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Profile of the cardiac repolarization in cervical spinal cord injury subjects performing physical exercise

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ABSTRACT. The aim of the study was to compare rest QT interval and QTcorrected intervals of electrocardiogram in trained men with and without cervical spinal cord injury (CSCI) and investigate cardiac electrocardiogram parameters in trained men with CSCI submitted to maximal effort test. Thirty men were separated into three groups: Control without CSCI (CON, 25.3 ± 4.1 yrs, strength training: 3 days week^{-1}; aerobic training 1day week^{-1}; n = 10), high volume exercise (30.5 ± 4.3 yrs, 3 day week^{-1} rugby specific exercises, 60min. day^{-1}; n = 12) and moderate volume of exercise (33.7 ± 5.9 yrs, 2 days week^{-1} specific rugby exercises, 60 min. day^{-1}; n = 8) with incomplete CSCI (C5-C7 cervical vertrebae) more than 12 months. Electrocardiogram was recorded in rest, during and after effort test. QT interval was significantly reduced ($p = 0.001$) in the high volume exercise group compared to control. Corrected QT interval showed no difference between moderate vs. high volume exercise group ($p > 0.05$). No changes were observed in QT, corrected QT, PR and QRS intervals of electrocardiogram between rest and post effort ($p > 0.05$). Thus, effort test does not change electrocardiogram parameters in CSCI subjects. High volume of week exercise promotes abnormalities in cardiac repolarization compared to a moderate training program.

Keywords: cervical spinal cord injury, physical training, electrocardiogram, venticular repolarization.

Perfil da repolarização cardíaca de sujeitos com lesão medular cervical submetidos a exercícios físicos

RESUMO. O objetivo do presente estudo foi comparar o perfil dos intervalos QT e QT corrigido (QTc) em homens treinados com e sem lesão medular cervical (LMC) e investigar o perfil eletrocardiográfico de homens treinados com LMC submetidos ao teste de esforço máximo. Trinta homens foram separados em três grupos: controle sem LMC (CON, indivíduos fisicamente ativos; n = 10), LMC praticantes de alto volume de exercícios (praticantes de *rugby* em cadeira de rodas 180 min. Semana^{-1}; n = 12) e LMC praticantes de moderado volume de exercícios (praticantes de *rugby* em cadeira de rodas 120 min. Semana^{-1}; n = 8). Todos os participantes do grupo LMC apresentavam lesões incompletas (C5-C7) mais do que 12 meses. Eletrocardiograma foi registrado em repouso, durante e após o teste de esforço. O intervalo QT apresentou redução significativa ($p = 0{,}001$) no grupo de alto volume de exercícios quando comparado ao controle. O QTc não mostrou diferença entre os distintos volumes de exercícios ($p > 0{,}05$). Ambos os grupos LMC não apresentaram mudanças significativas no intervalo QT, QTc, intervalos PR e QRS entre o repouso e pós-esforço ($p > 0{,}05$). Concluimos que o alto volume de exercícios semanais parece promover anormalidades na repolarização cardíaca.

Palavras-chave: lesão medular cervical, treinamento físico, eletrocardiograma, repolarização ventricular.

Introduction

Spinal cord injury (SCI) is a traumatic event that compromises physical, psychological and social well-being of patients, and shake substantial financial burden on health care systems (Saunders, Clarke, Tate, Forchheimer, & Krause, 2015). The average age at the time of injury is comprehended between 20 to 40 years, and the male/female ratio is 4:1, respectively (Biering-Sorensen, Bickenbach, El Masry, Officer & Von Groote, 2011; Krug, Sharma, & Lozano, 2000). The major incidence of SCI are related to cervical trauma (55%), which shows higher prevalence from traffic accidents (40 – 50%), assault (10 – 25%), falls (20%), work-related injuries (10 – 25%), and sports/recreation-related injuries (10 – 25%) (Biering-Sorensen et al., 2011;Surkin, Gilbert, Harkey, Sniezek, & Currier, 2000; Yang et al., 2013). A document published by the World Health Organization (Biering-Sorensen et al., 2011) shows that global SCI incidence is about 40 - 80 new cases per million, which corresponds to 250,000 to 500,000 new cases per year around the world.

