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Review

Cardiac Magnetic Resonance Imaging of the Myocardium in Chronic Kidney Disease

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Abstract
Early stages of chronic kidney disease (CKD) are often underdiagnosed, while their deleterious effects on the cardiovascular (CV) system are already at work. Thus, the assessment of early CV damage is of crucial importance in preventing major CV events. Myocardial fibrosis is one of the major consequences of progressive CKD, as it may lead to reentry arrhythmias and long-term myocardial dysfunction predisposing to sudden death and/or congestive heart failure. Subclinical myocardial fibrosis, with a potential key role in the development of uraemic cardiac disease, can be measured and characterised by appropriate cardiac magnetic resonance (CMR) techniques. Fibrosis detection was initially based on the contrast agent gadolinium, due to the superiority in sensitivity and accuracy of contrast-based methods in fibrosis assessment relative to native techniques. However, the severe consequences of gadolinium administration in uraemia (nephrogenic systemic fibrosis) have forced practitioners to re-evaluate the methodology. In the present overview, we review the possible contrast-based and contrast agent-free CMR techniques, including native T1 relaxation time, extracellular volume and global longitudinal strain measurement. The review also summarises their potential clinical relevance in CKD patients based on recently published studies.

Cardiovascular disorder in chronic kidney disease

Chronic kidney disease (CKD) is a common cardiovascular (CV) risk factor. Early stages of CKD are often underdiagnosed, whereas their deleterious effects on the cardiovascular system are already at work. According to the large meta-analysis by the Chronic Kidney Disease Prognosis Consortium, the slow, gradual increase in cardiovascular risk is already present in CKD patients at 60-75 ml/min/1.73m^2 glomerular filtration rates [1], with CKD

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Table 1. Traditional and CKD-related cardiovascular risk factors [2,3]

Traditional CV risk factors	CKD-related (non-traditional) risk factors
Older age	Type (diagnosis) of CKD
Male gender	Decreased GFR
White race	Proteinuria (albuminuria)
Hypertension	Renin-angiotensin system activity
Higher LDL cholesterol	Extracellular fluid volume overload
Lower HDL cholesterol	Electrolyte imbalance
Diabetes mellitus	Dysregulation of calcium and phosphate homeostasis
Smoking	Dyslipidaemia
Physical inactivity	Anaemia
Menopause	Malnutrition
Psychosocial stress	Inflammation
Family history of CV disease	Infection
	Thrombogenic factors
	Oxidative stress
	Homocysteine
	Uremic toxins

rightly deserving its designation as a silent killer. Thus, assessment of the early cardiovascular damage and risk conferred by CKD in its early stages is of crucial importance with regard to prevention of major cardiovascular events.

The cause of cardiovascular disease in CKD is multifactorial. Conventional and non-conventional risk factors both contribute to the increase in CV morbidity and mortality (Table 1).

With the progression of CKD, risk factors resulting from decreased kidney function gradually gain importance over the traditional risk factors. This prominence has been elegantly shown by the relative efficacy of lipid lowering therapy in CKD patients [4, 5] suggesting a different causality in cardiovascular diseases in the CKD and non-CKD population.

Endocrine abnormalities – such as increased parathyroid hormone and fibroblast growth factor 23 levels, dysregulation of calcium and phosphate homeostasis along with poor vitamin K status [6], concomitant vascular calcification, increased arterial stiffness [7-9], anaemia as well as hemodynamic fluctuations – may contribute to the progression of cardiovascular disease, left and right ventricular [10], cardiac disease, left ventricular hypertrophy (LVH) and myocardial fibrosis [2, 3, 11, 12].

Cardiac magnetic resonance (CMR) is a useful imaging tool not only to characterise ventricular volumes but also to assess the properties and consequential pathology of myocardial tissue. Using tissue characterisation properties, Mark et al. identified non-ischemic, uraemia-specific LVH in 72% of dialysed patients [13].

However, although increased left ventricular mass is often recognised as a surrogate endpoint of all-cause mortality [14, 15], a recent meta-analysis by Badve et al. [16] involving 6732 CKD patients concluded that there was no clear evidence of an association between the change in left ventricular mass and mortality. Thus there is an urgent need for complementary markers of myocardial function and damage in all patients alters [17].

