Echocardiographic signs of subclinical cardiac function impairment in Duchenne dystrophy gene carriers

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Research

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Abstract

Aim to assess subclinical cardiac function impairment in Duchenne dystrophy (DMD) female carriers Methods Forty-four female subjects proved as DMD carriers underwent echocardiographic examination including tissue Doppler imaging (TDI) of mitral and tricuspid annulus. Seventeen age-matched healthy female subjects served as controls. Results A significant differences in peak systolic annular velocity (Sa) between carriers and controls were found for lateral and septal part of the mitral annulus and for tricuspid annulus (0.09 vs 0.11 m/s, p<0.001, 0.08 vs 0.09 m/s, p<0.01 and 0.13 vs 0.14 m/s, p=0.02 respectively). There was also difference in early diastolic velocity (Ea) of the septal part of the mitral annulus (0.11 vs 0.13 m/s, p=0.03). Conclusion The subclinical deterioration of systolic function is presented even in asymptomatic DMD female carriers.

Introduction

Duchenne (DMD) and Becker (BMD) muscular dystrophies are hereditary diseases linked to the X chromosome. Thus, manifestation of skeletal muscle wasting, but also cardiomyopathy, occurs in males, while female carriers of the defective *DMD* gene are perceived healthy. Nevertheless, they have only one functional variant of the gene on one of the X chromosomes.

In male patients, dystrophy has a prevalence of 1/3500-6000 (Mah et al., 2014), and it primarily affects skeletal muscles, but heart impairment may also occur as a cardiomyopathy (McNally, 2007). Cardiac involvement manifests as a progressing decline in diastolic function, systolic ejection fraction, and fractional shortening (Markham et al., 2006). Myocardial fibrosis is related, with muscle contraction impairment (Panovský et al., 2019)

There are a number of proposed mechanisms of the disease's etiology. Primary sarcolemmal tears (Danialou et al., 2001) as a consequence of a non-functional dystroglycan complex has a number of consequences, e.g. increased oxidative stress, ion channel disturbances as well as numerous molecular pathway alterations (Berry et al., 2013; Jelinkova et al., 2019; Mu et al., 2015). These eventually lead to impaired heart muscle regeneration, possibly due to stem cell depletion (Pesl et al., 2020). The severity of cardiomyopathy does not always correlate with skeletal myopathy, and cardiac impairment occurs long before clinical symptoms appear (Li et al., 2009). In female carriers, the clinical symptoms are mostly not presented, thus cardiac function has not been studied in depth. Nevertheless, case studies have published severe heart failure episodes in different settings such as peripartum cardiomyopathy, perioperative stress and others (Cheng and Prior, 2013; Finsterer et al., 2018; Florian et al., 2016; Kerr et al., 2001; Papa et al., 2016), possibly leading even to heart transplantation (Melacini et al., 1998). However, complex prospective randomized studies are still lacking.

In our previously published study (Panovský et al., 2019) focused on young males with manifest Duchenne dystrophy, we used cardiac magnetic resonance (CMR) to assess the cardiac function and early signs of affection of the heart by T1 mapping because echocardiography is associated with some

difficulties due to skeletal deformities and narrow intercostal spaces. Female carriers do not present rib cage anomalies, thus we used echocardiography with tissue Doppler imaging as the first line method to assess subclinical cardiac dysfunction. The aim of this study was to assess detectable changes of tissue Doppler parameters in comparison with healthy control subjects.

Patients And Methods

Forty-four female subjects with a genetically diagnosed presence of *DMD* allele underwent an echocardiography examination on a standard Vivid 9 (GE Healthcare, Wisconsin, USA ultrasound device). Measurements of heart dimensions, left ventricular (LV) ejection fraction (EF), valvular morphology and parameters and tissue Doppler imaging of mitral and tricuspid annular velocities were performed. The dimensions were measured from the parasternal long axis view, while EF was calculated in accordance with Simpsons rule. Tissue Doppler curves were obtained from a standard apical four-chamber view, and the peak systolic (Sa), early diastolic (Ea) and late diastolic (Aa) velocities of the lateral and septal parts of the mitral annulus and lateral tricuspid annulus were obtained. The ratio between the early diastolic (E) wave of transmitral flow and the average of the mitral annular lateral and septal velocities (E/Ea) was calculated. The demographic and clinical characteristics of the cohort are presented in Table 1. The echocardiographic parameters were compared to a control group of 17 healthy female subjects who had no known or echocardiographically detectable heart disease, with a mean age of 36 years.

