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The role of native T1 values on the evaluation of cardiac manifestation in Japanese Fabry disease patients

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ABSTRACT

Aims: T1 mapping in cardiac magnetic resonance imaging enables us to distinguish various myocardial diseases showing left ventricular hypertrophy. Fabry disease is a lysosomal storage disorder causing the accumulation of glycosphingolipids into various organs, including the heart, which can be detected by native T1 values in T1 mapping. However, there is no report for the systematic evaluation of native T1 values in Fabry disease in Japan.
Methods and results: We analyzed native T1 values of 30 Fabry disease patients (14 males and 16 females) obtained by 3-T cardiac magnetic resonance imaging. Averaged T1 values were significantly lower in male patients (septal T1: 1149.5 ± 63.3 ms; total T1: 1145.1 ± 59.5 ms) than in female patients (septal T1: 1210.5 ± 45.5 ms; total T1: 1198.8 ± 51.8 ms) ($p < 0.01$). We compared the native T1 values of Fabry disease patients with those obtained from 15 hypertrophic cardiomyopathy patients (9 males and 6 females). Native T1 values effectively differentiate Fabry disease from hypertrophic cardiomyopathy (septal T1: sensitivity 93.3% and specificity 80.0%; total T1: sensitivity 86.7% and specificity 73.3%). In addition, native T1 values had a significant negative correlation with the left ventricular mass index in male patients at the pre-hypertrophic stage ($p < 0.05$). In male and female patients without late-gadolinium enhancement, native T1 values also had a significant negative correlation with the left ventricular mass index ($p < 0.05$).
Conclusion: These results suggest that native T1 values can be used to discriminate Fabry disease from hypertrophic cardiomyopathy and can reflect the accumulation of glycosphingolipids in cardiomyocytes.

1. Introduction

Fabry disease is a hereditary metabolic disorder due to a deficiency in alpha-galactosidase A activity [1]. The resulting accumulation of glycosphingolipids in various organs can cause clinical manifestations [2]. In childhood and adolescence, acroparesthesia, hypo/anhidrosis, angiokeratoma and cornea opacities are typical signs of Fabry disease. In adulthood, major organ involvement, such as the kidney, heart and central nervous system, is important and can determine the prognosis of Fabry disease [3]. Cardiac involvement is particularly crucial to manage, as more than half of the mortalities due to Fabry disease are attributed to cardiovascular complications [4,5]. Advances in cardiac magnetic resonance (CMR) have enabled us to diagnose various heart diseases. Late-gadolinium enhancement (LGE) determined by contrast-enhanced CMR is widely used for the differential diagnosis of cardiac diseases with left ventricular hypertrophy (LVH) [6]. In Fabry disease, LGE in the posterolateral region of the left ventricle is a typical finding; however, the presence of LGE indicates the progression of myocardial

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damage to fibrosis [7]. T1 mapping is a new method for quantifying the characteristics of myocardium and can be used to diagnose various heart diseases [8]. Without contrast medium, native T1 values can be determined in myocardium; these values depend on the main disorder in cardiac muscles. Native T1 values are known to be high with edema, fibrosis and amyloid, whereas they are low in cases with lipid and iron overload [9]. In Fabry disease, the accumulation of glycosphingolipids, such as globotriaosylceramide (Gb3) [10], results in low native T1 values. Indeed, some reports have clearly shown the discrimination of Fabry disease from other heart diseases using native T1 values [11]. However, most of those studies used 1.5-T magnetic resonance imaging (MRI) machines, and only 1 study using a 3-T MRI machine has been reported [12]. Furthermore, the native T1 values in Japanese Fabry disease patients have yet to be reported. In the present study, we examined native T1 values obtained by a 3-T MRI machine to evaluate the characteristics of cardiac manifestation and the potential for differentiation from hypertrophic cardiomyopathy (HCM) in Japanese Fabry disease patients.

2. Materials and methods

2.1. Population

Thirty Fabry disease patients (14 males and 16 females) with clinically and genetically diagnosed Fabry disease who underwent CMR from January 2018 to December 2019 in Jikei University Hospital were retrospectively included in the present study. The diagnosis of Fabry disease is based on the measurement of the alpha-galactosidase A activity and the mutation analysis of the *GLA* gene. In the same period, 15 HCM patients (9 males and 6 females) who underwent CMR were also included. The diagnosis of HCM was defined according to the guideline [13]. We also included 14 normal subjects (8 males and 6 females) (referred for CMR without any abnormal findings) to define normal native T1 reference ranges.

This study conformed to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the Ethics Committee of The Jikei University School of Medicine. Because of the nature of this retrospective study, informed consent was waived. Instead, we publicly posted a notice about the study design and contact information at a publicly-known space in our institution.

2.2. CMR protocol

CMR was performed using the 3-T clinical MRI system (MAGNETOM Skyra; Siemens Medical Solutions, Erlangen, Germany). Breath-hold steady-state free precession (SSFP) images were acquired in 6-mm long-axis slices and sequential 6-mm short-axis slices (4-mm gap) from the atrioventricular ring to the apex of the left ventricle. A modified Look–Locker inversion recovery (MOLLI) acquisition scheme was used to evaluate T1 mapping [14]. We used a modern MOLLI sequence of 5b (3s)3b with a flip angle of 35°, which has been reported to be preferable in clinical studies [15]. A region of interest (ROI) was manually drawn within the left ventricular myocardium to calculate native T1 values averaged between all pixels. Native septal T1 values were evaluated in cross-sections of the mid-ventricular septum, avoiding the anterior and inferior right ventricular insertion point. To evaluate native total T1 values, the ROI was also manually drawn at the cross-sections of the left mid-ventricle. We carefully removed any banding or motion artifacts from the images, which might have made the results harder to interpret. In a similar manner, anterior/lateral/posterior T1 values were evaluated in cross-sections of the mid-ventricular septum. Areas with LGE were not excluded from T1 analysis.

