Early effects of kidney transplantation on the heart - A cardiac magnetic resonance multi-parametric study ☆

Manvir K. Hayer [a],[*],[1], Ashwin Radhakrishnan [a],[1], Anna M. Price [a],[1], Shanat Baig [b],[1], Boyang Liu [b],[1], Charles J. Ferro [a],[1], Gabriella Captur [c],[1], Jonathan N. Townend [a],[1], James C. Moon [c],[1], Nicola C. Edwards [a],[1], Richard P. Steeds [a],[1]

[a] Birmingham Cardiorenal Group, Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom of Great Britain and Northern Ireland
[b] Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom of Great Britain and Northern Ireland
[c] Institute of Cardiovascular Science, University College London, United Kingdom of Great Britain and Northern Ireland

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ABSTRACT

Increased native myocardial T1 times in chronic kidney disease (CKD) may be due to diffuse interstitial myocardial fibrosis (DIF) or due to interstitial edema/inflammation. Concerns relating to nephrogenic systemic fibrosis with gadolinium-based contrast agents (GBCA) limit their use in end-stage kidney disease (ESKD) to measure extracellular volume (ECV) and characterise myocardial fibrosis. This study aimed to examine stability of myocardial T1 and T2 times before, and within 2 months after kidney transplantation; a time frame when volume status normalises but myocardial remodelling is unlikely to have occurred, and to compare these with ECV using GBCA after transplantation. Twenty-four patients with ESKD underwent serial cardiovascular magnetic resonance imaging, including T1 and T2 mapping. GBCA was administered on follow-up provided eGFR was >30 ml/min/1.73 m^2. Eighteen age- and sex-matched controls were studied at one timepoint. ECV (ECV 28 ± 2% vs. 24 ± 2%, p = 0.001) and T2 times were higher in ESKD compared to controls. After transplantation, septal T1 times increased (MOLLI 985 ms ± 25 vs. 1002 ms ± 30, p = 0.014; ShMOLLI 974 ms ± 39 vs. 992 ms ± 33, p = 0.113), LV volumes reduced (LVEDvol indexed 79 ± 24 vs. 63 ± 20 ml/m^2, p = 0.005) but LV mass was unchanged (LV mass index 89 g/m^2 ± 38 to 83 g/m^2 ± 23, p = 0.141). T2 times did not change after transplantation. Both ECV and myocardial T1 times are elevated in ESKD, supporting the theory that elevated T1 times are due to DIF, although a contribution from myocardial edema cannot be fully excluded. The lack of any fall in T1 or T2 times after transplantation suggests that myocardial T1 times are a stable measure of DIF in CKD.

1. Introduction

Cardiovascular (CV) disease is the leading cause of mortality in patients with chronic kidney disease (CKD). Most of the excess CV mortality in patients with end-stage kidney disease (ESKD) arises from heart failure, arrhythmia and sudden cardiac death rather than atherothrombotic events such as myocardial infarction; these events are thought to be attributable to uremic cardiomyopathy (UC) [1]. Histological and imaging studies have shown that this specific heart muscle disease is characterised by left ventricular hypertrophy (LVH)

and interstitial fibrosis causing left ventricular (LV) systolic and diastolic dysfunction, and is almost universal in the hemodialysis population. Studies using cardiac magnetic resonance imaging have shown changes consistent with coarse replacement fibrosis and diffuse interstitial fibrosis (DIF) in both early and advanced CKD [2–5]. More recently, the use of gadolinium-based contrast agents (GBCA) in ESKD has been restricted following case reports of nephrogenic systemic fibrosis. As a result, myocardial characterization has been investigated using native T1 mapping. This technique measures relaxivity that is characteristic of the tissue studied but does not distinguish between the intracellular and extracellular compartments. Emerging data show that native myocardial T1 times are prolonged in hemodialysis patients and in early stage CKD. These findings have been interpreted as due to DIF however this assumption is complicated by the fact that native T1 times can also be prolonged by free water in the myocardium (interstitial and extracellular edema, inflammation) [4,6,7]. This is especially pertinent in ESKD, when patients are often chronically volume overloaded. Studying renal transplant recipients shortly after kidney transplantation provides