Patients with cervical SCI are a high-risk group, with the highest mortality rate reported in spinal trauma, by suffer significant damage in the cardiac autonomic system, when compared to thoracic or lumbar spine injuries (Yang et al., 2013). Cervical SCI promote a loss, either temporary or permanent, in the sensory-motor response, autonomic and bladder/bowel function (Grossman et al., 2012; Santos, Santos Filho, Possatti, Bittencourt, Fontoura, & Botelho, 2012).These complications are related to forces that are required to fracture the spine, consequently, suffer significant peripheral and neurological damages that can be or not fatal. Two types of SCI could be described: complete, which contributes to loss of function below the level of the injury, and incomplete, that result in some feeling below the point of injury (Harkey, White, Tibbs, & Haines, 2003).

In this way, cardiovascular instability, such as heart rate and arterial blood pressure (Sisto et al., 2012), are common in SCI subjects, especially after cervical. It results in increased morbidity and mortality, but the instability is directly related to the type and degree of the injury, maintaining parasympathetic input to the heart intact while the spinal sympathetic system loses supraspinal autonomic control. The interruption of cardiac sympathetic innervation and parasympathetic control intact promotes bradycardia, reduces myocardial contractility and cardiac arrest occur due to a vago–vagal reflex, that contribute for autonomic dysfunction can lead to ventricular arrhythmias (Lehmann, Shandling, Yusi, & Froelicher, 1989; Ravensbergen, Walsh, Krassioukov, & Claydon, 2012).

Electrocardiographic ventricular repolarization (QT interval) parameters have been used as predictors of increased risk of ventricular arrhythmias and sudden death in patients with SCI (Akbal et al., 2014; La Fountaine et al., 2010; Ravensbergen et al., 2012). Acute phase of the cervical SCI and consequently increases in QT interval can be due to sympathetic nerves damage after separation from supraspinal control associated to parasympathetic nerves intact that negatively change cardiac autonomic control (La Fountaine et al., 2010). On the other hand, La Fountaine and colleagues (La Fountaine et al., 2010) found longer QTc intervals in paraplegia when compared to tetraplegia, and Chung et al. (2011) observed significant decreases of QT interval after 12 months of the cervical SCI. These results could be related to injury in the sympathetic innervation of the heart more that the unopposed parasympathetic activity thus helping to increase risk of atrioventricular blocks, ventricular arrhythmias and cardiac sudden death (Bartholdy et al., 2014). However, most studies measured the QT interval mainly during in the acute phase of the SCI, mainly after first month(Bartholdy et al., 2014; Chung et al., 2011; La Fountaine et al., 2010). On the other hand, subjects with cervical SCI and practitioners of physical exercise showed reduction of the myocardial atrophy due changes in the pressure and volume imposed to the heart exercise-induced (Anttonen et al., 2007). However, the relationship between the cervical SCI, physical exercise, and cardiac repolarization changes were not investigated.

Thus, the purposes of present study were 1) to compare rest QT and QTc intervals in trained men with and without cervical SCI and, 2) to investigate cardiac ECG parameters in trained men with cervical SCI submitted to a maximal arm ergometer test. We hypothesized that men with cervical SCI would have shorter QTc interval compared to men without SCI.

