Regional and transmural dispersion of repolarisation in patients with Emery-Dreifuss muscular dystrophy

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Abstract

Background: The development of malignant ventricular arrhythmias is a possible feature in Emery-Dreifuss muscular dystrophy (EDMD) patients with normal left ventricular systolic function. This event may be the cause of sudden cardiac death in EDMD patients. QTc dispersion (QTc-D), JTc dispersion (JTc-D) and Tpeak-end dispersion (TDR) could reflect the physiological variability of regional and transmural ventricular repolarisation and could provide a substrate for life-threatening ventricular arrhythmias.

Aim: The current study was designed to evaluate the heterogeneity of ventricular repolarisation in EDMD patients.

Methods: Echocardiograms and electrocardiograms from 40 EDMD patients (age 20 ± 13) were evaluated and compared to those of 40 healthy age-matched controls.

Results: The EDMD group, compared to the healthy control group, presented increased values of QTc-D (82.8 ± 44.1 vs. 53.3 ± 13.9, p = 0.003), JTc-D (73.6 ± 32.3 vs. 60.4 ± 11.1 ms, p = 0.001) and TDR (100.54 ± 19.06 vs. 92.15 ± 15.5 ms, p = 0.004). No correlation between QTc dispersion and ejection fraction (R = 0.2, p = 0.3) was found.

Conclusions: EDMD is associated with significantly increased regional and transmural heterogeneity of ventricular repolarisation, in the absence of impaired systolic and diastolic cardiac function.

Key words: Emery-Dreifuss muscular dystrophy (EDMD), sudden cardiac death, ventricular repolarisation, QTc dispersion, JTc dispersion, Tpeak-end dispersion, transmural dispersion of repolarisation

INTRODUCTION

Emery-Dreifuss muscular dystrophy (EDMD) — first described by Emery and Dreifuss in 1966 — is a hereditary muscle disorder characterised 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 [1–3]. 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 chromosome 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 [4]. Both patterns of inheritance result in a lack of the corresponding protein — emerin and/or lamin A/C — in nuclei. Cardiomyopathy is the most serious and life-threatening clinical manifestation of the disease; it can appear later compared to...
Dispersion of ventricular repolarisation in EDMD

Rhythm abnormalities commonly noted in EDMD include sinus node dysfunction, atrial flutter, atrial fibrillation, heart block, ventricular tachycardia and ventricular fibrillation. Sudden cardiac death (SCD) is common in patients with EDMD and attributed to the development of life-threatening arrhythmias which usually occur in the presence of normal left ventricular (LV) systolic function. Thus, electrical abnormalities may be the earliest manifestation of the histopathological process leading to the development of cardiomyopathy [7].

Assessment of the individual risk for sudden death in patients with EDMD remains a clinical challenge [5]. A significant increase of maximum P-wave duration and P dispersion in patients with EDMD with preserved systolic and diastolic cardiac function has been recently reported [8]. QTc dispersion (QTc-D), JTc dispersion (JTc-D) and Tpeak-end dispersion (TDR) have been proposed as a noninvasive method to measure the heterogeneity of ventricular repolarisation. Increased dispersion of ventricular repolarisation is considered to provide an electrophysiological substrate for life-threatening ventricular arrhythmias [9] in several clinical conditions [10–14].

The aim of our study was to investigate the ventricular repolarisation in EDMD patients by examining electrocardiographic parameters QTc-D, JTc-D and TDR, and the expression of regional and transmural heterogeneity of ventricular repolarisation.

