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Acute Kidney Injury and Mortality following Ventricular Assist Device Implantation

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Abstract

Background—Ventricular assist devices (VADs) are increasingly common and their surgical implantation predisposes patients to an increased risk of acute kidney injury (AKI). We sought to evaluate the incidence, risk factors, short and long term all cause mortality of patients with AKI following VAD implantation.

Methods—We identified all patients who underwent VAD implantation at the University of Chicago from January 1, 2008 to January 31, 2012. We evaluated the incidence of AKI, defined as a ≥50% increase in serum creatinine over the first 7 post-operative days (RIFLE Risk-Creatinine). A logistic regression model was used to identify risk factors for development of AKI and a cox proportional hazards model was used to examine factors associated with 30-day and 365-day all cause mortality.

Results—157 eligible patients had VAD implantations with 44 (28%) developing postimplantation AKI. In a multivariate analysis only diabetes mellitus $[OR=2.25 (1.03-4.94), P=0.04]$ was identified as a significant predictor of postoperative AKI. Using a multivariable model censored for heart transplantation, only AKI [HR= $3.01(1.15-7.92)$, P=0.03] and cardiopulmonary bypass time $[HR = 1.01(1.001-1.02), P = 0.02]$ were independent predictors of 30-day mortality. Pre-operative Body Mass Index [HR=0.95(0.90-0.99), P=0.03], pre-operative diabetes mellitus $[HR=1.89 (1.07-3.35), P=0.03]$ and post-implantation AKI $[HR=1.85 (1.06-3.21); P=0.03]$ independently predicted 365-day mortality.

Conclusion—AKI is common following VAD implantation and is an independent predictor of 30-day and 1-year all cause mortality.

Keywords

Acute Kidney Injury; Cardiac Surgery; Mortality; Ventricular Assist Device; RIFLE

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Introduction

Acute Kidney Injury (AKI) is common following traditional cardiac surgery [coronary artery bypass grafting (CABG) and/ or valve replacement] and is an independent risk factor for post-operative mortality [1,2]. Additionally, AKI has been associated with higher patient morbidity, longer length of stay, higher costs [1,3-5]. Multiple pre-operative risk stratification systems have been developed to predict the development of AKI following traditional cardiac surgery, however their role and application in the setting of ventricular assist device (VAD) implantation is unclear [6-9].

Since the Randomized Evaluation of Mechanical Assistance for the treatment of congestive heart failure (REMATCH) trial [10] there has been an increased number of VADs being implanted, with nearly 6000 VADs being implanted since June 2006 [11]. The first generation VADs were pulsatile and presumably more "physiologic", however they were associated with higher infection and thrombosis rates, lower durability and even lower cardiac transplant rates in comparison to continuous flow devices [12]. This has lead to a transition away from pulsatile flow devices to continuous flow devices which now make up for > 90% implants in the United States [13]. While the increasing numbers of implants , have improved our understanding of the impact of AKI during the peri-operative period; its etiology, predictors and short and long term consequences require further investigation. Previous studies have been difficult to interpret, as many have not used consensus definitions of AKI [14-19]. Utilizing consensus definitions of AKI, we performed a singlecenter, retrospective, longitudinal cohort study to evaluate the incidence of AKI following VAD implantation and to identify risk factors as well as assessing its impact on 30 and 365 day survival.

Methods

The Institutional Review Board of The University of Chicago approved this study. We performed a single center, retrospective chart review, of all patients who underwent a ventricular assist device placement at our institution from January 1, 2008 through January 31, 2012. Patients with End Stage Renal Disease (ESRD), those who were already on renal replacement therapy (RRT) for AKI prior to VAD implantation and those who died intraoperatively were excluded.

Observations and Measurements

Demographic, biochemical and clinical profiles were obtained from the INTERMACS national registry , Society of Thoracic Surgeons (STS) database and the University of Chicago electronic medical record (EMR) [20]. We collected preoperative data on age, race, sex, body mass index (BMI), baseline renal function (estimated glomerular filtration rate (eGFR) using MDRD) [21], past medical history, hemodynamic numbers; intraoperative data including cardiopulmonary bypass time and receipt of blood products, post-operative data including length of stay, post-operative complications (e.g. sepsis, thromboembolic events), need for RRT and in-hospital mortality. Baseline creatinine was defined as the listing creatinine data obtained from the INTERMACS registry, if INTERMACS did not contain a preoperative serum creatinine then the last serum creatinine in the EMR prior to

device implantation was used . We collected information about the indication for VAD implantation [Bridge to Transplant (BTT) or Destination Therapy (DT)] as well as the type

Outcomes

of device implanted.

