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ORIGINAL ARTICLE
Myocardial Disease

Usefulness of Native T1 in Cardiac Magnetic Resonance Imaging and Echocardiographic Strain Parameters for Detecting Early Cardiac Involvement in Fabry Cardiomyopathy

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Background: Non-invasive diagnosis of disease stage in Fabry cardiomyopathy with multimodality imaging is pivotal when deciding on the appropriate time to initiate enzyme replacement therapy. However, this approach has not been well established.

Methods and Results: We enrolled 14 patients with Fabry disease. All patients were evaluated using echocardiography and contrast cardiac magnetic resonance (CMR), and were divided into either an early-stage group without left ventricular hypertrophy (LVH; wall thickness >12 mm) or late gadolinium enhancement (LGE; n=7; median age 37 years; 4 female), or an advanced-stage group with LVH and/or LGE (n=7; median age 66 years; 7 female). Strain data from echocardiography and T1 mapping on CMR were compared between the groups. In the advanced-stage group, all strain data were impaired. In the early-stage group, localized longitudinal strain in the basal posterolateral segment was already reduced but both localized and global circumferential strain remained preserved. On CMR analysis, global and localized native T1 shortening were observed in the early-stage group, but were pseudo-normalized in the advanced-stage group. In logistic regression analysis, localized circumferential strain had significant diagnostic value for differentiating between early- and advanced stage (P=0.037) and significantly improved the predictive power of the model containing localized native T1 in CMR.

Conclusions: A combination of localized native T1 in CMR and echocardiographic strain parameters could be useful for staging Fabry cardiomyopathy.

Key Words: Cardiac magnetic resonance; Combination diagnosis; Echocardiographic strain parameters; Fabry cardiomyopathy; Native T1

Fabry disease is a rare X-linked lysosomal storage disease caused by deficient activity of the alpha-galactosidase A (α-GLA) enzyme and is characterized by progressive intracellular accumulation of neutral glycosphingolipids in various organs, including the heart.[1,2] Cardiac involvement is one of the main causes of mortality in patients with Fabry disease.[3] Fabry cardiomyopathy is characterized by progressive left ventricular hypertrophy (LVH), and involvement starts from the basal posterolateral segment.[2,4] Furthermore, accumulation of glycosphingolipids affects both ventricles.[5] Enzyme replacement therapy (ERT) is essential in Fabry disease, but it may be too late to start ERT when LVH or myocardial fibrosis detected by late gadolinium enhancement (LGE) on a cardiac magnetic resonance (CMR) examination appears.[4,6,7] Recently, early initiation of ERT has been identified to be beneficial for controlling disease progression and improving symptoms.[6] Therefore, early detection of cardiac involvement before LVH and LGE are observed seems to be important.[8]

There has been growing interest in echocardiographic strain imaging and parametric mapping in CMR, including T1, T2, and extracellular volume (ECV), as tools for the diagnosis of myocardial damage and characterization of

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tissue.[3] Shortening of the native T1 is particularly useful for identifying early cardiac manifestations of Fabry disease.[4,9] In clinical settings, multimodality imaging, including echocardiography and CMR, is pivotal for diagnosing Fabry cardiomyopathy and disease staging but has not been well established, especially in the early-stage of the disease.

In this study, we investigated the usefulness of a combination of echocardiography and CMR for diagnosing disease stage in patients with Fabry cardiomyopathy.

Methods

Study Population

A single-center cohort of patients diagnosed with Fabry disease was evaluated between June 2016 and May 2022. Fourteen patients in this cohort who were diagnosed as having Fabry disease using genetic or enzymatic analysis and had both CMR and echocardiographic findings available were included in the study. Ten (71%) patients underwent a right ventricular (RV) biopsy. The 14 patients were divided into 2 groups according to the presence or absence of LVH on echocardiography and LGE on a CMR examination. In accordance with previous studies,[2,10–12] LVH was defined as a maximal left ventricular (LV) wall thickness of >12 mm. Patients with either LVH or LGE were classified as an advanced-stage group and those without LVH or LGE were defined as an early-stage group. In addition to standard blood and urine laboratory analyses, serum levels of α-GLA activity and globotriaosylsphingosine in lysosomes (Lyso-Gb3) were also measured. The study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (R2003-2). The study was designed to be carried out without obtaining individual informed consent according to the "opt-out" principle. We published a summary of the study protocol with the contact information for our office on the institution's website, which provided patients with the ability to refuse enrollment into the study.

CMR

CMR was performed on a 3.0-T system (MAGNETOM Verio and Vida; Siemens Healthcare GmbH, Erlangen, Germany) using a standard clinical protocol with LGE imaging.[13] Native T1 mapping was acquired on the base, mid, apex ventricular short-axis slices using a modified Look-Locker inversion recovery (MOLLI) pulse sequence according to a consensus statement by the Society for Cardiovascular Magnetic Resonance[14] prior to contrast bolus administration (0.1 mmol/kg body weight; Gadovist, Bayer Healthcare, Berlin, Germany). Post-T1 mapping was performed approximately 15 min after contrast administration for ECV quantification.

CMR Analysis

All images were centralized and analyzed using CVI42 software (Circle Cardiovascular Imaging Inc., Calgary, AB, Canada). All analyses were performed by an experienced cardiologist and radiologist who were blinded to the patients' clinical status. The presence of LGE was assessed by two independent observers. For native T1 analysis, a native T1 map was drawn automatically in each segment with a 20% offset, taking care to avoid the blood-myocardial boundary. The normal native T1 reference range (mean±2 SD) was 1,251±45 ms, which was defined using healthy volunteers at our center. ECV was calculated from the native T1 and the hematocrit value before and after administration of contrast. The normal ECV reference range was defined by reference to the literature.[15] In this study, global native T1 and global ECV were calculated by averaging all segmental values of native T1 and ECV. Local native T1 and ECV were defined as the average values of native T1 and ECV in the basal posterior and basal lateral segments.

