Autonomic Neuroscience: Basic and Clinical 195 (2016) 16–19

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Reproducibility of the QT-variability index in individuals with spinal cord injury

Hisham Sharif [a,b], David Allison [a,b], Deborah O'Leary [b,c], David Ditor [a,b,*]

[a] Department of Kinesiology, Brock University, 500 Glenridge Avenue, St Catharines, ON L2S 3A1, Canada
[b] Brock-Niagara Center for Health and Well-Being, Brock University, 130 Lockhart Dr, St. Catharines, ON L2T 1W4, Canada
[c] Applied Health Sciences, Brock University, 500 Glenridge Avenue, St Catharines, ON L2S 3A1, Canada

ARTICLE INFO

Article history:
Received 21 July 2015
Received in revised form 16 December 2015
Accepted 7 February 2016

Keywords:
Spinal cord injury
Electrocardiogram
Autonomic function
QT-interval

ABSTRACT

Purpose: To examine the day-to-day reproducibility of the QT-variability index (QTVI) and the QT-apex variability index (QTaVI) in individuals with spinal cord injury (SCI).
Methods: Ten individuals with SCI participated in the current study (C2-T10; AIS A-D; 8.6 ± 7.8 years post-injury). On two occasions, with a 10-day interval, a 10-minute resting electrocardiogram was obtained from each participant. The QTVI and QTaVI were analyzed from 256 electrocardiographic beats from all participants, and a separate analysis was performed on those with injuries above the 4th thoracic level. An intraclass correlation coefficient (ICC) test was performed to measure day-to-day reproducibility of these measures and a Bland–Altman test was performed on all participants in order to examine the skewness of the measures.
Results: The reproducibility values were found to be high for both the QTVI (all participants: $R = 0.892$; above T4: $R = 0.893$) and the QTaVI (all participants: $R = 0.908$; above T4: $R = 0.915$). In addition, the reproducibility of QTVI and QTaVI did not appear to be skewed as indicated by Bland–Altman plots.
Conclusion: Both the QTVI and the QTaVI may be used as reproducible means of assessing cardiac autonomic function in individuals with SCI. Further, a reduction in cardiac sympathetic regulation after high thoracic and cervical level SCI does not appear to influence the day-to-day reproducibility of these measures.
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1. Introduction

It is well documented that spinal cord injury (SCI) results in complete or partial loss of supraspinal control of the cardiovascular system, which therefore increases the risk for cardiovascular dysfunctions and mortality (Myers and Lee, 2007). Specifically, injuries above the 5th thoracic level (T5) may lead to compromised cardiac sympathetic innervation, which increases the susceptibility to cardiac arrhythmias (Collins et al., 2006; Lujan et al., 2010; Ravensbergen et al., 2012) and reduces exercise tolerance (Eriksson et al., 1988). In addition, studies have reported a reduction in cardiac parasympathetic outflow following SCI, believed to be partly attributed to a physiological adaptation in an attempt to maintain sympathovagal balance (Grimm et al., 1997; Wang et al., 2000). However, such a reduction in cardiac vagal outflow may be problematic, as it has been demonstrated through a wide range of indicators that reduced vagal activity is associated with increased risk of mortality and morbidity, independent of traditional risk factors (Thayer and Lane, 2007). Furthermore, the loss of supraspinal control over sympathetic preganglionic neurons that innervate the vascular bed is associated with both autonomic dysreflexia (characterized by episodic fluctuations in blood pressure) (Karlsson, 1999) and orthostatic hypotension, which may reduce functional capacity and the ability to engage in activities of daily living. Thus, it is imperative to develop reliable, non-invasive measures of cardiac autonomic activity in individuals with SCI in order to assess the integrity of cardiac autonomic regulation and potential changes over time.

