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Paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients: P wave duration and dispersion analysis

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Abstract. – OBJECTIVE: Myotonic dystrophy type 1 (MD1) is characterized by cardiac involvement, in about 80% of case, that predominantly affects the conduction system. Aim of our study was to evaluate the P-wave duration and dispersion (PD) in MD1 patients underwent pacemaker implantation with conserved systolic and diastolic function.

PATIENTS AND METHODS: We enrolled 60 MD1 patients (age 51.3 ± 5 years; 11 females) underwent dual chamber pacemaker implantation for various grade of atrioventricular (AV) block. Sixty sex-and age matched non-MD1 subjects were recruited as controls. P-wave duration and dispersion were carefully measured using 12-lead electrocardiogram.

RESULTS: Compared with healthy control group, MD1 patients presented increased maximum P wave duration (106.4 ± 20.9 vs 65.9 ± 8.2 ms, $p = 0.03$) and PD values (40.1 ± 11 vs 27.1 ± 4.2 ms, $p = 0.003$). No statistically significant difference was found in minimum P wave duration (69.7 ± 11.8 vs 65.4 ± 8.1 ms, $p = 0.4$). The MD1 patients with paroxysmal atrial fibrillation, compared with MD1 patients without evidence of atrial fibrillation, presented increased maximum P wave duration (108.1 ± 10.4 vs 78.1 ± 7.9 ms, $p = 0.001$) and PD values (41.1 ± 8.5 vs 33.2 ± 4.2 ms, $p = 0.003$). Minimum P wave duration (68.4 ± 8.2 vs 67.1 ± 4.9 ms, $p = 0.5$) didn't differ between the two groups.

CONCLUSIONS: Our data showed a significantly increased P wave duration and dispersion in MD1 patients compared with age and sex-matched healthy controls. We showed a statistically significant increase in PD and P max in MD1 patients subgroup with AF compared to MD1 patients with no arrhythmias.

Key Words:
Atrial fibrillation, Myotonic dystrophy, P wave dispersion, P wave duration, Electrocardiogram, Arrhythmias.

Introduction

Myotonic dystrophy type 1 (MD1), or Steinert disease, is a serious autosomal-dominant hereditary disease with an estimated incidence of 1 in 8000 births[1-2]. It is an autosomal dominant disorder caused by an abnormal expansion of an unstable trinucleotide repeat in the three-prime untranslated region of DMPK gene on chromosome 19[3]. The cardiac involvement is noticed in about 80% of cases, and it often precedes the skeletal muscle one. Predominantly affects the conduction system, while myocardial contractile function is less commonly impaired in MD1 patients. Heart failure (HF) often occurs late in the course of the disease as consequence of cardiac myopathy due to progressive scar replacement[4]. Heart block is the first and most clinically significant cardiac disease in this group of patients and it is related to fibrosis of the conduction system and fatty infiltration of the His bundle[5]. To prevent cardiac sudden death, implantation of a pacemaker (PMK) is required in 3-22% of cases[6]. According to literature, paroxysmal atrial arrhythmias such as atrial fibrillation (AF), atrial flutter, atrial tachycardia, frequently occur in 25% of MD1 patients[4,7,8]. P-wave dispersion (PD) is defined as the difference between the maximum (P max) and the minimum (P min) P wave duration on standard 12-lead electrocardiogram (ECG). PD is considered to reflect the discontinuous and inhomogeneous propagation of sinus impulses and the prolongation of atrial conduction time[9]. Previous studies[10-11] showed the role of PD as independent risk factor for AF development. To our knowledge, there are no data in literature about P wave dispersion in MD1 patients. The aim of our

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study was to evaluate P-wave duration and dispersion in MD1 patients with conserved systolic and diastolic function underwent pacemaker implantation.