Echocardiography

All patients underwent an echocardiographic examination using a commercially available system (Vivid 7 or E95; GE Vingmed Ultrasound AS, Horten, Norway). Images were obtained with a 3.3 MHz probe, and parameters were measured according to the most recent guidelines.[16] LV dimensions and wall thicknesses were measured on B-mode recordings in the parasternal long-axis view. The biplane method of discs (modified Simpson's rule) was used to obtain the LV ejection fraction (LVEF) and the maximal volume of the left atrium. LV mass was calculated according to the formula recommended by the guidelines[16] and was indexed to body surface area. A comprehensive assessment of RV geometry and systolic function was performed.

Standard 2-dimensional images of apical 4-chamber, 2-chamber, and 3-chamber views were obtained to evaluate LV global longitudinal strain (GLS). Parasternal short-axis views at the mitral valve, papillary muscle, and apex levels were used to assess LV global circumferential strain (GCS) and global radial strain (GRS). The RV-focused apical 4-chamber view was obtained for assessment of the RV free wall longitudinal strain (RVFWS).[17] LV GLS was calculated by averaging all segmental strain values from standard 3 apical views. LV GCS and GRS were calculated by averaging all segmental strain values from standard parasternal 3 short-axis slices. Localized longitudinal strain (LS), circumferential strain (CS) and radial strain (RS), which were averaged values in the basal posterior and lateral portions, were also evaluated, considering that Fabry cardiomyopathy progresses from these segments. RVFWS was calculated by averaging all RV free wall segmental strain values. Standard commercially available dedicated EchoPAC software (GE Vingmed Ultrasound AS) was used to automatically track and accept segments of good tracking quality while allowing the observer to manually override its decisions. To confirm the accuracy of the echocardiographic parameters, the measurements were repeated offline by two experienced sonographers blinded to clinical status. The normal ranges of LVEF, GLS, GCS, GRS, localized LS, CS, RS and RVFWS were defined by referring to the literature.[16,18]

Statistical Analysis

Values are expressed as the median with interquartile range. Continuous data were compared between groups using the Student's t-test or Wilcoxon test and categorical data using the Fisher's exact test as appropriate. The ability to predict early-stage Fabry cardiomyopathy was evaluated using logistic regression analysis and the C-statistic.[19] All tests were two-sided, and a P value <0.05 was considered statistically significant. A Bonferroni-corrected P value threshold (P=0.05/5=0.01) was used to compare global chi-square values between localized native T1 and localized native T1 plus additional echocardiographic parameters. All statistical analyses were performed using JMP 12 software (SAS Institute, Inc., Cary, NC, USA).

Table 1. Patient Demographics and Clinical Characteristics

	Overall (n=14)	Early-stage group (n=7)	Advanced-stage group (n=7)	P value
Age (years)	39 [31–66]	37 [17–38]	66 [40–67]	0.010
Sex (male)	3 (21)	3 (43)	0 (0)	0.192
History of hospitalization for HF	1 (7)	0 (0)	1 (14)	1.000
Hypertension	2 (14)	0 (0)	2 (29)	0.462
Diabetes	2 (14)	0 (0)	2 (29)	0.462
Dyslipidemia	2 (14)	0 (0)	2 (29)	0.462
Atrial fibrillation	0 (0)	0 (0)	0 (0)	N/A
Stroke/transient ischemic attack	3 (21)	1 (14)	2 (29)	1.000
Right ventricular biopsy	10 (71)	4 (57)	6 (86)	0.559
Family history	10 (71)	6 (86)	4 (57)	0.559
Laboratory data				
BNP (pg/mL)	11 [9–252]	10 [8–11]	172 [10–607]	0.011
eGFR (mL/min/1.73 m^2)	82 [69–94]	93 [76–111]	74 [59–82]	0.055
Blood urea nitrogen (mg/dL)	12 [9–15]	10 [8–13]	15 [9–19]	0.095
Hemoglobin (g/dL)	13.2 [12.8–14.0]	13.5 [12.8–14.5]	13.1 [12.6–13.7]	0.523
Hematocrit	41 [38–42]	42 [38–43]	40 [38–41]	0.563
Proteinuria	1 (7)	0 (0)	1 (17)	1.000
α-galactosidase A (nmol/h per mg protein)	10.5 [3.7–21.0]	14.0 [0.3–20.0]	7.0 [3.9–24.0]	0.949
Lyso Gb3 (ng/mL)	12.0 [10.0–27.0]	13.0 [8.7–113]	12.0 [10.5–23.0]	0.927
Medication				
Enzyme replacement therapy	6 (43)	4 (57)	2 (29)	0.592
ACE inhibitor/ARB	2 (14)	0 (0)	2 (29)	0.192
β-blocker	2 (14)	0 (0)	2 (29)	0.192
Antiplatelet drug	2 (14)	1 (14)	1 (14)	1.000
Anticoagulant drug	0 (0)	0 (0)	0 (0)	N/A

Unless indicated otherwise, data are presented as n (%). Continuous values are expressed as median [IQR]. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; Lyso Gb3, globotriaosylsphingosine in lysosomes.

Results

Clinical Characteristics of Patients With Fabry Cardiomyopathy

Clinical characteristics of the 14 patients with Fabry disease are summarized in **Table 1**. Seven of the 14 patients were classified as having early-stage cardiomyopathy and the remainder as having advanced-stage cardiomyopathy. Patients in the early-stage group were significantly younger than those in the advanced-stage group. In the early-stage group, none had underlying diseases, except for previous stroke in a male patient. There was no significant between-group difference in serum levels of α-GAL activity and Lyso-Gb3, although the serum B-type natriuretic peptide level was significantly lower in the early-stage group. Only 1 patient in the early-stage group was on ERT.