Several electrocardiogram (ECG)-based measures have been employed for non-invasive assessment of cardiac autonomic regulation after SCI, including spectral analysis of heart rate variability (HRV) and non-linear HRV. Although both measures have been shown to be reproducible in individuals with SCI (Ditor et al., 2005; La Fountaine et al., 2010a), not all parameters achieve that status, as high frequency power was shown to have poor reproducibility in this population (Ditor et al., 2005). In addition, the efficacy of some of these parameters in gauging cardiac sympathetic activity in the SCI population remains questionable (Cotie et al., 2010; Millar et al., 2010). More recently however, the QT-variability index (QTVI) has been developed as a non-invasive measure of beat-by-beat repolarization variability (Berger et al., 1997). This measure takes simultaneous QT and RR intervals into consideration, thus providing insight on both myocardial (QT-interval) and autonomic (*RR*-interval) activity. An elevation in QTVI suggests more repolarization variability, while a reduction in QTVI suggests more stable and less variable repolarization time. An increase in QTVI has been strongly associated with future cardiac events (Atiga

* Corresponding author at: Department of Kinesiology, Brock University, 500 Glenridge Ave, St Catharines, Ontario L2S 3A1, Canada.
E-mail address: dditor@brocku.ca (D. Ditor).

http://dx.doi.org/10.1016/j.autneu.2016.02.004
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et al., 1998; Tereshchenko et al., 2012), hypertension (Baumert et al., 2011), cardiac arrhythmias (Oosterhoff et al., 2011) and heart failure (Piccirillo et al., 2006). In addition, it is also augmented in non-pathological settings that are associated with changes in cardiac autonomic activity, such as aging (Piccirillo et al., 2009) and exercise (Boettger et al., 2010). In addition, the QTVI has been shown to be moderately reproducible in healthy humans (Starc et al., 2014) and patients with kidney failure (Gao et al., 2005).

The QTVI has been shown to be elevated in individuals with SCI (La Fountaine et al., 2010b), especially those with injuries above T5 and/autonomically complete injuries (Ravensbergen et al., 2012). A recent study from our laboratory has demonstrated the QTVI's ability to reflect both cardiac sympathetic and parasympathetic activity in individuals with tetraplegia (Sharif et al., 2015). Although the QTVI is a relatively novel method, it may be a promising method for gauging the amount of preserved cardiac autonomic function in individuals with SCI. However, autonomic decentralization following SCI may cause the cardiovascular system to operate on reflexes alone, rather than well regulated supraspinal signals. Hence, because the QTVI is highly influenced by cardiac autonomic activity (Piccirillo et al., 2009; Yeragani et al., 1999), autonomic decentralization may render the QTVI unstable. Therefore, before the QTVI can be effectively employed as a measure of cardiac autonomic activity in individuals with SCI, its reproducibility must be examined in this population. Accordingly, the purpose of this study was to examine the day-to-day reproducibility of the QTVI in individuals with SCI.

2. Methods

2.1. Participants

Electrocardiographic data from 10 individuals (6 male, 4 female; age 44.8 ± 15.0 years) with SCI (C2-T10; AIS A-D; 8.6 ± 7.8 years post-injury) were collected and analyzed for this study. Participant characteristics can be found in Table 1. All participants were at least 1 year post-injury and were recruited from a community based rehabilitation program for individuals with SCI (Power Cord, St. Catharines, Ontario). All participants were medically examined and had no existing cardiovascular disease or cardiac pacemakers, and other than the SCI, they were healthy and free from secondary health compilations.

2.2. Study protocol

Each participant visited the laboratory on two occasions (day 1 and day 2) within a 10 day period, and no two testing sessions were less than seven days apart. All testing sessions took place between the hours of 12 pm and 4 pm, and each participant was tested at the same time of day during both visits. Participants were asked to refrain from any alcohol consumption or smoking 24 h prior to testing and to avoid caffeine intake the morning of testing. In addition, any types of exercise, aside from morning stretches, were to be avoided 24 h prior to testing and each participant was at least 1 h post-prandial during data collection. Medications were not discontinued during data collection, however, participants were instructed to maintain the same dosage during both days of testing. Medications that participants were on during data collection included baclofen, senokot, midodrine and fludrocortisone. All participants were asked to empty their urine bags, bladders or bowels before arriving to the laboratory.

