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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

# How Important are Cardiac Electrical Abnormalities in Duchenne and Becker Muscular Dystrophy?

## Duchenne ve Becker Musküler Distrofi'de Kardiyak Elektriksel Anomaliler Ne Kadar Önemlidir?

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## Abstract

**Aim:** Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are neuromuscular diseases associated with progressive cardiac dysfunction. This study aims to determine the early markers of their cardiac involvement.

**Materials and Methods:** This retrospective study was conducted with 26 boys with DMD-BMD (study group) diagnosed with genetic analysis. Healthy controls were 44 age-matched boys evaluated with electrocardiography (ECG), ambulatory Holter monitoring, and echocardiography (ECHO) to obtain a sport license. Heart rate variability (HRV) (SDNN, SDANN, SDNN index, Rmssd, pNN50), ECG (Heart rate, V1R/S, corrected QT, QRS-T angle, and parameters associated with ventricular repolarization heterogeneity) and ECHO parameters (ejection and shortening fraction, peak early and peak late diastolic velocities, tricuspid annular plane systolic excursion) of children with DMD and BMD were compared with healthy controls. The study group was also divided into "ambulatory" and "non-ambulatory" subgroups and differences in terms of cardiological parameters were evaluated between these subgroups.

**Results:** ECG revealed shorter PR and higher V1R/S in the study group than in the control group ($p<0.003$ and $p<0.01$). Heart rate was higher in the study group with ambulatory Holter monitoring ($p<0.01$). There was no significant difference in ECHO parameters. Lower HRV values were found in the ambulatory subgroup than in the non-ambulatory subgroup ($p<0.05$).

**Conclusion:** Significant alterations in ECG and HRV in dystrophinopathies were showed compared to healthy children of similar age. Thus, electrical abnormalities may be the earliest manifestation of the histopathological process conducive to the development of cardiac dysfunction.

**Key Words:** Duchenne muscular dystrophy, Becker muscular dystrophy, Heart

## Öz

**Amaç:** Duchenne musküler distrofi (DMD) ve Becker musküler distrofi (BMD), ilerleyici kalp fonksiyon bozukluğunun da eşlik ettiği nöromusküler hastalıklardır. Bu çalışmada DMD ve BMD'de kardiyak tutulumun erken belirteçlerinin belirlenmesi amaçlanmıştır.

**Gereç ve Yöntem:** Moleküler genetik tanı yöntemleri ile distrofin geninde hastalık nedeni mutasyon tespit edilmiş 26 DMD-BMD hastası ve 44 sağlıklı kontrol çalışmaya dahil edildi. Yaş uyumlu sağlıklı kontroller rutin spor lisans muayenesi için başvuranlar arasından seçildi. Tüm katılımcıların elektrokardiyografi (EKG) (Kalp hızı, V1R/S, QT, QRS-T açısı, ventriküler repolarizasyon heterojenliği ile ilişkili parametreler), ekokardiyografi (EKO) (ejeksiyon fraksiyonu, fraksiyonel kısalma, erken ve geç diyastolik tepe velosite, tricuspid annular plane systolic excursion) ve mevcut kalp hızı değişkenliği (KHD) (SDNN, SDANN, SDNN index, Rmssd, pNN50) ölçümleri geriye dönük olarak kaydedilerek hasta ve kontrol grubu karşılaştırıldı. Ayrıca hasta grubu "ambulatuvar" ve "non-ambulatuvar" olarak yeniden gruplandırıldı ve kardiyak parametreler bu alt gruplar arasında da kıyaslandı.

**Bulgular:** EKG verilerinden hasta grubunda kontrollere göre PR daha kısa, V1R/S yüksek bulundu ($p<0,003$, $p<0,01$). Kalp hızı, Holter monitorizasyonu ile hasta grubunda yüksek saptandı ($p<0,01$). EKO verilerinde her iki grup arasında fark saptanmadı. KHD verileri kıyaslandığında parametreler ambulatuar grupta non-ambulatuvar gruba kıyasla daha düşüktü ($p<0,05$).

