

Renal Failure in Patients with Left Ventricular Assist Devices

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Summary

Implantable left ventricular assist devices (LVADs) are increasingly being used as a bridge to transplantation or as destination therapy in patients with end stage heart failure refractory to conventional medical therapy. A significant number of these patients have associated renal dysfunction before LVAD implantation, which may improve after LVAD placement due to enhanced perfusion. Other patients develop AKI after implantation. LVAD recipients who develop AKI requiring renal replacement therapy in the hospital or who ultimately require long-term outpatient hemodialysis therapy present management challenges with respect to hemodynamics, volume, and dialysis access. This review discusses the mechanics of a continuous-flow LVAD (the HeartMate II), the effects of continuous blood flow on the kidney, renal outcomes of patients after LVAD implantation, dialysis modality selection, vascular access, hemodynamic monitoring during the dialytic procedure, and other issues relevant to caring for these patients.

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Introduction

Heart failure and CKD are important public health problems with increasing overlap. According to an estimate published by the American Heart Association in 2010, there were approximately 5.7 million Americans living with heart failure (1). Nearly two-thirds of hospitalized patients with heart failure also have CKD, with 44% having stage 3 CKD, 14% with stage 4 CKD, and 7% with stage 5 CKD (2). Furthermore, the presence of renal impairment is an independent predictor of mortality in patients with heart failure such that for every 1-ml/min decline in renal function below creatinine clearance (CrCl) of 60 ml/min, there is a 1% increase in mortality (3).

One-year mortality for advanced heart failure can exceed 50% (4). Cardiac transplantation is the definitive treatment; however, <3000 donor organs are available per year while several hundreds die annually on the waiting list (4). In response to this problem, left ventricular assist devices (LVADs) have now become an accepted bridge to transplant (BTT) or as destination therapy (DT) for patients who are not candidates for heart transplantation (4,5). Less commonly, LVADs are temporarily placed in patients in the hope that left ventricular unloading leads to cardiac improvement—this indication is referred to as bridge to recovery (BTR). In patients with severe biventricular failure who are either in cardiogenic shock or in whom the degree of right ventricular failure is severe and felt to be irreversible (with imminent death), biventricular assist devices can be implanted as a BTT or BTR. According to data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), there were a total of 4311 LVADs implanted in participating centers

in the United States between June 2006 and September 2011, with a current rate of implantation at 1500 per year (6).

With the growing number of individuals receiving LVADs, it is expected that there will be a significant rise in the number of patients with renal complications, many of whom will require renal replacement therapy (RRT) temporarily and in some cases this requirement will be long term. More nephrologists will be faced with the challenge of managing the complex hemodynamic and volume needs of these patients in a variety of clinical settings. In this article, we discuss the different aspects of renal dysfunction (RD) in LVAD patients and the special issues that arise when caring for these patients when RRT is required. The term *renal dysfunction* is commonly used in the LVAD literature and most commonly defined as an estimated GFR (eGFR) of <60 ml/min per 1.73 m². For the majority of studies cited in this article, it was not possible to determine if preoperative RD refers to patients with CKD, AKI, or AKI superimposed on CKD. In those instances in which the nature of RD was further defined, more precise terms of renal impairment are utilized.

Overview of LVADs

Mechanics of LVADs

There are two main indications for ventricular assist device (VAD) insertion approved by the US Food and Drug Administration (FDA): BTT and DT. VADs have also been temporarily implanted as a BTR. The VAD can be used to support the function of either the left ventricle, right ventricle, or both. There have been several generations of VADs that are classified by the

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type of pump flow. The first generation of VADs was largely pulsatile devices (*e.g.*, Thoratec Paracorporeal, Thoratec Implantable, HeartMate Vented Electric) with chambers that filled with blood, emptying through one-way valves *via* pneumatic mechanisms. These VADs were associated with high failure rates, infection, and bleeding (7). The most recent generation consists of continuous-flow devices, including both axial-flow and centrifugal-flow designs (*e.g.*, HeartMate II, Jarvik 2000, HeartWare). Compared with the pulsatile devices, the continuous-flow ventricular devices are smaller, quieter, less thrombogenic, more durable, and are associated with improved survival and fewer infections, right heart failure, respiratory failure, and cardiac arrhythmias (8–11). According to the data from the INTERMACS registry, 95% of all LVADs implanted between January 2010 and June 2011 were continuous-flow devices (12).

The HeartMate II is one of the most commonly used long-term continuous-flow LVADs, approved by the FDA as a BTT and for DT in 2008 and 2010, respectively. The HeartMate II system has four major components: blood pump (HeartMate II), percutaneous lead, external power source (power base unit), and system controller (Figure 1). The blood pump itself is approximately 124 ml in size, and it is surgically implanted in a preperitoneal position relative to the left hemidiaphragm. The inflow cannula is attached to the apex of the left ventricle and blood enters the LVAD pump *via* this cannula from the left ventricle. In BTR recipients, the inflow cannula is similarly attached in order to achieve the maximum degree of left ventricular

mechanical unloading. The outflow cannula is sewn into the proximal ascending aorta, carrying blood from the LVAD into the systemic circulation. There is a rotor inside the pump containing three curved blades that spin in a magnetic field, with blood flowing from the left ventricle into the ventricular arm of the LVAD, through the pump and exiting into the aorta through the other LVAD arm. On average, the rotor spins 8600–9400 rpm with pressure differential of 80–100 mmHg, generating blood flows of 3–8 L per minute. Higher revolution rates are associated with an increased risk of negative pressure in the left atrium and ventricle (13). High revolution rates are also associated with diminished aortic valve opening, a risk factor for thrombotic complications due to stasis in the ascending aorta, proximal to the site of the LVAD outflow arm insertion (14). In contrast to the pulsatile pumps, the continuous LVADs cause constant unloading of the left ventricle, resulting in a diminished or absent pulse.

Morbidity and Mortality after LVAD Implantation

After LVAD implantation, the neurohormonal activation and other features of heart failure improve (15). Specifically, atrial natriuretic peptide, aldosterone, renin, and arginine vasopressin have all been shown to decrease after LVAD placement (16). Systemic perfusion improves, as evidenced by improvement in renal, hepatic, and neurocognitive function that occurs in most patients a few weeks after LVAD placement (17,18). Furthermore, patients with a LVAD experience enhanced quality of life and improved functional status for an extended period of time (18,19).

