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Disturbed Atrial Conduction in Patients with Duchenne Muscular Dystrophy

ABSTRACT

Background: Duchenne muscular dystrophy (DMD)-related cardiomyopathy is associated with hemodynamic and conduction abnormalities and begins at an early age with subtle symptoms.

Methods: The study population included 55 patients with DMD and 54 healthy controls. We compared electrocardiogram (ECG), conventional echocardiography, and tissue Doppler imaging (TDI) assessments between patients with DMD and healthy controls. Also, we investigated atrial electromechanical delay, which has not been previously studied in DMD patients. Mitral, septal, and tricuspid segments were analyzed by TDI.

Results: The mean age was 13.6 ± 2.5 years (range, 9.3-17.9 years) in the patient group and 12.8 ± 2.6 years (range, 8-17.5 years) in the control group ($P = .1$). Patients had higher heart rates, longer QTc intervals, and P-wave dispersion (PWD) than controls ($P < .001$, $P = .004$, $P < .001$, respectively). The patient group had larger left ventricular end-systolic dimension ($P < .001$), lower left ventricular ejection fraction (EF) ($P < .001$), MAPSE ($P < .001$), TAPSE ($P < .001$), and mitral-E/A ($P = .029$) values than control subjects. Myocardial performance index ($P < .001$) was higher, and the E'/A' ratio ($P < .001$) was lower at all 3 segments in the patient group. Also, atrial electromechanical delay was longer in the patient group at these segments ($P < .001$). Patients had significantly longer inter-atrial ($P = .033$) electromechanical conduction delays. EF was negatively correlated with atrial conduction time variables.

Conclusion: We have shown deterioration in systolic and diastolic function in both ventricles, PWD, and atrial conduction in children with DMD. Patients with DMD may be at risk of atrial arrhythmias due to disturbed atrial conduction.

Keywords: Duchenne muscular dystrophy, cardiomyopathy, tissue Doppler imaging, atrial electromechanical delay

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that occurs in 1/3500 to 1/5000 male births and is characterized by varying degrees of skeletal and cardiac muscle degeneration. Mutations in the dystrophin gene cause the disease, resulting in a marked reduction or absence of the sarcolemmal protein dystrophin.[1] To date, no curative treatment is available for DMD, and most patients die in the second to fourth decade of life due to respiratory or heart failure. Cardiomyopathy is the leading cause of death in DMD as a result of improvements in respiratory care.[1-3] In addition to cardiac dysfunction, insufficient myocardium is also at risk of rhythm abnormalities.[2-5] Dilated heart chambers and cardiac scarring are the main causes of malignant arrhythmias in this patient group.[4]

Atrial fibrillation and atrial flutter can occur in patients with DMD, often in those with dilated cardiomyopathy and cor pulmonale.[2] Hovewer, the incidence is very rare in the pediatric population.[5] Disturbance in the synchronization of atrial electrical and mechanical activities and prolonged durations of both intra- and inter-atrial conduction indicate irregular propagation of sinus impulses. This phenomenon, termed electromechanical delay, is the hallmark electrophysiological feature of fibrillation-prone atria. Essentially, it refers to the time interval from the onset of electrical signals to the subsequent contraction of the heart muscle.[6]

ORIGINAL INVESTIGATION

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We aimed to compare ECG, conventional echocardiography, and tissue Doppler imaging (TDI) assessments between patients with DMD and healthy controls and to investigate atrial conduction properties, which have not been previously studied using echocardiographic parameters in this patient group.

METHODS

Study Design and Population

A total of 62 boys diagnosed with DMD with a classic phenotype and confirmed by genetic testing were enrolled in this prospective, cross-sectional, case-control study. In addition, 54 healthy male subjects of similar age and body surface area (BSA) were included as a control group. BSA was calculated using the following formula: BSA = (4*weight + 7) / (90 + weight). Serum samples were collected from the patient group to measure levels of the cardiac enzymes creatine kinase (CK) and creatine kinase isoenzyme (CK-MB). All patients and healthy controls underwent an ECG and echocardiographic examination.

