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Increased dispersion of ventricular repolarization in emery dreifuss muscular dystrophy patients

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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G Funds Collection

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Summary

Background: Sudden cardiac death (SCD) is common in patients with Emery-Dreifuss muscular dystrophy (EDMD) and is attributed to the development of life-threatening arrhythmias that occur in the presence of normal left ventricular systolic function. Heterogeneity of ventricular repolarization is considered to provide an electrophysiological substrate for malignant arrhythmias. QTc dispersion (QTc-D) and JTc dispersion (JTc-D) are electrocardiographic parameters indicative of heterogeneity of ventricular repolarization. The aim of our study was to evaluate the heterogeneity of ventricular repolarization in patients with Emery-Dreifuss muscular dystrophy with preserved systolic and diastolic cardiac function

Material/Methods: The study involved 36 EDMD patients (age 20±12, 26 M) and 36 healthy subjects used as controls, matched for age and sex. Heart rate, QRS duration, maximum and minimum QT and JT interval, QTc-D and JTc-D measurements were performed.

Results: Compared to the healthy control group, the EDMD group presented increased values of QTc-D (82.7±44.2 *vs.* 53.1±13.7; *P=0,003*) and JTc-D (73.6±32.3 *vs.* 60.4±11.1 ms; *P=0.001*). No correlation between QTc dispersion and ejection fraction (R=0.2, P=0.3) was found.

Conclusions: Our study showed a significant increase of QTc-D and JTc-D in Emery-Dreifuss muscular dystrophy patients with preserved systolic and diastolic cardiac function.

key words: **Emery-Dreifuss muscular dystrophy (EDMD) • sudden cardiac death (SCD) • ventricular repolarization • QTc dispersion • JTc dispersion**

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Background

Emery-Dreifuss muscular dystrophy (EDMD) – first described by Emery and Dreifuss in 1966 – is a hereditary muscle disorder characterized by slowly progressive muscle wasting and weakness, with humero-peroneal distribution in the early stages, early contractures of the elbows, Achilles tendons and post-cervical muscles, and cardiomyopathy [1]. EDMD can be inherited either as an X-linked recessive disorder, caused by mutations in the STA gene that encodes the nuclear protein emerin on chomosome Xq28, or as an autosomal dominant trait caused by mutations in the gene encoding the nuclear protein lamin A/C (LMNA) on chromosome 1q21.2 [2]. Both patterns of inheritance result in the lack of the corresponding protein – emerin and/or lamin A/C – in muscle and skin nuclei [3]. Cardiomyopathy is the most serious and life-threatening clinical manifestation of the disease, and usually appears later compared with muscle impairment. Rhythm abnormalities commonly noted in the all forms of muscular dystrophies [4], especially in EDMD, include sinus node dysfunction, atrial flutter, atrial fibrillation, heart block, ventricular tachycardia, and ventricular fibrillation [5]. Sudden cardiac death (SCD) is common in patients with EDMD, and is attributed to the development of life-threatening arrhythmias which occur in the presence of normal left ventricular systolic function [6]. Thus, electrical abnormalities may be the earliest manifestation of the histopathological process conducive to the development of cardiomyopathy. The gene therapy [7,8], unfortunately, has not yet given the desired results up to this moment, so prevention of arrhythmic risk plays an important role in the current treatment of this rare form of muscular dystrophy. Assessment of the individual risk for sudden death in patients with Emery-Dreifuss muscular dystrophy remains a clinical challenge. SCD in EDMD patients has not received sufficient recognition in the literature, and its mechanism is potentially of great interest. QTc dispersion (QTc- D) and JTc dispersion (JTc- D) have been proposed as noninvasive methods to measure the heterogeneity of ventricular repolarization. Increased dispersion of ventricular repolarization is considered to provide an electrophysiological substrate for life-threatening ventricular arrhythmias [9,10] in several clinical conditions [11–16]. The aim of our study was to evaluate the heterogeneity of ventricular repolarization in EDMD by examining QTc-D and JTc-D, electrocardiographic parameters of spatial heterogeneity of ventricular repolarization, in EDMD patients with preserved systolic and diastolic function.

