Kidney Medicine

Cardiac Imaging in Dialysis Patients

Jeff Kott, Nathaniel Reichek, Javed Butler, Leonard Arbeit, and Sandeep K. Mallipattu

There is a well-established yet unexplained high prevalence of cardiovascular morbidity and mortality in individuals with end-stage kidney disease receiving dialysis. Potential causes include changes in cardiac structure and function, with increased left ventricular mass index as the best established cardiac structural change associated with this increase in mortality. However, in recent years, new echocardiographic and cardiac magnetic resonance imaging techniques have emerged that may provide novel markers that may better explain the mechanisms underlying the cardiovascular morbidity and mortality observed in end-stage kidney disease. This review outlines advances in cardiac imaging and the current status of imaging modalities, including echocardiography, cardiac magnetic resonance imaging, and cardiac positron emission tomography, to identify dialysis patients at high risk for cardiovascular mortality.

Complete author and article information provided before references.

Kidney Med. 2(5):629-638. Published online July 31, 2020.

doi: 10.1016/j.xkme.2020.05.010

INTRODUCTION

The incidences of cardiovascular morbidity and mortality in individuals with end-stage kidney disease (ESKD) receiving dialysis is greater than those in the general population.[1] The US Renal Data System estimates the prevalence of cardiovascular disease in patients with ESKD receiving hemodialysis (HD) at 70.6% and that in patients receiving peritoneal dialysis at 57.8%.[2] Furthermore, arrhythmia/cardiac arrest alone is the cause of death in ~40% of dialysis patients.[2] There is little evidence to support the effectiveness of traditional approaches to risk-factor modification using medications or lifestyle changes in this population. Further, coronary artery revascularization in patients with documented coronary artery disease did not alter rates of arrhythmic death.[3,4]

Given the high prevalence of cardiovascular death, there has been increased interest in the identification of structural changes within the heart that could be used to predict mortality risk in a given individual. Such structural changes, which have become part of the syndrome known as uremic cardiomyopathy, appear to be due to a combination of chronic inflammation, ischemia due to coronary microcirculatory dysfunction, anemia, volume and pressure overload, and myocardial fibrosis.[5-9]

Echocardiography is the most widely available, least invasive, and least expensive technology for the evaluation of myocardial structure and function in individuals with ESKD receiving dialysis at risk for cardiovascular disease.[10] In recent years, new echocardiographic techniques, as well as the emergence of cardiac magnetic resonance, have shown promise in identifying structural changes consistent with uremic cardiomyopathy. This article reviews these new techniques and their relationship to the unexplained cardiovascular mortality in the ESKD population.

PATHOPHYSIOLOGY OF CARDIAC FIBROSIS IN ESKD

The heart undergoes significant changes in structure and function beginning with the onset of chronic kidney disease (CKD) and worsening with progression to ESKD through multiple mechanisms involving endocrine dysfunction (alterations in calcium/phosphate homeostasis), increased arterial pressure, volume overload, uncontrolled inflammation, anemia, and changes in the cardiac microvasculature.[11-13]

These pathologic mechanisms persist and progress during the development of ESKD, in which further changes in cardiac microvasculature, along with the initiation of kidney replacement therapies, can accelerate myocardial fibrosis.[12,14] Qualitative postmortem evaluation of coronary arteries in a cohort of patients with ESKD compared with nonrenal controls with coronary artery disease demonstrated significantly more calcified plaque, as well as significantly greater media thickness.[15] However, there is evidence that up to 50% of uremic patients who presented with anginal symptoms had no evidence of clinically significant large-vessel coronary artery disease on cardiac catheterization, suggesting that changes to the microvasculature played a role in the development of cardiac structural changes.[14] Similar to the changes observed in human epicardial coronary arteries, changes to the wall thickness and wall to lumen ratio of small intramyocardial arteries occur in animal models with induction of uremia, accompanied by increased expression of vascular endothelial growth factor corrected for hypertension.[16-18]

Additionally, rat models of kidney failure have demonstrated capillary-myocyte mismatch, as well as cardiac hypertrophy in the setting of increased extracellular collagen deposition.[19,20] These findings were mirrored in dialysis-dependent individuals in a small post mortem case-control study.[9] Increased capillary density is typically a compensatory response to maintain blood supply in response to physiologic hypertrophy, such as exercise or pregnancy. However, in pathologic hypertrophy, decreased angiogenesis leads to microischemia and contributes to fibrosis.[21] Interestingly, the severity of the decrease in capillary supply noted in uremic animal models has not been demonstrated in animal models of essential hypertension.[14]

PLAIN-LANGUAGE SUMMARY

The development and progression of heart disease in individuals with end-stage kidney disease receiving maintenance dialysis remain poorly understood. Historically, through the use of cardiac imaging, enlargement of the heart has been associated with increased mortality in patients with kidney disease receiving dialysis. In recent years, new imaging methods have provided insight into the changes in the structure and performance of the heart that may begin to explain the increase in mortality observed in these patients. With further advances in understanding the changes to the heart structure and function, as well as the process that leads to these changes, there is a potential for early identification of patients receiving dialysis who are at risk for the development and progression of heart disease.

