



Relationship between Myocardial Extracellular Space Expansion Estimated with Post-Contrast T1 Mapping MRI and Left Ventricular Remodeling and Neurohormonal Activation in Patients with Dilated Cardiomyopathy

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Objective: Post-contrast T1 values are closely related to the degree of myocardial extracellular space expansion. We determined the relationship between post-contrast T1 values and left ventricular (LV) diastolic function, LV remodeling, and neurohormonal activation in patients with dilated cardiomyopathy (DCM).

Materials and Methods: Fifty-nine patients with DCM (mean age, 55 ± 15 years; 41 males and 18 females) who underwent both 1.5T magnetic resonance imaging and echocardiography were enrolled. The post-contrast 10-minute T1 value was generated from inversion time scout images obtained using the Look-Locker inversion recovery sequence and a curve-fitting algorithm. The T1 sample volume was obtained from three interventricular septal points, and the mean T1 value was used for analysis. The N-Terminal pro-B-type natriuretic peptide (NT-proBNP) level was measured in 40 patients.

Results: The mean LV ejection fraction was 24 ± 9% and the post-T1 value was 254.5 ± 46.4 ms. The post-contrast T1 value was significantly correlated with systolic longitudinal septal velocity (s'), peak late diastolic velocity of the mitral annulus (a'), the diastolic elastance index (Ed , $[E/e']/\text{stroke volume}$), LV mass/volume ratio, LV end-diastolic wall stress, and LV end-systolic wall stress. In a multivariate analysis without NT-proBNP, T1 values were independently correlated with Ed ($\beta = -0.351$, $p = 0.016$) and the LV mass/volume ratio ($\beta = 0.495$, $p = 0.001$). When NT-proBNP was used in the analysis, NT-proBNP was independently correlated with the T1 values ($\beta = -0.339$, $p = 0.017$).

Conclusion: Post-contrast T1 is closely related to LV remodeling, diastolic function, and neurohormonal activation in patients with DCM.

Index terms: Dilated cardiomyopathy; T1 mapping; Diastolic function

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INTRODUCTION

The development of dilated cardiomyopathy (DCM) requires the coexistence of myocardial dysfunction with a remodeling process that is mediated by wall stress and neurohormonal factors (1). DCM is an important cause of morbidity and mortality among patients with heart failure (2). Mortality rate of heart failure has decreased but remains at > 50% 5 years after the diagnosis (3). Both diastolic dysfunction and neurohormonal activation are important prognostic factors in patients with DCM. Markers of diastolic dysfunction correlate strongly with congestive symptoms and prognosis in these patients (4, 5). N-Terminal pro-B-type natriuretic peptide (NT-proBNP) is an

index of neurohormonal activation and is associated with higher mortality and hospitalization in patients with heart failure (6). Previous studies have shown that left ventricular (LV) remodeling is associated with the degree of myocardial fibrosis (7, 8). Cardiac fibrosis is an important contributor to diastolic dysfunction and is significantly correlated with NT-proBNP level (9, 10). The concentration of gadolinium in myocardium can be assessed from T1 measurements and used to quantify extracellular volume (ECV) of the myocardium (11). However, the structural determinants of diastolic dysfunction and neurohormonal activation remain undetermined in patients with DCM. We hypothesized that LV diastolic function and neurohormonal activation in patients with DCM are associated with post-contrast T1 measured using the Look-Locker (LL) sequences.

MATERIALS AND METHODS

Study Population

A total of 122 patients diagnosed with idiopathic DCM at our institution were retrospectively enrolled in this study from May 2003 to August 2010. Idiopathic DCM was diagnosed in the presence of LV dilation associated with systolic dysfunction, in the absence of coronary artery disease, valvular heart disease, or congenital heart disease. Exclusion criteria included poor cardiac magnetic resonance imaging (CMR) quality ($n = 14$), lack of LL imaging or late gadolinium enhancement (LGE) images ($n = 45$), and an estimated glomerular filtration rate < 30 mL/min ($n = 4$). Finally, 59 patients (41 men; mean age, 55 ± 15 years) were included in the study. All study participants underwent both transthoracic echocardiography and CMR. Data on NT-proBNP levels were available for 40 of these patients. CMR and echocardiography were performed, and NT-proBNP levels were determined within 1 month of diagnosis. A retrospective review of medical records was conducted to obtain clinical data, electrocardiographic findings, and biological marker levels. Twelve cases (10 men; mean age, 47 ± 18 years), who underwent CMR for an evaluation of chest pain but had no significant cardiovascular disease, were enrolled as a control group. All study participants in the control group also underwent transthoracic echocardiography and had normal LV systolic function. Mean LV ejection fraction was $65.7 \pm 5.5\%$ (range, 58–74%) in the control group. The study protocols were approved by our Institutional Review Board, and informed consent from patients was waived due to the retrospective nature of the study.

