ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2020:27(1):59-66 doi: 10.17343/sdutfd.554940

ASSESSMENT OF LEFT VENTRICULAR FUNCTIONS WITH STRAIN AND STRAIN RATE ECHOCARDIOGRAPHY IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY

DUCHENNE MUSKÜLER DİSTROFİLİ HASTALARDA SOL VENTRİKÜL FONKSİYONLARININ STRAIN-STRAIN RATE EKOKARDİYOGRAFİ İLE DEĞERLENDİRİLMESİ

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Cite this article as: Keskin M, Ceylan Ö, Özgür S, Örün UA, Doğan V, Yılmaz O, Şenocak F, Karademir S. Assessment of Left Ventricular Functions With Strain and Strain Rate Echocardiography in Children with Duchenne Muscular Dystrophy. Med J SDU 2020; 27(1): 59-66.

Öz

Amaç

Çalışmamızda konvansiyonel ekokardiyografi ile kalp fonksiyonları normal bulunan Duchenne Musküler Distrofili (DMD) hastaların miyokard fonksiyonlarının pulse wave doku doppler görüntüleme (PWDDG) ve strain/strain rate (S/SR) ekokardiyografi aracılığıyla ölçülmesi ve kontrol grubu ile karşılaştırılması amaçlandı.

Gereç ve Yöntem

Bu çalışmada; ortalama yaşı 85.2 ± 38.4 ay olan 32 DMD'li erkek hasta ve 89 ± 38.9 ay olan 31 sağlıklı çocuk değerlendirildi. Demografik özellikler olgular ve kontrol grubunda değerlendirildi. Cinsiyet, yaş, vücut kitle indeksi, konvansiyonel ekokardiyografi verileri, pulse wave doku Doppler görüntüleme (PW-TDI) verileri ve iki boyutlu (2D) longitudinal strain (LS) / longitudinal strain rate (LSR) ekokardiyografi değerleri karşılaştırıldı.

Bulgular

Hasta ve kontrol grupları arasında kalp hızı bakımından istatistiksel olarak anlamlı fark saptandı (p<0.001) ve DMD'li grupta kalp hızı daha yüksekti. Ventriküler septumda bazal ölçümlerinde Em, S amplitüdü, izovolümetrik relaksasyon zamanı (İVRZ), miyokard performans indeksi (MPİ) bakımından istatistiksel yönden anlamlı fark saptanırken (p<0.05), sol ventrikü serbest duvar bazalindeki ölçümlerde de Em, S amplitüdü ve İVRZ bakımından istatistiksel yönden anlamlı fark bulundu (p<0.05). Sol ventrikülün serbest duvar bazalindeki strain ve strain rate değerlerinde DMD'ligrup ve kontrol grubu arasında istatistiki yönden anlamlı fark saptandı (p<0.001). Yapılan apikal dört boşluk pozisyondaki global strain değerlerinde DMD'li grup ve kontrol grubu arasında istatistiki yönden anlamlı fark saptandı (p<0,001).

Sonuç

Transtorasik ekokardiyografide normal aralık içinde sol ventrikül sistolik fonksiyon saptanan DMD'li

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Müracaat tarihi/Application Date: 17.04.2019 • **Kabul tarihi/Accepted Date:** 09.06.2019
Available online at http://dergipark.gov.tr/sdutfd
Makaleye http://dergipark.gov.tr/sdutfd web sayfasından ulaşılabilir.

asemptomatik hastalarda kontrol grubu ile karşılaştırıldığında sol ventrikül anterolateral duvarında LS ve LSR değerleri anlamlı olarak düşük bulundu.

Anahtar Kelimeler: Longitudinal strain, longitudinal strain rate, Duchenne musküler distrofi

Abstract

Objective
The goal of our study was to detect the left ventricular functions of duchenne muscular dystrophy (DMD) patients using, pulsed-wave tissue Doppler imaging (PW-TDI, longitudinal strain (LS) and longitudinal strain rate (LSR) echocardiography who had normal left ventricular functions in standart echocardiography before, and to match them with the results of the control group.

