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The Prognostic Role of T1 Mapping Sequences: Can T1 Mapping Parameters Have a Role in Risk Stratification?

Eui-Young Choi[1], Chul-Hwan Park[2], Tae Hoon Kim[2]

[1]Division of Cardiology, Heart Center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Cardiovascular disease risk stratification and prognostication are very important for treatment planning. In addition, for a growing number of patients with overt symptomatic heart failure or asymptomatic but have structural heart disease, accurate risk stratification is essential. Conventional clinical cardiovascular risk factors, several biomarkers and echo-Doppler indexes are generally used to satisfy this need. However, non-invasive approaches to direct structural and tissue characterization of the myocardium have not produced satisfactory results. The recent development of the late gadolinium enhancement (LGE) imaging allows fibrosis or myocardial inflammation to be visualized. A growing body of evidence for LGE-based prognostication has been reported. However, not all patients with heart failure or at risk for it have been assessed with LGE. Moreover, the degree of diffuse fibrosis or inflammation cannot be easily quantified with LGE techniques. Recently, introduced T1 mapping-based quantification can provide the volume of extracellular space suggestive of the degree of diffuse tissue fibrosis or inflammation. Even without gadolinium contrast, native T1 values can provide quantitative information on myocardial tissue status. Here, we review current evidence for T1 mapping-based risk stratification and prognostication for various cardiac diseases that can lead to heart failure or lethal arrhythmic events.

Key words Cardiac magnetic resonance imaging · T1 mapping · Prognosis.

INTRODUCTION

Several studies have explored tissue validation of T1 mapping [1-3]. Currently, T1 relaxation time and calculated extracellular volume fraction (ECV) are accepted as reliable markers of the degree of diffuse interstitial fibrosis [4]. T1 mapping data are used in various clinical studies as early detectors of disease or imaging-based biomarkers guiding specific therapies. However, native T1, post-T1 and ECV values vary by equipment manufacturer and according to the magnetic field strength and mapping sequence used [5,6] So, compared to left ventricular (LV) mass, volume and late gadolinium enhancement (LGE) imaging data, multi-vender-based multicenter T1 mapping studies have

several limitations. Thus, standardization of T1 mapping is important. In this review, we focus on the prognostic role of T1 mapping for various clinical disease entities.

BASIC CONCEPTS AND TECHNICAL ASPECTS

The general principle of T1 mapping is to acquire multiple images with different T1 weights and to fit the signal intensities of the images to the equation for T1 relaxation. T1-weighted images are acquired at different times after inversion of the magnetization or at different times after a saturation pulse. Pixel intensities in the finally reconstructed T1 images correspond to the fitted T1 values [7]. T1 mapping has an advantage in that it is a pixel-wise map and is objective; one disadvantage is that partial volume effects can lead to artifacts, but motion correction and

co-registration techniques are helping to minimize these effects. T1 mapping provides an intrinsic signal from both the myocytes and the interstitial tissue. Native T1 is prolonged with fibrosis, edema and amyloid and is reduced in lipid accumulation (Anderson-Fabry disease), cardiac siderosis, and hemorrhage in acute infarction (Fig. 1) [7]. However, when using ECV and native T1, not only fibrosis but also combined myocardial inflammation should be considered [8]. Currently, most popular T1 pulse sequences are modified look-locker inversion recovery (MOLLI), shortened MOLLI (shMOLLI) and saturation recovery single single-shot acquisition (SASHA) (Fig. 2) [7]. As previously mentioned, standardization of results across different instruments and sequences is important for interpretation of data across various studies and centers. Currently, work is underway to standardize T1 mapping using a specialized phantom [9]. This effort can improve the precision and accuracy of the T1 mapping technique and can be used in multi-center studies. Another approach is to standardize T1 values by calculating a Z score, which is a standard score. In one study, converting T1 values to Z scores significantly improved the agreement between SASHA and shMOLLI techniques, particularly for post-contrast T1 and ECV [10]. In addition, the current consensus statement recommends that each center derive their own normal values [11].