Enhanced CMR was performed using the same 3-T clinical MRI system for the patients without contraindications and who did not refuse contrast medium. To obtain LGE images, the short-axis slices from the atrioventricular ring to the apex of the left ventricle were acquired at 15 min after the injection of 0.1 mmol/kg of gadolinium-DO3A-butriol (Gadovist; Bayer Schering Pharma AG, Berlin, Germany) using an inversion-recovery gradient echo sequence [7]. A semi-quantitative analysis of LGE was performed using the LGE score method, as previously described [16].

2.3. Echocardiography

Echocardiography was performed on all patients within six months of CMR. Basic characteristics, such as the chamber size, wall thickness and wall motion, were determined. To detect LVH, we calculated the left ventricular mass according to the following equation: left ventricular mass $= 0.8 \times 1.04 \times [(\mathrm{IVS} + \mathrm{Dd} + \mathrm{PW})^3 - (\mathrm{Dd})^3] + 0.6$ (g) [17]. The left ventricular mass normalized by the body surface area (left ventricular mass index [LVMI]) (g/m^2) was used to determine LVH. For male patients, an LVMI of >115 g/m^2 was used to detect LVH, whereas an LVMI of >95 g/m^2 was used to detect LVH for female patients [17].

2.4. Statistical analyses

Continuous variables were presented as the mean ± standard deviation and/or median (Q1, Q3). Categorical data were expressed as numbers and percentages. For the comparison of the two data sets, Student's *t*-test was used for continuous variables, and the chi-squared test was used for categorical data. A regression analysis was also performed to detect the correlation between two groups. A receiver operating characteristic (ROC) analysis was performed to evaluate the validity of the T1 values in order to discriminate Fabry disease from HCM. DeLong's test was performed to compare the validity of the ROC analysis between septal and total T1 values. The significance level was set at $P < 0.05$. All statistical analyses were performed using the SPSS software program (version 25, SPSS Japan Inc., Tokyo, Japan).

3. Results

3.1. The representative images of T1 mapping

Pseudo-color images of T1 mapping obtained from 3-T CMR were shown in Fig. 1. The image from a Fabry disease patient showed a purple-blue color in the left ventricular myocardium, indicating lower native T1 values (Fig. 1A and B). In this patient, the native septal T1

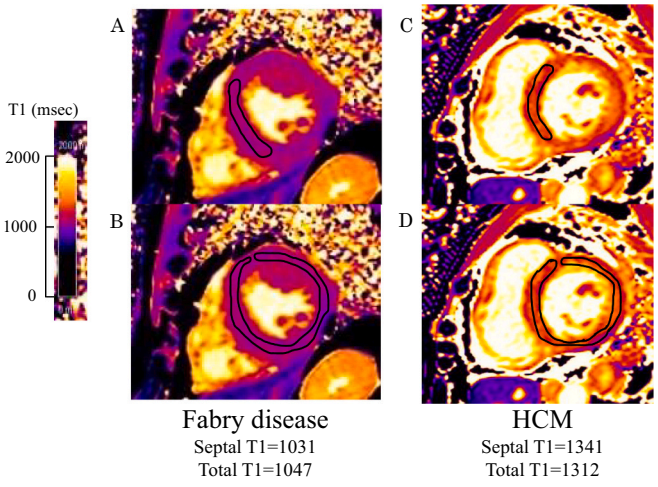

Fig. 1. Representative images of T1 mapping.
Pseudo-color images of T1 mapping at the short-axis slice of the mid-ventricular level are shown in a Fabry disease patient (A and B) and an HCM patient (C and D). A region of interest (ROI) was drawn within the septal area and the total area of the mid-ventricle.
HCM: hypertrophic cardiomyopathy.

value was 1031 msec, and the total T1 value was 1047 msec. In contrast, a red-yellow color was detected from the myocardium of an HCM patient, reflecting higher native T1 values (Fig. 1C and D). In this HCM patient, the native septal and total T1 values were 1341 and 1312 msec, respectively. The region of interest (ROI) at the septal area (Fig. 1A and C) and the total area (Fig. 1B and D) of the mid-ventricle was also shown.

Normal native T1 reference ranges were defined using 14 normal subjects. In 8 male subjects (age: 51.4 ± 21.7 years old), the mean normal septal T1 value was 1240.5 ± 36.2 msec, and the mean normal total T1 value was 1213.8 ± 37.6 msec. In 6 female subjects (age: 55.7 ± 15.2 years old), the mean normal septal and total T1 values were 1251.3 ± 34.8 msec and 1232.5 ± 40.0 msec, respectively.

3.2. Baseline characteristics of Fabry disease and hypertrophic cardiomyopathy patients

Table 1 shows the baseline characteristics of Fabry disease and HCM patients. Among all patients, the Fabry disease patients were younger and had lower systolic and diastolic blood pressure values and lower heart rates than the HCM patients. Various parameters evaluated by echocardiography did not differ significantly between Fabry disease and HCM patients. In Fabry disease patients, the left ventricular posterior thickness and LVMI were significantly smaller in female patients than in male patients. Genotyping of the *GLA* gene revealed a late-onset-type mutation in five male patients and a classical-type mutation in the other nine male patients and all female patients. The details of mutations in *GLA* genes of Fabry disease patients are presented in Supplemental Table 1. There were six male patients with major organ involvement, including three with heart failure, one with end-stage renal disease, and two with stroke. Among female patients, there were four cases of major organ involvement, including two with heart failure and two with stroke. Other symptoms of Fabry disease were observed in both male and female patients. Thirteen male patients and 10 female patients had been treated with enzyme replacement therapy (ERT) or chaperone therapy.

