Kidney Function Following Left Ventricular Assist Device Implantation: An Observational Cohort Study

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Rationale & Objective: Nearly half the patients with heart failure have chronic kidney disease. Implantation of a left ventricular assist device (LVAD) improves kidney function in some but not all patients, and lack of improvement is associated with worse outcomes. Preimplantation factors that predict change in kidney function after LVAD placement are not well described.

Study Design: Single-center observational study.

Setting & Participants: Consecutive patients undergoing LVAD implantation.

Predictors: 48 diverse preimplantation variables including demographic, clinical, laboratory, hemodynamic, and echocardiographic variables.

Outcomes: The primary outcome was change in estimated glomerular filtration rate (eGFR) at 1 month after implantation. Secondary outcomes included eGFR changes at 3, 6, and 12 months.

Analytic Approach: Univariable and multivariable linear regression.

Results: Among 131 patients, average age was 60 ± 13 years, 83% were men, 47% had preexisting chronic kidney disease, and mean preimplantation eGFR was 57 ± 23 mL/min/1.73 m^2. At 1-month following LVAD implantation, eGFR improved in 98 (75%) patients. Variables associated with 1-month increases in eGFR were younger age, absence of diabetes mellitus (DM), use of inotropes, lower implantation eGFR, and higher implantation serum urea nitrogen, alanine aminotransferase, bilirubin, and creatinine levels. In multivariable models, younger age (β = 7.14 mL/min/1.73 m^2 per SD; 95% CI, 3.17-11.10), lower eGFR (β = 7.72 mL/min/1.73 m^2 per SD; 95% CI, 3.10-12.34), and absence of DM (β = 10.36 mL/min/1.73 m^2; 95% CI, 2.99-17.74) were each independently associated with 1-month improvement in eGFR. Only younger age and lower eGFR were associated with improvements in eGFR at later months.

Limitations: Single-center study. Loss to follow-up from heart transplantation and death over duration of study.

Conclusions: Only younger age, lower eGFR, and absence of DM were associated with improvement in eGFR at 1 month. Thus, prediction of eGFR change at 1 month and beyond is limited by using preimplantation variables.

Visual Abstract included

Complete author and article information provided before references.

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Chronic kidney disease (CKD) affects approximately 30% to 50% of patients with heart failure and is strongly associated with mortality and adverse outcomes.[1] Many of the pathophysiologic processes promoting heart failure may also promote kidney failure, including hemodynamic perturbations, neurohormonal activation, inflammation, and oxidative stress. Moreover, many pharmacologic treatments for heart failure alter kidney function.[2-4] Conversely, the presence of intrinsic kidney disease can lead to fluid retention and cardiac structural alterations that may promote heart failure development.[2,5] Thus, these 2 end-organs are interconnected, and deciphering whether heart failure exacerbations are worsening kidney function or vice versa is challenging for the clinician.

Editorial, p. 324

Evaluation of changes in kidney function after left ventricular assist device (LVAD) implantation provides a unique opportunity to investigate the reciprocal relationship between cardiorenal disease in heart failure. With LVAD implantation, cardiac output is improved markedly and rapidly, largely ameliorating diminished kidney perfusion. Prior studies demonstrate that kidney function frequently improves immediately following LVAD implantation; however, there is considerable heterogeneity in this response, and some patients may not experience improvement in kidney function at all.[6-8] Furthermore, the clinical implications of changes in kidney function after LVAD implantation are not fully understood. Although an improvement in kidney function would suggest a favorable clinical response, some prior reports suggest that not only those with a lack of improvement in kidney function after LVAD implantation but also those with the most marked improvement in kidney function may have a worse prognosis.[6,9,10] Little is known about factors that are identifiable before LVAD implantation that may predict recovery of kidney function following LVAD implantation. Thus, we conducted this study among 131 consecutive patients undergoing LVAD implantation at our tertiary-care center to determine preoperative characteristics associated with changes in kidney function following LVAD implantation.

METHODS

Study Design

We conducted a single-center observational cohort study of successive patients who underwent implantation of an

PLAIN-LANGUAGE SUMMARY

Although implantation of a left ventricular assist device (LVAD) improves cardiac hemodynamics, changes in kidney function are variable. It is unknown whether factors measured preimplantation are associated with improvement in kidney function. We examined the association of 48 variables with changes in kidney function at 1 month after LVAD implantation and subsequently at 3, 6, and 12 months. Younger age, lower preimplantation estimated glomerular filtration rate (eGFR), and absence of diabetes were associated with improvements in kidney function at 1 month, whereas only younger age and lower eGFR were associated with improvement at later time points. These findings highlight the absence of reliable preimplantation factors that predict change in kidney function after LVAD implantation and the need for novel methods to assess kidney health.

