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Kidney health and function with left ventricular assist devices

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Abstract

Purpose of review—Mechanical circulatory support (MCS) is a group of evolving therapies used for indications ranging from temporary support during a cardiac procedure to permanent treatment of advanced heart failure (HF). MCS is primarily used to support left ventricle function, in which case the devices are termed left ventricular assist devices (LVADs). Kidney dysfunction is common in patients requiring these devices, yet the impact of MCS itself on kidney health in many settings remains uncertain.

Recent findings—Kidney dysfunction can manifest in many different forms in patients requiring MCS. It can be due to preexisting systemic disorders, acute illness, procedural complications, device complications, and long term LVAD support. After durable LVAD implantation, most persons have improvement in kidney function; however, individuals can have markedly different kidney outcomes, and novel phenotypes of kidney outcomes have been identified.

Summary—MCS is a rapidly evolving field. Kidney health and function before, during, and after MCS is relevant to outcomes from an epidemiologic perspective, yet the pathophysiology underlying this is uncertain. Improved understanding of the relationship between MCS use and kidney health is important to improving patient outcomes.

Keywords

kidney disease; cardiovascular disease; cardiac devices; mechanical circulatory support; left ventricular assist device

Introduction

Mechanical circulatory support (MCS) has evolved rapidly over the past 2 decades. While MCS devices can be used for right ventricular or biventricular support, left ventricular support—in which case the devices can be termed left ventricular assist devices (LVADs)—is by far the most common use. Durable MCS devices, used for long term support in persons with advance HF refractory to other therapies, have evolved from bulky first-generation devices with pulsatile flow and high complication rates to the latest generation device, a

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centrifugal flow device with magnetically levitated impeller. As the technology of durable MCS devices has evolved, the goals of use have changed as well. Initially, durable MCS was used almost exclusively to support survival to a desired outcome and device removal (bridge to heart transplantation, or bridge to myocardial recovery), whereas now the primary use is permanent management of advanced HF to improve quality and length of life.[1,2] Temporary MCS devices, used to provide circulatory support for a short term indications in a less invasive manner, have evolved as well in terms of technology and indications.[3] Several temporary MCS devices are available, with the newest being microaxial pumps enabling high blood flows with percutaneous placement.[4]

As the MCS landscape evolves, the links between cardiovascular and kidney health make nephrology research and clinical expertise critical. Comorbid heart and kidney disease is common in MCS recipients, and the effects of MCS on kidney health and function remain uncertain. In this review, we survey the most recent evidence on kidney health and function with durable and temporary LVAD use.

Types of MCS devices, indications, and trends

An understanding of the various device types and trends in their use is relevant to nephrology. Table 1 summarizes durable and temporary MCS devices. There is currently only one durable LVAD device available for implantation, a centrifugal flow device with a magnetically levitated rotor.[5,6] This device provides continuous flow, although it has some intrinsic pulsatility to reduce thrombosis formation in the device. This device was demonstrated in a randomized trial to be superior to the previously used axial flow device in that it required fewer pump replacements and had lower rate of disabling stroke, one of the most feared LVAD complications, in addition to improved 5 year survival.[7,8] This device can be used for biventricular or right ventricular support.[9]

While the fundamental indication for durable MCS with implantable LVADs (advanced HF refractory to other guideline directed therapies) has remained the same, the goals of therapy have changed greatly over the past 2 decades.[10] Implantable LVADs were initially used primarily for support until cardiac transplantation could be obtained (bridge to transplantation) or until a patient could be rehabilitated for cardiac transplantation listing (bridge to candidacy), and in a smaller number the strategy was temporary support of the heart until myocardial recovery could occur.[11] While a substantial portion of LVADs have been implanted for permanent support (destination therapy) for more than a decade, there has been a drastic increase in use for this indication in recent years.[12] In 2021 destination therapy was the goal for 81.1% of implantations in the US.[12] This marked shift has been driven at least partly by changes to the heart failure allocation system in 2018, which reduced the priority of implantable LVAD recipients because of their relatively good survival.[12]

