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Left ventricular volumes and function affected by myocardial fibrosis in patients with Duchenne and Becker muscular dystrophies: a preliminary magnetic resonance study

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Brief title:

The role of cardiac magnetic resonance in muscular dystrophies

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Introduction

Cardiac magnetic resonance (CMR) provides means for tissue characterization and has been used in different populations to assess global and regional functions, presence of edema, inflammation, necrosis and fibrosis of the heart chambers [1–4]. CMR can show early cardiac involvement when standard cardiovascular workup including 12-lead ECG, 24-hour ECG, and echocardiography, appears unrevealing [5]. The early identification of cardiac involvement in Duchenne muscular dystrophy (DMD) patients is important, as it allows for a timely introduction of cardioprotective therapy to slow down the progression of heart failure and to reduce symptoms [6]. Based on scarce data from limited cohort studies it is the fibrosis that is the most frequent and relevant abnormality evolving throughout patients' lifetime.

The aim of the study was to characterize cardiac involvement in Duchenne and Becker muscular dystrophy (BMD) patients across age groups.

Materials and Methods

We present a single centre cross-sectional observational study of the patients representing the DMD population from the entire country.

Inclusion and exclusion criteria as well as detailed CMR diagnostic procedure and protocol are presented in Supplementary Material.

The study was approved by the Institutional Bioethical Committee and all patients’ guardians gave their informed consent.

Statistical analysis was performed using Wizard Pro 1.9.33 (Evan Miller, Chicago, IL). Continuous variables are presented as mean (SD) or median (range) depending on the distribution. Chi-square test, Pearson and Spearman correlations were employed.
Results and Discussion

Out of 79 screened patients, 41 were enrolled considering inclusion/exclusion criteria and were successfully examined using CMR. They were all male, aged 12.0 (3.1) years, DMD 90.2%, n=37, BMD 9.8%, n=4. Left ventricle (LV) End Diastolic Volume index (LVEDVi) was 63.6 (17.4) ml/m2 and was decreased in 24% of patients. LV End Systolic Volume index (LVESVi) was 30.0 (9.0) ml/m2, abnormally high in 12% and abnormally low in 2% of patients. LV Stroke Volume index (LVSVi) was 37.0 (10.8) ml/m2, abnormally low in 39% and LV Ejection Fraction (LVEF) was 58% (6.4%), low in 44% of patients. Older patients had significantly lower LVEDVi-z \((r= -0.41, p=0.008, \text{Figure 1A})\) but not LVESVi-z \((p=0.16)\) (Figure 1B). Consequently, also negatively correlated with age were LVSVi-z \((r = -0.50, p < 0.001; \text{Figure 1C})\) and LVEF \((r = -0.36, p = 0.02, \text{Figure 1D})\). Also, the prevalence of patients with decreased LVSVi (Figure S1A), and decreased LVEF (Figure 1E) was growing in older age groups \((p = 0.001 \text{ and } p = 0.04 \text{ respectively})\).

Late gadolinium enhancement (LGE) was assessed in 39 patients and was positive in 38%, most often in mid-anterolateral 38%, basal-anterolateral 36%, basal-inferolateral 31%, mid-inferolateral 26% and apical-lateral segments 18% of the patients (Figure S2). In two, LGE images were termed non-diagnostic due to massive respiratory artifacts. LGE was significantly more prevalent in the older age groups \((p = 0.02, \text{Figure 1F})\). Also the fibrosis extensiveness positively correlated with age \((r = 0.036, p = 0.02, \text{Figure S1B})\). Noticeably no LGE was found in any of the BMD patients. The patients with positive LGE had significantly lower LVSVi-z \((-2.3 \text{ (1.0) vs -1.3 (1.1); } p = 0.02)\) and LVEF \((53.2 \text{ (5.5) vs 59.5 (5.3); } p < 0.001)\). Furthermore, the extent of fibrosis, irrespective of its pattern, correlated with decreased LVEF \((p < 0.001, r = -0.531, \text{Figure S1C})\). More detailed data can be found in Supplementary material (Tables S1-S4).
Our study presents preliminary cross-sectional data from a Polish cohort of DMD/BMD patients. In line with the previously published data [8,9] in DMD patients, we were able to show that LGE of the LV myocardium is associated with reduced LVEF. Moreover, our study confirmed that the extent of cardiac involvement increases with the disease progression resulting from advancing age, as previously demonstrated [10]. It is known that in DMD/BMD, myocardial necrosis starts from the posterobasal region of the left ventricle further progressing to other cardiac segments leading to heart remodeling, which is partly in line with our findings, where posterobasal and basal anterolateral regions of the LV were commonly involved, including the patients with smaller extent LGE.

Contrary to the previously published studies that suggested LV dilatation coupled with the reduction of LVEF [10], our observations showed decreased end-diastolic volumes with preserved end-systolic volumes, resulting in decreased stroke volume and LVEF, a pattern of involvement distinct from other cardiomyopathies. Enlargement of the LV was not noted as the study describes young population in an early stage of the disease whereas LV dilatation and overt heart failure tend to develop in the third decade of life in the majority of cases.

The presence, extent and distribution of LGE and its relation to LV function as assessed by LVEF in muscular dystrophy patients were previously studied by a number of authors [11,12]. In a study by Brunklaus et al., extensive but not minimal LGE was associated with reduced LVEF (48% vs 58%, respectively), suggesting more severe cardiomyopathy [12]. Our study confirms the correlation between the presence of any fibrosis and decrease in LVEF. However, the cardiac function may be preserved for many years in DMD, even with fibrosis progression [11,13]. Moreover, whether LGE extent at baseline predicts the pace of cardiac function impairment over the following years warrants further investigation. Given the limitations of physical activity with age in DMD, the affected individuals may not display clinical symptoms unless they are exposed to additional stress [14].
Finally, all the dot-plots also show a noticeable variability among the patients, (also of similar age), suggesting an uneven cardiac involvement of the patients. This observation forms the basis for further, longitudinal studies in the search of CMR parameters allowing for risk stratification and treatment escalation for those at risk.

In conclusion, in muscular dystrophy patients, fibrosis advances with age and is related to impaired LV function. CMR provides a detailed insight in chamber volumes, myocardial function and tissue characterization, all of which allow for the detection of subtle, subclinical cardiac involvement. Therefore, it may become a useful aid in determining the early cardioprotective therapy.

References:


Figure 1. The scatter plots show the correlations of left ventricular volume related parameters with age: end-diastolic volume (A), end-systolic volume (B), stroke volume (C) and ejection fraction (D). The bar charts represent the prevalence of abnormalities found in different age groups- decreased (< 55%) left ventricle ejection fraction (E), and patients with at least one LGE positive segment (F).