ORIGINAL ARTICLE

Comparison of QT-interval and variability index methodologies in individuals with spinal cord injury

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Study design: Within-group comparison.

Objectives: Individuals with spinal cord injury (SCI) demonstrate an elevated risk for cardiac arrhythmias as indicated by an elevated QT-variability index (QTVI). The methodology measuring the QTVI, however, is not standardized, and therefore the purpose of this investigation is to determine whether the threshold and tangent methods of QT-interval measurement, as well as the electrocardiographic (ECG) epoch duration, influence the QTVI in individuals with SCI.

Setting: Ontario, Canada.

Methods: Ten minutes of resting ECG data were collected and analyzed from 14 individuals with SCI (C2–L3; ASIA Impairment Scale (AIS) A–D; 11.5 ± 9.4 years post injury). The QTVI was analyzed via the threshold and tangent methods of QT-interval measurement, as well as from 1-, 5- and 10-min ECG epochs.

Results: The threshold method produced significantly higher QTVI values compared with the tangent method. The QTVI from a 1-min epoch was significantly higher compared with that from 5- and 10-min epochs. The QTVI values acquired from the threshold method were shown to have higher reproducibility compared with those from the tangent method. There were no differences in QTVI values between participants with lesions above and below T1, as shown by both methods of QT-interval measurement.

Conclusion: The method of QT-interval measurement and the length of ECG epoch influence QTVI values in individuals with SCI. The methodology of QTVI analysis must be standardized in studies involving SCI individuals to reduce the variability accounted by methodological inconsistency.

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INTRODUCTION

The electrocardiogram (ECG) has become an easily used noninvasive tool for the assessment of cardiac autonomic function and cardiac risk in several populations. Although conceptually, the QT-interval on the ECG incorporates ventricular depolarization and repolarization, it is used in the assessment of ventricular repolarization time because of its correspondence with ventricular cellular activity.^{1,2} In addition, beat-by-beat repolarization variability can be quantified mathematically via the QT-variability index (QTVI),³ which has been shown to strongly predict risk of sudden cardiac death in patients with symptomatic^{4,5} and asymptomatic heart disease.⁶ The QTVI is also able to predict the risk of ventricular arrhythmias in patients with acute⁷ and chronic heart disease,⁸ as well as reflect the degree of cardiac autonomic dysfunctions in experimental⁹ and patient populations.¹⁰ Spinal cord injury (SCI) is a condition that has been associated with altered cardiac electrophysiology and increased risk of cardiac arrhythmias,^{11–13} as well as cardiovascular morbidity.¹⁴ The QTVI has only been recently assessed in individuals with SCI^{15–17} and has demonstrated a higher risk for arrhythmia in this population compared with able-bodied individuals.^{15,16}

Similar to other traditional ECG-based indicators of cardiac risk, such as heart rate variability, assessment of the QTVI has not been completely standardized for individuals with SCI. For example, the

QTVI has been reported in individuals with SCI from 1-,¹⁵ 5-¹⁷ and 15-min¹⁶ epochs, and therefore it is difficult to compare results as it is unknown whether epoch length influences QTVI values. In addition, automated algorithms that measure the QT-interval mainly use two methods: (1) threshold-based measures where the T-end is determined at the intersection point of the isoelectric line and descending T-wave (see Figure 1a), and (2) tangent-based measures, where the intersection point of the isoelectric line and a tangent line down the descending T-wave is the T-end¹⁸ (see Figure 1b). Thus, it is possible that using different methods of measuring the QT-interval (determine the end of the T-wave) may yield different values for the QTVI in individuals with SCI. This could be problematic in clinical settings, as it may result in over- or underestimating the risk of cardiac events in this population. Therefore, before such a method is further used in clinical and physiological research, the methodology of its use must be examined and standardized. Accordingly, the purpose of this study is to examine the influence of different ECG epoch lengths on the QTVI in individuals with SCI and to compare QTVI values obtained from the threshold and tangent methods of QT-interval measurement.

MATERIALS AND METHODS

Participants

Fourteen individuals (9 males, 5 females; age: 47.9 ± 15.5 years) with SCI (C2–L3; ASIA Impairment Scale (AIS) A–D; 11.5 ± 9.4 years post injury) were

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Figure 1 (a) The QT-interval as measured via the threshold method. (b) The QT-interval as measured via the tangent method.