LV Size and Function in Fabry Cardiomyopathy

Echocardiographic and CMR parameters are shown in **Table 2**. The values of LV wall thickness and mass were higher in the advanced-stage group than in the early-stage group. However, there was no significant between-group difference in LV size, LV volume, or ejection fraction (EF) on echocardiography or CMR examination. GLS and GCS decreased in the advanced-stage group despite preserved EF (**Figure 1**). However, in the early-stage group, localized LS was reduced and GLS was just under the normal limit, although GCS and localized CS were preserved (**Figure 2**). GRS was just under the normal limit in the early-stage group and decreased in the advanced-stage group. However, there was no statistical difference between the two groups in GRS and localized RS (**Table 2**).

In terms of CMR parameters, localized and global native T1 shortening were found in the early-stage group (**Figure 2**), although the ECV value was at the upper limit of normal. In contrast, the native T1 value was within normal limits in the advanced-stage group, indicating pseudo-normalization (**Figure 1**). The ECV value increased and was slightly above normal limits.

RV Size and Function in Fabry Cardiomyopathy

Table 3 summarizes the RV parameters evaluated using echocardiography and CMR. The tricuspid annular plane systolic excursion (TAPSE) and RVFWS values, which indicate longitudinal function, were significantly lower in the advanced-stage group than in the early-stage group, although RV size was similar between the two groups. However, there were no significant between-group differences in fractional area change (FAC) on echocardiography or RVEF on CMR, which indicates global (longitudinal and transverse) RV function.

Distinguishing Between Early-Stage and Advanced-Stage Fabry Cardiomyopathy

Table 4 shows the results of the univariable logistic regression analysis of the ability of each echocardiographic and

Table 2. Echocardiography and CMR Parameters

	Early-stage group (n=7)	Advanced-stage group (n=7)	P value
Echocardiography			
Morphology			
LVEDD (mm)	45 [43–51]	46 [40–49]	1.000
LVESD (mm)	29 [27–31]	32 [27–33]	0.479
IVS (mm)	7 [5–9]	13 [10–13]	0.010
PW thickness (mm)	8 [6–9]	11 [8–13]	0.072
Relative wall thickness	0.33 [0.28–0.39]	0.52 [0.33–0.60]	0.097
LV mass index (g/m^2)	60 [48–84]	122 [80–166]	0.066
LAVI (mL/m^2)	29 [24–35]	47 [38–47]	0.008
Systolic function			
LVEF (normal range 63±5; %)	60 [60–63]	62 [55–63]	0.746
GLS (normal range 21.3±2.1; %)	17.4 [15.7–21.6]	11.1 [6.8–17.3]	0.097
Localized LS (basal posterolateral segments; %)	14.8 [13.3–16.1]	10.1 [7.7–13.1]	0.041
GCS (normal range 22.8±2.9; %)	19.4 [19.1–25.0]	13.8 [12.0–16.1]	0.003
Localized CS (basal posterolateral segments; %)	21.0 [13.0–23.3]	9.9 [6.9–11.0]	0.005
GRS (normal range 54.6±12.6; %)	44.0 [30.8–51.1]	27.8 [21.9–31.3]	0.100
Localized RS (basal posterolateral segments; %)	35.4 [25.0–70.9]	27.0 [17.7–32.0]	0.144
Diastolic function			
Mitral E velocity (cm/s)	90 [80–101]	72 [55–77]	0.084
Deceleration time (ms)	166 [143–220]	216 [165–274]	0.443
Septal mitral annular e′ velocity (cm/s)	10.3 [7.4–13.5]	2.8 [2.2–4.9]	0.005
E/e′ velocity ratio (septal)	9.5 [7.1–11.5]	22.1 [12.0–26.2]	0.018
CMR			
Morphology			
LVEDVI (mL/m^2)	67 [57–71]	72 [69–87]	0.055
LVESVI (mL/m^2)	22 [19–34]	25 [23–33]	0.371
LVEF (%)	64 [53–68]	65 [53–70]	0.609
LV mass index (g/m^2)	56 [42–68]	94 [73–107]	0.027
Tissue characterization			
Native T1 (average of all segments; normal range in our institution 1251±45; ms)	1,156 [1,131–1,245]	1,228 [1,181–1,274]	0.097
Localized native T1 (basal posterolateral segments; ms)	1,173 [1,108–1,215]	1,234 [1,194–1,297]	0.041
ECV (average of all segments; normal range 23–28; %)	27 [26–31]	31 [28–38]	0.276
Localized ECV (basal posterolateral segments; %)	29 [28–30]	29 [26–36]	1.000

Continuous values are expressed as mean ± SD, or median [IQR]. Each strain value is expressed as the absolute value. CMR, cardiac magnetic resonance; CS, circumferential strain; ECV, extracellular volume; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; IVS, interventricular septal thickness; LAVI, left atrial volume index; LS, longitudinal strain; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESVI, left ventricular end-systolic volume index; PW, posterior wall; RS, radial strain.

CMR parameter to distinguish early-stage from advanced-stage Fabry cardiomyopathy. Localized native T1 on CMR tended to have predictive ability (P=0.086). Among the echocardiographic variables, localized CS had significant value for distinguishing between early-stage and advanced-stage Fabry cardiomyopathy (P=0.037), but localized LS did not. GLS, GCS, and TAPSE tended to be related to the disease stage. The area under the curve for distinguishing early-stage from advanced-stage Fabry cardiomyopathy was 0.84 (95% confidence interval 0.62–1.00; P=0.035) for the localized native T1 and 0.96 (95% confidence interval 0.86–1.00; P=0.004) for the localized CS. The optimal cut-off values were 1,185 ms for localized native T1 (sensitivity 71%; specificity 86%) and −11.0% for localized CS (sensitivity 100%; specificity 86%).

