Cardiac Imaging in Chronic Kidney Disease Patients

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ABSTRACT

Cardiovascular disease is highly prevalent and it is associated with high morbidity and mortality rates in patients with chronic kidney disease (CKD). The implementation of various imaging modalities may help to risk stratify these patients with a potential ease on the burden of complications and the rising costs of care. In this article we review some of the modern imaging techniques to diagnose cardiac disease in patients affected by CKD.

Patients with chronic kidney disease (CKD) are at high-risk of cardiovascular disease and imaging plays a central role in assessing the severity of disease and providing risk stratification in these patients. Cardiovascular imaging has been used very successfully for such purpose in the general population, but has partial limitations in CKD patients. Traditional risk factors for atherosclerosis and factors more closely associated with progressive loss of renal function contribute to the high incidence of cardiovascular complications seen in these patients. As a result, myocardial dysfunction, both dependent and independent of coronary artery disease, is highly prevalent in CKD. In this article, we provide an overview of noninvasive imaging modalities used to diagnose myocardial disease and cardiac dysfunction in patients with advanced CKD.

Transthoracic Echocardiography

Echocardiography, based on ultrasound technology, is the primary noninvasive resource to evaluate the structure and function of the myocardium and cardiac valves. Left ventricular hypertrophy (LVH) is highly prevalent in CKD and its incidence increases as the estimated glomerular filtration rate (eGFR) declines over time. With echocardiography one can measure with good accuracy both left ventricular mass and volumes, and these allow characterization of the type of hypertrophy of the left ventricle: eccentric (due to volume overload) vs. concentric (due to increased afterload). Over 2/3 of patients receiving chronic dialysis (CKD-5D) with LVH die of heart failure or sudden cardiac death (1), hence the importance of an accurate estimation of this parameter.

Equally important is the assessment of left ventricular function. In fact, the prevalence of left ventricular systolic dysfunction in CKD-5D is approximately 15–18% (2). Several mechanisms have been invoked as potentially responsible for the development of systolic dysfunction of the left ventricle: coronary artery disease, chronic anemia, chronic volume overload, malnutrition, and hyperparathyroidism.

The simplest measure of left ventricular dysfunction is obtained with M-mode echocardiography and it is based on fractional shortening. This is estimated as the ratio of left ventricular end-diastolic minus end-systolic diameter divided by the end-diastolic diameter ([LVEDd-LVESd]/LVEDd). Normal fractional shortening values range between 25% and 44%. However, since these measures are obtained along the line of a single ultrasound beam as provided by M-mode echocardiography, there is a potential for substantial miscalculations if the ventricle presents areas of asymmetry such as can occur in coronary artery disease.

Instead of simple diameters, the left ventricular ejection fraction calculation makes use of volumes. The volumes are calculated based on several measurements made on two-dimensional echocardiography imaging and a number of assumptions that permit a close estimation of the left ventricular volumes in systole and diastole. The most frequently employed method is the method of disks or Simpson rule. After acquiring apical views in both systole and diastole, the left ventricle is divided along its length into a series of disks of equal height (Fig. 1). Each
disk’s volume is calculated from the diameter of the ventricle at its level and the height of the disk. The sum of all disk volumes in diastole minus the sum of all disk volumes in systole represents the stroke volume; the ratio of stroke volume over diastolic volume of the left ventricle*100 represents the ejection fraction of the left ventricle (LVEF). A normal LVEF is greater than 55%; a LVEF of 50–55% is considered borderline or low normal; a LVEF of 45–50% is considered as evidence of mild LV dysfunction, 35–45% moderate, and <35% severe LV dysfunction. These ranges have to be taken in the context of a 5–8% variability in the assessment of the parameter.

While two-dimensional measurements represent an improvement over linear measurements they are still subject to potential pitfalls. For instance, the apical views of the left ventricle could be foreshortened and this will hamper the attainment of reliable measurements. A definite improvement in the measurement of left ventricular volumes can be obtained by injecting an intravenous solution containing bubbles of inert gases (i.e., echo-contrast). The bubbles resonate when exposed to ultrasound and the vibration causes the release of harmonic sounds detected as a bright signal inside the ventricular cavity (Fig. 2). This enhanced signal allows a precise delineation of the endocardium thus rendering the volume calculation much more precise.