Material and methods

Subjects

Thirty men were recruitedand separated into three groups: Control without cervical SCI (CON, 25.3 ± 4.1 yrs, 179.2 ± 7.4 cm, 82.3 ± 8.1 Kg; BMI 26.3 ± 2.3 kg m^{-2}, n = 10), regularly engaged in strength training of 3 days $week^{-1}$ and low aerobic training of 1 day $week^{-1}$; High volume exercise with cervical SCI (HVE : 30.5 ± 4.3 yrs, 173.0 ± 11.1 cm, 65.7 ± 8.1 Kg; BMI 22.0 ± 2.9 kg m^{-2}; n = 12), practicing wheelchair rugby 3 day $week^{-1}$, 60 min. day^{-1}; and moderate volume of exercise with cervical SCI (MVE: 33.7 ± 5.9 yrs, 178.1 ± 4.3 cm, 73.6 ± 9.6 Kg; BMI 23.1 ± 2.5 kg m^{-2}; n = 8), practicing wheelchair rugby 2 days $week^{-1}$, 60 min. day^{-1}. All subjects of the HVE and MVE groups had incomplete cervical spinal cord injury (C5 - C7) with an average duration of more than 12 months. In the first phase of study, all subjects had electrocardiogram continuously recorded in rest (Control vs. HVE vs. MVE). In the second phase of study only HVE and MVE groups were submitted to maximal arm ergometer test.

All experimental procedures were carried out in accordance with the Declaration of Helsinki and were approved by the local ethical committee. All subjects gave written informed consent before data collection and were considered healthy on the basis of history, physical examination and normal resting electrocardiogram. The following additional exclusion criteria were adopted: (a) use of drugs that could affect cardiorespiratory responses, (b) no smoking (c) systemic hypertension (≥ 140/90 mmHg) induced by the concentration of urinary volume, (d) metabolic disease, (e) urinary tract infection.

Anthropometric and electrocardiogram (ECG) measurements

Volunteers attended the laboratory two times with 72 hours between visits. During the first visit, anthropometric data and ECGin rest were collected. In the second visit, HVE and MVE groups were submitted to a maximal arm ergometer test. All testing was performed between 1:00 - 3:00 p.m. and subjects received a light lunch 2 hours before each laboratory visit. Coffee, tea, alcohol, and tobacco intake were prohibited for 48 hours, and subjects avoided formal and strenuous exercise for 48 hours before each visit.

Body mass was measured to the nearest 0.01 kg using a calibrated physician's beam scale (model 448, Detecto, Webb City, Missouri, USA). Total mass from the subjects, dressing only underwear, in the wheelchair was determined first and after transferring the subject from the wheelchair. The wheelchair was weighted separately. Body weight of the subjects was determined by subtracting the weight of the wheelchair and total mass. Height was determined to the nearest 0.1 cm using a stadiometer scale (model 448, Detecto) with the subject in a 30° supine position, head in Frankfurt plane, legs stretched, and feet in dorsal flexion. Body-mass index (BMI) was calculated as body weight divided by height squared (kg / m^{-2}).

Electrocardiogram was continuously recorded in rest, at 1 kHz samplerate, 12-bit resolution, using a 12-lead ECG monitor system (25 mm s^{-1} paper speed at 10 mm mV^{-1} amplitude), during and after arm ergometer test (model 8000D; CONTEC, USA). Heart rate (HR) was measured in V5 lead from the ECG recording. The QT interval was measured manually in the 12 ECG leads and was rated with time interval between the initial deflection of the QRS complex and the point at which a tangent drawn to the steepest portion of the terminal part of the T wave crossed the isoelectric line. When U waves were present, the QT interval was measured to the nadir between the T and U waves, and when the end of the T wave could not be identified, the lead was discarded from analysis. Mean values of QT and QTc intervals in each lead were calculated from five consecutive cycles. The preceding RR intervals to the target heart cycles were measured and used to calculate the mean heart rate-corrected QT interval with Bazett's formula (Figure 1):

$$QTc = QT/\sqrt{RR}^{1/2}$$

Figure 1. Bazett's formula utilized to calculate corrected QT interval.

Repolarization parameters analyzed from QT measurements were:

QRS complex,

QT and QTc intervals obtained from lead II.

PR interval was measured from the beginning of the P-wave to the beginning of the R-wave and considered the mean of five consecutive beats taken from the lead II. Two independent and blinded evaluators carried out all measurements.

