

The effect of autonomic dysfunction on QT dispersion in patients with chronic spinal cord injury

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ÖZETKronik spinal kord yaralı hastalarda otonomik disfonksiyonun QT dispersiyonu üzerine etkisi

Amaç: Spinal kord yaralı(SKY) hastalarda otonomik disfonksiyonun ventriküler aritmilerin belirteci olan QT dispersiyonu üzerine etkisini inceleme ve hem istirahat hem de ürodinamik test sırasında aritmi riskini değerlendirmek. **Materyal ve Metod:** Bu prospektif çalışmaya 30 travmatik SKY ve 27 sağlıklı birey alınmıştır. Her iki gruptaki hastalara rutin fizik muayene ve 12 elektrotlu elektrokardiyografi(EKG) uygulanmıştır. Hasta grupta kan basıncı ve EKG kayıtları ürodinamik değerlendirme sırasında da uygulandı. QT intervalinin ölçümleri 2 kör araştırmacı tarafından yapıldı. QT ve düzeltilmiş QT (QTd) hesaplandı. SKY hastalar yaralanma seviyelerine ve ağırlığına göre ve ürodiamik ve otonomik testler sırasındaki otonomik disfonksiyonunun oluşumu muakayese edildi. **Bulgular:** QT ve QTd dispersiyon değerleri SKY hastalarda kontrollere daha yüksek idi. QT ve QTd arasındaki farklılık SKY ve sağlam bireyde anlamlı düzeyde değildi. **Sonuç:** QT dispersiyonu SKY hastalarda control grubuna göre daha yüksek idi. Bu durum bu hastalarda ventriküler aritmideki yüksek riske işaret edebilir, bununla beraber nörolojik yaralanma seviyesi, otonomik disfonksiyon ve yaralanmanın komplet olup olmaması bu riski arttırmaz.

Anahtar Kelimeler: QT dispersiyon, spinal kord yaralanması, otonomik disfonksiyon

SUMMARY

Objective: To provide data on patients with spinal cord injury (SCI) concerning the effect of autonomic dysfunction on QT dispersion as a predictor of ventricular arrhythmias, and to evaluate the risk of arrhythmia during both the resting state and urodynamic examination, which may increase the likelihood of autonomic dysreflexia due to bladder extension.

Materials and Method: This prospective, case-controlled study included 30 patients with traumatic SCI and 27 healthy individuals. SCI patients and healthy controls underwent routine physical examination and 12-lead electrocardiography. In the patient group blood pressure and ECG records were obtained during urodynamic assessment. Measurement of the QT interval was performed manually by 2 blinded investigators. QT and QT corrected (QTc) dispersion were calculated. The SCI patients were compared according to the injury level and severity, and the existence of autonomic dysfunction based on urodynamic or autonomic examination.

Results: QT and QTc dispersion values were higher in the SCI patients than in the controls. The difference in QT and QTc dispersion between the patients with and without autonomic dysfunction was not statistically significant.

Conclusions: QT dispersion in the SCI patients was higher than that in the controls. As such, the risk of ventricular arrhythmia may be higher in such patients; however, neurological injury level, autonomic dysfunction, and completeness do not contribute to this risk.