a unique opportunity to administer GBCA safely because of restored renal function. This allows measurement of ECV in ESKD at a time when uremic cardiomyopathy is unlikely to have changed. We hypothesised that both ECV and native T1 times would be elevated in subjects with ESKD studied shortly after transplantation. If so, this would provide evidence that the elevated T1 times previously reported in these subjects are likely to be due to DIF rather than to increased myocardial water content.

2. Methods

2.1. Study design and participants

Patients who were due to undergo living-donor kidney transplantation were recruited as part of an ongoing BHF-funded study (NCT03176862). All patients were in sinus rhythm. Subjects were excluded if they had a history or symptoms of CV disease or diabetes mellitus. CV disease was defined as any history of ischemic heart disease, peripheral vascular disease, stroke, heart failure, or LV ejection fraction <45% or more than mild valvular disease. All patients underwent exercise stress echocardiography or 99m technetium tetrofosmin single photon electron computed tomography (SPECT) to exclude silent myocardial ischemia. Demographic and medical comorbidity data and bloods were collected on both visits. Estimated glomerular filtration rate (eGFR) was assessed using the Modification of Diet in Renal Disease equation. Eighteen age- and sex-matched healthy controls were also recruited. Healthy subjects had normal kidney function (defined as an eGFR >60 ml/min/1.73 m^2 and the absence of structural or histological renal abnormality), no known chronic disease, and were not on regular medication. Subjects were recruited through advertisement at the University of Birmingham or University Hospitals Birmingham. Control subjects had blood tests and a CMR scan at baseline. Stress echocardiography or SPECT were not performed in these individuals.

2.2. Cardiac magnetic resonance imaging

Baseline CMR (1.5 T Magnetom Avanto, Siemens Healthcare, Germany) was performed before the transplant, and within 2 months following kidney transplantation. Cine images for LV and right ventricular (RV) volumes, function, and LV mass were acquired using breath-hold steady state free precession sequences as previously described [8]. T1 mapping was performed at basal and mid short axis (SAX) level in diastole using a Shortened Modified Look-Locker Inversion recovery sequence (ShMOLLI, Oxford) 5(1)1(1)1 heart beats and ECG-gated Modified Look-Locker Inversion recovery (MOLLI) sequence with a 3(3)3 (3)5 heart beats sampling protocol. ShMOLLI T1 maps were generated with variable inversion preparation time. Typical acquisition parameters were: TE = 1.05 ms, flip angle = 35°, matrix size 192 × 144, slice thickness 7 mm, voxel size = 1.9 × 1.9 × 7 mm, FoV = 360 mm. Typical acquisition parameters for the MOLLI sequence were: pixel bandwidth 977 Hz/pixel; TE = 1.1 ms; flip angle = 35°; matrix size = 144 × 256, slice thickness 7 mm, voxel size 2.5 × 2 × 7 mm. Motion correction and a non-linear least-square curve fitting were performed with the set of images acquired at different MOLLI inversion times to generate a parametric pixel-wise colour T1 map to quantitatively measure the longitudinal myocardial relaxation time. For T2 maps, 3 single shot images were acquired at different T2-preparation times (0 ms, 24 ms, and 55 ms, respectively) in the basal and mid SAX slices with the following typical acquisition parameters: ECG triggered, TE = 1.12 ms, flip angle = 70°, voxel size: 2.2 × 1.8 × 6.0 mm, slice thickness 6 mm. Motion correction and fitting were performed to estimate coefficients of the decay function, which were then used to estimate the T2 times. The T2 sequence was acquired later in our study and therefore only performed in 15 patients at baseline, but in all patients at follow up. LGE imaging was acquired using a standard inversion recovery sequence 7 to 10 min after administration of GBCA bolus (0.15 mmol/kg of Gadovist). Post-contrast MOLLI T1 images were acquired ≥15 min after GBCA administration at the same levels as pre-contrast. ShMOLLI T1 images were not acquired post-contrast. GBCA was administered on the follow up CMR scan provided eGFR had risen to >30 ml/min/1.73 m^2 and the patient consented.