HD can result in transient reductions to myocardial blood flow through hemodynamic shifts, which can lead to microvascular ischemia and long-term myocardial stunning.[7,22,23] Intradialytic hypotension, a common occurrence in HD, is associated with increased mortality. It also limits ultrafiltration and the efficacy of dialysis and is associated with endothelial dysfunction, increased arterial stiffness, and myocardial stunning.[24-26] Following intradialytic hypotension, reperfusion contributes to the creation of reactive oxygen species, which further exacerbates myocardial fibrosis.[26] Furthermore, increased myocardial afterload and compressive forces due to volume overload can increase myocardial energy expenditure, which also promotes cardiac remodeling.[26] However, peritoneal dialysis is associated with a lower incidence of cardiovascular disease compared with patients treated with HD.[2] Interestingly, a small prospective study of 10 peritoneal dialysis patients demonstrated less pronounced hemodynamic effects and thereby lower frequency of myocardial stunning.[27]

Cardiac Imaging in ESKD

Echocardiography

Echocardiography provides a noninvasive and cost-effective means of evaluating cardiac structure and function in the ESKD population (Table 1).[10] Additionally, due to the ease with which echocardiography can be performed, it can provide valuable information across various clinical situations.[28]

Volume and Pressure Abnormalities. Historically, aside from traditional markers of abnormal cardiac structure or function such as depressed ejection fraction, diastolic dysfunction, ventricular dilation, and left ventricular (LV) wall motion abnormalities, the echocardiographic finding of increased LV mass index (LVMI) has been a classic marker for increased cardiac mortality risk in patients with ESKD.[10,29] Bansal et al[30] used serial echocardiography to determine changes in cardiac structure and function and their relationship to mortality in a cohort of 417 patients with CKD as they progressed to ESKD. They observed an overall reduction in LVMI with an improvement in diastolic relaxation during a mean follow-up of 0.89 year after the initiation of kidney replacement therapy. However, despite the observed improvement after the initiation of kidney replacement therapy, the well-established association of increased LVMI as a risk factor for mortality was again demonstrated in this study.[30] In addition, they found a 4% decrease in LV ejection fraction (LVEF) and an 8% increase in LV end-systolic volume (another marker of LV function) after the initiation of dialysis. This decline in LVEF after the initiation of dialysis was also associated with an increase in postdialysis mortality.

Alterations in Cardiac Systolic Function. Speckle tracking echocardiography (STE) is a relatively new technique that can identify abnormal systolic myocardial LV function in the setting of normal LVEF in individuals with CKD.[31] STE tracks the motion of reflections within the myocardium to assess myocardial deformation during systole, or systolic strains. Both global average systolic LV myocardial circumferential, longitudinal, and radial strains and strain rates and segmental strain and strain rates can be assessed (Fig 1).[32]

Ravera et al[33] used STE to evaluate LV global longitudinal strain (LVGLS) in 70 individuals at various stages of CKD (defined as CKD stages 2-4, ESKD receiving dialysis, and post–kidney transplantation) and compared results with those found in patients with hypertension and healthy controls. Patients with ESKD demonstrated significantly abnormal LVGLS compared with both hypertensive individuals and controls. Abnormal LVGLS was most closely associated with 2 sequelae of volume and pressure overload, increased LVMI and with abnormal E/e′ ratio—the ratio of the peak velocity of early diastolic filling (E) to the early diastolic lengthening of the left ventricle (e′).

Sun et al[34] also used STE to evaluate strain as a potential predictor of adverse cardiac events in HD patients. In this study, 66 patients receiving HD for at least 6 months without a history of cardiac disease and 22 age- and sex-matched controls underwent 3-dimensional (3D)-STE. This cohort had significantly lower LVGLS and LV global radial strain with lower ejection fraction within the normal range as compared with controls during a 2-year follow-up period. However, after multivariate analysis, LVGLS and LVMI were the only echocardiographic parameters associated with an increased risk for cardiovascular events (odds ratio [OR], 3.94; 95% confidence interval [CI], 1.33-11.66 for LVGLS and OR, 1.04; 95% CI, 1.01-1.07 for LVMI). Interestingly, LVGLS greater than −17.2% was 87.0% sensitive and 79.1% specific for prediction of a major cardiovascular event.

Table 1. Markers of Cardiac Structure and Function in ESKD

Measure	Definition	Indicator	Related Studies
Left ventricular mass	Estimated mass of left ventricle	Left ventricular hypertrophy	10, 29, 30
Left ventricular mass index	Estimated mass of left ventricle divided by body surface area	Left ventricular hypertrophy	10, 29, 30, 44, 45, 46, 52, 55, 59
Left ventricular ejection fraction	The end-diastolic volume of left ventricle minus end-systolic volume, divided by end-diastolic volume	Left ventricular systolic chamber function	30, 35
Left ventricular end-systolic volume	Volume of blood in left ventricle at end of systolic ejection	Left ventricular systolic function	30
Left ventricular end-diastolic volume	Volume of blood in left ventricle at end of diastole	Left ventricular structure	47
E/e' ratio	The ratio of peak velocity of early diastolic filling (E) to early diastolic lengthening of left ventricle (e')	Left ventricular diastolic dysfunction	33, 35
Systolic strain	Percent shortening or lengthening of myocardium in systole in a given plane	Systolic myocardial function	
Global longitudinal strain	Strain in planes parallel to long axis of ventricle (negative systolic value due to systolic shortening)	Left ventricular systolic myocardial function	33, 34, 35, 38, 50, 58
Global radial strain	Transmural myocardial thickening, orthogonal to longitudinal stain and perpendicular to endocardium (a positive value)	Left ventricular systolic Myocardial function	34
Circumferential strain	Strain along circumference of short-axis planes perpendicular to length of the ventricle	Left ventricular systolic myocardial function	49, 50
Mechanical dyssynchrony	A prolonged delay between beginning and end of the onset of systolic strain or wall thickening in myocardium of a cardiac chamber	Systolic dysfunction that can be improved by resynchronization of contraction	34, 38, 39

Abbreviations: E/e′, the ratio of the peak velocity of early diastolic filling (E) to the early diastolic lengthening of the left ventricle (e′); ESKD, end-stage kidney disease. Definitions adapted from Feigenbaum's Echocardiography 7th edition.[69]

Furthermore, a recent cross-sectional single-center Chinese study used STE in an evaluation of the association of cardiac valve calcification and LV function in long-term HD patients of more than 5 years.[35] Despite normal ejection fractions in those with and without valve calcification, abnormal LVGLS was highly associated with valve calcification in this population (-0.18 ± 0.03 in the valve calcification population vs -0.25 ± 0.04; $P < 0.0001$).[35] This subtle myocardial dysfunction was accompanied by diastolic dysfunction with an increased septal E/e′.[35]