The primary outcome of AKI was defined as a 50% rise in serum creatinine over the preoperative baseline during the first 7 postoperative days as per the creatinine based RIFLE "Risk" Criteria [22]. The Acute Kidney Injury Network (AKIN) creatinine criteria [23,24] and urine output criteria were utilized for secondary analyses. All cause mortality was monitored over 1-year post implantation, with data reported at 30 and 365 days.

Statistical Methods—Qualitative data was recorded in a categorical fashion and quantitative covariates were measured as continuous variables. Differences between characteristics were analyzed either by an unpaired t-test or the Wilcoxon signed rank test as appropriate. Categorical variables were assessed by chi square analysis or the Fischer's exact test. Categorical variables were reported with their corresponding odds ratio (OR), hazards ratio (HR) and 95 percent confidence intervals. Continuous variables are represented with mean and their 95% CI values and hazards ratio (HR) when pertaining to survival data.

To assess determinants of AKI we first performed a univariate logistic regression analysis. Significant predictors $(p<0.10)$ were then included in a multivariate model.

Survival data was analyzed using cox proportional hazards modeling. All survival data was censored for cardiac transplantation. We analyzed survival at 30 and 365 days. Significant variables (p<0.10) were then included in a multivariate model. All statistical tests were 2 sided with the alpha set at 0.05 for statistical significance. STATA 11.2 (StataCorp LP, College Station TX) was used for all data analysis.

Results

Baseline Characteristics of those with acute kidney Injury

We identified 168 patients who underwent VAD implantation at our institution during the study period. Eleven subjects were excluded from the analysis with 8 patients having previous ESRD, 2 requiring pre-implant RRT for AKI and 1 subject with intra-operative mortality. In the final cohort of 157 a total of 44 (28%) patients developed AKI. Table 1a and 1b demonstrates the pre-, intra- and post-operative characteristics of those with and without AKI. Prior to implantation, there was no difference in age, baseline renal function (serum creatinine and eGFR), NYHA CHF class, preoperative hemodynamics, INTERMACS score, the presence of cardiogenic shock or inotrope use in those with and without AKI. However those with AKI tended to have more diabetes and cerebrovascular disease (CVD) and had higher pre-operative hematocrits (Table 1a). Intra-operatively there was no difference in cardiopulmonary bypass time, need for packed red blood cell (PRBC) transfusion or units of PRBC transfused between the two groups. Post-operatively there was no difference in complications including bleeding, cardiac tamponade, prolonged ventilation, postoperative sepsis, ischemic strokes (symptoms lasting greater than 24 hours) or pneumonia, however those with AKI had longer ICU stays and a higher in-hospital

mortality (Table 1b). Both groups had a net negative fluid balance by day 7. However patients with AKI had a significantly less net negative fluid balance by day 7 in comparison to the no AKI group $(p=0.02)$.

Table 2 demonstrates the varied AKI event rates in the complete cohort of 157 subjects, utilizing RIFLE and AKIN criteria. The incidence varied greatly depending of the AKI criteria (creatinine, urine output or both). (Table 2).

Predictors of AKI following VAD implantation

Utilizing univariate logistic regression modeling, diabetes and prior cerebrovascular disease were identified as significant predictors of the development of AKI (Table 3). However on a multivariate analysis only diabetes [OR= 2.27 (1.03-4.97), P=0.04] was identified as a significant predictor of postoperative AKI with prior cerebro-vascular disease and preoperative hematocrit demonstrating a trend towards significance (Table 3).

AKI and All-cause mortality: 30 day and 365 days

At 30 days, 11(26 %) of those with AKI had died compared to 8 (7%) without AKI (p=0.002). At 365 days, 21(48 %) of those with AKI had died compared to 34 (30%) without AKI (p=0.03). Figure 1 demonstrates the Kaplan Meier Survival Curves for those with and without AKI, with data censored for cardiac transplantation.

In a univariate model to identify predictors of 30 and 365-day mortality several variables were determined to be significantly associated with patient survival (Table 4 and 5). Using a multivariable model AKI [HR=3.01(1.15-7.91), p=0.03] and longer bypass time [1.01(1.001-1.02), P=0.02] were independent predictor of a higher 30-day mortality (Table 4). While AKI [HR=1.85(1.06-3.22); p=0.03] and diabetes mellitus [HR= 1.9(1.07-3.35), P=0.03] were associated with higher mortality at 365 days (Table 5). Higher preoperative BMIs were protective, and were associated with lower mortality at 365 days [0.95 $(0.90-0.99)$, p=0.03].

Discussion

Current literature on incidence of AKI in patients with VAD implantation and its outcomes are limited. Prior studies have defined AKI based the need for RRT while others have used non-standardized definitions [14-19,25-28]. Conducting a single center retrospective cohort study utilizing internationally accepted consensus definitions we identified the incidence of AKI as 28%(n=44) with a high portion of these patients receiving RRT (n= 9; 5.7% of the total cohort). Additionally, our study demonstrates that AKI is associated with short and long-term mortality following VAD implantation [29] .