Patients who were not compliant during the echocardiographic examinations, those for whom adequate images could not be obtained, and those taking medications that could affect heart rhythm and conduction, including beta-blockers, were excluded. Seven patients were excluded from the study because transthoracic echocardiography and TDI could not be performed due to obesity, scoliosis, and chest deformity. As a result, 55 patients were included in the patient group.

The study was approved by the Institutional Ethics Committee (18/03/2021, 2021-083) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from the parents of all participants. We did not use artificial intelligence or any assisted technologies such as large language models in this paper.

Electrocardiographic Measurements

The ECG parameters were analyzed by magnifying the stored digitized 12-lead surface ECG data on a high-resolution computer screen at a speed of 25 mm/s speed and an amplitude of 10 mm/mV amplitude. Maximum and minimum P-wave durations (P-max and P-min) were calculated from the standard ECG during sinus rhythm. The QTc duration was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). The P-wave duration is the time between the onset and endpoint of a P-wave. The onset and endpoints of the P wave were considered to be the intersection of the P-wave with the isoelectric line and the intersection of the endpoint of the P wave with the isoelectric line, respectively. P-wave dispersion (PWD) was calculated as the difference between P-max and P-min. Acceptable electrocardiography was defined as the ability to measure P-wave duration in at least 8 of the 12 electrocardiographic leads recorded simultaneously.

Echocardiographic Examinations

Using a Philips Affiniti 50 Cardiac Ultrasound with a 5-1 MHz transducer (Bothell, WA, USA), echocardiographic evaluations were conducted on all participants, including patients and control subjects. These examinations were carried out by a single pediatric cardiologist who remained unaware of the patients' clinical information. A continuous recording of a single-lead electrocardiogram was maintained throughout the echocardiographic studies. To assess ventricular systolic function, left ventricular ejection fraction (EF) was calculated by Simpson's biplane method. Additionally, fractional shortening (FS), mitral annular plane systolic excursion (MAPSE), and tricuspid annular plane systolic excursion (TAPSE) were measured, utilizing M-mode imaging as reliable indicators. To assess the diastolic function of the left ventricle, peak early (E) and late (A) wave velocities of the mitral valve and the E/A ratio were measured using pulsed-wave Doppler.

TDI was performed at 3 locations: the lateral mitral annulus, the septal mitral annulus, and the right ventricular tricuspid annulus (the mitral, septal, and tricuspid segments, respectively). Longitudinal peak annular velocities during systole (S'), early diastole (E'), and late diastole (A') were measured, and the E'/A' ratio was derived from these measurements. The myocardial performance index was calculated as follows: (isovolumic contraction time + isovolumic relaxation time / ejection time). The atrial electromechanical delay was defined as the time interval from the initiation of atrial electrical activity (indicated by the P-wave on surface electrocardiography) to the initiation of mechanical atrial contraction (the A' wave) (Figure 1). This parameter was measured in the same 3 segments mentioned earlier. The difference between mitral and tricuspid atrial electromechanical coupling intervals was termed inter-atrial conduction delay; the difference between mitral and septal atrial electromechanical coupling intervals was termed left-intra-atrial conduction delay, and the difference between septal and tricuspid atrial electromechanical coupling intervals was termed right-intra-atrial conduction delay.[7]

Statistical Analysis

The statistical analysis was conducted using SPSS for Windows, version 26.0 software (SPSS, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation or as median and interquartile range. Categorical variables were represented as percentages along with the corresponding number of cases. To compare categorical

HIGHLIGHTS

- Atrial electromechanical delay was longer in the patients at the mitral, septal, and tricuspid segments. P-wave dispersion (PWD) was increased in patients with DMD.
- Left ventricular EF was negatively correlated with atrial conduction time variables and PWD.
- We showed a deterioration in systolic and diastolic function in both ventricles and in atrial conduction in DMD patients. Patients with DMD may be at risk of atrial arrhythmias due to disturbed atrial conduction.

