Repolarization abnormalities in Duchenne-type muscular dystrophy

Duchenne musküler distrofisinde repolarizasyon anormallikleri

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Objectives: Duchenne-type muscular dystrophy (DMD) is an X-linked recessive inherited disease affecting mainly the skeletal and cardiac muscles. We aimed to seek associations between the incidence of ventricular arrhythmias and corrected QT (QTc) dispersion and its component, corrected JT (JTc) dispersion in patients with DMD.

Study design: The study included 43 consecutive male patients (mean age 8.8±3.0 years; range 3 to 17 years) with DMD. On standard 12-lead electrocardiograms (ECG) the QT and JT intervals and the corrected QT (QTc) and JTc dispersions were calculated. Ventricular extrasystoles were assessed on 24-hour Holter ECG recordings. Ventricular dysrhythmic patterns were evaluated according to the Lown-Wolf classification. The results were compared with those of a control group of 34 healthy children (mean age 9.5±3.1 years).

Results: The mean QTc and JTc dispersion values were significantly higher in DMD patients compared to controls (QTc: 78.0±20.6 msec *vs.* 50.9±16.5 msec; JTc: 77.6±20.5 msec *vs.* 50.8±17.7 msec; p<0.05). The results of Holter monitoring were evaluated in 36 patients and in 33 controls. Ventricular extrasystoles were found in six patients (16.7%) and in one (grade I) control subject (3%). The incidence of pathological findings was significantly higher in the study group (p<0.05), including grade I pathology in four patients, grade II pathology in one patient, and grade IV in one patient. QTc and JTc dispersion values of the patients with and without ventricular extrasystoles showed no statistically significant difference (p>0.05).

Conclusion: Similar QTc and JTc dispersion values detected in patients with and without ventricular extrasystoles may suggest that ventricular repolarization abnormalities occur in early life and may predispose to the development of ventricular arrhythmias in the long-term.

Key words: Arrhythmias, cardiac/etiology; child; electrocardiography; heart conduction system; muscular dystrophy, Duchenne.

Amaç: Duchenne musküler distrofisi (DMD), X'e bağlı resesif kalıtılan ve özellikle iskelet ve kalp kasını etkileyen genetik bir hastalıktır. Bu çalışmada, DMD'li hastalarda ventriküler aritmi varlığı ile düzeltilmiş QT (QTc) ve onun bileşeni olan düzeltilmiş JT (JTc) dağılımı (dispersiyon) arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya DMD'li ardışık 43 erkek hasta (ort. yaş 8.8±3.0; dağılım 3-17) alındı. Standart 12 derivasyonlu elektrokardiyografi (EKG) kayıtları üzerinden QT ve JT intervalleri ve düzeltilmiş QT (QTc) ve JTc dağılım değerleri hesaplandı. Yirmi dört saatlik Holter EKG kayıtlarında ventrikül ekstrasistolleri araştırıldı ve ventrikül ritim bozukluğu örnekleri Lown-Wolf sınıflamasına göre derecelendirildi. Sonuçlar 34 sağlıklı çocuktan (ort. yaş 9.5±3.1) oluşan kontrol grubuyla karşılaştırıldı.

Bulgular: Ortalama QTc ve JTc dağılım değerleri hasta grubunda kontrol grubuna göre anlamlı derecede yüksek bulundu (QTc için 78.0±20.6 msn ve 50.9±16.5 msn; JTc için 77.6±20.5 msn ve 50.8±17.7 msn; p<0.05). Holter kayıtları 36 hastada ve 33 kontrolde değerlendirmeye alındı. Ventrikül ekstrasistollerine altı DMD'li hastada (%16.7) ve kontrol grubunda bir kişide (%3, derece I) rastlandı. Holter kayıtlarında patolojik bulgu sıklığı DMD'li grupta anlamlı derecede fazlaydı (p<0.05). Patolojik bulgular dört hastada derece I, bir hastada derece II, bir hastada da derece IV olarak sınıflandırıldı. Ventrikül ekstrasistolü görülen ve görülmeyen hastalar arasında QTc ve JTc dağılım değerleri anlamlı farklılık göstermedi (p>0.05).

Sonuç: Ventrikül ekstrasistolü olan ve olmayan hastalarda benzer QTc ve JTc dağılım değerleri elde edilmesi, ventrikül repolarizasyon anormalliklerinin erken dönemde başladığı ve bunun uzun dönemde ventrikül ritim bozukluklarına temel oluşturduğu şeklinde yorumlanabilir.

Anahtar sözcükler: Aritmi, kardiyak/etyoloji; çocuk; elektrokardiyografi; kalp iletim sistemi; musküler distrofi, Duchenne.

