The Relationship between Myocardial T1 and T2 Values, Cardiac Function and 1-year Outcomes in Male Patients with Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) leads to myocardial tissue alterations that are associated with cardiac events and mortality. Cardiac magnetic resonance imaging (MRI) may be useful for noninvasively detecting myocardial abnormalities associated with CKD and its relationship with patients’ prognoses.

Objectives: The aim of this study was to evaluate the relationship between myocardial T1 and T2 values, cardiac function and 1-year outcomes in male patients with CKD.

Methods: Thirty-eight patients with CKD were examined using a 1.5T imager. The relationship between the patients’ native T1 or T2 values and their age, renal function, cardiac functional parameters measured by cardiac MRI, and 1-year outcomes was assessed. The 1-year outcomes was defined as cardiac events including hospitalization or death associated with coronary artery diseases or heart failure that occurred within 1 year after having a cardiac MRI.

Results: Native T1 and T2 values of the myocardium were significantly higher than those of our institutional reference standard (P < 0.05 for both). The patients’ T1 values were correlated with several cardiac functional parameters (P < 0.05). There were significant differences in the left ventricular end-diastolic volume (LVEDV) as well as the LVEDV index (LVEDVI) between patients with and without cardiac events within 1 year after having a cardiac MRI (P = 0.048 for both). A receiver operating characteristic analysis revealed that a LVEDV of 124 mL and a LVEDVI of 75.05 mL/m² were appropriate thresholds for identifying patients with CKD with poor 1-year outcomes.

Conclusions: T1/T2 mapping might be a useful tool to quantify myocardial tissue alterations specific for CKD and its cardiac function. LVEDV and LVEDVI are significantly related to 1-year outcomes in male patients with CKD.

Key words: chronic kidney disease, cardiac magnetic resonance imaging, T1 mapping, T2 mapping, cardiac events


1. Introduction

Chronic kidney disease (CKD) substantially increases the risks of death, cardiovascular disease, and hospitalization1-3. Therefore, CKD should be managed at its early stages to reduce the risk of cardiac events and improve survival and quality of life. In patients under dialysis with end-stage CKD, the typical pathological characteristics of the myocardium are left ventricular (LV) hypertrophy and diffused collagen or fibrosis deposition in the extracellular matrix4-6. Although myocardium biopsy is considered the reference standard for staging myocardial injuries, it is an invasive procedure that may lead to severe complications and suffer from sample error5-6; thus, it is not appropriate for identifying the myocardial tissue alteration associated with CKD.

Cardiac magnetic resonance imaging (MRI) is a noninvasive and useful tool with which to detect myocardial fibrosis because of its ability to characterize tissue. Myocardial fibrosis in patients with end-stage CKD is detected using late gadolinium enhancement MRI5-9. However, after emerging nephrogenic systemic fibrosis in patients with CKD or those under dialysis, gadolinium-based contrast agents are contraindicated9. T1 mapping is emerging as a valuable alternative to late gadolinium enhancement. Native T1 value has been shown to correlate with myocardial fibrosis as evaluated by histopathology10-11. Some previous studies demonstrate an increase in native T1 values in patients with CKD12-14. However, in another study, the T2 values between healthy controls and patients with end-stage CKD are different but native T1 values are not15. The etiologies for CKD (e.g., primary glomeru-
We used a modified National Kidney Foundation classification of CKD between August 2017 and July 2019. We included 38 consecutive male patients with CKD who underwent cardiac MRI for evaluating cardiac function in age from 47 to 86 years (mean age, 68.5 years) who occurred within 1 year after cardiac MRI death for coronary artery diseases or heart failure that study, cardiac events were defined as hospitalization or acquisition during 11-second breath-holding in short-axis pulse and 3s data were acquired after the second inversion pulse followed by a 3s interval, with a single-shot SSFP readout; 5s data were acquired during 11-second breath-holding in short-axis midventricular slices. The imaging parameters for MOLLI were as follows: TR, 2.7 ms; TE, 1.3 ms; flip angle, 35°; FOV, 300 × 300 mm²; imaging matrix, 152 × 150; and slice thickness, 10 mm. The delay time was 159.5 ms with an inversion time increment of 350 ms. T2 mapping was performed with multiecho gradient- and spin-echo (GRASE) sequences. The imaging parameters for GRASE were as follows: TR, 1 RR; effective TE, 7.7–69.2 ms with 9 echoes and an echo train length of 5; flip angle, 35°; FOV, 300 × 300 mm²; imaging matrix, 152 × 145; and slice thickness, 10 mm. A parallel imaging technique (i.e., sensitivity encoding) was used for all sequences.