LVAD between September 2010 and November 2017 at the University of California, San Diego. The study was approved by the Institutional Review Board (protocol #171215). Informed consent was waived because data were retrospectively collected. All authors have contributed to the report and had access to the data.

Study Population

Patients 18 years and older undergoing implantation of a permanent continuous-flow LVAD were included regardless of device type. Devices implanted at our institution included HeartMate II (Abbott), HeartMate III (Abbott), and HeartWare (HVAD, Medtronic). Exclusion criteria included placement of a total artificial heart, permanent biventricular assist devices, or receipt of renal replacement therapy before or at the time of LVAD implantation.

Data Collection

Clinical data from the electronic health record were abstracted and included age; sex; race; body weight; body mass index; clinical indication for LVAD (bridge to transplant vs destination therapy); cause of heart failure (ischemic vs nonischemic); smoking status (never vs current or prior use); Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification (dichotomized into classes 1 through 3 and 4 through 7)[11]; need for percutaneous mechanical circulatory support before LVAD implantation (none vs any); use of home inotropic support before LVAD implantation; inotrope use in the hospital admission before LVAD implantation; presence of implantable cardiac defibrillator; presence of cardiac resynchronization therapy; use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, or mineralocorticoid receptor antagonist; prior cardiac surgery; and medical history of diabetes mellitus (DM), atrial fibrillation, CKD, chronic obstructive pulmonary disease, peripheral arterial disease, or stroke.

We obtained data for left ventricular ejection fraction from the most recent echocardiogram before LVAD implantation, which were performed a median of 18 (interquartile range [IQR], 1-48) days before implantation. Similarly, we abstracted hemodynamic data from the most recent right heart catheterization procedure performed before LVAD implantation and included central venous pressure (CVP), pulmonary capillary wedge pressure, cardiac index, pulmonary vascular resistance, CVP to pulmonary capillary wedge pressure ratio, and pulmonary artery pulse index (pulmonary artery systolic − pulmonary artery diastolic pressure/CVP). Right heart catheterization data were obtained a median of 16 (IQR, 1-40) days before implantation.

Laboratory values abstracted were those before and closest to LVAD implantation and included serum urea nitrogen (SUN), serum sodium, bicarbonate, hemoglobin, N-terminal pro-B-type natriuretic peptide, aspartate aminotransferase, alanine aminotransferase (ALT), total bilirubin, hemoglobin A_{1c}, 24-hour urinary creatinine excretion, creatinine clearance, urinary blood on dipstick (none vs any), and urinary protein-creatinine ratio. Serum creatinine values were abstracted at the time of hospital admission for LVAD implantation and immediately before LVAD implantation. Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation.[12]

Outcomes

The primary outcome was change in eGFR at 1 month after LVAD implantation relative to eGFR on the day of LVAD implantation. We subtracted the eGFR at the time of LVAD implantation from the eGFR at 1 month, such that a positive number reflects improvement in kidney function. We chose the 1-month time point because this is when the greatest improvement in kidney function after LVAD implantation occurred in prior studies, change in eGFR at 1 month is associated with future outcomes, and this time point had the least loss to follow-up and censoring.[6,8,13] Our institutional practice for postimplantation care encompassed weekly follow-up for 1 month, then every 2 weeks for 2 months, then monthly thereafter, with kidney function assessments at each visit. We abstracted serum creatinine values at 1, 3, 6, and 12 months after implantation. Serum creatinine values measured within 7 days of and closest to the 1-month time point and 30 days of and closest to the 3, 6, or 12-month time points were used. All serum creatinine measurements were performed in the University of California, San Diego clinical laboratory and used an isotope dilution mass spectrometry–traceable protocol.

Patients were censored if they died, received a heart transplant, progressed and required dialysis therapy permanently, transferred care to another facility, or were

lost to follow-up. If a censoring event occurred before but within 30 days of a follow-up time point and a creatinine value was available, this value was used before censoring the patient from subsequent follow-up times. Patients who received temporary dialysis following LVAD implantation were included if they were liberated from dialysis for at least 1 week before the 1-month serum creatinine measurement.

Statistical Analysis

For descriptive purposes, we initially categorized participants into 2 groups by preimplantation eGFR ≥ 60 or <60 mL/min/1.73 m^2. We compared differences in baseline clinical, hemodynamic, and laboratory data across these 2 groups using t tests for normally distributed variables, Mann-Whitney U tests for non-normally distributed variables, and χ^2 or Fisher exact tests for categorical variables, as appropriate. Normality was assessed by visual inspection of distribution.

Similarly, we compared participants with and without an improvement in eGFR at 1 month after LVAD implantation. Next, to maximize statistical power, we used the 1-month change in eGFR as a continuous dependent variable in linear regression. We evaluated each independent variable with 1-month eGFR change in univariable analyses. Non-normally distributed independent variables were log-transformed before use in linear regression. Continuous variables were assessed per 1 standard deviation (SD) higher of that variable, facilitating comparison of strengths of associations across variables. For variables that were missing, we used multiple imputation methods before inclusion in multivariable models.