Table 1 Participant characteristics

Participant	Age (years)	Sex	Injury level	YPI	AIS
1	67	Male	C2–3	3	B
2	37	Male	C4	25	B
3	48	Male	C5	14	D
4	65	Male	C5–6	5	D
5	21	Male	C7	4	B
6	68	Male	C7	28	B
7	45	Female	C7	8	A
8	33	Female	T1	13	A
9	37	Female	T3	18	A
10	59	Male	T4	4	D
11	27	Female	T6	6	A
12	44	Male	T6	27	A
13	58	Male	T10	2.5	A
14	62	Female	L3	4	D

Abbreviations: AIS, ASIA Impairment Scale; YPI, years post injury.

recruited for the current study (Table 1). All participants were at least 1 year post injury and were recruited from a community-based rehabilitation center for individuals with SCI (Power Cord, St Catharines, ON, Canada). Seven of the 14 participants had tetraplegia, and according to the AIS,¹⁹ 10 out of the 14 participants had motor complete injuries (AIS A and B). 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 complications. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Study protocol

All testing sessions took place between 1200 and 1600 hours. Participants were asked to refrain from any alcohol consumption or smoking 24 h before 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 before testing and each participant was at least 1 h postprandial during data collection. All participants were asked to empty their urine bags, bladders or bowels before arriving to the laboratory. Medications were not discontinued during data collection; however, participants were instructed to maintain their normal dosages on testing days. The medications that the participants were taking during data collection were for the treatment of spasms, hypotension and bladder control.

Upon arriving to the laboratory, participants were transferred onto a plinth and a single lead ECG 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, Sydney, NSW, Australia). All ECG data were collected at a sampling frequency of 1000 Hz, and a bandpass filter of 0.5–50 Hz was used to reduce high-frequency noise and baseline wander.

QT-interval analysis

The QT-interval for QTVI analysis was determined by both the tangent and threshold methods. For the threshold method, the QT-interval was measured from the onset of the Q-wave until the intersection point of the descending T-wave and the isoelectric line (Figure 1a).²⁰ For the tangent method, the QT-interval was measured from the onset of the Q-wave until the intersection of the isoelectric line and a tangent line, fitted by least squares, over the descending slope of the T-wave (Figure 1b)²⁰ (Lab Chart 7; ADInstruments). Both methods were used to analyze the QTVI from 1-, 5- and 10-min epochs. The QTVI was calculated using the following formula developed by Berger *et al.*³:

$$QTVI = \text{Log}_{10}((QTv/QTm^2)/(RRv/RRm^2))$$

where QTv is the QT-interval variance, QTm² is the mean QT-interval squared, RRv is the RR interval variance and RRm² is the mean RR interval squared. Time domain analysis of cardiac parasympathetic activity (standard deviation of successive RR intervals: SNDD) analyses was also performed from the same ECG epochs used to examine QTVI.

Statistical analysis

A two-way (QT-interval measurement method X epoch length) repeated measures of analysis of variance was performed to calculate a difference in QTVI values obtained from both methods of QT-interval analysis and the different ECG epochs. Bonferroni's *post hoc* test was used to compare means if significant interactions or main effects were found. A three-level intraclass correlation was performed to examine QTVI reproducibility from both methods of QT-interval analysis. Two separate dependent sample *t*-tests were performed to compare QTVI values and SDNN from the first and last minute of the 10-min ECG recording. This was to ensure that the ECG data were recorded during stable cardiac autonomic activity because an increase in cardiac vagal outflow can reduce the QTV.^{9,17} A *t*-test was used to compare QTVI values obtained by the threshold and tangent methods between participants with injury levels above and below T1. In addition, the difference in QTVI between the methods was calculated by subtracting the tangent values from the threshold values and a *t*-test was used to detect significance in the difference between participants with injury levels above and below T1. Statistical significance was set at $P < 0.05$, and data were reported as mean $\pm$ s.d. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 21.0, IBM, Endicott, NY, USA) software.

RESULTS

The intraclass correlations were high for both the tangent and the threshold methods; however, the tangent method yielded better reproducibility than the threshold method (Table 2). In addition,

Table 2 QTVI values obtained by the tangent and threshold methods^a

QT method	1 min	5 min	10 min	R
Tangent	-1.04	-1.18	-1.16	0.92 ^b
Threshold	-0.5	-0.72	-0.78	0.88 ^b

Abbreviation: QTVI, QT-variability index.

^aFor various epoch lengths and the corresponding reproducibility.

^bSignificant intraclass correlation ($P < 0.05$).