Maximal arm ergometer test

Maximum exercise testing was carried out in arm ergometer (Top excite mode, Technogym, Gambetolla, Italy) at constant environment (22 ± 2°C). The test was started with a workload of 20 Watts and arm cadence cycling between 50 and 60 rpm. Increases in workloads occurred at every 1-minute stage between 2 to 5 watts (dependent of the functional capacity). The test was terminated when the participant voluntarily stopped. All subjects were similarly encouraged to exercise as long as possible. Subjects were allowed sufficient practice during preliminary testing to become familiar with the arm ergometer.

Testing was symptom limited and was terminated if subjects reported limiting symptoms of dyspnea, fatigue, chest pain or for medical reasons including horizontal or down-sloping ST-segment depression (≥ 1 mm), ST segment elevation (≥ 1 mm in non-Q wave lead), atrial fibrillation, or supraventricular tachycardia, suggestive left bundle branch block, fall in systolic blood pressure (≥ 20 mm Hg), variation in diastolic pressure under stress higher than 15 mmHg, presyncope, severe arrhythmias, presence of extra systoles, ataxia or ventricular ectopy (presence of 6 or more premature ventricular b.min^{-1} in recovery) and development of or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia.

Blood pressure, both systolic and diastolic, were measured at rest (at least 2 measurements on both arms after 10 minutes in the seat position), at each step of exercise, and after exercise in the first, second, and third minutes by a measure based on the I and V Kortok off sounds, respectively, using a cuff specially adapted to the enlarged upper arm girth as needed. Blood pressure was measured on the left arm according to the auscultatory methods with a mercury-column sphygmomanometer (Missouri® Equipment Co; Saint Louis, MO, USA).

Statistical analysis

All data are presented as mean ±standard deviation. The statistical analysis was initially performed using the Shapiro-Wilk normality test and the homoscedasticity test (Bartlett criterion).Inter-observer variability of QT interval, QRS complex, and PR interval were assessed by both Student's t-test and intraclass correlation coefficient (ICC). Comparisons within groups were performed with a one-way ANOVA for repeated measures followed by Tukey's post hoc tests. A two-way ANOVA was used to assess differences in QT interval, QTc interval, QRS complex, and PR interval between the MVE and HVE conditions. Bonferroni's post hoc were used to partition significant main effects. A Student's t-test was used to assess differences within conditions (rest vs following maximal exercise testing). Additionally, to determine the magnitude of the findings, effect size statistics were calculated for inter-groups (HVE*Vs.* MVE) responses for rest and post-effort. The effect size (ES) was calculated to determine the meaningfulness of the difference using the $f2$ for ANOVA. The magnitude of the ES was classified as small (< 0.1), medium (0.1 – 0.49) or large (> 0.5) (Cohen, 1988). The significance level was 0.05 and the software used for data analysis was GraphPad® (Prism 6.0, San Diego, CA, USA).

Results

The mean intra- and inter-observers absolute error for electrocardiograph parameters measurements was between 3 and 5 ms. The ICC for each individual observer was 0.94 ($p < 0.001$), whereas correlations among readers was 0.92 ($p < 0.001$).The mean duration of maximum exercise testing was of 9 ± 1.4 minutes. QT interval was significantly reduced ($p = 0.001$) in HVE compared to CON(Figure 2A). QTc interval showed no difference between groups (Figure 2B).

No significant changes were observed in ECG parameters intra- and inter-groups ($p > 0.05$) as shown in Figure 3.

The comparison of effect size of electrocardiograph parameters statistics between MVE and HVE groups were small and medium. ES statistics for all groups in the QTc interval (Control vs. HVE vs. MVE) presented moderate ES for Control vs HVE and MVE vs HVE. Table 1 shows the QT interval, QTc interval, QRS complex, and PR interval at rest and post-effort. The ES statistics for both groups (MVE vs HVE) presented small to medium values.

Table 1. Effect size values of electrocardiograph parameters of MVE and HVE groups.