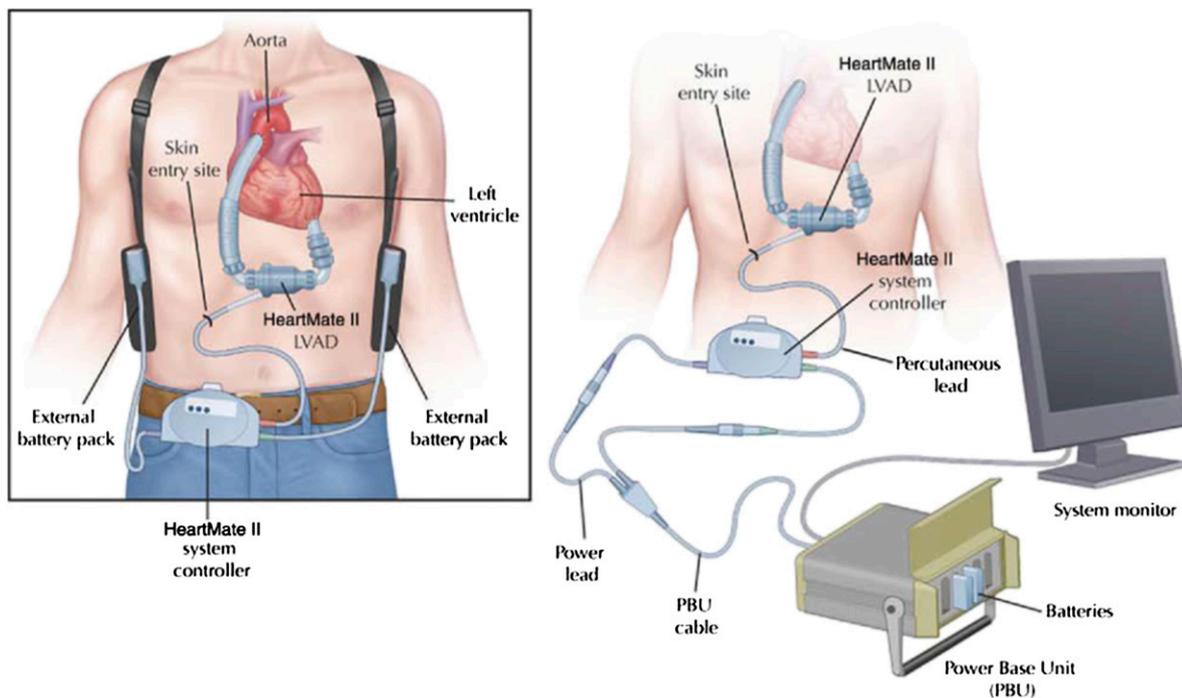


Figure 1. | HeartMate II Apparatus. The HeartMate II ventricular assist device consists of a blood pump, percutaneous lead, external power source, and system controller. The system controller can be connected to a display screen, which shows key parameters such as pump speed, pulsatility index, and pump power. Power may be delivered either through a power base unit or battery packs, which allow for increased mobility. LVAD, left ventricular assist device. Reprinted from reference 82, with permission.

In addition to improved hemodynamics and end-organ function, LVADs are associated with improved survival compared with medical therapy. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart (REMATCH) study was a landmark randomized controlled trial comparing survival outcomes with pulsatile-flow LVADs versus optimal medical therapy in 129 patients with class IV heart failure who were ineligible for cardiac transplantation. The survival rate in the LVAD group versus the medical management group was 52% versus 25% at 1 year and 23% versus 8% at 2 years ($P=0.002$ and $P=0.09$, respectively) (4). More recent studies have demonstrated 1-year survival rates of 73% and 85% for patients who have had a LVAD implanted as DT or BTT, respectively (20,21).

There are several drawbacks to LVAD support, making this therapy suitable for only a select group of patients. The Achilles' heel of LVADs is the percutaneous lead (Figure 1), also called the drive line, which is a port for infection into the pericardial cavity (22). In the REMATCH trial, sepsis was the leading cause of death in the LVAD arm of the study (4). In one study of 281 patients with continuous-flow LVADs, the infection rate from the percutaneous lead was about 14% (19). Approximately 9%–17% of LVAD recipients have complications of stroke, with ischemic stroke being more prevalent (11,19,23). The risk of hemorrhagic stroke is higher when RD is also present (23). Other complications after LVAD implantation include right-sided heart failure, hemolysis, bleeding, arrhythmias, and reoperation (11,19).

Renal Function and LVADs

This section focuses on the following aspects of renal function and LVADs: effect of RD on clinical outcomes after LVAD placement, effect of continuous blood flow perfusion on renal function, AKI after LVAD implantation, and improvement in RD after LVAD implantation.

Baseline RD and Survival after LVAD Placement

Factors that affect survival after LVAD implantation include but are not limited to choice of LVAD (continuous versus pulsatile), era of LVAD placement, and INTERMACS level of subsets of New York Heart Association functional class IV and advanced class III present at the time of LVAD placement (12). These factors guide the proper selection of patients who receive these expensive and medically complex devices. In this regard, early studies of LVAD implantation demonstrated that preimplantation RD was associated with a high mortality after implantation, ranging from 74% to 100% (24–28).

Recent studies using only continuous-flow LVADs are more relevant given that these devices have become the standard LVAD implanted (12). Sandner *et al.* reported that in LVAD recipients with baseline eGFR >60 ml/min per 1.73 m², survival at 1 month, 3 months, and 6 months was 91% (42 of 46), 80% (32 of 40), and 73% (14 of 19) versus 92% (37 of 40), 66% (23 of 35), and 48% (11 of 23), respectively, in recipients with baseline eGFR <60 ml/min per 1.73 m² (23). Furthermore, recipients with baseline eGFR >60 ml/min per 1.73 m² ($n=46$) compared with recipients with baseline eGFR <60 ml/min per 1.73 m²

($n=40$) had a higher BTT rate (63% versus 40%) and a lower requirement for postimplantation continuous RRT (CRRT) (28% versus 42%) (23). Yoshioka *et al.* reported a receiver operating characteristic curve analysis that demonstrated that a serum creatinine level of 1.96 mg/dl for 90-day mortality had a sensitivity of 80% and specificity of 82% (29). The cumulative survival rates of at 30 days, 90 days, and 1 year were 96%, 88%, and 77%, respectively, in patients with a serum creatinine of <1.96 mg/dl ($n=26$) versus 60%, 47%, and 31% in patients with serum creatinine >1.96 mg/dl ($n=15$) (29). Finally, Iwashima *et al.* demonstrated that VAD recipients with an eGFR ≥ 82 ml/min per 1.73 m² at 2 weeks postimplantation had an improved survival compared with recipients whose eGFR was <82 ml/min per 1.73 m². This study showed that the 2-week postimplantation eGFR was a stronger predictor of survival than baseline eGFR (30).