Patients and Methods

Study Population

From a large cohort of 150 MD1 patients, referred to Cardiomyology and Medical Genetics, Department of Experimental Medicine of Second University of Naples, we enrolled 60 MD1 patients (age 51.3 ± 5 years; 11 females) underwent dual chamber pacemaker implantation for various grade of atrioventricular (AV) block. Sixty sex-and age matched non-MD1 healthy subjects were also recruited as controls. MD1 patients with hypertension, diabetes mellitus or impaired glucose tolerance (IGT), obesity, electrolyte imbalance, valvular heart disease, heart failure, coronary artery disease, systolic and diastolic dysfunction, connective tissue disorders, left bundle branch block, hepatic, renal, thyroid diseases or sleep disorders, patent foramen ovale, atrial septal aneurysm, left atrial enlargement, persistent atrial fibrillation were excluded. 15 MD1 patients had history of paroxysmal AF detected by 12-lead surface ECG, 24-h ECG Holter monitoring or pacemaker stored electrogram (EGM). All patients were in sinus rhythm, and none of them was taking medications known to affect electrocardiographic intervals. The population study underwent medical history, physical examination, anthropometric evaluation, 12-lead surface ECG, Device interrogation and 2D color Doppler echocardiogram.

Electrocardiographic Measurements

All subjects underwent a routine standard 12-lead 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 took the ECG recordings at the same time (9:00-10:00 A.M.). The analysis was performed by one investigator only without knowledge of 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). P-wave duration measurement was manually performed with the use of computer software (Configurable Measurement System). Intra-observer coefficients of variation for P-wave variables were found to be less than 5% and not significant. In each electrocardiogram lead, the analysis included three consecutive heart cycles wherever possible. ECG with measurable P-wave in less than ten leads were excluded from analysis. The onset of P-wave was defined as the junction between the isoelectric line and the start of P-wave deflection; the offset of the P-wave was defined as the junction between the end of the P-wave deflection and the isoelectric line[9-12]. If starting and endpoints were not clear, the derivations including these points were taken as excluding criteria from the study. Maximum and minimum P-wave durations were measured. Maximum P-wave duration was defined as the longest P-wave duration, and minimum P-wave duration was defined as the shortest P-wave duration. PD was defined as the difference between the maximum and minimum P-wave durations.

Echocardiographic Measurements

All echocardiographic examinations were performed using a standard ultrasound machine with a 3.5-MHz phased-array probe (M3S). All patients were examined in the left lateral and supine positions by precordial M-mode, 2-dimensional and Doppler echocardiography. One lead ECG was recorded continuously. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVST) and left ventricular posterior wall thickness (LVPWT) were measured from M-mode in the parasternal long-axis views according to the standards of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated by using Devereux's formula, and was indexed for body surface area and height. Left atrium diameter (LAD) was measured during systole along the parasternal long-axis view from the 2-dimensional guided M-mode tracing; LA length was measured from the apical 4-chamber view during systole. The maximum LA volume (LAV) was calculated from apical 4- and 2-chamber zoomed views of the LA using the biplane method of disks. Ejection fraction was measured using a modified Simpson biplane method. Each representative value was obtained from the average of 3 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

Table I. Electrocardiographic characteristics of the study population. HR: heart rate.

Parameters	MD1 group	Control group	*p* value
HR (beats/min)	76.8 ± 5.4	75.7 ± 6.3	0.3
Max P wave duration (ms)	106.4 ± 20.9	65.9 ± 8.2	0.03
Min P wave duration (ms)	69.7 ± 11.8	65.4 ± 8.1	0.4
P wave dispersion (ms)	40.1 ± 11	27.1 ± 4.2	0.003

E/A ratio. Average values of these indices obtained from 5 consecutive cardiac cycles were used for analysis.

Device Interrogation

All MD1 patients underwent device interrogation and follow-up according to a standard protocol to evaluate sensing/pacing parameters, leads impedance and battery voltage. The devices were programmed to detect episodes of atrial tachycardia, and to record summary and detailed data, including atrial and ventricular electrogram (EGM). In all MD1 patients atrial preference pacing (APP) algorithm was disabled and minimal ventricular pacing algorithm was activated.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. Statistical analysis were performed using Student's t-test for unpaired data. *p*-values < 0.05 were considered to be statistically significant. Analysis were performed using the statistical package SPSS 11.0 software for Windows SPSS Inc. (Chicago, IL, USA).