2.3. Phantom studies

Phantom studies were also undertaken to assess the stability of our T1 sequences. The T1 Mapping and ECV Standardisation (T1MES) phantom was scanned every 2 weeks for 6 months as part of the T1MES multicentre study, according to the user manual instructions distributed to centres, and as previously described. Analysis was done offline as previously described [9].

2.4. Analysis of CMR scans

Offline analysis was performed using CVi 42® software (version 5.3.4, Circle Vascular Imaging, Canada) by an experienced reader blinded to clinical information. Manual planimetry of the short axis epicardial and endocardial borders in end-diastole and end-systole was performed using standardised methods for determination of LV ejection fraction, volumes and mass [10]. For analysis of parametric maps, endocardial and epicardial borders were manually drawn in the basal and mid short axis slices and a 20% offset was used to avoid blood pool contamination. Anterior and inferior septal borders were defined with semi-automated segmentalization of the LV in accordance with the AHA model.

All segments were assessed for quality and any segments containing LV outflow tract or artefact were excluded. A region of interest was drawn in the blood pool, taking care to avoid papillary muscle. ECV was calculated with the pre and post contrast T1 maps using a previously validated formula [4]. An inter-observer and intra-observer analysis of the MOLLI sequence only was also done by two experienced individuals to ensure there was no systematic bias in the T1 analysis technique. For analysis of global longitudinal strain smoothed endocardial and epicardial borders were drawn in the end-diastolic frame of all three long axis images and automatically propagated throughout the cardiac cycle using the feature tracking software. For global circumferential strain, smoothed endocardial and epicardial borders were drawn in the end-diastolic frame of SAX cines, and the anterior and inferior RV insertion points were defined on each SAX slice. The basal slice was taken as the first SAX slice without the LV outflow tract.

2.5. Statistical analysis

Data normality was assessed using the Shapiro-Wilk test. Continuous variables are expressed as mean ± SD (normal distribution) or median (interquartile range [IQR]; non-normal distribution). Paired group comparisons for continuous data were made using the paired samples t-test or the Wilcoxon Signed Rank test for parametric and non-parametric data respectively. Unpaired group comparisons for continuous data were made using the unpaired t-test or the Mann Whitney U test. Paired categorical data were compared using the McNemar test. Statistical tests were 2-tailed, and a p value <0.05 was considered to indicate statistical significance. A per protocol analysis was performed for the 21 patients with paired data. An intention-to-follow-up analysis was also done assuming variables did not change between baseline and follow up.

3. Results

3.1. Subject characteristics

Twenty-four patients were studied before kidney transplantation (median 8 days, IQR 4 to 11 days). The median time between baseline and repeat CMR scan was 7 weeks (IQR 6 to 9 weeks). Three patients were lost to follow up: 1 relocated to another geographical area and the other two had post-operative complications and withdrew consent for further CMR within 2 months. Table 1 describes the demographic details and subject characteristics for the CKD and control populations. Eleven patients were on hemodialysis prior to transplantation, three were on peritoneal dialysis, and ten underwent pre-emptive kidney transplantation. The median dialysis vintage was 15 months [IQR 8 to 24 months]. Hemodialysis patients were scanned 10 to 24 h after dialysis. At follow up, 14 patients consented to receive GBCA. The reason for refusal in the remaining subjects was anxiety about protecting their new kidney and avoiding unnecessary contrast agents. Two patients developed new onset diabetes after transplantation. The number of patients on antihypertensive medication reduced from 20 to 18, and the type of antihypertensive agents also changed (Table 1). Only one patient was on immunosuppression (prednisolone) before kidney transplantation. Following surgery, subjects were on a typical immunosuppressive regime of tacrolimus, mycophenolate mofetil and prednisolone. There was no difference in LV volumes at baseline between the CKD cohort and healthy controls, but LV mass was higher in ESKD. After transplantation, LV mass was unchanged, LV volumes were reduced, and there was a small increase in LV ejection fraction (Table 2).