Rest	0.25 (small)	0.35 (medium)	0.40 (medium)	0.32 (medium)
Post-effort	0.12 (small)	0.04 (small)	0.44 (medium)	0.03 (small)

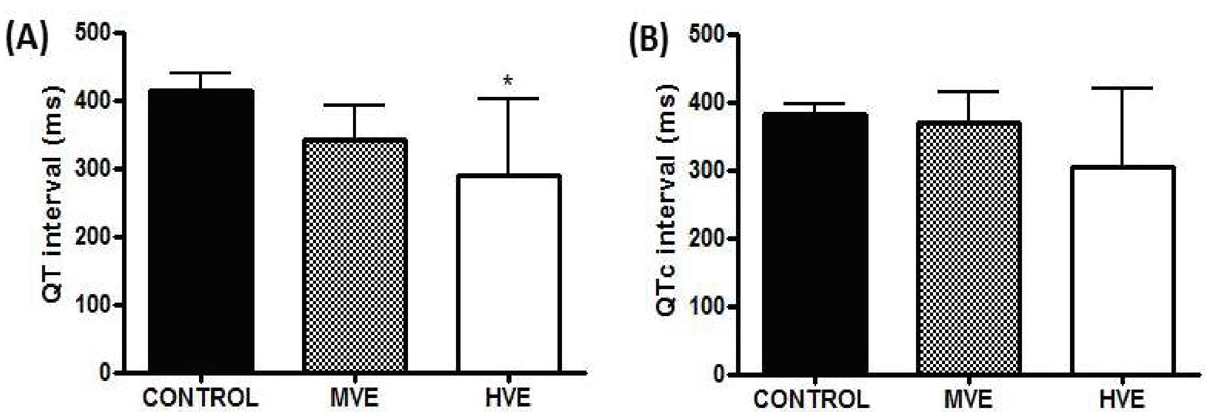

Figure 2. QT and QTc intervals, determined in rest of: control (CON; n = 10), high volume exercise (HVE; n= 12) and moderate volume of exercise (MVE; n= 8) groups. Values are expressed as mean ± standard deviation. *p < 0.001 versus control group.