Table 1. Characteristics of the Duchenne dystrophy carrier cohort
SD=standard deviation

N	44
Age, years (mean ± SD)	38.8 ±10.3
Body mass index (mean ±SD)	23.3±4
Heart disease, N (%)	0 (0%)
Hypertension, N (%)	2 (5%)
Diabetes mellitus, N (%)	2 (5%)
Hyperlipidaemia, N (%)	5 (11%)

Statistical analysis

The female carriers of the dystrophin loss-of-function mutation were statistically compared with age-matched female controls. Because most variables were either integers or did not follow for Gaussian distribution, a non-parametric Mann-Whitney U-test was used for making the statistical comparison. The value of α = 0.05 was set as the significance level in all tests. All analyses were performed using Statistica software (version 13.3, Tibco software, USA).

Results

Neither group differed in age, left and right ventricular end-diastolic diameter, interventricular septal, posterior wall and left atrial diameter, or ejection fraction. There was only a slight difference in the LV end-systolic dimension (carriers vs controls, 29 vs 27 mm, p=0.01). No serious valvular disease was found in the carrier group. The LV diastolic parameters (E/A and E/Ea ratio) were also without any significant difference. However, the tissue Doppler parameters showed differences in mitral Ea wave from the septal part of the mitral annulus, the Aa wave from both the septal and lateral mitral annulus, and the Sa wave from both parts of the mitral as well as the tricuspid annulus. All above-mentioned annular velocities were significantly lower in the carriers in comparison with the controls. The basic echocardiographic data are presented in Table 2, tissue Doppler parameters are presented in Table 3, and box and whisker plots of the Sa waves are shown in Figs. 1, 2 and 3.

Table 2. *Basic heart dimensions, ejection fraction and diastolic parameters.*

Data are presented as mean ± SD. DD – left ventricular end-diastolic diameter, DS – left ventricular end-systolic diameter, LA – left atrium diameter, IVS – interventricular septum diameter, PW – left ventricular posterior wall diameter, RV – right ventricular end-diastolic diameter, LV EF – left ventricular ejection fraction, E – transmitral early diastolic wave, A – transmitral late diastolic wave, E/A – ratio between the E and A waves, E/Ea - ratio between the E wave and the mean value of the Ea tissue Doppler wave from the lateral and septal mitral anulus.

	Carriers (N = 44)	Controls (N = 17)	p
DD (mm)	43±4	42±4	NS
DS (mm)	29±4	27±3	0.01
LA (mm)	34±4	34±4	NS
IVS (mm)	9±1	9±1	NS
PW (mm)	9±1	9±1	NS
RV (mm)	24±4	25±3	NS
LV EF (%)	64±4	65±4	NS
E (m/s)	0.81±0.13	0.85±0.18	NS
A (m/s)	0.53±0.11	0.6±0.1	NS
E/A	1.59±0.37	1.42±0.35	NS
E/Ea	6.6±1.3	6.1±1.2	NS

Table 3. *Tissue Doppler parameters*

Ea - peak early diastolic velocity, Aa - peak late diastolic velocity, Sa - peak systolic velocity, sept – the septal part of the mitral annulus, lat – the lateral part of the mitral annulus, tric – tricuspid annulus