Arrhythmia. Ventricular dyssynchrony, or heterogeneity of regional myocardial excitation and contraction due to an altered conduction system, can also predispose patients to cardiac arrhythmias.[36] Novel echocardiographic techniques are typically used to assess ventricular dyssynchrony in patients with depressed ejection fraction.[37] Sun et al[34] used 3D STE to compare ventricular dyssynchrony in age- and sex-matched healthy controls and patients with ESKD receiving HD. Although HD patients exhibited a significantly increased systolic dyssynchrony index, this was not a predictor of cardiovascular events (OR, 1.09; $P = 0.559$).[34]

A small cross-sectional study used the techniques of time to peak longitudinal strain and peak strain dispersion, as determined using 2-dimensional (2D) STE, to evaluate effects of peritoneal dialysis on cardiovascular disease in 31 patients with ESKD (aged >65 years) as compared with 49 age-matched healthy controls.[38] Time to peak longitudinal strain was significantly delayed in patients with ESKD, but peak strain dispersion was not significantly different between the groups.

The 2018 report of Hensen et al[39] attempted to explore the relationship between dyssynchrony and mortality by retrospectively evaluating the incidence of ventricular arrhythmia in 250 predialysis and dialysis-dependent patients (CKD 3B-5). Interestingly, 16 of the 250 patients had ventricular arrhythmias (defined as aborted cardiac arrest, documented sustained ventricular tachycardia, or ventricular fibrillation) or sudden cardiac death. STE demonstrated a significantly increased LVGLS ($-10\% \pm 4\%$ vs $-15\% \pm 5\%$; $P < 0.001$) and an increased LV mechanical dispersion (66 vs 52 milliseconds; $P = 0.004$) in the ventricular arrhythmia/sudden cardiac death group when compared with patients without cardiac events, suggesting that dyssynchrony may be a marker for cardiac events in dialysis patients. However, this study was retrospective and patients with prior cardiac disease were not excluded, thereby raising concerns for potential selection bias.

Cardiac Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) allows the measurement of many parameters of cardiac structure and function with greater reproducibility and additional quantitative

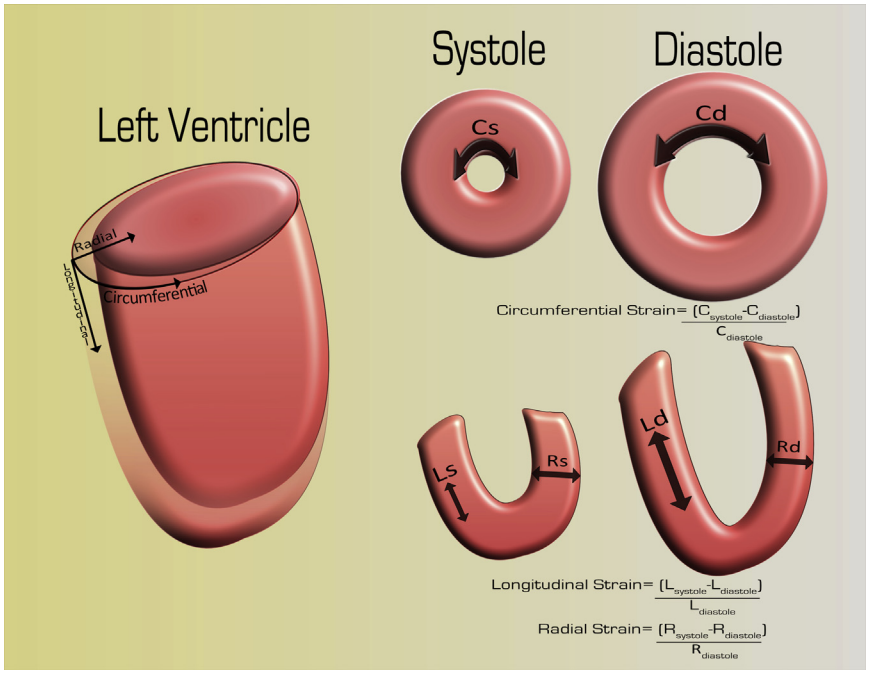

Figure 1. Visual depiction of myocardial strain in the radial, longitudinal, and circumferential directions. Image not anatomically to scale. Abbreviations: Cd, circumferential length in diastole; Cs, circumferential length in systole; Ld, longitudinal length in diastole; Ls, longitudinal length in systole; Rd, radial length in diastole; Rs, radial length in systole.

information on myocardial scar, interstitial fibrosis, coronary artery flow, and myocardial perfusion.[40] The increase in reproducibility in turn permits significant findings with smaller sample sizes using cardiac MRI (cMRI) than is possible using echocardiography. Due to the wealth of information provided, cMRI has become a reference standard for cardiac imaging and has become widely used to study the effects of CKD on cardiovascular outcomes (Table 2).[41]

Volume and Pressure Overload. cMRI allows volumetric imaging and quantitation of LV mass and volume without the geometric assumptions required using 2D echocardiography.[42,43] A small multicenter study of patients with ESKD and age- and sex-matched cohorts showed an increase in LV mass (with a tendency toward concentric remodeling) within 6 months of initiating dialysis.[44] Furthermore, a cross-sectional multicenter trial evaluated the effect of intradialytic changes in arterial pressure on LVMI as measured using cMRI.[45] Study participants were divided into 3 groups based on the mean change in systolic blood pressure (SBP) during dialysis over 1 month—those with increases in SBP ≥ 10 mm Hg, those with decreases in SBP ≥ 10 mm Hg, and those with intradialytic changes in SBP < 10 mm Hg. The authors observed that increases in SBP ≥ 10 mm Hg were significantly associated with increased LVMI.[45]