3.3. Discrimination of Fabry disease from hypertrophic cardiomyopathy

Fig. 2A and B show native T1 values from the septal (native septal T1) and total area (native total T1) among Fabry disease and HCM patients. The averaged septal and total T1 values were significantly lower in Fabry disease patients than in HCM patients (Table 2). Fig. 2C and D show the results of an ROC analysis to discriminate Fabry disease patients from HCM patients. With native septal T1, using a cut-off value of 1221.0 msec, the area under the curve (AUC) was 0.892, and the sensitivity and specificity were 93.3% and 80.0%, respectively (Table 3). With native total T1, using a cut-off value of 1197.5 msec, the AUC, sensitivity and specificity were 0.859, 86.7% and 73.3%, respectively (Table 3). We also analyzed the native anterior/lateral/posterior T1 values to evaluate the discrimination between Fabry disease and HCM (Supplemental Fig. 1). With native anterior T1, using a cut-off value of 1176.0 msec, the AUC was 0.936, and the sensitivity and specificity were 100.0% and 83.3%, respectively (Supplemental Fig. 1D). With native lateral T1, using a cut-off value of 1176.5 msec, the AUC, sensitivity and specificity were 0.647, 73.3% and 56.7%, respectively (Supplemental Fig. 1E). With native posterior T1, using a cut-off value of 1192.0 msec, the AUC, sensitivity and specificity were 0.652, 73.3% and 70.0%, respectively (Supplemental Fig. 1F).

We then further analyzed native T1 values in male and female patients separately. In male patients, both septal and total T1 values were able to clearly differentiate Fabry disease from HCM (Fig. 3A and B). In contrast, native T1 values of female HCM patients were distributed within the similar range of the values of female Fabry disease patients (Fig. 3A and B). Figs. 3C-F show the results of an ROC analysis in male and female patients to discriminate Fabry disease from HCM. High sensitivity and specificity were expected in male patients (Fig. 3C and D), while a relatively low sensitivity and specificity were expected in female patients (Fig. 3E and F). In male patients, the AUC, sensitivity and specificity were 0.980, 100.0% and 92.9%, respectively, using a cut-off value of 1216.5 msec in septal T1 and 0.956, 100.0% and 85.7%, respectively, using a cut-off value of 1191.0 msec in total T1 (Table 3). In female patients, the AUC, sensitivity and specificity were 0.797, 83.3% and 68.7%, respectively, using a cut-off value of 1221.0 msec in septal T1 and 0.781, 83.3% and 68.7%, respectively, using a cut-off value of 1203.5 msec in total T1 (Table 3). A comparison of the AUC of septal and total T1 values in an ROC analysis to discriminate Fabry disease from HCM did not reach statistical significance in any cases. Since we found that only anterior T1 values could be used to discriminate Fabry disease from HCM, we also used native anterior T1 values in male and female patients separately (Supplemental Fig. 2). In male patients, the AUC, sensitivity and specificity were 0.937, 100.0% and 75.6%, respectively, using a cut-off value of 1169.0 msec in anterior T1 (Supplemental Fig. 2B). In female patients, the AUC, sensitivity and specificity were 0.927, 100.0% and 87.5%, respectively, using a cut-off value of 1176.5 msec in anterior T1 (Supplemental Fig. 2C).

3.4. The relationship between native T1 values and the left ventricular mass index in Fabry disease

Fig. 4 shows native septal T1 values (Fig. 4A and C) and native total T1 values (Fig. 4B and D) plotted against the LVMI. In male patients, there was a clear difference in the relationship between native T1 values and the LVMI according to the existence of LVH. Before the establishment of LVH, there was a steep significant negative correlation of native T1 values with the LVMI ($R = -0.968$, $p = 0.02$ for septal T1; $R = -0.957$, $p = 0.03$ for total T1), whereas a weak non-significant positive correlation was found after the establishment of LVH ($R = 0.273$, $p = 0.513$ for septal T1; $R = 0.284$, $p = 0.496$ for total T1) (Fig. 4A and B). In female patients, there were no statistically significant correlation between native T1 values and the LVMI either before ($R = -0.071$, $p = 0.856$ for septal T1; $R = 0.364$, $p = 0.335$ for total T1) or after ($R = -0.014$, $p = 0.976$ for septal T1; $R = -0.014$, $p = 0.976$ for total T1) the establishment of LVH (Fig. 4C and D).

Nineteen Fabry disease patients (9 males and 10 females) underwent contrast medium-enhanced CMR to examine the existence of LGE. A semi-quantitative analysis of LGE revealed that the LGE score ranged 1 to 11, and LGE was mainly observed in the infero-posterior region of the left ventricle. This finding is essentially the same as was noted in our previous report [7]. Fig. 5 shows the native T1 values from the patients evaluated by enhanced CMR. Even in this small pool of patients, the Fabry disease patients without LGE showed a significant negative correlation of native T1 values with the LVMI in male patients ($R = -0.960$, $p = 0.040$ for septal T1; $R = -0.994$, $p = 0.006$ for total T1) (Fig. 5A and B) and in female patients ($R = -0.843$, $p = 0.035$ for septal T1; $R = -0.855$, $p = 0.030$ for total T1) (Fig. 5C and D). In contrast, the patients with LGE showed no significant correlation between native T1 values and the LVMI.

We also calculated LVMI from CMR images (MRI-LVMI) and re-evaluated the relationship between native T1 values and LVMI. Cut off values defining LVH are ≥ 91 g/m^2 in males and ≥ 77 g/m^2 in females according to the literature [18]. Supplemental Fig. 3 shows native septal T1 values (Supplemental Fig. 3A and C) and native total T1 values (Supplemental Fig. 3B and D) plotted against the MRI-LVMI. In male patients, there was a steep negative correlation of native T1 values with the LVMI before the establishment of LVH ($R = -0.729$, $p = 0.162$ for septal T1; $R = -0.748$, $p = 0.146$ for total T1), whereas a positive correlation was found after the establishment of LVH ($R = 0.575$, $p = 0.136$ for septal T1; $R = 0.701$, $p = 0.053$ for total T1) (Supplemental Fig. 3A and B). Supplemental Fig. 4 shows the native septal T1 values (Supplemental Fig. 4A and C) and native total T1 values (Supplemental Fig. 4B and D) plotted against the MRI-LVM from the patients evaluated by enhanced CMR. Fabry disease patients without LGE showed a