3.2. Myocardial function and tissue character

4% of shMOLLI segments and 4% MOLLI segments were excluded due to artefact, most commonly in inferior and lateral segments. At baseline, native global and septal T1 times and T2 times were higher in the CKD cohort than in healthy controls (Table 2). ECV was also higher in the CKD cohort than in healthy controls. On per protocol analysis there was a small but statistically significant increase in septal T1 times after kidney transplantation (Fig. 1(a) MOLLI; (b) ShMOLLI; Fig. 2). Global T1 times were unchanged (Table 2). Similar directional changes were seen regardless of the T1 sequence was used – T1 times increased in 14 subjects using both MOLLI and ShMOLLI. T2 times did not change after transplantation. Blood pool T1 times decreased following kidney transplantation, hemoglobin and hematocrit increased and heart rate was unchanged. Of the 14 patients who were given GBCA on follow

Table 1
Demographic data and subject characteristics in chronic kidney disease and healthy control cohorts.

	CKD		Controls (n = 18)
	Baseline (n = 24)	Follow up (n = 21)	
Age	46 ± 13	n/a	49 ± 17
Male n (%)	17 (71)	n/a	11 (61)
Dialysis vintage (months)	13 (8–33)	n/a	n/a
Weight (kg)	80.5 ± 13.9	80.2 ± 14.2	76.7 ± 7.7
Body surface area (kg/m²)	1.96 ± 0.21	1.96 ± 0.21	1.91 ± 0.14
Heat rate (beats/min)	73 ± 13	75 ± 14	75 ± 11
Systolic BP (mmHg)	133 ± 23	135 ± 18	125 ± 14
Diastolic BP (mmHg)	80 ± 14	83 ± 12	72 ± 12
Creatinine (mg/dL)	5.64 (5.02–7.53)	1.41 (1.29–1.66)*	0.90 (0.80–0.96)†
eGFR (ml/min/1.73 m²)	–	47 (36–61)*	83 (74–87)†
Hemoglobin (g/L)	124 ± 17	133 ± 15*	140 ± 17†
Hematocrit	0.37 ± 0.05	0.40 ± 0.04*	0.43 ± 0.29†
Ferritin (µg/L)	257 ± 162	186 ± 156	n/a
Cholesterol (mg/dL)	187 ± 036	195 ± 46	n/a
Primary glomerulonephritis n (%)	7 (29)	n/a	n/a
Vasculitis n (%)	1 (4)	n/a	n/a
Polycystic kidney disease n (%)	7 (29)	n/a	n/a
Hypertension n (%)	2 (8)	n/a	n/a
Other n (%)	7 (29)	n/a	n/a
Medications			
CCB	10	14	n/a
Beta blocker	7	7	
ACEi/ARB	5	0	
Diuretic	6	1*	
Statin	1	2	
Immunosuppression	1	21*	

n/a, not applicable; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

* Indicates p value <0.05 between paired data at baseline and transplant follow up (n = 21).

† Indicates p values <0.05 between unpaired data comparing the transplant cohort at baseline to healthy controls.

Table 2
CMR data for CKD patients at baseline and follow up with controls.