Echocardiography

All patients underwent a comprehensive echocardiographic examination, as described previously (12). LV end-diastolic and end-systolic diameters were obtained from the two-dimensional parasternal long-axis or short-axis view. The peak velocity of early diastolic filling (E), late diastolic filling, and deceleration time of the E wave velocity were measured using the pulsed-wave Doppler method at the level of the mitral valve leaflet tips in apical four-chamber views. Peak early diastolic velocity (e'), late diastolic velocity (a'), and peak systolic velocity of the mitral annulus (s') were measured by tissue Doppler imaging from the septal mitral annulus in apical four-chamber views. The E/ e' ratio was calculated to estimate LV filling pressure (13–15). We calculated the diastolic elastance index (Ed), estimated as E/ e' divided by the filling volume during diastole (stroke volume), as used in a previous study to measure diastolic function as a continuous variable (16). End-systolic pressure was estimated as $(2 \times \text{systolic pressure} + \text{diastolic pressure}) / 3$ (16, 17). All parameters were measured in three consecutive beats, and mean values were used for further calculations.

NT-proBNP Blood Sampling

The blood samples for plasma NT-proBNP levels were obtained by antecubital vein puncture, collected into ethylenediaminetetraacetic acid tubes, and placed on ice. Each sample was centrifuged for 5 minutes at $2000 \times g$ and at 4°C for 30 minutes. The plasma was separated, frozen, and stored at -80°C until assessment. NT-proBNP levels were measured with a proBNP assay on an Elecsys 2010 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). According to data provided by the manufacturer, the detection limit for this peptide was 5 pg/mL.

Cardiac MRI Protocols

Cardiac MR imaging was performed using a 1.5T Gyroscan Intera system (Philips Medical Systems, Best, the Netherlands). Steady-state free precession gated cine images were acquired during 8 seconds breath holds in the long-axis plane and sequential 10 mm short-axis slices, as described previously (18, 19). Contrast-enhanced delayed images were obtained 10–15 minutes after intravenous injection of 0.2 mmol/kg gadolinium diethylenetriamine pentaacetic acid. A standard mid-LV short-axis section orientation was used for inversion time (TI) scout images for LGE imaging with the LL inversion recovery sequence

T1 Measurement in Dilated Cardiomyopathy

(20, 21). LL single-slice TI scout imaging was performed 10 minutes after contrast injection. The LL sequence comprised 12 ms increments in the mid LV short-axis slice. Flip angle was 8°, echo time was 2.40 ms, and repetition time was 5.87 ms. LGE imaging was performed 15 minutes after contrast injection. Two-dimensional LGE imaging was used. The range of inversion recovery time was 220–300 ms. If myocardial signal intensity was higher than that of the shoulder muscle, inversion time was shortened by 10–20 ms, and the scan was repeated. Sequential, short-axis, 1-cm thick slices were obtained. Myocardial regions with abnormally high signals, as determined by two experienced radiologists, were considered positive for LGE. We used commercially available software (QMass MR, version 7.5, Medis, Leiden, the Netherlands) to quantify the post-contrast T1 values. The post-contrast 10-minute T1 value was generated from TI scout images obtained by the LL inversion recovery sequence using a curve-fitting algorithm (Fig. 1). About 0.6 x 0.6 cm sized round shaped region-of-interests were placed in the mid-wall of the upper- and lower-right ventricle-septal insertion site and mid-septum for T1 measurements regardless of the presence of LGE, because

movement of the ventricular septum was relatively less than in other LV areas. Then their average values were used for further analysis. T1 measurements were obtained twice by the same observer who was blinded to other clinical data in 10 selected cases. The ventricular volumes, LV ejection fraction, and stroke volume were measured by stacking endocardial and epicardial border tracings in each short-axis slice. Blood pressure and heart rate were also measured during CMR.