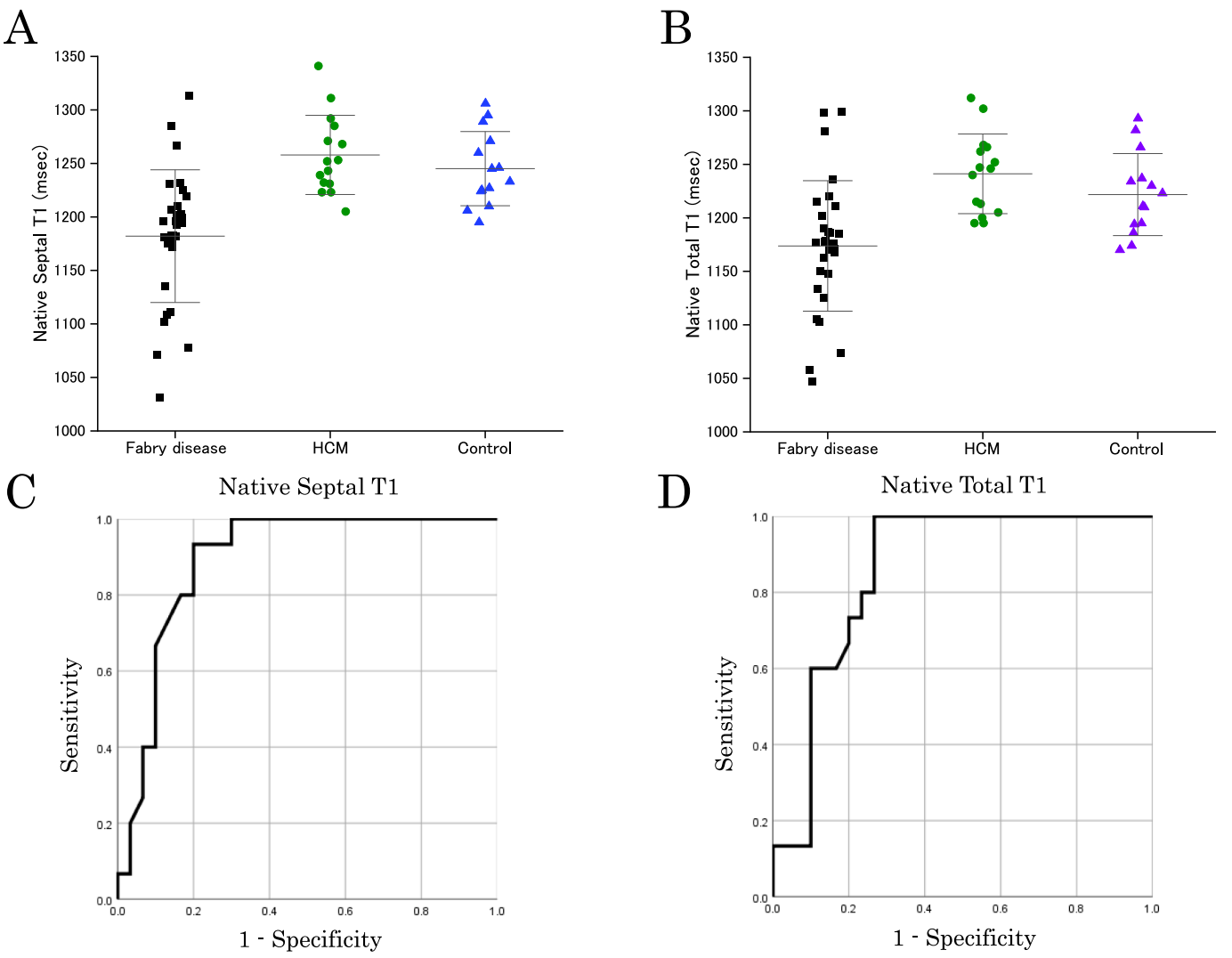

Fig. 2. A comparison of native T1 values between Fabry disease patients and hypertrophic cardiomyopathy patients.
A, B: Scatter plots of native septal T1 values (A) and total T1 values (B) in Fabry disease, HCM patients and control subjects.
C, D: An ROC analysis of the native septal T1 values (C) and total T1 values (D) to discriminate Fabry disease from HCM patients.
HCM: hypertrophic cardiomyopathy. ROC: receiver operating characteristic.

negative correlation of native T1 values with the LVMI in male patients (R = -0.976, $p = 0.024$ for septal T1; R = -0.923, $p = 0.077$ for total T1) (Supplemental Fig. 4A and B) and in female patients (R = -0.811, $p = 0.050$ for septal T1; R = -0.828, $p = 0.042$ for total T1) (Supplemental Fig. 4C and D). We found the similar tendency between the native T1 values and LVMI even when assessed using the CMR-based definition.

We then analyzed the findings/correlation of native T1 values with regard to age, the renal function and BNP value in Fabry disease. Supplemental Figs. 5–7 show the native T1 values plotted against the age (5A-5D), estimated glomerular filtration rate (eGFR) (6A-6D), and BNP (7A-7D). In male patients, there were no statistically significant correlation between native T1 values and the age ($R = 0.070$, $p = 0.812$ for septal T1; $R = -0.005$, $p = 0.986$ for total T1), eGFR ($R = 0.127$, $p = 0.066$ for septal T1; $R = 0.008$, $p = 0.978$ for total T1), or BNP ($R = 0.005$, $p = 0.986$ for septal T1; $R = 0.164$, $p = 0.574$, for total T1). In female patients, there was a negative correlation of native T1 values with the eGFR (R = -0.681, $p = 0.04$ for septal T1; $R = 691$, $p = 0.03$ for total T1), whereas there were no statistically significant correlations between native T1 values and age ($R = 0.403$, $p = 0.122$ for septal T1; $R = 351$, $p = 0.183$ for total T1) or BNP ($R = 0.120$, $p = 0.658$ for septal T1; $R = 0.452$, $p = 0.079$, for total T1).

4. Discussion

The differentiation of Fabry disease from HCM is very important, as there are specific therapeutic options available for Fabry disease patients. Various modalities, including electrocardiography [19,20], echocardiography [21,22] and CMR [23,24], have been used to identify cardiac manifestation of Fabry disease. In the present study, we clearly showed the utility of native T1 mapping of 3-T CMR to differentiate Fabry disease from HCM in a Japanese population.