More recently, three-dimensional (3D)-echocardiography has provided a significant advancement over 2D measurements of LV function and volumes especially in oddly shaped ventricles (3). However, there are relatively few data on the utility of 3D echocardiography in CKD over 2D methodologies. In a study of 76 patients with varying degrees of CKD, those with moderate to severe renal dysfunction showed a progressive decline in LVEF as the LV mass increased (4). Simultaneously, the left ventricular diastolic function deteriorated. However, no patient-level outcome data are available at this time based on 3D assessment of the LV function and structure in CKD patients.

Another prognostically important measurement that can be made with 2D echocardiography is the volume of the left atrium (LA). The volume of the LA increases as the severity of renal dysfunction deepens (5). An enlarged LA size is an independent marker of risk of mortality in the general population as well as in patients with CKD (5).

Echocardiography is the gold-standard, noninvasive imaging tool to diagnose cardiac valvular disease. Like many vascular territories, cardiac valves are frequently heavily calcified in patients with advanced CKD stages. With echocardiography it is possible to give a qualitative assessment of calcification besides gauging the severity of valvular stenosis or regurgitation (Fig. 3). In a cross-sectional study of 58 patients in CKD stage 4–5, 36 patients in CKD-5D, and 41 post-transplant patients, calcification of the aortic and mitral valve were present in 31%, 50%, and 29% of the subjects, respectively, compared to 12% of controls ($p = 0.001$) (6). Furthermore, there was an association between valvular calcification and increased carotid intima-media thickness, carotid plaques, coronary artery disease, and peripheral arterial disease (6). The detection of calcification of the mitral and aortic valve has important prognostic implications as patients with these findings have a higher mortality rate (7).

The velocity of displacement of moving objects can be measured with the Doppler technique. Examples of Doppler measurements utilized for assessment of cardiac function are the measurement of blood flow velocity across the mitral valve and the displacement of myocardial tissue. The diastolic function of the myocardium hinges on these Doppler measurements. Diastole is divided into a passive filling phase during which the LV relaxes and spontaneous filling occurs from the atrium, and an
active phase due to contraction of the left atrium. In hearts with normal diastolic function the passive phase is predominant and can be measured by Doppler as an early taller wave across the mitral plane called E wave; the second wave is smaller and is called A wave. In patients with reduced LV compliance the majority of filling occurs during the active atrial contraction phase and the E/A ratio, normally >1, is reversed (Fig. 4). Similarly, a modified Doppler technique can be applied to measure the speed of translation of the mitral valve ring during the diastolic phases. In this case, the Doppler beam is directed either toward the septum or the lateral wall of the LV from an apical 4 chamber view (Fig. 4A). Similar to the trans-mitral flow velocities, in hearts with normal diastolic function the early negative wave, known as E’, is larger than the later wave, known as A’. The ratio is again reversed in non-compliant ventricles (Fig. 4B).

Both in the general population and in CKD patients the outcome of patients with isolated abnormal diastolic heart function is as severe as that of patients with systolic dysfunction (8,9). In a recent study of 80 CKD patients (20 stage 1–2, 20 stage 3, 20 stage 4, and 20 stage 5D) and 24 controls, the prevalence of LV hypertrophy and diastolic dysfunction were extremely high (95% and 93%) (10). It would appear that LVH and diastolic dysfunction develop early in CKD and continue to progress despite optimal medical therapy (11). However, kidney transplantation has been shown to be followed by improvement of both systolic and diastolic LV function (9,12,13).