Table 1
Participant characteristics.

Participant	Gender	Age	Injury level	AIS classification	Years post-injury
1	M	21	C7	B	4
2	F	37	T3	A	18
3	M	41	C6	B	5
4	M	65	C5	D	5
5	M	67	C2	B	3
6	F	43	C7	C	9
7	F	45	C7	A	8
8	F	27	T6	A	6
9	M	44	T6	A	27
10	M	58	T10	A	5

AIS: ASIA Impairment Scale, where ASIA stands for the American Spinal Injury Association.

Upon arriving to the laboratory, participants were transferred onto a plinth and a single ECG lead (lead 2) was connected. Before data collection took place, the lights in the laboratory were dimmed and each participant was asked to lie down quietly in the supine position for 10 min in order for the participants to be in an autonomically relaxed state. Following 10 min of rest, 10 min of continuous ECG recordings were collected for later analysis of the QTVI (Power Lab, Lab Chart 7, ADInstruments). All ECG data were collected at a sampling frequency of 1000 Hz and a band-pass filter of 0.5-50 Hz was used in order to eliminate both high frequency noise and baseline wander, which can influence QT interval analysis.

2.3. QT interval analysis

Two hundred and fifty six stable artifact free beats were used for QTVI analysis for each participant. The QT interval was analyzed in 2 ways: i) from the onset of the Q wave to the intersection point of the isoelectric line and the tangent line down the descending limb of the *T*-wave, and ii) from the onset of the Q wave to the apex of the *T*-wave. The latter analysis, known as QTaVI (Baumert et al., 2011) is easier to detect and is less corrupted by noise compared to the end of the *T*-wave. The QTaVI method has been employed in assessing beat-to-beat repolarization variability in able-bodied (Piccirillo et al., 2001) and SCI individuals (La Fountaine et al., 2012).

Prior to further analysis, each beat was visually examined in order to ensure that the software marked the QT and QT-apex intervals appropriately. The QTVI was calculated using the following formula developed by Berger et al. (1997):

$$\mathrm{QTVI} = \mathrm{Log}_{10}\left[\left(\mathrm{QTv}/\mathrm{QTm}^2\right)/\left(\mathrm{RRv}/\mathrm{RRm}^2\right)\right]$$

where, QTv is the QT interval variance, QTm^2 is the mean QT interval squared, RRv is the RR interval variability and RRm^2 is the mean RR interval squared.

The QTaVI was calculated using the formula:

$$\mathrm{Log}_{10}\left[\left(\mathrm{QTav}/\mathrm{QTam}^2\right)/\left(\mathrm{RRv}/\mathrm{RRm}^2\right)\right]$$

where, QTav is the QT-apex interval variance and QTam^2 is the QT-apex interval mean squared, RRv is the RR interval variability and RRm^2 is the mean RR interval squared.

2.4. Statistical analysis

A dependent sample *t*-test was performed on all participants ($n = 10$) in order to compare Day 1 and Day 2 values for QTVI, QTaVI, RR interval and variability, QT interval and variability, as well as QT-apex interval and variability. Statistical significance was set at $p < 0.05$ and data are reported as means ± standard deviations. To calculate the test:retest reproducibility of QTVI and QTaVI, intra-class correlations (ICC) were performed for all participants ($n = 10$). Separate ICC's were also calculated for participants with injury levels above T4 ($n = 7$), as such injuries are associated with a greater loss of control over cardiac function due to compromised cardiac sympathetic innervation. In addition, Bland–Altman plots were performed for QTVI and QTaVI in order to assess possible skewness of the data, i.e., to determine if day to day differences depend on the magnitude of the QTVI or QTaVI values. All statistical analysis was performed using SPSS version 20 (SPSS Inc, Chicago).

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