In summary, these studies demonstrate a negative association between baseline RD and post-LVAD implantation survival. What are the implications of these observations? Should patients with severe RD be excluded as candidates for LVAD placement or should LVADs be placed in end stage heart patients with rising serum creatinine values before severe RD develops? As discussed below, patients with severe AKI pre-LVAD implantation (even those on CRRT) may show excellent improvement in renal function with improved survival outcomes after LVAD placement. Based on the poor outcomes of LVAD recipients who have RD and the observation that many LVAD recipients will improve their RD after implantation, it is imperative that heart failure patients with RD who are being considered for LVAD placement undergo a nephrologic evaluation before surgery to determine if the RD is functional and potentially reversible or represents intrinsic renal disease with an associated poor prognosis postoperatively.

Continuous Blood Flow and Renal Function

Continuous-flow LVADs are currently the predominant LVAD type placed in heart failure patients after it was demonstrated that these devices, compared with pulsatile-flow LVADs, are smaller, quieter, and have higher 2-year survival rates free of stroke and reoperation for device failure, in addition to fewer major adverse events such as infection, bleeding, right-sided heart failure, and renal failure (11,12). The evolution from pulsatile to continuous-flow LVADs has not been without concern due to the non-physiologic nature of continuous blood flow (31). In actuality, blood flow in continuous-flow LVAD recipients has some pulsatility, albeit low, from residual unloaded native left ventricular function (31,32). Continuous-flow LVADs increase diastolic pressure and flow and lower peak systolic pressure resulting in a dampening of pulsatility and an increase in laminar flow (33). This could result in stasis distal to atherosclerotic obstruction, which in turn could result in vascular occlusion (33). Initial belief that continuous-flow LVADs could be clinically effective was drawn from the successful use of short-term nonpulsatile cardiopulmonary bypass since the 1950s. However, in a model of cardiogenic shock in pigs, pulsatile bypass was more successful than continuous bypass in reversing reductions in renal cortical blood flow (34,35).

Implantation of continuous-flow LVADs into animals demonstrate stable renal function for periods as long as 340 days postimplantation but there is also evidence of renal arterial smooth muscle cell hyperplasia, peri-arterial inflammatory cell infiltration, and interstitial nephritis (36–40). In one study, plasma renin activity increased significantly after LVAD insertion, possibly as an adaptive response to a lack of pulse pressure (39). In another study, there was increased immunohistochemical staining of angiotensin II receptors and angiotensin converting enzyme in the endothelial and inflammatory cells infiltrating the peri-arterial and cortical interstitial areas of the animals (41). The applicability of these findings to LVAD patients is uncertain because animal studies have intact left ventricular function with different flow characteristics than heart failure patients who receive continuous-flow devices.

At the present time, a number of centers have reported their clinical experience with continuous-flow LVADs, including the effect of these devices on renal function. Most of these studies demonstrate either stable to improved renal function after implantation of continuous-flow LVADs for periods up to 3.7 years (11,19,42–46). In contrast, Hasin *et al.* reported on 83 patients who received a continuous-flow LVAD as either BTT or DT (47). Overall eGFR significantly improved from 53.2 ml/min per 1.73 m² at baseline to 87.4 ml/min per 1.73 m² at 1 month after implantation and then progressively declined to 77.6 ml/min per 1.73 m² and 71.2 ml/min per 1.73 m² at 3 and 6 months after implantation. Only 6 patients had continuation of the eGFR improvements, whereas 67 patients demonstrated either some decline of eGFR or no improvement in baseline RD. This pattern of initial improvement then subsequent decline was seen regardless of whether patients had baseline eGFRs <60 or >60 ml/min per 1.73 m². The authors speculate that the decline in eGFR after initial improvement could be due to a low muscle mass and hence low serum creatinine 1 month after surgery overestimating the true eGFR, which corrects at 3 and 6 months due to muscle mass accumulation or initiation of inhibitors of the renin angiotensin aldosterone system (RAAS) after implantation. Of greater concern is the possibility that this decline in eGFR represents an adverse renal effect of nonpulsatile blood flow (47). Welp *et al.* compared the effect of pulsatile- and continuous-flow LVADs on the RAAS in heart failure patients (48). As expected preimplantation, peripheral renin activity and plasma aldosterone concentrations were elevated in both LVAD groups. After implantation, levels of renin and aldosterone decreased into the normal range for both groups, although there was a greater decrease in patients who received the pulsatile-flow LVADs. Whether this disparity in normalization will have a long-term clinical effect remains unclear at the present time. Despite these encouraging initial reports, additional studies of renal function and histology will be necessary to confirm the long-term renal safety of continuous-flow LVADs in patients with end stage heart disease.