Although various studies have confirmed the validity of native T1 mapping in cardiac manifestation of Fabry disease, only one had proven the utility of 3-T CMR thus far [12]. That study using 3-T CMR included all patients with Fabry disease, irrespective of gender. We were able to distinguish Fabry disease from HCM among all patients; however, we found that the sensitivity and specificity for discriminating Fabry disease were much higher in male patients than in female patients when using native T1 mapping.

We also compared the validity of an ROC analysis for differentiating Fabry disease from HCM between septal and total T1 values. A previous report favored the use of septal T1 values because of the pseudo-normalization of T1 values due to fibrosis in posterolateral lesions of

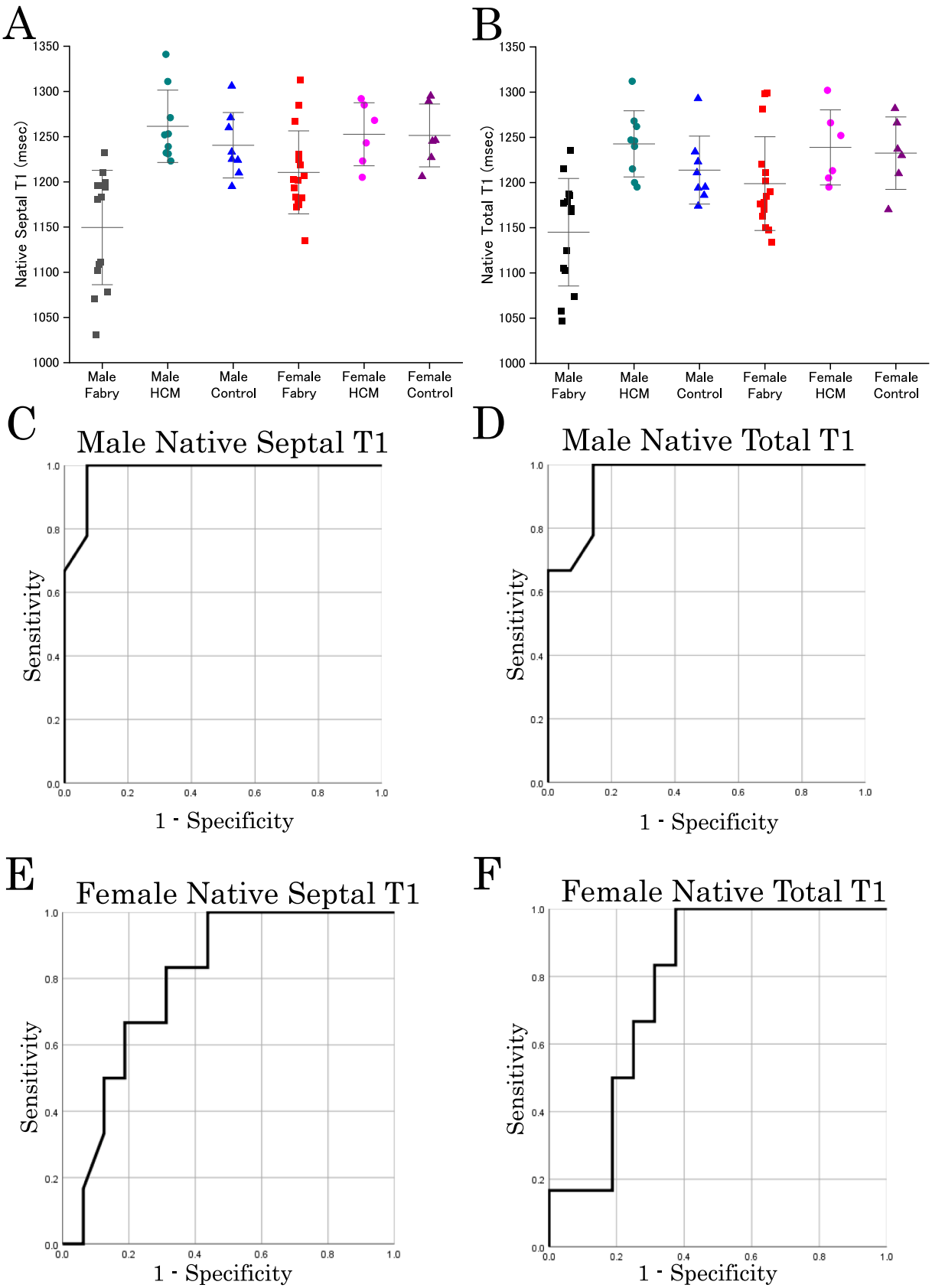

Fig. 3. A comparison of native T1 values between Fabry disease and hypertrophic cardiomyopathy in male and female patients.
A, B: Scatter plots of native septal T1 values (A) and total T1 values (B) in Fabry disease, HCM patients and control subjects.
C, D: An ROC analysis of the native septal T1 values (C) and total T1 values (D) to discriminate male Fabry disease from male HCM patients.
E, F: An ROC analysis of the native septal T1 values (C) and total T1 values (D) to discriminate female Fabry disease from female HCM patients.
HCM: hypertrophic cardiomyopathy. ROC: receiver operating characteristic.

Table 1
Baseline characteristics.