Usage of post-T1 requires correction by blood T1 to reduce time-dependent differences and effects of blood flow stasis [12]. ECV is calculated using gadolinium distribution mechanics after full saturation and steady status. Blood extracellular space should be considered using blood hematocrit (Hct) concentration to estimate intracellular volume space. As such, 1-Hct can be used as a proxy for the extracellular volume status of blood. Change in $1/T1$ in blood and tissue is expressed as change in longitudinal relaxation ($\Delta R1$) for blood ($\Delta R1blood$) and $\Delta R1$ for tissue ($\Delta R1tissue$), then ECV can be calculated as $(1-Hct) \times \Delta R1tissue/\Delta R1blood$ [11]. To make it more convenient in practice, a synthetic ECV method has recently been introduced [13]. The main mechanism of this method is pixel T1-based calculation of ECV without Hct concentration. The R1 of blood was found to have a linear relationship with blood Hct. The regression equations were: Synthetic $HctMOLLI = [866.0 \cdot (1/T1blood)] - 0.1232$; Synthetic $HctShMOLLI = [727.1 \cdot (1/T1blood)] - 0.0675$ [13].
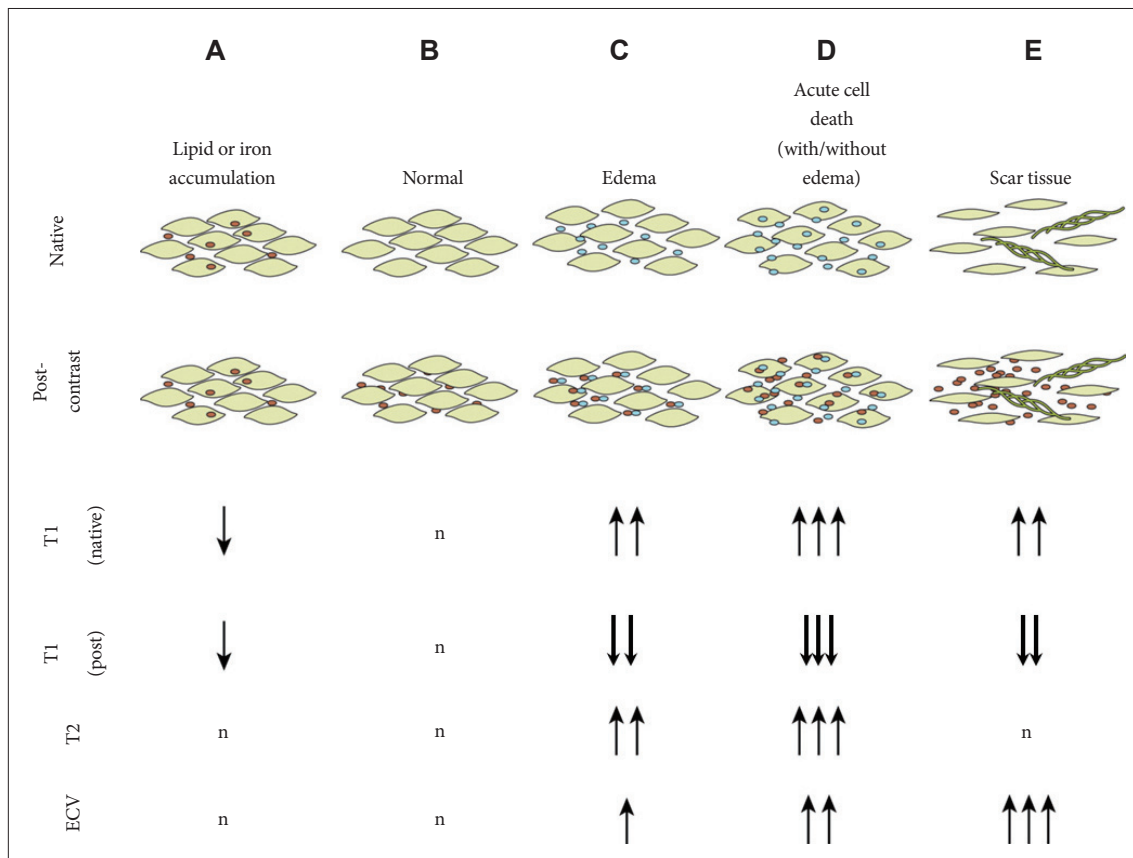

Fig. 1. A schematic representation of tissue changes in T1 measurements. (A) Lipid or iron accumulation (red dots) reduces native T1 values, irrespective of the T1 accuracy or T2 sensitivity of a given sequence. (B) Normal, minimal or no accumulation. (C and D) Accumulation of water (blue dots) leads to an increase in native T1, which is more pronounced in T2-sensitive sequences. (E) Similarly, scar tissue leads to increase in native T1. Conversely, accumulation of gadolinium contrast agents (GCAs) in extracellular space (green dots) leads to reduced post-contrast T1 (Adapted from Puntmann et al. Circ Res 2016;119:277-299. [4]). ECV: extracellular volume fraction.

RISK STRATIFICATION IN THE GENERAL POPULATION

Normal values of native T1, post-T1 and ECV

With MOLLI sequencing, which is the most popular T1 mapping sequence, normal myocardial native T1 ranges from 950 to 982 ms and thereby ECV is 25.0 to 26.9% in a 1.5 T magnetic field [5,6,14,15]. In a 3 T magnetic field, native T1 is somewhat prolonged to 1052 to 1159 ms [6,16]. Although reference values have been published in several studies, the current consensus statement recommends that each center should derive normal values for their specific center [11] Table 1 shows an overview of studies reporting normative ranges for T1-mapping indices.
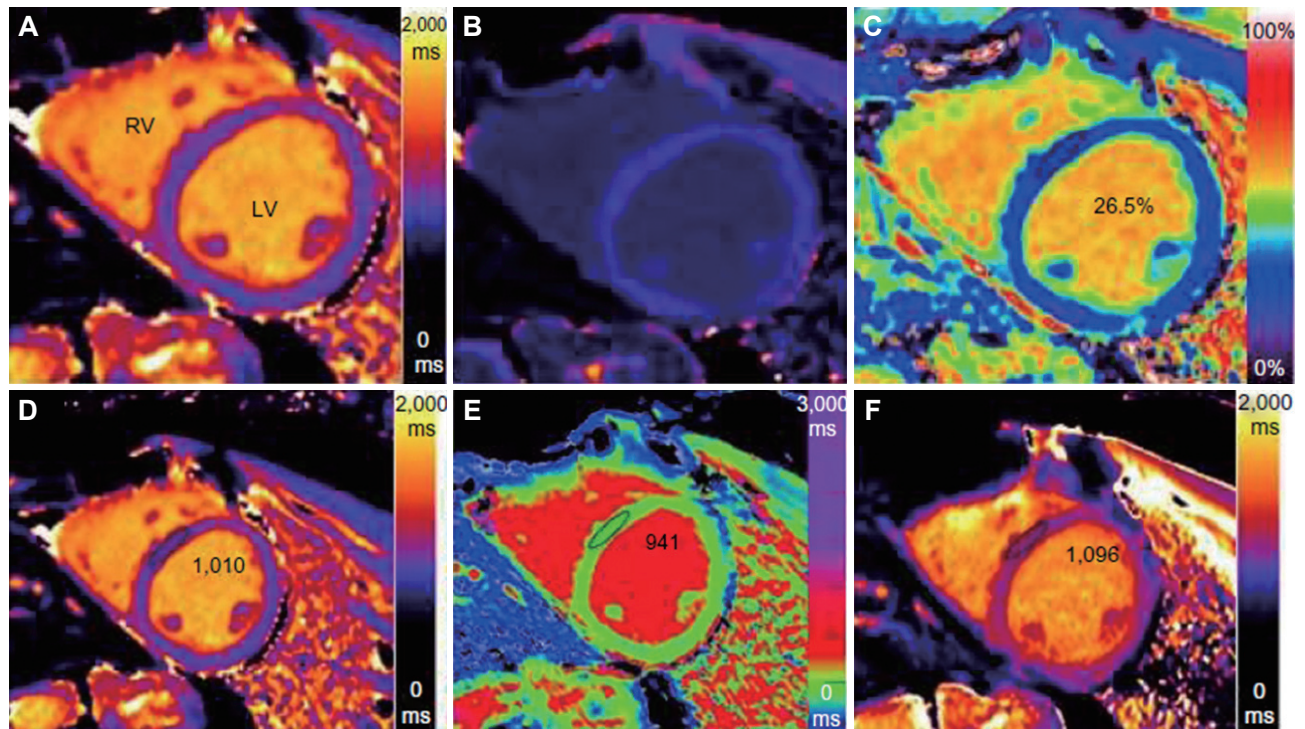