AKI and LVAD

Considering the hemodynamic instability characteristic of end stage heart patients, it is not surprising that AKI is frequently seen in patients after LVAD placement. The

incidence of AKI after LVAD implantation has been reported to range from 7% to 56% (Table 1) (20,21,23,26,29,44,47,49–58). There are multiple reasons for the large variation in AKI incidence, which include varying definitions for AKI, the time period during which the study was performed, the baseline severity of heart failure (INTERMACS level), and the incidence and severity of pre-existing RD. Even using RRT (usually CRRT) as a definition of AKI, the incidence of AKI has been reported to be as high as one-third of LVAD recipients (23,53). More recent studies using continuous-flow devices appear to be associated with a lower incidence (range, 7%–14%) of postimplantation AKI (Table 1) (20,21,29,47,57,58). Although several variables could be responsible for this reduction in AKI, it is unlikely that the choice of LVAD is critical because Sandner *et al.* reported a similar incidence of AKI with both pulsatile and continuous devices (44). Instead, it is more likely that the reduction in postoperative AKI is due to the trend to implant patients who are more hemodynamically stable (47). This premise is supported by a report of LVAD recipients who were segregated on their baseline characteristics as INTERMACS level 1 (critical cardiogenic shock) or INTERMACS levels 2 and 3 (progressive decline on inotropic support and stable but inotropic dependent) (29). The percentage of patients requiring postoperative CRRT was 29.3% (12 of 41) in the former group versus 7% (3 of 43) in the latter group. These observations suggest that LVAD implantation should be considered before extreme hemodynamic instability develops.

Mortality associated with postimplantation AKI is very high, ranging from 57% to 93% in initial studies (Table 1) (23,26,44,49,53,56). For example, Sandner *et al.* reported in a population of continuous-flow LVAD recipients that survival rates at 1, 3, and 6 months post-LVAD implantation were 83% (25 of 30), 49% (14 of 29), and 29% (5 of 17), respectively, for patients who required postoperative CRRT versus 96% (54 of 56), 87% (41 of 47), and 78% (20 of 26) for patients who did not require postoperative CRRT (23). In more recent studies, mortality from AKI has decreased but still remains significantly elevated (47,58). As with most causes of AKI, it remains uncertain if the AKI itself is directly responsible for the increased mortality, or if sicker patients (*i.e.*, patients in cardiogenic shock) are more likely to develop AKI and the increased mortality is really due to the greater comorbidities or associated multiorgan system failure in these patients. In addition to a greater mortality, patients with AKI postimplantation are also less likely to achieve BTT (49,53). Despite the higher mortality in LVAD recipients with AKI, the survival curves between LVAD recipients with and without AKI have been reported to be similar for the time periods extending from 1 year to 7 years postimplantation and after cardiac transplantation, suggesting that the association of AKI and mortality is primarily confined to the first year after implantation (53). Others have also shown that some patients who survive postimplantation AKI are ultimately transplanted but as noted, the likelihood of transplantation is diminished in AKI patients compared with non-AKI patients (58). Another negative effect of AKI postimplantation is a need for long-term hemodialysis, which in one series was reported in 50% (4 of 8) of patients who required postimplantation RRT (47).

Table 1. AKI after LVAD implantation				
Author (Reference)	LVAD Type	AKI Incidence (%)	Mortality (%)	Comments and Definition of AKI
McCarthy <i>et al.</i> (26)	Pulsatile	—	AKI: 63 No AKI: 14	AKI = RRT
Kaltenmaier <i>et al.</i> (49)	Pulsatile	55/227 (24)	AKI: 93 No AKI at 6 mo: 60	AKI = RRT Percentage achieving heart transplantation: 11% AKI versus 49% no AKI
Frazier <i>et al.</i> (50)	Pulsatile	158/280 (56)	—	AKI = SCr \geq 2.2 mg/dl or BUN \geq 50 mg/dl. Of 158 with AKI, 94 had RD before LVAD implantation
Haddad <i>et al.</i> (51)	Pulsatile	4/54 (7)	—	AKI = RRT
Deng <i>et al.</i> (52)	Pulsatile 90%	85/412 (21)	—	AKI = ND
Topkara <i>et al.</i> (53)	Pulsatile	65/201 (32)	AKI: 57 No AKI at 1 yr: 21	AKI = RRT BTT: 52% AKI versus 83% no AKI
Feller <i>et al.</i> (54)	Pulsatile Continuous	2/13 (15) 4/14 (29)	—	AKI = RRT
Miller <i>et al.</i> (55)	Continuous	18/133 (14)	—	AKI = ND
Sandner <i>et al.</i> (44)	Pulsatile Continuous	9/29 (31) 24/63 (38)	P: 78 C: 62 at 6 mo	AKI = RRT; 24% of AKI underwent heart transplantation
Alba <i>et al.</i> (56)	Pulsatile and continuous	24/53 (45)	AKI: 62 No AKI: 12	AKI = Fulfillment of any RIFLE criteria; 62.5% AKI required CRRT
Sandner <i>et al.</i> (23)	Continuous	30/86 (35)	AKI: 71 No AKI: 22	AKI = RRT
Genovese <i>et al.</i> (57)	Pulsatile and continuous	22/163 (13)	AKI: 68 No AKI at 1 yr: 35	AKI = ND; AKI associated 3-fold increased mortality
Demirozu <i>et al.</i> (58)	Continuous	15/107 (14)	40	AKI = RRT
Starling <i>et al.</i> (21)	Continuous	17/169 (10)	—	AKI = ND
Park <i>et al.</i> (20)	Continuous	51/414 (12)	—	AKI = ND
Hasin <i>et al.</i> (47)	Continuous	8/83 (10)	25	AKI = RRT 50% remained on chronic RRT
Yoshioka <i>et al.</i> (29)	Pulsatile and continuous	INTERMACS level 1: 12/41 (29); level 2/3: 3/43 (7)	—	AKI = RRT; percentage with continuous LVAD: level 1, 15%; level 2/3, 46%

LVAD, left ventricular assist device; AKI = RRT, AKI defined as need for RRT, usually as CRRT; SCr, serum creatinine; RD, renal dysfunction; AKI = ND, criteria for AKI not defined; BTT, bridge to transplantation; RRT, renal replacement therapy; P, pulsatile-flow LVAD; C, continuous-flow LVAD; CRRT, continuous renal replacement therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Given the high mortality, low BTT rate, and the potential outcome of long-term hemodialysis, it is important to identify LVAD candidate patients who are at high risk of postoperative AKI, especially AKI that requires CRRT. This is especially true for prognostic variables that are modifiable (57). Preimplantation serum creatinine has been investigated as a prognostic marker for AKI. Frazier *et al.* demonstrated that AKI occurred in 56% (158 of 280) of

their LVAD recipients; however, 59% (94 of 158) of this group had RD before implantation (50). Sandner *et al.* also reported a lower baseline GFR in patients who developed AKI versus those who did not (23). In contrast, other studies have not showed a difference in baseline serum creatinine between patients who did and did not develop AKI after implantation (53,56). Other variables that have been reported to predict AKI include preoperative use of

intra-aortic balloon pump, older age, higher LVAD risk scores, longer cardiopulmonary bypass times, intraoperative bleeding, and need for reoperation (53,56).