2. Patients and Methods

2.1. Patients

We enrolled 38 consecutive male patients with CKD (i.e., estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m², lasting more than 3 months), ranging in age from 47 to 86 years (mean age, 68.5 years) who underwent cardiac MRI for evaluating cardiac function or coronary disease between August 2017 and July 2019. We used a modified National Kidney Foundation Classification of CKD, which classifies eGFR. In the present study, cardiac events were defined as hospitalization or death for coronary artery diseases or heart failure that occurred within 1 year after cardiac MRI. Informed consent was given by all patients with CKD, and our institutional review board approved this retrospective study.

2.2. MRI

Cardiac MRI examinations were performed using a 1.5T unit (Ingenia 1.5 T, release 3.2.3; Philips Healthcare, Best, The Netherlands). A 28-channel cardiac multicoil was used for signal reception. ECG-gated breath-hold steady-state free-precession (SSFP) cine images with 2- and 4-chamber views were obtained. Thereafter, short-axis SSFP images encompassing the entire left ventricle were obtained using the following imaging parameters: repetition time (TR), 3.2 ms; echo time (TE), 1.6 ms; flip angle, 60°; field of view (FOV), 350 × 350 mm²; imaging matrix, 192 × 170; and slice thickness of 8 mm. T1 mapping was performed with a 5s (3s) 3s modified Look-Locker inversion recovery (MOLLI) sequence acquired with a single-shot SSFP readout; 5s data were acquired after the first inversion pulse followed by a 3s interval, and 3s data were acquired after the second inversion pulse. Therefore, 7 to 11 multicontrast images were acquired during 11-second breath-holding in short-axis midventricular slices. The imaging parameters for MOLLI were as follows: TR, 2.7 ms; TE, 1.3 ms; flip angle, 35°; FOV, 300 × 300 mm²; imaging matrix, 152 × 150; and slice thickness, 10 mm. The delay time was 159.5 ms with an inversion time increment of 350 ms. T2 mapping was performed with multiecho gradient- and spin-echo (GRASE) sequences. The imaging parameters for GRASE were as follows: TR, 1 RR; effective TE, 7.7–69.2 ms with 9 echoes and an echo train length of 5; flip angle, 35°; FOV, 300 × 300 mm²; imaging matrix, 152 × 145; and slice thickness, 10 mm. A parallel imaging technique (i.e., sensitivity encoding) was used for all sequences.

2.3. Data Collection

A cardiologist with 20 years of experience in cardiac imaging measured left ventricular (LV) functional parameters, such as LV mass (LVM), LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV) on short-axis cine SSFP images using a workstation (ViewForum, Philips Healthcare). These functional parameters except LVEF were indexed to body surface area (i.e., LVM index (LVMi), LVEDV index (LVEDVi), and LVESV index (LVESVi)). T1 and T2 mapping was generated automatically on the console (Fig. 1). A team of 3 radiological technologists divided the patients randomly, and each placed a region of interest (ROI) on the septal myocardium at the midventricular levels to be as large as possible in each patient; care was taken not to include the ventricular cavity within ROIs. A radiologist with 2 years of experience in cardiac MRI supervised the placement of the ROIs and confirmed the myocardial T1 and T2 values in each patient. Because a previous study demonstrated the absence of susceptibility artifacts and the high prevalence of fibrosis in the interventricular septum, we mainly investigated the septum.