	Carriers (N = 44)	Controls (N = 17)	p
Ea sept (m/s)	0.11±0.02	0.13±0.02	0.03
Aa sept (m/s)	0.09±0.02	0.10±0.02	0.05
Sa sept (m/s)	0.08±0.01	0.09±0.01	<0.01
Ea lat (m/s)	0.14±0.03	0.15±0.03	NS
Aa lat (m/s)	0.08±0.02	0.09±0.02	<0.01
Sa lat (m/s)	0.09±0.02	0.11±0.02	<0.001
Ea tric (m/s)	0.15±0.07	0.16±0.03	NS
Aa tric (m/s)	0.13±0.04	0.11±0.03	NS
Sa tric (m/s)	0.13±0.02	0.14±0.02	0.02

Discussion

The main result of our study was the fact that even asymptomatic DMD carriers without any significant systolic dysfunction have signs of subclinical systolic function impairment. Although strain and speckle tracking have become the most commonly used techniques for making a detailed assessment of cardiac function by echocardiography, tissue Doppler imaging (TDI) remains one of the most powerful and well proven methods in heart dysfunction diagnostics (Yu et al., 2007). The mitral annulus peak velocities are valuable indicators of long-axis left ventricular motion and thus of LV systolic and diastolic function (Henein and Gibson, 1999). Peak systolic velocity (Sa) is a very sensitive marker of LV dysfunction, even in subjects with preserved ejection fraction (EF) or in diabetic patients without any cardiac disease (Fang et al., 2004). Reduced TDI velocities were also found in asymptomatic carriers of hypertrophic cardiomyopathy mutations without any presence of cardiac hypertrophy (Nagueh et al., 2001). Early diastolic annular velocity is one of the most powerful predictive echocardiographic parameters (Richartz et al., 2002; Wang et al., 2005). The Ea parameter is a very sensitive marker of impaired diastolic function and it decreases in all stages of diastolic dysfunction (Yu et al., 2007). In advanced phases of diastolic failure, the Ea velocity remains low, but the E wave velocity is high as LV filling pressure increases, so the E/Ea ratio increases as well (Nagueh et al., 1997; Sohn et al., 1997). Although TDI values obtained from Duchenne dystrophy carriers in our study were in the normal range according to age (Chahal et al., 2010), a significant difference, particularly in systolic parameters (Sa), was found in comparison with the age-matched control group. Several subjects had Sa from the lateral mitral annulus below the 5th percentile of the normal value range. On the other hand, diastolic parameters did not differ so clearly; only septal Ea and Aa and lateral Aa were substantially lower. The E/Ea ratio was normal in both groups without any significant difference. The prevalence of cardiomyopathy in female DMD carriers widely varied and did not correlate with phenotype, muscle symptoms, creatinine kinase levels or age (Florian et al., 2016; Mccaffrey et al., 2017; Papa et al., 2016). In our study, only asymptomatic carriers without any developed cardiomyopathy were enrolled, but the slight impairment of systolic LV and RV parameters was presented even with normal diastolic function. This is in concordance with previous studies (Hoogerwaard et al., 2005), where impairment of systolic function was more pronounced than in diastolic echocardiographic parameters. However, this study assessed heart dimensions and fractional shortening, not tissue Doppler parameters. Also, the prevalence of dilated cardiomyopathy was relatively high (8.2%) in contrast with our study, which comprises asymptomatic subjects with a normal ejection fraction and without any

significant LV dilation. So, it is hypothesized that DMD, even in early stages, primarily affects the contractile function of cardiomyocytes, without having any real influence on the relaxing process or LV filling patterns. There were some limitations in our study. First, there was a small number of patients. But on the other hand, DMD is a rare disease, so it is difficult to enrol more subjects in a nationwide study within just the Czech Republic. Another limitation was the absence of the use of strain in echocardiography, but in the case of diffuse myocardial impairment, tissue Doppler echocardiography provides sufficient information about heart dysfunction and it is easier and faster to obtain.

Conclusion

The subclinical deterioration of systolic function is present even in asymptomatic DMD female carriers. Tissue Doppler echocardiography is a very appropriate, fast, simple and non-invasive method that can be used to assess subclinical cardiac dysfunction in DMD carriers. Larger studies with a follow-up of the subjects are needed.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the recommendations of the Masaryk University Ethics Committee and was approved by the Institutional Ethics Committee at University Hospital Brno, issuing approval nr. 20130410–03. All subjects gave full informed consent before enrolment into the study.