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QT dispersion is defined as the difference between the longest (QT_{max}) and the shortest (QT_{min}) QT intervals on a standard 12-lead electrocardiogram (ECG). It reflects regional differences in ventricular repolarization and reveals the heterogeneity in myocardial repolarization.[1,2] Patients with increased QT dispersion have been reported to have a high risk for serious ventricular arrhythmias and sudden death, especially those in high risk groups with ischemic heart disease, chronic congestive heart failure, long-QT syndrome, and cardiomyopathies.[3-7]

Duchenne-type muscular dystrophy (DMD) is an X-linked recessive inherited disease primarily affecting the skeletal and cardiac muscles.[8,9] Cardiac muscle degeneration is associated with fibrous tissue replacement and fatty infiltration.[10] Fibrosis in the myocardium may lead to heart failure and pulmonary congestion, a common cause of death at further stages.[10-12] Additionally, cardiac fibrosis can cause dilated cardiomyopathy and conduction abnormalities, which may induce fatal arrhythmias and worsen the clinical outcome.[13-15] Cardiac symptoms usually become appreciable after the age of 10 years and increase in incidence with age.[16] Unfortunately, there is no clinical finding until the standard 12-lead ECG or Holter ECG monitoring reveal ECG pathologies and dysrhythmias.[17] Tall R wave, increased R/S ratio, deep and narrow Q waves have been clearly defined as classical ECG findings in patients with DMD.[15,18-21]

Regional damage to the myocardial tissue causes a regional change in the ventricular repolarization, reflecting as abnormal QT dispersion.[1,22] There are few publications concerning QT dispersion in patients with DMD.[22,23] In this study, we aimed to seek associations between the incidence of ventricular arrhythmias and dispersion of corrected QT (QTc) dispersion and its component, corrected JT (JTc) dispersion in patients with DMD.

PATIENTS AND METHODS

Forty-three consecutive patients with DMD were studied, who were referred to the pediatric cardiology department from 1996 to 2005. All the patients were males (mean age 8.8±3.0 years; range 3 to 17 years). The patients' medical history, 12-lead ECG and 24-hour Holter ECG recordings were obtained. Diagnosis of DMD was made based to the established criteria including genetic analysis, muscular biopsy, or typical clinical findings (neurologic signs, increased creatine phosphokinase levels, and typical calf hypertrophy).[24] Female carriers were excluded. Three patients were receiving digoxin and four patients were receiving diuretic therapy. Patients taking antiarrhythmic drugs were excluded. The study protocol was approved by the hospital ethics committee.

The results were compared with those of a control group consisting of 34 male healthy children (mean age 9.5±3.1 years; range 4 to 16 years).

QTc and JTc analysis. A standard 12-lead ECG was obtained at a paper speed of 25 mm/sec and an amplitude of 10 mm/mV (Nihon-Kohden ECG 6511, Tokyo, Japan). All ECG recordings were evaluated by one observer blinded to the clinical status and all measurements were performed using hand calipers. The QT interval was measured from the onset of the QRS complex to the end of the T wave. Biphasic T waves were measured to the time of the final return to the baseline. If U waves were present, the QT interval was measured to the base point of the curve between the T and U waves. At least three cycles were measured on each ECG recording. Extrasystolic and post-extrasystolic cycles were ignored. Heart rate-corrected QT and JT intervals (QTc and JTc) were calculated by the Bazett's formula (QTc: $QT/\sqrt{R\text{-}R}$). QTc and JTc dispersions were calculated as the differences between the maximum and minimum measurements of QTc and JTc, respectively. The QTc and JTc dispersion values were compared between the study and the control groups.

Analysis of 24-Hour Holter monitoring. 24-hour recordings were obtained at the Pediatric Cardiology Department using a Schiller MT-200 Holter ECG V2.04 (Schiller AG, Baar, Switzerland) device. All recordings were evaluated by a pediatric cardiologist. Ventricular dysrhythmic patterns determined by 24-hour monitoring were evaluated according to the Lown-Wolf classification.[25,26] This classification consists of the following grades: grade 0: no ventricular premature beats; grade 1: ≤30 ventricular premature beats/hr; grade II: >30 premature beats/hr; grade III: multiform premature ventricular beats; grade IVa: presence of ventricular couplets; grade IVb: presence of ventricular tachycardia of three or more beats; grade V: presence of the R-on T-phenomenon.

The results of Holter ECG monitoring were evaluated in 36 patients (83.7%) and in 33 controls (97.1%). Seven patients were not taken into consideration due to technical problems of the device or detachment of electrodes during 24 hours of monitoring.

Statistical analysis was performed using the SPSS version 11.5 software program. Data were expressed

as mean±standard deviation or percentage where appropriate. Differences between the two groups were assessed by the unpaired t-test or chi-square test. A *p* value less than 0.05 was considered to be statistically significant.

RESULTS

The mean QTc dispersion was 78.0±20.6 msec in the study group and 50.9±16.5 msec in the control group, being significantly higher in the former (p<0.05). Similarly, JTc dispersion was significantly greater in the study group (77.6±20.5 msec *vs*. 50.8±17.7 msec; p<0.05).