**METHODS**

Electrocardiograms (ECGs) and echocardiograms from 40 EDMD male subjects (age 20 ± 13 years), followed in four different myological and/or cardiomyological centres, two of them Italian (Cardiomiologia e Genetica Medica, Second University of Naples and Department of Cardiological and Neurological Sciences, University of Cagliari) and two Polish (Mossawkowski Medical Research Centre, Polish Academy of Sciences and Cardiological Institute of Warsaw University), and from 40 age-matched healthy subjects recruited as controls, were evaluated by three independent observers, unaware of the clinical status of the subjects. Selected parameters were measured according to the American Society of Echocardiography recommendations in M-mode from the parasternal long-axis view: LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), interventricular septum end-diastolic thickness (IVSEDT), and LV posterior wall end-diastolic thickness (LVPWEDT). LV mass (LVM) was calculated using Devereux’s formula, and was indexed for body surface area and height. Ejection fraction was measured using the modified Simpson’s biplane method. Each representative value was obtained from the average of three measurements. Pulsed-wave Doppler examination was performed to obtain the following indices of LV diastolic function: peak mitral inflow velocities at early (E) and late (A) diastole and E/A ratio. Average values of these indices obtained from five consecutive cardiac cycles were used for analysis.

**Electrocardiographic measurements**

At least 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, was available for each patient and healthy controls. The analysis was performed by one single investigator, unaware of the subject’s clinical 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, USA). QRS duration, QT interval, JT interval and Tpeak-end interval were evaluated using computer software (Configurable Measurement System) using digitizer 34180 (Calcomp, Anaheim, CA, USA). The inter-measurement variability was not statistically significant (0.32 ± 5 ms). The standard correlation was 95% (95% CI 25.63–6.31). In each ECG lead, the analysis included three consecutive heart cycles, whenever possible. The QRS interval was measured from the start of the Q wave or, in the absence of the Q wave, from the start of the R wave to the end of S wave, (return to isoelectric line). The QT interval was measured from the initial deflection of the QRS complex to the end of the T wave (return to isoelectric line). When the 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 T waves were flat or of very low amplitude, measurements were not done and leads excluded from the analysis. The JT interval was derived by subtracting the QRS duration from the QT interval. QTd was defined as the difference between the maximal and the minimal QT value in all leads. The difference between the maximal and the minimal JT value in all leads was defined
as JTd. The Tpeak-end interval was defined as the interval from the maximum T-wave amplitude to the end of the T-wave. TDR was defined as the difference between the maximal and minimal Tpeak-end interval in all leads. All measurements were adjusted for heart rate by the Bazett’s formula (QTc = QT/√RR; JTc = JT/√RR).

**Statistical analysis**
Continuous variables are expressed as mean ± standard deviations. The data in each group have a Gaussian distribution. Statistical analysis was performed using Student’s t-test for unpaired data; p values < 0.05 were considered as statistically significant. Pearson’s simple correlation allowed study association between two variables. Analyses were performed using the statistical package SPSS 11.0 software for Windows (SPSS Inc., Chicago, IL, USA).

**RESULTS**
Clinical and echocardiographic characteristics of the study population are summarised in Table 1. The EDMD group did not significantly differ from the healthy control group in body mass index (BMI), heart rate or blood pressure. No significant differences in LVPWEDT, IVSEDT, LVEDD, LVESD, LVM/he- ght, LV fractional shortening or ejection fraction were observed between the two groups, indicating a normal systolic function also in the EDMD group. Furthermore, compared to controls, the EDMD group did not show significant variations in E wave, A wave or E/A ratio (Table 1), indicating a normal diastolic function.

**Electrocardiographic measurements (QTc-D, JTc-D, TDR)**
Electrocardiographic characteristics of the study population are shown in Table 2. Because no statistically significant differences in QTc-D, JTc-D and TDR were found between emerino-pathy EDMD patients and laminopathy EDMD patients, they were considered as a single group. Compared to the healthy controls, the EDMD group presented increased values of QTc-D, JTc-D and TDR (Fig. 1). The intra-observer variability of QTc-D, JTc-D and TDR measurements was 7 ± 4 ms, 4 ± 2 ms, and 3 ± 1 ms, respectively. No statistically significant correlation was found between QTc-D, JTc-D, TDR, BMI (p = 0.2), LVM (p = 0.3) or ejection fraction (p = 0.1).