Multivariable models forced and retained age, sex, and race. In addition, we included variables that were found to be statistically significantly associated with 1-month change in eGFR in univariable analysis. Parallel analyses using the multivariable model for 1-month change in eGFR were then conducted for the outcomes of changes in eGFR from LVAD implantation to months 3, 6, and 12 among the subset of participants who were not censored and had serum creatinine values available for analyses at these time points. All statistics were performed using STATA/SE, version 11.2 (Stata Corp), and SPSS, version 25 (IBM Corp). $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

Between September 2010 and November 2017, a total of 145 individuals underwent LVAD implantation at our center, but only 131 (90%) had serum creatinine values available at 1 month. These participants defined the study sample for this analysis. Additionally, there were 127 (88%), 106 (73%), and 66 (46%) individuals with serum creatinine values available at 3, 6, and 12 months after LVAD implantation, respectively. Table S1 shows reasons for censoring at each time point.

Among the 131 individuals, average age was 60 ± 13 years, 83% were men, 49% had an ischemic cause of heart failure, 47% had pre-existing CKD, and 41% had DM. Regarding implant characteristics, 43% of patients received LVADs as a bridge to transplant, 79% were INTERMACS classes 1 to 3, 83% were using inotropes preceding LVAD implantation, 62% received HeartMate II LVADs, 27% received HVAD, and 11% received HeartMate III LVADs. Mean serum creatinine level was 1.47 ± 0.48 mg/dL immediately before LVAD implantation, with eGFR of 57 ± 23 mL/min/1.73 m^2, and median urinary protein-creatinine ratio was 0.13 (IQR, 0.06-0.32) g/g creatinine (Table 1). When compared with those with preimplantation eGFRs ≥ 60 mL/min/1.73 m^2, those with lower eGFRs were older, were more likely to receive an LVAD as destination therapy, more often had DM, used inotropes at home, and had higher preimplantation SUN and N-terminal pro-B-type natriuretic peptide concentrations (Table 1).

At 1 month, eGFRs increased from the preimplantation value in 98 (75%) patients. Individuals whose eGFRs increased had significantly lower INTERMACS status, higher use of inotropes in the hospital, lower prevalence of prior stroke, lower hemoglobin levels before implantation, and lower preimplantation eGFRs. eGFRs at hospital admission were not significantly different between patients with and without improvements in eGFR post–LVAD implantation. When comparing eGFRs at hospital admission and before LVAD implantation, eGFRs increased in both groups on average between admission and implantation. The increase in eGFRs between admission and implantation was numerically greater in patients who subsequently did not experience an improvement in eGFRs after LVAD implantation; however, this finding did not reach statistical significance ($P = 0.06$).

Figure 1A shows changes in mean eGFRs for all patients during the 12 months following LVAD implantation. Mean eGFR increased from 57 ± 23 mL/min/1.73 m^2 immediately before LVAD implantation to 73 ± 28 mL/min/1.73 m^2 at 1 month, then steadily decreased to 67 ± 26, 62 ± 23, and 58 ± 22 mL/min/1.73 m^2 at 3, 6, and 12-months, respectively. Figure 1B shows changes in mean eGFRs over 12 months stratified by pre–LVAD implantation eGFRs < 60 and ≥60 mL/min/1.73 m^2. Trajectories were similar in the 2 strata, albeit the rate of increase in eGFRs appeared exaggerated in those with lower eGFRs at the time of LVAD implantation.

Predictors of Improvement in eGFR After LVAD Implantation

In univariable analysis, older age (β coefficient = −4.14 per 1 SD increase [13 years]; 95% CI, −7.79 to −0.49; $P = 0.03$) and presence of DM (β coefficient = −8.34; 95% CI, −15.77 to −0.91; $P = 0.03$) were associated with lower

Table 1. Baseline Characteristics of the Study Population Overall and Stratified by Preimplantation eGFR ≥ 60 and <60 mL/min/1.73 m^2