In addition, the 2017 prospective cohort study of Ross et al[46] followed up 67 Canadian long-term HD patients for 1 year using cMRI and biomarkers at intake and again 1 year later. The 57 participants completed the imaging portion of the study (with cardiac biomarkers available for 53). The study longitudinally evaluated the relationship between blood pressure, biomarkers (N-terminal pro hormone B-type natriuretic peptide and cardiac troponin I, high-sensitivity C-reactive protein, fibroblast growth factor 23, parathyroid hormone, phosphorus, and calcium levels), dialysis parameters (such as ultrafiltration volume and interdialytic weight gain), and cMRI findings. There was a significant negative association ($r = -0.27$; $P = 0.043$) between interdialytic weight gain and LV end-diastolic volume (a marker of LV structure), whereas there were significant positive correlations between SBP and LVMI ($P < 0.001$), cardiac troponin I level ($P = 0.02$), and N-terminal pro hormone B-type natriuretic peptide level ($P = 0.029$). SBP was also positively correlated with the ratio of LV mass to end-diastolic volume or concentric remodeling.[47] There were no correlations with markers of inflammation (high-sensitivity C-reactive protein level), fibrosis (fibroblast growth factor 23 level), or endocrine dysfunction (parathyroid hormone, phosphorus, or calcium levels), leading the authors to conclude that the changes in cardiac structure and function in patients with ESKD are more related to dialysis-associated factors.

Alterations in Cardiac Systolic Function. The cMRI equivalent of echocardiographic STE is feature tracking MRI, which is less operator dependent and more reproducible than STE.[48] In addition, there are a number of other cMRI research methods for strain imaging that have still higher reproducibility, accuracy, and spatial resolution than STE or feature tracking MRI but require specialized image acquisitions.

Table 2. Summary of Key Findings in Studies Using cMRI in Patients With ESKD

Study	Study Type	Patient Characteristics	Imaging Parameter	Results	Limitations
Odudu et al[44] (2016)	Cross sectional multicenter study	54 HD patients and 29 age- and sex-matched controls	LVMI, systolic circumferential strain, EF	Reduced global systolic function by EF (51% ± 10% in HD vs 59% ± 5% in controls; $P < 0.001$) and peak systolic circumferential strain (15.9% ± 3.7% in HD vs 19.5% ± 3.3% in controls; $P < 0.001$); LVMI was increased in HD patients vs controls (63; 95% CI, 54-79 vs 46; 95% CI, 42-53 g/m^2; $P < 0.001$)	Cross sectional design; small study population
Shamir et al[45] (2018)	Cross-sectional multicenter study	80 adult patients on maintenance HD stratified by average change in SBP during HD in 1-mo period	LVMI	Intradialytic HTN (SBP increase >10 mm Hg during dialysis) was associated with LVMI (12.5; 95% CI, 3.6-21.5 g/m^2; $P = 0.01$)	Cross-sectional design; only 7 of 80 patients in cohort had intradialytic HTN
Stromp et al[58] (2018)	Cross-sectional single center study	33 patients on HD and 44 healthy controls	Myocardial fibrosis, LVMI	Novel magnetization-transfer weighted images used to quantitate myocardial fibrosis: increased myocardial fibrosis in ESKD patients than in controls ($P < 0.001$); LVMI increased in ESKD patients and correlated with severity of fibrosis ($P = 0.014$)	Imaging modality not previously validated; small sample size
Ross et al[46] (2017)	Prospective 2-center cohort study	67 maintenance HD patients	LVMI	Volume overload: intradialytic weight gain and ultrafiltrate volume correlated with LVEDV at baseline and 12 mo; intradialytic weight gain correlated longitudinally with LVEDV ($r = -0.27$; $P = 0.043$) Pressure overload**:** elevated SBP correlated to LVMI at baseline, 12 mo, and longitudinally ($r = 0.64$; $P < 0.001$) Cardiac remodeling: SBP correlated with ratio of LVM:LVEDV at baseline, 12 mo, and longitudinally ($r = 0.37$; $P = 0.005$)	Small sample size; nongeneralizable cohort
Ong et al[49] (2019)	Prospective 2-center cohort study	67 Patients on conventional HD. 37 converted to INHD, 30 remained on conventional HD	GCS	Compared to baseline MRI, at 12 mo, INHD showed improvement in GCS compared to conventional HD ($P = 0.025$)	Not randomized; small sample size
Buchanan et al[50] (2017)	Randomized prospective crossover pilot trial	12 patients randomized 1:1 to either HD or HDF for 2 wk; subsequently crossed over to other kidney replacement modality	GCS and GLS	Significant reductions in intradialytic GLS and GCS from baseline regardless of kidney replacement modality	Small sample size

(Continued)

Table 2 (Cont'd). Summary of Key Findings in Studies Using cMRI in Patients With ESKD

Study	Study Type	Patient Characteristics	Imaging Parameter	Results	Limitations
Rutherford et al[55] (2017)	Prospective single-center cohort study	22 maintenance HD patients on dialysis for <1 y	Myocardial fibrosis, LVMI	No significant change in myocardial fibrosis. septal native T1 time unchanged from baseline to 6 mo; LVMI significantly reduced at 6 mo (baseline: 78.3 g/m^2; 6 mo, 67.9 g/m^2; $P < 0.0001$)	Small sample size; single center

Abbreviations: CI, confidence interval; cMRI, cardiac magnetis resonance imaging; EF, ejection fraction; ESKD, end-stage kidney disease; GCS, global circumferential strain; GLS, global longitudinal strain; HD, hemodialysis, HDF, hemodiafiltration; HTN, hypertension; INHD, in-center nocturnal hemodialysis; LVEDV, left ventricular end-diastolic volume; LVM, left ventriculat mass; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; SBP, systolic blood pressure.

A recent prospective 2-center study evaluated the effects of in-center nocturnal HD compared with conventional HD on LV strains and torsion over 1 year.[49] Global circumferential strain was significantly decreased in the nocturnal HD group; however, when compared with the conventional HD group, there was no significant difference. In addition, the 2017 crossover study of Buchanan et al[50] used serial cMRI to evaluate responses to either HD or hemodiafiltration on the myocardium. Twelve patients with ESKD were assigned to either 2 weeks of HD or hemodiafiltration and underwent serial cMRI before, during, and 30 minutes after a single dialysis session. The participants were then crossed over to the opposite modality for 2 weeks before repeating the series of scans. There were significant reductions in both global circumferential and longitudinal strains regardless of kidney replacement modality. In the postdialytic cMRI, strain returned to baseline in some but not all affected patients. Furthermore, there were no significant changes in mean myocardial perfusion during dialysis. However, there were significant differences between baseline perfusion and nadir intradialytic perfusion in both HD and hemodiafiltration. They found no significant change in coronary artery blood flow during dialysis sessions.[50] Although these studies were conducted in a small cohort, they highlight the potential role of cMRI in evaluating myocardial changes in patients with ESKD during dialysis.

