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Native T1 and T2 provide distinctive signatures in hypertrophic cardiac conditions – Comparison of uremic, hypertensive and hypertrophic cardiomyopathy

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ABSTRACT

Aims: Profound left ventricular (LV) hypertrophy with diastolic dysfunction and heart failure is the cardinal manifestation of heart remodelling in chronic kidney disease (CKD). Previous studies related increased T1 mapping values in CKD with diffuse fibrosis. Native T1 is a non-specific readout that may also relate to increased intramyocardial fluid. We examined concomitant T1 and T2 mapping signatures and undertook comparisons with other hypertrophic conditions.

Methods: In this prospective multicentre study, consecutive CKD patients (n = 154) undergoing routine clinical cardiac magnetic resonance (CMR) imaging were compared with patients with hypertensive (HTN, n = 163) and hypertrophic cardiomyopathy (HCM, n = 158), and normotensive controls (n = 133).

Results: Native T1 was significantly higher in all patient groups, whereas native T2 in CKD only ($p < 0.001$ vs. all groups). Native T1 and T2 were interrelated in patient groups and the strength of association was condition-specific (CKD r = 0.558, HTN r = 0.324, both $p < 0.001$; HCM r = 0.157, p = 0.05). Native T1 and T2 were similarly correlated in all CKD stages (S3 r = 0.501, S4 0.586, S5 r = 0.424, $p < 0.001$ for all). Native T1 was the strongest myocardial discriminator between patients and controls (area under the curve, AUC HCM: 0.97; CKD: 0.97, HTN 0.98), native T2 between CKD vs HCM (AUC 0.90) and native T1 and T2 between CKD vs HTN (AUC: 0.83 and 0.80 respectively), $p < 0.001$ for all.

Conclusions: Our findings reveal different CMR signatures of common hypertrophic cardiac phenotypes. Native T1 was raised in all conditions, indicating the presence of pathologic hypertrophic remodelling. Markedly raised native T2 was CKD-specific, suggesting a prominent role of intramyocardial fluid.

1. Introduction

Cardiovascular disease is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1,2]. Phenotypically, it is characterized by profound eccentric left ventricular (LV) hypertrophy, diastolic dysfunction and heart failure (HF) [1,3]. Interstitial diffuse myocardial fibrosis is a recognised pathophysiological factor; post-mortem studies revealed 'diffuse non-coronary interstitial fibrosis' in

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most patients on haemodialysis (HD) and those with less severe CKD, but not in non-hypertensive, non-diabetic controls [4]. More recent studies with T1 mapping, a novel imaging marker of abnormal myocardium with cardiovascular magnetic resonance (CMR), reported raised values, providing a non-invasive means of in-vivo recognition of pathologic remodelling in CKD [5,6]. Yet, T1 mapping is a sensitive measure of myocardial pathology, it is non-specific with regards to the underlying substrate; in addition to fibrosis, it can also relate to myocardial oedema or infiltration [7]. On the contrary, T2 mapping is a specific marker of increased myocardial water content [8]. Whereas studies focused on T1 mapping, the role of T2 mapping in hypertrophic conditions is generally less well understood. Since myocardial fluid overload has been demonstrated to impact myocardial function [9], possibly inducing structural changes within the interstitium [10], we hypothesize that increased myocardial fluid overload may also play a relevant role in the pathogenesis of CKD-related myocardial changes. The aim of the present study was to examine the detectable tissue characteristics in different types of myocardial hypertrophy, by exploring the T1 and T2 mapping signatures in CKD-related cardiomyopathy, and by comparisons with other hypertrophic model diseases, including the genetically driven myocardial remodelling in hypertrophic cardiomyopathy (HCM) [11,12] and due to increase in wall stress in essential hypertension (HTN) [13].