Detecting myocardial fibrosis with cardiac magnetic resonance in chronic kidney disease

Myocardial fibrosis is a hallmark consequence of progressive CKD. Uraemic myocardial fibrosis may cause reentry arrhythmias and long-term myocardial dysfunction predisposing to sudden death and/or congestive heart failure in end-stage renal disease. Accordingly, Charytan et al. [18] observed a 12% increase in myocardial fibrosis in stage 3-4 CKD patients and a 77% increase in stage 5 CKD comparatively to patients with preserved renal function.

Current treatment modalities for CKD do not adequately correct for fibrosis, apoptosis and capillary degeneration. Earlier detection of myocardial changes should therefore allow elaborating new strategies for a more effective intervention.

Subclinical myocardial fibrosis with a potential key role in the progression of uraemic cardiac disease can be measured and characterised by appropriate cardiac CMR techniques.

Late gadolinium enhancement (LGE) was heralded as a promising tool for the detection of myocardial fibrosis. LGE is based on the delayed contrast agent wash-in and wash-out in tissues with increased extracellular space. LGE was originally developed to detect chronic infarcted myocardium, such as fibrous scar tissue, but has also been found useful in the diagnosis of cardiomyopathies. Accordingly, while LGE was observed in only 6% of cases in early CKD patients (stage 2-3) with no clinical evidence of cardiovascular disease, in the aforementioned Charytan et al. study with 72% LVH incidence in the stage 5 CKD group, the occurrence of LGE was found as high as 28%. The authors described the pathological LGE type as less intense than the infarction pattern without subendocardial dominance. The importance of the new uraemic pattern of LGE is that it may help differentiate CKD-related diffuse fibrosis from ischemic scarring in the CKD population. Diffuse fibrosis identified by LGE has been associated with increased LV mass suggesting that left ventricular hypertrophy in stage 5 CKD patients is pathological [13].

However, LGE is not sufficiently sensitive to detect the diffuse form of myocardial fibrosis since the technique relies on relative differences in signal intensities, notably considering the lowest myocardial signal intensity as normal (regardless of the degree of fibrosis). Further investigations and developments were planned in the field of contrast (gadolinium) - enhanced fibrosis detection.

Nephrogenic Systemic Fibrosis in CKD patients

In 2006, the safety of gadolinium-enhanced magnetic resonance imaging became questionable in CKD patients based on observations of fatal cases of Nephrogenic Systemic Fibrosis (NSF) with a possible causal relationship to gadolinium use [19-21].

NSF typically begins on the skin and may involve underlying joints. This loss of skin flexibility and joint contractures can result in permanent pain and decreased mobility. A rapid progression has been observed in 5% of NSF patients, with internal organs such as lung, heart, liver and kidney also potentially affected [22].

The use of the highly toxic gadolinium as contrast agent is made possible by its embedding into chelates. Given that the chelates are excreted by the kidney, the duration of chelate exposure is hence related to renal function. In CKD patients, chelates have sufficient time to release into the extracellular fluid. However, there is a difference between linear and macrocyclic gadolinium chelates with regard to their gadolinium binding affinity. The linear gadolinium-based agents dissociate more easily, thus releasing gadolinium more rapidly. They are consequently more toxic, resulting in a more potent fibroblast stimulation than the more stable macrocyclic agents [23]. Based on these properties, current guidelines distinguish between high, medium and low risk agents. According to the European Medicines Agency guideline, the use of high risk gadolinium agents in patients with severe renal impairment (eGFR ≤30 ml/min/1.73m^2) is contraindicated and there are strong warnings regarding the use of medium and low NSF risk gadolinium agents in patients with severe renal impairment. Given the absence of specific and effective treatment, therapeutic activity is limited to palliation and prevention.

In recent years, due to the mandatory assessment of renal function prior to MRI and caution in patients with severe renal impairment, the number of reported NSF cases has drastically decreased.

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Assessment of uraemic myocardial disease after the NSF era

Given the limitations of contrast-based myocardial CMR in CKD patients, the development of new diagnostic strategies was initiated along two directions. The first was to detect early myocardial CMR changes in predialytic patients (eGFR ≥15 ml/min/1.73m^2) using gadolinium-based contrast agents. The second approach focused on the development of new native (contrast-free) CMR methodologies in CKD patients with moderate to severe renal impairment (eGFR ≤60 ml/min/1.73m^2).

In the following subsections, we will first review certain CMR techniques that may potentially detect myocardial fibrosis or dysfunction in non-CKD patients. The common goal of these techniques is to identify the high-risk patients who were undetected by traditional LGE assessment. Secondly, we will briefly review the most recent results obtained by the use of these techniques.