Key words: QT dispersion, Spinal cord injury, Autonomic dysfunction

Introduction

Spinal cord injury (SCI) is associated with increased risk of mortality (1). Following pneumonia and septicemia, cardiovascular disorders are the leading cause of death in patients with SCI (2). A relatively sedentary lifestyle and a high prevalence of other cardiovascular risk factors, including obesity and diabetes, increase cardiovascular-related morbidity and mortality rates in SCI patients. The autonomic nervous system modulates cardiac function, and abnormalities in autonomic function are known to increase the risk of ventricular arrhythmias (3). Autonomic dysfunction may cause increase in the heart rate, variability of blood pressure, and life-threatening hypertension attacks. Those are associated with a condition known as autonomic dysreflexia (4). In patients with cervical and high thoracic SCI (above T6) autonomic control of the cardiovascular system is impaired (5) as imbalanced reflex sympathetic discharge causes a disruption in cardiac sympathetic output. Rodenbaugh et al. reported that SCI increases susceptibility to ventricular tachyarrhythmias via altering cardiac function and an abundance of Ca²⁺ regulatory proteins. Moreover, cardiac arrhythmias and unstable blood pressure may occur during episodes of autonomic dysreflexia (6,7). Early repolarization, premature ventricular contraction, right bundle branch block, bradycardia, and ventricular excitation are examples of those cardiac arrhythmias (5,8,9).

Recent studies support the value of QT dispersion in predicting the risk for ventricular arrhythmias (10). Given the relationship between autonomic dysfunction in SCI and cardiac arrhythmias, QT dispersion may have a role as a predictor of ventricular arrhythmias in the clinical practice of physicians concerned with preventing further probable impairment in SCI patients. The aim of the present study was to determine whether autonomic dysfunction in SCI patients affects QT dispersion or not. There are two stages of the study. The first stage was the comparison of SCI patients and healthy controls for the presence of QT dispersion in the resting state. The second stage included the assessment of QT dispersion in SCI patients during an urodynamic examination, which may possibly trigger an attack of autonomic dysreflexia secondary to noxious stimulus of bladder extension.

Material and Methods

Study population

The study population included 30 patients with traumatic SCI and 27 gender and age matched healthy controls. A computerized sample size analysis program (PS3) was used to es-

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timate the number of patients in each group. According to the study by Galetta F et al. (34) the expected difference between the study and control groups was 27 and SD was 12. To obtain a power of 0,80 using a cut-off value of 0,05 for alpha it was calculated that it was necessary to have 4 patients in the study group and 4 patients in the control group. Therefore it was estimated that 30 patients in the study group would be sufficient for subgroup analyses considering possible drop-outs and possible SD changes. SCI patients were randomly selected from inpatients at our SCI rehabilitation unit and healthy controls were selected from outpatients who were non-smokers without any cardiac disease. All patients were assessed by a cardiologist and a physiatrist, based on physical examination and electrocardiography. American Spinal Injury Association (ASIA) assessment was used for neurological classification of the level and completeness of SCI (11). Patients with a history of myocardial infarction or angina pectoris, atrial fibrillation (AF), left ventricular dysfunction, left ventricular hypertrophy, valvular heart disease, chronic obstructive pulmonary disease, ventricular pre-excitation, atrioventricular conduction abnormalities, abnormal thyroid function, glucose metabolism, or serum electrolytes were excluded from the study. Subjects with pain, pressure sores, or any infection (urinary, respiratory etc.) were also excluded. None of the patients were taking medications that might have affected QT intervals. There was no history of familial arrhythmia, recurrent syncope, or sudden death from ventricular arrhythmias in any patient. Biochemical analysis of blood glucose, serum albumin, plasma calcium, and potassium in the patients and controls were within normal limits. The patients with symptoms or electrocardiographic findings of myocardial ischemia and a history of alcoholic abuse were excluded.

Autonomic Examination

Head-up tilt-table testing, heart rate variation with respiration, and the Valsalva maneuver were performed to examine autonomic dysfunction in the SCI patients (12). The patients with abnormal results in 2 of these 3 examinations were considered to have autonomic dysfunction.

1. **Head-up tilt-table testing;** After baseline blood pressure was established the patients were positioned on a tilt table at an incline of 80° from the horizontal for 5 min, and then blood pressure was measured again. A reduction from baseline in systolic blood pressure (≥ 20 mmHg) or diastolic blood pressure (≥ 10 mmHg) after 5 min was considered orthostatic hypotension a positive test result (12,13).