Results

Clinical and Echocardiographic Parameters

Clinical and echocardiographic characteristics of the population study didn't significantly differ between MD1 patients (51 ± 4 years; BMI: 22 ± 4) and control group (50 ± 5 years; BMI: 23± 3). The left ventricular posterior wall end diastolic thickness (LVPWEDT: 9.8 ± 1.7 *vs* 9.7 ± 1,3 mm; $p = 0.9$), inter- ventricular septum end diastolic diameter thickness (IVSEDT: 9.5 ± 1.2 vs 9.8 ± 1.28 mm; $p = 0.7$), left ventricular end diastolic diameter (LVEDD: 41.7 ± 8 *vs* 45.22 ± 4 mm; $p = 0.09$) and ejection fraction (EF: 63.39 ± 8.1% *vs* 64.56 ± 5.1%; $p = 0.1$) did not significantly differ between the two groups observed. Compared with controls, MD1 group did not show significantly E wave (81.3 ± 15.5 *vs* 91.4 ± 9.8 cm/s; $p = 0.2$), A wave (56.9 ± 10.5 *vs* 51.03 ± 7.72 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 conserved systolic and diastolic function in the MD1 group.

P-wave Duration and Dispersion

Electrocardiographic characteristics of the population study are shown in Table I. Compared to healthy control group, MD1 patients presented increased maximum P wave duration (106.4 ± 20.9 *vs* 65.9 ± 8.2 ms, $p = 0.03$) and P-wave dispersion values (40.1 ± 11 *vs* 27.1 ± 4.2 ms, $p = 0.003$). No statistically significant difference was found in heart rate (76.8 ± 5.4 bpm *vs* 75.7 ± 6.3 bpm, $p = 0.3$) and minimum P wave duration (69.7 ± 11.8 *vs* 65.4 ± 8.1 ms, $p = 0.4$). MD1 patients with paroxysmal atrial fibrillation, compared with MD1 patients without evidence of atrial fibrillation, presented increased maximum P wave duration (108.1 ± 10.4 *vs* 78.1 ± 7.9 ms, $p = 0.001$) and P-wave dispersion values (41.1 ± 8.5 *vs* 33.2 ± 4.2 ms, $p = 0.003$). Minimun P wave duration (68.4 ± 8.2 *vs* 67.1 ± 4.9 ms, $p = 0.5$) didn't differ between the two subgroups (Table II).

Table II. Electrocardiographic characteristics in the two subgroups of Steinert patients separated according to the device and the ECG Holter monitoring results.

Parameters	MD1 FA (+)	MD1 FA (-)	*p* value
Patients (n)	15	45	
Max P wave duration (ms)	108.1 ± 10.4	78.1 ± 7.9	0.001
Min P wave duration (ms)	68.4 ± 8.2	67.1 ± 4.9	0.5
P wave dispersion (ms)	41.1 ± 8.5	33.2 ± 4.2	0.003

Discussion

MD1 and Supraventricular Arrhythmias

The most frequent clinical event in MD1 patients is the development of a supraventricular arrhythmia, that is a common finding on 12 lead ECG or during 24 hour Holter monitoring and may be asymptomatic[13]. Most common supraventricular arrhythmias are atrial fibrillation, atrial flutter and atrial tachycardia, observed in up to 25% of patients both as unsustained and sustained forms[13]. Our previous studies showed that: AF episodes increase in MD1 patients with a high percentage of right ventricular pacing and a lower percentage of atrial stimulation[14]; right atrial septal stimulation in the Bachmann's bundle region is a safe and feasible procedure[15-17], with less atrial pacing and sensing defects than the right atrial appendage stimulation, but it does not seem to provide significant benefit for prevention of paroxysmal atrial fibrillation[18,19]. The atrial overdrive stimulation with APP algorithm prevents paroxysmal AF in MD1 patients who underwent dual-chamber PMK implantation for AV conduction disorder and reduces the AF burden over long term follow-up[20-22].

Electrocardiographic Findings in MD1

Previous studies documented several electrocardiographic abnormalities in MD1 patients[4,23-26]. The most common electrocardiographic findings were long PR interval with a prevalence of 20-40% and wide QRS complex with a prevalence of 5-25% in different studies depending on patients selection criteria[4,23]. Groh et al[24] in 406 MD1 patients showed severe ECG abnormalities characterized by no sinus rhythm, PR interval prolongation (> 200 ms), QRS prolongation (> 120 ms), second or third degree AV block. A diagnosis of atrial arrhythmias was commonly, especially in patients with severe ECG abnormalities. According to their results severe ECG abnormality and clinical diagnosis of atrial tachyarrhythmia are independent risk factor for sudden cardiac death (SCD) with a sensitivity of 81.5% for the prediction of sudden death, a specificity of 59.4%, a positive predictive value of 12.5%, and a negative predictive value of 97.8%. They also showed that SCD was more common in patients with advanced age and a higher muscle impairment score, indicating more severe disease. Melancini et al[25] hypothesized the relationship between risk of arrhythmias and genetic variables concluding that ECG abnormalities were directly proportional to the expanded triplet repeat seize; data not confirmed by Jaspert et al[26] in a small clinical study on 14 MD1 patients.