	Fabry disease			HCM		
	All	Male	Female	All	Male	Female
N	30	14	16	15	9	6
Age	45.0 ± 14.3	41.7 ± 13.7	47.8 ± 14.7	63.6 ± 8.5*	63.2 ± 8.6*	64.2 ± 9.2*
[Median (Q1,Q3)]	46.5(35.3,54.5)	44.5(28.8,52.0)	48.5(36.5,61.0)	66.0(56.0,70.0)	66.0(54.0,70.5)	66.5(55.3,72.3)
Genotype						
Classical	25	9	16			
Late-onset	5	5	0			
Organ Involvement						
Heart Failure	5	3	2			
End-stage Renal Disease	1	1	0			
Stroke	4	2	2			
Symptoms						
Acroparesthesia	9	6	3			
Hypohidrosis	12	7	5			
Angiokeratoma	6	5	1			
Corneal opacity	11	3	8			
Proteinuria	8	6	2			
ERT or Chaperone	23	13	10			
Duration	9.0 ± 5.3	8.8 ± 5.7	9.3 ± 4.9			
[Median (Q1,Q3)]	10.0(4.3,13.9)	8.6(2.8,14.2)	10.6(5.3,13.2)			
Systolic BP (mmHg)	105.7 ± 13.8	106.0 ± 10.3	105.5 ± 16.5	127.0 ± 11.1*	127.4 ± 11.6*	126.3 ± 11.3*
Diastolic BP (mmHg)	60.5 ± 9.9	59.2 ± 9.6	61.6 ± 10.3	73.9 ± 14.7*	75.6 ± 16.8*	71.3 ± 11.8
Heart rate (bpm)	63.3 ± 15.5	63.9 ± 14.6	62.7 ± 16.7	73.8 ± 15.1*	75.0 ± 15.6	72.0 ± 15.6
eGFR (ml/min/1.73m^2)	79.0 ± 27.0	78.1 ± 33.8	79.8 ± 20.4	68.7 ± 21.9	67.1 ± 18.6	71.0 ± 28.0
BNP (pg/mL)	122.4 ± 166.5	111.6 ± 129.0	131.8 ± 197.4	127.6 ± 230.8	55.6 ± 44.2	235.6 ± 350.2
Echocardiography						
IVS (mm)	12.1 ± 4.7	13.6 ± 5.4	10.9 ± 3.5	14.2 ± 1.6	14.7 ± 1.4	13.4 ± 1.8
PW (mm)	11.6 ± 4.4	13.7 ± 5.5	9.8 ± 1.9#	10.3 ± 1.2	10.4 ± 1.0	10.1 ± 1.5
Dd (mm)	43.7 ± 5.0	44.3 ± 5.6	43.1 ± 4.4	45.0 ± 4.7	46.8 ± 4.4	42.2 ± 3.8
Ds (mm)	27.3 ± 4.7	27.7 ± 4.1	26.9 ± 5.2	28.1 ± 4.2	29.6 ± 4.6	25.9 ± 2.5
EF (%)	67.8 ± 8.1	67.8 ± 5.6	67.9 ± 10.0	67.5 ± 7.3	66.4 ± 8.4	69.0 ± 5.7
LVMI (g/m^2)	122.5 ± 58.0	144.8 ± 69.1	102.9 ± 38.5#	120.1 ± 22.8	123.7 ± 26.9	114.7 ± 15.5

HCM: hypertrophic cardiomyopathy. ERT: enzyme replacement therapy. BP: blood pressure. eGFR: estimated glomerular filtration rate. BNP: brain type natriuretic peptide. IVS: inter ventricular septum. PW: posterior wall. Dd: end-diastolic diameter. Ds: end-systolic diameter. EF: ejection fraction. LVMI: left ventricular mass index.
* $p < 0.05$ vs Fabry disease.
# $p < 0.05$ vs Male.

Table 2
Native T1 values in Fabry disease and HCM.

	Fabry disease			HCM		
	All	Male	Female	All	Male	Female
N	30	14	16	15	9	6
Septal T1 (msec)	1182.0 ± 62.0	1149.5 ± 63.3	1210.5 ± 45.5#	1257.9 ± 37.0*	1261.4 ± 40.0*	1252.7 ± 38.9
Total T1 (mesc)	1173.7 ± 61.0	1145.1 ± 59.5	1198.8 ± 51.8#	1241.2 ± 37.2*	1242.8 ± 36.6*	1238.8 ± 41.6

HCM: hypertrophic cardiomyopathy.
* $p < 0.05$ vs Fabry disease.
# $p < 0.05$ vs Male.

Table 3
ROC analysis to discriminate Fabry disease from HCM.

	AUC	Cutoff	Sensitivity	Specificity
Septal T1				
All	0.892	1221.0	93.3%	80.0%
Male	0.980	1216.5	100.0%	92.9%
Female	0.797	1221.0	83.3%	68.7%
Total T1				
All	0.859	1197.5	86.7%	73.3%
Male	0.956	1191.0	100.0%	85.7%
Female	0.781	1203.5	83.3%	68.7%

ROC: receiver operating characteristic. HCM: hypertrophic cardiomyopathy. AUC: area under the curve.

left ventricle in the progressive stage of Fabry disease [11]. We noted no significant differences in the validity of the ROC analysis between septal and total T1 values. This result might reflect the less progressed stage of our patients than those in the previous reports.

Another important finding of the present study is the gender differences in native T1 values among Fabry disease patients. Although higher native T1 values in the myocardium of female subjects without cardiac diseases had been reported using 1.5-T CMR [23], another report observed no gender differences in native T1 values using the same 1.5-T CMR machine [24]. We found significantly higher native T1 values in female Fabry disease patients than in male patients. This gender-based difference in native T1 values may have been due to the nature of cardiac involvement rather than a simple gender difference. A recent report classified Fabry disease patients into various stages using a multimodality imaging technique [25]. Because early treatment with ERT is recommended to improve various complications and the prognosis in Fabry disease [26,27], the identification of patients in the pre-