Consent for publication

No persons personal data have been published.

Availability of data and material

The data that support the findings of this study are available from corresponding author V.K. upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest

Authors contributions

VK and RP conceived of the study and VK was the major contributor in writing the manuscript. VK, RP, MP and LM contributed in the study design. MP, LM, JH, LJ, contributed in patient recruitment and inclusion. VK and RP performed echo examinations and data analysis, JM performed statistical analysis. All authors read and approved the final manuscript.

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Figures

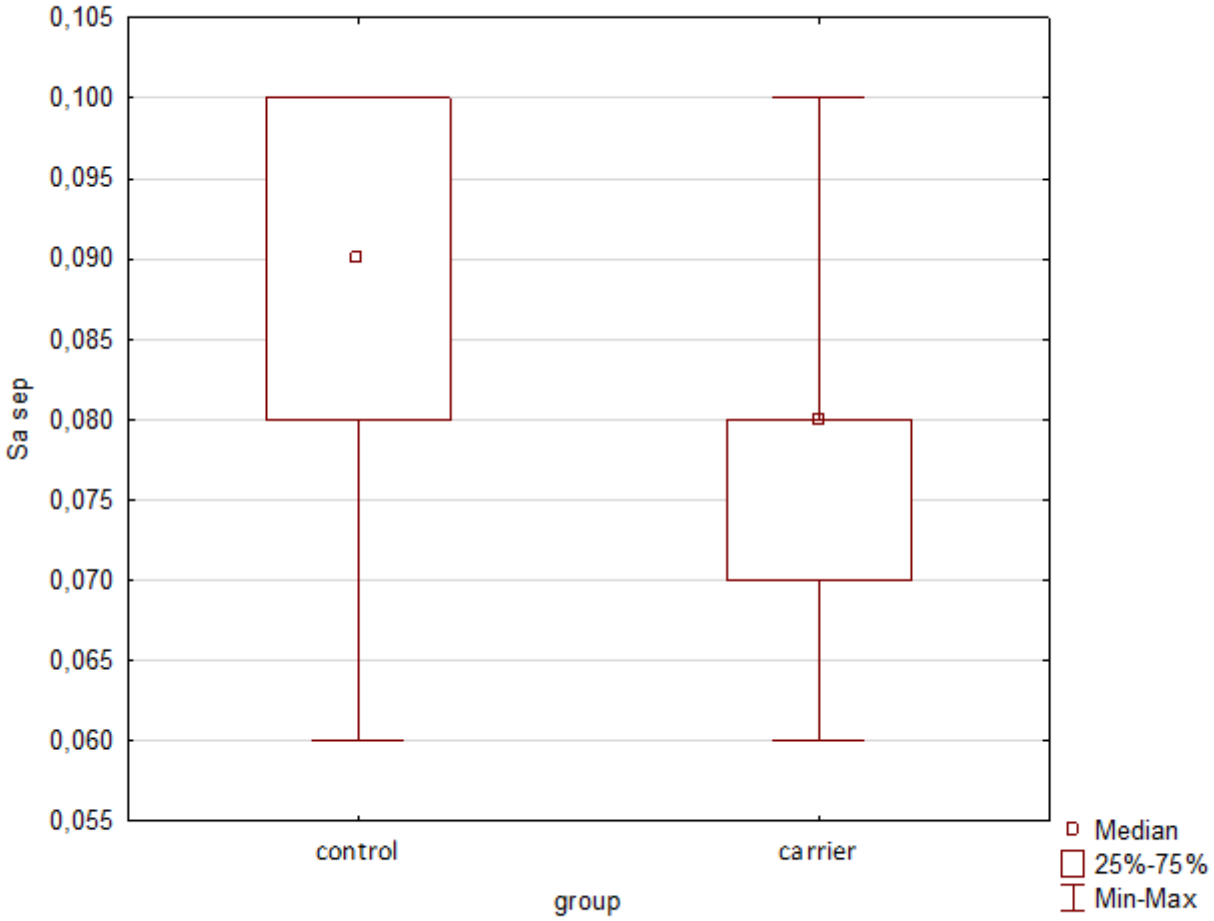

Figure 1

Box and whisker plot of Sa from the septal part of the mitral annulus. Significant difference between the groups p <0.01 (Sa – tissue Doppler peak systolic annular velocity)

