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LETTERS TO THE EDITOR

CMR Detects Subclinical Cardiomyopathy in Mother-Carriers of Duchenne and Becker Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder, leading to reduced/abnormal dystrophin. Becker muscular dystrophy (BMD) is a milder form, caused by the same mutation, with a nearly normal life expectancy, but with a 50% chance of cardiac involvement (CI) (1). Although female carriers are usually free of symptoms, they may develop peripheral myopathy and cardiomyopathy, contributing to heart failure (HF) (1).

Our aim was to evaluate the possibility of myocardial damage in genetically confirmed mothers-carriers of Duchenne muscular dystrophy (DMDc) and Becker muscular dystrophy (BMDc) using cardiac magnetic resonance (CMR).

Thirty-five mothers, mean age 50 years (range: 32 to 68 years), without known comorbidities, except mild hypertension (systolic blood pressure 160 to 170 mm Hg in 1 DMDc and 1 BMDc), were studied. DMDc (n = 25) and BMDc (n = 10) were prospectively evaluated by CMR using a 1.5-T General Electric Signa HDxt (Milwaukee, Wisconsin). A standard steady-state free-precession (SSFP) sequence (FIESTA) (echo time = 1.5 ms, repetition time = 3.1 ms, flip angle = 70°, slice thickness = 8 mm) was used to measure the left ventricular ejection fraction (LVEF). To assess fibrosis, 0.2 mmol/kg gadolinium diethylenetriamine penta-acetic acid was administered, and late gadolinium-enhanced (LGE) images were taken 15 min later, using a 3-dimensional–T1-turbo field echo sequence (flip angle = 15°, echo time = 1.4 ms, repetition time = 5.5 ms, inversion time 225 to 275 ms as individually optimized to null myocardial signal, gap = 0, slice thickness = 6 mm). A threshold of >6 SD exceeding the mean was used to define LGE images (2). Summing the planimetered LGE areas in all short-axis slices yielded the total volume, expressed as a proportion of left ventricular (LV) myocardium (percentage of LGE).

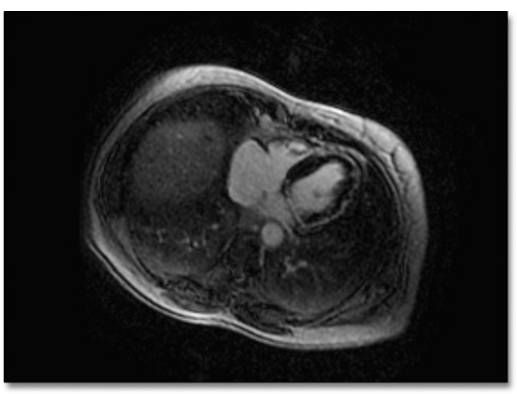

Figure 1. Late Gadolinium-Enhanced Image of a Becker Muscular Dystrophy Carrier With Mild Epicardial Fibrosis in the Lateral Wall of the Left Ventricle

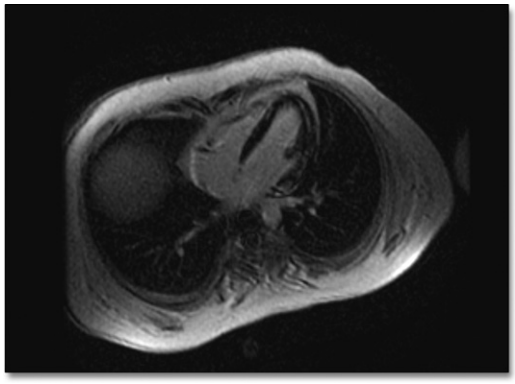

Figure 2. Late Gadolinium-Enhanced Image of a Duchene Muscular Dystrophy Carrier With Severe Epicardial Fibrosis in the Lateral Wall of the Left Ventricle

Measurements were expressed as mean ± SD or mean (range). Statistical significance was investigated by unpaired Student *t* test. Correlation was sought with Pearson correlation coefficient. The Mann-Whitney test and Spearman correlation coefficient were used for nonparametric data. Statistical significance was considered $p < 0.05$.

Eight DMDc and 1 BMDc presented with muscle weakness, recognized by the subjects, but which did not affect daily activities. Cardiac symptoms were documented only in 5 of 25 DMDc. Creatine kinase (CK) was measured in all carriers. CK values of 290 ± 120 IU/l (normal values <190 IU/l) were identified in 15 of 35 (42.8%) carriers (13 [52%] DMDc and 2 [20%] BMDc). CMR documented decreased LVEF in 10 DMDc and subepicardial LGE images in posterolateral and/or septal LV wall in 18 DMDc and 5 BMDc (Figs. 1 and 2). No difference in LGE morphology was identified between DMDc and BMDc. LGE images correlated negatively with LVEF ($p < 0.001$) and were greater in DMDc compared with BMDc (16 ± 2% vs. 3 ± 1%, $p < 0.001$, respectively). Carriers >40 years old had more extensive lesions compared with those <40 years old (14 ± 2% vs. 3 ± 1%, $p < 0.001$). The lack of comorbidities that could be possibly related to CMR findings strengthens the role of abnormal dystrophin in their pathogenesis. Carriers' characteristics are presented in Table 1.