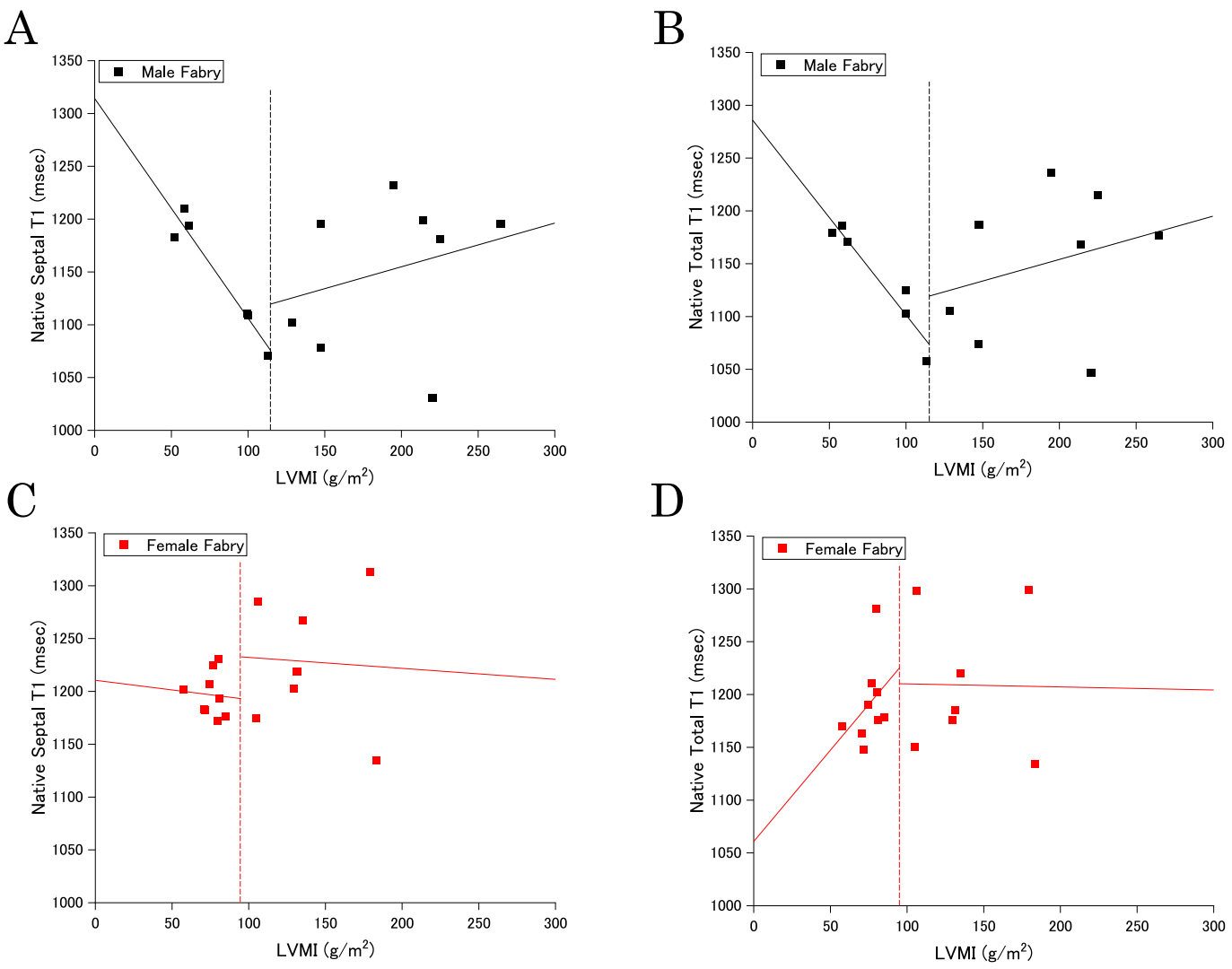

Fig. 4. Native T1 values of Fabry disease patients plotted against left ventricular mass index.
A, B: Native septal T1 values (A) and total T1 values (B) were plotted against the LVMI in male Fabry disease patients.
C, D: Native septal T1 values (C) and total T1 values (D) were plotted against the LVMI in female Fabry disease patients.
Dotted lines show the cut-off values for detecting left ventricular hypertrophy. Solid lines show the results of the regression analysis between native T1 values and the LVMI before and after the existence of left ventricular hypertrophy in each figure.
LVMI: left ventricular mass index.

hypertrophy to early hypertrophy stages is an important issue. We noted a negative correlation of T1 values with the LVMI in pre-hypertrophic male Fabry patients, and this relationship was reversed after the establishment of LVH. Therefore, native T1 values are useful for not only to diagnosing Fabry disease but also for identifying patients who are effective targets of ERT to improve their prognosis, especially in male Fabry disease patients. In contrast, female Fabry disease patients showed no significant correlation between T1 values and the LVMI, even in the pre-hypertrophic state. This result might indicate the heterogeneous accumulation of glycosphingolipids in the myocardium of female Fabry disease patients due to skewed X-chromosome inactivation [28] or the methylation status of the *GLA* gene [29].

A subgroup analysis of the patients who underwent enhanced CMR revealed that native T1 values were negatively correlated with the LVMI in both male and female patients who did not have LGE, indicating that the accumulation of glycosphingolipids exacerbated LVH without inducing myocardial damage in this population. In addition, the increase in native T1 values reflected myocardial damage as determined by LGE, especially in the patients with LVH. Therefore, Fabry disease patients with low T1 values, even those with LVH, can also be effectively treated with ERT.

The most important limitation of our study is the significant differences in patients' age between Fabry disease and HCM. Because some previous reports indicated age-dependent differences in native T1 values [30], our findings of higher native T1 values in HCM patients than in Fabry disease might reflect an older patients' age instead of the nature of the disease. To overcome this problem, we also compared the native T1 values between Fabry disease and control subjects, whose ages were not significantly different from those of Fabry disease patients. The averaged native T1 values were significantly lower in Fabry disease patients than in control subjects (Fig. 2A and B). An ROC analysis revealed that the respective AUC, sensitivity and specificity were 0.848, 78.6% and 80.0% using 1221.5 msec as a cut-off value in septal T1 and were 0.768, 78.6%, and 73.3% using 1192.0 msec as a cut-off value in total T1 (Supplemental Fig. 8A and B). In male patients, the respective AUC, sensitivity and specificity in septal T1 were 0.924, 87.5% and 85.7% using a cut-off value of 1204.5 msec, and those in total T1 were 0.844, 87.5%, and 71.4% using a cut-off value of 1182.5 msec (Supplemental Fig. 8C and D). In female patients, the respective AUC, sensitivity and specificity in septal T1 were 0.802, 83.3% and 75.0% using a cut-off value of 1226.0