Wall Stress Index

The LV mass index was calculated as: LV mass/body surface area. LV-end diastolic wall stress (LVEDWS, mm Hg) was calculated as: (estimated LV end-diastolic pressure) / {([LVEDV + LV mass] / LVEDV)^{2/3} - 1} from LaPlace's law, where the estimated LV end-diastolic pressure was calculated from the equation (1.9 + 1.24 x [E/e']) (15, 22). Similarly, LV-end systolic wall stress (LVESWS, mm Hg) was calculated as (estimated end-systolic pressure) / {([LVESV + LV mass] / LVESV)^{2/3} - 1}. Where, LVEDV and LVESV means left ventricular end-diastolic volume and left ventricular end-systolic volume, respectively.

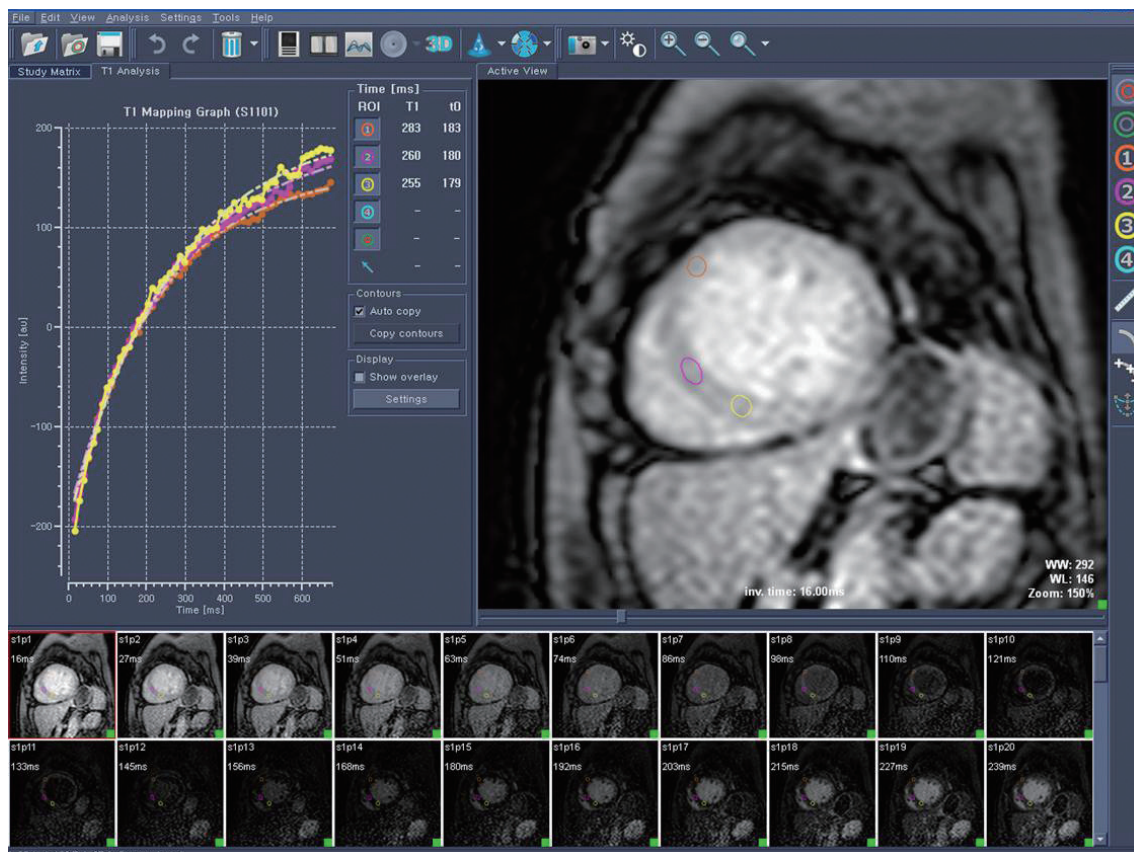


Fig. 1. Representative case of measuring post-T1 value in Look-Locker-based inversion time scout images.

