REVIEW

Non-invasive electrocardiographic assessments of cardiac autonomic modulation in individuals with spinal cord injury

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Study design: Review.

Objectives: The purpose of this review is to discuss the utility of linear and non-linear heart rate variability (HRV) as well as the QT-variability index (QTVI) as indices of cardiac autonomic control in individuals with spinal cord injury (SCI).

Setting: Brock University, Department of Kinesiology, St Catharines, Ontario, Canada. Brock-Niagara Centre for Health and Well-being, St Catharines, Ontario, Canada.

Methods: Literature review.

Conclusion: Non-invasive markers determined from the electrocardiogram, such as linear and non-linear HRV, and, more recently, the QTVI have all shown some promise as indices of cardiac autonomic regulation in the SCI population. However, there are inconsistencies in the literature that call to question their true validity in this regard. Studies using pharmacological blockade, sympathetic manoeuvres and exercise suggest that both linear and non-linear HRV reflect cardiac parasympathetic activity, whereas their ability to quantify cardiac sympathetic outflow remains uncertain. The QTVI, although a novel method, correlates with both limbs of the autonomic nervous system and therefore may hold value as a measure of both cardiac sympathetic and parasympathetic activity in individuals with SCI; however, more research is required to confirm its utility.

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INTRODUCTION

Developing a method that quantifies cardiac autonomic activity in individuals with spinal cord injury (SCI) has been a topic of significant interest over the past two decades. Although there has been many advances, there remains a lack of consensus on a single, non-invasive measure of cardiac autonomic function in this population. SCI presents a unique model of autonomic dysfunction that is associated with a variety of impairments, including broncho-pulmonary dysfunction¹ reduced bladder control,² sexual dysfunction^{3,4} and gastrointestinal issues.⁵ In addition, autonomic dysfunction contributes both directly and indirectly to the increased risk for cardiovascular morbidity and mortality in the SCI population.^{6,7} In general, an injury above the 5th thoracic level results in reduced cardiac autonomic regulation due to reduced supraspinal control over preganglionic sympathetic neurons.⁸ In contrast, cardiac parasympathetic outflow is preserved as the vagus nerve is not interrupted by the SCI. Therefore, it is important to develop valid measures of cardiac autonomic activity to gauge the cardiac sympathetic function and to assess cardiac autonomic imbalances as they may have detrimental consequences.^{6,9,10}

Beat-to-beat control of HR is tightly regulated by autonomic activity;^{11,12} thus, the electrocardiogram may represent a non-invasive method to assess the cardiac autonomic function. The purpose of this review is, therefore, to discuss three electrocardiogram-based methods currently used to quantifying the cardiac autonomic function in individuals with SCI: heart rate

variability (HRV), non-linear heart rate dynamics and the QT-variability index (QTVI). Although these indices are used in clinical and investigative settings, the physiological correlates of some still remain equivocal, and the use of some may provide false results.¹³ As such, this review will discuss the physiological basis of these measures, their clinical applicability, their use in the SCI population and recommendations for their utility.

VALIDITY OF CARDIAC AUTONOMIC MEASURES

Heart rate variability

Heart rate demonstrates normally occurring oscillations in beat-to-beat variability that reflect modulation of sympathetic and parasympathetic inputs.¹⁴ Time- and frequency-domain techniques have been developed to utilise such HRV as an indirect marker of cardiac autonomic modulation. Time-domain HRV can be mathematically calculated through methods such as standard deviation of all RR intervals (SDNN), standard deviation of the averages of RR intervals from a 5-min segment and root mean square of differences between RR intervals.¹⁵ For analysis of frequency-domain HRV, successive RR intervals from an electrocardiogram are plotted against time to create a tachogram, which is then evaluated through spectral density analysis. In healthy humans, resting successive RR intervals oscillate around 2 main frequencies: low frequency (LF; 0.04–0.15 Hz; centre frequency: 0.1 Hz) and high frequency (HF; 0.15–0.40 Hz; centre frequency: 0.25 Hz).¹⁶

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Although studies using stress manoeuvres suggest that HF power reflects cardiac parasympathetic outflow, whereas LF represents sympathetic activity,¹⁷ other research has questioned the validity of these measures. Early results from Pomeranz and colleagues showed that atropine, a cholinergic blocker that reduces cardiac parasympathetic activity, almost completely abolished HF power and significantly reduced LF power during supine resting conditions.¹⁸ Likewise, while standing, LF power was significantly reduced after infusion of propranolol, a β -blocker that reduces cardiac sympathetic activity; however, LF power was further attenuated after additional atropine administration. These findings suggest that LF power is influenced by both cardiac sympathetic and parasympathetic activity, whereas HF power reflects the latter. Thus, the LF:HF ratio has been used for the estimation of cardiac sympathovagal balance.¹⁹ However, a recent review provides substantial evidence negating the use of LF power and the LF:HF ratio for their purported purposes,¹³ and these limitations are discussed in more detail below.

Non-linear heart rate dynamics

Cardiac sympathetic and parasympathetic interactions on HR are complex and are not always reciprocal or linear.^{20,21} This has stimulated interest in variability measures based on chaos theory and non-linear systems theory in the hopes of elucidating a marker that more accurately quantifies cardiac autonomic modulation and clinical risk. The non-linear measures most frequently used in physiological and clinical trials²² have been created to assess signal complexity or randomness (for example, approximate entropy, sample entropy), self-similarity (for example, detrended fluctuation analysis, power-law exponent) or fractal dimensions (for example, correlation dimension, Poincare plot). Evidence for weak relationships between linear and non-linear measures of HRV^{23–25} may suggest that non-linear measures offer unique or complimentary information regarding the modulation of HR.