Fibrosis. Additionally, cMRI allows for the assessment of visible macroscopic fibrosis seen using the late gadolinium enhancement technique, such as myocardial scars due to ischemic infarction, which extend from the endocardium into the midwall or become transmural, and the mid- and subepicardial scars found in disorders such as hypertrophic and dilated nonischemic cardiomyopathies. However, it also enables the detection and quantitation of the microscopic interstitial fibrosis seen in many disorders using T1 relaxation mapping with and without gadolinium administration to calculate myocardial extracellular volume or, if gadolinium cannot be given, simply using native T1 mapping. Ventricular fibrosis due to cardiac ischemia has long been known to be a nidus for arrythmogenicity. However, it has become apparent that any condition that causes either a midwall or subepicardial scar or interstitial fibrosis can share that potential.[51] Unfortunately, the risk for nephrogenic systemic fibrosis has precluded the use of gadolinium in patients with glomerular filtration rates < 30 mL/min/1.73 m^2.

Before the recognition of nephrogenic systemic fibrosis, earlier studies using gadolinium-enhanced imaging identified both patients with a pattern of nonischemic midwall late gadolinium enhancement that correlated with an increase in LV mass and patients with ischemic heart disease who had the subendocardial pattern in the distribution of a coronary artery typically observed in ischemic cardiomyopathy.[52] The relationship of nonischemic scar to an increase in LV mass was further validated in HD patients without traditional cardiac risk factors.[52] However, given the need to avoid gadolinium in patients with ESKD, native T1 mapping has been used more recently and can detect both interstitial space increases consistent with scar or interstitial fibrosis and myocardial edema related to tissue water increase.[53]

Rutherford et al[54] found that both global and septal T1 times were significantly elevated in HD patients compared with age-matched healthy controls in their 2016 cross-sectional study, thereby demonstrating that increased global cardiac fibrosis is associated with uremic cardiomyopathy. Rutherford et al[55] conducted an additional prospective observational study to evaluate the change in fibrosis (using septal T1 time on cMRI) in 22 HD patients after a 6-month follow-up period. Although the authors observed an improvement in LVMI at 6 months, no significant changes in T1 times were observed, indicating that maintenance kidney replacement therapy had no significant effect on the fibrotic changes.[55]

It should be noted that there have been variable observations on native T1 mapping and volume status. Graham-Brown et al[56] concluded that native T1 mapping was a reproducible marker of myocardial fibrosis, independent of volume status, in HD patients in a small single-center cross-sectional study. Conversely, Antlanger et al[57] found that T1 mapping was significantly influenced by volume status, as determined using bioimpedence spectroscopy, when comparing hypovolemic with euvolemic HD patients. These

studies highlight the critical need for further studies to determine the effectiveness of native T1 mapping to differentiate myocardial fibrosis and edema in ESKD.

The 2018 study of Stromp et al[58] presented a relatively novel gadolinium-free method of quantitating cardiac fibrosis and its relationship to cardiac function declines in patients with ESKD. Thirty-three patients with ESKD receiving dialysis showed a significantly greater level of myocardial fibrosis using a novel 2-point balanced steady-state free precession method with magnetization transfer weighting.[59] LVMI was increased in the ESKD cohort compared with controls and was positively correlated with the degree of fibrosis ($P = 0.014$). Global longitudinal strain was the only cardiac function index that was significantly reduced in the ESKD cohort but it did not correlate with fibrotic changes. Nonetheless, among the few patients with ESKD who returned for the 1-year follow-up, there was an association between the initial fibrosis burden and subsequent declines in global longitudinal strain at 1 year. Collectively, these data suggest a potential prognostic role for noncontrast cMRI in evaluating the progression of myocardial fibrosis in the ESKD population.

Positron Emission Tomography

There has been limited research into positron emission tomography (PET) in the setting of ESKD. The use of radiotracer uptake has largely been used to evaluate myocardial perfusion and identify areas of ischemia or infarction. However, it also can provide valuable information on areas of viability, as well as inflammation.[60]

Alterations in Coronary Vasculature. PET has also been used to assess coronary flow reserve (CFR). CFR, calculated as the ratio of myocardial blood flow during stress to myocardial blood flow at rest, is a marker of the coronary circulation's ability to meet increased myocardial oxygen demand. CFR was used to evaluate changes in the coronary microcirculation and mortality in a cohort of 168 dialysis-dependent patients.[61] After a median follow-up of 3 years, the median CFR value in this study population was 1.4, with 80% of the cohort having values < 2.0, a value previously recognized as the low-risk cutoff in other study populations.[62] Those with CFR < 1.4 demonstrated increased all-cause and cardiovascular mortality as both an independent and an incremental risk factor, even after adjustment for prior cardiac disease.

Paz et al[63] prospectively used dipyridamole pharmacologic stress PET myocardial perfusion imaging and CFR to assess 131 patients with ESKD undergoing evaluation for kidney transplantation. Of the 131 patients, 29.8% had abnormal myocardial perfusion imaging results (defined as qualitative ischemia/infarct, stress electrocardiogram ischemia, or transient ischemic dilation), while 59% had abnormal CFR (defined as <2.0). Furthermore, 34 patients in the cohort underwent left heart catheterization, of whom 68% had abnormal CFR and 68% had at least 1 coronary stenosis > 70%. Ultimately, there was no association between abnormal CFR and abnormal PET myocardial perfusion imaging results ($P = 0.13$) or obstructive coronary artery disease ($P = 0.26$), demonstrating that abnormal CFR results do not require epicardial coronary artery stenosis in the ESKD population. This was a prospective study but did not report the relationship between CFR and cardiovascular mortality.