Statistical Analysis

The statistical analysis was performed using SPSS ver. 18.0 for Windows software (SPSS Inc., Chicago, IL, USA). All continuous variables are expressed as mean \pm standard deviation. Discrete variables were compared using Fisher's exact test. Continuous variables were compared using the independent *t* test. Pearson's correlation analysis was used for the univariate analysis to find the determinants of post-contrast T1 relaxational time, and a stepwise multiple linear regression analysis was used for the multivariate analysis. Variables with a *p* value $<$ 0.05 in the univariate analysis were included in the multivariate analysis. LV mass was not included in the multivariate analysis for post-contrast T1 values without NT-proBNP due to significant colinearity with the LV mass/volume ratio, which is a better correlate for post-contrast T1. A two-sided probability value of *p* $<$ 0.05 was considered significant.

RESULTS

Baseline Clinical Characteristics and CMR Findings

Thirty-seven (68.5%) of 59 patients were classified New York Heart Association class III or IV. LV dilatation (LVEDV, 308.3 ± 129.0 mL; LVESV, 239.7 ± 116.9 mL) with severely reduced ejection fraction ($23.8 \pm 9.3\%$) was measured by CMR. Mean velocity was also significantly reduced (3.8 ± 1.2 cm/s). The mean E/e' value increased to 19.7 ± 9.4 . Plasma NT-proBNP levels ranged from 33 pg/mL to 18077 pg/mL, and the median value was 3034 pg/mL. Of the 59 patients, 38 (64%) showed LGE on CMR. Septal and mid-wall LGE patterns were seen in 29 (49.2%) and 19 patients (32.2%), respectively. The mean T1 value was 254.5 ± 46.4 ms (Table 1). Mean post-contrast T1 value was significantly longer in the control group, than that in the DCM group (303.3 ± 48.1 ms vs. 254.5 ± 46.4 ms, *p* = 0.002). The intraclass correlation coefficient for the post-T1 value between the 10 selected cases was 0.9.

Presence of LGE, Diastolic Function, and NT-proBNP

Patients with LGE had significantly lower post-contrast T1 values and higher NT-proBNP levels than those without. In addition, patients with LGE had a lower LV mass/volume ratio, e', a', s', and LV ejection fraction and higher E/e', LVEDWS, and LVESWS than patients without LGE (Table 2).

Correlation with Post-Contrast T1 Values

Among the echocardiographic variables, s' (*r* = 0.419, *p*

= 0.002), a' (*r* = 0.364, *p* = 0.023), and Ed (*r* = -0.288, *p* = 0.027) were significantly correlated with post-contrast T1 values. The correlation between the ejection fraction and post-contrast T1 values was not statistically significant. LV mass (*r* = 0.297, *p* = 0.019), LV mass/volume ratio (*r* = 0.388, *p* = 0.002), LVEDWS (*r* = -0.298, *p* = 0.023), and LVESWS (*r* = -0.380, *p* = 0.004) determined by CMR were also significantly correlated with post-contrast T1 values. The NT-proBNP values measured in 40 patients were significantly correlated with the post-contrast T1 value (*r* = -0.464, *p* = 0.003) (Table 3). In these patients, s', e', a', Ed, LV mass, LVEDWS, and NT-proBNP were significantly correlated with the post-contrast T1 values. In the multivariate analysis without NT-proBNP, Ed (β = -0.466, *p* = 0.013) and LV mass/volume ratio (β = 0.694, *p* = 0.018) were significantly correlated with the post-contrast T1 values. However, in the multivariate analysis with NT-proBNP, only NT-proBNP was significantly and most strongly correlated with the post-contrast T1 values (β = -0.423, *p* = 0.029) (Table 4). In addition, the association between the T1 value, the LV mass/volume ratio, and NT-proBNP remained significant even after further adjustment for LGE, septal LGE, and mid-wall LGE (Table 5). In the subgroup analysis of patients without LGE, post-contrast T1 values were significantly correlated with the LV mass/volume ratio (*r* = 0.494, *p* = 0.023). Furthermore, NT-proBNP was significantly correlated with LVEDWS. However, when LGE or the post-contrast T1 values were considered in a subgroup analysis, a significantly weaker relationship was noted (β = 0.237, *p* = 0.124 after post-contrast T1). However, the relationship between post-contrast T1 and NT-proBNP remained significant after adjusting for LVEDWS (β = -0.381, *p* = 0.016).