The following incremental benefits of echocardiographic parameters in the diagnosis of early-stage Fabry cardiomyopathy were identified. The additional echocardiographic parameters of localized CS and GCS significantly improved the predictive power of the model containing localized native T1 even after Bonferroni correction, although addition of localized LS, GLS, or TAPSE did not (baseline model 1, localized native T1, chi-square 4.7; model 2, plus localized LS, chi-square 7.8; P=0.078; model 3, plus GLS, chi-square 11.2; P=0.011; model 4, plus localized CS, chi-square 19.4; P<0.001; model 5, plus GCS, chi-square 19.4; P<0.001; and model 6, plus TAPSE, chi-square 10.1; P=0.020; **Figure 3**).

Discussion

This study had two important findings (**Figure 4**). The first was that a reduction in localized LS in the basal posterolateral segment and shortening of the native T1 were key

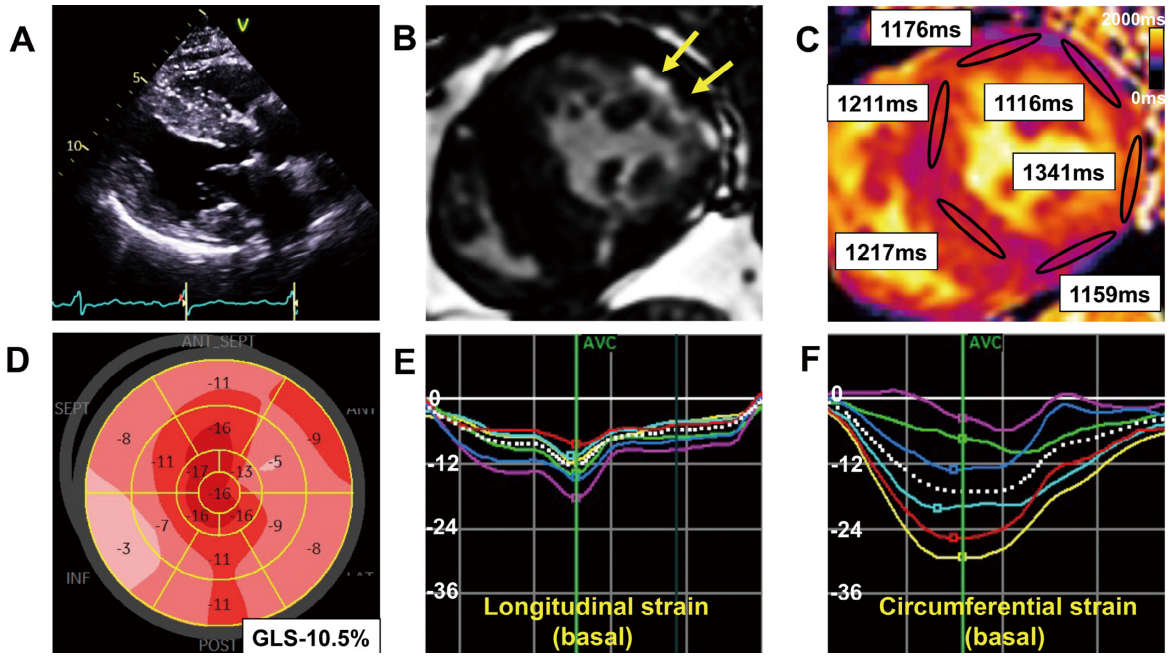

Figure 1. A representative case of a 66-year-old woman with advanced Fabry cardiomyopathy. (**A**) Two-dimensional echocardiography showing left ventricular hypertrophy. (**B**) Cardiac magnetic resonance showing late gadolinium enhancement in the basal posterolateral segment (yellow arrow). (**C**) Global native T1 was pseudo-normalized, and localized native T1 was prolonged, especially in the basal posterolateral segment. (**D**–**F**) Localized longitudinal strain, circumferential strain, global longitudinal strain (GLS), and global circumferential strain values were reduced.

