BRIEF COMMUNICATION

Myocardial T₁-mapping and Extracellular Volume Quantification in Patients and Putative Carriers of Muscular Dystrophy: Early Experience

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To assess myocardial fibrosis associated with muscular dystrophy, T₁-mapping and extracellular volume fraction (ECV) quantification was prospectively performed using cardiovascular MR (CMR) imaging in 6 male patients with muscular dystrophy and 5 female putative carriers of Duchenne or Becker muscular dystrophy. Five patients and all putative carriers had an elevated ECV (>29.5% for men and >35.2% for women), suggesting that ECV has a potential to detect diffuse fibrotic changes in patients and putative carriers of muscular dystrophy.

Keywords: cardiovascular magnetic resonance imaging, T₁-mapping, extracellular volume fraction, muscular dystrophy, putative carrier

Introduction

Muscular dystrophy is characterized by progressive wasting and weakness of skeletal muscles that result from mutations in many genes affecting striated muscle. For many muscular dystrophies, cardiac complications are a major cause of morbidity and mortality. The most common form of cardiac involvement in muscular dystrophy is dilated cardiomyopathy, presenting as an age-related progression of left ventricular (LV) dysfunction and myocardial fibrosis detected by late gadolinium enhancement (LGE) cardiovascular MR (CMR) imaging. Accurate evaluation of myocardial fibrosis could be useful for risk stratification and determining early initiation of cardioprotective treatment in patients with muscular dystrophy. Cardiomyopathy associated with muscular dystrophy has also been reported in female carriers of Duchenne and Becker muscular dystrophy. These female carriers are basically asymptomatic, and their myocardial fibrosis are likely to precede the development of LV dysfunction. Although LGE is well established for detecting myocardial fibrosis, LGE cannot detect diffuse fibrotic changes in the myocardium. The image contrast in LGE strongly depends on the difference in post-contrast signal intensity between diseased and normal myocardium, which is attenuated by diffuse myocardial fibrosis. Previous studies suggested that native T₁ values and extracellular volume fraction (ECV) mapping using CMR might be more suitable for detecting diffuse myocardial fibrosis. Therefore, this study aimed to detect diffuse myocardial fibrosis in patients and putative carriers of muscular dystrophy by myocardial T₁-mapping CMR.

Materials and Methods

Patients with muscular dystrophy and female putative carriers of Duchenne or Becker muscular dystrophy were prospectively recruited at Hokkaido University Hospital, Japan, between August 2019 and March 2020. Inclusion criteria in the patient group were: (1) patients diagnosed with muscular dystrophy based on a clinical examination, dystrophin gene analysis, muscle biopsy, or family history of muscular dystrophy; (2) ≥6 years of age; and (3) referred for clinically indicated CMR. Inclusion criteria in the putative carrier group were women ≥20 years of age who had a first-degree male relative with a confirmed diagnosis of Duchenne or Becker muscular dystrophy. Exclusion criteria were participants with renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m²), contraindications to CMR, or limited life expectancy. The study was approved by the Institutional Review Board of Hokkaido University Hospital.
Results

Six patients with muscular dystrophy and five female putative carriers of Duchenne or Becker muscular dystrophy participated in this study. Characteristics of study participants are shown in Table 1. All 6 patients were male with a median age of 16 (range, 8.6–34.4) years, while the median age of 5 putative carriers was 46 (range, 43.0–51.7) years. The patient group was included patients with Duchenne muscular dystrophy (n = 2), Becker muscular dystrophy (n = 3), and myotonic dystrophy (n = 1). Four patients were being treated with angiotensin-converting enzyme inhibitor, and 2 of these 4 patients were also treated with β-blocker. All putative carriers were mothers of confirmed male patients with Duchenne or Becker muscular dystrophy without any symptoms and known comorbidities, and all of them had normal levels of cardiac biomarkers including NT-proBNP and troponin T. Of the 11 participants, Case 3 was the brother of Case 4, and Case 9 was the mother of Case 2. Four of the patients and 1 of the putative carriers had a reduced LV ejection fraction (<55%).