DISCUSSION

This study confirmed the relationship between LGE and more advanced systolic and diastolic dysfunction, higher LV wall stress, LV remodeling, and elevated NT-proBNP levels, in patients with non-ischemic DCM. Furthermore, the post-contrast T1 relaxational time, an index of extracellular myocardial volume expansion, was reliably measured from TI scout images widely used in all CMR machines without additional imaging. Post-contrast myocardial T1 relaxational time was related to LV remodeling, LV compliance, and neurohormonal activation as assessed by elevated plasma NT-proBNP levels independent of LGE.

Table 1. Clinical, Echocardiographic, and CMR Findings of Study Populations

	DCM	Control	P
Clinical findings			
Age (years)	55.3 ± 15.4	46.7 ± 18.0	0.091
Male	41/59 (69.5%)	10/12 (83.3%)	0.488
Initial NYHA	2.8 ± 0.7	1.2 ± 0.4	< 0.001
Systolic blood pressure (mm Hg)	110.8 ± 18.2	121.3 ± 10.6	0.059
Diastolic blood pressure (mm Hg)	71.0 ± 13.9	72.1 ± 6.1	0.674
Hypertension	15/52 (28.8%)	6/12 (50%)	0.185
Diabetes	15/51 (29.4%)	2/12 (16.7%)	0.487
eGFR (mL/min)	70.3 ± 23.1	86.7 ± 27.3	0.033
NT-proBNP (pg/mL, n = 40)	4067.3 ± 4063.6 (median)	-	-
Aspirin	32/53 (60.4%)	4/12 (33.3%)	0.114
Beta-blocker	36/54 (66.7%)	3/12 (25%)	0.011
Diuretics	50/54 (92.6%)	4/12 (33.3%)	< 0.001
Angiotensin converting enzyme inhibitor	52/54 (96.3%)	6/12 (50%)	< 0.001
Echocardiographic findings			
E velocity (cm/s)	81.4 ± 28.2	76.7 ± 17.6	0.492
A velocity (cm/s)	57.0 ± 24.3	58.3 ± 21.1	0.882
E/A	1.7 ± 1.0	1.3 ± 0.4	0.091
s' (cm/s)	3.8 ± 1.2	8.0 ± 2.2	< 0.001
e' (cm/s)	4.5 ± 1.6	8.7 ± 3.0	0.001
a' (cm/s)	5.4 ± 2.2	8.8 ± 2.8	< 0.001
E/e'	19.7 ± 9.4	9.4 ± 5.0	0.001
Echocardiographic + CMR findings			
LVEDWS (mm Hg)	102.4 ± 63.2	26.7 ± 2.9	0.095
LVESWS (mm Hg)	281.9 ± 100.6	101.0 ± 17.7	0.006
CMR findings			
LVEDV (mL)	308.3 ± 129.0	146.9 ± 42.3	< 0.001
LVESV (mL)	239.7 ± 116.9	55.3 ± 18.9	< 0.001
Stroke volume (mL)	66.4 ± 24.0	91.7 ± 27.5	0.004
LV ejection fraction (%)	23.8 ± 9.3	62.2 ± 6.3	< 0.001
LV mass (g)	145.9 ± 53.4	80.8 ± 6.1	< 0.001
LV mass/volume ratio (g/mL)	0.5 ± 0.19	0.8 ± 0.33	0.246
LGE	38/59 (64.4%)	0/12 (0%)	< 0.001
Septal LGE	29/59 (49.2%)	0/12 (0%)	0.001
Mid-wall LGE	19/59 (32.2%)	0/12 (0%)	0.028
Post-contrast T1 value (ms)	254.5 ± 46.5	303.3 ± 48.1	0.002