**DISCUSSION**
We evaluated QTc dispersion, JTc dispersion and TDR considered as electrocardiographic markers of regional and trans-mural ventricular repolarisation heterogeneity in EDMD patients. Echocardiographic data showed a preserved systolic and diastolic function in all patients. QTd and JTd are expressions of regional differences in cellular action potential duration and in ventricular recovery time. TDR is an expression of a preferential prolongation of the M cell action potential, which can be estimated as the interval between the peak and the end of the T wave [15]. The increase in QTd,
JTd and TDR increases the risk of the development of malignant ventricular arrhythmias, probably via two mechanisms: firstly by facilitating the transmural propagation early after depolarisation; secondly causing intramural functional conduction blocks that predispose to re-entrant polymorphic ventricular tachyarrhythmias. An increase in QT dispersion is a possible substrate for ventricular arrhythmias and SCD in patients with chronic heart failure [11], LV hypertrophy [16], diabetes mellitus [17], prolonged QT interval [18], obesity [19], aortic coarctation [20], dilated cardiomyopathy [21] and in subjects older than 55 years of age. Several studies have suggested that JTc-D is clinically useful in assessing the risk of arrhythmia [9, 22] because it is less dependent on ventricular depolarisation and reflects the ventricular repolarisation heterogeneity better than QTc-D, in patients with intra-ventricular conduction abnormalities [23]. It is well known that a high incidence of SCD occurs in patients carrying STA and lamin A/C gene mutations, due to the development of life-threatening arrhythmias, probably related to the specific histopathological pattern characterised by diffuse fibrosis and fatty acid infiltration [24, 25].

**Previous studies**

Previous experimental studies have shown in ECGs recorded in conscious, restrained knockout LMNA−/− mice, a slight decrease of heart rate with significant prolongations of PQ, QRS and QT intervals compared to controls. These ECG changes resemble some aspects of the ECG recorded in patients with EDMD. To the best of our knowledge, no information is present in the literature about TDR, QTc and JTc dispersion values in EDMD patients.

**Main findings**

Our data showed that the electrocardiographic parameters, both regional (QTc-D, JTc-D) and transmural (TDR), proposed to estimate the ventricular repolarisation heterogeneity, were significantly increased in EDMD patients when compared to age and sex-matched healthy controls. These findings suggest that cardiac diffuse fibrosis and fatty acid infiltration can _per se_ influence regional and transmural dispersion of repolarisation, even when systolic and diastolic cardiac functions are preserved.

**Limitations of the study**

QT interval and JT interval were measured on 12-lead ECGs, through a computer software and digitiser by an experienced cardiologist. However, in the absence of indisputable, generally accepted criteria for the definition of the end of T wave, some degree of error in measurements can remain. Furthermore, 12-lead surface ECG, compared to body surface mapping or vectorcardiography, gives an incomplete picture of cardiac electric activity, so that QTd could not be a true manifestation of the local repolarisation heterogeneity.