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**Sonuç:** Bu çalışmada, distrofinopatilerde EKG ve KHD'de benzer yaştaki sağlıklı kontrollere göre anlamlı değişiklikler gösterilmiştir. Elektriksel anormallikler, kardiyak disfonksiyon gelişiminde histopatolojik sürecin en erken belirtisi olabilir.

**Anahtar Kelimeler:** Duchenne Musküler Distrofi, Becker Musküler Distrofi, Kalp

## Introduction

Duchenne muscular dystrophy (DMD; OMIM: 310200) is the most common hereditary neuromuscular disease in the childhood period with an incidence of 1/3500-5000 (1,2). In Turkey, there is no comprehensive study about the incidence and prevalence of DMD and Becker muscular dystrophy (BMD), though it is noticed that nearly half of childhood neuromuscular patients comprise DMD/BMD patients (3). In situations where the mRNA reading framework is preserved, BMD (OMIM: 300376) is observed with milder clinical progression due to partially functional dystrophin synthesis. Additionally, some mutations in limited areas of the dystrophy gene are associated with X-linked dilated cardiomyopathy (4).

In recent years, the average life expectancy has increased with the improvement in the standards of care (5,6). While respiratory failure is the leading cause of death, an increase in death rates due to cardiac causes was recorded after introduction of glucocorticoid treatment and ventilator support (7). Cardiac failure emerges in the second half of the second decade and becomes more evident with time (8). However, histopathological changes begin earlier. Awareness of cardiac involvement and initiation of treatment are important for prognosis. However, cardiac involvement may not be noticed before the emergence of clinical findings (9).

In skeletal and cardiac muscle, dystrophin is a part of the large glycoprotein complex located on the cytoplasmic surface of sarcolemma and ensures structural support of the cell. Additionally, it plays a role in regulation of blood flow to skeletal muscle by providing emplacement of nitric oxide synthetase on the sarcolemma. The absence of dystrophin in cardiac muscle causes progressive degeneration of muscle fibrils linked to membrane instability, fibrosis and fatty infiltration (10). This situation results in cardiac dysfunction and dilated cardiomyopathy. Additionally, cardiac conduction anomalies and linked fatal arrhythmias may be seen (11). Determining the decrease in left ventricle functions might be inadequate for early detection of cardiac involvement (12). Electrical abnormalities may be the earliest reflection of histopathologic changes in the development process of cardiomyopathy as arrhythmias may emerge without disruption of left ventricle systolic functions (13). Heart rate variability (HRV) consists of changes between consecutive heartbeats and indexes neurocardiac function (autonomic nervous system) which allow the cardiovascular system to rapidly adjust to sudden physical and psychological challenges to homeostasis. Beside autonomic nervous system disorders, elevated HRV measurements should indicate the problems of cardiac conduction system which could be related to cardiac muscle diseases. In this study, the electrocardiography (ECG), echocardiography (ECHO) and HRV data from DMD/BMD patients were compared with healthy controls to determine easily accessible, early diagnostic markers.

## Materials and Methods

This study is a single-center retrospective study of genetically confirmed DMD/BMD patients and an age-matched healthy control group. Ethical approval was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (13/11/2020-B.30.2.ODM.0.20.08/692). From January 2019 to February 2020, files of DMD/BMD patients attending to our center were investigated and demographic data, treatments and Gross Motor Function Classification System (GMFCS), Vignos and Brooke scales and maximum motor capacity data were obtained from their last examination. Patients using angiotensin-converting enzyme inhibitor, angiotensin receptor antagonists, beta blockers, antiarrhythmics and tricyclic antidepressants affecting electrocardiographic intervals were not included in the study.

DMD-BMD patients are assessed with ECG and ECHO annually in our center and if the pediatric cardiologist deems necessary, 24-hour Holter monitoring is planned. Patients who were recommended cardiac medication but did not start using it due to poor drug adherence were selected. In our country, it is necessary for children to undergo a detailed cardiac examination in order to start professional sports. The control group was created from these healthy male children without any acute/chronic illness, not using any medication and age-matched to the study group. The assessments at the last visit of the patients were considered.