Fig. 2. Representative images of T1 mapping. (A) Native T1 MOLLI map (myocardial T1 1010 ms). (B) Post-contrast T1 MOLLI map (myocardial T1 615 ms). (C) ECV map (ECV=26.5%). (D) Native T1 map by MOLLI. (E) ShMOLLI and (F) SASHA (Adapted from Abdel-Gadir et al. Res Rep Clin Cardiol 2014;5:339. [69]). MOLLI: modified look-locker inversion recovery, ECV: extracellular volume fraction, ShMOLLI: shortened MOLLI, SASHA: saturation recovery single-shot acquisition, RV: right ventricular, LV: left ventricular.

Table 1. Overview of studies reporting normative ranges for T1 mapping indices

Study (n=participants)	Pulse sequence	GCAs (dose and type)	T1 index	1.5 T Myocardium	1.5 T Blood	3.0 T Myocardium	3.0 T Blood
Messroghli et al. [5] (n=43)	MOLLI 3(3)3(3)5 (FA 50°)	0.15 mmol/kg gadopentetate dimeglumine	Native T1, ms	982±46			
Piechnik et al. [14] (n=342)	MOLLI 5(1)1(1)1 (FA 35°)	0.15 mmol/kg gadopentetate dimeglumine	Native T1, ms	962±25	1535±76		
Dabir et al. [6] (n=102)	MOLLI 3(3)3(3)5 (FA 50°)	0.1−0.2 mmol/kg gadobutrol	Native T1, ms; ECV, %	950±21; 25±4	1551±115	1052±23; 26±4	1736±139
Liu et al. [15] (n=1231)	MOLLI 3(3)3(3)5 (FA 35°)	0.15 mmol/kg gadopentetate dimeglumine	Native T1, ms; ECV, %	977±42; 26.9±2.8			
von Knobelsdorff-Brenkenhoff et al. [16] (n=60)	MOLLI 3(3)3(3)5 (FA 35°)	0.2 mmol/kg gadobutrol	Native T1, ms			1159±73	

The number of participants per group and mean values (mean±SD) are reported for the type of sequence, T1 index, field strength and T1-mapping indices. Post-contrast T1 measurements were typically obtained >15 minutes after contrast administration (Adapted from Puntmann et al. Circ Res 2016;119:277-299. [4]). ECV: extracellular volume fraction, FA: flip angle, GCA: gadolinium contrast agents, MOLLI: modified look-locker inversion recovery.