Material and Methods
İn this study compared 32 male patients with DMD whose mean age was 85.2 ± 38.4 months were matched with 31 healthy males whose mean age was 89.0 ± 38.9 months. The following demographic features were evaluated in both DMD patients and controls: gender, age, body mass index, standard echocardiography parameters, pulsed-wave tissue Doppler imaging (PW-TDI) findings, and two-dimensional (2D) LS/LSR echocardiography measurements.

Results
Asymptomatic boys with DMD were established to have high heart rate ($p<0.001$). In the calculations performed from the base of the ventricular septum, statistically significant differences were determined between the Em, S amplitude and isovolumetric relaxation time (IVRT), myocard performance index (MPI) values of the two groups ($p<0.05$). In the measurements made from the base of the left ventricular free wall, Em, S amplitude and IVRT, MPI values were demonstrated to be more considerably different ($p<0.05$). The results of the LS and LSR measurements done from the base of the left ventricular free wall were considerably different between DMD and control group ($p<0.001$), and in the global strain measurement performed from the four chamber apical position, considerable distinction was noted between the two groups ($p<0.001$).

Conclusion
In patients with DMD in whom standart echocardiography had assesed left ventricular systolic function within the normal range showed significantly lower LS and LSR values at the left ventricular anterolateral wall compared with the control group.

Keywords: Longitudinal strain, longitudinal strain rate, duchenne muscular dystrophy,

Introduction

Duchenne muscular dystrophy (DMD), the most common neuromuscular hereditary disease, affects all peoples and ethnic groups, and has a prevalence of 1 in 3600 live-born infants. Its mode of inheritance is X-linked recessive. The associated gene is located at the Xp21 locus on the X chromosome, and is one of the largest genes described so far (1).

In DMD patients, the most important cause of morbidity and mortality is the involvement of respiratory and heart muscles (1). Evaluation of left ventricular function in DMD with cardiac involvement is of critical importance for diagnosis, treatment, and prognosis. In spite of the presence of many related studies in the literature, the search for the most optimal assessment method still continues. The most commonly used imaging modality for the assesment of myocardial function is echocardiography, and the most commonly evaluated parameter is the ejection fraction (EF) (2). However, measurement of EF is subjective, and its value is limited due to poor reflection of the global characteristics of the heart by EF.

On the other hand, tissue Doppler imaging (TDI) is a more sensitive technique than EF measurement, but its inability to distinguish between active and passive movements of cardiac contraction may be problematic. However, some emerging techniques like longitudinal strain (LS) and longitudinal strain-rate (LSR) echocardiography may enable the evaluation of global and regional left ventricular myocardial systolic and diastolic functions (3,4). Our study purposed to asses the role LS and LSR echocardiography in the assessment of left ventricular functions in patients with DMD.

Material and Methods

A total of 32 patients (ages, 3–12 years) were selected from among the patients diagnosed with DMD who met the study criteria and were being followed in the Pediatric Cardiology and Neurology Departments of Dr. Sami Ulus Obstetrics, Gynecology, and Pediatric Health and Disease Training and Research Hospital, Ankara, Turkey. A total of 31 healthy children (ages, 3–12 years) who had been referred to our clinic for evaluation of a murmur and had no cardiac disease were contained our study as controls. Control and DMD grups gave written informed consent and local Ethics Commitee approved the study protocol. The study was approved by the Local Ethics Committee of the Institutional Review Board (approval number: 29-27.03.2012).

The following demographic characteristics were evaluated in both patients and controls: gender, age, body mass index, standard echocardiography parameters, pulsed-wave tissue Doppler imaging (PW-TDI) findings, and two-dimensional (2D) LS/LSR echocardiography measurements.

All echocardiographic examinations were performed by the same investigator to prevent from interobserver variability. For all of the study patients, the echocardiographic recordings were participated by monitoring DII derivation with an IE 33 echocardiograph (S5-1 probe, IE33, Philips, Andover, MA, USA) in the back-to-top or left lateral decubitus position by the same pediatric cardiologist. The myocardial function of the patients was assesed using conventional echocardiography (m-Mode echocardiography parasternal long axis), PW-TDI, and LS and LSR echocardiography.
Left ventricular dimensions and out flow tracts were evaluated in M-mode with 2D color Doppler echocardiography and LS/LSR echocardiography. Left ventricular asssesments were done according to the suggestions of the American Society of Echocardiography (2).