Variable	Overall (N = 131)	Pre-LVAD eGFR ≥ 60 mL/min/1.73 m^2 (n = 59)	Pre-LVAD eGFR < 60 mL/min/1.73 m^2 (n = 72)
Age, y (n = 131)[a]	60 (13)	54 (14)	65 (9)
Male sex (n = 131)	109 (83%)	47 (80%)	62 (86%)
African American (n = 131)	21 (16%)	10 (17%)	11 (15%)
Baseline weight, kg (n = 131)	80.3 (18.8)	81.2 (20.2)	79.6 (17.7)
Body mass index, kg/m^2 (n = 131)	26.0 (4.9)	26.4 (5.1)	25.7 (4.9)
Bridge to transplant (n = 131)[a]	56 (43%)	32 (54%)	24 (33%)
LVAD type (n = 131)			
HeartWare	35 (27%)	16 (27%)	19 (26%)
HeartMate II	81 (62%)	38 (64%)	43 (60%)
HeartMate III	15 (11%)	5 (9%)	10 (14%)
Ischemic cardiomyopathy (n = 131)	64 (49%)	29 (49%)	35 (49%)
Prior or current smoking (n = 130)[a]	79 (61%)	41 (71%)	38 (53%)
Diabetes mellitus (n = 131)[a]	53 (40%)	15 (25%)	38 (53%)
Atrial fibrillation (n = 130)	74 (57%)	30 (52%)	44 (61%)
Chronic kidney disease (n = 131)[a]	62 (47%)	6 (10%)	56 (78%)
Chronic obstructive pulmonary disease (n = 130)	26 (20%)	16 (28%)	10 (14%)
Peripheral arterial disease (n = 115)	11 (10%)	5 (9%)	6 (10%)
Stroke (n = 113)	15 (13%)	6 (12%)	9 (15%)
Prior cardiac surgery (n = 115)	37 (32%)	13 (25%)	24 (39%)
INTERMACS 1-3 (n = 130)	103 (79%)	47 (81%)	56 (78%)
Home inotropes (n = 114)[a]	33 (29%)	10 (19%)	23 (38%)
Inotropes in hospital (n = 115)	95 (83%)	44 (83%)	51 (82%)
MCS before LVAD (n = 131)	26 (20%)	14 (27%)	12 (20%)
ACEi/ARB use (n = 115)[a]	47 (41%)	30 (57%)	17 (27%)
β-Blocker use (n = 115)	46 (40%)	22 (42%)	24 (39%)
Mineralocorticoid receptor antagonist use (n = 115)	56 (49%)	30 (57%)	26 (42%)
Cardiac resynchronization therapy (n = 114)	27 (24%)	8 (15%)	19 (31%)
Implantable cardiac defibrillator (n = 126)[a]	113 (90%)	46 (82%)	67 (96%)
Creatinine (admission), mg/dL (n = 131)[a]	1.58 (0.68)	1.25 (0.46)	1.86 (0.71)
Creatinine (pre-LVAD), mg/dL (n = 131)[a]	1.47 (0.48)	1.07 (0.20)	1.79 (0.39)
eGFR (admission), mL/min/1.73 m^2 (n = 131)[a]	54 (24)	71 (23)	41 (14)
eGFR (pre-LVAD), mL/min/1.73 m^2 (n = 131)[a]	57 (23)	78 (16)	40 (10)
24-h urinary creatinine, mg/d (n = 63)	1,057 (375)	1,098 (406)	1,030 (357)
24-h creatinine clearance, mL/min (n = 60)[a]	49 [33-67]	66 [50-96]	38 [31-59]
Urinary blood (n = 131)	20 (15%)	8 (14%)	12 (17%)
Urinary protein-creatinine ratio (n = 116)	0.13 [0.06-0.32]	0.14 [0.08-0.35]	0.13 [0.00-0.32]
Serum urea nitrogen, mg/dL (n = 131)[a]	30 [21-43]	24 [16-31]	39 [28-57]
Sodium, mmol/L (n = 131)	134 (6)	133 (6)	135 (4)
Bicarbonate, mmol/L (n = 131)	26 (4)	27 (4)	26 (4)
NT-proBNP, pg/mL (n = 111)[a]	3,406 [1,094-8,799]	2,693 [1,550-5,437]	4,032 [2,595-11,511]
Hemoglobin, g/dL (n = 131)	10.8 (2.0)	10.8 (2.0)	10.7 (2.0)
Hemoglobin A_{1c} (n = 113)[a]	6.4 (1.1)	6.0 (1.0)	6.6 (1.1)
Bilirubin, mg/dL (n = 131)	0.9 [0.6-1.4]	0.8 [0.6-1.4]	0.9 [0.6-1.4]
Alanine aminotransferase, U/L (n = 116)	23 [16-35]	24 [16-35]	22 [16-35]
Aspartate aminotransferase, U/L (n = 116)	26 [20-38]	24 [19-37]	27 [21-41]
Ejection fraction (n = 130)	19 (6)	19 (7)	20 (5)
Central venous pressure, mm Hg (n = 119)	12 (6)	12 (6)	12 (6)
Wedge pressure, mm Hg (n = 116)	25 (7)	25 (7)	25 (7)
Cardiac index, L/m^2 (n = 112)	1.9 (0.5)	1.8 (0.5)	1.9 (0.6)

(Continued)

Table 1 (Cont'd). Baseline Characteristics of the Study Population Overall and Stratified by Preimplantation eGFR ≥ 60 and <60 mL/min/1.73 m^2