2. Methods

This is a prospective multicentre study of consecutive CKD patients (n = 154) undergoing routine clinical assessment of cardiac function and structure, and presence of ischaemia by CMR (NCT03749551). CKD was defined by estimated glomerular filtration rate (eGFR) as assessed by the Modification of Diet in Renal Disease formula ≤60 ml/min/1.73 m^2 [14,15]. The participating centres included University Hospital Frankfurt, Kerckhoff Hospital and Bad Nauheim, Germany. All procedures were carried out in accordance with the Declaration of Helsinki (2013) and clinical management guidelines, including the use of GBCA [16,17] (macrocyclic agents in a minimal diagnostic dose, post-CMR haemodialysis (HD) within 24 h). Three control groups were included. Firstly, a group of consecutive HCM patients (n = 158, defined by LV wall thickness ≥ 15 mm, associated with a non-dilated LV and in the absence of increased LV wall stress or other cardiac or systemic disease that could result in a similar magnitude of hypertrophy [18]), consisting of subjects with an expressed phenotype, typically asymmetric septal hypertrophy, and a positive genotype, permitting unequivocal clinical diagnoses. Sixty HCM patients (38%) had evidence of LV outflow obstruction. Secondly, a further group of patients with established essential hypertension (HTN, n = 163; systolic blood pressure (BP) >140 mmHg; diastolic BP >95 mmHg) [13] and compensated concentric left ventricular hypertrophy (LVH), defined as >12 mm in the basal septal and infero-lateral segments, without evidence of dilated LV cavity (end-diastolic diameter ≤ 5.4 cm for women, ≤5.9 cm for men) on transthoracic echocardiography [19]. Lastly, healthy controls consisted of normotensive age-gender matched healthy subjects (n = 133), not taking any regular medications, with normal routine blood tests, urine samples and CMR findings including normal LV mass indices. Subjects with hypertrophic phenocopies (determined phenotypically by imaging, endomyocardial biopsy or genetic testing, including myocardial amyloidosis, iron accumulation, lipid-storage disease, arrhythmogenic right ventricular cardiomyopathy, non-compaction cardiomyopathy) or significant (≥grade III) valvular heart disease, were excluded from this study. HCM patients with previous septal ablation or myectomy were also excluded. Exclusion criteria for all subjects were the remaining contraindications to CMR (MR-unsafe implantable devices, cerebral aneurysm clips, cochlear implants). The protocol was reviewed and approved by institutional ethics committees. Written informed consent was obtained from all participants.

2.1. CMR image acquisition and analysis

All subjects underwent a routine clinical scan protocol using a 3-Tesla clinical scanner (Skyra, Siemens Healthineers, Erlangen, Germany). After standardized patient specific planning, myocardial T1 and T2 mapping were performed in a single midventricular short axis (SAX) slice [6]. Volumetric cavity assessment was performed by whole-heart coverage of SAX slices followed by myocardial perfusion imaging (Regadenosone 400 μg/5 ml, Gadovist® 0.1 mmol/kg) and late gadolinium enhancement (LGE). T1 mapping was performed using modified Look-Locker Imaging (FFM-MOLLI) [20,21]. For T2 mapping, a FLASH sequence was employed [22]. All sequence types and parameters have been validated and reported previously [22-24].

Assessment of cardiac volumes, function and mass, interpretation of myocardial perfusion and LGE images was performed following standardized recommendations. LGE was characterized based on the presence and predominant pattern as ischaemic or non-ischaemic. Quantitative tissue characterization was performed by the core-lab, blinded to the underlying subject group allocation. Rates of T1 and T2 relaxation were measured in the septal myocardium of midventricular SAX using the ConSept approach [24,25]. Areas of LGE were excluded from region of interest to avoid false inflation of values due to inadvertent inclusion of replacement scar. Inter- and intraobserver reproducibility and agreement of post-processing approaches have been reported previously [24,25]. All patients underwent venous blood sampling immediately prior to CMR study. Plasma samples were frozen at −80 °C and analysed subsequently using standardized commercially available test kits. Analysis of NT-proBNP, as an indirect marker of fluid status, was performed using standardized clinical platforms (Elecsys 2010®, Roche, Basel, Switzerland).

2.2. Statistical analysis

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA, version 24.0). Departures from normality were examined using Shapiro-Wilk's test. Data are presented as counts (percentages), mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Comparisons of means were performed using independent samples *t*-test or one-way ANOVA and Mann-Whitney test, as appropriate. Chi^2 and Fischer's exact tests when appropriate were employed for proportions. The associations were analysed by linear regressions. Binary logistic regression and receiver operator curve (ROC) analyses were used to test the ability of CMR measures to discriminate between the groups; the purpose of showing area under the curves (AUCs) should be read in the context of a study more oriented to explanation and aetiology rather than prediction. Collinearity diagnostics was used to examine the variance inflation factor analysis. All tests were two-tailed and p-value of <0.05 was considered statistically significant.