The results of 24-hour Holter ECG monitoring were divided into two groups as normal and pathological findings, according to the Lown-Wolf classification, where grade 0 was accepted to be normal and grades I to IV were accepted to be pathologic. Pathologic findings were observed in six patients (16.7%) and in one (grade I) control subject (3%). The incidence of pathological findings was significantly higher in the study group (p<0.05), including grade I pathology in four patients, grade II pathology in one patient, and grade IV in one patient.

Comparison of QTc and JTc dispersion values of the patients with and without ventricular extrasystoles during Holter ECG monitoring showed no statistically significant difference (p>0.05; Table 1).

DISCUSSION

In the present study, we found that repolarization abnormalities occurred in the early period of DMD. Cardiac dysrhythm abnormalities have been reported to have a major role in mortality and morbidity in patients with DMD.[19,27,28] Ventricular repolarization abnormalities may be a marker for ventricular arrhythmias. Thus, various ECG parameters such as QT dispersion and JT dispersion, which were formerly used in other cardiac diseases, have been investigated in individuals with DMD.[22,23,29] QT dispersion reflects regional differences in ventricular repolarization and has a heterogenic feature in myocardial repolarization.[1,2] Increased dispersion of recovery time is believed to be associated with increased risk for serious ventricular arrhythmias compared to the individuals with dispersion of recovery time in normal ranges.[2-5] Regional damage to the myocardial tissue causes a regional change in the ventricular repolarization which plays a major role in the formation of QT dispersion. There are few publications concerning QT dispersion in patients with DMD.[22,23] In one study, 24-hour Holter ECG monitoring of the patients with DMD (mean age 20.5±4.7 years) was performed and ventricular dysrhythmias were classified according to the Lown-Wolf classification.[22] QT dispersion values obtained from the standard ECG were compared with those obtained from Holter monitoring and grade III or higher ventricular dysrhythmias were found to be correlated with QT dispersion.

Table 1. Comparison of QTc and JTc dispersion values of patients with and without ventricular extrasystole during Holter ECG monitoring

	Ventricular extrasystole		
	Present (n=6) Mean±SD	Absent (n=30) Mean±SD	*p*
QTc dispersion (msec)	86.0±14.0	77.9±22.8	>0.05
JTc dispersion (msec)	80.6±21.1	78.1±22.6	>0.05

QT dispersion can also be calculated using the QTc interval which is the correction of the QT interval for heart rate using the Bazett's formula.[1,23,30] QTc can be calculated more easily with the Bazett's formula, yet there are other formulas used in high heart rates.[1] In our study, QTc values were calculated using the Bazett's formula. The mean QTc values in the patient and control groups were 78.0±20.6 msec and 50.9±16.5 msec, respectively. There was a statistically significant difference between the two groups. In a study involving 25 children (mean age 8.7 years) with idiopathic benign ventricular ectopy, the mean QTc dispersion was found to be 83.8±32 msec compared to 58.9±14.8 msec in the control group.[30] This study involved patients whose mean age was similar to that in our study. In our study, no correlation was found between OTc dispersion and the incidence of ventricular dysrhythmia. This finding could be due to the fact that the incidence of ventricular dysrhythm was low in the early phase of DMD. It has been shown that grade III and above scores are significantly correlated with dispersion of repolarization, while lower scores do not show such a correlation.[22]

QTc value includes both depolarization and repolarization time of the ventricles. JTc interval reflects ventricular repolarization more accurately compared to the QTc interval.[30,31] Both QTc and JTc intervals have been frequently used to assess abnormalities of the ventricular conduction system. Like QTc dispersion, JTc dispersion, assessed by subtracting the shortest JTc distance from the longest distance, also reflects the regional repolarization changes in myocardial repolarization. Thus, in many studies it has

been used with QTc dispersion to assess ventricular dysrhythmias and the risk for sudden death.[1,30] To our knowledge, JTc dispersion has not been used in DMD patients. Das and Sharma[30] reported significantly higher QTc and JTc dispersion values in children with idiopathic ventricular ectopy compared to normal controls. Similarly, both the QTc and JTc dispersion values were significantly higher in our patients ($p<0.05$). Although JTc dispersion has been reported to reflect ventricular repolarization pathologies associated with increased risk for ventricular dysrhythmia,[30] we found no difference in JTc dispersion values between patients with and without ventricular dysrhythm. This finding may be due to the fact that ventricular repolarization abnormalities occur in early life and form the basis of ventricular dysrhythmias in the long-term. Therefore, long-term follow-up of these patients is necessary with 12-lead ECG and 24-hour Holter ECG monitoring.

In conclusion, although both the QTc and JTc dispersions were found to be abnormal in children with DMD, we could not find any relationship between the QTc/JTc dispersions and the occurrence of ventricular dysrhythmias. This finding may suggest that ventricular repolarization abnormalities occur in early life and may predispose to the development of ventricular arrhythmias in the long-term. Since 24-hour Holter recordings are not sensitive enough to detect this kind of dysrhythmias, new techniques are needed to detect these dysrhythmias in patients with DMD. Our study is limited by its retrospective nature. A large prospective study with a longer Holter ECG monitoring (48-72 hours) may be required.

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