AKI groups (no AKI, AKI without RRT, and AKI with RRT) and the outcome of interest, risk for all-cause mortality. Kaplan–Meier plots were utilized to show death-free survival by AKI category. Patients who did not die were censored on the date of their last known creatinine. Regarding electrolyte changes, we report the number and percent of patients who experienced electrolyte abnormalities during induced hypothermia in the first 24 hours of VA ECMO and then during the warming period 24–72 hours after initiation of VA ECMO. Targeted cooling was defined as an average temperature during a 1-hour period of <34°C. A warming period was defined as an average temperature during a 1-hour period >36°C, with an hourly average <34°C either 6, 12, 18, or 24 hours prior. All analyses were conducted using the R Statistical Computing Environment.

Results

Of the initial 143 patients initiated on VA ECMO, 116 were included in our analysis. In total, 22 patients were excluded due to death within 24 hours, and five patients were excluded because they carried a diagnosis of ESKD. Baseline characteristics are presented in Table 1. Patients with a previous history of hypertension had a significantly higher incidence of AKI. Otherwise, a previous history of diabetes or cardiovascular disease was not associated with higher incidence of AKI.

Among the 116 patients, 33 (28%) did not develop AKI or the need for RRT. In this population, mortality was 52% (17 out of 33) at 30 and 365 days. Of the 83 patients that developed AKI, 28 required RRT. Of those receiving RRT, 21 (75%) patients died within 30 days of VA ECMO initiation. The four patients who survived were all initiated on RRT >48 hours after initiation of ECMO. Among the 55 patients with AKI but without need for RRT, 37 (67%) died within 30 days and two (4%) died 31–365 days after their cardiac arrest (Table 1, Figure 1).

Regarding electrolyte derangements, results showed abnormalities in potassium and phosphate balance with cooling and rewarming. Of the 107 patients with measured potassium levels, 62 patients (64%) had marked hypokalemia with potassium <3 mmol/L in the first 24 hours associated with cooling. Additionally, 47 out of 82 (57%) patients developed hypophosphatemia with phosphate <2 mg/dl (Figure 2).

With rewarming, phosphate and potassium measurements were obtained in 51 and 67 patients, respectively. Rebound hyperkalemia and hyperphosphatemia was observed in a proportion of patients. In total, 47% (24 out of 51) of patients had hyperphosphatemia with levels >5.5 mg/dl. Rebound hyperkalemia was less frequent, with 15% (10 out of 67) of patients developing potassium >5.5 mmol/L (Figure 2).

Discussion

Current literature regarding cardiac arrest and AKI encompasses a wide range of patients including those requiring intra-aortic balloon pump, patients who suffer in-hospital cardiac arrest or postcardiac surgery arrest, and patients who may not require any mechanical support (4–6). In this study, we provide new data regarding a unique population of patients with AKI in the setting of refractory out-of-hospital cardiac arrest who have been treated with prolonged CPR, mechanical circulatory support via VA ECMO, coronary angiogram and percutaneous coronary intervention, and therapeutic hypothermia.

Our findings in this patient population demonstrate a high incidence of AKI with an associated increased risk of mortality, albeit this was not statistically significant. In terms of electrolyte changes, cooling was associated with development of hypokalemia, and hypophosphatemia and rewarming resulted in either normalization of potassium and phosphate or hyperkalemia and hyperphosphatemia. In terms of risk factors for development of AKI, we observed that patients with hypertension had a higher

| Table 1. Baseline characteristics of patients and survival by AKI/RRT status |
|--------------------------|----------|---------------|------------------|--------|
| Characteristics           | No Acute Kidney Injury | Acute Kidney Injury | Acute Kidney Injury-Renal Replacement Therapy | P Value |
| n                        | 33       | 55            | 28               |        |
| Age, yr                  | 54.8 (13.1) | 57.5 (11.7)  | 57.4 (11.2)      | 0.57   |
| Sex, M                   | 26 (79%) | 41 (75%)      | 26 (93%)         | 0.14   |
| Baseline creatinine, mg/dl| 1.1 (0.4) | 1 (0.3)       | 1.1 (0.2)        | 0.07   |
| Diabetes                 | 10 (30%) | 14 (25%)      | 7 (25%)          | 0.86   |
| Hypertension             | 10 (30%) | 34 (62%)      | 22 (79%)         | <0.001 |
| Cardiovascular disease   | 13 (39%) | 25 (45%)      | 13 (46%)         | 0.82   |
| Downtime to EMS, min     | 5 [4, 7], NA 13 | 6 [5, 9.5], NA 16 | 5 [4.75, 11.25], NA 12 | 0.17   |
| Overall 365 day mortality| 17 (52%) | 39 (71%)      | 24 (86%)         |        |
| Death within 30 days     | 17 (52%) | 37 (67%)      | 21 (75%)         |        |

Median (interquartile range) unless otherwise indicated. M, male; EMS, emergency medical services.
incidence of AKI. Hypertension has previously been demonstrated as a risk factor for patients who suffer an acute myocardial infarction (7). This increased risk may be due to impaired renal vasculature autoregulation in patients with chronic hypertension, resulting in renal function that is more sensitive to hypotension (8).