Variable	Overall (N = 131)	Pre-LVAD eGFR ≥ 60 mL/min/1.73 m^2 (n = 59)	Pre-LVAD eGFR < 60 mL/min/1.73 m^2 (n = 72)
Pulmonary vascular resistance, Woods units (n = 89)	4.0 (2.6)	4.4 (3.2)	3.7 (2.1)
Central venous pressure/wedge, mean (SD) (n = 115)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)
Pulmonary artery pulse index (n = 118)	3.1 (2.8)	2.6 (1.6)	3.4 (3.4)

Note: Values expressed as mean (standard deviation), number (percent), or median [interquartile range].
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]$P < 0.05$ comparing pre-LVAD eGFR >60 vs. <60 ml/min/m2.

eGFRs at 1 month after LVAD implantation, whereas higher SUN levels (β coefficient = 5.28 per 1 SD increase [0.23 log SUN]; 95% CI, 1.68 to 8.89; $P < 0.01$) was significantly associated with greater improvement in eGFRs at 1 month (Table 2). Additionally, higher concentrations of total bilirubin (β coefficient = 5.84 per 1 SD increase [0.32 log bilirubin]; 95% CI, 2.25-9.42; $P < 0.01$) and ALT (β coefficient = 4.28 per 1 SD increase [0.29 log ALT]; 95% CI, 0.30-8.27; $P = 0.04$) at time of implantation were both significantly associated with 1-month increases in eGFRs. A higher creatinine level (β coefficient = 5.56 per 1 SD increase; 95% CI, 1.97-9.15; $P < 0.01$) and conversely, lower eGFR (β coefficient = 4.67 per 1 SD increase; 95% CI, 1.04-8.30; $P = 0.01$) immediately before LVAD implantation were associated with 1-month increases in eGFRs. Last, use of inotropes in the hospital was associated with an increase in eGFRs at 1 month (β coefficient = 12.97; 95% CI, 2.57-23.37; $P = 0.02$). Associations of variables found not to be significantly associated with 1-month change in eGFR included the rest of the demographic, clinical, laboratory, and echocardiographic and all hemodynamic variables (Table S2).

In the multivariable model, we included 7 variables that were found to be significantly associated with eGFR changes in univariable analysis along with sex and race. In this model, younger age (β coefficient = 7.14 per 1 SD; 95% CI, 3.17-11.10; $P < 0.01$), absence of DM (β coefficient = 10.36; 95% CI, 2.99-17.74; $P < 0.01$), and lower pre-LVAD eGFR (β coefficient = 7.72 per 1 SD; 95% CI, 3.10-12.34; $P = 0.01$) were each independently associated with an increase in eGFR at 1-month postimplantation (Table 2). ALT levels approached but did not reach statistical significance in this multivariable model ($P = 0.06$).

We next evaluated the associations of these same variables with eGFR changes from baseline to 3, 6, and 12 months after LVAD implantation. Lower pre-LVAD eGFR was significantly associated an increase in eGFR at each time point. Younger age was significantly associated with increases in eGFRs at each time point except the 6-month time point but was close ($P = 0.054$). The rest of the variables were not independently associated with increases

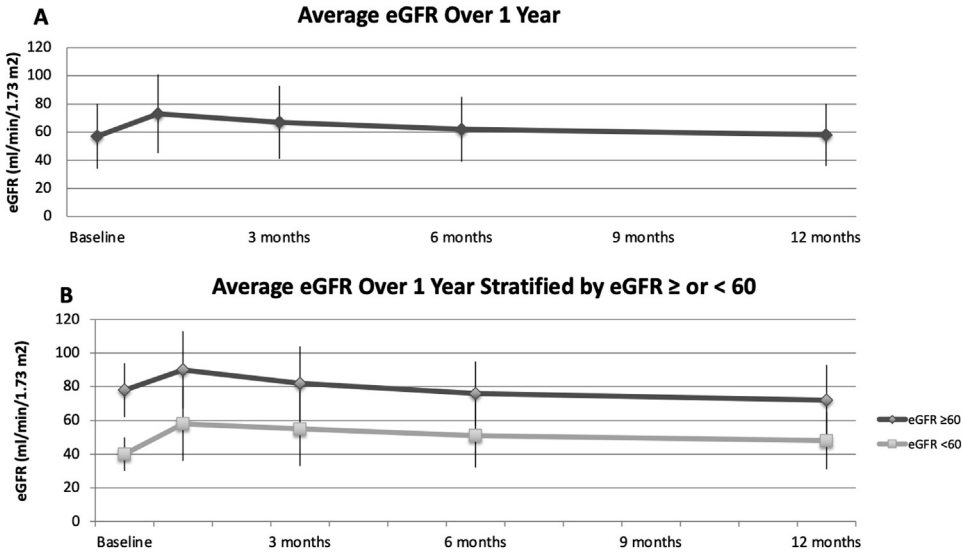

Figure 1. Average estimated glomerular filtration rate (eGFR) from before left ventricular assist device (LVAD) implantation to 12 months after implantation. Change in (A) entire cohort and (B) separated by eGFR ≥ 60 or <60 mL/min/1.73 m^2 before LVAD implantation.