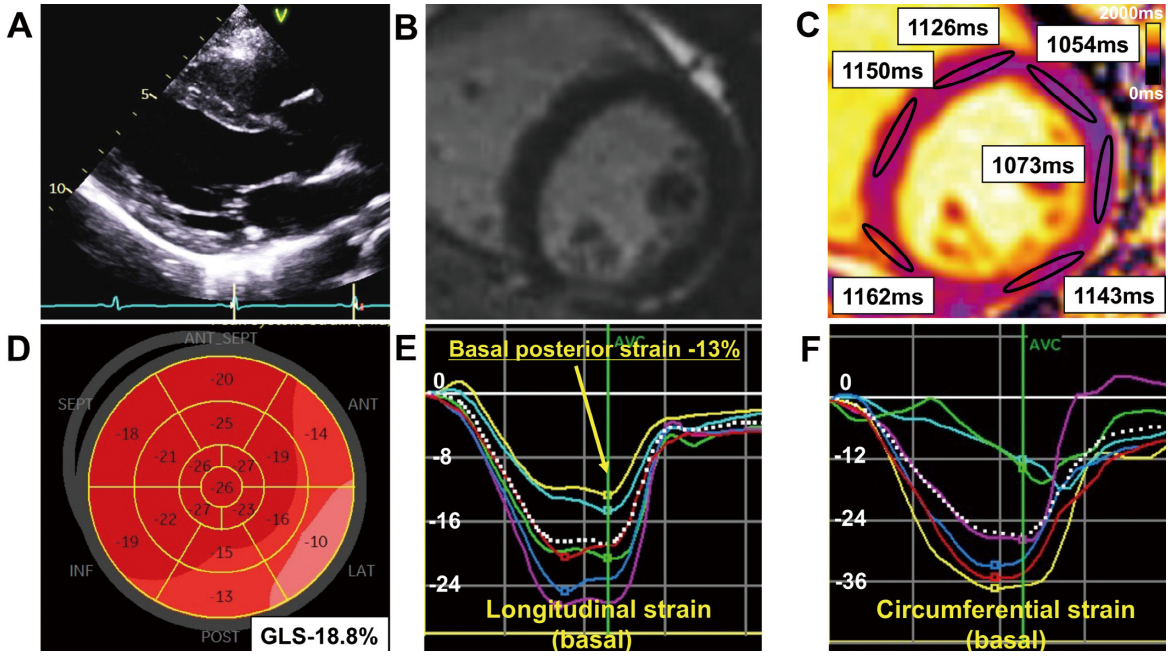

Figure 2. A representative case of a 36-year-old woman with early Fabry cardiomyopathy. The woman was referred to National Cerebral and Cardiovascular Center with a family history of Fabry disease. (**A**) Two-dimensional echocardiography showed no left ventricular hypertrophy. (**B**) Cardiac magnetic resonance showed no late gadolinium enhancement; however, the native T1 was found to be shortened, especially in the basal posterolateral segment (**C**). (**D**–**F**) Localized longitudinal strain in the basal posterolateral segment was reduced, although global longitudinal strain (GLS), localized circumferential strain, and global circumferential strain were preserved.

Table 3. RV Parameters

	Early-stage group (n=7)	Advanced-stage group (n=7)	P value
Echocardiography			
RVEDD (mm)	27 [26–29]	30 [29–31]	0.027
RVOT diameter (proximal; mm)	25 [21–29]	25 [22–28]	0.847
TAPSE (mm)	21.7 [20.8–22.5]	16.0 [13.9–20.4]	0.022
FAC (%)	46 [42–48]	44 [41–47]	0.609
RV free wall strain (normal range 29.0±4.5; %)	28.9 [27.8–31.0]	20.8 [18.9–23.8]	0.003
CMR			
RVEDVI (mL/m^2)	76 [58–83]	71 [59–86]	0.702
RVESVI (mL/m^2)	42 [26–43]	29 [27–40]	0.443
RVEF (%)	49 [46–55]	51 [44–58]	0.443

Continuous values are expressed as median [IQR]. Each strain value is expressed as the absolute value. CMR, cardiac magnetic resonance; FAC, fractional area change; RV, right ventricular; RVEDD, right ventricular end-diastolic dimension; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion.

Table 4. Logistic Regression Analysis for Predicting Early-Stage Fabry Cardiomyopathy

	OR (95% CI)	Chi-square value	P value
GLS (0.1%)	1.028 (0.997–1.060)	5.0	0.079
Localized LS (basal posterolateral segments; 0.1%)	1.025 (0.993–1.069)	3.2	0.129
GCS (0.1%)	1.104 (0.993–1.227)	12.3	0.068
Localized CS (basal posterolateral segments; 0.1%)	1.038 (1.002–1.075)	9.5	0.037
TAPSE (1 mm)	1.825 (0.924–3.606)	6.8	0.083
RV free wall strain (0.1%)	1.504 (0.503–4.500)	16.0	0.466
Native T1 (average of all segments; 1 ms)	0.984 (0.963–1.005)	3.0	0.125
Localized native T1 (basal posterolateral segments; 1 ms)	0.983 (0.963–1.002)	4.7	0.086

CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 2,3.

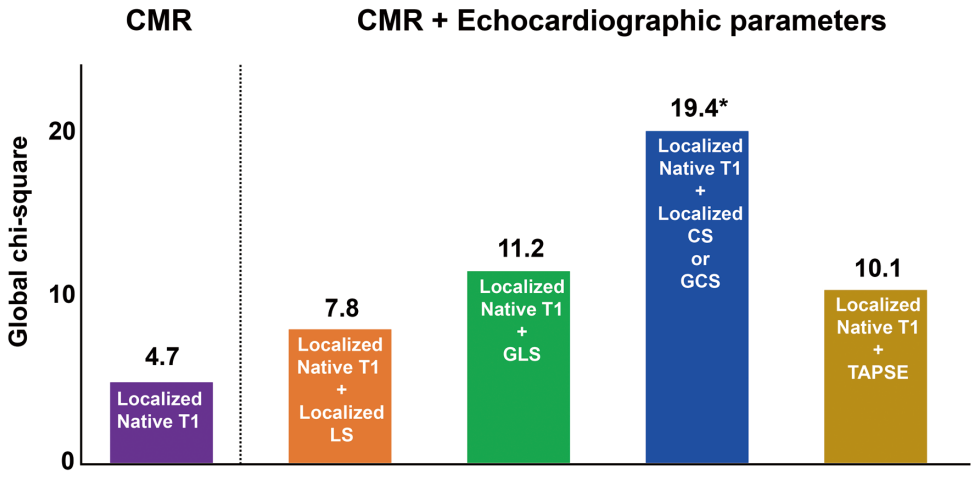

Figure 3. Incremental prognostic value of echocardiographic parameters when added to localized native T1. The change in the global chi-square value in sequential Cox models incorporating echocardiographic parameters is shown. The additional echocardiography parameters of localized circumferential strain (CS) and global circumferential strain (GCS) significantly improved the predictive power in a model containing localized native T1. *P<0.01 (Bonferroni correction). CMR, cardiac magnetic resonance; GLS, global longitudinal strain; LS, longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