Relation to sex, age and cardiovascular risk factors

There are a few general population-based studies in which the relationships between T1 value and conventional cardiac risk factors such as gender, age, diabetes, hypertension or dyslipidemia are reported [15,17]. The recent Multi-Ethnic Study of Atherosclerosis (MESA) showed post-T1 was correlated with age and risk factors [15]. In that study, women had a significantly greater partition coefficient, ECV and native T1 than men, as well as lower post-contrast T1 values (all p<0.05). In general, linear regression analyses demonstrated that a greater partition coefficient, native T1 values and ECV were associated with older age in men (multivariate regression coefficients=0.01; 5.9 ms; and 1.04% per 10 year change; all p<0.05). ECV was also significantly associated with age in women after multivariate adjustments [15]. In another MESA study, 25-minute post-gadolinium T1 time showed more statistically significant associations with cardiovascular disease risk scores (10/14 scores, 71%) compared to other cardiac magnetic resonance (CMR) imaging indices (e.g., native T1; 7/14 scores, 50%) and the partition coefficient (7/14, 50%) in men [17]. Risk scores, particularly the new 2013 American Heart Association/AtheroSclerotic Cardiovascular Disease risk score, did not correlate with any CMR fibrosis index [17]. Bulluck et al. [18] recently reported that myocardial native T1 values correlated with blood T1 and heart rate. However, even after adjustment for heart rate and blood T1, females had higher native T1 values, so gender-specific T1 values should be established at each center. Association with age is controversial but, in women, age correlated with native T1 values in that study. Due to short-term follow-up after acquisition of T1 mapping, there is currently no prognostic role for T1 mapping in the general population.
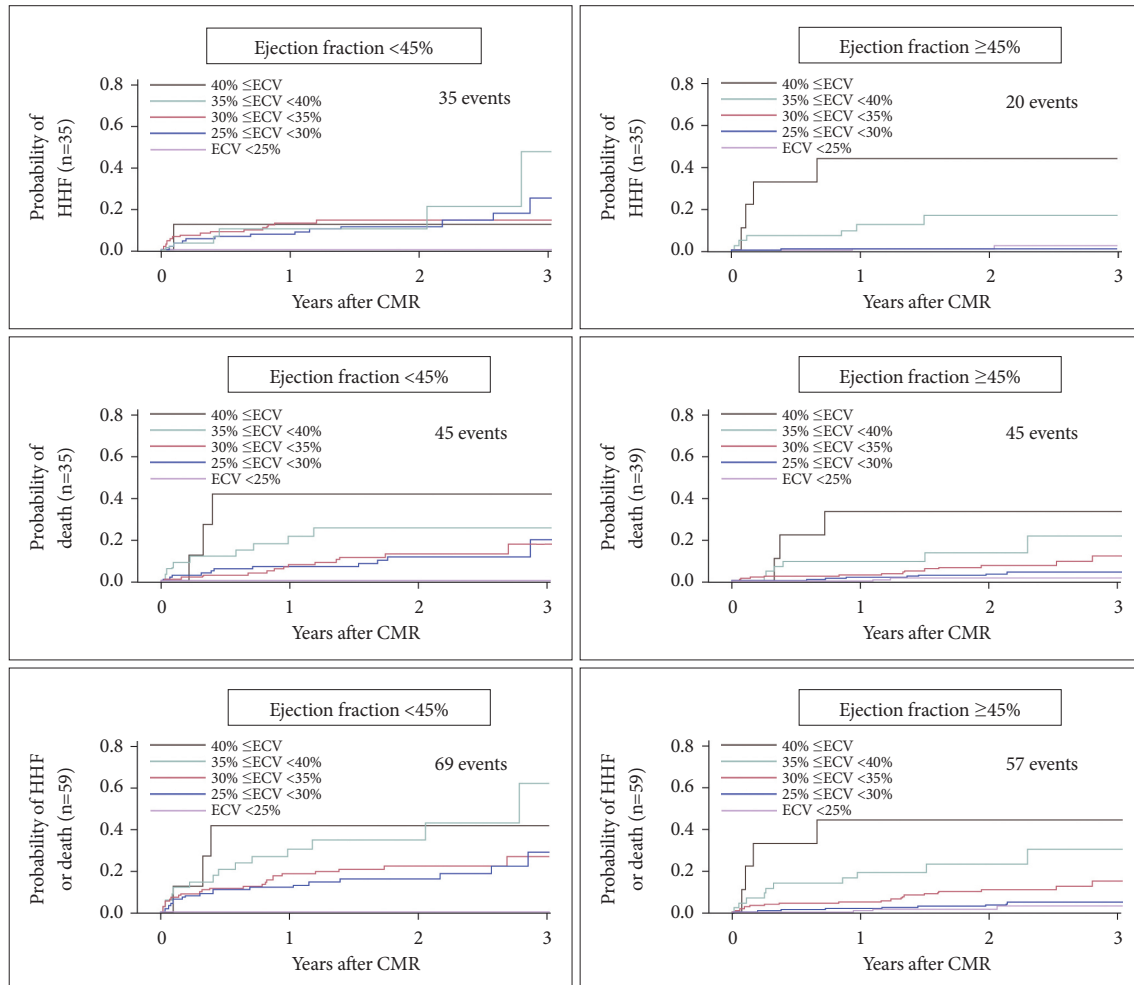

Fig. 3. ECV was significantly associated with adverse outcomes in univariate Cox regression models (p<0.05 for all), whether EF was reduced (<45%) or preserved (EF≥45%). Despite the decreased statistical power occurring with subgroup analysis, the basis for the statistically significant interactions between ECV and EF was evident qualitatively. Associations between ECV measures at the lower end of the ECV spectrum and events appeared strengthened when EF was reduced (Adapted from Schelbert et al. J Am Heart Assoc 2015;4:e002613. [20]). ECV: extracellular volume fraction, EF: ejection fraction, CMR: cardiac magnetic resonance, HHF: hospitalization for heart failure.

Heart failure with preserved ejection fraction (HFpEF) or reduced EF

An early study showed that CMR-based post-contrast T1 time [hazard ratio (HR), 0.99; 95% confidence interval (CI): 0.98−0.99; p=0.046], left atrial area (HR, 1.08; 95% CI: 1.03−1.13; p<0.01) and pulmonary vascular resistance (HR, 1.01; 95% CI: 1.00−1.01; p=0.03) were significantly associated with cardiac events in patients with heart failure (HF) with preserved ejection fraction (HFpEF) [19]. Patients with post-T1 times below the median (<388.3 ms) were at greater risk of cardiac events than the rest of the group (p<0.01). The extracellular matrix from LV biopsies as quantified using TissueFAXS technology correlated with T1 time. Thus, post-contrast T1 time was associated with prognosis in HFpEF, suggesting post-contrast T1 as a possible biomarker for HFpEF [19]. In another study, Schelbert et al. [20] reported myocardial fibrosis with ECV measures in 1172 consecutive patients without amyloidosis, hypertrophic or stress cardiomyopathy and assessed associations with outcomes using Cox regression (Fig. 3). Adjusting for age, gender, renal function, myocardial infarction size, ejection fraction (EF), hospitalization status, and HF stage, higher ECV was associated with hospitalization for HF (HR, 1.77; 95% CI: 1.32−2.36 for every 5% increase in ECV), death (HR, 1.87; 95% CI: 1.45−2.40) or both (HR, 1.85; 95% CI: 1.50−2.27). ECV improved classification of persons at risk and improved model discrimination for outcomes. This suggested that myocardial fibrosis measured by ECV was associated with hospitalization for HF, death, or both. Myocardial fibrosis may represent a principal phenotype of cardiac vulnerability that improves risk stratification. It has been suggested that myocardial fibrosis can be reversed, and cells and enzymes regulating collagen could be potential therapeutic targets [20]. However a more recent prospective study showed that MOLLI-ECV in HFpEF accurately reflected histological ECV and correlated with markers of disease severity; ECV≥28.9% (median) was associated with shorter event-free survival (log-rank, p=0.028), but not after adjustment for important clinical and invasive hemodynamic parameters (Table 2) [21]. The problems to be solved are that conventional echo-based diastolic functional parameters such as E/e' were not included in the multivariate analysis and many patients were excluded due to previous pacemaker/implantable cardioverter-defibrillator (ICD) implantation, estimated glomerular filtration rate (eGFR)<30 mL/min, claustrophobia, immobility and premature discontinuation of CMR scanning. Even in the excluded patients, echo-derived E/e' and blood N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement are possible. Thus, in clinical practice, prognostication in HFpEF patients needs further improvement for patient convenience.