Electrocardiogram was performed after adjusting the device to 10 mm/mV with a recording speed of 25 mm/s, using NIHON KOHDEN ECG-1250K Cardiofax S Electrocardiograph. Heart rate (HR), V1R/S, corrected QT, QRS-T angle, and parameters associated with ventricular repolarization heterogeneity (QT dispersion, Tpeak-to-Tend interval, and Tpeak-to-Tend /QT ratio, fragmented QRS V1 and lateral Q D1) were calculated. In addition, QT interval measurements were calculated and adjusted according to the Bazett formula.

Echocardiographic examinations were performed by the same experienced pediatric cardiologist using a "General Electric Vivid 7" cardiac ultrasound machine using sector probes (4S ve 7S) suitable for the age and weight of patients.

Echocardiographic measurements were assessed according to the American Echocardiography Association Pediatric Echocardiography Guideline (14).

Left ventricular systolic function (ejection and shortening fraction) was calculated by measuring the left ventricular inner diameter, posterior wall, and interventricular septum thickness during systole and diastole with M mode in the parasternal 5-chamber position. Left ventricular diastolic function was measured in the apical four-chamber position by tissue Doppler imaging in which the cursor was placed on the lateral mitral annulus. Peak early and peak late diastolic velocities (E 'and A') were measured and the E'/A' ratio was calculated. Three different measurements were made for each tissue and the average was calculated. For right ventricular function, tricuspid annular plane systolic excursion (TAPSE) was measured by placing the M mode cursor over the lateral tricuspid annulus at apical four-chamber positions. For HRV, electrocardiographic data for 24 hours were evaluated with a 12-lead Holter device and Cardioscan software. Artifacts were manually eliminated by the pediatric cardiologist.

HRV parameters [standard deviation of NN intervals (SDNN), standard deviation of the average NN intervals (SDANN) for each 5 min segment of a 24 h HRV recording), SDNN index (mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording), root mean square of successive RR interval differences (rMSSD) and percentage of successive RR intervals that differ by more than 50 ms measurements (pNN50)] were determined automatically with the data processing program of the Cardioscan software.

## Statistical Analysis

SPSS version 24 was used for analysis of data. The Kolmogorov-Smirnov test was used to assess distribution of data. Quantitative data are shown as mean and standard deviation, while qualitative data are given as case number (n) and percentage. Analysis of parametric data for more than two variables used the ANOVA test, while analysis of non-parametric data used the Kruskal-Wallis test. Analysis of factors causing significance in analysis of more than two variables used the Mann-Whitney U test for two-way comparison of those positive according to Kruskal-Wallis test and the post-hoc Tukey test for those positive with ANOVA. Comparisons of two-way quantitative data used the Spearman correlation analysis. A p-value of 0.05 was accepted as significant.

## Results

The study included 26 patients [17 DMD (65.4%) and 9 BMD (34.6%)] and 44 healthy controls. Mean age was 7.1±3.8 years on the DMD group, 8.5±5.1 years on the BMD group and 8.7±4.5 years in the control group, with no statistical difference present (p=0.45). The minimum age in the patient group was 1.5 years, with maximum age 17 years. The age of diagnosis and follow-up duration were 3.3±1.9 and 3.8±3.2 years in the DMD group and 3.6±2 and 4.9±4.1 years in the BMD group, respectively (p=0.71 and p=0.56).

All participants had ECG and ECHO records available while 10 patients in the patient group (38.4%) and 41 healthy children in the control group (93.2%) had HRV records available. The ECG, ECHO and HRV data for patient and control group are given in Table 1. Of the ECG data, HR and V1RS was significantly high, while PR interval was short, in the patient group compared to the control group (p=0.019, p=0.00, p=0.003). There was no difference between the two groups in terms of ECHO data. When HRV data are compared, all parameters in the patient group were lower compared to the control group, while there was statistical significance for SDNN and SDANN (p=0.028, p=0.044).