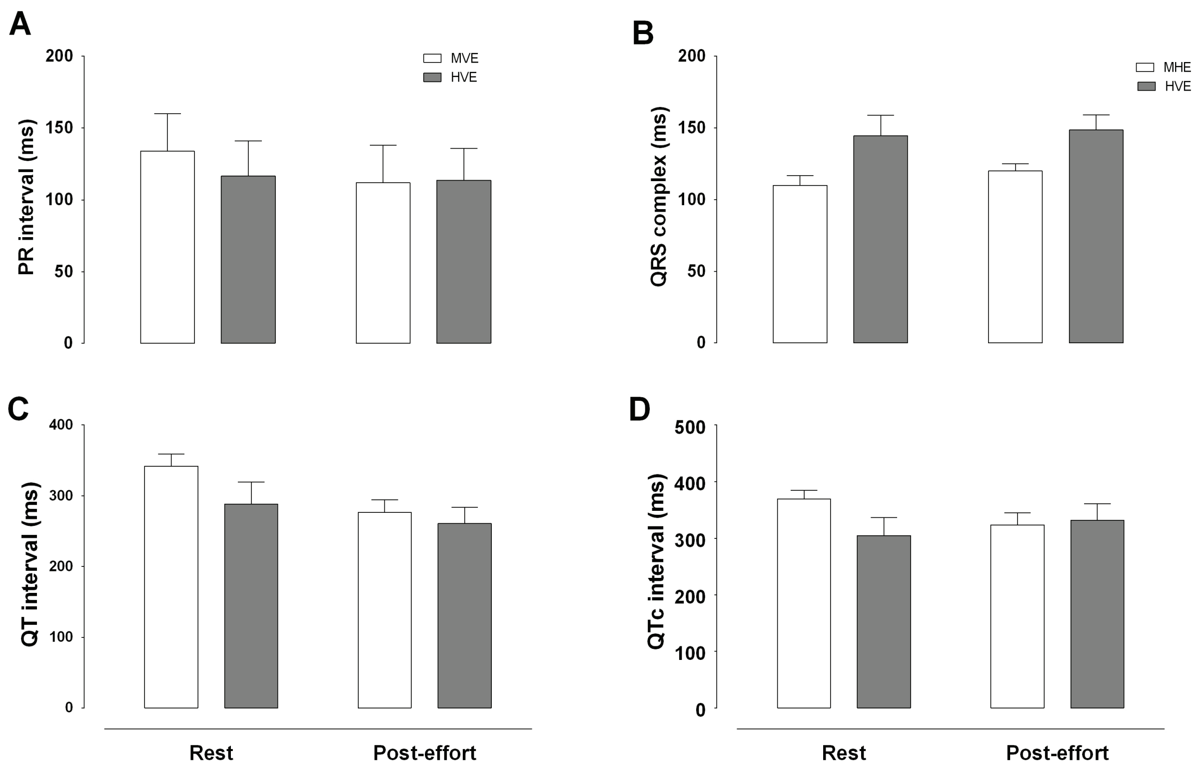

Figure 3. PR interval, QRS complex, QT and QTc intervals, measured in rest and in recovery period (post exercise testing). Values are expressed as mean ± standard deviation.

Discussion

This study presents an evaluation of the electrocardiographic parameters achieved at rest and after maximal exercise testing in a small sample of trained men with and without cervical SCI. The principal novel findings of this study are that subjects of the HVE group showed a significant decrease in QT interval, at rest, when compared with CON. On the other hand HVE showed smaller values of QTc interval at rest and after maximal arm ergometer test considering standard values (rest = 304.9 ± 100 ms; post effort = 332.1 ± 103.5 ms), while MVE showed lower QTc interval, in relation to standard values, only post effort (323.6 ± 60.9 ms). QT short is predictors of risk of arrhythmias in different patient populations (Anttonen et al., 2007; Kobza et al., 2009)and our data suggest that high volume of physical exercise in cervical SCI patients can contribute to repolarization ventricular abnormalities consequently high risk of ventricular arrhythmias and sudden death.

In male adultswith intact spinal cord, the normal values for QTc are shorter than 430 ms (ranging from 430 to 450 ms) (Maior et al., 2010). However, QTc interval shorter than 350 ms may also be a predictor of heart failure, ventricular tachycardia, ventricular fibrillation and syncope (Patel, Yan, & Antzelevitch, 2010; Viskin, 2009). Some studies showed that cervical SCI promote shortening of QT interval and increases in QT dispersion (Bartholdy et al., 2014; Saunders et al., 2015).The short QT interval shows uniformity in time and space in the ventricle, producing an exaggerated heterogeneity of repolarization, hastens recovery and reduced refractoriness in the ventricle (Patel et al., 2010).The ion channelopathies that cause SQTS (mutation in KCNH2, KCNQ1, KCNJ2 that encodes cardiac K^+ channel or mutation in CACNA1c, CACNB2b that encodes cardiac Ca^{2+} channel) not only abbreviate repolarization but they significantly increase dispersion of repolarization, thus creating the cellular basis for both the substrate and trigger necessary for the initiation of reentry (Patel et al., 2010). Rodenbaugh and colleagues (Rodenbaugh, Collins, Nowacek, & DiCarlo, 2003) observed that paraplegic rats showed high susceptibility to ventricular tachyarrhythmias via altering cardiac function and an abundance of Ca^{2+} regulatory proteins. However, increases in plasma endothelin-1 levels (commonly elevated in SCI) could have a little effect on the amplitude of contraction, calcium transients and influx through the L-type calcium channels in myocytes of SCI rats (Guo et al., 2010).It is still not clear the relation of cervical SCI and ion channel cardiac function.

