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P wave duration and dispersion and QT interval in multiple sclerosis

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Abstract
Introduction: Multiple sclerosis (MS) is one of the most frequent disorders of central nervous system, resulting in autonomic disturbances. Some electrocardiographic changes have been reported in these patients that can lead to arrhythmia. In this study we compared P wave duration and dispersion and QT interval of MS patients to healthy control subjects.
Material and methods: Eighty four multiple sclerosis patients and 84 healthy, age and sex-matched volunteers were included. A 12-lead electrocardiogram was undertaken in order to measure minimal and maximal P wave duration, P wave dispersion (PWD) and QT interval.
Results: In patient group, mean P wave duration, maximum P wave duration and PWD were significantly longer than control group. QT interval was longer in patient group but the difference was not significant.
Conclusion: In this study, P wave duration and P wave dispersion was found to be higher in MS patients than healthy control subjects.

1. Introduction

Multiple sclerosis is a chronic demyelinating inflammatory disorder, presumed to be of autoimmune etiology. Abnormalities of autonomic nervous system (ANS) function in multiple sclerosis (MS) have been reported in various studies (Flachenecker et al., 1999; Frontoni et al., 1996; Gunal et al., 2002; Merkelbach et al., 2001; Pentland and Ewing, 1987; Sterman et al., 1985).

The most common manifestations of the ANS in patients with MS include bladder dysfunction, sleep disturbances, sweating, gastrointestinal and cardiovascular disturbances. Another common symptom seen in patients of MS is fatigue. Orthostatic dizziness has been reported to occur in up to

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50% of MS patients (Anema et al., 1991; Vita et al., 1993). Autonomic dysfunction has an important impact on the disability that patients with MS experience and can substantially restrict the activities of daily living in these individuals.

Cardiovascular function will affect 10–50% of people with MS. On cardiovascular reflex testing it has been shown that both sympathetic as well as parasympathetic dysfunction can occur in patients with MS (Acevedo et al., 2000; Pomeranz et al., 1985).

We hypothesized that the patients with MS may be under the risk for ventricular and atrial arrhythmias. Therefore, this study was planned to investigate the P wave duration, P wave dispersion and QT interval in MS patients.

2. Material and methods

Eighty four patients with relapsing remitting MS who were admitted to outpatient neurology clinic of Imam Reza Hospital; affiliated to Kermanshah University of Medical Sciences, Iran, were included in this study. All of the patients with MS were diagnosed according to the 2005 McDonald's criteria (Reingold et al., 2005). All patients were in remission and have been without any significant new symptoms and/or signs for at least 2 months and were not received corticosteroid treatment in 2 months ago. The informed consent obtained from all the patients.84 genders and age matched healthy subjects as control group were included in this study. Physical examination, medical history of subjects was evaluated in two groups to exclude systemic diseases. Persons with thyroid dysfunction, anemia, electrolyte imbalance, hypertension, diabetes mellitus, heart failure, rheumatic valve disease, primary cardiomyopathy, chronic lung disease, coronary artery disease and left bundle branch block, atrioventricular conduction abnormalities on electrocardiogram (ECG) were excluded from the study. All of the subjects have sinus rhythm and none of them were taking medications like antiarrhythmics, tricyclic antidepressants, antihistaminics and antipsychotics. The 12-lead ECG was recorded at a paper speed of 50 mm/s and gain of 10 mm/2 mV in the supine position and were breathing freely but not allowed to speak during the electrocardiographic recording. Measurement of P duration and QT interval was carried out manually using a caliper. The starting point of P wave was referred as the positive deflection crossing the isoelectric line and the end-point was referred as the end of the deflection crossing the isoelectric line. P wave duration was measured from the onset to the offset of the P wave (Figure 1). The patients were excluded if these points were not clear. Maximum P wave duration is defined as the longest P wave duration and minimum P wave duration is defined as the shortest P wave duration. P wave dispersion defined as difference between maximum P wave duration and minimum P wave duration was also calculated. QT interval was measured from the onset of the QRS complex to the offset of the T wave. Maximum QT interval was selected and was adjusted according to heart rate ($QTC = QT + 1.75(HR - 60)$) (Hodges et al., 1983).

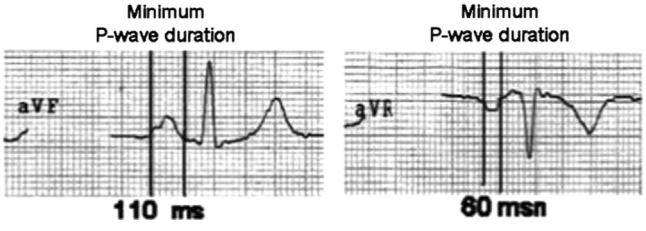

Figure 1 The P-wave durations (Pmax and Pmin) were calculated.

All the measurements were repeated three times and average values were accepted for each of electrocardiographic parameters. All of the measurements were performed by one experienced investigators unaware of the subject's clinical status. Intra and inter-observer coefficients of variation (standard deviation [SD] of differences between 2 observations divided by the mean value and expressed in %) were found as 4.1% and 4.2% for P wave dispersion. Intra and inter-observer coefficients of variation were found to be less than 5%.

The SPSS statistical software package (version 16.0) was used to perform all statistical calculations. Continuous variables were expressed as mean values ± SD, and categorical variables as percentages. Pearson correlations were used to compare associations between indexes. Categorical variables were compared by Pearson chi-square test. Comparisons of continuous variables between two groups have been performed by means of unpaired Student's *t* test. For all tests, a value of $p < 0.05$ was considered statistically significant.