Acute myocardial infarction and ischemic cardiomyopathy

In acute myocardial infarction patients, increased remote ECV, higher ECV in infarct and higher remote ECV were related to adverse remodeling, which suggests quantitative ECV can provide insight into the pathophysiology of LV remodeling and prognosis [22]. In ST elevation myocardial infarction patients, higher core native T1 was related to all-cause death or first hospitalization for HF post-discharge [23]. Although a sub-study of the Surgical Treatment for Ischemic Heart Failure trial failed to demonstrate the utility of pre-procedural viability assessment with dobutamine stress echocardiography or single-photon-emission computed tomography to guide revascularization in patients with ischemic cardiomyopathy [24,25], other studies support the identification of myocardial fibrosis as carrying important prognostic information [26]. Chen et al. [27] reported that native T1 was an independent predictor of ventricular arrhythmia in ischemic cardiomyopathy. The ongoing development of new techniques, particularly T1 mapping of the ECV, holds promise for the future as early studies suggested its complementary prognostic value and its avoiding contrast administration [28]. However, whether T1 mapping-guided revascularization imaging can improve disease prognosis has not been studied. A summary of T1 mapping-based prognostication studies in ischemic heart disease, cardiomyopathies and valvular heart diseases are de-

Table 2. Summary of prognostic value of T1 mapping in heart failure with preserved ejection fraction

Study	Parameter	End-point	Univariate	Multivariate	Co-variates	Exclusion (%)
Schelbert et al. [20] (n=1172)	ECV	Hospitalization for heart failure/death	p<0.001	p<0.01	Age, eGFR, myocardial infarction size, gender, heart failure stage	1765/597 (34)
Mascherbauer et al. [19] (n=100)	Post-T1	Hospitalization for heart failure or death from cardiovascular causes	p=0.01	p=0.046	Left atrial area Pulmonary vascular resistance NT-proBNP	Not mentioned
Duca et al. [21] (n=117)	ECV	Hospitalization for heart failure/death from cardiovascular causes	p=0.038	p=0.978	eGFR NT-proBNP Right ventricular end-diastolic volume, pulmonary vascular resistance	80/197 (41)

ECV: extracellular volume fraction, eGFR: estimated glomerular filtration rate, NT-proBNP: N-terminal pro-B-type natriuretic peptide

Table 3. Studies of T1 mapping-based prognostication in ischemic heart disease, cardiomyopathies and valvular heart diseases

Study	Disease	Parameter	End-point	Univariate	Multivariate	Co-variates	Exclusion Criteria
Carrick et al. [23] (n=288)	Acute ST elevation myocardial infarction	Native T1 (infarct core)	All cause death, first heart failure hospitalization	p<0.001	p<0.001	LV ejection fraction, infarct core T2, Myocardial hemorrhage	Contra-indications to contrast CMR (a pacemaker and eGFR ≤30 mL/min/1.73 m²)
McLellan et al. [31] (n=100)	HCM	Post-T1 (<440 ms)	NSVT or aborted sudden cardiac death	p=0.03 (for sudden cardiac death) p<0.001 (for NSVT)	p<0.01 (for NSVT)	Septal thickness	Ischemic heart disease, contra-indication tor CMR, eGFR <50 mL/min/1.73 m²
Barison et al. [42] (n=89)	DCM	ECV (>0.32)	Cardiovascular death, hospitalization for heart failure and appropriate defibrillator intervention	p=0.001	p<0.05 in each bivariate	Diabetes, duration of disease, NT-proBNP, heart rate, LV end-diastolic volume, LV ejection fraction, LV mass, LGE extent	Age <18 years, recent myocarditis, peripartum CM, severe primary valvular disease, arrhythmogenic RV CM, HCM, amyloidosis, eGFR<30 mL/min
Chen et al. [27] (n=130)	Non-ischemic DCM and ischemic CM (patients with ICD)	Native T1	ICD shock due to ventricular arrhythmia	p=0.021	p=0.001	QRS duration≥120 ms, LVEF≤35%, LGE amount, gray zone amount	ICD implantation for catecholaminergic VT, Brugada syndrome, long QT syndrome
Puntmann et al. [44] (n=637)	DCM	Native T1	All-cause mortality and heart failure admission	p<0.001	p<0.01	Extent of LGE, RV ejection fraction	Ischemic heart disease, infiltrative CM, contraindications to CMR
Banypersad et al. [49] (n=100)	Light chain amyloidosis	ECV (>0.45)	Mortality	p=0.004	p=0.01	E/é, LV ejection fraction, diastolic function grade, NT-proBNP	eGFR of <30 mL/min/1.73 m² (25% of patients)
Nadjiri et al. [56] (n=97)	Aortic stenosis undergoing TAVR	ECV (>30%) for conduction abnormalities	Arrhythmic events LBBB Complete AV-block Pacemaker implantation after TAVR, heart failure	p=0.036 (for conduction abnormalities) p=0.06 for heart failure	Not done	None	Patients with implanted pacemakers, unstable vital conditions, eGFR <30 mL/min, claustrophobia
Chin et al. [59] (n=203)	Aortic stenosis	iECV (>22.5 mL/m²)	All-cause mortality	p=0.009	p=0.01	Age≥70 years, sex, peak aortic jet velocity, LV mass index	Other valvular heart disease, significant comorbidities with limited life expectancy, contraindications to gadolinium-enhanced CMR, acquired or inherited non-ischemic cardiomyopathies

AV: atrio-ventricular, LBBB: left bundle branch block, CM: cardiomyopathy, LVEF: left ventricular ejection fraction, LV: left ventricular, NSVT: non-sustained ventricular tachycardia, HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, eGFR: estimated glomerular filtration rate, iECV: extracellular volume indexed by body surface area, TAVR: transcatheter aortic valve replacement, ICD: implantable cardioverter-defibrillator, RV: right ventricular, LGE: late gadolinium enhancement, ECV: extracellular volume fraction, CMR: cardiac magnetic resonance, NT-proBNP: N-terminal pro-B-type natriuretic peptide

scribed in Table 3.

