ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Impact of ventricular assist device placement on longitudinal renal function in children with end-stage heart failure

Lindsay J. May, MD,[a] Maria E. Montez-Rath, PhD,[b] Justin Yeh, MD,[c] David M. Axelrod, MD,[d] Sharon Chen, MD,[d] Katsuhide Maeda, MD,[e] Christopher S.D. Almond,[d] David N. Rosenthal, MD,[d] Seth A. Hollander, MD,[d] and Scott M. Sutherland, MD[f]

From the [a]Division of Pediatric Cardiology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah; [b]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California; [c]Division of Pediatric Cardiology, Department of Pediatrics, University of California San Diego, La Jolla, California; [d]Division of Pediatric Cardiology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California; [e]Division of Pediatric Cardiac Surgery, Department of Cardiothoracic Surgery, Stanford University, Palo Alto, California; and the [f]Division of Pediatric Nephrology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California.

KEYWORDS:
ventricular assist device;
end-organ dysfunction;
renal function;
children;
end-stage heart failure

BACKGROUND: Although ventricular assist devices (VADs) restore hemodynamics in those with heart failure, reversibility of end-organ dysfunction with VAD support is not well characterized. Renal function often improves in adults after VAD placement, but this has not been comprehensively explored in children.

METHODS: Sixty-three children on VAD support were studied. Acute kidney injury (AKI) was defined by Kidney Disease: Improving Global Outcomes criteria. Estimated glomerular filtration rate (eGFR) was determined by the Schwartz method. Generalized linear mixed-effects models compared the pre-VAD and post-VAD eGFR for the cohort and sub-groups with and without pre-VAD renal dysfunction (pre-VAD eGFR $<$ 90 ml/min/1.73 m^2).

RESULTS: The pre-VAD eGFR across the cohort was 84.0 ml/min/1.73 m^2 (interquartile range [IQR] 62.3–122.7), and 55.6% (34 of 63) had pre-VAD renal dysfunction. AKI affected 60.3% (38 of 63), with similar rates in those with and without pre-existing renal dysfunction. Within the cohort, the nadir eGFR occurred 1 day post-operatively (62.9 ml/min/1.73 m^2; IQR, 51.2–88.9 ml/min/1.73 m^2; $p < 0.001$). By Day 5, however, the eGFR exceeded the baseline (99.0 ml/min/1.73 m^2; IQR, 59.3–146.7 ml/min/1.73 m^2; $p = 0.03$) and remained significantly higher through the first post-operative week. After adjusting for age, gender, and AKI, the eGFR continued to increase throughout the entire 180-day study period ($\beta = 0.0025$; 95% confidence interval, 0.0015–0.0036; $p < 0.001$). Patients with pre-VAD renal dysfunction experienced the greatest improvement in the eGFR ($\beta = 0.0051$ vs $\beta = 0.0013$, $p < 0.001$).

CONCLUSIONS: Renal dysfunction is prevalent in children with heart failure undergoing VAD placement. Although peri-operative AKI is common, renal function improves substantially in the first post-operative week and for months thereafter. This is particularly pronounced in those with pre-VAD

Reprint requests: Lindsay J. May, MD, Division of Pediatric Cardiology, University of Utah, 81 N. Mario Capecchi Dr, Salt Lake City, UT 84113. Telephone: +801-213-7613. Fax: +801-213-7778.
E-mail address: lindsay.may@hsc.utah.edu

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2015.10.039

renal impairment, suggesting that VADs may facilitate recovery and maintenance of kidney function in children with advanced heart failure.
J Heart Lung Transplant 2016;35:449–456

Renal dysfunction is common in the setting of heart failure. Although this phenomenon has been best described in adults, it also occurs in pediatric patients with end-stage heart disease (ESHD), often as part of the cardiorenal syndrome.[1,2] The exact mechanism by which heart failure causes kidney dysfunction is poorly understood, but reduced renal perfusion, increased neurohumoral activation, and renal vein congestion with systemic venous hypertension have been implicated.[2–4] Irrespective of the mechanism, renal dysfunction is a well-recognized prognostic indicator for mortality in adults with heart failure.[5–8]

This association between renal dysfunction and poorer outcomes has been extrapolated to pediatric ESHD patients with significant ramifications. Use of a ventricular assist device (VAD) as a bridge to transplant or destination therapy has become more common in children with ESHD. As mechanical support evolves in the pediatric community, candidate selection hinges on end-organ assessment. End-organ dysfunction that is deemed irreversible may be considered a contraindication to VAD implantation.[9] However, renal recovery is challenging to predict, and several studies in adults have reported improved kidney function both in the short-term and long-term after VAD implantation.[10–16]

To date, the effect of VAD implantation on renal function has not been comprehensively studied in children. The goal of this study was to characterize renal function after VAD implantation in children with ESHD and describe the trajectory of renal function in the days and months after VAD placement. We hypothesized that children with ESHD commonly experience acute kidney injury (AKI) after VAD placement and that a sustained improvement in renal function would follow VAD implantation.

