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Original Article

Gender differences in QTc interval in young, trained individuals with lower spinal cord injury

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Study design: Cross-sectional comparison.
Objective: To examine gender differences in rate-corrected QT interval (QTc), an index of ventricular depolarization/repolarization, in young, trained men and women with lower spinal cord injury (SCI) and able-bodied (AB) controls.
Setting: University of Illinois at Urbana-Champaign, Exercise and Cardiovascular Research Lab, USA.
Methods: Subjects consisted of 16 athletes with SCI (eight men and eight women) and 16 age-matched AB active controls (eight men and eight women). QT interval dynamics was derived from ECG recordings and rate corrected using the Bazett formula.
Results: Men with SCI had QTc similar to that of AB men (369.3 ± 7.5 *versus* 357.9 ± 3.0 ms, $P > 0.05$). Women with SCI had QTc similar to that of AB women (400.0 ± 4.6 *versus* 385.2 ± 6.5 ms, $P > 0.05$). AB women had longer QTc interval than AB men, and SCI women had longer QTc than SCI men ($P < 0.05$).
Conclusions: Gender differences in ventricular depolarization/repolarization are present in trained individuals with SCI. Thus, similar to their AB gender-matched peers, women with SCI have longer QTc intervals and may be at greater risk for the development of untoward cardiac arrhythmias than men with SCI.
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Keywords: spinal cord injury; QT interval; heart rate; electrocardiogram

Introduction

Prolongation of the QT interval has been associated with an unfavorable electrophysiological milieu, increasing risk for cardiac arrhythmia and sudden cardiac death.[1] Individuals with spinal cord injury (SCI) may be at greater risk for development of arrhythmia.[2] As autonomic tone directly affects the ventricular myocardium and repolarization kinetics,[3] inherent alterations in cardiac autonomic control stemming from SCI may result in unfavorable prolongation of rate-corrected QT interval (QTc).

It is commonly accepted that QT interval, when corrected for differences in heart rate/RR interval (QTc), is longer in women compared to men.[4,5] This has been associated with greater susceptibility to the development of Torsades de Pointes in women.[6] However, recent findings suggest that factors other than autonomic tone, such as hormonal modulation, may be responsible for gender differences in QTc interval.[4] Thus, despite the potential autonomic disruption associated with SCI, gender differences in QTc interval may prevail.

The first purpose of this study was to compare QTc interval in men and women with and without SCI. We hypothesized that men and women with SCI would have longer QTc interval than men and women without SCI. A secondary purpose was to investigate gender differences in QTc interval in individuals with SCI and able-bodied (AB) controls. We hypothesized that women with and without SCI would have longer QTc interval compared to men with and without SCI.

Methods

Subjects

Thirty-two subjects with age between 18 and 32 years participated in this study. All subjects were free of known cardiovascular or metabolic disease. AB subjects (eight male and eight female) were recreationally active.

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Subjects with SCI (eight male and eight female) were members of collegiate wheelchair athletic teams (Table 1). SCI was caused by trauma ($n=6$ female; $n=4$ male), spina bifida ($n=3$ male), transverse myelitis ($n=2$ female), and neuroblastoma ($n=1$ male). Average time since injury was 16.5 ± 1.0 years. None were taking medications known to affect heart rate or blood pressure. Subjects did not smoke and had normal sinus rhythm. After explanation and familiarization with all aspects of the testing protocol, subjects gave written consent. This research was approved by the University Institutional Review Board.

Study design
All subjects abstained from caffeine and vigorous exercise for at least 24 h before testing. Subjects were required to rest quietly for a period of 10 min in a dimly lit, climate-controlled room. QT interval dynamics were derived from a stable, 180-s epoch via ECG with a single lead CM_5 configuration (Biopac Systems, Santa Barbara, CA, USA) and ensamble averaged (WinCPRS, Turku, Finland). The ECG was collected online at a sampling rate of 1000 Hz, in real time, and stored on a computer for off-line analysis. Breathing was paced at 12 breaths per minute.

Assessment of QT interval
Analysis of QT interval and ECG morphology was performed as previously described.[7] All analyses were carried out blindly and automatically using aforementioned software (WinCPRS, Turku, Finland). The QT interval was defined as the time difference between the Q-peak and the end of the T-wave. QT interval was rate corrected using the Bazett formula $\text{QTc} = \text{QT interval}/\sqrt{RRI}$. The QTa interval was defined as the onset of the Q wave to the apex of the T wave. QTa interval was rate corrected as previously described[7] using the following equation: $\text{QTac} = \text{QTa} + 1.11(\text{heart rate (b.p.m.)} - 60)$. Repeatability of QTc in our laboratory is 0.90.