PET can also use fluorodeoxyglucose F 18 (^{18}F-FDG) to detect and quantify inflammatory atherosclerotic disease using standardized uptake values.[64] A significant amount of data supports its use in the evaluation of atherosclerosis in both large and medium-sized arteries.[64,65] A cohort of 42 individuals, 21 with ESKD and 21 age- and sex-matched healthy patients, underwent ^{18}F-FDG PET/computed tomography to determine maximum and mean standardized uptake values in the ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, iliac arteries, and femoral arteries.[64] The maximum and mean standardized uptake values were significantly greater in all arterial segments in patients with ESKD, providing evidence of acceleration of atherosclerotic processes. Although the relationship between standardized uptake values and cardiovascular mortality was not reported, aortic FDG uptake has been retrospectively shown to predict future cardiovascular disease in other patient populations.[64]

Assa et al[66] presented a case report that used PET to compare the effects of stress induced by dialysis with the effects of pharmacologic stress (adenosine). The intradialytic PET scan showed new regional wall motion abnormalities associated with myocardial blood flow decreases in the same segments that were not observed after adenosine administration. Due to the intradialytic findings, the patient underwent cardiac catheterization and placement of a stent in the midright coronary artery. Although only a case report, these findings shed light on ischemia during dialysis that may contribute to alterations in cardiac structure and function, as well as the increase in eventual cardiovascular mortality in this population.

PET clearly has utility in evaluating myocardial blood flow, coronary reserve, atherosclerosis, and even cardiac structure in the ESKD population, but use has been limited, possibly due to uncertainty about the effects of kidney failure on the biodistribution of radiotracers such as ^{18}F-FDG.[67] Some studies report that kidney function has little effect on isotope kinetics, but further studies are required to substantiate these findings.[67,68]

FUTURE IMPLICATIONS

As demonstrated by this review, there has been important progress in identifying new imaging techniques that may provide additional insight into the changes in cardiac structure and function in patients with ESKD and explain the high prevalence of cardiovascular mortality in this population (Table 3). However, many of these were single-center cross-sectional

Table 3. Summary of Strengths and Limitations of Current Cardiac Imaging Modalities

Modality	Use	Advantages	Limitations	Reference
Echocardiography	Evaluation of function and structure of myocardium; evaluation of cardiac valves	Cost-effective; non-invasive; portable; can accurately assess for hypertrophy of myocardium	Operator dependent; prone to inaccuracy due to measurements being derived; no information of epicardial artery or microvascular disease; no information of interstitial tissue	40, 10, 28, 70
Cardiac magnetic resonance imaging	Evaluation of myocardial structure and function; cardiac valves; myocardial interstitium; and coronary artery flow	More accurate and reproducible than echocardiography; higher imaging quality compared to echocardiography; the gold standard of cardiac imaging	More expensive; less accessible; use of gadolinium-based contrast associated with nephrogenic systemic fibrosis	40, 70
Positron emission tomography	Evaluation of myocardial perfusion, micro- and macrovasculature, and left ventricular function	Reliable assessment of ischemia; allows for evaluation of microvasculature	Variability of radiotracer uptake contributes to variations in results; little research into distribution of radiotracer uptake in the setting of kidney failure	60, 70

studies with small sample sizes. Larger prospective multicenter studies would greatly advance the evaluation of these imaging techniques as potential indexes of mortality risk in the ESKD population.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Jeff Kott, MD, Nathaniel Reichek, MD, Javed Butler, MD, MPH, MBA, Leonard Arbeit, MD, and Sandeep K. Mallipattu, MD.

Authors' Affiliations: Division of Nephrology, Department of Medicine, Stony Brook University, Stony Brook (JK, LA, SKM); Cardiac Imaging Program and Research Department, St. Francis Hospital-The Heart Center, Roslyn (NR); Division of Cardiology, Department of Medicine (NR), and Department of Biomedical Engineering, School of Engineering and Applied Mathematics (NR), Stony Brook University, Stony Brook, NY; Department of Medicine, University of Mississippi Medical Center, Jackson, MS (JB); and Renal Section, Northport VA Medical Center, Northport, NY (SKM).

Address for Correspondence: Sandeep K. Mallipattu, MD, Department of Medicine/Nephrology, Stony Brook University, 100 Nicolls Rd, HSCT16-080E, Stony Brook, NY 11794-8176. E-mail: sandeep.mallipattu@stonybrookmedicine.edu

Support: This work was supported by funds from Dialysis Clinic Inc to Drs Arbeit and Mallipattu.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received December 15, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form May 3, 2020.

REFERENCES

1. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int*. 2003;63(3):793-808.
2. US Renal Data System. *USRDS 2018 Annual Data Report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
3. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(6):572-586.
4. Herzog CA, Strief JW, Collins AJ, Gilbertson DT. Cause-specific mortality of dialysis patients after coronary revascularization: why don't dialysis patients have better survival after coronary intervention? *Nephrol Dial Transplant*. 2008;23(8):2629-2633.
5. Dubin RF, Deo R, Bansal N, et al. Associations of conventional echocardiographic measures with incident heart failure and mortality: the Chronic Renal Insufficiency Cohort. *Clin J Am Soc Nephrol*. 2017;12(1):60-68.
6. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. *J Am Soc Nephrol*. 2001;12(5):1079-1084.
7. McIntyre CW. Haemodialysis-induced myocardial stunning in chronic kidney disease - a new aspect of cardiovascular disease. *Blood Purif*. 2010;29(2):105-110.
8. Simmons EM, Langone A, Sezer MT, et al. Effect of renal transplantation on biomarkers of inflammation and oxidative stress in end-stage renal disease patients. *Transplantation*. 2005;79(8):914-919.
9. Amann K, Breitbach M, Ritz E, Mall G. Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol*. 1998;9(6):1018-1022.
10. Arrigo M, Cippa PE, Mebazaa A. Cardiorenal interactions revisited: how to improve heart failure outcomes in patients with chronic kidney disease. *Curr Heart Fail Rep*. 2018;15(5):307-314.
11. Lopez B, Gonzalez A, Hermida N, Laviades C, Diez J. Myocardial fibrosis in chronic kidney disease: potential benefits of torasemide. *Kidney Int Suppl*. 2008;111:S19-S23.
12. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. *Lancet*. 2016;388(10041):276-284.
13. Wang X, Shapiro JI. Evolving concepts in the pathogenesis of uraemic cardiomyopathy. *Nat Rev Nephrol*. 2019;15(3):159-175.
14. Amann K, Ritz E. The heart in renal failure: morphological changes of the myocardium - new insights. *J Clin Basic Cardiol*. 2001;4:109-113.
15. Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant*. 2000;15(2):218-223.
16. Amann K, Neususs R, Ritz E, Irzyniec T, Wiest G, Mall G. Changes of vascular architecture independent of blood