Prognostic value for various non-ischemic cardiomyopathies

Hypertrophic cardiomyopathy (HCM)

Many previous studies have shown that the amount of LGE was related to future cardiovascular events, especially sudden death due to ventricular arrhythmic events [29,30]. The amount of LGE, especially more than 15% of the LV mass, can be an indication that ICD implantation might be able to prevent such an event [29]. However, whether a T1 map-based ECV provides additive prognostic value for the LGE amount is not known. Because about two thirds of hypertrophic cardiomyopathy (HCM) patients have LGE, the role of T1 mapping for prediction of prognosis may be focused on the remaining 30% non-LGE patients or remote myocardium in cases with LGE. In addition, whether the average ECV or T1 value of the whole myocardium is better than the LGE amount for prognostication is not known. Only one study showed that the average of whole LV post-contrast ventricular T1 relaxation time was significantly reduced in patients with non-sustained ventricular tachycardia and patients with aborted sudden cardiac death [31]. Although the value for prognostication is limited, native T1 data can be helpful for discriminating infiltrative cardiomyopathies, such as Fabry cardiomyopathy or hemochromatosis from HCM in patients with thickened myocardium [32-35]. Compared to other disease entities, the native T1 value is uniquely decreased in Fabry cardiomyopathy [33] and hemochromatosis [35]. Native T1 data were shown to be independent discriminators between HCM and hypertension or an athlete's heart, over and above ECV, LV wall thickness and indexed LV mass [36,37]. Native T1 was also useful for separating positive genotype but not negative phenotype subjects from controls [36]. In HCM, contrast-enhanced CMR with T1 mapping can non-invasively evaluate regional and diffuse patterns of myocardial fibrosis. These patterns of fibrosis occur independently of each other and exhibit distinct clinical associations. HCM patients with recognized genetic mutations have significantly more regional but less diffuse myocardial fibrosis compared to those without [38].

Dilated cardiomyopathy (DCM)

The role of T1 mapping is promising for non-ischemic dilated cardiomyopathy (DCM) because a typical mid-wall LGE pattern is not as prevalent as seen in HCM. Generally 44% (21 to 70%) of non-ischemic DCM patients have been shown to have LGE [39], so theoretically, ECV might be useful in DCM patients without LGE. In addition, in all DCM patients, remote non-LGE area ECV could provide significant additive information for risk stratification and prognostication. For instance, in one study, a post-T1 value >450 ms was an independent predictor of LV reverse remodeling at follow-up (LV systolic volume index Δ=24.6 mL/m^2 standard error 14.6 mL/m^2, p=0.0480) in patients despite the presence of LGE, even after adjusting for their Seattle Heart Failure Score [40]. While DCM patients with focal LGE demonstrated greater adverse LV remodeling than those without focal fibrosis, diffuse fibrosis independently predicted LV reverse remodeling in DCM patients despite the presence of focal fibrosis [40]. Our group also observed that post-contrast T1 is closely related to LV remodeling, diastolic function and neurohormonal activation, measured by NT-proBNP level [41]. Barison et al. [42] showed myocardial ECV was an independent prognostic predictor beyond all other conventional clinical, electrocardiographic and echocardiographic parameters. Also, Chen et al. [27] demonstrated that quantitative myocardial tissue assessment using T1 mapping was an independent predictor of ventricular arrhythmia in both ischemic and non-ischemic cardiomyopathies. Regarding cardiac resynchronization therapy response, focal scar burden detected by LGE-CMR was associated with a poor response to cardiac resynchronization therapy. A previous study showed that diffuse interstitial fibrosis assessment by T1 mapping, however, was not independently predictive of cardiac resynchronization therapy response [43]. Recently, an important prospective multicenter longitudinal study in 637 consecutive patients with DCM {mean age 50 years [interquartile range (IQR) 37−76 years]; 395 males [62%]} underwent CMR with T1 mapping and LGE at 1.5 T and 3.0 T field strengths. During a median follow-up period of 22 months (IQR 19−25 months), a total of 28 deaths (22 cardiac) and 68 composite HF events were observed. T1 mapping indices (native T1 and ECV), as well as the presence and extent of LGE, were predictive of all-cause mortality and HF endpoint (p<0.001 for all). Multivariate analyses showed native T1 was the sole independent predictor of all-cause and HF composite endpoints (HR, 1.1; 95% CI: 1.06−1.15; HR, 1.1; 95% CI: 1.05−1.1; p<0.001 for both), followed by the models including the extent of LGE and right ventricular EF, respectively (Fig. 4) [44].

Cardiac amyloidosis and sarcoidosis

Although native T1 and ECV data are helpful for early detection of cardiac involvement in systemic amyloidosis or suspected cardiac amyloidosis [45-47], the prognostic value of T1 mapping is rarely reported. T1 mapping can also provide information about disease severity and serve as a monitoring tool for chemotherapy in amyloid light-chain amyloidosis [48]. Banypersad et al. [49] showed ECV was independently predictive of mortality (HR, 4.41; 95% CI: 1.35−14.4) after adjusting for E/e', EF, diastolic dysfunction grade and NT-proBNP, but not with native T1 data in light chain amyloidosis. Greulich et al. [50] reported that sarcoid patients had a higher median native T1 (994 vs. 960 ms;

p<0.001), lower post-T1 (491 vs. 526 ms; p=0.001), expanded extracellular volume (28 vs. 25%; p=0.001), and higher T2 values (52 vs. 49 ms; p<0.001) compared with controls. Thus, patients with sarcoidosis demonstrated higher T1 values, extracellular volume, and T2 values compared to healthy controls, with the most significant differences seen in native T1 and T2 data.