Currently published studies on AKI associated with LVAD surgery are limited by the variable definitions of AKI utilized, uncertainty about exact onset of AKI (preoperatively or postoperatively), absence of specific details of RRT utilized, and the duration of RD preoperatively and postoperatively. Additional limitations include a failure to separate patients who develop AKI who have pre-existing functional (reversible) renal impairment versus intrinsic renal disease (permanent), failure to identify prognostic factors that predict postimplantation AKI, and an inadequate description of long-term clinical outcomes of survival, achievement of cardiac transplantation, and development of ESRD. It is hoped that future studies examining renal outcomes of LVAD recipients will address these limitations.

Improvement of RD after LVAD Placement

Considering the low flow states that characterize end stage heart disease, it is not surprising that these patients frequently have evidence of impaired renal function (59). In theory, improvements in cardiac output after implantation of LVAD would be expected to improve renal perfusion and hence renal function. Thus, a number of clinical studies have examined the effect of LVAD placement on renal function (Table 2). In most of these studies, improvement in renal function to “normal” values (serum creatinine 1.0–1.3 mg/dl) was demonstrated in patients when pre-existing RD was mild to moderate (serum creatinine 1.4–1.9 mg/dl), regardless of whether a pulsatile or continuous-flow LVAD was implanted (17,27,45,46,50,60). In addition, several studies have demonstrated dramatic improvements in renal function after LVAD implantation in patients with baseline creatinine values of 3.1–4.1 mg/dl and even in those dependent on CRRT before LVAD implantation (23,27,47,58,61–64).

Illustrative case series of renal function improvement are as follows. Khot *et al.* reported their experience with 18 patients who had severe RD (mean serum creatinine 4.0 mg/dl) and cardiogenic shock before receiving an LVAD as BTT (62). Seven of the 18 patients required CRRT in the LVAD peri-implantation period. Of the 18 LVAD recipients, 7 died before cardiac transplantation and 4 of these patients had resolution of their AKI with a mean serum creatinine of 1.9 mg/dl before death. The other 11 patients underwent cardiac transplantation and their mean serum creatinine at time of LVAD placement was 4.1 mg/dl, falling to a mean of 1.6 mg/dl at time of cardiac transplantation with improvement in renal function lasting at least 6 months after transplantation. Butler *et al.* reported paired CrCl analyses in patients with a CrCl <50 ml/min before implantation (27). The CrCl increased from 36.7 ml/min before implantation to 60 ml/min 1 week after implantation and from 59.7 ml/min to 66.8 ml/min from weeks 1–2 after implantation. Sandner *et al.* reported on 86 patients with heart failure and RD (eGFR <60 ml/min per 1.73 m²) who underwent continuous-flow LVAD placement as BTT (23). Paired sample analysis revealed the following improvements in eGFR postimplantation: implant to month 1, from 44.6 to 80.7 ml/min per 1.73 m²; implant to month

3, from 40.8 to 70.9 ml/min per 1.73 m²; and implant to month 6, from 41.7 to 62.7 ml/min per 1.73 m². The decline in renal function over time again raises concerns about the long-term safety of continuous-flow LVADs on renal function.

Singh *et al.* reviewed their experience with 116 patients who underwent implantation of a pulsatile-flow (the majority) or continuous-flow LVAD, remained on LVAD support for 60 days, and subsequently underwent cardiac transplantation (64). Patients were divided into the following tertiles according to their preimplantation CrCl: group 1 had CrCl <45 ml/min; group 2 had CrCl >45 ml/min to <65 ml/min; and group 3 had CrCl >65 ml/min. Changes in CrCl from baseline to 6 months were as follows: group 1, from 34.1 to 73.5 ml/min; group 2, from 56.7 to 66.2 ml/min; and group 3, from 79.4 to 78 ml/min. The improvements in groups 1 and 2 were seen during the first month postimplantation and no further improvements occurred thereafter. The authors speculate that the lack of further improvement in renal function after the first month may be due to residual chronic renal disease from hypertension, diabetes, renovascular disease, or injury from prolonged ischemia. Finally, Demirozu *et al.* described 15 patients who required RRT after LVAD implantation (58). After LVAD implantation, renal function improved in 10 patients sufficiently to allow removal of RRT—most had RRT removed by 1 month, but two patients required 6 months of RRT before removal. For the five patients who did not have RRT discontinued after LVAD implantation, mortality was 80%. For the group as a whole, the preimplant eGFR was 46.9 ml/min per 1.73 m², increasing to 73.2 ml/min per 1.73 m² at 2 months postimplant and was 61.8 ml/min per 1.73 m² at 12 months postimplant.

Improvement in renal function has been reported in as many as 74% of implant patients with baseline RD (23,27,64) although the likelihood of improvement is less with more severe preimplant RD (64). Not surprisingly, patients who recover renal function have a dramatically improved survival compared with those whose AKI did not recover (23,62). A more surprising observation is that patients who recover renal function postimplantation compared with patients without RD preimplantation have similar survival curves 6 months after LVAD placement, from placement to the time of cardiac transplantation, and up to 1 year after transplantation (62). In general, improvement in RD is usually seen during the first month postimplantation and has been shown to remain stable for periods up to 1 year (58). Patients who demonstrated the greatest improvement in renal function had lower preimplant cardiac indexes and were more likely to have received inotropic support than those who did not improve (23,27). This implies that if renal function remains significantly impaired despite attainment of a reasonable cardiac index on medical therapy preimplant, a careful assessment for intrinsic renal disease should be conducted (27). In this regard, patients with RD and diabetes are less likely to improve renal function postimplantation (23).