3. Results

The demographic and clinical characteristics of the MS patients and the control subjects are shown in Table 1. There was no significant difference between the two groups with regard to gender, age, heart rate or blood pressure. In MS patients, the mean disease duration was 6 ± 5.8 years (range 0.25–23). All patients were treated with disease-modifying treatments (interferon beta).

Maximum P wave duration and P wave dispersion were significantly higher in MS patients than control groups.

Table 1 The demographic and clinical characteristics of the MS patients and control subjects.

	MS patients ($n=84$)	Control group ($n=84$)	*p* Value
Female	73	71	0.564
male	11	13	0.525
Age (years)	35 ± 10	35.3 ± 10	0.231
Heart rate (beat/min)	77 ± 7	74 ± 5	0.121
Systolic BP (mmHg)	124 ± 13	123 ± 13	0.345
Diastolic BP (mmHg)	78 ± 9	77 ± 8	0.234
Disease duration (years)	6 ± 5.8		

Data are means ± SD, BP indicates blood pressure.

Table 2 Electrocardiographic measurements of the MS patients and controls.

	MS patients ($n=84$)	Control group ($n=84$)	p Value
Minimum P wave duration (ms)	60.48±15.29	62.41±11.85	0.506
Maximum P wave duration (ms)	125.78±15.78	111.57±15.34	0.000
P wave dispersion (ms)	65.30±18.76	49.16±16.62	0.000
QT interval (ms)	422.92±26.14	416.55±19.36	0.077

Data are means±SD.

However, minimum P wave duration and QT interval were not significantly different between the groups (Table 2).

4. Discussion

Multiple sclerosis is a progressive and disabling neurological condition associated with documented dysfunction of the autonomic nervous system. Frequent studies have shown abnormalities of cardiovascular reflexes in MS patients (Pentland and Ewing, 1987; Anema et al., 1991; Nordenbo et al., 1989).

P wave dispersion is a new electrocardiographic marker that has been associated with the heterogeneous and discontinuous propagation of sinus impulses. Furthermore, the correlation between the presence of intra atrial conduction abnormalities and the induction of paroxysmal AF has been well documented (Dilaveris et al., 2000, 1998; Dilaveris and Gialafos, 2001; Leier et al., 1978; Cheema et al., 1990). Prolonged P wave duration and increased PWD have been reported to carry an increased risk for atrial fibrillation (Dilaveris et al., 2000, 1998; Dilaveris and Gialafos, 2001; Aytemir et al., 2000). Therefore, it has been suggested that PWD can be used to diagnose patients with a high risk of AF (Dilaveris et al., 2000, 1998; Dilaveris and Gialafos, 2001). This study shows that maximum P wave duration and PWD are higher in MS patients than control subjects. The significance of an increased P wave duration and PDW in our patients is unknown. Kocer et al. (2005) investigated P wave duration and dispersion in 31 MS patients and compared with 33 healthy subjects, their study showed that P wave duration and dispersion were prolonged significantly in MS patients compared to control subjects. We cannot find other studies which investigated P wave changes in MS patients. Tukek et al. (2000) suggested that increased sympathetic activity may cause significant increase in PWD. P wave dispersion may be associated with increased sympathetic nervous system activity in patients with MS. On the surface electrocardiogram, QT interval reflects time for repolarization. Several studies have shown a relationship between prolonged QTc (QT interval corrected for heart rate) and life threatening arrhythmias (Bonnet et al., 2006). Drouin et al. (1998) investigated ventricular repolarization for the first time in 48 multiple sclerosis patients using measurement of QTc interval on standard electrocardiographic recordings. Their study showed that the repolarization process was prolonged significantly in MS compared to control subjects ($p=0.0001$).We found that there was no statistically significant difference in QT interval between MS patients and control subjects. This result may be due to difference in the QT correction formulas in two studies. In Drouin et al. study correction of the QT-interval for heart rate was according to Bazett's (1920) formula. Rate correction of QT intervals using the standard Bazett formula can introduce significant errors in the QT interval measurement. It overestimated the change in QT. Numerous references recommend 420–440 ms as the threshold for reporting prolonged QTc when using Bazett's formula. Based on this database, 30% of apparently normal ECGs would be reported as having abnormal QT intervals for the 440 ms threshold, or 10% if 460 ms is chosen, compared to $<2\%$ for the other formula (Bonow and Mann, 2012). It was also noted that QT has a linear trend with heart rate but not with RR interval. However this study population is relatively small and therefore our results should not be extrapolated to all MS patients.

Obviously, measurement errors performed during manual evaluation may be one limitation of the study. Although acceptable intraobserver and interobserver errors in the manual measurement of P-wave duration in 12-lead ECGs have been reported (Dilaveris et al., 1998), well-known difficulties in defining P-wave onset and offset may restrict the accuracy and reproducibility of the measurements. It is better to resort to signal averaging of P-waves. However, lack of the Holter recordings may be another potential limitation of the study.

5. Conclusions

Involvement of the heart may be seen in MS patients even in the absence of clinical cardiac manifestations. In this study, P wave duration and P wave dispersion was found to be higher in MS patients than healthy control subjects. However, whether the patients with MS prone to development of atrial conduction abnormalities should be established by further large scale studies.

Conflict of interest

There is no financial interest to report.

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