The overall rate of AKI in our group was 72%, higher than a previous meta-analysis that demonstrated a 61% incidence of AKI in patients who received VA ECMO (included patients who were non–cardiac arrest) (9). Regarding mortality, a previous review of AKI in patients undergoing VA ECMO for cardiac arrest demonstrated no difference in the mortality between patients with AKI (70%) and those without (71%) (4). Our mortality rate of 76% for patients with AKI is similar; however, mortality in the prior study in patients without AKI is higher than the 52% mortality in our study. This may demonstrate a tipping point, where patients with excellent resuscitation are supported with VA ECMO and mortality is reduced. However, comparisons with both previous studies are not ideal because the circumstances of cardiac arrest and initiation of VA ECMO varied.

Overall, this is a critically ill group of patients, most of whom developed multiorgan system dysfunction (liver, pulmonary, cardiac) (10). These patients had prolonged duration of CPR before initiation of hemodynamic support with VA-ECMO and vasopressors, given that their arrest occurred outside the hospital (10,11). Additionally, all patients underwent coronary angiography, exposing them to intravenous contrast media, which can directly contribute to kidney injury. These factors likely played a critical role in the reported mortality rate and incidence of AKI.

Regarding timing of initiation of RRT, because there were no survivors among the 11 patients who initiated RRT within 48 hours of ECMO initiation, the need for early RRT may reflect severe end-organ injury and portend a poor prognosis.

Previous literature has described electrolyte abnormalities related to therapeutic cooling—particularly hypokalemia and hypophosphatemia. In a review of 21 patients with severe head trauma who underwent induction of hypothermia, significant hypokalemia and hypophosphatemia was observed. The authors described hypothermia-induced polyuria as a main driver of electrolyte depletion, along with intracellular shifting as a result of cooling (12). An additional study of patients who underwent cooling after cardiac arrest also described hypokalemia during cooling (13). One proposed mechanism is that cooling promotes increased endogenous catecholamine production, resulting in shifting of potassium intracellularly (14). In our study, we had similar findings of
hypoventilation, hypokalemia, and hypophosphatemia associated with cooling. With rewarming, we identified rebound hyperphosphatemia.

Overall, the clinical significance of these fluctuations is not completely clear. Potassium abnormalities do carry a risk of ventricular arrhythmia, and hypophosphatemia carries both neurologic and cardiac risk (12,13). Thus, repletion of these electrolytes may be of benefit, but close monitoring is warranted given the risk of hyperkalemia and hyperphosphatemia with rewarming. The protocol at our institution prohibits potassium replacement when serum potassium is >3.0 mmol/L in an effort to reduce the risk of rebound hyperkalemia.

There are multiple limitations of this study. The size of the study population is small and generalizability may be limited given the single-center nature of this study using a unique clinical protocol. Further, our exclusion of patients who died early likely eliminates a portion of the AKI population because these patients likely suffered severe injury leading to their death. However, the higher mortality rate observed in those with AKI is despite the immortal time bias before developing AKI. Additionally, our definition of AKI did not include patients with Kidney Disease Improving Global Outcomes Stage 1 AKI. Thus, we may have underestimated the number of patients with AKI. However, we did not want to misclassify patients as having AKI if they had small fluctuations in creatinine because it is unclear how to interpret these changes in this complex patient population.

AKI is associated with a high rate of mortality in this unique patient population undergoing VA ECMO. It remains unclear if the presence of AKI is purely prognostic with a relationship to the severe injury caused by cardiac arrest, or if AKI directly worsens mortality. In addition, there are fluctuations in potassium and phosphate associated with therapeutic cooling and rewarming. This study raises questions regarding the management of patients with out-of-hospital cardiac arrest who are supported with VA ECMO. It remains unknown if early initiation of RRT for early management of potassium, phosphate, and volume would provide benefit. As techniques evolve in both CPR and ECMO, we could see changes in rates of mortality and AKI in this patient population. In the interim, ongoing data collection is needed to identify the ideal management approach for these patients who develop AKI.

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Author Contributions
J. Bartos, P. Drawz, S. Murray, and D. Yannopoulos conceptualized the study; S. Murray, P. Ravipati, and D. Yannopoulos were responsible for data curation; P. Drawz was responsible for the formal analysis; J. Bartos and P. Ravipati wrote the original draft; and J. Bartos, P. Drawz, P. Ravipati, and D. Yannopoulos reviewed and edited the manuscript.

References

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