Tachycardia-induced cardiomyopathy

A recent study showed that compared with controls, atrial tachycardia with low EF patients had reduced global LV corrected post-T1 times (442±53 vs. 529±61 ms; p<0.05), consistent with diffuse fibrosis. Tachycardia-mediated cardiomyopathy patients exhibited differences in LV structure and function including diffuse fibrosis long after arrhythmia cure, indicating

that recovery was incomplete [51].

Acute and chronic myocarditis

Limited data are available regarding the degree of normalization of CMR parameters during the course of the disease and the time window during which quantitative CMR should be most reasonably implemented for diagnostic work-up. Regarding this question, Luetkens et al. [52] reported that there was a significant and consistent decrease in all inflammatory CMR parameters over the course of the disease (p<0.01 for all parameters). Myocardial T1 and T2 relaxation times-indicative of myocardial edema-were the only single parameters showing significant differences between myocarditis patients and control subjects at the 5.5±1.3-week follow-up (native T1: 986.5±44.4 vs. 965.1±
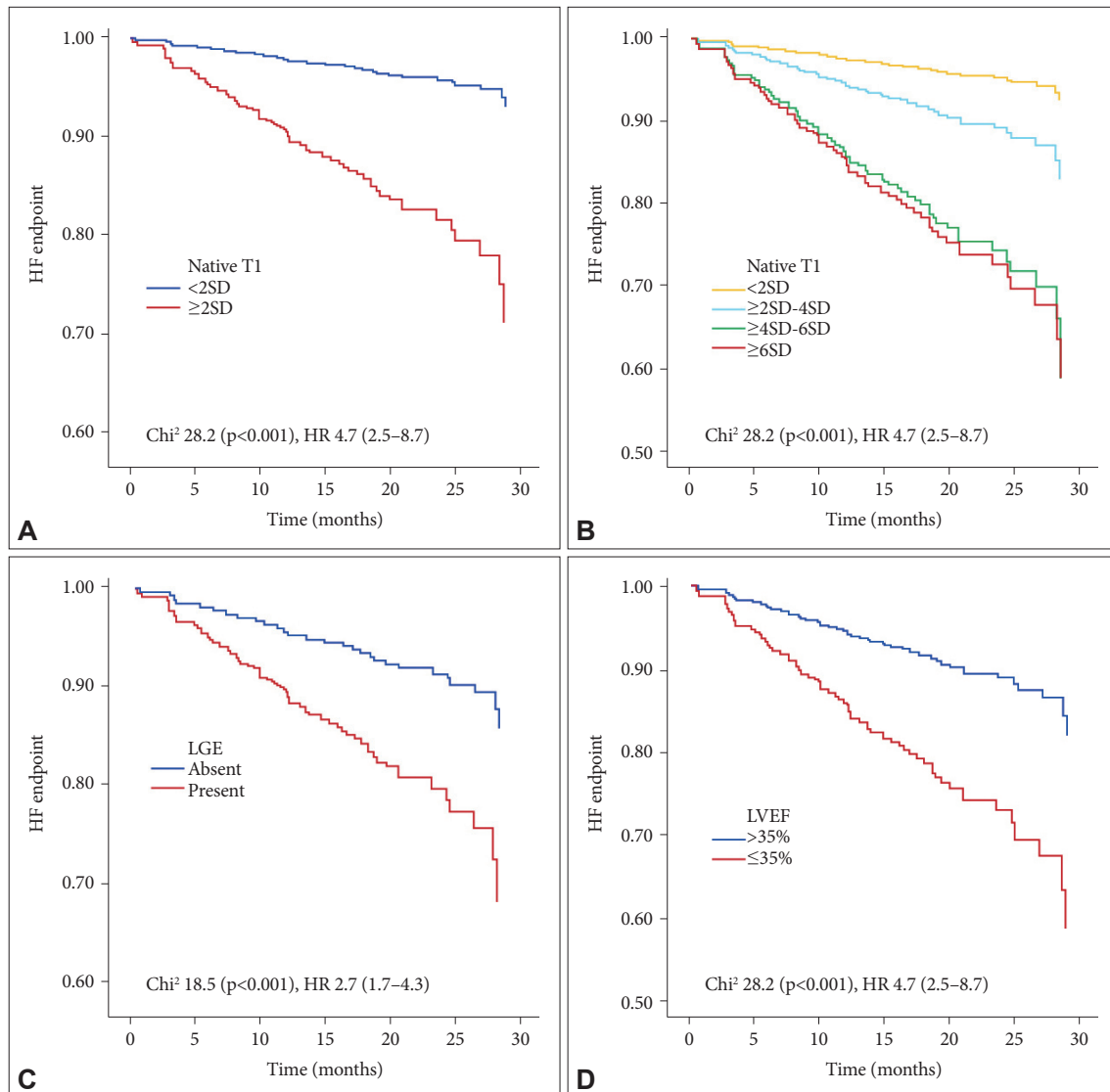

Fig. 4. (A) Native T1 [normal vs. abnormal myocardium, based on >2 standard deviations (SD) above the mean of the normal reference range]. (B) Native T1 ranked by 2n-times SD (ranks of SD: <2, ≥2 to 4, ≥4 to 6, ≥6), (C) LGE present vs. absent and (D) LVEF <35% (Adapted from Puntmann et al. JACC Cardiovasc Imaging 2016;9:40-50. [44]). HR: hazard ratio, LGE: late gadolinium enhancement, LVEF: left ventricular ejection fraction, HF: heart failure.

28.1 ms, p=0.022; T2: 55.5±3.2 vs. 52.6±2.6 ms, p=0.001). They concluded that myocardial native T1 and T2 relaxation times were the only active inflammation/edema parameters that could discriminate between myocarditis patients and control subjects even during the convalescent stage of the disease. von Knobels-dorff-Brenkenhoff et al. [53] reported that although both T2 and T1 mapping reliably detected acute myocarditis, only T2 mapping discriminated between acute and healed stages, underlining the incremental value of T2 mapping.