2.4. Statistical Analysis

All data were checked for normality using a Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation; nonparametric data are presented as median with interquartile range. First, we evaluated the relationship between native T1 or T2 values and the ages, body mass index (BMI), eGFR, length of time on dialysis including both hemodialysis and peritoneal dialysis, or cardiac functional parameter in the patients using a Pearson correlation or Spearman rank correlation analysis. Next, we evaluated the differences in the clinical characteristics, native T1 and T2 values of the myocardium, and cardiac function between patients with and without cardiac events. The intergroup comparisons of continuous and categorical variables were achieved using an unpaired Student t, Mann–Whitney U, or χ² test, respectively. A receiver operating characteristic (ROC) analysis was used to define the threshold of some parameter related to the cardiac events: the 1-year outcome.
A risk ratio was calculated for the factors increasing the cardiac events. A stepwise regression analysis was used to determine the factors related to cardiac events, if necessary. All statistical analyses were conducted using SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA). *P* < 0.05 was considered significant for all statistical analyses.

3. Results

3.1. Patient Characteristics

We completed cardiac MRI studies successfully for all of the 38 patients with CKD. Three patients were excluded from further analysis because they had hypertrophic cardiomyopathy, sarcoidosis, or acute myocardial infarction. One patient with a history of myocardial infarction was included for the following analyses because it was an apical focal lesion on cine images. Table 1 summarizes the clinical characteristics of 35 patients with CKD.

3.2. Relationship between myocardial T1 or T2 values and the age of the patients, their BMI, eGFR, length of time on dialysis, and cardiac function

Native T1 and T2 values of the septal myocardium were 1081 ± 43 ms and 54 ± 4 ms, respectively, in the male patients with CKD, which were significantly longer than the reference standard of our institution (1049 ± 31 ms in 10 healthy men (mean age, 41.8 years), *P* = 0.035 for native T1 and 47 ± 2 ms in 8 healthy men (mean age, 39.1 years), *P* < 0.01 for T2; Fig. 1). Table 2 summarizes the relationship between T1 or T2 values and the patients’ clinical backgrounds and cardiac function. Neither native T1 nor T2 values correlated with the age of the patients, their BMI, eGFR, the length of time on dialysis, or any laboratory data (*P* > 0.05 for all). Native T1 values were correlated with LVMI (*r* = 0.376, *P* = 0.026), LVEDV (*r* = 0.377, *P* = 0.026), LVEDVI (*r* = 0.349, *P* = 0.04; Fig. 2), LVESV (*r* = 0.431, *P* = 0.01), LVEF (*r* = 0.413, *P* = 0.014), and inversely correlated with LVEF (*r* = −0.44, *P* < 0.01; Fig. 3). T2 values inversely correlated with only septal thickness (*r* = −0.379, *P* = 0.025).

3.3. Relationship between the clinical characteristics, myocardial T1 or T2 values, cardiac functional parameters and cardiac events

Three patients were excluded from this analysis because 2 patients died of surgeries for dissecting aortic aneurysm and 1 patient dropped from our follow-up. Table 3 summarizes the relation of the patients’ clinical characteristics or MRI findings to the cardiac events. The cardiac events occurred within 1 year after cardiac MRI in 6 (18.8%) of the 32 patients with CKD: coronary artery diseases in 4 and heart failure in 2. There were significant differences in LVEDV and LVEDVI between patients with and without cardiac events (*P* = 0.048 for both, Fig.
4). Although native T1 and LVEDV or LVEDVI correlated, there were no significant differences in the T1 between the patients with and without cardiac events \((P = 0.27)\). A ROC analysis revealed that LVEDV of 124 mL (sensitivity of 0.833, specificity of 0.615, an area under the curve of 0.763) and LVEDVI of 75.05 mL/m\(^2\) (sensitivity of 0.833, specificity of 0.769, an area under the curve of 0.763; Fig. 5) were appropriate thresholds for identifying the patients with poor 1-year outcome.

Increased LVEDV and LVEDVI increased the risk of cardiac events with the risk ratio 3.692 (95% confidence interval [CI], 0.601 to 22.671) and 4.615 (95% CI, 0.762 to 27.964), respectively.

4. Discussion

The present study demonstrated that native T1 values were correlated with several cardiac functional parameters in patients with CKD. There were significant differences in LVEDV and LVEDVI between patients with and without cardiac events that occurred within 1 year after cardiac MRI. A ROC analysis revealed that LVEDV of 124 mL and LVEDVI of 75.05 mL/m\(^2\) were appropriate thresholds for identifying the patients with CKD with poor 1-year outcome.