	CKD (n = 21)		Controls (n = 18)
	Baseline	Follow up	
LVEDvol indexed (ml/m²) (n = 21)	79 ± 24	63 ± 20*	65 ± 13†
LVESvol indexed (ml/m²) (n = 21)	26 ± 16	20 ± 15	19 ± 6
LVEF (%) (n = 21)	68 ± 9	73 ± 9*	70 ± 8
LV mass indexed (g/m²) (n = 21)	89 ± 38	83 ± 23	55 ± 11†
Septal T1 MOLLI (ms) (n = 18)	985 ± 25	1002 ± 30*	962 ± 22†
Global T1 MOLLI (ms) (n = 18)	981 ± 29	983 ± 25*	946 ± 30†
Blood pool T1 MOLLI (ms) (n = 18)	1593 ± 74	1520 ± 96*	1462 ± 67†
Septal T1 ShMOLLI (ms) (n = 18)	974 ± 39	992 ± 33	916 ± 20†
Global T1 ShMOLLI (ms) (n = 18)	963 ± 45	960 ± 33*	907 ± 23†
Blood pool T1 ShMOLLI (ms) (n = 18)	1586 ± 108	1570 ± 94	1497 ± 51†
Septal T2 (ms) (n = 15)	55.5 ± 4.0	54.6 ± 2.1	50 ± 2†
Global T2 (ms) (n = 15)	58.1 ± 7.3	59.1 ± 4.3	50 ± 2†
Blood pool T2 (ms) (n = 15)	201 ± 26	199 ± 38	190 ± 32
Septal ECV (%) (n = 14)	n/a	28 ± 2	24 ± 2§
Global ECV (%) (n = 14)	n/a	27 ± 2	24 ± 2§
Septal ICV (%) (n = 14)	n/a	72 ± 2	76 ± 2§
Global ICV (%) (n = 14)	n/a	73 ± 2	76 ± 2§
2D GLS (%) (n = 21)	15.6 ± 3.0	16.3 ± 2.5	19.0 ± 2.9†
2D GCS (%) (n = 21)	16.6 ± 3.2	17.2 ± 2.8	20.8 ± 3.8†

n/a, not applicable; LVEDvol, left ventricular end-diastolic volume; LVESvol, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; ECV, extracellular volume fraction; ICV, intracellular volume fraction; GLS, global longitudinal strain; GCS, global circumferential strain.
These data are from a per-protocol analysis, excluding the 3 patients at baseline who did not go on to have a follow up scan.

* Indicates p value <0.05 between paired data at baseline and transplant follow up.

† Indicates p values <0.05 between unpaired data comparing the transplant cohort at baseline to healthy controls.

§ Indicates p values <0.05 between unpaired data comparing the transplant cohort at follow up to healthy controls.

up scans, 1 patient had LGE in a mid-wall distribution and 3 patients had right ventricular insertion point LGE, including one of the patients with new onset diabetes. There were no significant differences in LV volumes, mass, ejection fraction, myocardial T1/T2 times or ECV in patients with LGE compared to those without. The subject with midwall LGE had extensive contrast uptake (LGE 34 g, 15 g/m², 22% total), with elevated T1 in the region with contrast uptake (Supplementary Fig. 1). There was no systemic bias detected on Bland Altman Analysis of T1 between readers, with an inter-reader difference of −1 ± 7 ms (−13 to 11), and an intra-reader difference of −1 ± 6 ms (−12 to 10).

3.3. Phantom data

25 ShMOLLI and MOLLI phantom datasets were collected over the study period (Supplementary Fig. 2). The scanner room temperature was stable throughout the test period at 20.96 ± 0.98 °C. Unadjusted for temperature, ShMOLLI and MOLLI T1 times across the 9 tubes were stable with coefficients of variation ranging between 0.511% to 1.585% and 0.436% to 0.872% respectively. Stability of both sequences improved further with temperature correction (0.500% to 1.495% and 0.436% to 0.868% respectively).

4. Discussion

This is the first study in ESKD to comprehensively examine myocardial structure and tissue character, including T2 mapping and ECV measurement, early after kidney transplantation. Patients with ESKD exhibited higher global and septal T1 and T2 times than healthy controls and there was a small increase in T1 time after kidney transplantation. At 8 weeks after transplantation, ECV measured using GBCA was elevated in patients with ESKD. These findings support the hypothesis that the elevated myocardial T1 times in ESKD are due to DIF. The small elevation in T2 times in patients with ESKD compared to controls means that it is not possible to exclude a contribution from myocardial oedema to the increased T1 times. However it is important to note that ECV is not particularly affected by T2 times since most myocardial water is in the intracellular or intravascular spaces and not in the interstitial space [11]. Although not performed here, a longitudinal measurement of T2 times looking for late normalisation might clarify the importance of myocardial edema in this population.