Methods

The Human Subjects Research and Institutional Review Board at Stanford University approved this investigation.

Study location and patient population

This single-center, retrospective review was performed at the Lucile Packard Children's Hospital (Stanford University Medical Center, Palo Alto, CA), a quaternary care pediatric hospital. The study included all patients aged $<$ 21 years with ESHD who underwent VAD implantation between May 2005 and November 2013. VADs were placed as a bridge to heart transplantation, recovery, decision, or as a destination therapy. Data were extracted from the electronic medical record, including demographics and anthropometrics, clinical characteristics, the need for renal replacement therapy, and serum creatinine and blood urea nitrogen (BUN) values pre-operatively, daily for post-operative days (PODs) 1 to 7, POD 14, and every month for the duration of VAD support for each patient. Clinical data were stored and managed using REDCap 4.5.2 (Vanderbilt University, Nashville, TN), a Web-based application designed to support data capture for research studies.[17]

Defining AKI and serial determination of renal function

AKI was defined according to the Kidney Disease: Improving Global Outcomes serum creatinine criteria.[18] Estimated creatinine clearance (estimated glomerular filtration rate [eGFR]) was determined according to the Schwartz formula.[19,20] AKI was diagnosed and staged during the first 7 post-operative days:

- Stage 1 AKI was defined as an elevation in serum creatinine by $\geq$ 0.3 mg/dl ($\leq$ 48 hours) or 1.5- to 1.9-times above baseline.
- Stage 2 AKI was defined as an increase in serum creatinine by 2- to 2.9-times above baseline.
- Stage 3 AKI was defined as an increase in serum creatinine by 3-times above baseline, a decrease in the eGFR to $<$ 35 ml/min/1.73 m^2, or initiation of renal replacement therapy.

Based on Kidney Disease: Improving Global Outcomes definitions,[21] pre-VAD renal dysfunction was defined as an eGFR $<$ 90 ml/min/1.73 m^2 immediately before VAD implantation.

Statistical analysis

The primary outcome measure was the change in the pre-operative eGFR to various post-operative time points. The incidence of peri-operative AKI was a secondary outcome measure. These outcomes were assessed across the entire cohort as well as in the sub-groups of patients with and without pre-VAD renal dysfunction. Student's *t*-tests or chi-square tests were applied to normally distributed data, and signed rank analysis or Fisher's exact tests were applied to data that did not follow a normal distribution. We report median (interquartile range [IQR]) and mean (standard deviation [SD]) for non-normally and normally distributed data, respectively.

Patients who underwent transplant or died were included in the analysis until this outcome occurred. The eGFR measurements presented as non-normal (right skewed) with non-constant variance over time; therefore, a generalized linear mixed-effects model was used, assuming a gamma distribution with log link (Appendix I, available on the jhltonline.org Web site). The approach used a patient-level random intercept representing each individual's deviation from the overall mean level in the response variable after adjusting for age, gender, and post-operative development of AKI. An interaction between pre-VAD renal dysfunction and time was included in the model to test whether baseline the eGFR modified the association of the change in the eGFR over time. We computed and plotted the predicted mean eGFR over time (when the random intercept was 0) to show the average predicted eGFR curve over time. To assess differences in the eGFR levels over time compared with baseline after adjustment, we modeled time as a categoric variable and computed the differences in the marginal

predictions, using the "margins" command in Stata MP 13 software (StataCorp LP, College Station, TX), which represents the discrete change in the eGFR levels from baseline. This analysis was stratified by pre-VAD renal dysfunction. All p-values ≤ 0.05 were considered statistically significant. Analyses were performed using Stata MP 13 software.

Results

Demographics and clinical data

The analysis included 63 patients (63.5% male) who underwent VAD implantation between May 2005 and November 2013. Baseline characteristics are reported in Table 1. Patients were a median age of 6.2 years (IQR, 0.64–14.4 years). The most common diagnoses were dilated cardiomyopathy (37 [58.7%]) and failed palliation of congenital heart disease (15 [23.8%]). All patients had New York Heart Association/Ross Functional Classification IV[22–24] heart failure at the time of VAD implantation. Medical management and the proportion of patients with chronic heart failure were similar in the sub-groups with and without pre-VAD renal dysfunction.

The EXCOR (Berlin Heart AG, Berlin, Germany) was the most commonly used device (31 [49.2%]). Support was with a continuous-flow device in 20.6% of the cohort. Temporary VADs were used in 5 patients (1 Impella [Abiomed, Danvers, MA] and 4 centrifugal devices). Four of these 5 patients were exclusively on centrifugal VADs support. The fifth patient was transitioned from the Impella device (after 2 weeks) to a HeartMate II (Thoratec, Pleasanton, CA). Renal function data for this patient reflect the HeartMate II implant only, because the Impella is the only device not requiring cardiopulmonary bypass at the time of implant. This enabled comparisons that included the potential insult of cardiopulmonary bypass.

Five patients had single-ventricle physiology requiring VAD support for the systemic ventricle. Bridge to transplant (54 [85.7%]) was the most common indication for implantation. The median duration of support was 57 days (IQR, 28.3–118.3 days); the mechanical circulatory support course in 12 patients exceeded 150 days.