3. Results

Characteristics of the study population are summarized in Table 1. CKD patients had more CV-risk factors, higher systolic blood pressure and lower eGFR ($p < 0.001$). Significant dyspnoea (NYHA ≥II) was observed in approximately half of all patients, which was similarly proportioned between the hypertrophic groups. CMR measurements are provided in Table 1. All patient groups had increased LV wall thickness, LV mass and left atrial size. CKD patients had increased LV volumes and generally preserved global systolic function ($p < 0.01$). LGE was more frequently identified in HCM than in CKD or HTN patients (65% vs. 23%, vs. 21%, $p < 0.001$), in HCM prevalently of the non-ischaemic type. Compared to controls, native T1 was significantly raised in all

Table 1
Subjects' characteristics. CMR measurements of function and structure and tissue characterization. BP – blood pressure, CAD – coronary artery disease, AF – atrial fibrillation, GLS-global longitudinal strain, GRS -global radial strain, GCS-global circumferential strain, eGFR – estimated glomerular filtration rate, LV – left ventricular, LVWT- LV wall thickness, LGE – late gadolinium enhancement.

Variables	Controls (n = 133)	CKD (n = 154)	HCM (n = 158)	HTN (n = 163)	Sig (p-value)
Age (years)	53 ± 18	53 ± 13	55 ± 16	54 ± 16	0.642
Sex (females, n,%)	57(43)	62(40)	66(42)	72(44)	0.148
BMI (kg/m^2)	24 ± 7	28 ± 9	27 ± 8	28 ± 2	0.119
Hypertension (n,%)	0(0)	150(98)§	76(48)	163(100)	<**0.001**
Dyslipidemia (n,%)	0(0)	99(68)§	57(38)	66(41)	<**0.001**
Diabetes Mellitus (n,%)	0(0)	76(49)§	10 (6)	41(25)	<**0.001**
Type II (n,%)	0(0)	70(45)	8(5)	37(23)	<**0.001**
Smokers (n,%)	25(19)	68 (44)§	36(23)	55(34)	<**0.001**
Known CAD (n,%)	0(0)	45(29)	3(2)	52(32)	<**0.001**
Known AF (n,%)	0(0)	38(25)	18(11)	14(9)	<**0.001**
Heart rate (bpm)	66 ± 11	68 ± 12	68 ± 12	70 ± 21	0.147
Systolic BP (mmHg)	118 ± 9	140 ± 22§	129 ± 17	139 ± 17	<**0.001**
eGFR (ml/min/1.78 m^2)	90(67–110)	29(6–57)	76(57–109)	84(61–112)	NA
Stage 1 (>90 ml/min/1.78 m^2) n,%	89(67)		64 (41)	76 (47)	
Stage 2 (89–60 ml/min/1.78 m^2) n,%	44(33)		94(59)	87(53)	
Stage 3 (59–30 ml/min/1.78 m^2) n,%		54 (35)			
Stage 4 (29–15 ml/min/1.78 m^2) n,%		62 (40)			
Stage 5 (<14 ml/min/1.78 m^2) n,%		40 (25)			
Dialysis dependent (n,%)	/	38(24)	/		/
Haematocrit (%)	43.8 ± 4.9	40.2 ± 8.5	44.8 ± 5.5	40.8 ± 8.5	<**0.001**
NT-proBNP (ng/l)	39(12–69)	1553(1289–3815)	241(117–594)	102(81–139)	<**0.001**
NYHA ≥II (n,%)	0(0)	89 (58)	88(56)	91(56)	0.666
LV-EDVi (ml/m^2)	79 ± 15	99 ± 29*,§	74 ± 18	78 ± 15	<**0.001**
LV-ESVi (ml/m^2)	33 ± 8	47 ± 30*,§	29 ± 15	31 ± 9	<**0.001**
LV-EF (%)	59 ± 5	54 ± 15*,§	63 ± 12	61 ± 7	<**0.001**
RV-EF (%)	56 ± 6	56 ± 13	63 ± 13*	59 ± 8	<**0.001**
LA area, cm^2	17 ± 3	31 ± 3*,§	29 ± 4*	23 ± 5	<**0.001**
LVWT (mm)	8 ± 1	14 ± 7*,§	17 ± 6	12 ± 5	<**0.001**
LV mass (index) (g/m^2)	55 ± 14	89 ± 26*	94 ± 30*	78 ± 15	<**0.001**
LGE presence (n,%)	/	11 (7)§	31 (65)	34(21)	<**0.001**
Ischemic type (n,%)	/	7 (4)	3 (2)	20(12)	<**0.001**
Non-ischemic type (n,%)	/	4(2)§	90(56)	14(9)	<**0.001**
Native T1 (ms)	1062 ± 39	1161 ± 55*,§	1154 ± 56*	1102 ± 42	<**0.001**
Native T2 (ms)	35.8 ± 2.3	41.8 ± 5.2*,§	33.7 ± 5.8*	37.4 ± 2.5	<**0.001**