Table 2. Association of Predictors for Change in eGFR Post–LVAD Implantation in Univariable and Multivariable Analysis

	Univariable Analysis	Multivariable Analysis			
	1 mo (n = 131)	1 mo (n = 131)	3 mo (n = 127)	6 mo (n = 106)	12 mo (n = 66)
Variable[a]	β Coefficient (95% CI)	β Coefficient (95% CI)	β Coefficient (95% CI)	β Coefficient (95% CI)	β Coefficient (95% CI)
Age	−4.14 (−7.79 to −0.49)	−7.14 (−11.10 to −3.17)[b]	−4.76 (−8.93 to −0.59)[b]	−3.90 (−7.86 to 0.07)	−5.60 (−9.50 to −1.69)[b]
Male sex	7.21 (−2.63 to 17.04)	3.33 (−5.53 to 12.19)	6.27 (−3.21 to 15.76)	1.49 (−7.84 to 10.81)	8.31 (−1.55 to 18.17)
African American	−3.37 (−13.46 to 6.72)	−3.85 (−12.59 to 4.88)	0.07 (−9.28 to 9.41)	−5.87 (−15.39 to 3.66)	0.23 (−9.17 to 9.64)
Diabetes mellitus	−8.34 (−15.77 to −0.91)	−10.36 (−17.74 to −2.99)[b]	−3.57 (−11.47 to 4.34)	1.01 (−6.62 to 8.64)	4.42 (−4.11 to 12.96)
Inotropes in hospital vs not receiving inotropes	12.97 (2.57 to 23.37)	5.07 (−4.53 to 14.66)	7.83 (−2.14 to 17.80)	2.58 (−6.69 to 11.85)	2.16 (−8.22 to 12.54)
Log SUN (SD = 0.23 log units)	5.28 (1.68 to 8.89)	2.84 (−1.50 to 7.18)	1.13 (−3.45 to 5.71)	−1.67 (−5.98 to 2.63)	−3.05 (−8.40 to 2.30)
Log bilirubin (SD = 0.32 log units)	5.84 (2.25 to 9.42)	2.31 (−1.21 to 5.83)	−0.13 (−3.86 to 3.60)	2.48 (−1.09 to 6.04)	4.00 (0.18 to 7.82)[b]
Log ALT (SD = 0.29 log units)	4.28 (0.30 to 8.27)	3.29 (−0.15 to 6.72)	2.27 (−1.47 to 6.01)	−0.41 (−3.71 to 2.87)	−1.71 (−5.95 to 2.54)
Pre-LVAD eGFR	−4.67 (−8.30 to −1.04)	−7.72 (−12.34 to −3.10)[b]	−8.54 (−13.43 to −3.66)[b]	−10.16 (−14.76 to −5.56)[b]	−9.71 (−14.48 to −4.93)[b]
Pre-LVAD creatinine	5.56 (1.97 to 9.15)				

Abbreviations: ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; LVAD, left ventricular assist device; SD, standard deviation; SUN, serum urea nitrogen.
[a]Continuous variables are reported per 1 SD increase.
[b]Values in multivariable analysis have $P < 0.05$.

in eGFRs at these later time points except higher preimplantation bilirubin level was associated with an increase in eGFR at the 12-month time point.

DISCUSSION

In 131 sequential LVAD recipients at a single tertiary-care hospital, we sought to identify preimplantation variables associated with an increase in eGFR following LVAD implantation. Overall, mean eGFR increased by 16 mL/min/1.73 m^2 at 1 month after LVAD implantation, then progressively decreased thereafter. Mean eGFR remained higher than pre–LVAD implantation at all time-points up to 12 months after implantation, though there was considerable heterogeneity in eGFR trajectories from one LVAD recipient to the next. These findings were evident in patients with eGFRs ≥ 60 or <60 mL/min/1.73 m^2 before LVAD implantation.

In multivariate analysis, among 48 variables evaluated, only younger age, lower preimplantation eGFR, and the absence of DM were associated with 1-month increases in eGFRs, while only lower eGFR and younger age were associated with increased eGFRs at later time points. Because lack of improvement in kidney function after LVAD implantation is associated with subsequent adverse outcomes and very few variables were associated with eGFR trajectories among the diverse 48 variables evaluated here, we believe these findings highlight a need for novel methods to assess kidney health at the time of LVAD implantation.