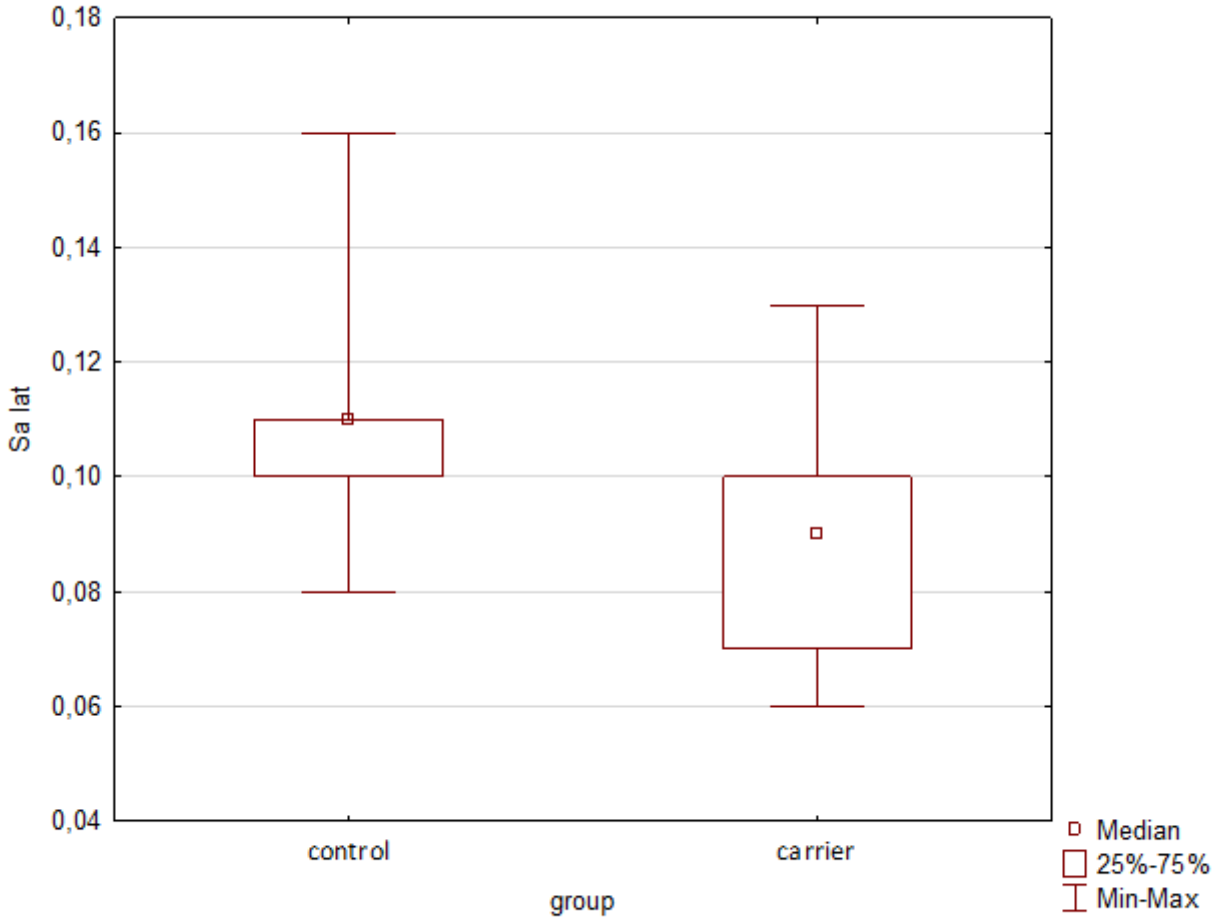

Figure 2

Box and whisker plot of Sa from the lateral part of the mitral annulus. Significant difference between the groups p <0.001 (Sa – tissue Doppler peak systolic annular velocity)