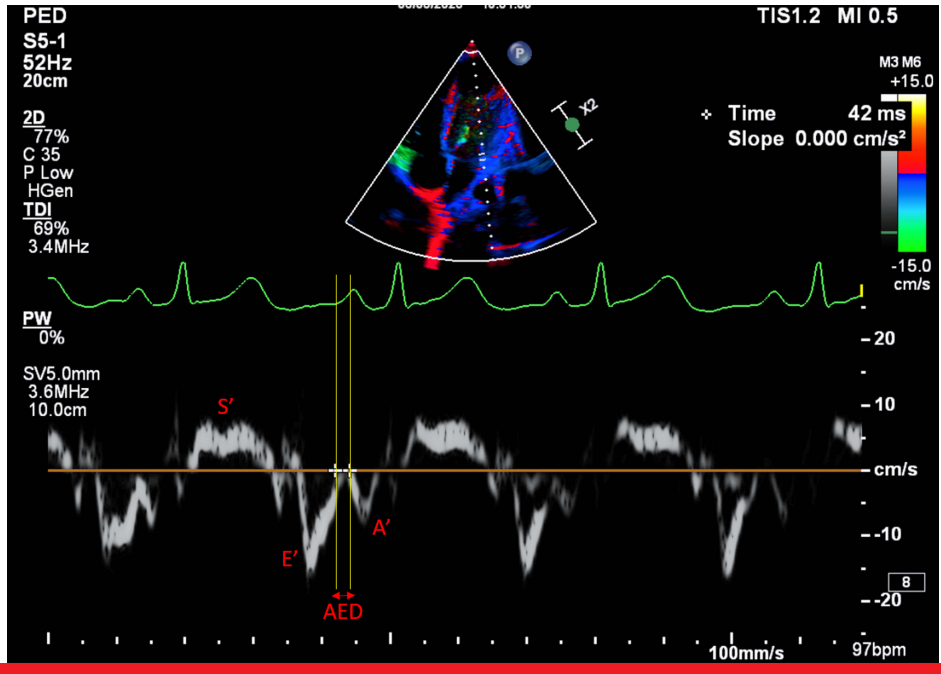

Figure 1. Measurement of the atrial electromechanical delay from the onset of the P-wave on the surface electrocardiogram (ECG) to the beginning of the A'-wave on the tissue Doppler echocardiogram. AED, atrial electromechanical delay; E', peak early diastolic velocity; A', peak late diastolic velocity; S', peak early systolic velocity.

data, the Chi-Square test was employed. For continuous variables, the Student's *t*-test or the Mann–Whitney *U*-test was applied depending on the normal distribution of the data, determined through the Kolmogorov–Smirnov test. The Pearson correlation test for normally distributed groups and the Spearman correlation test for non-normally distributed groups assessed the relationships among the test parameters. A *P* value less than .05 was considered statistically significant.

RESULTS

The mean age was 13.6 ± 2.5 years (range, 9.3-17.9 years) in the patient group and 12.8 ± 2.6 years (range, 8-17.5 years) in the control group ($P = .1$). The median CK and CK-MB levels were 3610 (479-22 605) U/L and 152.8 (29-901) U/L, respectively, in the patient group. Thirty-one (56%) of the patients were non-ambulatory and had been on prednisone treatment. Also, they were prescribed angiotensin-converting enzyme inhibitor therapy at the age of 10 years. Patients on beta-blockers were excluded from the study due to concerns about their effects on atrial conduction characteristics and echocardiographic measurements.