Representative CMR images are shown in Fig. 1. Four patients and 2 putative carriers showed visually detected LGE. The median LGE extent was 6.2% (range, 5.3–14.6%) of LV mass in the patient group. Five patients and all putative carriers had an elevated ECV. The median values of ECV in the patient and putative carrier groups were 34.8% (range, 27.6–43.8%) and 37.4% (range, 36.1–39.8%), respectively. When comparing CMR findings between patients and putative carriers in the same family, a similar distribution of LGE was observed in both families: Case 3 and 4 (brothers with Becker muscular dystrophy) showed subepicardial hyperenhancement in the lateral wall; Case 2 and 9 (mother and son with Duchenne muscular dystrophy) showed midwall hyperenhancement in the septal and lateral walls (Fig. 1).

Discussion

This study showed that diffuse myocardial fibrosis detected by elevated ECV was observed both in patients with muscular dystrophy and female putative carriers. Previous studies have shown the utility of myocardial T1 values and ECV for detecting myocardial fibrosis in patients with Duchenne and Becker muscular dystrophy.10,15,17,18 In the present study, elevated ECV was observed even in female putative carriers without LGE. Furthermore, mild diffuse fibrosis detected ECV appears to precede the development of LV dysfunction or substantial LGE, suggesting that myocardial tissue characterization by T1-mapping and ECV may be more sensitive to detect cardiac involvement in muscular dystrophy compared to conventional CMR techniques.

The similarity of LGE findings between female carriers of Duchenne or Becker muscular dystrophy and their male relatives was in agreement with previous studies.7 Although
### Table 1  Characteristics of study participants

| Characteristics                  | Patients                  | Putative carriers          |
|----------------------------------|---------------------------|-----------------------------|
|                                  | Case 1  | Case 2  | Case 3  | Case 4  | Case 5  | Case 6  | Case 7  | Case 8  | Case 9  | Case 10 | Case 11 |
| Age (years)                      | 8.6     | 13.3    | 13.7    | 18.3    | 20.1    | 34.4    | 43.0    | 44.4    | 46.0    | 46.5    | 51.7    |
| Sex                              | Male    | Male    | Male    | Male    | Male    | Male    | Female  | Female  | Female  | Female  | Female  |
| Type of muscular dystrophy       | Duchenne | Duchenne | Becker  | Becker  | Myotonic | Becker  | Becker  | Becker  | Becker  | Duchenne |
| Body mass index (kg/m²)          | 15.5    | 16.3    | 17.8    | 23.8    | 17.9    | 21.7    | 20.8    | 19.5    | 21.8    | 19.9    | 21.3    |
| Wheelchair bound                 | No      | Yes     | No      | No      | No      | No      | No      | No      | No      | No      | No      |
| Medications                      | None    | Enalapril 10 mg/day | None    | Enalapril 10 mg/day, Bisoprolol 1.25 mg/day | Enalapril 5 mg/day, Carvedilol 5 mg/day | None |
| Blood data                       |         |         |         |         |         |         |         |         |         |         |         |
| Creatine kinase (IU/L)           | 6509    | 2739    | 1430    | 2158    | 240     | 328     | 66      | 76      | 192     | 71      | 93      |
| NT-proBNP (pg/mL)                | 189     | 80      | NA²     | 302     | 26      | 7       | 99      | 47      | 67      | 39      | 51      |
| Troponin T (ng/mL)               | 0.059   | 0.115   | 0.024   | 0.073   | 0.046   | 0.005   | ≤0.014  | ≤0.014  | ≤0.014  | ≤0.014  | ≤0.014  |
| Hematocrit (%)                   | 40.8    | 40.8    | 38.0    | 40.8    | 47.9    | 47.5    | 37.5    | 40.2    | 40.6    | 42.6    | 38.8    |
| CMR findings                     |         |         |         |         |         |         |         |         |         |         |         |
| LVEF (%)                         | 57.6    | 54.0    | 56.5    | 31.8    | 46.4    | 53.7    | 56.2    | 61.0    | 49.6    | 60.3    | 65.3    |
| LVEDVI (mL/m²)                   | 53.5    | 50.5    | 49.4    | 115.0   | 68.9    | 53.9    | 51.1    | 65.7    | 62.5    | 58.6    | 54.0    |
| LVESVI (mL/m²)                   | 22.7    | 23.2    | 21.5    | 78.4    | 37.0    | 25.0    | 22.3    | 25.6    | 31.5    | 23.3    | 18.7    |
| LV mass (g)                      | 23.7    | 36.8    | 30.9    | 79.3    | 33.4    | 44.8    | 37.6    | 28.7    | 39.9    | 29.8    | 53.0    |
| LVMi (g/m²)                      | 26.7    | 32.6    | 23.7    | 46.7    | 21.2    | 27.2    | 26.5    | 19.4    | 26.4    | 18.3    | 33.3    |
| LGE extent, % of LV mass§        | NA³     | 6.8     | 6.2     | 14.6    | 0       | 5.3     | 0       | 2.3     | 19.8    | 0.5     | 1.2     |
| Native T₁ value (ms)             |         |         |         |         |         |         |         |         |         |         |         |
| Basal (mean)                     | 1292    | 1326    | 1325    | 1316    | 1279    | 1195    | 1269    | 1306    | 1293    | 1267    | 1259    |
| Mid-ventricular (mean)           | 1276    | 1377    | 1300    | 1264    | 1240    | 1207    | 1336    | 1341    | 1334    | 1330    | 1269    |
| Apical (mean)                    | 1354    | 1480    | 1315    | 1452    | 1357    | 1297    | 1312    | 1408    | 1341    | 1407    | 1287    |
| ECV (%)                          | 32.3    | 39.7    | 37.0    | 43.8    | 32.6    | 27.6    | 38.7    | 39.8    | 36.1    | 37.4    | 36.7    |