A = late diastolic transmitral inflow, a' = late diastolic mitral annular velocity, CMR = cardiac magnetic resonance imaging, DCM = dilated cardiomyopathy, E = early diastolic transmitral inflow, e' = early diastolic mitral annular velocity, eGFR = estimated glomerular filtration rate, LGE = late gadolinium enhancement, LV = left ventricular, LVEDWS = left ventricular end-diastolic wall stress, LVESWS = left ventricular end-systolic wall stress, NT-proBNP = N-Terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, s' = systolic mitral annular velocity

Non-Invasive Measurement of Extracellular Space Expansion

Late gadolinium enhancement imaging is widely used to detecting extracellular space expansion or replacement fibrosis. The presence of LGE or various patterns of LGE in patients with non-ischemic cardiomyopathy provides important insight into myocardial pathology. However, current LGE imaging cannot provide the degree of diffuse

interstitial fibrosis or expansion, which exists in all patients with non-ischemic DCM. Because LGE is present in only 30–60% of patients with DCM and the amount of LGE reaches at most 10% of the entire LV myocardium, an accurate assessment of the tissue characteristics of non-LGE myocardium is essential for understanding the microscopic structure and functional interaction. Direct T1 values measured with T1 mapping can provide information on

Table 2. Comparison of Left Ventricular Systolic, Diastolic Function, Wall Stress, and Post-Contrast T1 Values According to Presence of Late Gadolinium Enhancement

	LGE Absence (n = 21)	LGE Presence (n = 38)	P
E/A ratio	1.22 ± 0.82	1.99 ± 1.03	0.017
e', cm/s	5.12 ± 1.58	4.21 ± 1.52	0.033
E/e'	16.1 ± 5.73	21.64 ± 10.43	0.028
s', cm/s	4.34 ± 1.27	3.54 ± 1.10	0.026
a', cm/s	6.91 ± 1.97	4.60 ± 1.98	0.001
LVEDWS, mm Hg	82.97 ± 38.79	145.69 ± 84.03	< 0.001
LVESWS, mm Hg	272.27 ± 96.78	302.91 ± 108.13	0.289
LV mass/volume ratio	0.58 ± 0.19	0.47 ± 0.18	0.034
LV ejection fraction, %	27.5 ± 10.6	20.2 ± 6.8	0.008
Log NT-proBNP, pg/mL	2.89 ± 0.66	3.56 ± 0.41	< 0.001
Post-T1, ms	256.3 ± 40.7	250.8 ± 57.9	0.024

A = late diastolic transmitral inflow, a' = late diastolic mitral annular velocity, E = early diastolic transmitral inflow, e' = early diastolic mitral annular velocity, LGE = late gadolinium enhancement, LV = left ventricular, LVEDWS = left ventricular end-diastolic wall stress, LVESWS = left ventricular end-systolic wall stress, NT-proBNP = N-Terminal pro-B-type natriuretic peptide, s' = systolic mitral annular velocity

Table 3. Association with Post-Contrast T1 Value by Univariate and Multivariable Analysis without NT-proBNP (n = 59)

	Univariate Analysis		Multivariate Analysis*	
	r	P	β	P
Age	0.05	0.709		
eGFR	-0.09	0.496		
LVEDV	-0.039	0.767		
LVESV	-0.071	0.592		
Stroke volume	0.169	0.201		
LV ejection fraction	0.245	0.061		
LV mass (CMR)	0.297	0.019		
LV mass/volume ratio	0.388	0.002	0.495	0.001
E/e'	-0.159	0.228		
s'	0.419	0.002		
e'	0.254	0.052		
a'	0.364	0.023		
E/e'/stroke volume (= Ed)	-0.288	0.027	-0.351	0.016
LVEDWS	-0.298	0.023		
LVESWS	-0.380	0.004		