Elevated native T1 relaxation time (T1). Myocardial interstitial volume expansion (diffuse or focal fibrosis, cardiomyopathy or amyloid) and oedema may represent the pathological background of elevated native T1. In order to obtain consistent and comparable results, native T1 measurements should be performed at the same field strength, cardiac phase and cardiac region [24]. Although native T1 is highly dependent on technical parameters, there are studies supporting its clinical relevance (including predictive value or correlation with histological fibrosis). Native myocardial T1 is correlated with serum cardiac biomarkers of disease severity in amyloidosis and is predictive of mortality in this patient group [25]. Native T1 values are also increased in patients with aortic stenosis. In this patient group, the length of T1 values is correlated with the increase in left ventricular mass index (LVMi) as well as with the degree of biopsy-quantified fibrosis [26].

Extracellular volume (ECV) assessment. ECV is a T1-derived histologically validated CMR parameter. Estimation of ECV requires the measurement of myocardial and blood T1 before and after administration of contrast agents. ECV values may be more reproducible between different field strengths and acquisition techniques than both native and post-contrast T1 [27, 28].

Although there is a strong correlation between ECV and the histological extent of myocardial fibrosis [27], its main disadvantage lies in that ECV measurement is based on the use of contrast agent. ECV can nonetheless be useful in several patient groups, for example for differentiating hypertrophic cardiomyopathy (HCM) from athlete's heart. In athlete's heart, hypertrophy is associated with a reduction in ECV, as opposed to an increase in ECV in HCM patients. ECV may also be of prognostic value in selected populations. In a large diabetic study, ECV was associated with mortality and/or incident hospitalisation for heart failure [29].

Use of dynamic parameters to describe myocardial properties. In addition to T1 and its derivatives, dynamic parameters can also be used to describe myocardial status. Strain imaging can quantify myocardial mechanics such as shortening and torsion. CMR is usually considered the reference standard for myocardial strain, although echocardiography is more readily available in the clinical setting and shows reasonable agreement with CMR.

Global longitudinal strain (GLS) represents the most accurate strain parameter for identifying subclinical myocardial dysfunction in echocardiography studies [30]. Although impaired GLS is associated with an increased risk of mortality in stage 4-5 CKD patients, there is no clear evidence to date confirming the early predictive value of GLS in patients with ≥60 ml/min/1.73m^2 [31, 32].

Assessment of myocardium using gadolinium-based contrast agent (GBCA) in CKD patients

After a long quiet period, Edwards et al. in 2015 presented the first study assessing diffuse interstitial fibrosis using T1-mapping in 43 stage 2-4 CKD patients with no history or symptoms of cardiovascular disease or diabetes [33]. In addition to routine assessment and native T1 evaluation, the authors assessed ECV using low dose macrocyclic GBCA.

The CKD group displayed an increased ECV compared to controls as well as hypertensive subjects with normal kidney function (CKD: 0.28; hypertensive: 0.25; control: 0.25, respectively; $p < 0.05$). The ECV frequency histogram for CKD patients was shifted rightward with a higher mean septal ECV. Such elevation of ECV in early CKD, but not in hypertensive patients, suggests that the development of diffuse interstitial fibrosis is not dependent on increased blood pressure.

Furthermore, both ECV and native T1, considered as parameters of diffuse fibrosis in the above study, have also shown an association with global longitudinal systolic strain (GLS), a more sensitive predictor of both overall and CV mortality than the routinely-used ejection fraction in patients with CKD stage 4-5 [34].

Assessment of the myocardium without contrast agent in CKD patients

As stated earlier, myocardial fibrosis detection was initially based on the contrast agent gadolinium. The sensitivity and accuracy of these methods in fibrosis assessment is superior to native techniques. However, the severe consequences of gadolinium administration forced a return to the primarily-used native T1 time measurement. This resulted in a long period in which no studies on contrast-free myocardial fibrosis detection in CKD patients were available, possibly due in part to methodological uncertainties.

In 2016, Graham-Brown et al. and Rutherford et al. [35, 36] published promising results in dialysis populations using native T1 as a novel CMR technique. Not only were the studies conducted in parallel, but both groups also used the same methodology. The assessments were perfomred on a 3-Tesla magnet using a modified look-locker inversion recovery sequence (which was manufacturer-specific). This similarity hence enabled the comparison of these two studies without serious T1-specific limitations.