Besides the implantable centrifugal pump, the only other U.S. Food and Drug Administration (FDA)-approved durable MCS device is a total artificial heart (TAH), which replaces both ventricles and the 4 native heart valves.[13] This device consists of rigid ventricles and pneumatic displacement pumps that provide pulsatile flow, and receives

limited use because of high complication rates, limited durability, and limited quality of life.[14] It is currently approved for use for bridge to transplantation, and a trial for use as destination therapy is ongoing. Another TAH, designed to be less thrombogenic than the existing device and to mimic native ventricular function by adjusting contractility in response to preload, is undergoing testing in humans.[15] Because of the perennial shortage of donor organs, development of TAHs more suitable for permanent use is an area of active interest.[14]

In contrast to the few devices used for durable MCS, for temporary MCS there are a range of device types (Table 1). Indications have expanded from supportive therapy in cardiogenic shock to use for temporary support in a wide variety of cardiac procedures[16] and for support prior to cardiac transplantation.[17] These devices vary in the amount of support they provide and their invasiveness, and range from intra-aortic balloon pumps (which can provide modest flow increases, on the order of 1L/minute, and are relatively easily placed and removed) to venoarterial extracorporeal membrane oxygenation (ECMO) and a percutaneous centrifugal flow device (which can provide high blood flow, and require substantial procedures for placement). In between these extremes are microaxial pumps, which can be placed percutaneously and can provide up to 5 L/minute of flow.[16] While use has expanded greatly, evidence for effectiveness of these devices in various scenarios is limited.

Kidney health and LVADs – durable MCS

Combined heart and kidney dysfunction is extremely common; thus, it is no surprise that kidney dysfunction is a common challenge in implantable LVAD recipients. Despite long-standing recognition of the importance of kidney dysfunction to LVAD recipient outcomes, and the sometimes deleterious effects of LVAD implantation on kidney function, this remains an area filled with uncertainty and in need of further research.[18] Table 2 summarizes possible mechanisms of beneficial and deleterious effects of temporary and durable MCS on the kidneys.

Kidney dysfunction prior to LVAD implantation

Kidney dysfunction (assessed generally using serum creatinine, derived estimated glomerular filtration rate [eGFR], or blood urea nitrogen [BUN]) is common prior to LVAD implantation and associated with adverse outcomes.[19,20] Various measures of pre-implantation kidney function are used in most prognostic models developed to risk stratify persons prior to LVAD implantation.[21] Dialysis prior to LVAD implantation is associated with adverse outcomes, and permanent kidney disease (kidney failure with replacement therapy [KFRT]) is associated with particularly poor outcomes.[22,23] The possible reasons underlying this relationship between pre-implantation kidney dysfunction and adverse outcomes are many, and different factors and combinations are likely predominant in different patients.[24] Pre-existing kidney dysfunction could potentially be an indicator of overall health and disease severity, indicating more severe cardiovascular disease, or severe comorbid conditions (particularly diabetes).[25] Additionally, pre-existing kidney dysfunction likely plays a causal role in adverse outcomes in the perioperative period and later. This

is due to the myriad important functions that a healthy kidney performs to optimize homeostasis, from acid base management and intravascular volume control to control of red blood cell production. In most cohorts, it is quite challenging and often impossible to differentiate (or attribute proportions to) acute kidney decompensation before LVAD implantation and pre-existing irreversible kidney disease. Thus, these tend to be necessarily combined in many analyses. However, some recent publications have attempted to separate different groups. One way of determining chronicity of kidney disease has made use of administrative diagnostic codes to identify and differentiate chronic kidney disease. A recent publication used the Medicare 5% sample to identify nearly 500 people carrying various CKD diagnoses, and compared this to those with KFRT.[22] While persons with CKD had better outcomes than those with KFRT, comparisons were not made to persons with AKI or no kidney disease.[22]

Acute kidney injury following LVAD implantation

Cardiac surgery with cardiopulmonary bypass, such as LVAD implantation, is a prototypical acute kidney injury-inducing insult. With increasing recognition of the importance of parenchymal kidney injury assessment, a study using a urine cell cycle arrest biomarker score (calculated by multiplication of the urine concentrations of insulin-like growth factor-binding protein 7 [IGFBP7], and tissue inhibitor of metalloproteinases-2 [TIMP-2]) found that elevated score 6 hours after LVAD implantation was an independent predictor for development of moderate or severe AKI within 48 hours of implantation; levels prior to LVAD implantation were not a predictor of this outcome.[26] An AKI prediction model for cardiac surgery was recently successfully developed and validated in large cohorts; however, it excluded LVAD recipients.[27] Extending an AKI prediction model to LVAD recipients may enable targeted supportive care, and eventually possibly enriched enrollment for trials of management strategies.