pressure in experimental uremia. *Am J Hypertens*. 1995;8(4, pt 1):409-417.
17. Amann K, Kronenberg G, Gehlen F, et al. Cardiac remodelling in experimental renal failure–an immunohistochemical study. *Nephrol Dial Transplant*. 1998;13(8):1958-1966.
18. Tornig J, Gross ML, Simonaviciene A, Mall G, Ritz E, Amann K. Hypertrophy of intramyocardial arteriolar smooth muscle cells in experimental renal failure. *J Am Soc Nephrol*. 1999;10(1):77-83.
19. Amann K, Wiest G, Zimmer G, Gretz N, Ritz E, Mall G. Reduced capillary density in the myocardium of uremic rats–a stereological study. *Kidney Int*. 1992;42(5):1079-1085.
20. Amann K, Neimeier KA, Schwarz U, et al. Rats with moderate renal failure show capillary deficit in heart but not skeletal muscle. *Am J Kidney Dis*. 1997;30(3):382-388.
21. Gogiraju R, Bochenek ML, Schafer K. Angiogenic endothelial cell signaling in cardiac hypertrophy and heart failure. *Front Cardiovasc Med*. 2019;6:20.
22. Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol*. 2011;6(6):1326-1332.
23. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol*. 2008;3(1):19-26.
24. Chao CT, Huang JW, Yen CJ. Intradialytic hypotension and cardiac remodeling: a vicious cycle. *Biomed Res Int*. 2015;2015:724147.
25. Dubin R, Owens C, Gasper W, Ganz P, Johansen K. Associations of endothelial dysfunction and arterial stiffness with intradialytic hypotension and hypertension. *Hemodial Int*. 2011;15(3):350-358.
26. Zuidema MY, Dellsperger KC. Myocardial stunning with hemodialysis: clinical challenges of the cardiorenal patient. *Cardiorenal Med*. 2012;2(2):125-133.
27. Selby NM, McIntyre CW. Peritoneal dialysis is not associated with myocardial stunning. *Perit Dial Int*. 2011;31(1):27-33.
28. Loutradis C, Sarafidis PA, Papadopoulos CE, Papagianni A, Zoccali C. The ebb and flow of echocardiographic cardiac function parameters in relationship to hemodialysis treatment in patients with ESRD. *J Am Soc Nephrol*. 2018;29(5):1372-1381.
29. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol*. 1995;5(12):2024-2031.
30. Bansal N, Roy J, Chen HY, et al. Evolution of echocardiographic measures of cardiac disease from CKD to ESRD and risk of all-cause mortality: findings from the CRIC Study. *Am J Kidney Dis*. 2018;72(3):390-399.
31. Kramann R, Erpenbeck J, Schneider RK, et al. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. *J Am Soc Nephrol*. 2014;25(10):2351-2365.
32. Geyer H, Caracciolo G, Abe H, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr*. 2010;23(4):351-369; quiz 453-455.
33. Ravera M, Rosa GM, Fontanive P, et al. Impaired left ventricular global longitudinal strain among patients with chronic kidney disease and end-stage renal disease and renal transplant recipients. *Cardiorenal Med*. 2018;9(1):61-68.
34. Sun M, Kang Y, Cheng L, et al. Global longitudinal strain is an independent predictor of cardiovascular events in patients with maintenance hemodialysis: a prospective study using three-dimensional speckle tracking echocardiography. *Int J Cardiovasc Imaging*. 2016;32(5):757-766.
35. Li J, Li A, Wang J, Zhang Y, Zhou Y. Early left ventricular dysfunction detected by speckle tracking in long-term hemodialysis patients with valvular calcification. *Cardiorenal Med*. 2018;9(1):22-30.
36. Cheng A, Helm RH, Abraham TP. Pathophysiological mechanisms underlying ventricular dyssynchrony. *Europace*. 2009;11(suppl 5):v10-v14.
37. Missiri A. Echocardiographic assessment of left ventricular mechanical dyssynchrony – a practical approach. *Egyptian Heart J*. 2014;66(3):217-225.
38. Shi F, Feng S, Zhu J, Wu Y, Chen J. Left ventricular strain and dyssynchrony in young and middle-aged peritoneal dialysis patients and healthy controls: a case-matched study. *Cardiorenal Med*. 2018;8(4):271-284.
39. Hensen LCR, Goossens K, Podlesnikar T, et al. Left ventricular mechanical dispersion and global longitudinal strain and ventricular arrhythmias in predialysis and dialysis patients. *J Am Soc Echocardiogr*. 2018;31(7):777-783.
40. Chiu DY, Green D, Abidin N, Sinha S, Kalra PA. Cardiac imaging in patients with chronic kidney disease. *Nat Rev Nephrol*. 2015;11(4):207-220.
41. Hunold P, Vogt FM, Heemann UW, Zimmermann U, Barkhausen J. Myocardial mass and volume measurement of hypertrophic left ventricles by MRI–study in dialysis patients examined before and after dialysis. *J Cardiovasc Magn Reson*. 2003;5(4):553-561.
42. Harnett JD, Murphy B, Collingwood P, Purchase L, Kent G, Parfrey PS. The reliability and validity of echocardiographic measurement of left ventricular mass index in hemodialysis patients. *Nephron*. 1993;65(2):212-214.
43. Stewart GA, Foster J, Cowan M, et al. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int*. 1999;56(6):2248-2253.
44. Odudu A, Eldehni MT, McCann GP, Horsfield MA, Breidthardt T, McIntyre CW. Characterisation of cardiomyopathy by cardiac and aortic magnetic resonance in patients new to hemodialysis. *Eur Radiol*. 2016;26(8):2749-2761.
45. Shamir AR, Karembelkar A, Yabes J, et al. Association of intradialytic hypertension with left ventricular mass in hypertensive hemodialysis patients enrolled in the Blood Pressure in Dialysis (BID) Study. *Kidney Blood Press Res*. 2018;43(3):882-892.
46. Ross BA, Wald R, Goldstein MB, et al. Relationships between left ventricular structure and function according to cardiac MRI and cardiac biomarkers in end-stage renal disease. *Can J Cardiol*. 2017;33(4):501-507.
47. Gaasch WH, Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *J Am Coll Cardiol*. 2011;58(17):1733-1740.
48. Gotte MJ, Germans T, Russel IK, et al. Myocardial strain and torsion quantified by cardiovascular magnetic resonance tissue tagging: studies in normal and impaired left ventricular function. *J Am Coll Cardiol*. 2006;48(10):2002-2011.
49. Ong JP, Wald R, Goldstein MB, et al. Left ventricular strain analysis using cardiac MRI in patients undergoing in-centre nocturnal hemodialysis. *Nephrology (Carlton)*. 2019;24(5):557-563.
50. Buchanan C, Mohammed A, Cox E, et al. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. *J Am Soc Nephrol*. 2017;28(4):1269-1277.