Figure 2 QTVI values (collapsed across methods) for 1-, 5- and 10-min ECG epoch lengths. *Significantly different than 1 min. $P < 0.05$.

the two-way analysis of variance revealed no significant (QT-interval measurement method X epoch length) interaction ($P = 0.37$). Despite these results, there was a significant main effect for method (collapsed across epoch lengths) where QTVI values obtained by the threshold method were significantly higher compared with those obtained by the tangent method (-0.67 ± 0.13 vs -1.13 ± 0.11 ; $P = 0.01$). There was also a significant main effect for epoch length ($P = 0.01$) (collapsed across methods), and *post hoc* analysis showed that QTVI from a 1-min epoch was significantly higher than QTVI values obtained from 5- ($P = 0.03$) and 10-min ($P = 0.03$) epochs (Figure 2). To confirm that there were no changes in cardiac parasympathetic outflow during the test, cardiac autonomic function via QTVI and SDNN was used to compare values from the first minute and the tenth minute of the ECG recordings. There were no significant differences in QTVI values between the first minute and the tenth minute as measured by the tangent method (-1.04 ± 0.59 vs -1.08 ± 0.56 ; $P = 0.70$); however, the threshold method showed that QTVI from the first minute was significantly higher compared with that of the tenth minute (-0.50 ± 0.64 vs -1.12 ± 0.55 ; $P = 0.01$). In addition, standard deviation of successive RR intervals did not significantly change between the first minute and the tenth minute (44.69 ± 19.29 vs 39.35 ± 25.30 ms; $P = 0.18$). Comparison between participants with injury levels above and below T1 showed no significant differences in QTVI values as obtained by the tangent ($P = 0.13$) and threshold methods ($P = 0.61$) (Table 3), as well as the difference between these two measures ($P = 0.1$) (Table 3).

DISCUSSION

The purpose of this study was to determine whether the QTVI in individuals with SCI is influenced by the method of QT-interval measurement and the length of the ECG epoch used for analysis. The main results were as follows: (1) the threshold method of measuring the QT-interval produced significantly higher QTVI values compared with those obtained by the tangent method, (2) both methods of QT-interval measurement showed high reproducibility for QTVI;

Table 3 Comparison of QTVI methods between lesions above and below T1

Participant	Injury level	Tangent	Threshold	Difference
1	C2-3	-0.71	-0.67	0.04
2	C4	-1.27	-0.74	0.54
3	C5	-1.22	-0.76	0.46
4	C5-6	-0.75	-0.69	0.05
5	C7	-1.49	-1.13	0.36
6	C7	-1.17	-0.68	0.49
7	C7	-0.50	0.03	0.53
	Ave	-1.02 ± 0.36	-0.66 ± 0.35	0.35 ± 0.22
8	T1	-1.70	-0.85	0.85
9	T3	-1.85	-1.58	0.26
10	T4	-0.81	-0.43	0.39
11	T6	-1.59	-1.10	0.50
12	T6	-1.55	-0.86	0.69
13	T10	-1.08	-0.18	0.90
14	L3	-0.89	-0.45	0.44
	Ave	-1.35 ± 0.42	-0.78 ± 0.45	0.57 ± 0.24
	P-value	0.13	0.61	0.10

Abbreviation: QTVI, QT-variability index.

however, better reproducibility was reported from the tangent method and (3) the length of the ECG epoch used for analysis influences the QTVI value, as 1-min epochs yielded significantly higher values compared with 5- and 10-min epochs.

The QTVI has recently been shown to be elevated in individuals with SCI,^{15,16} thus suggesting that this population may be at a relatively higher risk for sudden cardiac events.^{4,5} Traditional ECG-based predictors of sudden cardiac death, such as heart rate variability,²¹ rely on the detection of RR intervals; however, the QT-interval is more difficult to discern,²² as the T-wave terminal is not as explicit, nor is it as standardized as the R peak, and it is easily subjected to noise. Although the heart rate variability methodology may be easier to execute, the QTVI may be superior, as our laboratory has already established that it has good reproducibility, which may be better than that of heart rate variability,²³ it is an able gauge of the degree of preserved cardiac sympathetic and parasympathetic function,¹⁷ and it can provide information regarding repolarization variability in ischemic conditions where heart rate variability cannot.²⁴ Although automated measures of the QT-interval have demonstrated higher reproducibility than manual assessment,²⁵ automated algorithms do not always accurately assess morphologically compromised T-waves²⁶ and the QT-interval can be corrupted by the slightest amount of noise,²⁷ as well as by T-wave amplitudes, U-waves and even filtering bandwidths.²⁰ This holds true especially for individuals with SCI, because even in the best possible circumstances these individuals are prone to noise in the ECG from uncontrolled spasms or muscle tone. As such, it is important to elucidate methodologies that control for such confounding effects to obtain more robust measures of QTVI in this population.