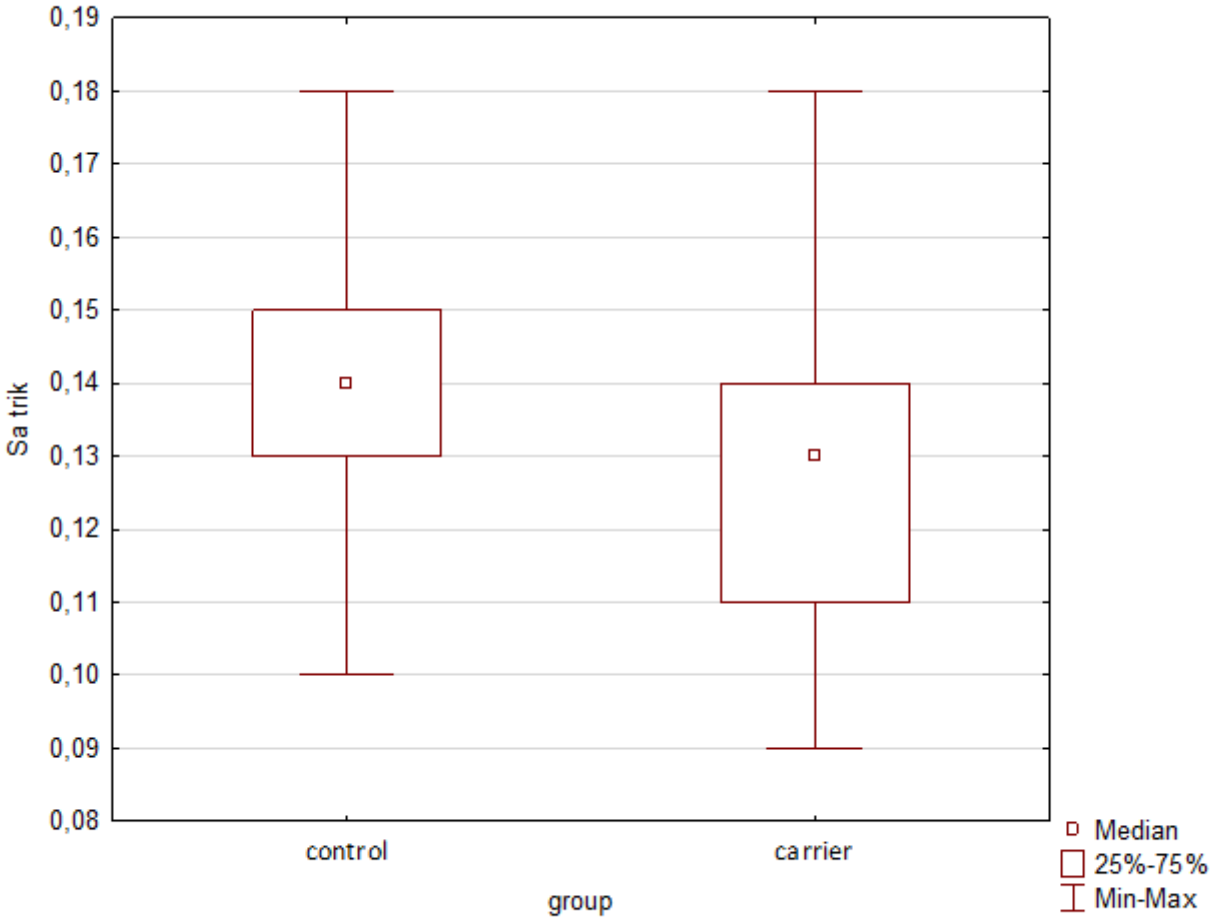

Figure 3

Box and whisker plot of Sa from the tricuspid annulus. Significant difference between the groups p = 0.02 (Sa – tissue Doppler peak systolic annular velocity)