The patient group was divided in two as ambulatory (n=21) and non-ambulatory (n=5) cases. Age, motor capacity and cardiac data are compared in Table 2. HRV records were available for 8 patients in the ambulatory group (30.8%) and 2 patients in the non-ambulatory group (7.7%). The mean age of non-ambulatory patients was significantly older than the ambulatory group (p=0.005). QRS was identified to be significantly longer in the non-ambulatory group (p=0.01). For ECHO data, mitral E value was significantly lower in the non-ambulatory group (p=0.015). When HRV data are examined, all parameters were observed to be low in the non-ambulatory group (p<0.05). Only 1 DMD patient was observed to have wall movement anomaly with left ventricle systole disorder findings.

Seven patients (26.9%) were receiving only prednisolone, 4 patients (15.4%) were receiving prednisolone and idebenone, 1 patient (3.85%) was receiving translarna treatment and 14 patients (53.85%) were not receiving treatment. When the groups receiving and not receiving treatment are compared, the mean age (5.5±3.6 years) and follow-up duration (2.7±2.4 years) were lower in the group not receiving treatment compared to the mean age (10±3.7) and follow-up duration (6±3.8 years) in the group receiving treatment (p=0.004, p=0.009). When ECG, ECHO and HRV data are compared in these groups, mitral E and A were observed to be significantly lower in the group receiving treatment (p=0.03, p=0.041). There was no significant difference identified in terms of the other parameters.

There were positive correlations between the IVSd with Brooke and GMFCS scores, between IVSs with Brooke score, between LVPWd with Brooke and GMFCS scores and between LVIDd with Brooke, Vignos and GMFCS scores (p<0.05). For the 10 patients with HRV records, there were negative correlations between age, Brooke, Vignos and GMFCS values with SDNN, SDANN, SDNN index, rMSSD and pNN50 values, though these were not statistically significant (p<0.05).

## Discussion

Surveillance of the heart in children with dystrophinopathy and taking the necessary medical precautions in time is important. Overlooking of heart failure findings due to limited ambulation, involvement of other organ systems coming to the forefront and the lack of immediate pronounced cardiac symptoms are negative factors in terms of cardiac surveillance (15). Cardiac symptoms are reported in 28% of patients under 18 years of age and frequency is 57% among adults (15). Left ventricular dysfunction is an important indicator for mortality and occurs in up to 40% of DM patients, reflecting an increased propensity to develop cardiomyopathy and heart failure in DMD (16,17). ECHO may identify cardiac dysfunction in the advanced stages of disease; however, there is no adequate diagnostic tool for identification of early-period cardiovascular involvement (18). Cardiac symptoms are only observed in 30% of patients at time of diagnosis in DMD, while left ventricular dilatation is rarer (19). A large study with EF showed left ventricular dysfunction at mean 15.2 years (20). Our study is in line with this information with ECHO data of LVIDd and LVIDs showing left ventricle diameter, EF and KF showing systole function and mitral E, A and E/A values showing diastole function within normal limits. There was no significant difference between the patient and control groups.