The records that showed the best examples and highest amplitude signals with color tissue Doppler echocardiography were evaluated. Left ventricular images for color tissue Doppler were gained in the apical 4-chamber view. It were adjusted as the Nyquist limit is at interval of -20 cm/s to +20 cm/s, and high frame rates are bigger than 100 frames/s. The sample volumes were taken from the basal segments of the septum and the left ventricular free wall by color tissue Doppler echocardiography. The following parameters were evaluated with color-coded tissue Doppler: S, Am, and Em waves; ejection time (ET); isovolumetric contraction time (IVCT); and isovolumetric relaxation time (IVRT). The myocardial performance index (MPI) was calculated as follows: MPI = IVCT + IVRT/ET.

Apical four-chamber images were recorded, and the data were analyzed. Measurements were obtained for LS/LSR echocardiography. The electrocardiography records included five consecutive cardiac cycles. The 33 iE device and speckle-tracking echocardiography software (QLAB version 6.0, TMQ; Philips Medical Systems) automatically calculated the LS and LSR of the myocardial tissue after the endocardial borders were manually identified. From the apical four-chamber view, the LS and LSR of the basal aspect of the anterolateral left ventricular wall and the left ventricular global strain were determined.

Statistical Analysis
Statistical analysis was performed using SPSS (version 16.0 for Windows; SPSS, Inc., Chicago, IL). The data are given as means ± standard deviation. Student's t-test was used to compare normally distributed parameters between groups. Values of $p < 0.05$ point out statistical significance.

Results

A group of 32 male patients with DMD (ages, 3–12 years) constituted the patient group, and 31 male controls with normal EF (ages, 3–12 years) constituted the control group. Demographic data, echocardiographic measurements, and heart rates are given in Table 1. The mean ages in the patient and control groups were 85.2 ± 38.4 months (range, 36–144 months) and 89 ± 38.9 months (range, 36–144 months). The EF, shortening fraction (SF), heart rate, and end-diastolic diameter of the left ventricular posterior wall differed significantly between the patient and control groups ($p < 0.05$). However, no statistically considerable differences were found in The interventricular septum end-diastolic diameter, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and left ventricular mass index were not considerably different between the two groups ($p > 0.05$).

Pulse-wave Tissue Doppler Measurements
Pulse-wave tissue Doppler imaging was performed in the apical 4-chamber view by placing the cursor at the baseline of the interventricular septum and left ventricular free wall with electrocardiography. Em, Am, E/A, S, ET, IVRT, IVCT, and MPI were measured. The PW-TDI measurements are given in Table 2. Among the measurements taken at the base of the interventricular septum, the following showed significant differences ($p < 0.05$) between the patient versus control groups: Em (10.7 ± 1.39 vs. 12.5 ± 1.8 cm/s), S (6.79 ± 0.84 vs. 7.6 ± 1 cm/s), amplitude and IVRT (55.6 ± 11.9 vs. 49 ± 8.57 m/s), and MPI (0.46 ± 0.08 vs. 0.42 ± 0.06). There was no significant difference in Am, ET, E/A, or IVCT ($p > 0.05$) between the groups. Among the measurements taken at the base of the left ventricular free wall, the following were significantly different between the patient versus control groups: E (14.2 ± 2.3 vs. 15.7 ± 2.2 cm/s), S (7 ± 1 vs. 7.8 ± 1.1 cm/s), and amplitude and IVRT (58.7 ± 11.5 vs. 50.9

± 9.8 m/s) (p < 0.05). Values for A, ET, E/A, IVCT, and MPI did not differ significantly between the two groups (p > 0.05).