Thirty-four patients (54.0%) had pre-existing renal dysfunction (eGFR $<$ 90 ml/min/1.73 m^2) with a median eGFR of 63.8 ml/min/1.73 m^2 (IQR, 44.3–73.3 ml/min/1.73 m^2). Pre-operative renal function was within normal reference ranges (eGFR $\geq$ 90 ml/min/1.73 m^2) in 29 patients (46.0%); the median eGFR of this sub-group was 126.7 ml/min/1.73 m^2 (IQR, 106.7–151.3 ml/min/1.73 m^2).

Forty-one patients (65.0%) in the overall cohort underwent heart transplant. There were 15 deaths while on VAD support; mortality was similar in those with an eGFR $\geq$ 90 ml/min/1.73 m^2 (6 of 29 [20.7%]) and those with an eGFR $<$ 90 ml/min/1.73 m^2 (9 of 34 [26.5%], $p = 0.59$). Myocardial recovery occurred in 1 patient in the entire cohort, and the VAD was explanted. Six patients remained on VAD support at the time of analysis.

Table 1 Baseline Characteristics and Outcomes

Patient characteristics[a]	Entire cohort ($N = 63$)	Baseline eCrCl $<$ 90 mL/min/1.73m^2 ($n = 34$)
Male gender	40 (63.5)	21 (61.8)
Diagnosis		
Dilated cardiomyopathy	37 (58.7)	22 (64.7)
Restrictive cardiomyopathy	4 (6.3)	2 (5.9)
ARVC	1 (1.6)	0
Congenital heart disease	15 (23.8)	7 (20.6)
Myocarditis	4 (6.3)	2 (5.9)
Transplant, graft failure	2 (3.2)	1 (2.9)
Time from heart failure diagnosis to VAD implant, months	1.5 (0.29–5.18)	1.4 (1.42–3.3)
Chronic heart failure[b]	20 (31.7)	10 (29.4)
Baseline medications		
ACE inhibitor	15 (23.8)	4 (11.8)
β-Blocker	11 (17.5)	3 (8.8)
Diuretic	12 (19.0)	6 (17.6)
Milrinone	0	0
Incomplete records	10 (15.9)	6 (17.6)
Medications 48 hours before VAD		
ACE inhibitor	3 (4.8)	1 (2.9)
β-Blocker	5 (7.9)	3 (8.8)
Diuretic	22 (34.9)	13 (38.2)
Milrinone	28 (44.4)	15 (44.1)
Dopamine	23 (36.5)	12 (35.3)
Epinephrine	10 (15.9)	6 (17.6)
Incomplete records	28 (44.4)	15 (44.1)
Support type		
LVAD	44 (69.8)	24 (70.6)
RVAD	5 (7.9)	3 (8.8)
BiVAD	14 (22.2)	7 (20.6)
Device		
Berlin EXCOR	31 (49.2)	17 (50.0)
HeartWare HVAD	4 (6.3)	1 (2.9)
HeartMate II	9 (14.3)	2 (5.9)
Thoratec PVAD	14 (22.2)	10 (29.4)
Other[c]	5 (7.9)	4 (11.8)
Intent		
Bridge to transplant	54 (85.7)	30 (88.2)
Bridge to decision	2 (3.2)	1 (2.9)
Bridge to recovery	3 (4.8)	2 (5.9)
Destination therapy	4 (6.3)	1 (2.9)
Outcomes		
Transplantation	41 (65.1)	20 (58.8)
Explant	2 (3.2)	1 (2.9)
Ongoing support-inpatient	2[d] (3.2)	0
Ongoing support-outpatient	3[e] (4.8)	0
Death	15 (23.8)	13 (38.2)

ACE, angiotensin-converting enzyme; ARVC, arrhythmogenic right ventricular cardiomyopathy; BiVAD, biventricular assist device; eCrCl, estimated creatinine clearance; LVAD, left ventricular assist device; RVAD, right ventricular assist device; VAD, ventricular assist device.

[a]Categoric data are presented as number (%) and continuous data as median (interquartile range).

[b]Chronic heart failure defined as 3 months or longer.

[c]Other: 4 centrifugal VADs and 1 Abiomed Impella.

[d]One patient was transferred to another hospital.

[e]Patients received VADs as destination therapy.

Acute kidney injury

Rates of AKI in the first 7 post-operative days are reported in Table 2. AKI developed post-operatively in 38 patients (60.3%). Among patients with AKI, 24 of 38 (63.1%) experienced severe AKI (Stage 2 or greater): Stage 2 occurred 6 of 38 (15.8%), and Stage 3 in 18 of 38 (47.3%). Notably, 4 patients (6.3%) required renal replacement therapy during the first post-operative week. Rates of AKI were not significantly different in the sub-groups with (51.7%) and without (67.0%) pre-existing renal dysfunction ($p = 0.9$).