Non invasive Electrocardiographic Predictors of Arrhythmic Risk in MD1

P wave dispersion is a non invasive indicator of intra-atrial conduction heterogeneity producing substrate for reentry, which is a pathophysiological mechanism of atrial fibrillation[10-11]. PD has been studied in some clinical conditions such as obesity[27], dilated cardiomyopathy[28], myocardial infarction[29], Beta-thalassemia major[30-31] and Emery-Dreifuss muscular dystrophy[32]. Morner et al[33] showed that an absolute PR + QRS duration of more than 320 ms predicted mortality of MD1 patients with a specificity of 84%. To our knowledge, there are no data in literature about the P wave duration and dispersion in MD1 patients with conserved systolic and diastolic function. QTc dispersion (QTcD) and JTc dispersion (JTcD) have been proposed as noninvasive methods to measure the heterogeneity of ventricular repolarization[34-35]. Increased dispersion of ventricular repolarization is considered to provide an electrophysiological substrate for life-threatening ventricular arrhythmias in several clinical conditions such as dilated cardiomyopathy[36-33], obesity[38-39], congenital disease[40-42] and cardiomyopathies[43-47]. Park et al[48] suggested that the higher incidence of sudden cardiac death in MD1 population was associated with the observed prolonged QTc interval in those patients. Magrì et al[49] showed a significant difference in the QT variability index (QTVI) between MD1 patients and healthy controls. According to their results, the QTVI and age were independently associated with PR interval and CTG repeat. Heart Rate Variability (HRV) is a reliable index to asses sympathovagal balance and can be used to stratify arrhythmic risk in several clinical conditions[50-53] and cardiomyopathies[54-56]. However previous studies on autonomic modulation of heart rate in MD1 patients have obtained conflicting results[57-61].

Main Findings

To our knowledge, the current study is the first report that investigated the P wave duration and dispersion in myotonic dystrophy patients with conserved systolic and diastolic function underwent dual chamber pacemaker implantation for various grade of AV block. Our data confirmed that the electrocardiographic parameters proposed to estimate the discontinuous and

inhomogeneous propagation of sinus impulses and the prolongation of atrial conduction time (P max and PD) were significantly increased in MD1 patients when compared with age and sex-matched healthy controls. We showed a statistically significant increased PD and P max in MD1 patients subgroup with AF compared to MD1 patients with no arrhythmias. We suggested the hypothesis that atrial fibrosis degeneration and fatty infiltration pattern may be responsible of intra-atrial conduction heterogeneity producing substrate for reentry which predispose to the onset and the perpetuation of atrial fibrillation in MD1 patients.

We would like to underline that PD reflects only the intra-atrial conduction heterogeneity but not provides the other atrial electrophysiological properties better reflected by atrial electromechanical delay (AEMD)[62-63]. The relatively small number of patients included is certainly a limitation, and a more extensive study is needed to confirm these data. PD measurement errors done with manual evaluation may be a potential bias for observed results although, according to Dilaveris et al[10], scanning and digitizing ECG signals from paper records using an optical scanner is a feasible and accurate method for measuring P-wave duration.

Conclusions

Our study showed a significant increase of electrocardiographic parameters considered to reflect the discontinuous and inhomogeneous propagation of sinus impulses and the prolongation of atrial conduction time in MD1 patients with conserved systolic and diastolic function underwent dual chamber pacemaker implantation for various grade of AV block. We hypothesize that P max duration and P wave dispersion may be simple electrocardiographic parameters for identify high risk atrial fibrillation MD1 patients. For these patients, we suggest to perform a careful cardiac monitoring with seriate ECG Holter recordings or periodical evaluation of device stored electrograms to early detect atrial fibrillation onset and to evaluate the opportunity of prophylactic anticoagulation treatment or non pharmacologic approaches for stroke prevention[64-66].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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