51. Disertori M, Mase M, Ravelli F. Myocardial fibrosis predicts ventricular tachyarrhythmias. *Trends Cardiovasc Med*. 2017;27(5):363-372.
52. Mark PB, Johnston N, Groenning BA, et al. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int*. 2006;69(10):1839-1845.
53. Germain P, El Ghannudi S, Jeung MY, et al. Native T1 mapping of the heart - a pictorial review. *Clin Med Insights Cardiol*. 2014;8(suppl 4):1-11.
54. Rutherford E, Talle MA, Mangion K, et al. Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. *Kidney Int*. 2016;90(4):845-852.
55. Rutherford E, Bell E, Mangion K, Patel RK, McComb C, Mark PB. Heart function and structure during the first year of haemodialysis treatment: Cardiac Uraemic Fibrosis Detection in Dialysis Patients, an observational prospective study [abstract]. *Lancet*. 2017;389(suppl 1):S86.
56. Graham-Brown MP, Rutherford E, Levelt E, et al. Native T1 mapping: inter-study, inter-observer and inter-center reproducibility in hemodialysis patients. *J Cardiovasc Magn Reson*. 2017;19(1):21.
57. Antlanger M, Aschauer S, Kammerlander AA, et al. Impact of systemic volume status on cardiac magnetic resonance T1 mapping. *Sci Rep*. 2018;8(1):5572.
58. Stromp TA, Spear TJ, Holtkamp RM, et al. Quantitative gadolinium-free cardiac fibrosis imaging in end stage renal disease patients reveals a longitudinal correlation with structural and functional decline. *Sci Rep*. 2018;8(1):16972.
59. Stromp TA, Leung SW, Andres KN, et al. Gadolinium free cardiovascular magnetic resonance with 2-point Cine balanced steady state free precession. *J Cardiovasc Magn Reson*. 2015;17:90.
60. Lau JMC, Raptis DA, Laforest R, et al. Cardiac positron emission tomography-magnetic resonance imaging: current status and future directions. *J Thorac Imaging*. 2018;33(3):139-146.
61. Shah NR, Charytan DM, Murthy VL, et al. Prognostic value of coronary flow reserve in patients with dialysis-dependent ESRD. *J Am Soc Nephrol*. 2016;27(6):1823-1829.
62. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124(20):2215-2224.
63. Paz Y, Morgenstern R, Weinberg R, et al. Relation of coronary flow reserve to other findings on positron emission tomography myocardial perfusion imaging and left heart catheterization in patients with end-stage renal disease being evaluated for kidney transplant. *Am J Cardiol*. 2017;120(11):1909-1912.
64. Bural GG, Torigian DA, Sozmen M, Houseni M, Alavi A. Comparison of atherosclerotic inflammation and calcification in subjects with end stage renal disease (ESRD) on hemodialysis to normal controls utilizing (18)F-FDG PET/CT. *Hell J Nucl Med*. 2018;21(3):169-174.
65. Davies JR, Izquierdo-Garcia D, Rudd JH, et al. FDG-PET can distinguish inflamed from non-inflamed plaque in an animal model of atherosclerosis. *Int J Cardiovasc Imaging*. 2010;26(1):41-48.
66. Assa S, Dasselaar JJ, Slart RH, et al. Comparison of cardiac positron emission tomography perfusion defects during stress induced by hemodialysis versus adenosine. *Am J Kidney Dis*. 2012;59(6):862-864.
67. Minamimoto R, Takahashi N, Inoue T. FDG-PET of patients with suspected renal failure: standardized uptake values in normal tissues. *Ann Nucl Med*. 2007;21(4):217-222.
68. Kode V, Karsch H, Osman MM, Muzaffar R. Impact of renal failure on F18-FDG PET/CT scans [abstract]. *Front Oncol*. 2017;7:155.
69. Armstrong WF, Ryan T, Feigenbaum H. *Feigenbaum's Echocardiography*. 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.
70. Raggi P, Alexopoulos N. Cardiac imaging in chronic kidney disease patients. *Semin Dial*. 2017;30(4):353-360.