**Table 1: Cardiac parameters in Duchenne and Becker muscular dystrophy (DMD/BMD) patients versus controls**

| | DMD&BMD (n=26) | Healthy controls (n=44) | p-value |
|---|---|---|---|
| **Electrocardiography** | | | |
| Heart rate/min | 104.2±26.3 | 90.0±18.2 | **0.019** |
| PR interval (ms) | 116.2±24.6 | 133.8±18.3 | **0.003** |
| QRS (ms) | 84.8±13.6 | 84.8±10.9 | 0.997 |
| QTC (ms) | 317.5±27.8 | 381.0±23.6 | 0.714 |
| QT dispertion (ms) | 24.2±10.1 | 23.8±9.0 | 0.888 |
| QRS T angle | 30.5±33.0 | 27.0±24.3 | 0.614 |
| Tpeak to Tend (ms) | 60.5±50.5 | 46.50±15.6 | 0.092 |
| Tpeak to Tend/QT | 0.18±0.15 | 0.18±0.08 | 0.866 |
| V1RS | 1.49±1.0 | 0.54±0.31 | **0.000** |
| Fragmented QRS V1 | 7.7% | 4.5% | 0.357 |
| Lateral Q DI | 11.5% | 6.8% | 0.310 |
| **Echocardiography** | | | |
| EF (%) | 69.7±4.2 | 69.3±7.2 | 0.803 |
| FS (%) | 39.4±4.7 | 38.5±5.9 | 0.475 |
| Mitral E wave (cm/s) | 93.5±13.0 | 93.7±14.5 | 0.398 |
| Mitral A wave (cm/s) | 57.6±10.5 | 55.16±12.8 | 0.307 |
| IVSd (mm) | 7.5±1.6 | 7.06±1.6 | 0.264 |
| IVSs (mm) | 15.2±20.1 | 9.37±2.2 | 0.059 |
| LVPWd (mm) | 7.2±2.2 | 6.75±1.6 | 0.245 |
| LVPWs (mm) | 10.9±2.4 | 9.89±1.9 | 0.052 |
| LVIDd (mm) | 38.5±6.3 | 38.1±5.6 | 0.796 |
| LVIDs (mm) | 23.2±4.8 | 23.3±4.21 | 0.959 |
| TAPSE (mm) | 19.5±3.01 | 20.23±4.21 | 0.519 |
| **Heart rate variability** | | | |
| SDNN (ms) | 92.7±33.9 | 131.5±51.2 | **0.028** |
| SDANN (ms) | 83.2±35.9 | 115.7±46.2 | **0.044** |
| SDNN index | 48.1±16.8 | 63.4±25.0 | 0.072 |
| rMSSD (ms) | 32.7±12.1 | 45.8±20.1 | 0.054 |
| pNN50 (%) | 11.9±9.3 | 20.0±13.9 | 0.088 |

Min: Minute, EF: Ejection fraction, FS: Fractional shortening, IVS: Inter-ventricular septum thickness, LVPW: Left ventricle posterior wall, LVID: Left ventricle internal diameter, -d = In diastole. -s = In systole, TAPSE: Tricuspid annuler plane systolic excursion, SDNN: Standard deviation of NN interval, SDANN: Standard deviation of the 5 minute average NN intervals, rMSSD: Root of square mean of successive NN interval, pNN50: Number of NN intervals with less than 50 ms, pNN50: Percentage of number of NN interval with less than 50 ms

Scar tissue formed by myocardial fibrosis causes electrical conductivity disorders. Fibrosis may be shown by magnetic resonance imaging; however, this investigation is not always possible at all times and locations due to requirements for sedation and institutional inadequacies. ECG is an easily accessible and cheap test reflecting the pattern of myocardial injury. We think it still preserves its importance in the present day for this purpose. Abnormal electrocardiogram findings had a frequency of 52.4% for asymptomatic patients under 10 years of age according to Nigro et al. (15) and 84.8% according to Takami et al. (21).

As in our patients, increased HR, short PR interval and high R wave in V1 derivation (V1rs) on ECG are reported in the literature (21). Thomas et al. (22) reported increased HR was associated with the onset of cardiomyopathy, and may be associated with myocardial fibrosis and autonomic dysfunction. High R wave on V1 derivation is thought to be due to selective scar tissue and atrophy in the posterobasal areas and adjacent lateral walls,