Material and Methods

Study population

The study enrolled 36 EDMD subjects (26 men; age 20±12 years) recruited from the Cardiomyology and Medical Genetics Section of the 2nd University of Naples. Thirty-six age- and sex-matched non-EDMD healthy subjects were also recruited as controls. Exclusion criteria were: history of hypertension (systolic and diastolic blood pressure >140/90 mmHg), obesity, previous atrial fibrillation, electrolyte imbalance, valvular heart disease, diabetes mellitus or impaired glucose tolerance, chronic renal disease, thyroid disorders, chronic obstructive pulmonary disease, cardiomyopathy, connective tissue disorders, heart failure, left bundle branch block or atrioventricular conduction abnormalities on electrocardiogram (ECG), congenital heart disease, congestive heart failure, pericarditis, pulmonary embolism, sick sinus syndrome, and preexcitation syndromes. All patients were in sinus rhythm, and none of them was taking medications known to affect electrocardiographic intervals. All subjects gave their written informed consent.

Study protocol

Medical history, physical examination, anthropometric evaluation, 12-lead surface ECG, 2D color Doppler echocardiogram and ECG Holter monitoring were performed in the study population. The patients were rested for at least 15 min before cardiovascular assessments, including electrocardiography and echocardiography.

Electrocardiographic measurements

All subjects underwent a routine standard 12-lead body surface ECG, recorded at a paper speed of 50 mm/s and gain of 10 mm/mV in the supine position, and were breathing freely but not allowed to speak during the ECG recording. To avoid diurnal variations, we generally performed the ECG recordings at the same time (9:00 A.M. to 10:00 A.M.). The analysis was performed by 1 investigator, without knowledge of subjects' clinic status. ECGs were transferred to a personal computer by an optical scanner and then magnified 400 times by Adobe Photoshop software (Adobe Systems Inc., San Jose, CA). QRS duration, QT interval and JT interval were evaluated with the use of computer software (Configurable Measurement System) using digitizer 34180 (Calcomp, Anaheim, CA, USA). The variability of the measurements was 0.32±5 ms, which was not statistically significant. The standard correlation was 95% (95% CI 25.63 to 6.31). In each electrocardiogram lead, the analysis included 3 consecutive heart cycles, wherever possible. Leads were excluded from analysis when the end of the T-wave was not clearly distinguishable, or the signal quality was too poor for analysis. The QRS interval was measured from the start of the Q wave, or, in the absence of the Q wave, from the start of R wave to the end of S (to its return to the isoelectric line). The QT interval was measured from the initial deflection of the QRS complex to the end of the T wave (to the point where the T wave returned to the isoelectric line). When U wave was present, the QT was measured to the nadir of the curve between the T and U waves. If the end of the T wave could not be reliably determined, or if the T waves were isoelectric or of very low amplitude, measurements were not done and these leads were excluded from analysis. The JT interval was derived by subtracting the QRS duration from the QT interval [17]. QTd was the difference between the maximal and the minimal QT value in all leads [18]. The difference between the maximal and the minimal JT value in all leads was defined as JTd. All measurements were corrected for heart rate using Bazett's formula ($QTc=QT/\sqrt{RR}$; $JTc=JT/\sqrt{RR}$) [19].

Echocardiographic evaluation

Images were gathered with a standard ultrasound machine with a 3.5-MHz phased-array probe (M3S). All the echocardiographic studies were digitally stored, and all the measurements were performed off-line by 2 independent observers who were blinded to the clinical status of the subjects. Selected

Table 1. Clinical and echocardiographic characteristics of the study population.

	EDMD patients	Control group	*P*
Patients (n)	36	36	
Age (years)	20±12	20±12	
BMI (Kg/m^2)	20±5	19±4	*0.03*
Sex (male/female)	26/10	26/10	
SBP (mmHg)	122.7±12	119±11	*0.6*
DBP (mmHg)	69.7±8	67±12	*0.7*
HR (bpm)	77.8±5.3	74.9±6.5	*0.3*
EF (%)	63.4±8.1	64.6±5.1	*0.1*
FS (%)	32.3±4.2	34.8±4.1	*0.2*
LVEDD (mm)	49.4±5.1	43.4±4.5	*0.3*
LVESD (mm)	34.4±5.7	32.2±4.8	*0.4*
IVSEDT (mm)	7.5±1.2	6.3±0.8	*0.4*
LVPWEDT (mm)	7.2±0.8	5.9±1.2	*0.3*
LVM/H 2.7 (g/m 2.7)	35.7±10	32.5±9	*0.3*
E wave (cm/s)	82.3±16.5	87.4±13.8	*0.2*
A wave (cm/s)	57.9±12.5	52.03±9.72	*0.3*
E/A ratio	1.5±0.4	1.8±0.38	*0.3*