Bold indicates P value < 0.05.
* p < 0.05 vs. controls.
§ p < 0.05 vs. HCM.

patients' groups (p < 0.01, Fig. 1A). Native T2 was significantly increased in CKD and HTN but not HCM patients (p < 0.001, Fig. 1B); analysis of CKD substages revealed step-wise rise in both native T1 and T2 values with severity of CKD (Fig. 1C and D).

3.1. Analysis of relationships

Analysis of group-based bivariate correlations (age, gender, CMR measures) revealed no significant associations in controls. In both CKD and HCM, native T1 was positively associated with LV mass (r = 0.308 and r = 0.38, p < 0.001). Significant correlations with native T2 were restricted to CKD group and included positive relationships with LV-EDV, LV mass and LVWT (r = 0.231, 0.366 and 0.21 p < 0.01, respectively). Native T1 and T2 were interrelated in patient groups; the strength of association was markedly condition-specific (CKD r = 0.558, p < 0.001, HTN: r = 0.324, p < 0.001; HCM r = 0.157, p = 0.050), whereas there was no native T1-T2 relationship in controls (r = 0.038, p = 0.662) (Fig. 2C). Native T1 and T2 were similarly correlated in CKD stages (S3 r = 0.501, S4 0.586, S5 r = 0.424, p < 0.001 for all). There was a significant association between native T1 and NT-proBNP in CKD and HCM (r = 0.37 and r = 0.29, p < 0.001), whereas native T2 and NTproBNP were associated in CKD only (r = 0.369, p < 0.001).

Results of binary logistic regression and ROC analyses for discrimination between groups are presented in Table 2. Compared to normal myocardium of healthy controls, native T1 was the strongest discriminator of pathological myocardium of separate patient groups (Supplementary Fig. 1A, D and E). On the contrary, native T2 was the only discriminator between pathological myocardium of the CKD against HTN or HCM patient groups (Supplementary Fig. 1B and C). The strength of discrimination was similar when compared with CKD subgroup in stage 5.

4. Discussion

Our findings reveal differential phenotypical pathophysiological signatures of hypertrophic cardiac conditions, which are commonly encountered in clinical practice. Firstly, native T1 was the strongest discriminator between myocardium of patients and healthy controls, reiterating its sensitivity for detection of pathological myocardium. Secondly, significantly raised native T2 was found in CKD (and to a lesser extent in HTN), but not in HCM. Together with a strong interrelationship between native T1 and T2 in CKD (and less so in HTN), this finding suggests a prominent role of intramyocardial fluid in addition to diffuse fibrosis, in driving the change in native T1 in the conditions with primarily LV volume overload. On the contrary, weak relationship between native T1 and T2 in HCM suggests that the predominant source of signal in native T1 is mediated through diffuse myocardial fibrosis. Our findings lend support to the potential of quantitative tissue characterization in providing non-invasive readouts of the distinctive underlying pathophysiology. Future research is required to examine whether detecting distinctive hypertrophic phenotypes could support differential treatment.