Native T1 and T2 values were not correlated to the age of the patients, their BMI, eGFR or length of dialysis in patients with CKD. Nonetheless, native T1 and T2 were prolonged in the male patients with CKD, compared to the male controls. Prolonged myocardial T1 is induced by diffuse interstitial fibrosis, edema, or inflammation in several types of cardiomyopathies\(^{20, 21}\). T2 relaxation time is related to water content, macromolecules or some tissue alterations in the myocardium\(^{22-24}\). In contrast to the present results, Hayer et al.\(^{25}\) have reported that myocardial...
Native T1 values were correlated with several cardiac functional parameters in patients with CKD\textsuperscript{12, 20}. Native T1 values of the septal myocardium may reflect myocardial injuries related to cardiac dysfunction in patients with CKD. The abnormally prolonged native T1 values may also be related to an increase in LVM that is commonly and convincingly associated with cardiovascular and all-cause mortality in patients with CKD\textsuperscript{26, 27}. The myocardial T2 values inversely correlated with only septal thickness. In general, septal thickness becomes thinner as the LVEDV or LVESV increases. The septal thickness was measured at the center line, while an ovoid ROI was placed on the interventricular septum for T2 quantification, which might influence the present result. The present findings indicate that prolonged T2 does not necessarily reflect myocardial edema, which can lead to myocardial hypertrophy. Changes in macromolecules, interstitial expansion associated with myocardial fibrosis, cellular hypertrophy or vessel dilatation might prolonged T2 of the myocardium in patients with CKD\textsuperscript{23, 34}. Arcari et al.\textsuperscript{28} have reported that an increase in myocardial T2 is specific for myocardial injuries related to CKD.

There were significant differences in LVEDV and LVEDVI between patients with and without cardiac events. We showed the appropriate thresholds of the two factors for identifying the CKD patients suffering from cardiac events. Because body surface area is affected by gender, obesity and body size, both volumetric values and their indexed values were evaluated in our CMR study\textsuperscript{20}. Myocardial T1 was moderately correlated with LVEDV and LVEDVI, but not to cardiac events. The history of heart failure, lower eGFR, lower LVEF and increased LVMI did not reach statistical significance between the patients with and without cardiac events, whereas Go et al.\textsuperscript{19} reported that reduced eGFR was associated with increased cardiac events and sharply for subjects with an eGFR of less than 45 ml/min/1.73 m\textsuperscript{2}. Mimura et al.\textsuperscript{29} have shown that dilatation of the left ventricle and increase in myocardial fibrosis are related to cardiovascular events in the patients with hemodialysis. Increased LVEDV and LVEDVI, which raised the risks of cardiac events in our patients with CKD, can be induced by not only myocardial fibrosis but also by volume overload, hypertension, anemia, and other pathophysiologic factors. In the daily practice, the CKD patients with increased LVEDV or LVEDVI should be treated and followed up intensely. Our results indicated that the native T1, a histologic MRI variable, was related to cardiac dysfunction, but its relation to the 1-year outcome was not straightforward. Nonetheless, early intervention can be applied to the patients with prolonged native T1 of the myocardium, while a longitudinal study with more population with CKD should be necessary to determine whether native T1 values prolong at the early stage of CKD: prolonged T1 precedes the increase in LVEDV or LVEDVI.

There were some limitations to this study. First, the sample size was relatively small and only men are examined. The percentage of the patients with cardiac events in our study was close to that of the previous study with many patients with CKD\textsuperscript{3}. Rauhalammi et al.\textsuperscript{17} reported that native T1 decreased with increasing age in females but not in males. Indeed, the sample size might attribute to the 95\% CI 1 below 1. Second, native T1 and T2 values may be affected by magnetic field strength or imaging sequences. Thus, we cannot extrapolate our results to other studies using 3.0 T or other T1 mapping techniques such as saturation recovery sequences. Third, no biopsy has been performed in this study. The ischemic changes, uremic cardiomyopathy, and fibrosis may be mixed and indistinguishable in our CKD patients.

5. Conclusion

In conclusion, T1T2 mapping is useful for identifying the myocardial tissue alterations related to cardiac function, and LVEDV and LVEDVI are significantly related to 1-year prognosis in the male patients with CKD.

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