Failure to improve renal function after LVAD implantation could be due to ongoing multiorgan failure, residual damage from AKI, or the presence of pre-existing intrinsic renal disease from hypertension, diabetes, renovascular disease, or long-standing ischemia from a low cardiac

Author (Reference)	LVAD Type	Participants (N)	Improvement in Renal Function	Duration of Follow-Up, Days, Mean (Range)	Comments
Burnett <i>et al.</i> (61)	Pulsatile	11	SCr: 3.1 → 1.5	115 (31–233)	2 of 4 dialysis-dependent patients preimplantation able to discontinue dialysis postimplantation
Farrar <i>et al.</i> (17)	Pulsatile	22	SCr: 1.7 → 1.2	60–248	Patients with continued MOF postimplantation demonstrated worsening of renal function
Bank <i>et al.</i> (60)	Pulsatile	20	SCr: 1.6 → 1.0	12–193	
Frazier <i>et al.</i> (50)	Pulsatile	271	SCr: 1.5 → 1.1	112 (1–691)	
Khot <i>et al.</i> (62)	Pulsatile	11	SCr: 4.1 → 1.6	180	7 patients were CRRT dependent in peri-implant period. None were CRRT dependent after LVAD implantation at time of death/transplantation
Aaronson <i>et al.</i> (63)	Pulsatile	13	—	NA	8 of 13 CRRT-dependant patients preimplantation recovered renal function postimplantation
Butler <i>et al.</i> (27)	Pulsatile	220	CrCl: 77 → 107	28	Subset patients' baseline CrCl <50, 37 → 67 at week 2 postimplant
Russell <i>et al.</i> (46)	Continuous	78	SCr: 1.8 → 1.4	180	
Kamdar <i>et al.</i> (45)	Continuous	40	SCr: 1.9 → 1.3	30	
Sandner <i>et al.</i> (23)	Continuous	40	eGFR: 42 → 63	180	65% of patients with baseline eGFR <60 recovered renal function: eGFR 46 → 84
Demirozou <i>et al.</i> (58)	Continuous	15	eGFR: 47 → 62	360	15 patients required CRRT after LVAD implantation → 10 able to stop RRT by 6 months
Singh <i>et al.</i> (64)	Pulsatile and continuous	116	CrCl: 58 → 74	180	
Hasin <i>et al.</i> (47)	Continuous	83	eGFR: 53 → 71	180	8 patients required CRRT postimplant: 2 recovered renal function, 2 died, and 4 required chronic hemodialysis

LVAD, left ventricular assist device; SCr, serum creatinine (mg/dl); MOF, multiorgan failure; CRRT, continuous renal replacement therapy; NA, not available; CrCl, creatinine clearance (ml/min); eGFR, estimated GFR (ml/min per 1.73 m²).

output state (17). The possibility that long-standing low flow (ischemia) can result in irreversible CKD is suggested by the observation that patients with hepatorenal syndrome who receive an orthotopic liver transplant usually improved renal function if the duration of pretransplantation RD was not long standing (65). Future studies are needed to better define predictors of patients who have AKI that will improve after LVAD implantation and to evaluate long-term renal function and survival in DT patients. This information is important given the costs of LVAD implantation, that cardiac transplant eligibility is often dependent on acceptable renal function (often an eGFR ≥ 50 ml/min per 1.73 m²) (66,67), and that use of calcineurin inhibitors will cause progressive renal damage in a significant number of heart transplant recipients (64,68). The ability of LVADs to improve comorbidities that are contraindications to cardiac transplantation, such as RD, indicates that another benefit of LVAD placement is as a bridge to candidacy (69,70).

Although it has been repeatedly demonstrated that LVAD implantation improves renal function, the precise mechanisms for this improvement have not been fully defined. Iwashima *et al.* performed renal Doppler sonography in pulsatile-flow LVAD recipients who after implantation showed improvement in their mean eGFR (from 42.7 to 64.1 ml/min per 1.73 m²) (71). Mean peak systolic velocity decreased and mean end diastolic velocity increased, resulting in a significant improvement in the resistive index. These findings could be explained by improvements in elevated right heart and renal vein pressures, which increase interstitial pressures that in turn decrease cross-sectional area of intrarenal vessels and diastolic flow. Improvements in renal function by LVADs appears to be mediated by several factors, including reductions in vascular resistance within the kidney from changes in renal venous pressure, RAAS, and sympathetic activity, as well as improvements in cardiac output (48,71–73).

Management of RRT in LVAD Patients

There are challenging and unique issues that arise in the course of delivering RRT to an LVAD patient in either the inpatient or outpatient setting. The cardiothoracic surgeon, heart failure physician, and LVAD nurses should be closely involved in educating the dialysis unit team, nephrologist, patient, and family members about LVAD management during RRT. In this section, we discuss the challenging issues that arise when managing LVAD patients who require RRT.

RRT Modality

In a critical care setting, RRT is often initiated using CRRT; however, once a LVAD patient becomes hemodynamically stable, he or she can be transitioned to intermittent hemodialysis or peritoneal dialysis. Because older larger pulsatile LVADs were implanted in the peritoneal cavity or abdominal wall, peritoneal dialysis was contraindicated since peritonitis has the potential to develop into a lethal infection of the pericardial cavity. Moreover, intraperitoneal placement of these older pulsatile LVADs has been associated with bowel erosion, bowel obstruction,

and hernia, which all can further complicate peritoneal dialysis (74). The newer LVADs such as the HeartWare HVAD (commercially available in Europe but currently pending approval by the FDA in the United States) or HeartMate II can be implanted in an intrapericardial (HVAD) or pre-peritoneal (Heart Mate II) location below the left rectus muscle, making peritoneal dialysis a possible option. Advantages of peritoneal dialysis in an LVAD patient requiring chronic RRT include gentle ultrafiltration, rarity of bacteremia secondary to a peritoneal catheter infection, and home RRT obviating the logistic obstacles of placement of an LVAD patient in an outpatient hemodialysis unit (75). Although hemodialysis and peritoneal dialysis are both options for RRT in an LVAD patient, the superiority of one over the other is undetermined at the present time. However, if hemodialysis is utilized, the authors recommend placement of a dialysis graft (see below) as soon as possible to minimize the risk of bacteremia from a tunneled dialysis catheter.