Results from the current study demonstrate significantly higher QTVI values obtained from the threshold method of QT-interval measurement compared with the tangent method. Although it is not clear as to which method more accurately represents the amount of repolarization variability, we speculate that the higher values obtained by the threshold method are due to a methodological issue rather than physiological in nature. Although the ECG data were collected in the best possible circumstances, unpreventable noise from the

mentioned reasons was found near the T-wave terminus in most of our participants. The threshold method does not correct for noise near the T-wave terminus; however, this issue is circumvented by the tangent method, as it takes the descending slope of the T-wave into account. Therefore, we speculate that the QTVI values obtained from the threshold method are overestimating the true degree of myocardial repolarization variability. A recent animal study showed that the area between the T-peak and T-end may be modulated by the sympathetic nerve activity.²⁸ In addition, Ravensbergen *et al.*¹⁶ reported higher T-peak–T-end variability and QTVI in those with lesion levels above T5. As the tangent method takes the whole T-wave into account, whereas the threshold method eliminates a portion of the descending limb, QTVI values obtained by the tangent method may be subjected to more variability in those with blunted/or low cardiac sympathetic outflow. However, the data show that there were no differences in QTVI values, as obtained by both methods, between participants with injury levels above and below T1. A potential explanation for the inconsistency between our results and those by Ravensbergen *et al.*¹⁶ is that they used T5 as their level of cardiac sympathetic dysfunction, whereas we used T1. In addition, it is possible that participants in the current study did not have ablated cardiac sympathetic outflow, whereas the participants in the study by Ravensbergen *et al.*¹⁶ included autonomically complete individuals, as shown by autonomic tests. Further, although QTVI values were shown to be highly reproducible, as assessed by both methods of QT-interval measurement, the tangent method yielded higher QTVI reproducibility compared with the threshold method. This is in agreement with previous reports showing the tangent methods to be more reliable than threshold-based measures for QT-interval analysis in able-bodied individuals.^{18,20}

The current investigation also showed that the duration of the ECG epoch used for analysis affects the QTVI value in individuals with SCI. One-minute epochs resulted in significantly higher QTVI values compared with 5- and 10-min epochs, with no difference between the latter two. In addition, the finding that there was no significant difference in QTVI between first and tenth minute, as assessed by the tangent method, suggests that the differences in QTVI are a product of the number of ECG beats used for analysis rather than an increase in cardiac vagal activity. However, this may be open to further interpretation, as the tangent method showed significant differences in QTVI between minute 1 and minute 10. Although it is difficult to discern which method of QT-measurement for QTVI more accurately assesses cardiac parasympathetic outflow (tangent or threshold), the finding of no changes in QTVI, via the tangent method, was further supported by no changes in SDNN. This suggests that there were no significant changes in cardiac parasympathetic outflow between the first- and the tenth-minute recordings, and therefore the significant changes in QTVI obtained via the threshold method are likely a result of a methodological limitation rather than physiological in nature. La Fountaine *et al.*¹⁵ reported QTVI values in individuals with SCI from 1-min recordings, whereas Ravensbergen *et al.*¹⁶ did so from 15-min recordings, and a recent study from our laboratory reported it from 5-min recordings.¹⁷ According to the results from the current investigation, it is difficult to compare QTVI values in the SCI literature, as differences in the results could be attributed to the varying methodologies used. In addition, it is important to note that the ECGs from the current investigation were sampled at a rate of 1000 Hz. It is unknown whether different sampling rates would influence the QTVI values and further research is warranted in this area.

As the validity¹⁷ and reliability²³ of the QTVI as a gauge of cardiac autonomic activity in SCI have been examined, future work certainly

needs to focus on its validity in assessing cardiac risk in this population. In addition, the methodology of QT-interval measurement and analysis needs to be standardized, as they clearly influence QTVI values in individuals with SCI. Therefore, the following are the recommendations we put forward for QT-interval analysis for the purposes of quantifying QTVI in individuals with SCI. We also note that using a different methodology for QT-interval or QTVI analysis is not incorrect; however, these recommendations are meant to reduce the amount of methodological variability within the measure: (1) only use ECG data with the least amount of noise possible, (2) if using an automated program for measurement of the QT-interval, use an algorithm that uses the tangent method, as it results in less variability and thus will not overestimate the QTVI, and (3) use a minimum of 5-min ECG epoch, as shorter length may falsely overestimate the QTVI.

Accordingly, the QTVI in individuals with SCI is influenced by the length of ECG epoch and the method of measuring the QT-interval. One-minute epochs resulted in significantly higher QTVI values compared with 5- and 10-min epochs. In addition, the threshold method of measuring the QT-interval produced QTVI values that were significantly higher and less reproducible than those obtained by the tangent method.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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