An interesting, novel development of Doppler echocardiography is the measurement of strain and strain rate; this represents the degree of deformation (shortening, stretching, and torsion) in space and time of the myocardial fibers during systole and diastole (Fig. 5) (14). During systole the LV myocardium shortens, squeezes, and twists producing the necessary force to propel a bolus of blood (the stroke volume) out of the ventricle. During diastole, the LV unwinds creating the necessary suction to produce diastolic filling. This information can be accurately assessed with strain imaging obtained via Doppler tissue imaging or, more modernly, speckle tracking (speckle tracking echocardiography: STE). In STE, specialized software is utilized to follow the motion in space of “speckles”, i.e., the bright reflections of ultrasound beams bouncing off myocardial fibers. A reduced strain indicates a reduced deformability, hence reduced contractility and increased stiffness of the LV. Reduced strain can be detected very early in CKD before obvious changes in LV function become apparent as a drop in ejection fraction or reduced compliance by Doppler (15–18). In a recent study, reduced strain was associated with all-cause mortality in a cohort of 447 patients with various degrees of severity of CKD (19). Finally, STE can also be utilized to assess left atrial and right ventricular function (14,20).

Functional assessment of the presence and severity of coronary artery disease (CAD) can be performed with stress echocardiography. During stress (performed on a treadmill, a stationary bike, or induced pharmacologically) the motion of various segments of the LV wall is assessed visually and compared to the motion of the same segments at rest. The appearance of one or more new hypokinetic or akinetic segments is considered evidence...
that obstructive CAD is present. Stress echocardiography performs well in CKD patients as in the general population. An abnormal response during stress echocardiography confers a 1.5–4 fold increased risk of cardiac events in the ensuing 2–4 years of follow-up (21,22). However, an accurate selection of patients to be submitted to testing based on risk factors increases the accuracy of stress echocardiography (22). The sensitivity and specificity of stress echocardiography for the detection of obstructive CAD in kidney transplant candidates are similar to that of nuclear stress testing (23), and likewise their prognostic value in this setting is equivalent (24). Of interest, the prognostic value of noninvasive stress testing in transplant candidates was superior to direct coronary angiography in several publications (25–27), suggesting that pre-operative risk stratification based on direct invasive angiography is likely to be the wrong approach.

Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI) is the reference standard for the noninvasive assessment of myocardial ischemia due to CAD (28). It can be performed via single-photon emission computed tomography (SPECT) or positron emission tomography (PET). The latter has a reportedly higher sensitivity and specificity for the detection of obstructive CAD. Radioactive tracers are injected intravenously at rest and after stress, and are extracted by myocytes in proportion to the flow of blood in the coronary arteries. However, different tracers demonstrate different extraction characteristics and may therefore provide imaging data of substantially different quality (28). Rest and stress perfusion images are compared for the presence of reversible or irreversible defects in tracer uptake in various myocardial segments corresponding to specific coronary artery territories (Fig. 6). Besides global and segmental myocardial perfusion, PET and SPECT provide information on myocardial function and both left ventricular volumes and ejection fraction can be calculated.
Furthermore, PET allows a precise assessment of myocardial blood flow and flow reserve (i.e., ability to increase myocardial blood flow in response to stress). The latter can be very helpful in differentiating a normal perfusion study from a study that appears normal although the “normality of flow” is due to an equally reduced flow in all coronary artery territories due to severe triple vessel disease; this phenomenon is also known as “balanced ischemia” (Figures S1A, B).

MPI has been shown to have diagnostic and prognostic utility in various stages of CKD, including incident and prevalent dialysis patients (29,30). A normal MPI scan in patients with CKD is associated with a worse cardiovascular prognosis than in patients with normal renal function (31). Al-Mallah et al. (32) showed that patients with worsening degrees of CKD demonstrate larger and more severe perfusion defects on MPI. The mortality of patients with CKD increased with worsening renal function, and there was a significant interaction between eGFR and perfusion abnormalities on MPI, suggesting that the effect of CKD on outcomes is explained in part by the abnormalities detected by MPI (32). Furthermore, MPI provided incremental prognostic information in CKD (31,32). Kasama et al. (33) showed in 299 patients with an eGFR<60 ml/m/1.73² that the extent of perfusion deficit of the LV and the end-systolic volume of the LV measured on MPI were the best independent predictors of cardiac death.