Vascular Access

Arteriovenous graft placement is the preferred long-term dialysis access option. Although we did not identify any studies to support this statement, we have had several LVAD patients in whom arteriovenous grafts were placed, remained patent, and were used successfully to perform intermittent hemodialysis. It is possible that the requirement of chronic anticoagulation in these patients may contribute to graft patency. Every effort should be made to avoid long-term use of dialysis catheters in these patients due to the increased risk of bloodstream infection with subsequent spread to the pericardial cavity and the LVAD itself. Although there are no studies looking at arteriovenous fistula maturation in LVAD patients, theoretical considerations of nonpulsatile flow lead us to conclude that arteriovenous fistula should not be considered a vascular access option. In this regard, Amir *et al.* found that nonpulsatile flow was associated with decreased flow-mediated vasodilation compared with pulsatile flow (8). Another challenge in the care of LVAD patients with renal failure is accurate evaluation of access patency. Because many patients with a continuous-flow LVAD have an absent pulse and thrill, we suggest the use of ultrasonography with Doppler or needle puncture of the access to evaluate access patency before concluding that the access has thrombosed.

BP Monitoring

The standard methods of obtaining BP using auscultation of Korotkoff sounds and automatic BP machines often fail to accurately measure BP in a patient with a continuous-flow LVAD unless there is a significant pulse pressure present from preserved left ventricular function (14). The pulse pressure in a continuous-flow LVAD depends on pump speed, the residual native left ventricle contractility, aortic valve opening and closing, and preload/afterload pressures (76). Myers *et al.* showed that the automatic BP machine provided both systolic and diastolic readings when pulse pressure was $>12.8 \pm 4.8$ mmHg (76). However, readings obtained using an

automatic BP machine are often unreliable because many of them rely on oscillometric pulsations, which are created by the native left ventricular contractions (77,78). Comparison of automatic BP cuff readings with arterial line measurements in 35 patients with a continuous-flow LVAD revealed significant differences in systolic, diastolic, and mean BPs, with the automatic cuff readings of systolic and diastolic measurements consistently lower than those obtained using an arterial catheter (14,76). For practical reasons, Doppler audible ultrasonography is a commonly used means to record BP in patients with continuous-flow LVADs, especially when residual left ventricular pulsatility is so low that automated devices have difficulty in displaying a reproducible reading. In these instances, the start of blood flow auscultated with Doppler ultrasonography is commonly regarded as the mean arterial pressure (77). The blood pressure can be measured by placing the Doppler probe over the brachial artery below an inflated blood pressure cuff using the non-access arm of a hemodialysis patient.

Patients with an LVAD often have increased systemic vascular resistance. Unlike pulsatile-flow VADs, continuous-flow devices are sensitive to elevated afterload (76). Increased afterload can reduce pump output and/or cause retrograde flow through the LVAD due to the absence of valves in the device (33). Therefore, it is important to monitor for elevated BP and treat accordingly. The optimal mean arterial pressure is between 70 and 80 mmHg and must not be allowed to exceed 90 mmHg in order to avoid impaired LVAD output (14). When initiating antihypertensive therapy, negative inotropes should be used with caution and in collaboration with the LVAD treatment team. The antihypertensive agents of choice in this population are angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

LVAD Monitoring During Hemodialysis or CRRT

During hemodialysis or CRRT, the system driver should be connected to a display screen, which shows key parameters such as pump flow, pump speed, pulsatility index (PI), and pump power. These parameters should be recorded throughout the hemodialysis or CRRT treatment. It is useful to obtain an individualized range of target values for each of these parameters from the LVAD monitoring team.

Pump Speed. The pump speed is the rate of revolution of the rotor. The pump speed is set by the LVAD team, and is generally kept in the range of 8000–10,000 rpm for most patients implanted with the HeartMate II, although the maximum set speed is 15,000 rpm. Increasing the pump speed leads to an increase in pump blood flow. A pump speed that is too high can result in left ventricle and atrium collapse by completely unloading the left ventricle, causing hemodynamic instability. Furthermore, the prolonged closure of the aortic valve during the cardiac cycle can lead to aortic valve fusion and aortic insufficiency. In the case of LVADs that return blood to the descending aorta, stagnant flow in the aortic root proximal to the entry of blood from the LVAD can occur, causing supraventricular thrombosis or occlusion of coronary arteries (76). Other potential adverse effects of high pump speed include intravascular hemolysis, platelet activation, and

interventricular septal shift with decreased right ventricular function (76).

Pump Flow. Pump flow, expressed in liters per minute, ranges from 3 to 10 L/min. Pump flow is derived from pump speed and power and is not directly measured (\uparrow speed = \uparrow flow; \downarrow speed = \downarrow flow). Pump flow is dependent on both preload and afterload. The flow of the HeartMate II is directly related to the pump speed and is inversely related to the pressure differential across the pump. As speed increases, the flow increases. The pressure differential across the pump refers to the difference between the pressure at the aortic outlet and the left ventricular inlet (Figure 2) (79).

Pulsatility Index. The PI is a dimensionless quantity that is derived from the LVAD pump in the Heart Mate II system. Despite the presence of an LVAD, the native ventricle has residual pulsatile activity that transiently increases flow within the LVAD resulting in a flow pulse. These flow pulses are averaged over intervals of 15 seconds and the resulting value is termed the PI. The formula is: $[(\text{flow maximum} - \text{flow minimum}) / \text{flow average}] \times 10$, and usually ranges from 1 to 10 for a HeartMate II (80). When the ventricle has abundant native contractile function, then the resulting flow pulses will cause the PI to increase. When there is less contractile function of the native ventricle, then there are fewer flow pulses and hence, a lower PI (80). The PI can also reflect preload, and an understanding of this is critical in performing ultrafiltration in an LVAD patient. When the preload increases, the contractility of the left ventricle increases, resulting in flow pulses that increase the PI. The opposite holds true for situations of low preload—the PI decreases. Inadequate preload from other variables, such as excessive ultrafiltration during hemodialysis or CRRT, may result in decreased PI and the pump flow drops (Table 3). Negative inotropes such as β -blockers as well as non-dihydropyridine calcium channel blockers should be used with caution because they can reduce right ventricular function and thus preload (81). Other factors that decrease preload include drug-induced venodilation, volume depletion, sepsis, lateral decubitus position, and reverse Trendelenburg position (80). Overall, the PI can serve as a surrogate marker for preload during RRT. These parameters for monitoring should be individualized and discussed with the LVAD team. The PI can also be regarded as a surrogate marker of LVAD support. With increased LVAD support, PI decreases and *vice versa* (80).