In this study we demonstrate the different tissue characteristics in pathophysiological different types of myocardial hypertrophy. These differential phenotypic signatures may be helpful, for example in

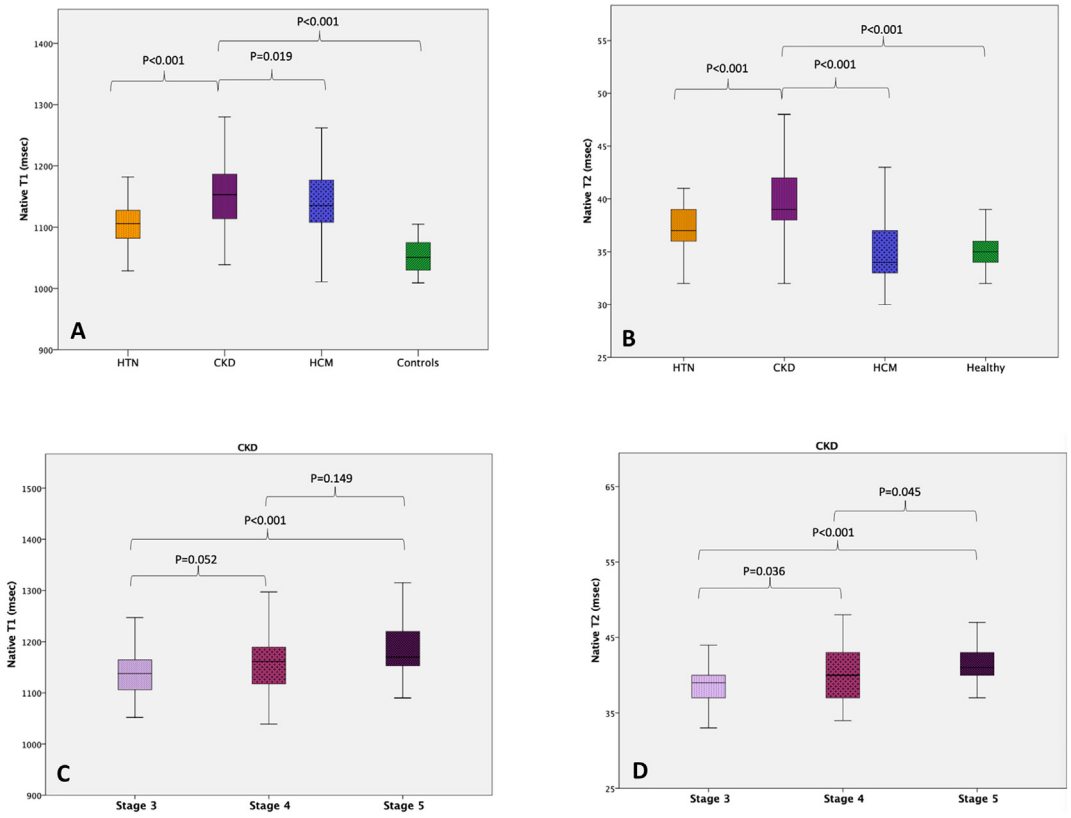

Fig. 1. Group specific mean values of native T1 and T2 in the study groups as well as according to CKD stages. Native T1 was significantly raised in all patients' groups (A), whereas native T2 was significantly higher in CKD only (B). Step-wise increase in both native T1 (C) and T2 (D) was observed with progressively decline of kidney function.