Peri-operative renal function

The observed eGFR trend across the entire study period is shown in Figure 1 and Appendix II (available on the jhltonline.org Web site). The median eGFR for the entire cohort before VAD implant was 84.0 ml/min/1.73 m^2 (IQR, 62.3–122.7 ml/min/1.73 m^2) and reached a nadir on POD 1 (62.9 ml/min/1.73 m^2; IQR, 51.2–88.9 ml/min/1.73 m^2; $p < 0.001$). Over the course of the first post-operative week, the eGFR rapidly returned to and exceeded baseline values. The median eGFR on POD 5 was 99.0 ml/min/1.73 m^2 (IQR, 59.3–146.7 ml/min/1.73 m^2; $p = 0.03$ vs pre-operative value), and the eGFR remained significantly higher than baseline through POD 7. The eGFR trend for the sub-groups with (eGFR < 90 ml/min/1.73 m^2) and without (eGFR ≥ 90 ml/min/1.73 m^2) pre-VAD renal dysfunction are shown in Figure 2. In patients without pre-VAD renal dysfunction, nadir eGFR occurred on POD 1 (90 ml/min/1.73 m^2; IQR, 78.4–111.1 ml/min/1.73 m^2; $p < 0.001$). After POD 2, there was an upward trend in the eGFR, and by POD 4, the eGFR was not significantly different than baseline. Patients with pre-VAD renal dysfunction also reached a nadir eGFR on POD 1 (52.7 ml/min/1.73 m^2; IQR, 41.1–62.9 ml/min/1.73 m^2; $p = 0.004$). By POD 2, the eGFR had returned to baseline ($p = 0.41$); by POD 3, the eGFR was significantly higher than baseline (68.6 ml/min/1.73 m^2; IQR, 44.0–91.9 ml/min/1.73 m^2; $p = 0.04$). In this group with pre-existing renal dysfunction, the eGFR remained significantly higher than baseline, with a maximum value of 90.8 ml/min/1.73 m^2 (IQR, 67.5–124.1 ml/min/1.73 m^2; $p < 0.001$) on POD 7.

Table 2 Acute Kidney Injury in the First Post-Operative Week After Ventricular Assist Device Implantation

Acute kidney injury stage[a]	No. (%)
Stage 1	14 (22.2)
Stage 2	6 (9.5)
Stage 3	18 (28.6)
Total	38 (60.3)

[a]Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes criteria.[18]

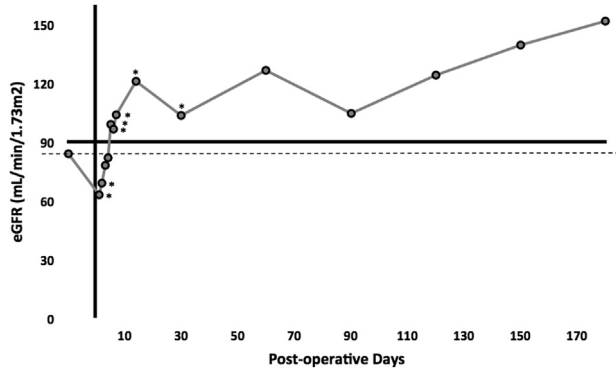

Figure 1 Estimated glomerular filtration rate (eGFR) trajectory across the entire ventricular assist device (VAD) cohort. Median eGFR values are shown for the entire cohort pre-operatively and post-operatively. The dashed line represents baseline eGFR before VAD placement. *Indicates the eGFR values that are significantly different from baseline ($p < 0.05$).

Longitudinal renal function

Figure 1 depicts longitudinal evaluation of the observed eGFR values during 180 post-operative days across the entire cohort, in which the eGFR remained at or above pre-implantation values for the entire 180-day study period. The eGFR was significantly higher than baseline through POD 30 (103.5 ml/min/1.73 m^2; IQR, 84.0–146.7 ml/min/1.73 m^2; $p = 0.01$). Although the eGFR continued to trend upward for 180 days, this trend did not reach statistical significance. Among patients with pre-VAD renal dysfunction, the eGFR was significantly higher than baseline through POD 90 (99.0 ml/min/1.73 m^2; IQR, 90.0–110.9 ml/min/1.73 m^2; $p = 0.004$) and continued to trend upward through 180 post-operative days (Figure 2B). In the sub-group with a baseline eGFR > 90 ml/min/1.73 m^2, the eGFR remained equivalent to baseline between PODs 7 and 180.

After adjustment for age, gender, and post-operative development of AKI, we found that the eGFR increased significantly after VAD placement ($\beta = 0.0025$; 95% confidence interval [CI], 0.0015–0.0036; $p < 0.001$). However, this increase was modified by pre-VAD renal dysfunction; the eGFR increased significantly both for patients with normal pre-VAD renal function ($\beta = 0.0013$; 95% CI, 0.0001–0.0025, $p = 0.03$) and for those with pre-VAD renal dysfunction ($\beta = 0.0051$; 95% CI, 0.0033–0.0070; $p < 0.001$). As evidenced by the coefficients, the rate of rise was greater in patients with pre-VAD renal dysfunction (Figure 3).