Healthy and nonischemic myocytes utilize fatty acids as the preferred source of energy supply, switching to glucose only in times of stress. An iodine-labeled tracer (¹²³I- β-methyl iodophenyl-pentadecanoic acid; BMIPP) makes use of this physiological property of the myocyte energy cycle. Due to the long-term effect of ischemia on the utilization of fatty acids by the myocyte, BMIPP can be injected some time after an ischemic episode and still show a perfusion defect. Zen et al. (34) employed BMIPP in 677 asymptomatic hemodialysis patients without known CAD, and showed that perfusion defects on MPI predicted hard cardiovascular events better than diabetes mellitus and peripheral arterial disease.

Although MPI has traditionally been used to identify perfusion abnormalities due to obstructive CAD, perfusion deficits can occur due to microcirculatory or endothelial dysfunction (35). PET is especially suited to provide this type of information and global and segmental perfusion abnormalities can appear in the absence of obstructive epicardial CAD. Using PET imaging Fukushima et al. (36) showed that in patients with CKD without epicardial coronary artery disease, there is a reduced myocardial blood flow reserve suggesting significant endothelial dysfunction even in the absence of obstructive disease.

Risk stratification prior to renal transplantation remains one of the most frequent indications for MPI in patients with advanced CKD (37). Patel et al. retrospectively examined the cardiovascular outcome of 174 patients with CKD-5D submitted to SPECT MPI for risk stratification. Patients with abnormal SPECT studies had a fivefold greater risk of cardiac event rate than those with normal studies (p = 0.006) (38). Furthermore, an abnormal MPI

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Fig. 6. Myocardial perfusion stress test obtained with single photon emission tomography (SPECT) technique. (A) The left sided images show a severe perfusion defect of the inferior and apical segments of the left ventricle both after stress and at rest (the defect is marked by an asterix in the images). (B) To the right, the polar maps of the left ventricle (i.e., the sum of all segments of the left ventricle displayed as a 2D image) make it easier to appreciate that the perfusion defect is mostly fixed and shows a minimal amount of reversibility (i.e., the dark area in the rest images at the bottom is slightly smaller than in the stress images). This suggests the presence of a prior myocardial infarction with mild peri-infarct ischemia. [Color figure can be viewed at wileyonlinelibrary.com]
was the single best predictor of an unfavorable outcome (39). In a study of 150 patients being evaluated for kidney transplantation, abnormal MPI results (decreased LV function or abnormal perfusion) and diabetes mellitus were the best independent predictors of death, whereas the presence of obstructive CAD on invasive coronary angiography was not (40). A few studies suggested that screening prior to transplantation does not offer any advantage over clinical evaluation and/or invasive angiography in assessing cardiac risk in these patients (1,41,42). Therefore, the appropriateness of screening for CAD by MPI or other noninvasive and invasive techniques prior to kidney transplantation remains nebulous.

In summary, although stress MPI is an excellent method to risk stratify patients whether it should be performed in all patients undergoing dialysis prior to transplantation and how often it should be repeated while awaiting on the transplant list, remains unclear at this stage (43).

The most recent K/DOQI guidelines date back to 2005 and call for screening in patients with clinical and electrocardiographic evidence of CAD, asymptomatic diabetic patients and patients with prior incomplete revascularization (44). Repeat testing should be entertained every 12 months for all, or every 3 years in patients who underwent a successful coronary artery by-pass surgery. The guidelines released by the American College of Cardiology and American Heart Association in 2012 recommend testing all symptomatic CKD-5D patients and CKD-5D asymptomatic patients with 3 or more risk factors (45); however, they discourage periodic screening. A variety of other guidelines are also available from national and international organizations, but the recommendations are sometimes conflicting.

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) has become established as the most accurate noninvasive method to assess left ventricular mass, volume and ejection fraction without the need for contrast administration or radiation exposure. CMR further allows the assessment of severity of valvular regurgitation and stenosis with a high degree of accuracy (2). Currently, CMR can be safely performed in the presence of coronary or peripheral artery stents and prosthetic heart valves. Additionally, MRI-safe pacemakers and internal defibrillators have been introduced recently in clinical practice.