LS and LSR Measurements

Five or more consecutive heart cycles were recorded by electrocardiography in the apical 4-chamber view. The global LS and LSR were measured at the base of the left ventricular free wall. Values for LS (-14.5 ± 4.7 vs. -27.3 ± 6.5) and LSR (-0.24 ± 0.5 vs. -0.83 ± 0.27) at the base of the left ventricular free wall differed considerably between the patient versus control groups (p < 0.001) (Table III). Global strain in the apical four-chamber position (-13.7 ± 2.8 vs. -18.8 ± 2.3) also differed significantly between the two groups (p < 0.001) (Table 3).

Table 1 Demographic Data, Echocardiographic Measurements, And Heart Rates

		Patient (N=32)	Control (N=31)	P value
Demographiccharacteristics				
Meanage	months	85.2± 38.4	89± 38.9	0.69
Body weight	(kg)	24.4± 6.8	28.9± 13.3	0.06
Height	(cm)	116 ± 10,8	125±22.4	0.06
Echocardiographic measurements and heart rate				
EF	(%)	70.9 ±5,5	76.5± 5.85	0.0001
SF	(%)	39.7±5.2	44.8± 5.8	0.0001
EDDLVPW	(mm)	4.4± 0.8	5.5±1.2	0.06
IVSEDD	(mm)	4±0.8	5.9±1.4	0.01
LVESD	(mm)	20.9±3.7	19.7±4.1	0.21
LVEDD	(mm)	34.7±5	35±5.4	0.82
HR	/dk	99.1±8.6	86.1±7.6	0.0001
LVMI	Gr/m2	103.6±35.7	111.8±29.5	0.08

EF: ejection fraction, SF: shortening fraction, EDDLVPW: end-diastolic diameter of the left ventricular posterior wall, IVSEDD: interventricular septum end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVEDD: left ventricular end-diastolic diameter, HR: Heart rate, LVMI: left ventricular mass index

Table 2 Comparison Of PW-TDI Results Between The Patient And Control Groups

PW-TDI	Patient (N = 32)	Control (N = 31)	P	Patient (N = 32)	Control (N = 31)	P
	SB	SB		LVB	LVB	
E (cm/sn)	10.7±1.39	12.5±1.8	0.0001	14.2±2.3	15.7±2.2	0.01
A (cm/sn)	5.7±1.3	6.3±1,6	0.09	7.0±1.2	7.3±1.37	0.36
ET (m/sn)	234.5±16,4	235.2±22	0.88	237.4±15.2	238.3±26	0.85
E/A	1.94±0.43	2.03±0.35	0.39	2.03±0.36	2.17±0.32	0.13
S (cm/sn)	6.79±0.84	7.6±1	0.001	7±1	7.8±1.1	0.001
IVRT (m/sn)	55.6±11.9	49±8.57	0.01	58.7±11.5	50.9±9.8	0.004
IVCT (m/sn)	55.9±10.2	51.6±8.7	0.07	58.7±12.7	54.2±9,8	0.12
MPI	0.46±0.08	0.42±0.06	0.03	0.48±0.1	0.44±0.08	0.10

PW-TDI: pulse-wave tissue Doppler imaging,IVRT: isovolumetric relaxation time, IVCT: isovolumetric contraction time, MPI:myocardial performance index, SB: septum basal, LVB: left ventricular basal

Table 3 Comparison Of S And SR Between The Patient And Control Groups

	Patient (N = 32)	Control (N = 31)	P
LVBLS	-14.5±4.7	-27.3±6,5	0.0001
GLOBS	-13.7±2.8	-18.8±2.3	0.0001
LVBLSR	-0.24±0.5	-0.83±0.27	0.0001

LVBLS: left ventricular basolateral of free wall strain, GLOBS: global strain,
LVBLSR: left ventricular basolateral of free wall strain rate

Discussion

DMD, the most common neuromuscular hereditary disease, affects all peoples and ethnic groups, and is inherited as an X-linked recessive trait. The abnormal gene is located at the Xp21 locus on the X chromosome (1). In addition to skeletal muscle, this disease can involve the respiratory and heart muscles, accounting for the morbidity and mortality among patients with this illness. Although myocardial involvement can be subclinical, cardiomyopathy (CMP) and heart failure can develop.