Anticoagulation, Bleeding, and Hemolysis

Thromboprophylaxis remains an important therapy in continuous-flow device support and anticoagulation is generally recommended with various combinations of heparin, warfarin, aspirin, and dipyridamole for the prevention of clot formation unless there is a contraindication such as gastrointestinal bleeding (9). Bleeding after LVAD implantation is not uncommon and is due to required anticoagulation and acquired von Willebrand's disease. There are multiple case reports of gastrointestinal bleeding from arteriovenous malformation in patients with a continuous-flow LVAD (33). The development of arteriovenous malformations with bleeding may be due to the combination of a lack of pulse pressure in continuous-flow LVADs (in a

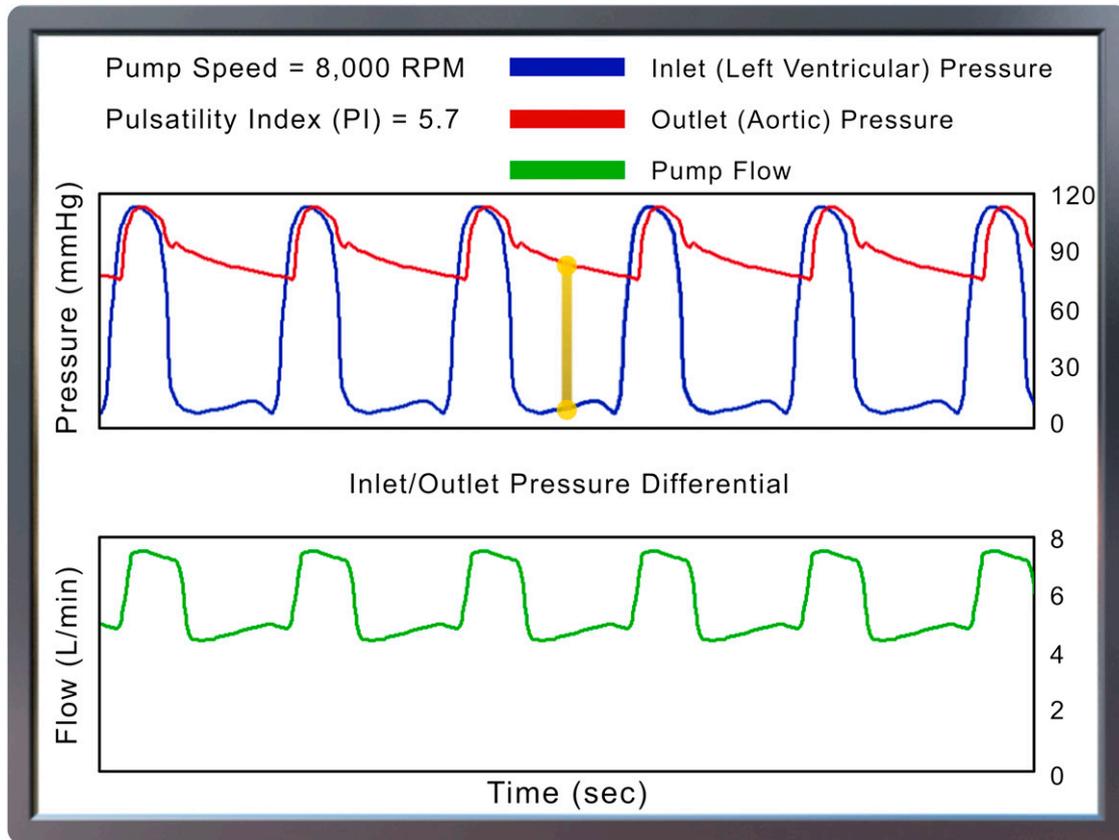


Figure 2. | Relationship between LVAD flow and pressure. The pump flow is inversely related to the pressure differential across the pump, which is the difference between the pressure measured at the outflow cannula (*i.e.*, aortic pressure, as shown by the red line) and that at the inflow cannula (*i.e.*, left ventricular pressure, as shown by the blue line). As the pressure difference between these two locations decreases (during systole), the pump flow (green line) is increased. As the pressure differential increases (during diastole), the pump flow (green line) is decreased because the pump must overcome this increased pressure difference (yellow line) in order to propel blood forward. Reprinted from reference 79, with permission.

Condition	LVAD Parameter Outcome
Uncontrolled hypertension	↑ Afterload → ↓ PI and ↓ pump flow
Excessive volume removal	↓ Preload → ↓ PI and ↓ pump flow
Trendelenburg position or saline infusion	↑ Preload → ↑ PI and ↑ pump flow

LVAD, left ventricular assist device; PI, pulsatility index.

manner analogous to that proposed for arteriovenous malformations in patients with aortic stenosis or Heyde’s syndrome) and destruction of high molecular-weight von Willebrand multimers (14,33). In general, an international normalized ratio between 1.5 and 2.5 is associated with reduced risk of stroke while minimizing the risk of bleeding (14). Hemolysis, another potential complication of LVAD is uncommon due to the low shear stress of current

continuous-flow LVADs but may become clinically significant if thrombus develops within the LVAD.

Conclusion

A dual diagnosis of heart failure and RD is frequently observed and is associated with significant morbidity and mortality. Heart failure unresponsive to medical therapy is increasingly being treated with LVADs. Current LVADs utilize continuous blood flow, which is nonphysiologic. To date, renal function in most studies does not appear to be adversely affected by continuous blood flow. However, some studies have observed a decrease in renal function during prolonged observation after LVAD implantation raising uncertainties about the long-term effects of continuous blood flow on renal function and histology. AKI after LVAD placement is common and is associated with a high mortality. In contrast, improvement in RD, including discontinuation of CRRT, is commonly seen and is associated with improved survival. Nonetheless, some LVAD recipients with RD will require long-term RRT. Patients with LVADs requiring CRRT in the acute setting or long-term hemodialysis or peritoneal dialysis provide unique challenges in their management and require an understanding of the hemodynamic and physiologic consequences

of the LVAD in order to optimize the dialysis prescription and deliver high-quality nephrology care that minimizes patient morbidity and mortality.

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