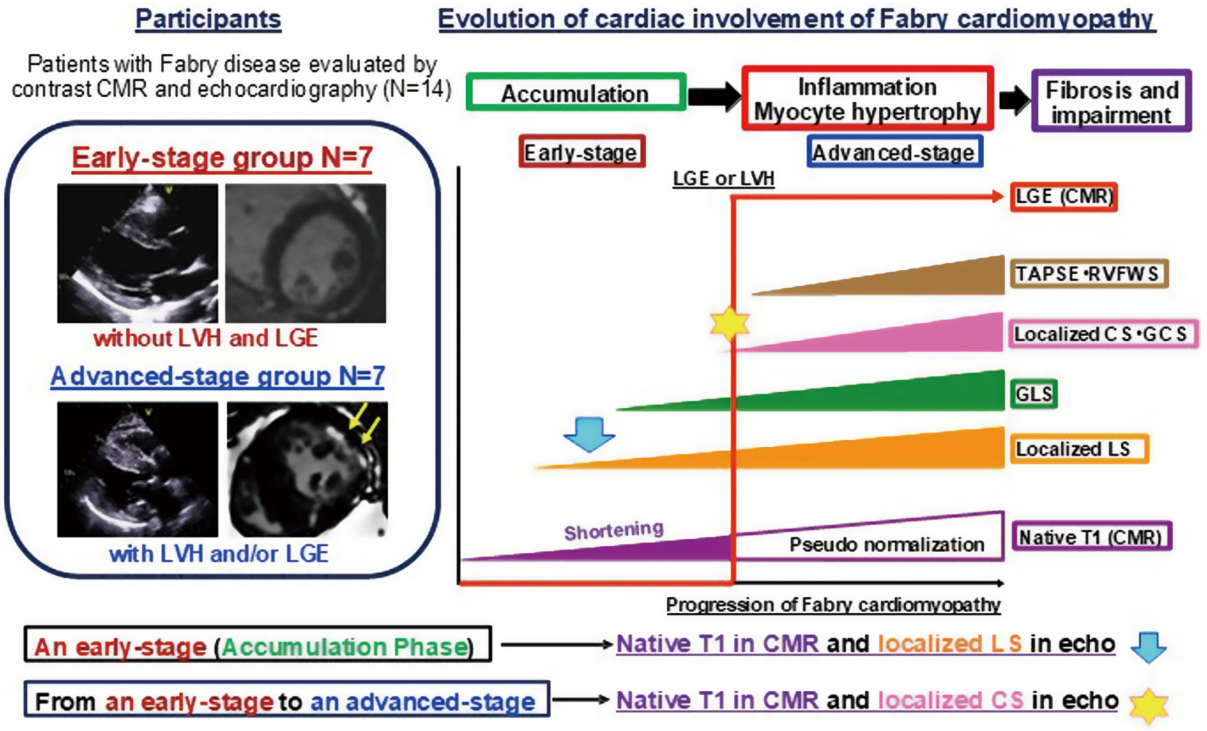

Figure 4. Usefulness of a combination of cardiac magnetic resonance (CMR) and echocardiography for staging Fabry cardiomyopathy. (**Left panel**) The 14 study participants. The early-stage group included 7 patients without left ventricular hypertrophy (LVH) or late gadolinium enhancement (LGE). The advanced-stage group included 7 patients with LVH and/or LGE. (**Right panel**) The relationship between progression of Fabry cardiomyopathy and CMR and echocardiographic parameters. Shortening of the native T1 and reduction in localized longitudinal strain in the basal posterolateral segment were key parameters for detecting early-stage Fabry cardiomyopathy (light blue arrow). Reduction of localized circumferential strain (CS) in the basal posterolateral segment was the most useful echocardiography parameter for differentiating early-stage and advanced-stage Fabry cardiomyopathy (yellow star). GCS, global circumferential strain; GLS, global longitudinal strain; LS, longitudinal strain; RVFWS, right ventricular free wall strain; TAPSE, tricuspid annular plane systolic excursion.

parameters for early detection of Fabry cardiomyopathy; this was observed even when GLS, GCS, localized CS, ECV, and RV function were within the normal ranges at this stage. The second was that a reduction of localized CS was the most useful echocardiographic parameter for differentiating between early-stage and advanced-stage Fabry cardiomyopathy. This parameter notably enhanced the predictive accuracy of the model that incorporated localized native T1 in CMR.

Evolution of Cardiac Involvement in Fabry Disease and Importance of Early Initiation of ERT

Three phases of cardiac involvement in Fabry disease have been proposed: an accumulation phase, an inflammation and myocyte hypertrophy phase, and a fibrosis and impairment phase.[2,3] First, in the accumulation phase, accumulation of Gb3 affects all cardiac cells and tissues. Second, in the inflammation and myocyte hypertrophy phase, accumulation of Gb3 in the myocardium leads to localized LVH, and involvement of intramural vessels or conduction tissue induces myocardial ischemia or conduction disturbances. Last, in the fibrosis and impairment phase, progression to diffuse LVH and/or fibrosis results in ventricular arrhythmias.[3] In the present study, the early-stage is consistent with the accumulation phase, and the inflammation and myocyte hypertrophy and fibrosis and impairment phases are included in the advanced-stage. Previous studies have already demonstrated that ERT is more effective and contributes to an extension of life if it is started before reaching an advanced-stage of diffuse LVH and myocardial fibrosis identified using LGE on CMR.[6,7] However, ERT requires patients to attend hospital every 2 weeks, and most patients seen in clinical settings have no desire to start ERT unless they are symptomatic or have organic dysfunction. Therefore, early detection of Fabry cardiomyopathy using non-invasive multimodality imaging is essential so that patients can appreciate their disease stage and make the decision of early initiation of ERT.