2. **Heart rate variation with respiration;** Patients in the supine position, with the head elevated to 30°, breathed deeply 6 respirations min⁻¹ (5 s for inspiration and 5 s for expiration). The average of the six ratios of the longest and shortest R-R interval within each of the six respirations was calculated. The outcomes were compared with the normal values (12).

3. **The Valsalva maneuver;** Each patient, with their head slightly elevated to 30°, performed the Valsalva maneuver for 15 s, and then relaxed and breathed comfortably for 45 s. Electrocardiographic records were obtained during all these tests. The ratio of maximal to minimal heart rate was calculated; ratios < 1.2 were accepted as abnormal (12).

Electrocardiographic Measurement

A 12-lead electrocardiogram (ECG) was recorded for all the patients and controls (rate: 50 mm s⁻¹) while in the resting su-

pine position. While each SCI patient was examined urodynamically, blood pressure and electrocardiograms were obtained at the stages of initial sensation of vesical filling, micturition desire, and maximal bladder capacity by another researcher. Signs of autonomic dysreflexia, such as hypertension, headache, excessive sweating, flushing, and piloerection during urodynamic examination were recorded.

All annotations on the electrocardiograms were masked and assigned a number. Measurement of the QT interval was performed manually by 2 blinded investigators. To improve accuracy the measurements were performed with calipers and a magnifying lens to define electrocardiographic deflection. The QT interval was measured from the start of the QRS complex to the point at which the T-wave intersected the isoelectric line. The corrected QT interval (QTc) for heart rate was calculated using Bazett's formula: $QTc = QT/\sqrt{RR}$ (14). QT and QTc dispersion were calculated as the difference between the maximum QT interval and minimum QT interval (15).

Statistical analysis

Continuous variables are expressed as mean \pm SD and categorical variables are expressed as a percentage. QT and QTc dispersion values from resting ECG recordings in the control and patient groups were compared using Student's t test. Those values were also compared between patient subgroups, which were designated according to the injury level and severity (completeness, injury level), the existence of autonomic dysreflexia during urodynamic examination, and the existence of autonomic dysfunction during head-up tilt-table testing, heart rate variation with respiration testing, and the Valsalva maneuver. Comparisons between the patient and control groups were made using Student's t test. Change over time in QT dispersion or QTc dispersion, and the probable effect of autonomic factors were evaluated with the general linear model-repeated measures analysis of variance. A value of $p < 0.05$ was considered statistically significant.

Results

There was no difference in age between the patients with traumatic SCI (age: 29.43 ± 7.00 years) and the healthy controls (age: 32.18 ± 6.82 years) ($P > 0.05$). The SCI patients and controls were predominantly male ($n = 22, 73.3\%$; $n = 21, 77.8\%$, respectively). There was no difference in gender between the two groups ($P > 0.05$). In total, 19 (63.3%) of the SCI patients were paraplegic, 11 (36.7%) were tetraplegic, and 16 (53.3%) had complete lesions. Of the total patients, 43.3% ($n = 13$) had lesions at the level of T6 or above. Mean elapsed time from the incident that caused SCI to hospitalization in our center was 38.7 months (10-170 months).

QT and QTc dispersion values were higher in the SCI patients than in the controls ($P < 0.001$). There was no significant difference in QT or QTc dispersion values between the patients with complete and incomplete lesions ($P > 0.05$). There was no difference in QT or QTc dispersion values between the tetraplegic and paraplegic patients ($P > 0.05$). Furthermore, QT and QTc values did not differ significantly between the patients with and without autonomic dysfunction ($P > 0.05$). All the patients with autonomic dysfunction experienced autonomic dysreflexia during urodynamic examination. QT and QTc dispersion values in the patients that experienced autonomic dysreflexia during urodynamic examination were not significantly different from those in the other patients during resting electrocardiography ($P > 0.05$). Patients with an injury level

Table 1. Examinations of QT and QTc dispersions in the resting ECG records.