The associations of age, DM, and pre-LVAD eGFR with changes in kidney function after LVAD implantation are physiologically logical. The decline in kidney function with aging is well described.[14] Older individuals with cardiorenal syndrome may have experienced greater lifetime kidney ischemia and/or may have more severe intrinsic kidney damage and fibrosis. Perhaps for these reasons, older patients may be less likely to recover eGFR after LVAD implantation. Others have reported an association between age and change in kidney function after LVAD implantation. Hasin et al[7] also found that older age was significantly associated with less improvement in eGFRs at 1 month among 72 individuals receiving an LVAD; however, this finding did not remain statistically significant in their multivariable models.

DM is the leading risk factor for end-stage kidney disease in the United States. Similar to advanced age, the association of DM with lack of improvement in kidney function may also be because DM may be marking the presence of intrinsic kidney disease. Interestingly, urinary protein-creatinine ratio and hematuria on urinalysis are other biomarkers often used to evaluate for intrinsic kidney disease. These factors were not associated with eGFR trajectories in our study. Although diabetic nephropathy classically leads to proteinuria, it is widely recognized that diabetes has other adverse consequences on the kidney and a substantial portion of patients with progressive kidney disease and DM do not have proteinuria.

Last, the association of lower preimplantation eGFR with an increase in eGFR 1 month after LVAD implantation fits with the current hemodynamic understanding of cardiorenal syndrome. Venous congestion from elevated CVP is a well-known cause of worsening kidney function, and relief of congestion can improve kidney function.[15,16] Low cardiac output less often contributes to declining kidney function in cardiorenal syndrome except in the late stages of heart failure and cardiogenic shock, a setting many patients with heart failure are in at the time of LVAD implantation.[17,18] LVAD implantation generally allows optimization of both cardiac output and CVP, reversing the hemodynamic drivers of cardiorenal syndrome. Thus, individuals experiencing the greatest decline in kidney function before LVAD implantation from cardiorenal syndrome are the most likely to have an improvement in kidney function after LVAD implantation, with reversal of these adverse cardiac hemodynamics.

Despite evaluating 48 variables, including demographics, cardiac hemodynamics, and standard clinical laboratory test results, very few factors were associated with improvement in eGFR after LVAD implantation. Although lower preimplantation eGFR is logically associated with a greater likelihood of improvement after LVAD implantation, it still does not give insight into who may or may not have reversible cardiorenal syndrome before LVAD implantation. The variables of age and DM give some additional subtle clues to the clinician but they are unlikely to be sufficiently robust to definitively predict subsequent eGFR trajectory. We do not advocate making LVAD decisions based on these parameters at this time. Although these 3 factors make physiologic sense, it remains possible that some were observed by chance due to our evaluation of 48 variables in a relatively small data set with a potential loss of power from censoring at later time points. However, despite the risk for type 1 errors (false positives) due to multiple comparisons, it is particularly noteworthy how few were associated with eGFR changes. Thus, we find that preimplantation variables are not reliable predictors of eGFR changes, and our findings support the need for discovery of novel biomarkers and imaging modalities that can discriminate kidney injury and damage from more benign and reversible hemodynamic changes in kidney function and the pathophysiologic drivers of kidney dysfunction in individual patients with heart failure.[19-21]

Strengths of the current study include its relatively large sample size when compared with other studies evaluating kidney function changes after LVAD implantation, the comprehensive number of clinical variables available to assess relationships with changes in kidney function, and the availability of repeat measures of eGFR at protocol-driven time points, allowing us to extend evaluation of changes in kidney function to 12 months after LVAD implantation.

The study also has important limitations. This is a single-center study that may not reflect practice patterns or participant characteristics at other centers. Although many variables were measured immediately before LVAD implantation, some, including right heart catheterization variables and echocardiography measurements, may not have been proximate. These variables may therefore appear less accurate for predicting eGFR changes and should be reevaluated in future studies. Some variables evaluated had missing data; however, results were similar using a complete case analysis versus multiple imputation.

As described previously, testing 48 variables raises the risk for type 1 errors, yet our overall findings are the opposite. Despite an extensive search, we did not find that preimplantation variables can reliably predict changes in eGFR. Although most participants provided data for evaluation of eGFR after implantation, only approximately half had eGFR measurements available at 12 months, limiting the strength of analyses at these time points. Intervening cardiac transplants and deaths were the leading causes of missing data at 12 months and represent significant competing risks that are not fully accounted for.