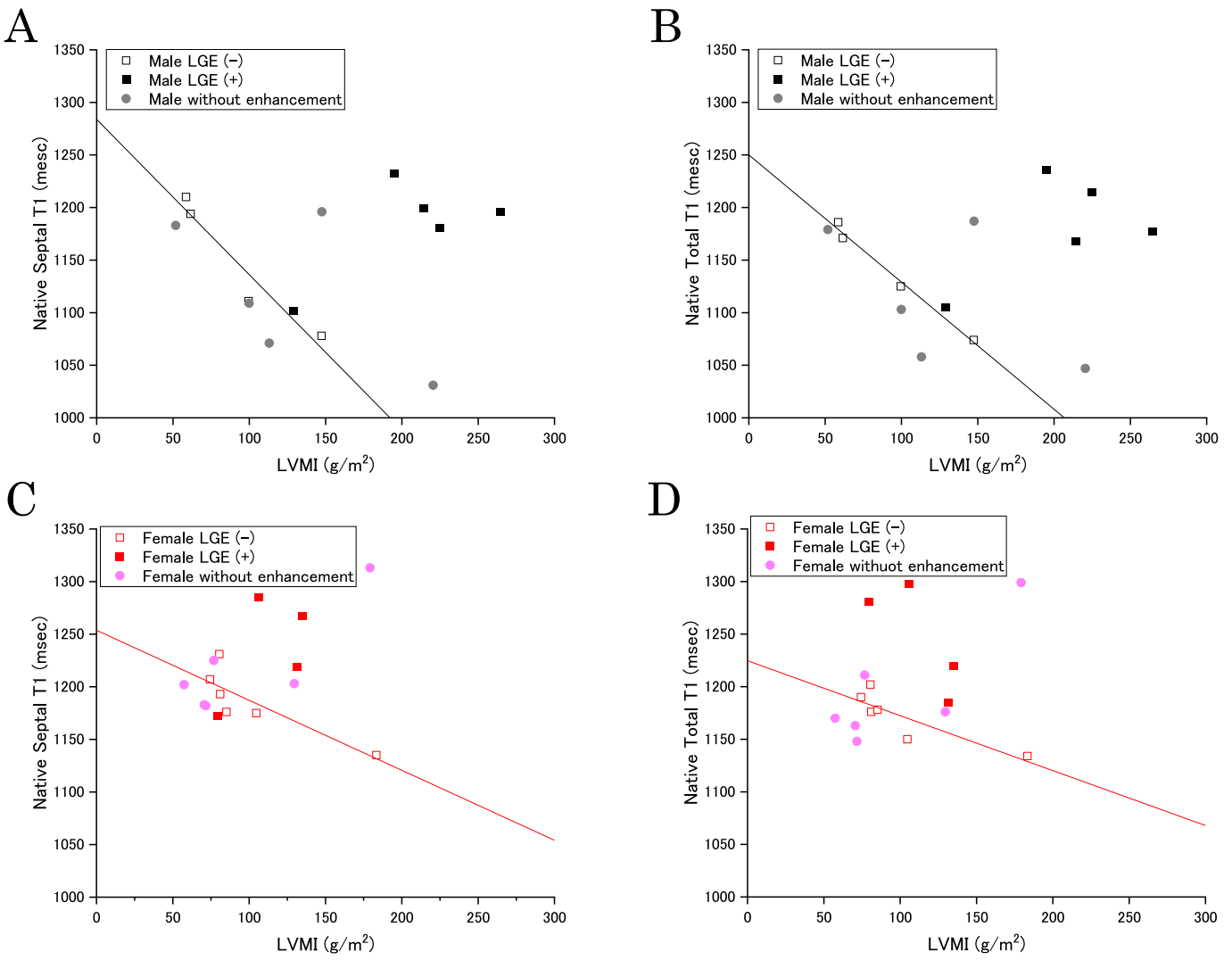

Fig. 5. Native T1 values in Fabry disease patients with and without late-gadolinium enhancement.
A, B: Native septal T1 values (A) and total T1 values (B) were plotted against the LVMI in male Fabry disease patients.
C, D: Native septal T1 values (C) and total T1 values (D) were plotted against the LVMI in female Fabry disease patients.
Open squares show the patients without LGE, and closed squares show the patients with LGE. Closed circles show the patients who did not have gadolinium enhancement. Solid lines show the results of the regression analysis between native T1 values and the LVMI in the patients without LGE.
LVMI: left ventricular mass index. LGE: late-gadolinium enhancement.

msec, and those in total T1 were 0.714, 83.3%, and 68.7% using a cut-off value of 1206.0 msec (Supplemental Fig. 8E and F). In contrast, we were not able to discriminate HCM from control subjects using native T1 values (data not shown).

Several other limitations associated with the present study warrant mention. The present study retrospectively examined only patients in the same institution, and the number of such patients was small. Only some of the patients were able to undergo gadolinium enhancement due to contraindications or patients' preferences. Therefore, the comparison of native T1 values and the confirmation of the existence of LGE was limited. We did not perform other sequences of CMR, such as T2 mapping, to evaluate the inflammatory state of myocardium.

5. Conclusions

Native T1 values obtained by 3-T CMR effectively differentiated Fabry disease from HCM in a Japanese population. The utility of native T1 values was greater in male patients than in female patients, and male patients had a higher sensitivity and specificity for discriminating Fabry disease. Native T1 values had a negative correlation with the LVMI in the male patients in a pre-hypertrophic state. In addition, native T1 values also had a negative correlation with the LVMI in patients without LGE. Therefore, Fabry disease patients with low T1 values are ideal targets for effective treatment with ERT.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2022.100858.

Declaration of Competing Interest

Kenichi Hongo, Hiroyuki Ida and Yoshikatsu Eto received research funding from Sanofi Genzyme Corporations and Sumitomo Dainippon Pharma. Toya Ohashi received research funding from Sanofi Genzyme Corporations, Sumitomo Dainippon Pharma and Amicus Therapeutics, and conducted joint research with JCR Pharmaceuticals. Toya Ohashi is also an adviser of JCR Pharmaceuticals.

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