| | Study population (n=30) | Healthy population (n=27) | |
|-----------------------|--|--|--------|
| QT dispersion | 52.53±15.41 | 32.75±7.90 | <0.001 |
| QTc dispersion | 58.39±17.85 | 36.19±7.11 | <0.001 |
| | The patients with complete lesions (n=16) | The patients with incomplete lesions (n=14) | |
| QT dispersion | 55.87±16.45 | 48.71±13.73 | >0.05 |
| QTc dispersion | 62.38±19.32 | 53.82±15.42 | >0.05 |
| | Tetraplegic patients (n=11) | Paraplegic patients (n=19) | |
| QT dispersion | 53.63±13.98 | 51.89±16.53 | >0.05 |
| QTc dispersion | 57.94±17.86 | 58.65±18.32 | >0.05 |
| | The patients with the injury level of T6 or above (n=13) | The patients with the injury level of T7 or below (n=17) | |
| QT dispersion | 50.98±14.92 | 53.71±16.13 | >0.05 |
| QTc dispersion | 55.03±18.40 | 60.96±17.52 | >0.05 |
| | The subjects with autonomic dysfunction or dysreflexia (n=9) | The subjects without autonomic dysfunction or dysreflexia (n=21) | |
| QT dispersion | 52.88±15.44 | 52.38±15.78 | >0.05 |
| QTc dispersion | 58.14±19.97 | 58.49±17.39 | >0.05 |

of T6 or above had similar QT and QTc dispersion values as those with an injury level of T7 or below ($P > 0.05$).

Comparison between resting electrocardiograms and electrocardiograms recorded during the stages of urodynamic examinations (Figure 1)

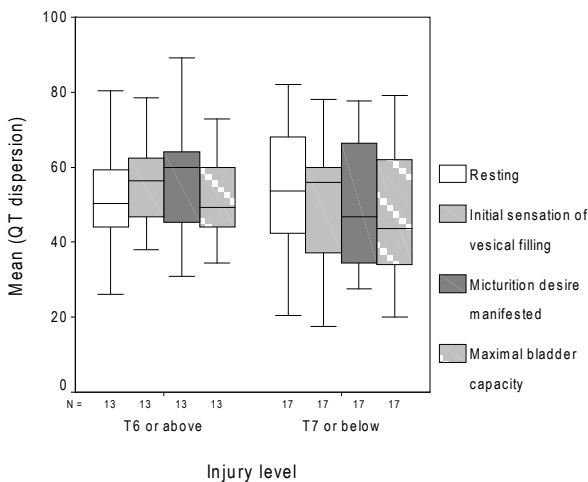


Figure 1. Comparison of QT dispersion of patients with injury level of T6 or above and those with T7 or below in the resting electrocardiograms and the electrocardiograms recorded during the stages of urodynamic examinations.

Repeated measures of QT and QTc dispersion did not statistically differ during resting electrocardiograms and electrocardiograms recorded during the stages of urodynamic examination (initial sensation of vesical filling, micturition desire, and maximal bladder capacity) ($P > 0.05$) (Figures 1-4). Completeness, injury level, and autonomic dysfunction did not significantly

affect the repeated measurements, based on between-subject analysis of variance ($P > 0.05$).

Discussion

In the present study, our findings show that subjects with SCI were found to have higher QT dispersion values than the control subjects. QT dispersion was not found to be affected by neurological level or completeness or by autonomic dysfunction. Several studies have reported that completeness of lesions, as determined by ASIA score, does not necessarily indicate the integrity of autonomic pathways (16,17). Likewise, we also observed that there was no relationship between completeness of injury and QT dispersion values in SCI patients.