In the Graham-Brown et al. study, native T1 and strain parameters were measured on a global and segmental level in 35 haemodialysis patients. The authors found elevated native global T1 times and septal-nonseptal differences (septal T1 1293 vs. non-septal T1 1252 ms respectively). Elevated global T1 levels were correlated with global strain parameters while septal native T1 was correlated with septal systolic strain. Graham-Brown et al. not only presented the possibility of non-invasive T1 mapping in a haemodialysis population, but also suggested that the interventricular septum is the most sensitive region with regard to the development of myocardial fibrosis [35].

Rutherford et al. [36] found that global, septal and midseptal native T1 values were significantly higher in haemodialysis patients compared to healthy volunteers (global 1171 vs. 1154 ms; septal 1184 vs. 1163 ms; midseptal 1184 vs. 1161 ms respectively) and that native T1 was correlated with left ventricular mass indices. Although these authors found no differences in native T1 at the segmental level (in contrast to Graham-Brown et al. [35]), a correlation was observed between septal native T1 and clinical parameters (troponin level and corrected QT interval). An important finding of the study featured the demonstration of a significant correlation between native T1 and LVMi (global T1: $R=0.452$, $p= 0.008$, septal T1 $R=0.449$, $p= 0.009$, midseptal T1 $R=0.498$ $p= 0.003$ respectively). Moreover, global longitudinal strain was significantly reduced and correlated with LVMi ($R= 0.426$), along with a trend toward a correlation of GLS with galectin-3 ($R=0.344$, $p=0.05$) a biomarker of cardiac fibrosis.

As previously mentioned, one of the most important determinants of native T1 is oedema. Although native T1 times are elevated in dialysis patients, the reproducibility of native T1 has not been investigated in this population group with highly variable fluid status. Most recently, Graham-Brown et al. [37] published a study on the reproducibility of T1 mapping in haemodialysis patients in which they found excellent inter-study, inter-observer and intra-observer variability of native T1. In dialysed patients, changes in body weight between the examinations (reflecting the fluid status of the patients) was correlated with changes in LV end-diastolic volume (LVEDV) ($r = 0.682$; $P = 0.03$). However, based on linear regression analysis, T1 change was unaffected by LVEDV or weight fluctuation. The

authors concluded that myocardial native T1 is reproducible in haemodialysis patients and unaffected by alterations in fluid status.

In contrast, a recent study on native T1 measurement in CKD patients published by Wang et al. [38] failed to show significant differences in native T1 in patients with end-stage renal disease compared to controls. The higher control native T1 levels compared to the other above 3-Tesla studies (Wang et al.: 1253.1 ± 71.6 ms, Graham-Brown et al.: 1085.2 (1066–1109.2) ms, Rutherford et al.: 1154 ± 32 ms) highlight not only the difficulties associated with native T1 measurements, but also raise the question of the comparability of native T1 in different studies. Wang et al. also reported on the value of native T1-rho sequences in CKD patients. The "rho" in the sequence name refers to a "ro"tating frame with the sequence having elements of both T1 and T2 weighting. They found significantly higher values in dialysed patients compared to controls (52.2 ± 4.0 ms vs. 49.4 ± 2.6 ms, P = 0.001). The authors concluded that T1-rho might be associated with myocardial fibrosis and may better characterise myocardial injury than T1 and T2. However, the significance and predictive value of T1 rho measurement in CKD patients still remain to be clarified.

Conclusion

Recent CMR studies have identified markers of subclinical left ventricular disease in chronic kidney disease. While these studies do not confirm the establishment of a particular and singular powerful tool for myocardial assessment, the combination of these safe imaging techniques (native T1 time, T1-rho, longitudinal strain, LVMi) and biomarkers (troponin, brain natriuretic peptide, galectin-3) should help practitioners perform highly predictive risk assessment in CKD patients.

Disclosure Statement

The authors declare no conflict of interest regarding the publication of this article.

Abbreviations

CKD (chronic kidney disease); CMR (cardiac magnetic resonance); CMRI (cardiac magnetic resonance imaging); CV (cardiovascular); eGFR (estimated glomerular filtration rate); ECV (extracellular volume); GBCA (gadolinium based contrast agent); GFR (glomerular filtration rate); GLS (global longitudinal strain); HDL (high density lipoprotein); HCM (hypertrophic cardiomyopathy); LDL (low density lipoprotein); LGE (late gadolinium enhancement); LVEDV (left ventricular end-diastolic volume); LVH (left ventricular hypertrophy); LVMi (left ventricular mass index); MRI (magnetic resonance imaging); NSF (Nephrogenic Systemic Fibrosis); T1 (T1 relaxation time).

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