Kidney dysfunction after LVAD implantation

While lower pre-LVAD implantation kidney function appears to be associated with adverse outcomes, a common clinical question is how kidney function is expected to change following LVAD implantation. Average kidney function trajectories after LVAD placement tend to show early increase in eGFR, up to a maximum value generally at about one month follow-up, followed by subsequent decline up to about 3 months and then stabilization. Additional recent studies have confirmed this general pattern.[19,28] There have been attempts to identify pre-implantation characteristic that may identify patients whose kidney function will improve following implantation. In an observational cohort study by Wettersten et al, a few non-modifiable pre-implantation factors such as younger age, lower eGFR, and absence of diabetes mellitus (DM) were associated with post-implantation eGFR improvement at the 1-month mark.[28] Although these patterns of early eGFR increase and later decline are widely observed, a new analysis of INTERMACS data from our group used a method (latent class mixed models) to identify kidney function trajectories that may be obscured by the dominant patterns.[29] This analysis found that while the majority of LVAD recipients did fall into these dominant patterns of early improvement followed by later decline in kidney function, a sizable minority experienced significantly different trajectories following LVAD implantation. The three novel trajectories that were found displayed: 1. Low pre-

LVAD eGFR followed by initial worsening and later stabilization; 2. Low pre-LVAD eGFR followed by marked increase and stabilization, and 3. Mid-range pre-LVAD eGFR followed by wide swings.[29] When examination of related baseline factors and outcomes was performed, it was found that these 3 novel trajectories may correspond to distinct pathophysiologic mechanisms: low pre-LVAD eGFR followed by post-LVAD worsening may perhaps correspond to severe pre-existing parenchymal kidney disease; low pre-LVAD eGFR followed by substantial and sustained eGFR increase may represent a class type 1 cardiorenal syndrome with hemodynamically-induced kidney dysfunction corrected by the LVAD; and the unstable eGFR pattern seemed to correlate with new onset right ventricular failure, one of the feared complications of LVADs that is addressed in more detail later.[29]

Another study examining the importance of kidney function following LVAD implantation provides additional insight. In the randomized trial comparing the magnetically levitated centrifugal pump LVAD to the prior generation, axial flow device, kidney function at time of discharge from the implantation hospitalization was found to be associated with higher risk of rehospitalization.[30] AKI during the implantation hospitalization has been shown to be associated with higher rates of overall and cause specific readmissions as well.[31]

While numerous studies have examined changes in eGFR following LVAD implantation, little is known about other aspects of kidney function and health following LVAD implantation. Kidney biopsy results following LVAD implantation are quite rare, given the tenuousness of the patients and need for anticoagulation. However, use of kidney biomarkers and multi-omics investigations hold the potential to give additional insight into other aspects of kidney health across the LVAD recipient life course.

A limitation of reliance on eGFR is the potential confounding of eGFR by body composition and fluid changes. A recently reported study performed in 88 persons measured GFR before LVAD implantation, 3-6 months after LVAD implantation, and then 1 year following heart transplantation.[32] This found that in the subset of those implanted in more recent years, measured GFR increased following LVAD implantation and heart transplantation. However, it is unclear how this finding in a relatively small number of selected patients relates to the usually observed eGFR change pattern, and to outcomes.

Kidney dysfunction and right heart failure after LVAD implantation

The importance of congestion and central venous pressure to kidney function in HF is widely recognized, and there are several potential mechanisms underlying this.[33] This is particularly relevant for LVAD recipients, as right heart failure (RHF) after LVAD implantation is a common and feared complication, affecting up to 40% of recipients.[34] Recent studies have investigated the diversity of RHF after LVAD implantation, which can vary in terms of timing of onset (early or late after LVAD implantation, often dichotomized at a 30 day time point), and in terms of persistence of the RHF.[35] The details of how these RHF outcomes affect kidney health and function remain to be investigated. It has been demonstrated that onset of RHF after LVAD implantation is associated with both lower pre-implantation eGFR and with lower subsequent eGFR after development of RHF.[36]