Prognostic value in valvular heart diseases

Aortic stenosis

As patient numbers increase, the role of prognostication becomes important, especially in fragile patients. Current issues include peri-surgical aortic valve replacement or peri-trans-catheter aortic valve replacement (TAVR) risk stratification. From this point of view, LGE presence and amount provides useful prognostic information [54,55], but the additive prognostic value of T1 mapping remains unclear. Some previous reports revealed that ECV or native T1 values could be helpful for the prediction of arrhythmic events or complete atrio-ventricular (AV)-block after the TAVR procedure [56]. For example, patients with post-TAVR conduction abnormality (left bundle branch block, AV-block or pacemaker implantation) had statistically significantly lower ECV values compared to those without an event. Patients with an event had a mean ECV of 28.1±3.16%; patients without an event had a mean ECV of 29.8±4.53% (HR, 0.56; 95% CI: 0.32-0.96, p=0.036). In this study, elevated myocardial ECV was a trending predictor of HF; CMR may be helpful in identifying patients at high risk for post-TAVR cardiac decompensation benefitting from intensified post-interventional surveillance [56]. So CMR-T1 mapping can guide selection of TAVR-valve type, which results in less conduction system compromise in cases with a high risk of conduction disturbance. In addition, elderly persons and those with chronic kidney disease are very common in cases with severe aortic stenosis, so native T1 without contrast could provide helpful information without the use of gadolinium contrast media [57,58]. Chin et al. [59] used total extracellular volume indexed by body surface area (iECV) was together with LGE to categorize patients with normal myocardium (iECV<22.5 mL/m^2; 51% of patients), extracellular expansion (iECV≥22.5 mL/m^2; 22%), and replacement fibrosis (presence of mid-wall LGE, 27%). In that study, categorization by ECV was of prognostic value with stepwise increases in unadjusted all-cause mortality (8 deaths/1000 patient-years vs. 36 deaths/1000 patient-years vs. 71 deaths/1,000 patient-years, respectively; p=0.009).

Mitral regurgitation and aortic regurgitation

A few studies have shown that the presence of preoperative myocardial fibrosis assessed with LGE-CMR was an independent predictor of increased adverse clinical outcomes in patients with chronic degenerative mitral regurgitation [60,61]. Chaikriangkrai et al. [61] reported that preoperative LGE may be of clinical utility for the prediction of outcomes during peri-mitral valve repair. Myocardial ECV was increased (32±7% vs. 25±2%, p<0.01) in severe mitral regurgitation patients compared to healthy controls. ECV was associated with increased LV end-systolic volume index (r=0.62, p<0.01), left atrial volume index (r=0.41, p<0.05), lower LV EF (r=-0.60, p< 0.01), longitudinal function (mitral annular plane systolic excursion, r=-0.46, p<0.01) and peak VO2 max (r=-0.51, p<0.05). A multivariate regression model showed LV end-systolic volume index and left atrial volume index were independent predictors of ECV (r^2=0.42, p<0.01) [58,62]. A recent study by Bui et al. [63] reported that patients with mitral valve prolapse with complex ventricular arrhythmia (ComVA) had significantly shorter post-T1 times when compared with patients with mitral valve prolapse without ComVA [324 (IQR 296−348) vs. 354 (IQR 327−376) ms; p=0.03] and only 5/14 (36%) had evidence of papillary muscle LGE. Mitral valve prolapse may be associated with diffuse LV myocardial fibrosis as suggested by reduced post-T1 times. They concluded that diffuse interstitial derangement was linked to subclinical systolic dysfunction, and may have contributed to ComVA in mitral valve prolapse-related mitral regurgitation, even in the absence of focal fibrosis. Prediction of LV function after mitral valve or aortic valve surgery in cases with severely depressed LV function is challenging. Due to prediction uncertainty for LV function recovery, several parameters are potential predictors [64]. The basic concept of reversibility prediction is based on degree of myocardial fibrosis, especially diffuse interstitial fibrosis. At this point, ECV or native T1 values are helpful indexes. However, few studies have examined this issue. LGE positive signal in CMR is a potential predictor of persistent cardiac failure after aortic valve replacement for patients with severe chronic aortic regurgitation and an extremely dilated LV chamber. This has an intimate relationship with malignant arrhythmia and sudden death, which makes this a valuable technique in preoperative evaluation and risk stratification [60,65]. However, no T1 mapping-based prognostication studies in severe aortic regurgitation patients have yet been conducted.

Perspectives and challenges

Because there is already a great deal of evidence for LGE prognostication, T1 mapping-based parameters should provide additive information beyond that provided by LGE. However, quantification of LGE amount for various cardiac diseases, especially in cardiomyopathies, shows measurement variability

[66,67]. In contrast, measurement of average ECV or native T1 in whole LV myocardium is more convenient for researchers. Therefore, a head-to-head comparison asking which parameter (amount of LGE and average T1) is better for prognostication is needed, because there is an increase in the number of HF patients, an aging population and an increasing prevalence of concomitant kidney disease. Although a far improvement for avoiding systemic nephrogenic fibrosis, gadolinium usage is still limited in patients with glomerular filtration rates less than 45 mL/min/m^2. In those cases, native T1-based imaging would provide safe and reliable information about myocardial tissue characteristics [68]. After establishment of a standardization protocol for image acquisition and motion correction algorithm, it could be used in various centers and multi-nations around the world. Most importantly, the protocol could be used as a sensitive and reliable tool to demonstrate the effects of new treatments.

CONCLUSION

In regard to risk stratification and prognostication for cardiovascular events including sudden death, current evidence is mainly focused on non-ischemic cardiomyopathy such as HCM and DCM. However, a growing number of studies have demonstrated the role of T1 in risk stratification in various disease entities, including ischemic and valvular heart disease.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

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