Changes in Echocardiographic and CMR Parameters With Progression of Fabry Cardiomyopathy

As demonstrated in the present study and in previous studies, the native T1 in CMR is shortened even in the accumulation phase before onset of LVH.[4,9,20] In particular, as described in the representative case shown in **Figure 2**, the native T1 is shortened from the basal posterolateral segment, where myocardial change first develops. The native T1 value was within normal limits in patients in the present study with advanced-stage Fabry cardiomyopathy, as shown in **Figure 1**. This indicates that inflammation and/or

fibrosis of cardiomyocytes, especially in the basal posterolateral segment, prolong the native T1 (pseudo-normalization). Therefore, shortening of the native T1 is a valuable parameter for detecting early-stage Fabry cardiomyopathy (i.e., the accumulation phase). However, as the disease progresses, the pseudo-normalized native T1 makes it difficult to distinguish patients at an advanced-stage from normal subjects if it were not for the findings of LGE on CMR. ECV in CMR is also an important parameter for detecting dilated interstitial spaces between cells.[15,21] However, Fabry disease is predominantly an intracellular storage disease; therefore, ECV is typically normal or at the upper limit.[3,21] Use of the native T1 may be more useful than ECV for detecting patients with Fabry cardiomyopathy, especially when it is at an early-stage.

In terms of echocardiographic parameters, a significant correlation between strain parameters (GLS and GCS) and severity of myocardial fibrosis was found in patients with advanced heart failure.[22] We found that localized LS was already reduced in the basal posterolateral segment in patients at an early-stage (accumulation phase), although GLS, localized CS, and GCS were at a normal or lower limit. This reflects the fact that accumulation of Gb3 initiates from the basal posterolateral segment and leads to a reduction in localized LS despite normal GLS. The reduction of localized LS might start at a very early-stage; therefore, this parameter is useful for the early detection of Fabry cardiomyopathy. In contrast, reduction of GLS, localized CS, and GCS may be a red flag for progression from an early-stage to an advanced-stage.[23,24] Regarding RS, no statistical differences were shown between the 2 groups in the present study, and usefulness for measuring RS in patients with hypertrophy is controversial, and there are few previous studies related to radial function.[25–27] Therefore, RS was not included in the present study in useful echocardiographic parameters for distinguishing the early-stage from the advanced-stage.

RV Function in Fabry Cardiomyopathy

Several studies have reported RV involvement in Fabry cardiomyopathy.[10,28,29] However, the relationship between disease progression and RV parameters has been unclear. In the present study, TAPSE and RVFWS, which reflect RV longitudinal function, were reduced at an advanced-stage, although FAC using echocardiography and RVEF using CMR indicated no change in global RV function. Early phase RV dysfunction may be better detected by RV longitudinal function than by global RV function. Given that the wall of the RV is thinner than that of the LV, it is difficult to evaluate the native T1 value in the RV wall in CMR for early detection of Fabry cardiomyopathy. Reduction of RV longitudinal function may be a red flag indicating progression from an early-stage to an advanced-stage, as well as strain parameters in the left ventricle.

Combination of Echocardiographic and CMR Parameters for Distinguishing Between Early-Stage and Advanced-Stage Fabry Cardiomyopathy

As mentioned earlier, it is essential to be able to recognize the stage of Fabry cardiomyopathy, particularly before it reaches an advanced-stage with LVH and/or LGE. Recognition of disease progression makes it possible to lead patients to ERT before appearance of any symptoms or advanced cardiac dysfunction. Even in the accumulation phase (early-stage), shortening of the native T1 and reduction of local LS have already started. Considering our findings, diagnosis using a combination of shortening of the localized native T1 in CMR and reduction of localized CS or GCS in echocardiography is useful for detecting progression of disease from an early-stage to an advanced-stage. Using the native T1 alone is not appropriate because pseudo-normalization is seen at an advanced-stage. Therefore, diagnosis based on a combination of CMR and echocardiography is ideal for staging Fabry cardiomyopathy and making a decision regarding the timing of starting ERT.

Study Limitations

The present study has several limitations. First, in line with the rarity of the disease, the study included a small number of patients with Fabry disease from a single center. Second, the number of male patients was small, and all of them were in the early-stage group. Third, echocardiographic and CMR parameters were not compared with histological findings. Fourth, the longitudinal transition of each patient could not be followed. The stage was judged at the time of diagnosis when echocardiography and CMR were performed. Moreover, the relationship between parameters of imaging modalities and prognosis was not investigated.[30] Last, native T1 values and echocardiographic strain parameters are specific to the instruments.[15,18] In the present study, CMR and echocardiography were performed using the same instrument in each patient; thus, there were no differences in instruments that needed to be considered. However, the specificities of instruments are major barriers when multicenter studies are conducted, and this is the main reason why the present study evaluating native T1 values and echocardiographic strain parameters is conducted in a single center and with a small number of patients.

Conclusions

A combination of localized native T1 on CMR and echocardiographic strain parameters could be useful for staging Fabry cardiomyopathy.

Acknowledgments

None.

Disclosures

The authors have nothing to disclose in connection with this article.

IRB Information

The National Cerebral and Cardiovascular Center ethics committee approved this study (Study no. R2003-2).

Data Availability

The data that support the findings of the present study are available from the corresponding author (M. Amano) on reasonable request. The individual deidentified participant data will be shared immediately following publication, with no end date. The data will be shared on a request basis for anyone who wishes to access the data. The data can be applicable for any kind of analyses and will be shared as Excel via email or URL link for downloading.