The ECV levels observed in patients with ESKD are consistent with previously published myocardial histology data for patients with ESKD that demonstrated DIF in uremic cardiomyopathy [12]. The number of patients in our study who had LGE was too small to determine whether high T1 in ESKD alone could be used as a surrogate marker for coarse replacement fibrosis, although in the single case with mid-wall enhancement, elevated T1 was detected that mapped to the area. Both global and septal T1 times, were elevated in the CKD cohort compared to healthy controls, which are consistent with other data from hemodialysis patients [5,7]. Native myocardial T1 times increased very slightly early after kidney transplantation indicating a change in myocardial tissue composition. Given the trend to decreasing LV mass observed in this study despite rising T1 times, it is possible that myocardial cellular regression occurred. This would have increased the ratio of ECV to ICV, thereby increasing myocardial T1 times, but could also be a reflection of increased water content as measured by T2 mapping. The absolute increase in T1 times early after kidney transplantation was small, and the clinical significance of this change is unknown.

Previous studies of LV structure and function after kidney transplantation are conflicting with echo studies showing improvement in LV mass and ejection fraction [13–15] but CMR studies showing no
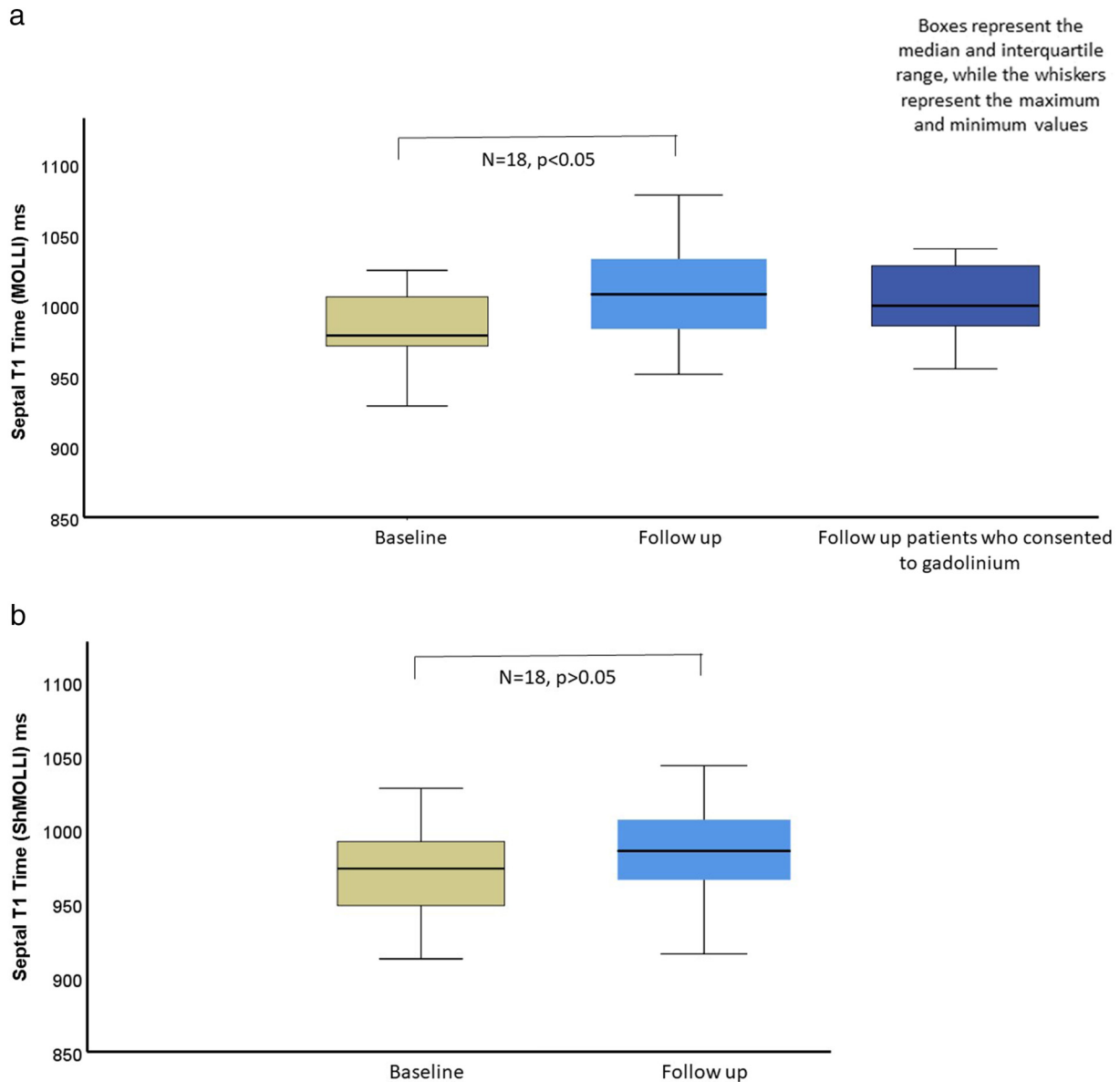
a