*Stepwise multiple regression analysis. A = late diastolic transmitral inflow, a' = late diastolic mitral annular velocity, CMR = cardiac magnetic resonance imaging, E = early diastolic transmitral inflow, e' = early diastolic mitral annular velocity, Ed = end-diastolic elastance, eGFR = estimated glomerular filtration rate, LGE = late gadolinium enhancement, LV = left ventricular, LVEDWS = left ventricular end-diastolic wall stress, LVESWS = left ventricular end-systolic wall stress, NT-proBNP = N-Terminal pro-B-type natriuretic peptide, s' = systolic mitral annular velocity

myocardial tissue characteristics. The extracellular contrast distribution mechanism allows for obtaining information about the degree of extracellular space expansion using the post-contrast T1 value (23). Therefore, the post-contrast T1 value can be used as a surrogate marker of the ECV fraction. The most common approach to measure LV T1 values by CMR is the LL sequence. The LL sequence has been widely implemented by MRI scanner manufacturers for many years. The recently introduced modified LL inversion

recovery (MOLLI) sequence is currently the most widely used gold standard for T1 mapping. The MOLLI sequence has the advantage of determining T1 during the same phase of the cardiac cycle, with potential for a more accurate T1 measurement with less heart rate dependence. However, the MOLLI technique has limited availability, whereas the LL sequence is commonly used as a sequence for TI scout images. Therefore, an abundance of retrospective data is available for the LL sequence. As our study was designed

Table 4. Univariate and Multivariable Analysis with NT-proBNP (n = 40) Showing Association with Post-Contrast T1 Values

	Univariate Analysis		Multivariate Analysis	
	r	P	β	P
Age	0.037	0.820		
eGFR	0.160	0.324		
LVEDV	0.086	0.598		
LVESV	0.054	0.741		
Stroke volume	0.224	0.164		
LV ejection fraction (CMR)	0.229	0.156		
LV mass (CMR)	0.346	0.029	0.388	0.005
LV mass/volume ratio	0.304	0.057		
E/e'	-0.296	0.064		
s'	0.466	0.003	0.447	0.002
e'	0.345	0.029		
a'	0.500	0.008		
E/e'/stroke volume (Ed)	-0.360	0.023		
LVEDWS	-0.348	0.028		
LVESWS	-0.304	0.057		
NT-proBNP	-0.464	0.003	-0.339	0.017

a' = late diastolic mitral annular velocity, CMR = cardiac magnetic resonance imaging, E = early diastolic transmitral inflow, e' = early diastolic mitral annular velocity, Ed = end-diastolic elastance, eGFR = estimated glomerular filtration rate, LV = left ventricular, LVEDV = left ventricular end-diastolic volume, LVEDWS = left ventricular end-diastolic wall stress, LVESV = left ventricular end-systolic volume, LVESWS = left ventricular end-systolic wall stress, NT-proBNP = N-Terminal pro-B-type natriuretic peptide, s' = systolic mitral annular velocity

Table 5. Correlation with Post-Contrast T1 Values after LGE Adjustment

	Standardized Coefficient	P
Adjustment by presence of LGE		
LV mass/volume ratio	0.339	0.010
NT-proBNP	-0.340	0.034
Adjustment by septal LGE		
LV mass/volume ratio	0.360	0.006
NT-proBNP	-0.419	0.008
Adjustment by mid-wall LGE		
LV mass/volume ratio	0.387	0.003
NT-proBNP	-0.473	0.002

LGE = late gadolinium enhancement, LV = left ventricular, NT-proBNP = N-Terminal pro-B-type natriuretic peptide

retrospectively, we only had LL sequence data. One study showed that LL-based T1 measurements agree well with T1 using MOLLI (24) and it has been used in several studies (25). Therefore, use of LL-based T1 measurements is justified in this study.

Myocardial Fibrosis and Diastolic Dysfunction in Patients with Non-Ischemic DCM

Diastolic function is a well-known important prognostic factor (4, 5, 26) and is correlated with myocardial fibrosis in patients with DCM (10). The presence of fibrosis reduces

compliance of the ventricle and impairs diastolic function by increasing filling pressure (27). Our study confirmed that LV compliance decreased and diastolic wall stress increased in patients with LGE. In addition, post-T1, a surrogate marker of ECV, was independently related to the diastolic functional index, the LV remodeling index, and serum biomarkers of diastolic function, independent of LGE. Therefore, the combination of LGE and direct T1 value measurements in non-LGE myocardium can potentially provide better information about all myocardial tissue characteristics. One of the interesting findings of this study is that gadolinium distribution could be quantified using this LL T1 measurement technique, which added quantitative information to the LGE qualitative evaluation at the same time and location within the myocardium. The post-T1 measurement and its association with clinical outcomes need to be further investigated in longitudinal studies of patients with DCM.