Kidney health and LVADs – temporary MCS

Despite the increasing use of temporary MCS devices, and the theoretical benefits to kidney function from a macrocirculatory perspective, there is limited data available on the effects of temporary MCS on kidney health and outcomes. The diversity of temporary MCS devices, widely varying indications, and lack of randomized trials make this a particularly challenging area. Potential mechanisms through which temporary MCS devices could harm the kidneys include through hemolysis and heme pigment nephropathy, systemic inflammation, and arterial emboli (Table 2).[37,38]

A propensity matched analysis comparing use of intraortic balloon pumps and percutaneous microaxial LVAD in persons with acute myocardial infarction complicated by cardiogenic shock was recently published.[39] This found markedly worse kidney outcomes with microaxial LVAD use at 30 days and 1 year: kidney replacement therapy was needed within 30 days in 12.2% of the microaxial LVAD group and 7.0% of the IABP group (odds ratio [OR] 1.88 [95% CI 1.30-2.73]), and within 1 year in 18.1% of the microaxial LVAD group and 10.9% of the IABP group (hazard ratio [HR] 1.95 [95% CI 1.35-2.83]).[39] These adverse kidney outcomes are in addition to worsened mortality and bleeding. Another recently published propensity-adjusted analysis used administrative claims data to compare rates of AKI in persons undergoing high risk percutaneous coronary intervention (PCI) supported with either microaxial LVADs or IABP, and found similar rates of AKI in the two groups.[40]

Venoarterial ECMO use tends to be associated with high complication rates, but this may be in part due to underlying patient factors leading to selection of this intensive strategy. A recent analysis from Germany of persons undergoing elective high risk PCI who were supported with VA ECMO or a microaxial device found higher risk of stage 1 AKI (by KDIGO criteria) with ECMO: 55% vs. 12%, $p = 0.03$.[41]

The diversity of temporary MCS devices, lack of randomized trials, and unclear and changing indications and usage patterns makes this an important area for future nephrology investigations.

Conclusions

The field of MCS continues to evolve rapidly. In the United States, the use and availability of devices for a variety of indications continues to expand. Due to the close relationship between the kidneys and the heart, and the sensitivity of the kidneys to numerous insults, further understanding of the effects of different management strategies on short and long term kidney outcomes is essential to ensuring optimal patient outcomes. Non-invasive assessments of kidney health using biomarker panels and multi-omics techniques holds promise for improved pathophysiologic understanding, diagnosis, and prognosis of kidney health in these settings.

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Key Points

1. Durable and temporary mechanical circulatory support use is rapidly evolving, and the effects on kidney health and function remain uncertain.
2. Despite improvement or maintenance of blood flow and central venous pressure levels that are expected to improve kidney function, mechanical circulatory support may have adverse effects on the kidneys. Precision nephrology approaches to understanding this are needed.
3. Nephrology plays a critical role in management of persons receiving mechanical circulatory support, both in clinical management and in research aimed at important knowledge gaps.

Table 1.

Mechanical circulatory support device types in common use

	Temporary				Durable	
Device type	Intra-aortic balloon pump	Microaxial flow pump	Percutaneous external centrifugal pump	Venoarterial extra corporeal membrane oxygenator (ECMO)	Implantable centrifugal pump	Total artificial heart
Expected Length of Use	Days	Days	Weeks	Weeks	Years	Months to years
Mechanism	Counterpulsation	Axial flow	Centrifugal pump	Centrifugal pump	Centrifugal pump	Pulsatile flow using displacement pumps
Notable complications	Spinal cord ischemia, limb ischemia, kidney ischemia, infection, and bleeding	Valvular lesions, hemolysis, stroke	Air embolism, limb ischemia	Limb ischemia, intracardiac thrombus formation, hemolysis, bleeding	Right heart failure, stroke	Driveline infections, mediastinitis, constrictive pericarditis causing transplantation complications
Considerations	Can only pump 1 L/minute	Can pump up to 5 L/minute	Can pump up to 5 L/minute. Appealing to avoid surgery	High mortality except in select patient populations	Has demonstrated reduced need for device replacement compared to previous generations	Only used for bridge to transplantation

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Table 2.

Potential mechanisms of LVAD effects on the kidney

Beneficial effects
Increased forward flow
Reduced central venous pressure
Harmful effects
Ischemia-reperfusion injury
Systemic and intrarenal inflammation
Systemic and intrarenal neurohormonal activation
Hemolysis
Microemboli