moderating the pretest-likelihood of subsequent diagnostic testing. Genetic testing for HCM is rarely performed as a first line test in patients with significant LVH; a signature of high native T1 with low T2 may point towards HCM. A further impetus for specific insight into pathophysiological differentiation of remodelling in hypertrophic conditions is due to their contribution to HF (especially with preserved ejection fraction, HFpEF) with an ongoing paucity of therapeutic options [26,27]. The main criticism of the many negative clinical trials in HFpEF was centred on the patient selection with poorly characterized myocardial abnormalities [28]. Tissue mapping imaging may provide a unique opportunity to discern the underlying myocardial substrates no-invasively. Myocardial fibrosis is a well-recognised histopathological substrate of failing heart, irrespective of underlying pathophysiology [29]. Several studies reported significantly elevated T1 mapping indices in HCM, in expressed phenotypes as well as in phenotypically subexpressed gene-carriers [11,19,31]. A marked difference in native T1 between HCM and HTN has also been reported, pointing out underlying differences between the pathologic hypertrophy due to genetically driven pro-fibrotic myocardial remodelling in the former condition [17]. Several studies further reported raised T1 mapping values in CKD patients [30,32,33]. We expand on these previous observations in several ways. Firstly, we included CKD patients across all disease stages, including those with eGFR<30, and performed LGE analysis in all of them, which was omitted in the above studies due to the limited use of GBCA in severe CKD in light of NSF [16]. Recent regulatory statements cleared the macrocyclic agents – used in the present study - in the lowest permissible doses for diagnostic use, thus providing a safe framework across all CKD stages. Meanwhile, several CMR-based indications, primarily assessment of myocardial ischaemia and heart failure, by myocardial perfusion and LGE imaging, respectively, were endorsed in cardiological practice guidelines [18,27,34]. These indications are especially relevant to CKD population, a group recognised to be at very high risk of CVD due to the clustering and amplification of atherosclerotic risk factors [35]. Technically, visualization by LGE (in addition to native T1) remains as important, as it allows separation between dense regional replacement scar and diffuse fibrosis [7], by LGE and native T1 respectively. Moreover, inclusion of LGE into T1 mapping ROIs falsely inflate the native T1 measurements, and visualization helps to avoid its inclusion.

Myocardial oedema represents an important myocardial substrate in CKD. A recent report in a small number of HD-dependent patients revealed dynamic changes in T1 and T2 mapping values with volume-removal [36]. We demonstrate that this is CKD-specific, as not found in HCM (and less so in HTN) and is conditioned by CKD-presence and severity. This finding provides novel insights into the pathophysiology of uremic cardiomyopathy and has thus-far it has not been shown comparatively for hypertrophic conditions. This indicates that the markedly different pathophysiological background cannot be distinguished solely based on abnormal T1 mapping values. Comparison of CKD-stages significantly expand this view, by showing that increase in native T2 is not limited to stage-5, but readily detectable in earlier stages of CKD. A further important finding is that native T1 and native T2 are significantly interrelated with differentially strong associations between hypertrophic conditions. This suggests that the two imaging measures are partially driven by a similar signal, the intracardial fluid content, with the association beibg markedly condition-specific; whilst prominent in CKD $r = 0.558$, $p < 0.001$, and less so in HTN: $r = 0.324$, $p < 0.001$, the association in HCM is much weaker $r = 0.157$, $p = 0.050$. Water-sensitivity of T1 mapping sequences is well-recognised for MOLLI sequences and viewed critically in the past, primarily as an indirect sign of poor T1 accuracy, a term often used in MR physics to relate to the gold standard T1 weighted measurements, acquired in phantoms [37,38]. The findings of the present study reiterate the contrary view [7], that in vivo myocardial T1 mapping measurements benefit from a sequence that in part depends on water signal, allowing complementary information on diffuse fibrosis and oedema. Increased total body fluid