Figure 4 demonstrates the adjusted percentage change from baseline in the eGFR between the 2 sub-groups. Patients without pre-operative renal dysfunction experienced a significant drop in the eGFR from baseline (change of –57 ml/min/1.73 m^2, $p < 0.0001$). During the next 180 days, their renal function returned to, but never significantly exceeded, baseline. Patients with pre-operative renal dysfunction also experienced a decrement in the eGFR after VAD placement, albeit a less pronounced and statistically insignificant change (–6 ml/min/1.73 m^2, $p = 0.228$). The eGFR in this group rapidly returned to and significantly exceeded baseline.

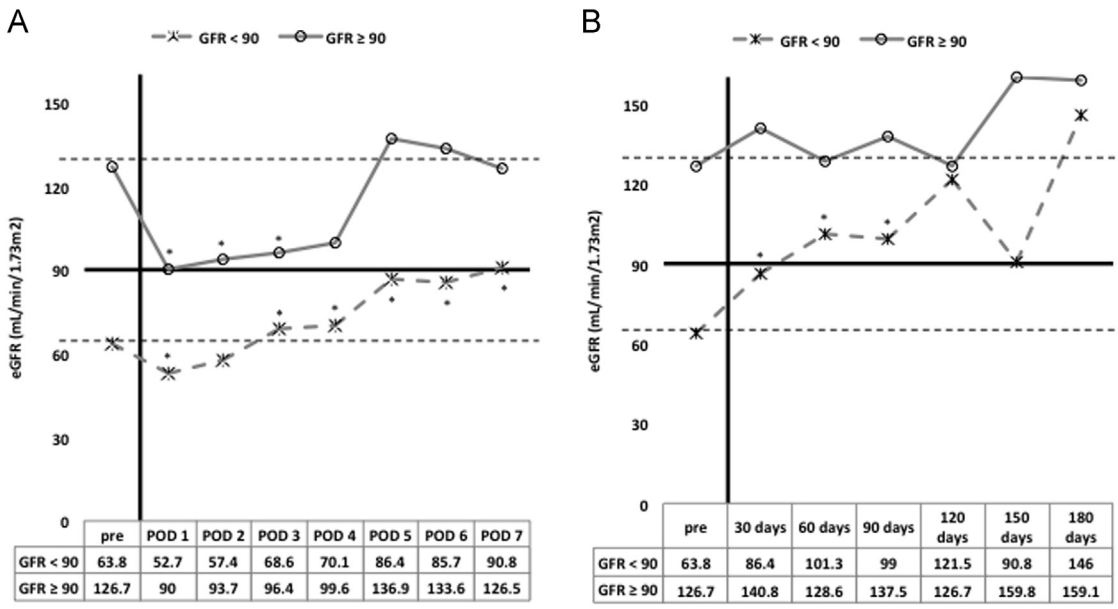

Figure 2 Estimated glomerular filtration rate (eGFR) trajectory by pre-ventricular assist device (VAD) eGFR sub-group. The median eGFR values for patients with (eGFR $<$ 90 ml/min/1.72 m^2) and without (eGFR $\geq$ 90 ml/min/1.72 m^2) pre-VAD renal dysfunction are shown (A) for the first post-operative week and (B) for the entire 180-day follow-up period. The dashed lines represent baseline eGFR before VAD placement. *Indicates the eGFR values that are significantly different from baseline ($p < 0.05$). POD, post-operative day.

Discussion

Our study demonstrates that VAD implantation can improve short-term and long-term renal function in children with ESHD. We found that children with advanced heart failure commonly have renal dysfunction at the time of VAD placement. More than 50% of this population had a baseline eGFR of $<$ 90 ml/min/1.73 m^2; the median eGFR in this sub-group was 63.8 ml/min/1.73 m^2, consistent with Stage 2 chronic kidney disease (CKD).[18] Although AKI occurred in 60% of children after VAD implantation, renal function recovered relatively quickly, returning to or exceeding baseline by the end of the first week after implant. Patients with intact pre-VAD renal function maintained this function throughout the study period. More impressively, patients with pre-VAD renal dysfunction experienced a significant improvement in eGFR as early as POD 4 and sustained this improvement through POD 180.

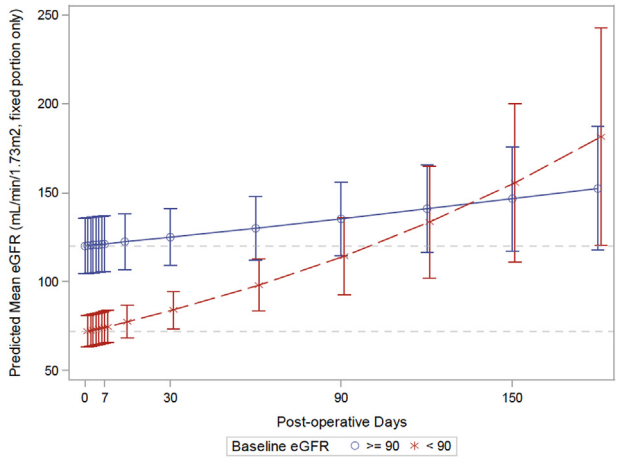

Figure 3 Effect of ventricular assist device (VAD) placement over time by estimated glomerular filtration rate (eGFR) sub-group. The predicted mean eGFR when the random intercept equals 0 (fixed portion only) with 95% confidence intervals (I-bars). The eGFR increased in both sub-groups post-VAD, and this was more pronounced in those with pre-operative renal dysfunction (increase of 5.1×10^{-3} vs 1.3×10^{-3} ml/min/1.73 m^2 per day after surgery). The dashed lines represent predicted mean eGFR before VAD placement (fixed portion only).