Morbidity and mortality related to cardiovascular causes increase after SCI, as compared to those in the general population (18,19). Metabolic disorders that are more commonly seen in SCI patients than in ambulatory patients are the cause of most cardiovascular diseases (20). In addition, autonomic nervous system dysfunction may cause malignant ventricular arrhythmias and sudden death (21). Changes of autonomic neural tone may influence depolarization and repolarization kinetics of myocardial cells, and then QT dispersion may increase (22). This is considered to reflect regional variation in ventricular recovery times. This spatial dispersion of repolarization may cause ventricular instability and ventricular arrhythmias (23,24). The present study that revealed that higher QT dispersion in SCI supports the view of a higher risk of arrhythmias in SCI patients compared to healthy individuals. The increase in QT dispersion, that is the risk of arrhythmias, was similar for paraplegic and tetraplegic patients. Similarly, complete or incomplete lesions did not have any effect on QT dispersions.

There is a correlation between QT dispersion and autonomic imbalance (25). A reduction in QT interval dispersion du-

ring treatment with beta-blocking agents has confirmed this finding indirectly (26). The autonomic nervous system plays an important role in electrophysiological heterogeneity (27,28). Sympathetic activation may precipitate or enhance ventricular arrhythmias, whereas vagal tone may suppress their occurrence (27,29). As such, modulation of autonomic tone may play a significant role in protecting against spontaneous and ischemic ventricular arrhythmias (30,31). Myocardial necrosis and injury may cause a dispersion of myocardial refractoriness that, in conjunction with heightened sympathetic tone, creates electrical instability and cardiac arrhythmias (32). It has been shown that anxiety is associated with changes in neuroautonomic control, and this neuroautonomic imbalance may lead to QT dispersion (33). Galeta et al. reported that patients with clinical hypothyroidism have sympathovagal imbalance and higher non-homogeneity of ventricular recovery times, and that the assessment of QT dispersion in these patients may represent a useful tool for monitoring cardiovascular risk (34). Given the findings of the present study, the QT dispersion value may also be a predictor for arrhythmias in SCI.

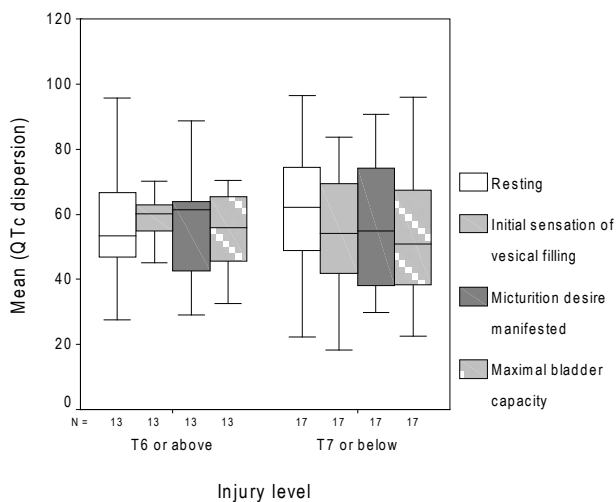


Figure 2. Comparison of QTc dispersion of patients with injury level of T6 or above and those with T7 or below in the resting electrocardiograms and the electrocardiograms recorded during the stages of urodynamic examinations.

Normally, there is a balance between the sympathetic and parasympathetic nervous systems. Although various neurotransmitters, such as norepinephrine, pass through systemic circulation due to sympathetic outflow, compensatory vasomotor brainstem reflexes increase parasympathetic stimulation. Autonomic dysfunction due to SCI shows the disturbance of this balance. As such, SCI is a good model for investigating the effects of autonomic dysfunction on cardiac electrophysiology, although, to the best of our knowledge the present study is the first study to investigate QT dispersion (a predictor of ventricular arrhythmia) in patients with SCI.