Systolic and diastolic blood pressure values were similar between the 2 groups ($P = .4$ and $P = .4$, respectively). ECG analyses revealed significantly higher heart rates and longer QTc intervals in the patient group compared to controls ($P < .001$ and $P = .004$, respectively) (Table 1). ECG abnormalities associated with DMD were as follows: sinus tachycardia in 20 (36%), sinus arrhythmia in 15 (27%), incomplete right bundle branch block in 10 (18%), tall R waves or increased R/S ratio in V1-2 in 10 (18%), and deep Q waves in V5-6 in 6 (10%) of the patients. Two patients had ventricular extrasystoles on ECG, and Holter monitoring showed only rare ventricular extrasystoles without pairs or runs. P-max and PWD values were significantly longer in the patient group compared to the control group ($P < .001$ and $P < .001$, respectively). A comparison of the ECG and echocardiographic parameters of both groups is presented in Table 1. Patients with DMD had significantly larger left ventricular end-systolic dimension ($P < .001$), lower left ventricular EF ($P < .001$), MAPSE ($P < .001$), and TAPSE ($P < .001$) values than control subjects. In addition, mitral E/A was significantly lower in the patient group compared to controls ($P = .029$). In the patient group, the left ventricular EF was between 45% and 55% in 12 (2.1%) patients and below 45% in 5 (0.09%) patients.

TDI examinations revealed impairment in both systolic and diastolic function parameters in DMD patients. The patient group had a statistically significant higher myocardial performance index and lower E'/A' levels compared to healthy controls at all 3 segments we evaluated ($P < .001$) (Table 2).

The patient group had a significantly longer atrial electromechanical delay time than controls in the mitral, septal, and tricuspid segments ($P < .001$). Also, inter-atrial conduction delay was significantly prolonged in the patients with DMD ($P = .033$).

Correlation analyses of left ventricular EF with atrial conduction time variables are shown in Table 3. In the study group, while MAPSE was positively correlated with EF, there was a negative correlation between EF and PWD, left ventricular end-diastolic dimension, mitral, septal, and tricuspid atrial electromechanical delay times, and inter-atrial conduction time.

Table 1. Comparison of Demographic, Electrocardiographic, and Conventional Echocardiographic Characteristics Between Groups

Variables	Patient Group	Control Group	*P*
Age (years)	13.6 ± 2.5	12.8 ± 2.6	.118
Height (cm)	154.6 ± 12.2	150.3 ± 18.6	.164
Weight (kg)	48.8 ± 5.7	47.1 ± 6.4	.526
BSA (m^2)	1.38 ± 0.22	1.33 ± 0.3	.364
SBP (mm Hg)	109.3 ± 10.6	111.2 ± 13	.396
DBP (mm Hg)	64.4 ± 8	63 ± 8.3	.385
HR (min^{-1})	95.5 ± 13.2	83.3 ± 15.7	< .001
PR (ms)	129 ± 15	132 ± 15	.242
QTc (ms)	402.7 ± 17.3	393.2 ± 15.7	.004
P-min (ms)	95.2 ± 8.8 (70-135)	91.7 ± 7.8 (60-120)	.072
P-max (ms)	142.4 ± 18.2 (95-200)	115.6 ± 17.6 (75-165)	< .001
PWD	90.1 ± 12.2	53.5 ± 14.7	< 0.001
EF (Simpson) (%)	55.1 ± 8.2	68.3 ± 2.9	< .001
FS (%)	29.5 ± 5.7	39.6 ± 2.9	< .001
LVEDd (mm)	41.6 (37.4-44.6)	40.8 (38-45.4)	.937
LVEDs (mm)	28.2 (25-32)	24.9 (22.5-27.3)	< .001
LVPWd (mm)	6.5 ± 1.7	6.9 ± 1.3	.251
LADd (mm)	31.1 ± 3.9	28.1 ± 3.6	< .001
RADd (mm)	34.1 ± 2.9	33.4 ± 3.1	.182
RVEDd (mm)	13.7 ± 1.8	13.4 ± 1.2	.364
Mitral-E/A	1.7 ± 0.5	1.9 ± 0.5	.029
TRV (m/s)	2.3 (2.2-2.4)	2.2 (2.1-2.3)	.040
TAPSE (mm)	17.3 ± 3.1	22.9 ± 3.2	< .001
MAPSE (mm)	9.6 ± 1.7	14.1 ± 2.5	< .001