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; EF – ejection fraction; SF – shortening fraction; LVEDD – left ventricular end diastolic diameter; LVESD – left ventricular end systolic diameter; IVSEDT – interventricular septal end diastolic thickness; LVPWEDT – left ventricular posterior wall end diastolic thickness; LVM/H – left ventricular mass/height.

parameters were measured according to the American Society of Echocardiography recommendations [20] in M-mode from parasternal long-axis view: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPT). LV mass (LVM) was calculated by using Devereux's formula, and was indexed for body surface area and height [21]. Ejection fraction was measured using a modified Simpson's biplane method. Each representative value was obtained from the average of 3measurements. Pulsed-wave Doppler examination was performed to obtain the following indexes of LV diastolic function: peak mitral inflow velocities at early (E) and late (A) diastole and E/A ratio. Average values of these indexes obtained from 5 consecutive cardiac cycles were used for analysis.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). The data in each group has a Gaussian distribution. Statistical analysis was performed using Student's t test. P values <0.05 were considered to be statistically significant. Pearson's simple correlation allowed studying the association between 2 variables. Analyses were performed using the statistical package SPSS 11.0 software for Windows SPSS Inc. (Chicago, IL, USA).

Table 2. Electrocardiographic characteristics of the study population.

Parameters	EDMD group	Control group	P
HR (bpm)	77.8±5.3	74.9±6.5	0.3
QRS max (ms)	119.09±6.3	105.9±6.9	0.5
QRS min (ms)	88.1±22.01	68.01±9.8	0.2
QTc max (ms)	462.4±75.3	442.1±26.9	0.04
QTc min (ms)	379.9±75.6	388.9±32.3	0.7
QTc-D (ms)	82.7±44.2	53.1±13.7	0.03
JTc max (ms)	352.36±28.02	339.9±23.7	0.2
JTc min (ms)	241.3±62.2	279.6±17.7	0.7
JTc-D (ms)	73.6±32.3	60.4±11.1	0.001

Results

Clinical and echocardiographic parameters

Clinical and echocardiographic characteristics of the study population are summarized in Table 1. The healthy control group did not significantly differ from EDMD group in BMI, heart rate and blood pressure (BP). No significant differences in LVPWEDT (7.2±0.8 *vs.* 5.9±1.2 mm, *P=0.3*), IVSEDT (7.5±1.2 *vs.* 6.3±0.8 mm, *P=0.4*), LVEDD (49.4±5.1 *vs.* 43.4±4.5 mm, *P=0.3*), LVESD (34.4±5.7 *vs.* 32.2±4.8 mm, *P=0.4*), LVM/H (35.7±10 *vs.* 32.5±9 g/m 2.7, *P=0.3*), left ventricle fractional shortening (FS; 34.8±4.1 *vs.* 32.3±4.2%, *P=0.2*) and ejection fraction (EF 64.6±5.1 *vs.* 63.4±8.1%, *P=0.1*) between the 2 groups were observed. These data indicate compensated normal systolic function in the EDMD group. Compared with controls, the EDMD group did not show significant E wave (82.3±16.5 *vs.* 92.4±10.8 cm/s; *P=0.2*), A wave (57.9±12.5 *vs.* 52.03±9.72 cm/s; *P=0.3*) and E/A ratio (1.5±0.4 *vs.* 1.8±0.38; *P=0.3*) variations. These data indicate normal diastolic function in the EDMD group.

QTc and JTc dispersion

Electrocardiographic characteristics of the study population are shown in Table 2. Compared to the healthy control group, the EDMD group presented increased values of QTc-D (82.7±44.2 *vs.* 53.1±13.7; P=0.003) and JTc-D (73.6±32.3 *vs.* 60.4±11.1 ms; *P=0.001*) (Figure 1). Absolute value of intraobserver variability of QTc and JTc dispersion measurement was 7±4 ms and 4±2 ms, respectively. No statistically significant correlation between QTc-D, JTc-D, BMI (P=0.2), LVM (P=0.3) and ejection fraction (P=0.1) was found. No statistically significant differences in QTc-D (92.5±39.3 *vs.* 70.6±48.7 ms, *P=0.4*) and JTc-D (61.73±16.46 *vs.* 64.72±14,12 ms, *P=0.4*) between the laminopathy EDMD subgroup and the emerinopathy EDMD subgroup were found.