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Fig. 1. (a). Comparison of myocardial T1 times between baseline and follow up using MOLLI. The rectangle in each box and whisker plot represents the interquartile range. The line inside each box represents the median value, and the lines at either end of the whiskers represent the maximum and minimum values. (b). Comparison of myocardial T1 times between baseline and follow up using ShMOLLI. The rectangle in each box and whisker plot represents the interquartile range. The line inside each box represents the median value, and the lines at either end of the whiskers represent the maximum and minimum values.

significant change in LV mass, volume or function at one year after transplantation [16]. Our data showed a reduction in LV end-diastolic volume and an accompanying improvement in ejection fraction at 2 months following kidney transplantation but no change in LV mass.

Left ventricular hypertrophy was highly prevalent in our CKD cohort, mirroring the situation in the general ESKD population where it occurs due to a combination of haemodynamic factors (arterial stiffness, increased preload, activation of the renin angiotensin aldosterone system) and circulating factors (hyperuricaemia, elevated levels of parathyroid hormone and fibroblast growth factor-23) [2,17,18]. It is unlikely that LVH contributed significantly to the changes in T1 times or ECV seen here. We have previously shown that hypertensive patients with LVH but no renal impairment have lower T1 times than patients with early stage CKD [4]. Additionally, physiological LVH as a result of exercise training is not associated with increased T1 times [19]. These data suggest that raised LVMI alone cannot account for the increased T1 times seen in ESKD.

The results of this study are consistent with the results of previously published studies using T1 mapping in CKD. Two studies have shown that native myocardial T1 times are elevated in hemodialysis patients compared to healthy controls, although these were performed at 3 T [5,7]. A longitudinal follow-up study of patients showed no change in T1 time despite a reduction in LV mass and improvement of myocardial deformation after initiating dialysis [20]. Our earlier work has shown that ECV is also higher in patients with early stage CKD compared to healthy and hypertensive controls [4]. Although ECV is the preferred non-invasive biomarker to measure DIF, the necessity for GBCA precluded its measurement in our pre-transplant population.