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**Table 2. Electrocardiographic characteristics of the study population**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>EDMD group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate [bpm]</td>
<td>78.5 ± 5.1</td>
<td>73.9 ± 6.9</td>
<td>0.3</td>
</tr>
<tr>
<td>QRS max [ms]</td>
<td>121.06 ± 6.4</td>
<td>107.9 ± 6.5</td>
<td>0.5</td>
</tr>
<tr>
<td>QRS min [ms]</td>
<td>88.6 ± 22.3</td>
<td>67.05 ± 9.4</td>
<td>0.2</td>
</tr>
<tr>
<td>QTc max [ms]</td>
<td>466.4 ± 75.7</td>
<td>448.1 ± 27.1</td>
<td>0.04</td>
</tr>
<tr>
<td>QTc min [ms]</td>
<td>380.9 ± 75.8</td>
<td>386.5 ± 32.3</td>
<td>0.7</td>
</tr>
<tr>
<td>QTc-D [ms]</td>
<td>82.8 ± 44.1</td>
<td>53.3 ± 13.9</td>
<td>0.03</td>
</tr>
<tr>
<td>JTc max [ms]</td>
<td>355.3 ± 28.07</td>
<td>339.5 ± 23.4</td>
<td>0.2</td>
</tr>
<tr>
<td>JTc min [ms]</td>
<td>241.5 ± 62.6</td>
<td>279.3 ± 17.5</td>
<td>0.7</td>
</tr>
<tr>
<td>JTc-D [ms]</td>
<td>73.6 ± 32.3</td>
<td>60.4 ± 11.1</td>
<td>0.001</td>
</tr>
<tr>
<td>TDR [ms]</td>
<td>100.54 ± 19.06</td>
<td>92.15 ± 15.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Figure 1. Differences (mean values) in dispersion of repolarisation (QTc-D, JTc-D, TDR) between Emery-Dreifuss muscular dystrophy (EDMD) group and healthy control group**
CONCLUSIONS
Our study showed a significant increase in QTc-D, JTc-D and Tpeak-end dispersion values, all parameters considered to reflect the regional and transmural heterogeneity of the ventricular repolarisation in EDMD patients preserved systolic and diastolic function.

These results suggest that diffuse fibrosis and fatty acid infiltration may per se increase ventricular electrical instability and produce the electrophysiological substrate for ventricular malignant tachyarrhythmias and SCD. However, further studies are necessary to assess the relationship between these parameters and SCD in EDMD patients.

Conflict of interest: none declared

References
Regionalna i prześcienna dyspersja repolaryzacji komór u chorych z dystrofią mięśniową Emery’ego-Dreifussa

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Streszczenie

Wstęp: Jednym z możliwych powikłań dystrofii mięśniowej Emery’ego-Dreifussa (EDMD) u chorych z prawidłową czynnością skurczową lewej komory jest wystąpienie złośliwej arytmii komorowej. To zdarzenie może być przyczyną naglej śmierci sercowej u chorych z EDMD. Dyspersja odstępu QTc (QTc-D), odstępu JTc (JTc-D) i końca załamka T (TDR), mogąca odzwierciedlać fizjologiczną zmienność regionalnej i prześciennnej repolaryzacji komór, jest potencjalnym podłożem rozwoju zagrażających życiu komorowych zaburzeń rytmu.

Cel: Celem niniejszej pracy była ocena zróżnicowania w zakresie repolaryzacji komór u chorych na EDMD.

Metody: Oceniono i porównano echokardiogramy i elektrokardiogramy 40 chorych na EDMD (w wieku 20 ± 13 lat) i 40 odpowiednio dobranych zdrowych osób stanowiących grupę kontrolną.

Wyniki: W grupie chorych na EDMD QTc-D (82,8 ± 44,1 vs. 53,3 ± 13,9; p = 0,003), JTc-D (73,6 ± 32,3 vs. 60,4 ± 11,1 ms; p = 0,001) i TDR (100,54 ± 19,06 vs. 92,15 ± 15,5 ms; p = 0,004) były większe niż w grupie kontrolnej. Nie stwierdzono korelacji między dyspersją odstępu QTc i frakcją wyrzutową (R = 0,2; p = 0,3).

Wnioski: Dystrofia mięśniowa Emery’ego-Dreifussa wiąże się z istotnym zwiększeniem zróżnicowania w zakresie regionalnej i prześciennjej repolaryzacji komór u chorych z prawidłową skurczową i rozkurczową czynnością serca.

Słowa kluczowe: dystrofia mięśniowa Emery’ego-Dreifussa, nagły zgon sercowy, repolaryzacja komór, dyspersja odstępu QTc, dyspersja odstępu JTc, dyspersja końca załamka T, prześcienna dyspersja repolaryzacji

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