Autonomic dysreflexia, which is characterized by massive imbalance in reflex sympathetic discharge in patients with SCI above the splanchnic sympathetic outflow, is the best indicator of autonomic dysfunction due to SCI. A noxious stimulus can induce autonomic dysreflexia, and it is known that the most effective stimulus for inducing excessive sympathetic spinal outflow is bladder extension (35). The pro-arrhythmogenic effect of autonomic dysreflexia causing sympathetic hyperactivity and high vagal tone has been reported (7). The results of

the present study indicate that there was no relationship between autonomic dysfunction or dysreflexia, and QT dispersion in SCI patients. This may be related to the fact that all SCI patients in the study had more or less an impacted autonomic nervous system. However, the methods used in the study were not sufficient to reveal all autonomic dysfunctions, for example if it was minimal, but enough to elicit higher QT dispersion. Similarly, recent studies on the predictive role of prolonged QTc or increased QT dispersion in diabetic patients have reported conflicting results, although most have reported that prolonged QTc, but not increased QT dispersion, is a predictor of mortality related to ventricular arrhythmias in both non-diabetic and diabetic patients (36). Lo et al. studied patients with chronic primary autonomic failure in order to evaluate the effects of autonomic failure on the QT interval and dispersion (22). Patients with primary autonomic failure were associated with prolonged QT intervals, but a relationship between QT dispersion and chronic primary autonomic denervation was not observed.

There is a balance between the two limbs of the autonomic nervous system, and any alteration to this balance may result in changes in QT intervals. Sympathetic dysfunction is likely to be more significant than parasympathetic dysfunction in patients with primary autonomic dysfunction (22). However, a study that evaluated whether the autonomic nervous system affected the QT interval showed that vagal tone increased the intrinsic dependence of QT as the cycle length increased, whereas sympathetic tone did not (37).

When the resting electrocardiograms and the electrocardiograms recorded during the stages of urodynamic examinations were compared, some interesting findings were observed. Noxious stimulation that originated from the urinary tract did not cause an increase in QT dispersion. Parasympathetic down-regulation might have immediately intervened and reduced the sympathetic effect on the heart, and balance might have been regained. On the other hand, the SCI patients' parasympathetic systems might have been vigilant due to the extreme and permanent reaction of their sympathetic nervous systems. As such, parasympathetic control would have been dominant at the beginning of urodynamic examination.

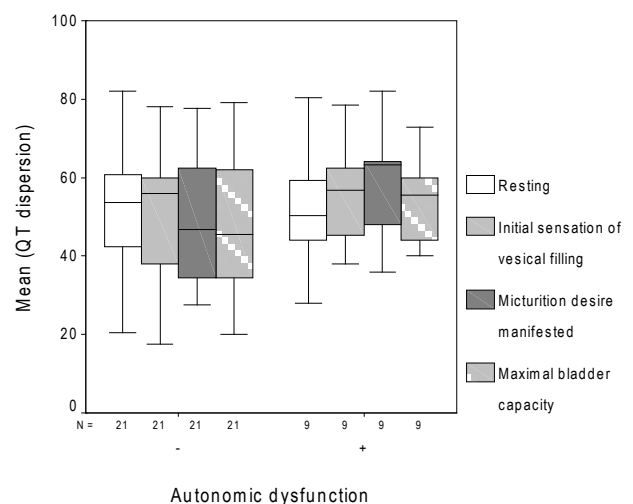


Figure 3. Comparison of QT dispersion of patients with autonomic dysfunction (all patients who had autonomic dysfunction in examination tests experienced autonomic dysreflexia during urodynamic examinations) in the resting electrocardiograms and the electrocardiograms recorded during the stages of urodynamic examinations.

Autonomic dysfunction in patients with SCI is a heterogeneous parameter. Therefore, standard deviations in the subgroups of patients were more than expected, so statistical power was low in the subgroup analysis. The high variability in QT dispersion in the healthy subjects and the possibility of inter-rater variability in scoring QT dispersion across clinical settings may be limitations of this study. However, it is thought that these findings may lead to more comprehensive studies.

Conclusion

In this study, subjects with SCI were found to have a greater QT dispersion on the ECG than healthy individuals suggesting an increased risk of developing ventricular arrhythmia. Neither neurological completeness, injury level or autonomic dysfunction were found to affect QT dispersion.

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