BSA, body surface area; DBP, diastolic blood pressure; EF, ejection fraction; FS, fractional shortening; HR, heart rate; LADd, left atrial end-diastolic dimension; LVEDd, left ventricular end-diastolic dimension; LVEDs, left ventricular end-systolic dimension; MAPSE, mitral annular plane systolic excursion; Mitral-A, mitral late diastolic velocity; Mitral-E, mitral early diastolic velocity; PR, PR interval; P-min, minimum P-wave duration; P-max, maximum P-wave duration; PWD, P-wave dispersion; QTc, corrected QT duration; RADd, right atrial end-diastolic dimension; RVEDd, right ventricular end-diastolic dimension; SBP, systolic blood pressure; TAPSE, systolic displacement of the lateral portion of the tricuspid annular-plane systolic excursion; TRV, tricuspid regurgitation velocity.

Table 2. Comparison of the Patient and Control Groups' Tissue Doppler Imaging Parameters and Atrial Electromechanical Delay Characteristics

Variables	Patient Group	Control Group	*P*
Mitral E/E'	7.9 ± 3.9	6.8 ± 1.8	.730
Mitral E'/A'	2.1 ± 0.8	2.6 ± 0.6	< .001
Mitral MPI	0.58 ± 0.2	0.34 ± 0.6	< .001
Septal E'/A'	1.9 ± 0.6	2.2 ± 0.5	< .001
Septal MPI	0.53 ± 0.1	0.35 ± 0.1	< .001
Tricuspid E'/A'	1.2 ± 0.4	1.7 ± 0.3	< .001
Tricuspid MPI	0.54 ± 0.1	0.34 ± 0.1	.001
Mitral AED (ms)	49.5 ± 11.6	36.6 ± 8.2	< .001
Septal AED (ms)	36.1 ± 8.9	25.6 ± 6.2	< .001
Tricuspid AED (ms)	23.1 ± 7.5	14.6 ± 5.5	< .001
Inter-atrial conduction delay (ms)	25.9 ± 10.5	24.1 ± 8.2	.033
Right-intra-atrial conduction delay (ms)	12.8 ± 7	10.9 ± 5.9	.142
Left intra-atrial conduction delay (ms)	13.1 ± 8	11 ± 5	.116

A' peak late diastolic velocity; AED, atrial electromechanical delay; E, mitral early diastolic velocity by pulsed-wave Doppler; E' peak early diastolic velocity; MPI, myocardial performance index.

DISCUSSION

As expected, our cross-sectional study revealed that DMD patients had impaired conventional echocardiographic and TDI parameters of both systolic and diastolic function. They also had a significantly higher PWD and atrial electromechanical delay obtained by TDI examinations than healthy controls.

Cardiac involvement manifests with dilated cardiomyopathy, congestive cardiac failure, and arrhythmias in patients with DMD. Deficiency of the subsarcolemmal dystrophin causes progressive muscle fibrosis and necrosis in skeletal and cardiac muscles in these patients.[8-10] DMD-related cardiomyopathy has a markedly prolonged subclinical phase of myocardial fibrosis beginning early in the disease course, leading to overt heart failure in the second decade.[11] The incidence increases with age, affecting one-third of patients by age 14, and is universal by age 18.[12] However, cardiomyopathy remains clinically silent due to severe physical limitations in these patients.[12,13] Previous studies have shown that early detection of cardiac involvement and treatment with angiotensin-converting enzyme inhibitors and/or beta-blockers can delay irreversible myocardial remodeling and prevent death from cardiac disease in patients with DMD.[14]

Advanced DMD cardiomyopathy is characterized by arrhythmias similar to those in other cardiomyopathies, including atrial fibrillation/flutter, ventricular tachycardia, and ventricular fibrillation. The incidence of arrhythmias

Table 3. Correlation of Left Ventricular Ejection Fraction with Atrial Conduction Time Variables