Studies commented that physical activity in individuals with SCI is effective to improve of task-specific self-efficacy (Keyser, Rasch, Finley, & Rodgers, 2003), caloric balance control, increases in lean body mass (Gorla et al., 2015) and maximum constant work rate tests time (Gaffurini et al., 2013; Keyser et al., 2003; Pelletier, Jones, Latimer-Cheung Warburton, & Hicks, 2013). Furthermore, myocardial atrophy associated with cervical SCI may be reversed by changing the pressure and volume to the heart, imposed with physical activity (Nash et al., 1991). In relation to cardiac electrophysiology, our results showed short QT interval with high volume of exercise (HVE = 304,9 ± 114,1 ms), but normal values were found with moderate volume of exercise (MVE = 369,5 ± 43,4 ms). However, others (Heffernan et al., 2007) suggest that increased physical activity in lower SCI may not alter QTc interval kinetics. On the other hand, it is not known the effect volume / intensity of exercise in cardiac electrophysiological responses of individuals with cervical spinal cord injury. This way, is necessary more studies to possible conclusions. But we can hypothesize that multiple autonomic changes occurs simultaneously during exercise, it is impossible to determine the relative contributions of changes in the sympathetic and parasympathetic balance that contribute to the short QT interval (Magnano, Holleran, Ramakrishnan, Reiffel, & Bloomfield, 2002).

Regarding QRS complex duration, we found that high volume exercise seems to increase the duration of QRS complex comparing to moderate exercise (HVE= 144.6 ±51.6 ms vs MVE = 110.1 ± 19.6 ms). It is particularly important since some studies showed QRS duration increases as left ventricular function worsens (Iuliano et al., 2002; Stellbrink et al., 1999). Others (Freudenberger, Sikora, Fisher, Wilson, & Gold, 2004; Shamim et al., 1999; Silverman, 1995), demonstrated that patients with QRS prolongation have higher all-cause mortality and possibly a higher incidence of sudden death (or cardiac death) than those with narrow QRS complexes. On the other hand, PR interval duration did not differ between high and moderate exercise(HVE = 116.6 ± 24.5 ms vs. MVE = 134.1 ± 26.1 ms), but the HVE group showed lower limits of PR compared to recommended standard values(between 120 ms - 200 ms). Short PR interval can be related to AV junctional rhythms, ectopic atrial rhythms and pre-excitation syndrome (MacKenzie, 2005). However, combination short PR interval and wide QRS complexes more the broad slur on the upstroke of the R wave, taken together, are and ECG characteristic of individuals with the commonest form of ventricular pre-excitation in Wolff-Parkinson-White syndrome (Munger et al., 1993).This syndrome promotes an abnormal cardiac electrical conduction that stimulates premature ventricular contractions, resulting in a unique type of supraventricular tachycardia called atrioventricular reciprocating tachycardia (Fitzsimmons, McWhirter, Peterson, & Kruyer, 2001). However, sudden cardiac death risk in people with WPW is less than 0.6%, and is usually caused by the propagation of an atrial tachydysrhythmia to the ventricles, by the accessory pathway (Fitzsimmons et al., 2001; Munger et al., 1993).

Limitations of the present study showed a small number of patients. However, it was not possible to include more patients in the MVE and HVE groups since this study prospectively included consecutive patients admitted with a cervical SCI, so the inherent nature of the study makes this potential bias inevitable. Further investigation could give information about how the heart adapts to physical exercises in a situation of damage to sympathetic innervation and which patients are especially vulnerable to the cardiac instability resulting of the cervical SCI.

Conclusion

We concluded that short QTc interval and increase in the duration of QRS complexin subjects with cervical SCI and practitioners of high volume of exercise, suggesting the presence of ventricular repolarization abnormalities. Furthermore, PR interval depression may indicate atrial injury. Evaluation of electrocardiographic repolarization parameters at rest and post-exercise could provide diagnostic and prognostic information about the risk of cardiac arrhythmias and sudden cardiac death in healthy subjects with cervical SCI.

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