References

1. Zarate YA, Hopkin RJ. Fabry's disease. *Lancet* 2008; **372:** 1427–1435.
2. Nordin S, Kozor R, Medina-Menacho K, Abdel-Gadir A, Baig S, Sado DM, et al. Proposed stages of myocardial phenotype development in Fabry disease. *JACC Cardiovasc Imaging* 2019;

12: 1673–1683.
3. Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovac AC, et al. Cardiac involvement in Fabry disease: JACC Review Topic of the Week. *J Am Coll Cardiol* 2021; **77:** 922–936.
4. Militaru S, Ginghina C, Popescu BA, Saftoiu A, Linhart A, Jurcut R. Multimodality imaging in Fabry cardiomyopathy: From early diagnosis to therapeutic targets. *Eur Heart J Cardiovasc Imaging* 2018; **19:** 1313–1322.
5. Sheppard MN, Cane P, Florio R, Kavantzas N, Close L, Shah J, et al. A detailed pathologic examination of heart tissue from three older patients with Anderson-Fabry disease on enzyme replacement therapy. *Cardiovasc Pathol* 2010; **19:** 293–301.
6. Kampmann C, Perrin A, Beck M. Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: Cardiac outcomes after 10 years' treatment. *Orphanet J Rare Dis* 2015; **10:** 125.
7. Krämer J, Niemann M, Störk S, Frantz S, Beer M, Ertl G, et al. Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease. *Am J Cardiol* 2014; **114:** 895–900.
8. Kobayashi M, Ohashi T, Sakuma M, Ida H, Eto Y. Clinical manifestations and natural history of Japanese heterozygous females with Fabry disease. *J Inherit Metab Dis* 2008; **31:** 483–487.
9. Pica S, Sado DM, Maestrini V, Fontana M, White SK, Treibel T, et al. Reproducibility of native myocardial T1 mapping in the assessment of Fabry disease and its role in early detection of cardiac involvement by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2014; **16:** 99.
10. Lillo R, Graziani F, Panaioli E, Mencarelli E, Pieroni M, Camporeale A, et al. Right ventricular strain in Anderson-Fabry disease. *Int J Cardiol* 2021; **330:** 84–90.
11. Meucci MC, Lillo R, Del Franco A, Monda E, Iannaccone G, Baldassarre R, et al. Prognostic implications of the extent of cardiac damage in patients with Fabry disease. *J Am Coll Cardiol* 2023; **82:** 1524–1534.
12. Hiwot T, Hughes D, Ramaswami U. Guidelines for the treatment of Fabry disease. https://bimdg.org.uk/store/lsd//FabryGuide_LSDSS_Jan2020_700523_11032020.pdf (accessed May 6, 2024).
13. Hashimura H, Kimura F, Ishibashi-Ueda H, Morita Y, Higashi M, Nakano S, et al. Radiologic-pathologic correlation of primary and secondary cardiomyopathies: MR imaging and histopathologic findings in hearts from autopsy and transplantation. *Radiographics* 2017; **37:** 719–736.
14. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017; **19:** 75.
15. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: A comprehensive review. *J Cardiovasc Magn Reson* 2016; **18:** 89.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28:** 1–39.e14.
17. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: A consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2018; **19:** 591–600.
18. Takigiku K, Takeuchi M, Izumi C, Yuda S, Sakata K, Ohte N, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circ J* 2012; **76:** 2623–2632.
19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988; **44:** 837–845.
20. Camporeale A, Pieroni M, Pieruzzi F, Lusardi P, Pica S, Spada M, et al. Predictors of clinical evolution in prehypertrophic Fabry disease. *Circ Cardiovasc Imaging* 2019; **12:** e008424.
21. Sado DM, Flett AS, Banypersad SM, White SK, Maestrini V, Quarta G, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. *Heart* 2012; **98:** 1436–1441.
22. Cameli M, Mondillo S, Righini FM, Lisi M, Dokollari A, Lindqvist P, et al. Left ventricular deformation and myocardial fibrosis in patients with advanced heart failure requiring transplantation. *J Card Fail* 2016; **22:** 901–907.
23. Gruner C, Verocai F, Carasso S, Vannan MA, Jamorski M, Clarke JT, et al. Systolic myocardial mechanics in patients with Anderson-Fabry disease with and without left ventricular hypertrophy and in comparison to nonobstructive hypertrophic cardiomyopathy. *Echocardiography* 2012; **29:** 810–817.
24. Esposito R, Galderisi M, Santoro C, Imbriaco M, Riccio E, Maria Pellegrino A, et al. Prominent longitudinal strain reduction of left ventricular basal segments in treatment-naïve Anderson-Fabry disease patients. *Eur Heart J Cardiovasc Imaging* 2019; **20:** 438–445.
25. Spinelli L, Giugliano G, Imbriaco M, Esposito G, Nappi C, Riccio E, et al. Left ventricular radial strain impairment precedes hypertrophy in Anderson-Fabry disease. *Int J Cardiovasc Imaging* 2020; **36:** 1465–1476.
26. Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W, et al. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study. *Circulation* 2003; **108:** 1299–1301.
27. Shanks M, Thompson RB, Paterson ID, Putko B, Khan A, Chan A, et al. Systolic and diastolic function assessment in Fabry disease patients using speckle-tracking imaging and comparison with conventional echocardiographic measurements. *J Am Soc Echocardiogr* 2013; **26:** 1407–1414.
28. Niemann M, Breunig F, Beer M, Herrmann S, Strotmann J, Hu K, et al. The right ventricle in Fabry disease: Natural history and impact of enzyme replacement therapy. *Heart* 2010; **96:** 1915–1919.
29. Graziani F, Lillo R, Panaioli E, Pieroni M, Camporeale A, Verrecchia E, et al. Prognostic significance of right ventricular hypertrophy and systolic function in Anderson-Fabry disease. *ESC Heart Fail* 2020; **7:** 1605–1614.
30. Orsborne C, Bradley J, Bonnett LJ, Pleva LA, Naish JH, Clark DG, et al. Validated model for prediction of adverse cardiac outcome in patients with Fabry disease. *J Am Coll Cardiol* 2022; **80:** 982–994.