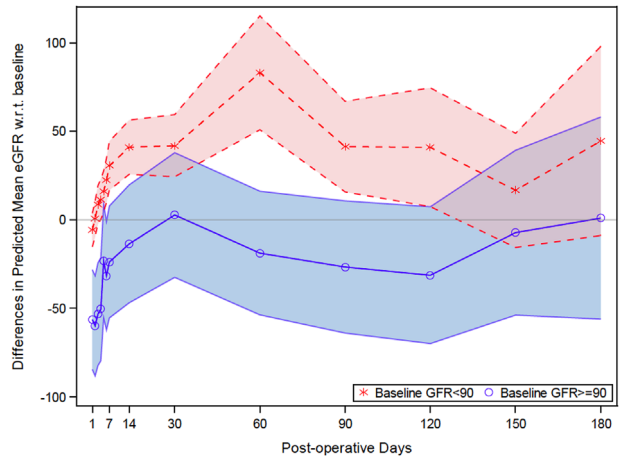

Figure 4 Estimated glomerular filtration rate (eGFR) percentage change from baseline by sub-group. Differences in predicted mean eGFR with respect to baseline, when the random intercept equals 0 (fixed portion only) with 95% confidence band. After ventricular assist device (VAD) implant, patients without pre-operative renal dysfunction (eGFR $\geq$ 90 ml/min/1.72 m^2) experienced a pronounced fall in the eGFR, which returned to baseline over the first postoperative week; over the next 6 months, the eGFR did not exceed baseline. Patients with pre-VAD renal dysfunction (eGFR $<$ 90 ml/min/1.72 m^2) experienced a less pronounced drop in eGFR, followed by rapid improvement with an eGFR that exceeded baseline.

The phenomenon of short-term improvements in renal function after VAD implant has been illustrated in several adult studies. Yoshioka et al[7] and Butler et al[8] each demonstrated significant improvements in renal function in the first 2 weeks after LVAD implantation. Significantly improved renal function has been reported in the first month post-VAD in adults,[11,12,15] and those with the worst pre-operative renal function show the most marked improvement.[10,15] However, this issue has not been systemically explored in children with end-stage heart failure, who differ from their adult counterparts with respect to heart failure etiologies, duration, and other associated comorbidities. Here we demonstrate the short- and long-term effects of VAD support on renal excretory function in children with heart failure.

Our longitudinal data corroborate our early post-operative findings. In those with preserved pre-VAD eGFR, VAD implantation maintained normal renal function, even 6 months after implantation. In patients with pre-existing renal dysfunction, the eGFR significantly exceeded baseline through 90 days post-VAD. This was sustained through 180 days; however, statistical significance was not achieved because of the decreasing size of the cohort. These findings are in agreement with several longer-term VAD studies in adults. Several studies have reported improved renal function in the initial months after VAD implant,[11,15,16] with sustained improvements 12 to 15 months after implant.[11,13,16] Hasin et al[12] found renal function was significantly improved 1-month after VAD implant. Although the improvement in renal function was not sustained, the GFR values at 6 months were significantly better than the pre-operative values.[12] Long-term data from the Interagency Registry for Mechanically Assisted Circulatory Support registry illustrated that adults experienced a substantial improvement in eGFR within a few weeks of implantation, but this was not sustained beyond 1 year of VAD support for most patients.[25]

Pediatric data on longer-term VAD support are limited. One small, single-center study demonstrated that children experienced substantial improvements in renal function in the first week of VAD (Berlin EXCOR) or extracorporeal membrane oxygenation support[26]; however, this study found that renal function deteriorated in the VAD population after 7 days. Another relatively small study of 37 children found improved renal function in the first 30 days after VAD implant.[27] A recent study of Organ Procurement and Transplant Network data suggested that children awaiting heart transplant may have equivalent rates of worsening renal failure irrespective of the use of VAD support, but this sub-group and the available data were not well-characterized.[28] Clearly, there is a paucity of data regarding short-term and long-term renal performance in children on VAD support, and our study addresses these comprehensively with rigorous assessments of AKI and eGFR.