According to previous studies, 12% of BMDc presented with muscle weakness, and CK was increased in 30% to 62% (1,3,4). In our study, although some BMDc had muscular symptoms and increased CK, the majority was asymptomatic with normal CK. The prevalence of CI on electrocardiography (ECG) and echocardiography and the possibility of dilated

Table 1. DMDc and BMDc Clinical Characteristics and Comorbidities

	DMD (n = 25)	BMD (n = 10)
Age (yrs) (median, range)	48 (33–65)	52 (31–69)
Height (cm) (median, range)	170 (158–175)	168 (160–172)
Weight (kg) (median, range)	70 (62–78)	74 (65–80)
Diabetes mellitus	0	0
Hypertension (SBP 160–170 mm Hg)	1/25	1/10
Dyslipidemia	0	0
Smoking	0	0
Alcohol consumption	0	0
Infections that could possibly induce myocardial damage	0	0
Valvular disease	0	0
BMI (kg/m^2) (median, range)	23 (18–26)	24 (19–27)
ECG	1. Nonspecific ST-changes (6/25) 2. Negative T in leads V_4 to V_6 (6/25)	Nonspecific ST-changes (2/10)
24-h ECG recording	1. Sinus tachycardia (10/25) 2. Supraventricular extrasystolic beats (10/25) 3. Ventricular extrasystolic beats (5/25) 4. Bigeminy (3/25) 5. Couples (2/25)	Supraventricular extrasystolic beats (2/10)
ECHO (LV dysfunction)	6/25	0
CMR (normal LV function)	15/25 LVEF 69.4 ± 4.3% LVEDV 131.9 ± 33.0 ml LVESV 40.2 ± 13.6 ml	10/10 LVEF 70.3 ± 2.5% LVEDV 174.5 ± 31.3 ml LVESV 51.0 ± 14.1 ml
CMR (LV dysfunction)	10/25 LVEF 45.0 ± 2.9% LVEDV 186.4 ± 46.0 ml LVESV 107.1 ± 29.8 ml	0
LGE (+)	18/25 (10 with low LVEF/8 with normal LVEF)	5/10 (all with normal LVEF)
Abnormal serum CPK	13/25 (52%)	2/10 (20%)

Values are n, median (range), or mean ± SD, unless specified otherwise.
BMDc = Becker muscular dystrophy carriers; BMI = body mass index; CMR = cardiac magnetic resonance; CPK = creatine protein kinase; DMDc = Duchenne muscular dystrophy carriers; ECG = electrocardiography: ECHO = echocardiography; LGE = late gadolinium-enhanced; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; SBP = systolic blood pressure.

cardiomyopathy (dCMP) varied widely (3,4). CI in BMDc appears after the age of 16 years and may remain subclinical with advancing age in up to two-thirds of subjects. It can be manifested as ECG changes in two-fifths or as dCMP in up to one-fifth of cases (3). Our BMDc findings were in agreement with previous studies identifying normal ECG and echocardiographic results in the majority of subjects.

DMDc are more likely to develop dCMP at a young age (3). A 2002 consensus estimated that 10% of all DMDc or BMDc develop dCMP, even without skeletal muscle involvement (3). However, the impact of increased dCMP risk on life expectancy is still unclear (3). Although only a minority of our patients presented with muscular involvement, some DMDc already had LV impairment and rhythm disturbances. These findings were in agreement with previous studies supporting that CI is independent of muscular disturbances in DMDc (3).

Recently, CMR has been successfully used to identify myocardial fibrosis in subclinical DMDc or BMDc (4,5). However, except for case reports (4,5), there are not enough data about CMR in dystrophinopathy carriers. In our study, we identified myocardial fibrosis in the majority of carriers, with a significant superiority in severity of DMDc over BMDc and older carriers over younger carriers. The inverse correlation of fibrotic area, identified by LGE imaging, with LVEF supports the role of fibrosis in the development of HF (1,2). Furthermore, CMR proved to be of great significance documenting CI in a percentage higher than that identified by routine assessment.

The study limitations were that the population of studied carriers was small, young female carriers were not included, and long-term follow-up was not available.

To conclude, CMR documented myocardial fibrosis in the majority of dystrophinopathy carriers, although the usual assessment was mildly abnormal. However, the clinical implications of CMR and the necessity for early cardiac treatment need further evaluation.