Diabetes has been shown to increase the risk of AKI following traditional cardiac surgery [6,7]. In a multivariate analysis we identified diabetes as the sole predictor of AKI after VAD implantation. Previous studies in VADs had identified age, baseline eGFR and perfusion time as other risk factors for the development of post implant AKI [30,31]. However similar to the Borgi and colleagues [32] we were unable to demonstrate perfusion time as a risk factor for AKI. Our inability to replicate differences in baseline eGFR may

stem from our utilization of the standardized creatinine based definition of AKI rather than more subjective definitions [14-19].

In our study, predictors of 30-day mortality included AKI and perfusion time. Our findings mirror those of *Borgi et al.*, a smaller single center study (n=100), and demonstrate that post-VAD AKI is also a predictor of 1-year mortality [32]. After our adjusted analyses these findings further strengthen the pre-existing literature demonstrating the long-term consequences of AKI in a variety of clinical settings[33,34]. Additionally, we observed that patients with a higher pre-operative BMI had lower 1-year mortality; corroborating the findings of *Butler et al* who demonstrated that in a univariate analyses the 180 and 365-day survival after VAD implantation was significantly higher among patients with higher BMIs. However, unlike our study this effect was no longer significant following multivariate analysis. [35]

Age, baseline eGFR, gender and African American race have been previously reported to have an impact on AKI and mortality. However we did not identify these to be significant AKI risk factors (Tables 4,5). The recently published fifth INTERMACS report: identified age to be a predictor of mortality although the actuarial survival of patients older than 70 years was reported to be only modestly inferior to those older than age 50 [13] .Similarly we were unable to identify baseline eGFR as predictor for short and long term survival. Even after stratifying pre-implant eGFR to < 60 ml/minute and ≤ 60 ml/minute we found no significant difference in long-term mortality (Data not shown). This was contrary to the study done by Sandner et al, which reported worse survival for group with e GFR $<$ 60 ml/ minute [36]. Our inability to demonstrate eGFR as a risk factor may stem from the lower than previously published eGFR in our cohort (49.7 ml/min). Traditionally African Americans have been noted to have worse outcomes after cardiac surgeries [37,38], but our study as well two recently published studies showed no difference in outcomes in patients who had a VAD placed [39,40]. Women have also been reported to be at higher risk for mortality after traditional cardiothoracic surgery, but we did not appreciate that in any of our analysis [6,41,42].

Haase et al demonstrated no difference in diagnosing AKI following traditional cardiac surgery when comparing the RIFLE and AKIN criteria [43]. However, unlike our cohort, in their prospective observational study, less than 25% of all patients had an eGFR less than 60 ml/min. Our study demonstrated clear differences between the AKIN and RIFLE criteria defined AKI; with over 67 (42.7%) subjects developing AKIN serum creatinine based Stage-1, compared to 28% for RIFLE-Risk. In a secondary analysis the use of AKIN-stage-1 (creatinine criteria) was not associated with a significant risk of mortality 30-day [HR=1.88 (0.76-4.67, P=0.17)] or 365-day [HR=1.41 (0.83-2.41, P=0.2)] survival. This analysis suggests the use of a 0.3 mg/dl increase in serum creatinine to identify post-VAD AKI may be inferior to RIFLE- Risk (50% increase) from a prognostic perspective. Similarly despite the high proportion of patients with AKI defined by urine output, $n=119(75.8\%)$, Stage-1 <0.5 ml/kg/h for 6 hours) (Table 2) we did not note any statistically significant impact on 30 and 365-day survival (data not shown). A recent study in a general ICU cohort has raised the question whether the urine output criteria for defining AKI is too liberal. Similar to our observation the authors were unable to show an impact of AKI as defined by urine output

criteria to have a significant impact on 1 year mortality $[44]$. However these findings need to be validated in larger multicenter prospective trials.

Questions remain about the effects of pulsatile versus continuous flow devices on renal function. While pulsatile flow is physiologic and theoretically better, based on the limited published human data, renal outcomes have not differed across the 2 modalities [25]. Perhaps counter-intuitively, continuous flow devices have been associated with lower device related complications and improved outcomes [28,45,46]. The further investigation of this issue has proven difficult, with greater than 90% of U.S. VAD implantations being continuous flow devices [13].

Our study has several strengths in that to our knowledge this is the largest cohort study of VAD patients to employ a consensus definition of AKI, including analyzing AKI endpoints defined by urine output. Additionally compared to previously published papers we have a significant number of African American patients as well as DT VAD patients. Both these sub-populations that are steadily increasing [11]. Our study suffers from all the inherent limitations of a single center retrospective review. However it is these same single-center factors that allowed us to have excellent patient follow-up and complete, demographic, postoperative serum creatinine and urine output data. Additional strengths include utilization of our single center electronic medical record and access to INTERMACS to validate the true pre-implantation baseline creatinine/eGFR. Included in our limitations is the low numbers of patients who developed severe AKI (RIFLE I or F), and this limits our ability to make any conclusions about severe AKI.