5. Limitations

There are several limitations to acknowledge. Patients with ESKD in this study may not be representative of the general kidney transplant population as they were highly selected, relatively young, and all were
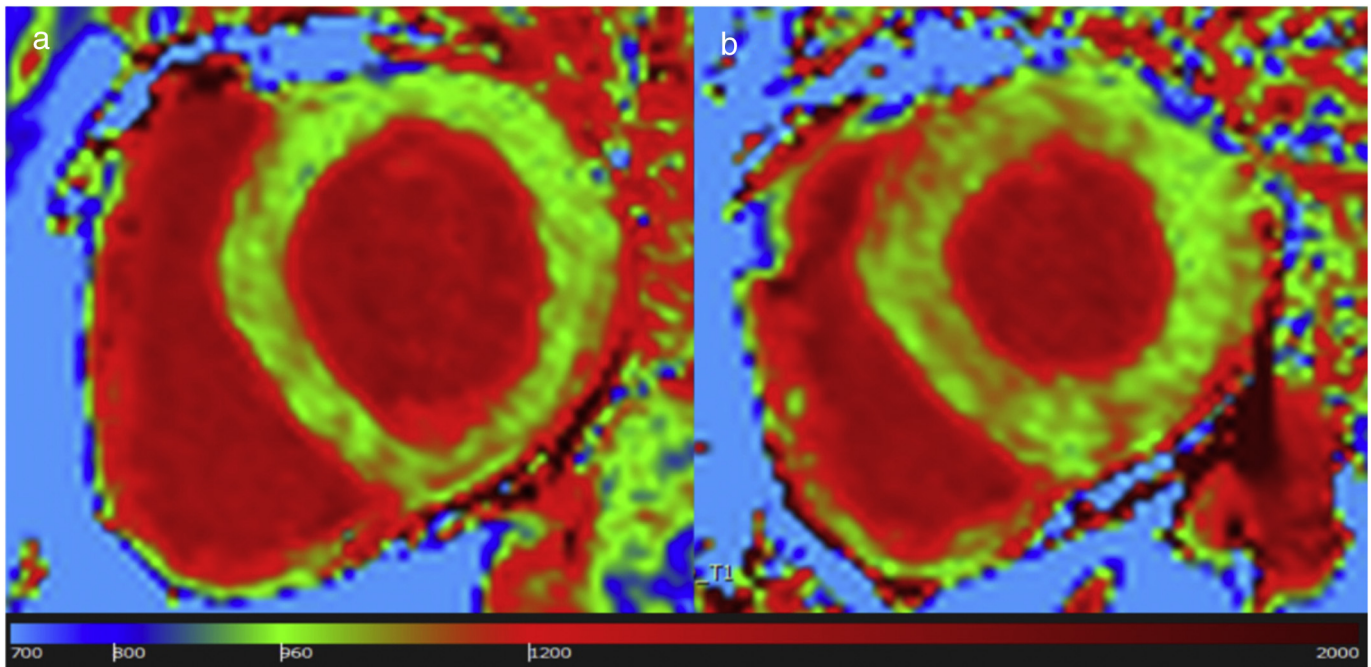
Fig. 2. A typical example of T1 maps before and after kidney transplantation. Panel a is an example of a basal MOLLI map acquired in a patient before kidney transplantation. Panel b is a basal MOLLI map acquired from the same patient after kidney transplantation. The colour scale at the bottom shows what T1 times the different colours represent. Normal myocardium appears green, with red representing elevated T1 times.

recipients of living kidney donation. These data cannot be extrapolated to ESKD with diabetes, previous cardiovascular events and coronary artery disease. While our study enables conclusions to be drawn about 'pure' myocardial disease in ESKD, it is likely that a typical group of dialysis patients will have a higher prevalence of both sub-endocardial and mid wall LGE and of valvular disease. Moreover, our control population was small and did not include patients with increased LVMI. It is now recommended that for small-magnitude biological changes, as is likely the case with diffuse myocardial fibrosis in ESKD, high precision is required for native T1 and T2 mapping and that control populations should be larger [21].

6. Conclusion

In conclusion ECV is elevated in kidney transplant recipients compared to controls, supporting the suggestion that high myocardial T1 times in ESKD are indicative of DIF. The contribution of myocardial edema toward the raised T1 times and ECV cannot be excluded since T2 times were also mildly elevated.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.007.

Declaration of Competing Interest

None.

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