Determination of myocardial function in DMD patients with heart involvement is critical for diagnosis, treatment, and prognosis, but the most appropriate method is still under debate. Measurement of the EF is not sufficient because it is subjective and of limited value, due to the global assessment of the heart. The EF is preserved in the early stages of DMD, and responses to treatment are better during this time. However, occult systolic dysfunction is reportedly present in this stage (5,6). Despite the preserved EF and SF in patients with DMD in this study, there were considerable differences in LS and LSR between patients and controls; thus, occult systolic dysfunction was thought to be present. Tissue Doppler imaging is a more sensitive method than EF measurement. However, the inability to distinguish between active and passive movements of heart contraction is problematic. LS and LSR echocardiography is an emerging technique that allows for the assessment of global and regional myocardial systolic and diastolic functions (3,4).

In the present study, the patient and control groups had similar ages, body weights, and heights, and the EF and SF were within the normal ranges in both groups. Nevertheless, these measurements differed significantly between the DMD and controls. In previous reports, patients with an SF >28% have been considered to be normal (5-7) In addition, significant differences weren't found between patients and controls in terms of EF and SF in these studies (5-11). In a study by Mori et al.(10), PW-TDI was compared with the conventional method in 14 patients with DMD. Mertens et al. (8), studied 32 patients with DMD, aged 3–12 years, and compared the anterolateral left ventricular anterolateral wall LS and LSR obtained by PW-TDI with those obtained by the conventional method. This latter study was consistent with our study in terms of the number and ages of patients and the results.

In the literature, ıt was shown in only one study that significant differences were found in EF and SF between patients and controls (11). In the present study because the EF and SF were within the normal ranges in all groups, the significant differences between the patient and control groups were not considered to be important. Notably, we had already targeted the examination to patients with asymptomatic DMD and normal EF/SF values. LVESD and LVEDD did not differ considerably between the DMD and controls. These results indicate that dilated CMP had not yet developed in our patients. The posterobasal and lateral anterior walls of the left ventricle have been reported as the areas that are first affected and first to show the development of fibrosis in patients with DMD; however, these areas are not initially affected homogeneously (12-14). In our study, left ventricular end-diastolic diameter of the left ventricular posterior wall (EDDLVPW) did not differ considerably between the patient and control groups. This finding may be important in terms of showing that fibrosis had begun in the early stages, when patients were asymptomatic. In other studies comparing EDDLVPW between patient and control groups, lower values were measured in the patient group, but the differences were not significant (5-11).

Sinus tachycardia is the first electrocardiographic finding in patients with DMD. This is because fibrosis and fat accumulation affect the transmission system of the heart, especially the sinoatrial node (15). In addition, autonomic dysfunction in these patients contributes to tachycardia (16). The elevation of circulating catecholamines and sympathetic hyperactivity in DMD patients are due to autonomic dysfunction (1-17). In the present study, heart rate differed significantly between the patient and control groups. No arrhythmia other than sinus tachycardia was detected in our study. The heart rate decreased with age in the control group but not in the patient group. One previous study demonstrated a correlation between heart rate and cardiac dysfunction, and the heart rates of patients who were followed for 5 years increased with the development of CMP (7). Left ventricular dysfunction is thought to be aggravated in this condition. Thus, beta-blockers have been used in treatment (18,19).

TDI is a more sensitive method than EF measurement, but the inability to distinguish between active and passive movements of heart contraction is problematic. Moreover, as in all Doppler methods, the PWDD method is dependent on the angle. In patients with DMD, TDI may indicate diastolic dysfunction but not systolic dysfunction. Markham et al. (5), studied 26 patients with DMD, aged 5–14 years, with no CMP and normal EF and SF values; they reported significant differences in the A wave, E wave, E/A ratio, IVRT, and S wave between the patient and control groups. In the present study, the E wave, S wave, and IVRT were measured from the basal septum and basal aspect of the left ventricular free wall, and MPI was measured from the base of the septum. All of these measurements differed significantly between the DMD and control groups. This is generally consistent with previous reports (7,12,16,20). The A wave, E/A ratio, ES, and MPI measured from the base of the left ventricular free wall showed no considerable differences between the two groups, in agreement with the findings of Mertens et al. (8) and Mori et al.(10), but incompatible with others' results.