Our AKI findings, although not the primary focus of the study, warrant exploration given the increased morbidity and mortality associated with AKI.[29–34] The AKI burden in our cohort was substantial, with an incidence (60.3%) that exceeds AKI rates in other pediatric cardiac cohorts as well as adult VAD recipients. For example, rates of AKI among children undergoing corrective cardiac surgery have been reported between 20% and 56%.[35–38] Furthermore, adult studies report AKI rates between 10% and 38% after VAD implant,[7,12,14,15,39,40] although they used a variety of definitions of AKI that can complicate comparisons.[41] Surprisingly, rates of AKI in our study were equivalent in patients with and without pre-VAD renal dysfunction; this is in contrast to several adult studies that demonstrate that CKD is a potent risk factor for AKI development.[42–44] Our findings may be related to the age of our population and lack of multiple comorbidities, although suggesting that some of the renal dysfunction seen in children with ESHD is related to hemodynamic factors associated with severe heart failure, which improve on VAD support. We hypothesize that the improved cardiac output after VAD placement and the subsequent restoration of adequate renal blood flow mitigates the increased risk of AKI observed in populations with CKD. Across the entire cohort, renal function returns to normal within the first post-VAD week, and in those with poor renal function at baseline, the eGFR significantly improves by POD 3, after several days of improved renal perfusion.

There appears to be no significant difference in the pre-VAD medical management in patients with and without pre-existing renal dysfunction. The sub-groups are too small for statistical analyses but appear similar in their baseline heart failure therapies and the escalated medical management immediately pre-VAD. In addition, the proportion of patients with chronic heart failure was similar between the groups with and without pre-VAD renal dysfunction. This sub-group had presumably longer duration of exposure to diuretics and nephrotoxic medications as well as a longer period of abnormal hemodynamics. The even distribution of these patients across the cohort improves generalizability of the results and suggests that even patients with chronic heart failure and renal dysfunction can have improved renal performance after VAD implant.

It is important to interpret our findings in the context of the study limitations. This is a relatively small cohort, and our analysis is retrospective. Thus, our findings describe associations and cannot determine causality. Despite the single-center nature of this study, we examined a diverse group of patients and included a variety of devices. This represents a realistic reflection of pediatric heart failure management and implies that our findings may be generalizable to other centers.

Another consideration is the potential for era effect in patient management and perhaps most significantly in device selection. The use of continuous-flow devices for children is increasing, mirroring the trend in adults,[45] and contemporary adult data describing renal recovery is based on these VADs.[3,5–8,12,46] However, other studies have demonstrated equivalent long-term improvements in renal function for pulsatile and continuous-flow devices.[14,25] Future pediatric studies will reflect this trend toward continuous-flow durable devices.

Irreversible end-organ injury may be considered a contraindication to heart transplant.[9,47] Projecting end-organ recovery after VAD implant is often challenging in pediatric patients, and there is a scarcity of literature to guide this decision. In this study, we demonstrate that children with poor renal function had the most significant improvement in eGFR and continued to maintain stable renal function well beyond the first post-operative week. This may imply that patients with sub-optimal renal function in end-stage heart failure may stand to gain the most from VAD support, and have the capacity not only for recovery but also potential normalization of their renal excretory function.

In conclusion, renal dysfunction is common in pediatric ESHD patients who require VAD placement. Although AKI is common after implantation, renal recovery tends to occur in the first post-operative week, potentially due to improved hemodynamics on VAD support. Renal function remains stable in the post-operative period, without significant deterioration in patients with preserved pre-VAD renal function. Importantly, patients with poorer renal function at baseline experience brisk and significant improvements in renal excretory function that are maintained for months while on VAD support. Although these findings suggest that VADs may improve and sustain kidney function in this population, further studies may be useful to correlate these improvements with clinical outcomes.

Disclosure statement

D.N.R. serves as a paid member on the committee of the Berlin Heart Post Approval Study. None of the remaining authors have a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at www.jhltonline.org.