Among patients with heart failure undergoing implantation of continuous-flow LVADs, from 48 variables measuring demographic, clinical, laboratory, and hemodynamic parameters, only younger age, lower preimplantation eGFR, and the absence of DM were associated with improvement in eGFRs at 1 month, and only younger age and lower preimplantation eGFR were associated with eGFR changes at later time points. Determining clinical factors that identify patients likely to have long-term improvements in kidney function after LVAD remains elusive. Future studies evaluating kidney biomarkers that can differentiate between intrinsic kidney damage versus hemodynamic changes and novel measure of renal venous congestion should be high priorities for future research to identify whether they can predict which individuals are most likely to have improvements in kidney function after LVAD implantation.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Timeline of Participant Censorship During Follow-up

Table S2: Association of Variables That Were Found Not to Be Statistically Significantly Associated With Change in eGFR at 1 Month in Univariate Analysis

ARTICLE INFORMATION

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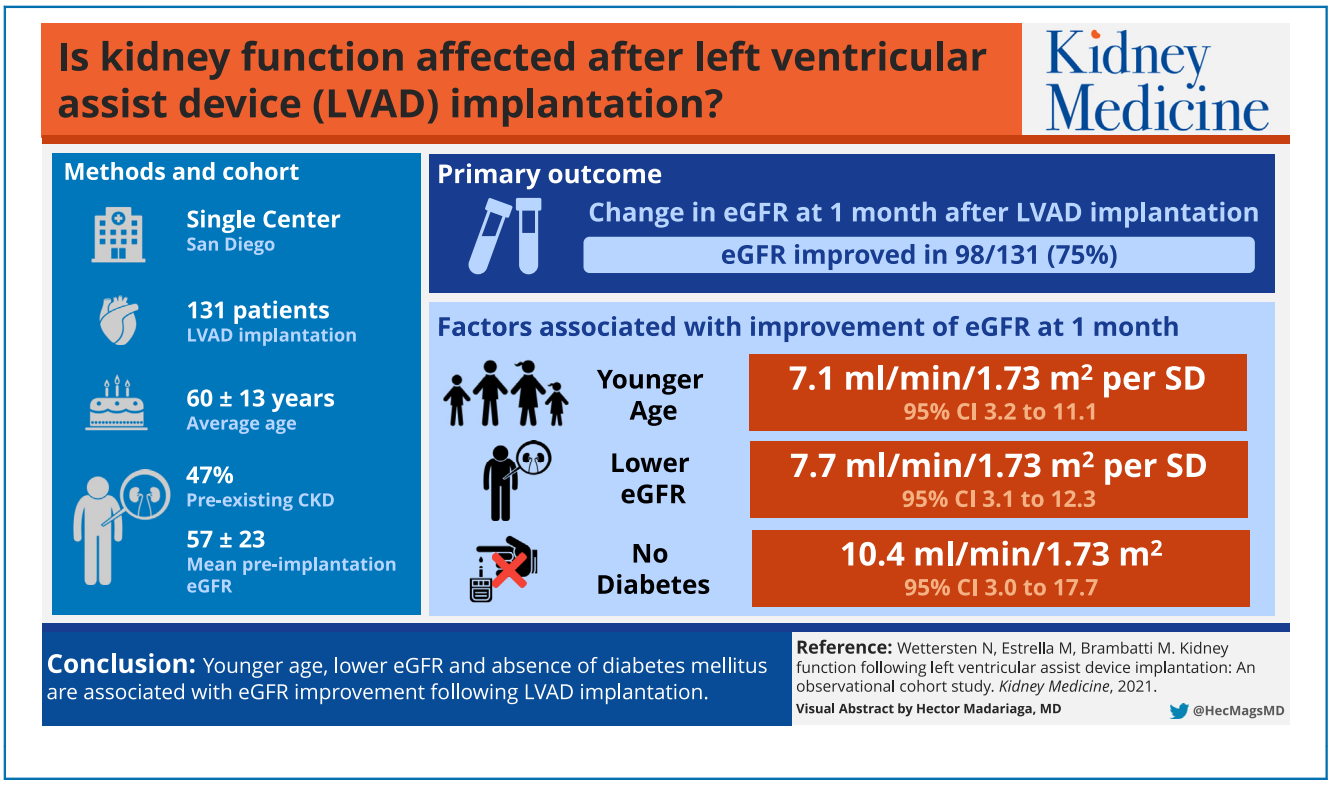
Is kidney function affected after left ventricular assist device (LVAD) implantation?
Kidney Medicine
Methods and cohort
Single Center
San Diego
131 patients
LVAD implantation
60 ± 13 years
Average age
47%
Pre-existing CKD
57 ± 23
Mean pre-implantation eGFR
Primary outcome
Change in eGFR at 1 month after LVAD implantation
eGFR improved in 98/131 (75%)
Factors associated with improvement of eGFR at 1 month
Younger Age
7.1 ml/min/1.73 m2 per SD
95% CI 3.2 to 11.1
Lower eGFR
7.7 ml/min/1.73 m2 per SD
95% CI 3.1 to 12.3
No Diabetes
10.4 ml/min/1.73 m2
95% CI 3.0 to 17.7
Conclusion: Younger age, lower eGFR and absence of diabetes mellitus are associated with eGFR improvement following LVAD implantation.
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