Despite its broad range of applications, TDI has some limitations. The main limitation is that the measured rate of the target myocardial segment is affected by the movement of the adjacent myocardial segments and the rotational movement of the heart. New methods such as S and SR attempt to be overcome this limitation. TDI also has insufficient quality to evaluate the PWDD because the apex of the heart is partly still. Ultrasound waves are required for the adjustment parallel to myocardial motion, which sometimes makes it difficult to utilize this method. In addition, because of the dependence of this method on the angle, the evaluation of movements along the long and short axes of the heart is not possible (4,17,20,21). Because conflicting results have been published, more reliable methods have been researched, and S and SR have been used for this purpose in recent years.

In recent years, cardiological treatment of patients with DMD has begun after the development of CMP. Treatment only slows the progression of CMP and cannot prolong the life of patients. CMP usually begins after the age of 12 years and affects more than 90% of patients with DMD after the age of 18 years (12). In recent years, it has been demonstrated that occult systolic and diastolic dysfunction in patients with DMD may develop in the early period and that early treatment can significantly delay the development of dilated CMP. Moreover, early treatment can extend the survival time of affected patients (22,24) Hitoko et al. (25), started treatment with beta-blockers and ACE inhibitors in 40 asymptomatic patients, and none had died by the end of a 10.9-year follow-up. For these reasons, new methods of treatment for occult systolic and diastolic dysfunction in the asymptomatic period of DMD have been explored. Based on the results obtained thus far, LS and LSR measurements have been determined to be one of the most reliable methods.

In the majority of studies on LS and LSR measurements in groups with DMD, the left ventricular posterior wall has been used. (6,8,11) Hitoko et al. (25), studied 13 patients with DMD, reported significant differences in S and SR between patients and controls . Giatrikos et al. (9), studied only SR. The present study used S and SR of the base of the left ventricular free wall and the apical four-chamber global strain values. Significant differences in LVBLS, LVBLSR, and global strain were detected between the patient and control groups. Mertens et al. (8) reported significant differences in the values of the base of the left ventricular free wall, apical and midlateral strain, and strain rates between patient and controls. Different from our study, the midlateral and apical regions were also studied. Mertens et al.(8), and Spurney et al. (26), measured the midlateral left ventricular free wall S and SR in mice with DMD and found significant differences compared with the control group. Recent reports showed the importance of basal longitudinal strain in aortic stenosis and tachycardia induced cardiomyopathy. Decreased basal longitudinal strain is a considerable predictor of future aortic valve surgery, in asymptomatic patients with aortic stenosis. Decreased basal longitudinal strain is also a predictor of future recovery in groups with tachycardia. The basal function has an important role of left ventricular function (27).

Our patients were asymptomatic, with normal EF and SF values. An abnormal S/SR measurement is important to show occult myocardial damage. In this way, patients are presented the opportunity to start treatment early. LS and LSR echocardiography is more sensitive and specific than conventional echocardiography and TDI evaluation. However, few studies have been conducted in patients with DMD.

Limitations of our study included the limited case and the relatively wide age range of DMD group. Our study only one pediatric cardiologist studied the echocardiographic parameters but we did not measure intraobserver variabilities.

In summary, asymptomatic patients with DMD in whom conventional echocardiography had detected left ventricular systolic function within the normal range showed significantly lower LS and LSR values at the left ventricular anterolateral wall compared with the control group. Based on these results, we believe that the identification of subclinical dysfunction using echocardiographic methods such as LS/LSR measurements in addition to conventional methods will be beneficial in terms of treatment timing and follow-up in these patients.

Financial support
The authors received no financial support for the research or authorship of this article.

Conflicts of interest
MK, OC, SO, UAO, VD, OY, FS, SK declare that they have no conflict of interest.

Human rights statements and informed consent
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients for being included in the study.

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