References

1. Price JF, Goldstein SL. Cardiorenal syndrome in children with heart failure. Curr Heart Fail Rep 2009;6:191-8.
2. Jefferies JL, Goldstein SL. Cardiorenal [corrected] syndrome: an emerging problem in pediatric critical care. Pediatr Nephrol 2013;28:855-62.
3. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577-85.
4. Firth JD, Raine AE, Ledingham JG. Raised venous pressure: a direct cause of renal sodium retention in oedema? Lancet 1988;1:1033-5.
5. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. Circulation 2010;121:2592-600.
6. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527-39.
7. Yoshioka D, Sakaguchi T, Saito S, et al. Predictor of early mortality for severe heart failure patients with left ventricular assist device implantation: significance of INTERMACS level and renal function. Circ J 2012;76:1631-8.
8. Butler J, Geisberg C, Howser R, et al. Relationship between renal function and left ventricular assist device use. Ann Thorac Surg 2006;81:1745-51.
9. Kirklin J. ISHLT guidelines for the management of pediatric heart failure. Birmingham, AL: University of Alabama at Birmingham Printing; 2014.
10. Singh M, Shullo M, Kormos RL, et al. Impact of renal function before mechanical circulatory support on posttransplant renal outcomes. Ann Thorac Surg 2011;91:1348-54.
11. Deo SV, Sharma V, Altarabsheh SE, et al. Hepatic and renal function with successful long-term support on a continuous flow left ventricular assist device. Heart, Lung Circ 2014;23:229-33.
12. Hasin T, Topilsky Y, Schirger JA, et al. Changes in renal function after implantation of continuous-flow left ventricular assist devices. J Am Coll Cardiol 2012;59:26-36.
13. Radovancevic B, Vrtovec B, de Kort E, Radovancevic R, Gregoric ID, Frazier OH. End-organ function in patients on long-term circulatory support with continuous- or pulsatile-flow assist devices. J Heart Lung Transplant 2007;26:815-8.
14. Sandner SE, Zimpfer D, Zrunek P, et al. Renal function after implantation of continuous versus pulsatile flow left ventricular assist devices. J Heart Lung Transplant 2008;27:469-73.
15. Sandner SE, Zimpfer D, Zrunek P, et al. Renal function and outcome after continuous flow left ventricular assist device implantation. Ann Thorac Surg 2009;87:1072-8.
16. Demirozu ZT, Etheridge WB, Radovancevic R, Frazier OH. Results of HeartMate II left ventricular assist device implantation on renal function in patients requiring post-implant renal replacement therapy. J Heart Lung Transplant 2011;30:182-7.
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.
18. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84.
19. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr 1984;104:849-54.
20. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr 1985;106:522-6.
21. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089-100.
22. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th edition. Boston: Little, Brown & Co; 1994.
23. Ross RD, Daniels SR, Schwartz DC, Hannon DW, Shukla R, Kaplan S. Plasma norepinephrine levels in infants and children with congestive heart failure. Am J Cardiol 1987;59:911-4.
24. Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatr Cardiol 2012;33:1295-300.
25. Brisco MA, Kimmel SE, Coca SG, et al. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. Circ Heart Fail 2014;7:68-75.
26. Prodhan P, Bhutta AT, Gossett JM, et al. Comparative effects of ventricular assist device and extracorporeal membrane oxygenation on renal function in pediatric heart failure. Ann Thorac Surg 2013;96:1428-34.
27. Chen JM, Richmond ME, Charette K, et al. A decade of pediatric mechanical circulatory support before and after cardiac transplantation. J Thorac Cardiovasc Surg 2012;143:344-51.
28. Rajagopal SK, Yarlagadda VV, Thiagarajan RR, Singh TP, Givertz MM, Almond CS. Pediatric heart failure and worsening renal function: association with outcomes after heart transplantation. J Heart Lung Transplant 2012;31:252-8.
29. Alkandari O, Eddington KA, Hyder A, et al. Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study. Crit Care 2011;15:R146.

30. Axelrod DM, Sutherland SM. Acute kidney injury in the pediatric cardiac patient. Paediatr Anaesth 2014;24:899-901.
31. Li S, Krawczeski CD, Zappitelli M, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. Crit Care Med 2011;39:1493-9.
32. Morgan CJ, Zappitelli M, Robertson CM, et al. Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery. J Pediatr 2013;162:120-7e1.
33. Parikh CR, Devarajan P, Zappitelli M, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. J Am Soc Nephrol 2011;22:1737-47.
34. Sutherland SM, Ji J, Sheikhi FH, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clin J Am Soc Nephrol 2013;8:1661-9.
35. Gil-Ruiz Gil-Esparza MA, Alcaraz Romero AJ, Romero Otero A, et al. Prognostic relevance of early AKI according to pRIFLE criteria in children undergoing cardiac surgery. Pediatr Nephrol 2014;29:1265-72.
36. dos Santos El Halal MG, Carvalho PR. Acute kidney injury according to pediatric RIFLE criteria is associated with negative outcomes after heart surgery in children. Pediatr Nephrol 2013;28:1307-14.
37. Ricci Z, Di Nardo M, Iacoella C, Netto R, Picca S, Cogo P. Pediatric RIFLE for acute kidney injury diagnosis and prognosis for children undergoing cardiac surgery: a single-center prospective observational study. Pediatr Cardiol 2013;34:1404-8.
38. Lex DJ, Toth R, Cserep Z, et al. A comparison of the systems for the identification of postoperative acute kidney injury in pediatric cardiac patients. Ann Thorac Surg 2014;97:202-10.
39. Borgi J, Tsiouris A, Hodari A, Cogan CM, Paone G, Morgan JA. Significance of postoperative acute renal failure after continuous-flow left ventricular assist device implantation. Ann Thorac Surg 2013;95:163-9.
40. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57:1890-8.
41. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO Definitions. Clin J Am Soc Nephrol 2015;10:554-61.
42. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008;74:101-7.
43. Pannu N, James M, Hemmelgarn BR, et al. Modification of outcomes after acute kidney injury by the presence of CKD. Am J Kidney Dis 2011;58:206-13.
44. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009;20:223-8.
45. Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. J Heart Lung Transplant 2014;33:555-64.
46. Iwashima Y, Yanase M, Horio T, et al. Serial changes in renal function as a prognostic indicator in advanced heart failure patients with left ventricular assist system. Ann Thorac Surg 2012;93:816-23.
47. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 2006;25:1024-42.