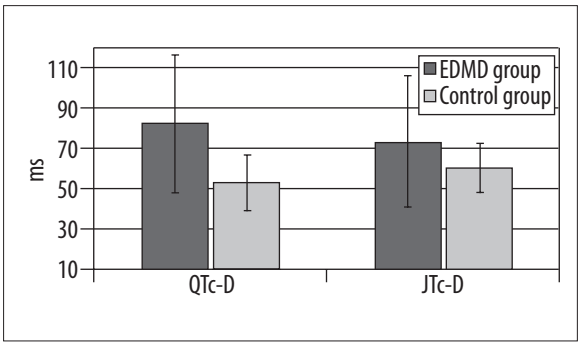

Figure 1. Differences in dispersion of repolarization index values (QTc-d; JTc-d) between Emery-Dreifuss Muscular Dystrophy (EDMD) group and non EDMD healthy control group.

Discussion

In our study we evaluated the QTc dispersion and JTc dispersion, electrocardiographic markers of ventricular repolarization heterogeneity, in Emery-Dreifuss muscular dystrophy patients with preserved systolic and diastolic function. QTd and JTd are expressions of regional differences in cellular action potential duration and in ventricular recovery time. Increase in QTd and JTd increases the risk of development of malignant ventricular arrhythmias, probably via 2 mechanisms. First, it facilitates transmural early afterdepolarization propagation; second, it could cause intramural functional conduction blocks that predispose to re-entrant polymorphic ventricular tachyarrhythmia**s**. An increase in QT dispersion is a possible substrate for ventricular arrhythmias and sudden cardiac death in patients with chronic heart failure [12], left ventricular hypertrophy [22], diabetes mellitus [23], prolonged QT interval [24], obesity [25] and in subjects who are 55 years of age or older [18]. Several studies suggested that JTc-D is clinically useful in assessing arrhythmia risk [10,26] because it is a parameter that is less dependent on ventricular depolarization and reflects the ventricular repolarization heterogeneities better than QTc-D in patients with intra-ventricular conduction abnormalities [27]. Less is known about the heterogeneity of ventricular repolarization in Emery-Dreifuss muscular dystrophy patients with preserved systolic and diastolic function.

Previous studies

Previous experimental studies have shown a slight decrease of heart rates, with significant prolongations of PQ, QRS and QT intervals compared with control recordings in conscious, restrained $LMNA^{-/-}$ mice ECG recordings. These ECG changes resemble some aspects of the ECG records from humans with EDMD (28). To our knowledge, no information is present in literature about QTc and JTc dispersion in EDMD patients with normal systolic and diastolic function. It is known that sudden cardiac death has a high incidence in patients carrying STA and Lamin A/C gene mutations. SCD is attributed to the development of life-threatening arrhythmias, probably related to the specific histopathological pattern characterized by diffuse fibrosis and fatty acid infiltration [29,30].

Main findings

Studying the QTc-D and JTc-D in EDMD patients without systolic or diastolic dysfunction, and without other clinically appreciable diseases, might have offered the unique clinical opportunity to exclude the influence of possible comorbidities on the evaluation of heterogeneity of ventricular repolarization in this population. Our data showed that the electrocardiographic parameters, proposed to estimate the ventricular repolarization heterogeneity (QTc-D, JTc-D), were significantly increased in EDMD patients when compared with age and sex-matched healthy controls. The significant increase in heterogeneity of ventricular repolarization parameters in EDMD patients suggests that cardiac diffuse fibrosis and fatty acid infiltration *per se* influences regional dispersion of repolarization, even when systolic and diastolic cardiac function are preserved.

Limitations

The small number of patients included is certainly a limitation, and a more extensive study is needed to confirm these findings. QT interval and JT interval were made on 12-lead ECGs, with the use of computer software and digitizer by an experienced cardiologist observer. However, there remains an absence of indisputable, generally accepted criteria for the definition of the end of T interval, implying some degree of possible error in the measurements. The 12-lead surface ECG, compared with body surface mapping or vector cardiography, gives an incomplete picture of cardiac electric activity, so QTd could not be a true manifestation of local heterogeneity of repolarization.

Conclusions

Our study showed a significant increase of QTc-D and JTc-D, electrocardiographic parameters considered to reflect the heterogeneity of the ventricular repolarization, in EDMD patients with normal systolic and diastolic function. Our results suggest the hypothesis that diffuse fibrosis and fatty acid infiltration, in the absence of systolic and diastolic dysfunction, may increase ventricular electrical instability and produce the electrophysiological substrate for ventricular malignant tachyarrhythmias and sudden cardiac death. Further studies are necessary to assess the effective relationship between QTc and JTc dispersion and sudden death in EDMD patients.

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