Variables	*r*	*P*
PWD	−0.486	< .001
LVEDd	−0.25	.009
LVEDs	−0.678	< .001
MAPSE	0.714	< .001
Mitral AED	−0.618	< .001
Septal AED	−0.549	< .001
Tricuspid AED	−0.551	< .001
Intra-atrial conduction delay	−0.093	.337
Inter-atrial conduction delay	−0.276	.004

AED, atrial electromechanical delay; LVEDd, left ventricular end-diastolic dimension; LVEDs, left ventricular end-systolic dimension; MAPSE, mitral annular plane systolic excursion; PWD, P-wave dispersion; *r*, correlation coefficient.

increases with increasing age and decreasing left ventricular EF.[5] Affected patients have circadian rhythm disruption, cardiac autonomic dysfunction, increased sympathetic activity, and reduced heart rate variability.[15-18] In our patient group, 2 patients had ventricular extrasystoles on ECG and Holter monitoring, but no further arrhythmia patterns were detected. However, tachyarrhythmias due to DMD-associated cardiomyopathy are likely to occur at an older age.

Impaired atrial conduction has an essential role in the pathophysiology of atrial fibrillation.[19] It can be assessed by both invasive (recording of atrial conduction during an electrophysiological study) and non-invasive indicators of atrial conduction (PWD on the ECG and measurement of atrial electromechanical delay by echocardiography).[20,21] These methods are thought to reflect atrial remodeling and predict atrial fibrillation.[22] Umapathi et al[23] reported that PWD was significantly higher in patients with DMD and Becker muscular dystrophy. They concluded that PWD is associated with systolic dysfunction in these patients and that the presence of cardiomyopathy in dystrophinopathies increases the risk of atrial arrhythmias. The patient group had significantly longer P-max and PWD than the control group in our study. Additionally, we showed a significantly longer duration of atrial electromechanical delay in the mitral, septal, and tricuspid segments in DMD patients compared to healthy control children. Furthermore, the inter-atrial conduction delay was significantly longer in the DMD group than in the control group. These findings may indicate an increased risk of atrial fibrillation in the future in these patients.

Transthoracic echocardiography (TTE) is the most commonly used diagnostic modality for DMD-related cardiomyopathy. However, conventional echocardiography rarely detects systolic dysfunction before the age of 10.[24] TTE lacks the ability to detect early myocardial fibrosis and visualize all heart segments. Left ventricular size and contractility also remain normal until widespread myocardial fibrosis is established. Recent studies have shown an improvement in the early diagnosis of DMD-related cardiomyopathy with newer TTE techniques such as TDI and 2D speckle echocardiography.[25] In line with previous studies, the left ventricular EF of patients in our study population was significantly reduced compared to healthy children and adolescents. Similarly, TDI studies revealed significant systolic and diastolic dysfunction parameters in DMD patients. DMD patients also showed signs of diastolic dysfunction in both ventricles.

Study Limitations

The current study has some limitations. First, our study was a single-center study with a relatively small number of patients, which may have affected the power of the study. Second, although none of the patients had atrial fibrillation during the study period, they could not be followed for the long-term development of atrial fibrillation. In addition, Holter monitoring was not performed in all patients with DMD. Finally, although all echocardiographic measurements were performed by a single experienced physician, intra-observer variability was not assessed.

CONCLUSION

The current study shows that DMD-related cardiomyopathy is associated with impairment of systolic and diastolic function in both the left and right ventricles by conventional echocardiography and TDI. While the atrial electromechanical delay was significantly increased in the mitral, septal, and tricuspid segments in patients with DMD, they had a longer inter-atrial conduction delay and PWD than the healthy controls. These findings are considered an indicator of impaired atrial conduction and may reflect atrial arrhythmias.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences, Antalya Training and Research Hospital (Approval No: 2021-083, Date: 18.03.2021).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer reviewed.

Author Contributions: Study conception and design: O.T., A.K.; data collection: O.T., A.K.; analysis and interpretation of results: O.T., A.K.; draft manuscript preparation: O.T., A.K.; Supervisor: A.K. All authors reviewed the results and approved the final version of the manuscript.

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