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Interval from the Onset of Transmitral Flow to Annular Velocity Is a Marker of LV Filling Pressure

Recently, the time interval between the onset of early diastolic transmitral flow velocity (E) and mitral annular velocity (e′) ($T_{E\text{-}e'}$) was proposed as a new index representing left ventricular (LV) relaxation. A problem with the measurement of $T_{E\text{-}e'}$ was that E and e′ could not be measured in the same beat. However, a novel dual Doppler echocardiographic method has been introduced that allows the measurement of both E and e′ in the same beat (1), and E/e′ and $T_{E\text{-}e'}$ can be instantly calculated. The aims of this study were to: 1) investigate the usefulness of single-beat $T_{E\text{-}e'}$ compared with invasive hemodynamic measurements; and 2) determine the impact of pre-load alterations by leg-positive pressure (LPP) on the relationship between $T_{E\text{-}e'}$ and increased LV filling pressure.

We designed a prospective study to assess 42 consecutive patients who underwent catheterization for diagnosis of stable angina pectoris. Twenty-one age- and sex-matched healthy volunteers served as the control group. Patients with atrial fibrillation, valve diseases, severe heart failure, LV systolic dysfunction (LV ejection fraction <40%), or a regional wall motion abnormality at the basal, lateral, or septal region were excluded.

A total of 63 pairs of echocardiographic examinations were performed at baseline and during LPP. We used an ultrasound machine EUB-7500 (Hitachi Medical Corporation, Kashiwa, Japan). A 5-F Millar transducer with single lumen was introduced into the LV. Tau and LV end-diastolic pressure (LVEDP) were determined from the LV pressure curve, and measurements were performed simultaneously with the echocardiographic measurements. We customized a commercially available leg massage machine (Dr. Medomer DM-5000EX, Medo Industries, Tokyo, Japan) because it could maintain the same pressure loading (90 mm Hg) for 5 min.

Values are expressed as mean ± SD. The diagnostic ability of echocardiographic parameters to discriminate elevated LVEDP (>16 mm Hg) was determined by analysis of receiver-operating characteristic (ROC) curves. Reproducibility was expressed as the intraclass correlation coefficients (ICC) in a group of 10 randomly selected subjects by 1 observer, and then repeated on 2 separate days by 2 investigators.

The clinical characteristics and the influence of LPP in both groups are shown in Table 1. A representative case is shown in Figure 1. There was a correlation between $T_{E\text{-}e'}$ and LVEDP at baseline ($r = 0.71$, $p < 0.001$) and during LPP ($r = 0.82$, $p < 0.001$). There was also a relationship between the change in LVEDP in response to LPP and the change in $T_{E\text{-}e'}$ ($r = 0.50$, $p < 0.001$). The $T_{E\text{-}e'}$ (standardized beta = 0.73, $p < 0.001$ at baseline and standardized beta = 0.89, $p < 0.001$ during LPP) was an independent predictor of the LVEDP in multivariate regression analysis with adjustment for age and sex. A ROC curve (area under the curve [AUC] = 0.93) was used to select a $T_{E\text{-}e'}$ cutoff of 38 ms (specificity: 91%; sensitivity: 85%) to predict elevated LVEDP (>16 mm Hg) during LPP. For differentiating elevated LVEDP during LPP, the AUC was significantly higher for the $T_{E\text{-}e'}$ compared with E/e′ (AUC = 0.93 vs. AUC = 0.72, $p = 0.004$). The $T_{E\text{-}e'}$ (standardized beta = 0.42, $p = 0.011$ at baseline and standardized beta = 0.71, $p < 0.001$ during LPP) were also independent predictors of tau in multivariate regression analysis with adjustment for age and sex. The ICC of intraobserver variability was 0.98 ($p < 0.001$), and interobserver variability was 0.95 ($p < 0.001$).

This study is the first to demonstrate that single-beat $T_{E\text{-}e'}$ correlated with invasively measured LV diastolic pressure, and that the $T_{E\text{-}e'}$ was a better predictor of LV filling pressure than E/e′. In addition, our study showed that $T_{E\text{-}e'}$ is pre-load–dependent compared with other Doppler parameters of LV diastolic function. $T_{E\text{-}e'}$ could be influenced by pre-load changes, especially with impaired LV relaxation.

We postulate that because the mitral E begins with the crossing of left atrial (LA) and LV pressures, an augmentation of LA pressure might shorten the time needed for LA and LV pressures to cross, and this would shorten the isovolumic relaxation time. The onset of e′ is influenced by LV active relaxation and the cardiac restoring forces in end diastole. As LV relaxation is delayed and early diastolic suction is reduced, the onset of e′ is delayed and follows the onset of the E wave. In addition, an augmentation in pre-load might prolong the duration of systole and delay the onset of e′. For these reasons, $T_{E\text{-}e'}$ was prolonged by a pre-load increase. The main limitation of this study was the small number of patients with elevated LVEDP at baseline (8 of 42).

Elevation of LVEDP prolongs $T_{E\text{-}e'}$, and this may be due to enhanced early diastolic mismatch between mitral inflow and annular motion. $T_{E\text{-}e'}$ is a sensitive noninvasive index for the estimation of LVEDP, and dual Doppler echocardiography is a practical method for the accurate measurement of this index in a single beat.

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