³Case 3 was the brother of Case 4, and Case 9 was the mother of Case 2. ²The normal reference ranges for NT-proBNP and troponin T are ≤55 pg/mL and ≤0.014 ng/mL, respectively. ³The plasma level of brain natriuretic peptide (normal reference range, ≤18.4 pg/mL) in Case 3 was 7.3 pg/mL. ⁴Case 1 did not have sufficient image quality for LGE analysis due to an incomplete breath-hold. BNP, brain natriuretic peptide; CMR, cardiovascular magnetic resonance; ECV, extracellular volume fraction; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMi, left ventricular mass index; NA, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide.
further studies are still needed to confirm this observation, CMR screening should be considered in putative female carriers who had male relatives with muscular dystrophy-related cardiomyopathy. Since the number of participants is small in this early experience, large-scale studies and long-term follow-up are needed to substantiate clinical utility of myocardial T₁-mapping, to adjust genetic background including the parent–child relationship, and to evaluate the long-term effects of myocardial ECV on changes in LV ejection fraction and outcomes in patients and putative carriers of muscular dystrophy.

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Conflicts of Interest

Dr. Aikawa was supported by postdoctoral fellowships from the Uehara memorial Foundation, the Kanzawa Medical Research Foundation, the Suginome Memorial Foundation, and the Nakayama Foundation for Human Science; and was affiliated with a department with endowments from Medtronic Japan and Win International.

Fig. 1 Representative images in a putative carrier of Becker muscular dystrophy (Case 10), a patient with Duchenne muscular dystrophy (Case 2), and the mother of Case 2 (Case 9; a putative carrier of Duchenne muscular dystrophy). Case 2 and 9 show nonischemic patchy hyperenhancement (yellow arrows) on the LGE image and abnormal pre- and post-contrast T₁ values located in the same areas. Both putative carriers had an elevated extracellular volume fraction (37.4% and 36.1%, respectively). LGE, late gadolinium enhancement.
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