Relationship between Extracellular Space Expansion, LV Remodeling, and Neurohormonal Activation

Late gadolinium enhancement is currently accepted as a non-invasive gold standard method for detecting replacement fibrosis. However, diffuse interstitial fibrosis, which exists in all patients with DCM of varying degrees, cannot be quantified with this technique. Although the

presence of LGE can be a marker of severe diffuse interstitial fibrosis in LGE-negative myocardium, as supported by our observations, it is not possible to quantify the degree of diffuse interstitial fibrosis or the degree of extracellular expansion. However, quantifying the degree of extracellular space expansion is very important because the non-LGE area represents 80–90% of the entire LV in a patient with DCM, suggesting that the non-LGE area could be a main determinant of LV structural remodeling and mechanical properties. The relationship between decreased post-T1, an index of increased ECV, and a decrease in the mass/volume ratio, an index of LV remodeling due to myocyte atrophy in patients with DCM, is consistent with a previous study (28). One of the interesting findings of this study is that the relationship between LVEDWS and NT-proBNP became significantly weaker after introducing LGE or post-contrast T1 values, whereas the post-contrast T1 values remained significant, suggesting that post-contrast T1 values or ECV could be an important determinant of the NT-proBNP level with a given LVEDWS. This finding also justifies the importance of tissue characterization of the non-LGE area using T1-measurements for further risk stratification or predicting the prognosis.

N-Terminal pro-B-type natriuretic peptide is secreted from the ventricles in response to excess stretching of cardiomyocytes modulated by calcium ions (29, 30). However, an opposite hypothesis can also be applied, as previous studies have shown that the stretch-induced production of NT-proBNP from fibroblasts modulates extracellular protein turnover and extracellular space or fibrosis. Our results partially support the role of NT-proBNP in ECV expansion and LV remodeling. Excess collagen deposition may increase stiffness, whereas excess collagen degradation may contribute to ventricular dilatation (29, 30). The relationship between the post-contrast T1 values and the LV mass/volume ratios became weaker after adjusting for NT-proBNP. In addition, the relationship between ECV and remodeling is partly mediated by neurohormonal activation and increased extracellular matrix turnover by NT-proBNP. Therefore, expansion of the ECV due to increased wall stress can directly trigger the release of NT-proBNP from cardiomyocytes or fibroblasts in the extracellular space. In this study, the correlation between post-contrast T1 values, ECV markers, LVEDWS, and post-contrast T1 values was weaker than that to the LV mass/volume ratio and NT-proBNP. ECV cannot be easily predicted using hemodynamic indices, and NT-proBNP level changed

due to volume status. Therefore, directly measuring ECV would provide the specific myocardial tissue characteristics without the effects of various hemodynamic factors. The clinical implications in terms of predicting the prognosis or further remodeling of higher ECV warrant further long-term follow-up studies.

Limitations

The major limitation of our study is the small sample size, cross-sectional design, and lack of follow-up data. The study lacked a control group, which is needed to demonstrate that our findings are unique to the DCM population. In addition, we were unable to measure pre-contrast (native) T1 values, and there were some time intervals between CMR, echocardiography, and NT-proBNP sampling. Particularly, NT-proBNP level and echo Doppler measures were dependent on the patient's volume status. Finally, post-T1 values were affected by the contrast dose, scan timing, renal function, hematocrit, and heart rate. The T1 values measured in our study were lower than those of a previous study; probably because we used post-10 minutes images rather than post-15 minutes images, which have been used in most other studies. However, the same MRI scanner with the same protocol was used when performing CMR to avoid further limitations. Prospective studies with a larger sample size are required.

Conclusions

The degree of extracellular space expansion as assessed by post-contrast T1 values was closely related to LV remodeling, diastolic function, and neurohormonal activation as determined by NT-proBNP level, independent of systolic function and LGE.

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