CMR shows a significantly lower interobserver variability compared to echocardiography for the assessment of LV volumes and mass (46), and it would appear that the LV mass is generally overestimated with echocardiography when compared to CMR (2). Given the high prognostic value of LV mass measurements in patients with CKD, it is important to use a diagnostic tool with the greatest accuracy. Several studies have assessed left ventricular mass in CKD patients using CMR; a high prevalence (72%) of LV hypertrophy was been observed in a pivotal study of patients receiving chronic hemodialysis (47), and was largely confirmed in later studies (48). Alterations in both pre-load and after-load conditions are the main determinants of LV hypertrophy in CKD patients (49); these include swinging volume loads, a high prevalence of arterial hypertension, and increases arterial stiffness. Volume overload leads to LV dilatation, but also to an increase in LV mass. In patients undergoing hemodialysis there are continuous variations in cardiac chamber volumes, depending on loading conditions. In a recent study in which CMR was conducted during dialysis sessions, the authors reported a drop in myocardial volumes, systolic function, and myocardial perfusion, and also noted the appearance of segmental wall motion abnormalities of the LV (50). Pre- and immediately postdialysis blood pressures are a better predictor of LV mass index (indexed to body surface area) and LV hypertrophy than ambulatory blood pressure monitoring (51).

CMR has a unique capability to assess myocardial fibrosis and scarring; the most validated sequence used is a T1-weighted image obtained 10–15 minutes after gadolinium administration (late gadolinium enhancement – LGE). LGE is observed in as many as 28% of end-stage renal disease patients (47). In general, there are two different patterns of LGE in patients with CKD: a subendocardial pattern and a diffuse pattern. Subendocardial LGE is indicative of ischemic myocardial injury, i.e., myocardial infarction, and its presence denotes coronary artery disease. Thus, it is observed more frequently in CKD patients with concomitant atherosclerotic risk factors, such as hypercholesterolemia or diabetes mellitus, or known ischemic heart disease (47). Of note, like in the general population (52), the presence of silent myocardial infarction is not uncommon in CKD patients (47).

Diffuse LGE is not associated with typical risk factors for atherosclerosis and represents focal myocardial fibrosis, also seen in other diseases affecting the myocardium either directly, i.e., myocarditis, infiltrative diseases, or through the pathophysiological consequences of volume or pressure overload due to conditions such as aortic insufficiency (volume overload), and systemic hypertension or aortic stenosis (pressure overload) (53). Diffuse LGE, however, does not exclude the possibility of coronary artery disease, and in some patients both patterns of LGE can be present. Subendocardial LGE is associated with increased LV mass, increased LV dimensions, and reduced LV systolic function (47); in many of these patients ischemic cardiomyopathy is the major determinant of cardiac performance. Diffuse LGE is associated with increased LV mass and LV dilatation, often with preserved LV systolic function (47).
For LGE, gadolinium administration is needed. This is a major concern in patients with end-stage renal disease, because of risk of nephrotoxic systemic fibrosis (NSF). A novel technique called T1 mapping has been introduced recently for the assessment of myocardial fibrosis without GBCA administration (Figure S2). T1 mapping estimates myocardial T1 relaxation time, which differs in diseased/fibroed compared to normal myocardium. Noncontrast native (i.e., without GBCA) T1 relaxation time shows a good correlation with cardiac fibrosis found on histology (54).

In a pivotal study, patients with early CKD had increased native T1 times compared to controls (55). T1 times were correlated with impaired systolic function as assessed by global longitudinal systolic strain (55). These results were recently reproduced in hemodialysis patients (56,57). T1 mapping has already proved its clinical value in patients with other cardiovascular diseases, especially those with cardiac amyloidosis (58), in whom renal impairment is usually encountered. More data will be necessary to assess whether T1 mapping will play a role not only for the assessment of myocardial fibrosis in patients with CKD but as a tool that provides prognostic information as well (59).

In clinical practice stress MRI, performed with vasodilating agents or dobutamine, is utilized to test the presence of CAD via induction of myocardial ischemia. However, the demonstration of perfusion is usually encountered. More data will be necessary to determine whether T1 mapping will play a role only for the assessment of myocardial fibrosis in patients with CKD but as a tool that provides prognostic information as well (59).

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**Supporting Information**

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