Statistical analysis
All data are reported as means $\pm$ SEM. *A priori* significance was set at $P<0.05$. One-way ANOVA was used to assess differences in age, height, weight, heart rate (HR), QT, QTc, QTa, and QTac between genders. Lesion status (ie complete *versus* incomplete) may impact overall findings. Thus, one-way ANOVA was used to assess differences in aforementioned variables between subjects with complete *versus* incomplete lesions. Moreover, ANCOVA was performed to assess gender differences in variables when co-varying for lesion status (ie complete *versus* incomplete). When significant differences were detected, *post* hoc analyses were made using Schefe to determine specific group differences. All data analyses were carried out using Statistical Package for the Social Sciences (SPSS, v 12.0.1, SPSS Inc., Chicago, IL,USA).

Results

Subject characteristics are presented in Tables 1 and 2. There were no group differences in age. AB and SCI men were matched for height and weight. AB and SCI women were also matched for height and weight. AB women were lighter than AB men ($P<0.05$). SCI women were lighter and shorter than both SCI and AB men ($P<0.05$). Resting HR in women with SCI was not different from resting HR in men with SCI (Table 3).

Table 1 Descriptive characteristics of subjects

	Male SCI	*Male AB*	*Female SCI*	*Female AB*
Age (years)	21.5 ± 0.7	23.0 ± 1.0	22.6 ± 1.5	22.6 ± 1.8
Height (cm)	168.4 ± 4.1	175.7 ± 2.5	157.0 ± 3.2[a]	164.9 ± 1.8
Weight (kg)	70.1 ± 6.4	79.5 ± 5.0	51.1 ± 3.8[a]	62.2 ± 3.3[a]

SCI = spinal cord injured; AB = able bodied
[a]Significantly different from male AB ($P<0.05$)

Table 2 Lesion level and functional level (spinal bifida) in subjects with SCI

*Subject (*n*, gender)*	*Lesion level*	*Complete/incomplete*
$n=6$ female, 1 male	T12-L1	Complete
$n=1$ female	T7-T9	Complete
$n=1$ male	L4-L5	Complete
$n=1$ female, 1 male	T10-T12	Incomplete
$n=1$ male	T6-T7	Incomplete
$n=4$ male	L1-L5	Incomplete

Table 3 HR, QT interval, and QTa interval in SCI and AB men and women

	Male SCI	*Male AB*	*Female SCI*	*Female AB*
HR (bpm)	81.6 ± 3.5[a,b]	60.4 ± 3.5	78.1 ± 2.5[a,b]	62.6 ± 2.5
QT (ms)	334.4 ± 8.6[b]	355.0 ± 11.5	361.3 ± 7.9	380.0 ± 9.3
QTa (ms)	261.9 ± 8.1[b]	294.4 ± 11.6	310.0 ± 5.6	300.7 ± 11.2

SCI = spinal cord injured; AB = able bodied; HR = heart rate
[a]Significantly different from male AB ($P<0.05$)
[b]Significantly different from female AB ($P<0.05$)

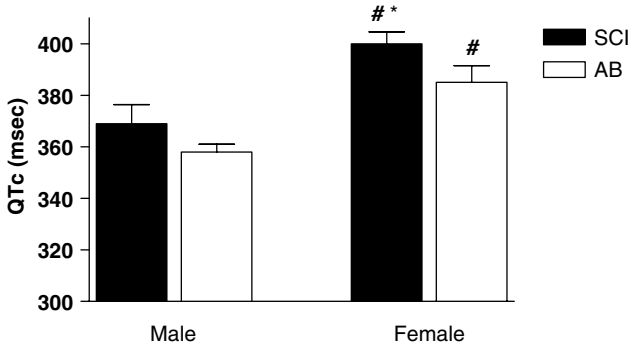

Figure 1 QTc interval in SCI and AB men and women. #Significantly different from male AB, *significantly different from male SCI

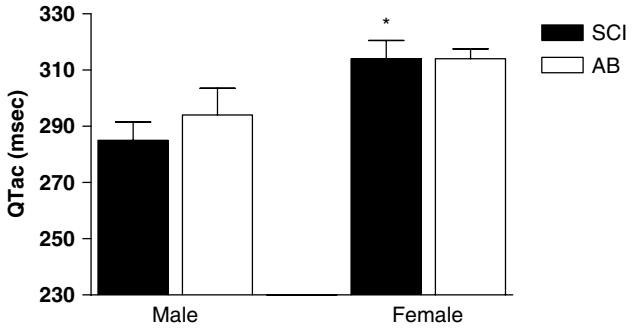

Figure 2 QTac interval in SCI and AB men and women. #Significantly different from male AB, *significantly different from male SCI