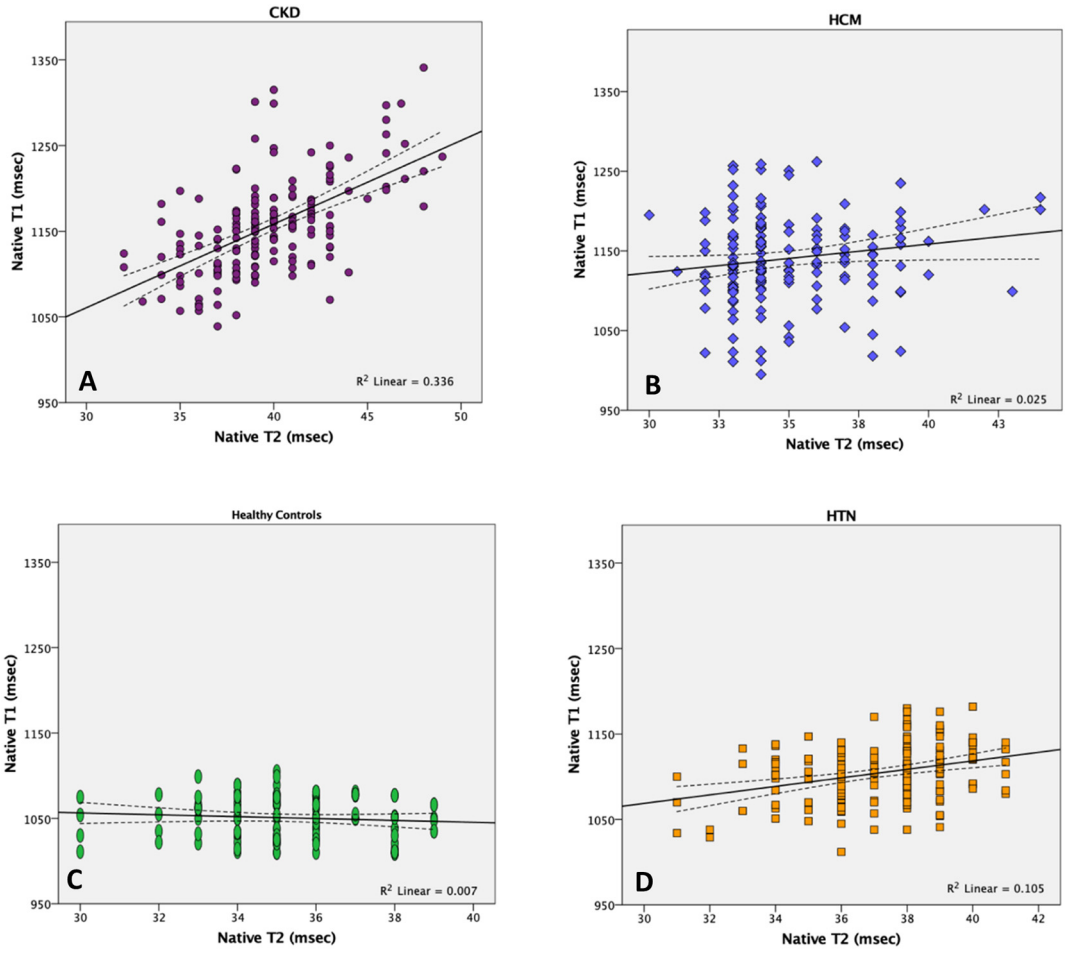

Fig. 2. Association between native T1 and T2 is condition-specific. There is a significant correlation between native T1 and T2 in all patients' groups (A, CKD; B HCM; C, HTN), most pronounced in CKD (A), whereas relatively weak in HCM (C). In healthy controls (D), no significant correlation was observed.

in CKD may be an obvious source in chronic uraemia in HD-dependent patients (i.e. stage 5). Furthermore, increased native T2 in early stages may reflect increased vascular permeability due to microvascular disease and endothelial dysfunction [39,40]. Whilst increase in native T2 was most pronounced in the CKD group, it was also detectable in HTN. In concert with our previous observation of raised native T2 in

Table 2
Analysis of relationships. Results of ROC analyses and multivariate binary logistic regression to test the ability of CMR measures to discriminate between the groups controls and patients, as well as between patient groups. In multivariate analyses, all CMR measures (LV-EDV, LV-ESV, LVEF, LVWT, LVmass, LGE and native T1 and T2) were included in construction of the models, we only provide the outputs showing the significant predictive variables (up to two models). * denotes $p < 0.05$, **denotes $p < 0.01$.