In conclusion, we identified the incidence of AKI following VAD implantation to be 28% and those who developed AKI had increased risk for both short and long term mortality. Further investigations are needed to tease out the differences between the risks of AKI following traditional cardiac surgery versus VAD implantations. Additionally, given high AKI event rates and the mounting evidence linking AKI to mortality following VAD implantation, the use of biomarkers to identify those at risk may have a role. Larger prospective multicenter trials are needed to develop a risk stratification system to identify patients at risk for developing post VAD implantation AKI.

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Figure 1.

The figure demonstrates the 1-year survival curves for patients with and without AKI. The hash marks denote censoring. At 365 days, 21(48%) of those with AKI had died compared to 34 (30.1%) of those without AKI p=0.03.

eGFR – Estimated Glomerular Filtration Rate

RAP- Right Atrial Pressures

RVSP- Right Ventricle Systolic pressure

PASP – Pulmonary artery Systolic Pressure.

PADP- Pulmonary artery diastolic pressure

PCWP – Pulmonary capillary wedge pressure.

PVAD/RVAD- Paracorporeal ventricular /Right ventricular assist device.

Data presented as either mean \pm SD or median (inter-quartile range) as appropriate

CPB- Cardiopulmonary bypass

PRBC- Packed red blood cells

RRT- Renal replacement therapy

Data presented as either mean \pm SD or median (inter-quartile range) as appropriate

SCr – Serum Creatinine

RIFLE[22] - Risk of renal dysfunction, Injury to the Kidney, Failure or Loss of kidney function, and End Stage renal disease. (AKI assessed over 7 days)

AKIN[23] – Acute Kidney Injury Network (AKI assessed over 48 hours)

Table 3

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 \mathbf{BMI} – \mathbf{Body} Mass Index BMI – Body Mass Index eGFR - estimated glomerular filtration rate eGFR – estimated glomerular filtration rate

PRBC-Packed red blood cells PRBC- Packed red blood cells

PVD-Peripheral vascular disease PVD- Peripheral vascular disease

CVD-cerebrovascular disease CVD- cerebrovascular disease

CHF-congestive heart failure CHF- congestive heart failure

eGFR – estimated glomerular filtration rate

PRBC- Packed red blood cells

PVD- Peripheral vascular disease

CVD- Cerebrovascular disease

CHF- Congestive heart failure

BMI- Body Mass Index

PCWP- Pulmonary capillary wedge pressure

UNIVARIATE COX PROPORTIONAL HAZARDS MODEL	HR (95%CI)	P-value
Age	$1.00(0.99 - 1.03)$	0.53
Male Sex	$1.12(0.58 - 2.19)$	0.72
Black Race	$0.99(0.56 - 1.72)$	0.96
e GFR	$0.99(0.98 - 1.00)$	0.29
AKI	$2.01(1.16 - 3.48)$	0.01
BMI	$0.96(0.92 - 1.00)$	0.08
Diabetes	$1.66(0.97-2.84)$	0.06
CHF	$0.63(0.27-1.48)$	0.29
Hypertension	$1.26(0.74 - 2.16)$	0.31
Cardiogenic Shock	$1.06(0.60 - 1.88)$	0.81
Cerebrovascular Disease	$1.25(0.57 - 2.77)$	0.58
Perfusion Time	$1.00(1.00-1.01)$	0.04
Hematocrit	$1.00(0.95 - 1.05)$	0.99
Intraoperative PRBC use	$1.25(0.73 - 2.16)$	0.40
Right Atrial Pressure	$0.99(0.95 - 1.04)$	0.86
PCWP.	$1.00(0.97-1.04)$	0.92
Cardiac Output	$1.02(0.85 - 1.23)$	0.80
MULTIVARIATE COX PROPORTIONAL HAZARDS		
AKI	$1.85(1.06 - 3.22)$	0.03
BMI	$0.95(0.90 - 0.99)$	0.03
Diabetes	$1.90(1.07-3.35)$	0.02
Perfusion Time	$1.00(0.99 - 1.01)$	0.07

Table 5 Hazard Ratios for 365-day All-Cause Mortality following VAD Implantation

eGFR – estimated glomerular filtration rate.

PRBC- Packed red blood cells.

PVD- Peripheral vascular disease.

CVD- Cerebrovascular disease.

CHF- Congestive heart failure.

BMI- Body Mass Index.

AKI- Acute Kidney Injury.

PCWP- Pulmonary capillary wedge pressure.