Resting HR in AB women was not different from resting HR in AB men (Table 3). SCI men and women had higher HR than AB men and women ($P<0.05$). Women with SCI had longer QT and QTa than men with SCI ($P<0.05$; Table 3). QTc interval was longer in SCI women than in SCI and AB men (Figure 1; $P<0.05$). QTc interval was also longer in AB women than in AB men ($P<0.05$). QTac interval in SCI women was longer than in SCI men (Figure 2; $P<0.05$). QTac in AB women was longer than in SCI men, but this did not reach statistical significance ($P=0.058$).

When comparing subjects with complete *versus* incomplete lesions, there were no group differences in QT, QTa, QTc, and QTac. When controlling for lesion status, women with SCI still had longer QTc and QTac than men with SCI ($P<0.05$). Although women with SCI had longer QT and QTa than men with SCI, after controlling for lesion status, this did not reach statistical significance ($P=0.080$ and $P=0.067$).

Discussion

The main findings of the present study are as follows: (1) men with SCI have similar QTc compared to AB men of similar age; (2) women with SCI have similar QTc as AB women of similar age; and (3) gender differences in QTc interval kinetics are still present in trained young individuals with lower SCI, with women having longer QTc interval than men.

It has been suggested that individuals with SCI are at greater risk for development of arrhythmia and this may be related to impaired cardiac autonomic control.[1] Indeed, individuals with SCI have altered autonomic modulation of HR[8] and our findings of greater resting HR in men and women with SCI are consistent with previous reports[9] and support this contention. SCI individuals with high-level injury who have complete disruption of central sympathetic outflow have altered ventricular repolarization manifesting as ST elevation.[10,11] Case reports of atrial fibrillation associated with autonomic dysreflexia have also been reported in apparently healthy (ie no known cardiac or metabolic disease) persons with high-level SCI.[12] However, large cross-sectional investigations note no differences in the occurrence of ECG abnormalities in men with low-level SCI (T6 and below) *versus* their AB counterparts.[13] Our findings note that young, trained men and women with low-level SCI have similar QTc interval as their AB gender-matched counterparts, suggesting comparable ventricular repolarization/depolarization kinetics.

Several investigations have reported gender differences in QTc interval.[4,5] Similar to these previous reports in AB individuals, QTc interval is larger in women with SCI than in men with and without SCI. Based on the present findings of similar QTc interval prolongation in women with and without SCI, greater propensity for arrhythmogenesis in women with SCI may be similar to that seen in AB women, but this needs further investigation.[6] Women with lower SCI also had increased QTac interval. The ventricular myocardium consists of three distinct cell types: epicardial, endocardial, and midmyocardial cells. As prolongation of the QTa interval is due to delayed epicardial cell layer repolarization,[14] our findings suggest possible gender differences in the duration of epicardial cell action potentials (ie early repolarization) in persons with lower SCI. Genetic polymorphisms or mutations of the hERG potassium channel have been associated with duration of QTc in female subjects.[15] In the human heart, hERG channel distribution is more abundant in the epicardium compared to that in the midmyocardium.[16] Our finding of longer QTac in women with SCI *versus* men with SCI supports the possibility of ion channel differences in the epicardium.

All participants with SCI in this investigation were highly active. Thus, we are limited in our ability to extend findings to a sedentary SCI population. The fact that no differences in QTc interval were found within genders may be due to the training status of our subjects with SCI. However, findings from cross-sectional investigations have revealed that QTc interval is not impacted by exercise training as it is similar in highly trained and sedentary AB individuals.[17,18] Our findings suggest that increased physical activity in lower SCI may not alter QTc interval kinetics. Additional limitations include the cross-sectional nature of this investigation and our small sample size.

Conclusions

QTc interval is similar in men with SCI compared to their age matched AB counterparts. Likewise, QTc interval is similar in women with SCI compared to their age matched AB counterparts. Gender differences in ventricular depolarization/repolarization are still present in young, trained individuals with lower SCI, and QTc interval is longer in women with SCI than in men with SCI. Thus women with SCI may be at greater risk for the development of cardiac arrhythmias than men with SCI.

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