**Table 2: Cardiac parameters in non-ambulatory versus ambulatory muscular dystrophy patients**

| | Non-ambulatory (n=5) | Ambulatory (n=21) | p-value |
|---|---|---|---|
| Age (years) | 12.1±2.7 | 6.5±3.8 | **0.005** |
| Brooke score | 3.2±1.9 | 1.2±0.5 | **0.010** |
| Vignos score | 7±3.5 | 1.8±1.0 | **0.012** |
| GMFCS score | 4.2±1.3 | 1.2±0.4 | **<0.001** |
| **Electrocardiogarphy** | | | |
| Heart rate/min | 109±15.2 | 103.1±28.5 | 0.850 |
| PR interval (ms) | 119.8±31.7 | 115.4±23.5 | 0.705 |
| QRS (ms) | 94.6±4.3 | 82.5±14.1 | **0.010** |
| QTC (ms) | 386±27.1 | 382.6±25.6 | 0.717 |
| QTdispertion (ms) | 24±6.2 | 24.2±10.9 | 0.850 |
| QRS T angle | 41.4±65.5 | 28±21.6 | 0.801 |
| Tpeak to Tend (ms) | 62±24.8 | 60.2±55.7 | 0.575 |
| Tpeak to Tend/QT | 0.19±0.09 | 0.19±0.17 | 0.845 |
| V1RS | 1.5±0.8 | 1.5±1.3 | 0.682 |
| **Echocardiography** | | | |
| EF (%) | 69.6±6.9 | 69.8±3.6 | 0.753 |
| FS (%) | 43±8.3 | 38.6±3.2 | 0.157 |
| Mitral E wave (cm/s) | 80±15 | 96.8±10.4 | **0.015** |
| Mitral A wave (cm/s) | 51.8±14.5 | 59±9.1 | 0.178 |
| IVSd (mm) | 8.6±5 | 7.3±21 | 0.178 |
| IVSs (mm) | 12.9±2.3 | 15.8±22.5 | 0.272 |
| LVPWd (mm) | 9.1±3.1 | 6.9±1.8 | 0.121 |
| LVPWs (mm) | 12.3±2.8 | 10.6±2.2 | 0.243 |
| LVIDd (mm) | 42±6.7 | 37.7±6.1 | 0.272 |
| LVIDs (mm) | 25.5±5.6 | 22.7±4.7 | 0.447 |
| TAPSE (mm) | 19.6±4.3 | 19.6±2.8 | 0.613 |
| **Heart rate variability** | | | |
| SDNN (ms) | 50±14.1 | 103.4±28.3 | **0.037** |
| SDANN (ms) | 41±21.2 | 93.8±31 | **0.048** |
| SDNN index | 27.5±2.1 | 53.3±14.7 | **0.037** |
| rMSSD (ms) | 18.5±2.1 | 36.3±10.9 | **0.035** |
| pNN50 (%) | 1.5±0.7 | 14.5±8.6 | **0.036** |

GMFCS: Gross Motor Function Classification System, EF: Ejection fraction, Min: Minute, FS: Fractional shortening, IVS: Inter-ventricular septum thickness, LVPW: Left ventricle posterior wall, LVID: Left ventricle internal diameter, -d = In diastole. -s = In systole, TAPSE: Tricuspid annuler plane systolic excursion, HRV: Heart rate variability, SDNN: Standard deviation of NN interval, SDANN: Standard deviation of the 5 minute Average NN intervals, rMSSD: Root of square mean of successive NN interval, pNN50: Number of NN intervals with less than 50 ms, pNN50: Percentage of number of NN interval with less than 50 ms

rather than from right ventricular hypertrophy (23). Sanyal et al. (24) proposed that dystrophic changes in the conduction system may cause left axis deviations and short PR intervals. This study also investigated the QT dispersion, QRS-T angle, Tpeak-to-Tend, Tpeak-to-Tend/QT, Fragmented QRS V1, and Lat Q DI. In previous studies, f-QRS was shown to reflect intraventricular conduction delay caused by myocardial fibrosis and regional myocardial injury and was associated with the degrees of left ventricle dysfunction, fibrosis and ventricular arrhythmia (25,26). QT dispersion shows regional repolarization heterogeneity and was shown to be a risk factor for severe ventricular arrhythmia in DMD and BMD patients (27). Tpeak-to-Tend interval shows the spatial and transmural distribution of repolarization, while corrected Tpeak-to-Tend interval is associated with lengthened ventricular arrhythmia and increased sudden cardiac death (28). Yoo et al. only found a significant difference in fQRS prevalence between patients and controls under 10 years of age; with differences in fQRS, HR, Tpeak-to-Tend/QT and corrected Tpeak-to-Tend for those aged 11-15 years; and significant differences for all parameters over 16 years (29). In our study, no difference was identified between patient and control group. The reason for this may be considered to be the low mean age in the study group or the low patient numbers.