Univariate	AUC (95%CI)	AUC (95%CI)	AUC (95%CI)	AUC (95%CI)	AUC (95%CI)	AUC (95%CI)
	Controls vs CKD	Controls vs HCM	Controls vs HTN	CKD vs HCM	CKD-HD vs HCM	CKD vs HTN
LV-EDV (10 ml/m^2)	0.61*(0.55–0.66)	0.39**(0.35–0.41)	0.63**(0.57–0.70)	0.69**(0.63–0.75)	0.74**(0.67–0.82)	0.71**(0.64–0.73)
LV-ESV (10 ml/m^2)	0.60(0.42–0.68)	0.32**(0.29–0.36)	0.70**(0.65–0.74)	0.68**(0.62–0.72)	0.69**(0.61–0.73)	0.65**(0.59–0.69)
LVEF (%)	0.37**(0.15–0.43)	0.65**(0.58–0.71)	0.36**(0.29–0.43)	0.30**(0.24–0.35)	0.33**(0.25–0.42)	0.36**(0.59–0.42)
LVWT (1 mm)	0.87**(0.82–0.90)	0.93**(0.89–0.96)	0.79**(0.71–0.84)	0.42**(0.32–0.44)	0.39**(0.35–0.41)	0.52 (0.45–0.59)
LV massi (10 g/m^2)	0.65**(0.58–0.71)	0.82**(0.77–0.87)	0.66**(0.59–0.72)	0.29**(0.25–0.34)	0.33**(0.25–0.41)	0.62*(0.55–0.68)
LGE presence	0.68*(0.63–0.74)	0.82**(0.77–0.87)	0.68**(0.61–0.74)	0.40**(0.33–0.46)	0.31**(0.23–0.40)	0.57(0.51–0.64)
Native T1 (10 ms)	0.97**(0.95–0.98)	0.97**(0.92–0.99)	0.98**(0.93–0.99)	0.57**(0.50–0.63)	0.64**(0.55–0.72)	0.83**(0.81–0.86)
Native T2 (ms)	0.91**(0.85–0.96)	0.43*(0.36–0.50)	0.88**(0.85–0.93)	0.90**(0.85–0.93)	0.91**(0.56–0.94)	0.80**(0.72–0.83)

Multivariate	Exp(B) (95%CI)		Exp(B) (95%CI)		Exp(B) (95%CI)		Exp(B) (95%CI)		Exp(B) (95%CI)
Controls vs CKD		Controls vs HCM		Controls vs HTN		CKD vs HCM		CKD vs HTN	
Model 1									
Native T1 (10 ms)	1.1(1.06–1.11)	Native T1 (10 ms)	1.06(1.04–1.07)	Native T1 (10 ms)	1.1(1.08–1.16)	Native T2 (1 ms)	1.7(1.51–1.9)	Native T1 (10 ms)	1.04(1.03–1.06)
Model 2									
Native T1 (10 ms)	1.1(1.06–1.12)	Native T1 (10 ms)	1.05(1.03–1.08)	Native T1 (10 ms)	1.1(1.07–1.16)	Native T2 (1 ms)	1.7(1.5–2.0)	Native T1 (10 ms)	1.03(1.02–1.05)
Native T2 (1 ms)	1.8 (1.4–2.4)	LGE (present)	5.4(2.4–18.6)	Native T2 (1 ms)	1.7(1.23–3.32)	LGE (present)	0.14(0.1–0.3)	Native T2 (1 ms)	1.3(1.10–1.4)

patients with severe aortic stenosis [8], it suggests a commonality in pressure-overload hypertrophic remodelling. Further studies are required to investigate whether tissue mapping with native T1 and T2 can provide a signature of progressive cardiac involvement and myocardial injury [41] in patients with CKD, as well as potentially modifiable treatment targets.

5. Limitations

A few limitations may apply. All our patients were recruited through a real-life clinical service. Because we are committed to minimize the overall scanning time (i.e. patient's table-time) for patient comfort and image quality, we focused on the measurements that are relevant for patients' management and also feasible in real clinical CMR service, which may have us to sacrifice many acquisitions that have not shown to add clinical value [6]. Selected patients' in HTN and HCM groups with expressed phenotypes provide a representative and unambiguous model of disease. Although comparisons with tissue samples have not been made in the present study, we reported associations with diffuse fibrosis for both sequences previously [8]. Histological assessment of myocardial oedema is difficult owing to the dehydration technique of tissue fixation with formaldehyde [42].

6. Conclusions

Our findings reveal differential phenotypical pathophysiological signatures of common hypertrophic cardiac conditions. Native T1 was the strongest discriminator between myocardium of patients and healthy controls, reiterating its sensitivity for detection of pathological myocardium. Significantly raised native T2 was found in CKD (and to a lesser extent in HTN), but not in HCM. Together with a strong interrelationship between native T1 and T2 in CKD (and less so in HTN), this finding suggests a prominent role of intramyocardial fluid in driving the change in native T1 in the conditions with primarily LV pressure, but also volume overload. On the contrary, weak relationship between native T1 and T2 in HCM suggests that the predominant source of signal in native T1 is mediated through diffuse myocardial fibrosis.

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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