Reduced HRV is reported to be an indicator of cardiovascular disease (30). Twenty-four-hour Holter records are the gold standard for SDNN risk classification and predict mortality and morbidity (31). SDNN <50 ms is classified as unhealthy, 50-100 ms is compromised health and values above 100 are healthy (32). The incidence of arrhythmia increased with increasing age in DMD patients (33). When HRV data are compared, all parameters in the patient group were low compared to the control group, but only SDNN and SDANN were at levels significant in statistical terms. When HRV data are compared between ambulatory and non-ambulatory groups, all parameters were lower in the non-ambulator group. Though there were negative correlations between age, Brooke, Vignos and GMFCS scores with SDNN, SDANN, SDNN index, rMSSD and pNN50 values, none of these correlations were statistically significant. This indicates an indirect association between the increasing motor function loss with age and cardiac involvement. Similar to our findings, HRV and short-term HRV data were reported to be low in DMD patients (34-36). Hypotheses proposed for this situation include fatty infiltration of the sinoatrial node or nitric oxide alteration (37,38). SDANN and maximum HR were shown to be associated with late gadolinium involvement on cardiac MRI. A study by Inoue et al. (35) frequently encountered autonomic dysfunction while left ventricle functions and BNP were normal on ECHO.

Additionally, while cardiac MRI was normal for ambulatory patients from 5-10 years, HRV abnormalities were identified and the researchers noted that HRV was disrupted before development of failure findings (39). In our study, the marker for left ventricle systole function of EF was identified to be normal in all patients. This situation leads to consideration that cardiovascular changes primarily form in the rhythm system of the heart and that contractility alterations occur in later periods.

In our study, non-ambulatory patients showed remarkable results in terms of QRS duration and mitral E. QRS interval prolongation is an important parameter in arrhythmic evaluation and an independent predictor of sudden death in DMD (40,41). QRS prolongation is likely due to late depolarization of tissue within islands of patchy fibrosis (42). Progression of myocardial fibrosis also contributes to impairment in the passive component of diastole leading to deteriorated ventricular compliance and the development of systolic dysfunction (43). A relatively low-velocity E wave reflects the impaired relaxation of the left ventricle and decreased early diastolic suction. In this study, QRS prolongation and decreased mitral E were observed in the non-ambulatory subgroup. This situation, which is probably associated with increased fat accumulation in myocardial tissue with immobility, suggests that more frequent and careful cardiac evaluation is required for non-ambulatory DMD patients. Limitations of the study are the limited numbers and retrospective planning. Thus this is a pilot, exploratory study in a small heterogeneous cohort of patients, whose results need to be confirmed in further prospective studies. Assessment of all ECG, HRV, and ECHO data along with motor functions are strong aspects of this study.

## Conclusion

Treatment with angiotensin-converting enzyme inhibitors in the early period is proven to reduce mortality (44). Easily accessible and cheap indicators showing early cardiac involvement will be beneficial to clinicians in this process. For this purpose ECG and HRV monitoring remain important for ambulatory and non-ambulatory groups.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (13/11/2020-B.30.2.ODM.0.20.08/692).

**Informed Consent:** Retrospective study.

**Peer-reviewed:** Externally peer-reviewed.

### Authorship Contributions

Concept: İ.O.Ş., Ü.A., A.A., Design: İ.O.Ş., Ü.A., A.A., Data Collection and Processing: G.Ö.T., İ.O.Ş., Analysis or Interpretation: A.A., Literature Search: A.A., Writing: G.Ö.T.

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