The current data on non-linear measures are limited and conflicting with regard to its reproducibility and physiological basis. The reproducibility of non-linear measures over time has been both confirmed^{26–29} and refuted,³⁰ whereas the physiological background of non-linear HRV is also poorly understood due to conflicting results from studies employing autonomic blockade or stimuli. For example, measures of HR complexity while under vagal blockade have been shown to be unaffected,^{31,32} reduced²⁰ or almost completely abolished.^{33–35} Further, HR complexity is reduced by standing³⁶ and increased during low-intensity dynamic exercise²⁵ but unaltered during sympathetic blockade,³⁵ passive head-up tilt²⁵ or autonomic stress.³⁵ Differences in circulating catecholamine concentrations evoked by each stimulus have been proposed to explain divergent complexity responses,²⁵ but this concept requires further investigation. Examination of the short-term fractal scaling exponent (α_1) determined by detrended fluctuation analysis has also produced conflicting results. This measure, which quantifies the fractal-like correlation properties of the HR signal, has been shown to be reduced by norepinephrine infusion,³⁷ cold face immersion³⁸ or progressive dynamic exercise³⁶ and increased during standing,³⁶ low-intensity dynamic exercise,²⁵ passive head-up tilt²⁵ or cold hand immersion,³⁸ and unaffected³⁵ or increased^{25,32} by atropine administration. Nonetheless, similar to linear HRV, the majority of non-linear measures of HR appear to be impacted more by cardiac vagal than sympathetic modulation.

QT-variability index

The QTVI is a measure of beat-by-beat repolarisation variability that was initially developed for the purposes of assessing repolarisation lability³⁹ and as a prognostic tool for risk of ventricular arrhythmia in cardiac patients.⁴⁰ However, because the QTVI takes the QT and RR intervals into account (both intervals being influenced by autonomic activity),^{11,18,41} this measure has been proposed to hold some efficacy in assessing cardiac autonomic activity.

The QTVI has been shown to increase during conditions that augment cardiac sympathetic activity such as standing and isoproterenol infusion,⁴² autonomic stress⁴³ and hypertension,⁴⁴ as well as during situations that reduce vagal activity, such as cardiac autonomic neuropathy⁴⁵ and aging.⁴⁶ To date, the most compelling evidence for the physiological basis of the QTVI was an animal study by Piccirillo *et al.*⁴⁷ that demonstrated an inverse relationship between the QTVI and integrated vagal nerve activity during rest in dogs but a direct relationship between QTVI and integrated stellate ganglionic nerve activity during heart failure. Accordingly, such clinical and experimental studies suggest that the QTVI may reflect both cardiac sympathetic and parasympathetic activities, depending on the autonomic state of the individual.

CLINICAL UTILITY OF CARDIAC AUTONOMIC MEASURES

Heart rate variability

Several studies have demonstrated the prognostic value of HRV for identifying the risk of mortality in various cardiovascular populations. A reduction in time-domain HRV has been shown to be associated with an increased relative risk of all-cause mortality,⁴⁸ cardiac mortality⁴⁹ and sudden cardiac death^{7,50} in post-myocardial infarction patients. A reduction in HRV has also been shown in patients with hypertension⁵¹ congestive heart failure⁵² and diabetes.⁵³ With regard to frequency-domain HRV, both short-term⁵⁴ and long-term⁵⁵ recordings have shown to be useful for risk stratification and the prediction of sudden death in individuals with chronic heart failure.^{56–58} In addition, it has been reported that HRV has greater prognostic value than commonly used measures, such as left ventricular ejection fraction, wall motion abnormalities and exercise capacity.⁵⁹ Still, there is no widely accepted value for any frequency-domain measures of HRV that is used as a threshold of cardiac risk.

Non-linear heart rate dynamics

Accumulating evidence demonstrates a prognostic role for non-linear measures of HRV in identifying individuals at risk of cardiovascular events or mortality. This work has focused primarily on fractal-like correlation or self-similarity measures of HR behaviour, such as power-law slope and α_1 . These measures have demonstrated the ability to predict mortality in patients following myocardial infarction,⁵⁸ better than^{60,61} and independent of⁶² linear HRV. Further research has established a similar role for predicting vulnerability to ventricular tachycardia,⁶³ ventricular fibrillation,⁶⁴ arrhythmic and non-arrhythmic cardiac death,⁶¹ nonfatal coronary events⁶⁵ and heart failure admissions⁶⁶ in post-myocardial infarction patients. Premature mortality in other clinical populations is also associated with reduced measures of complexity.^{67,68} The utility of non-linear measures of HR dynamics is further emphasised by their ability to predict increased risk of cardiovascular causes of death better than traditional time- and frequency-domain indices in a random population of elderly individuals.⁶⁹

QT-variability index

Several investigations have reported the ability of the QTVI to predict risk of sudden cardiac death in clinical populations. A higher QTVI value is suggestive of greater repolarisation variability, which is indicative of a less stable myocardium, and thus, a greater risk for arrhythmogenesis. Conversely, a lower value is indicative of a more stable myocardium. The QTVI has been reported to be elevated in several conditions, including dilated cardiomyopathy³⁹ hypertension,⁴⁴ heart failure,⁷⁰ anxiety and depression.⁷¹ In addition, Atiga *et al.*⁴⁰ reported that the QTVI was a sensitive predictor of future arrhythmia and a more accurate predictor of sudden cardiac death compared with spatial QT dispersion, HRV and ejection fraction in patients with heart disease. The prognostic value of QTVI for cardiac mortality has also been demonstrated in asymptomatic heart failure patients⁷² and in the general population.⁷³ Moreover, the QTVI was shown to be a useful tool in stratifying severities of cardiac autonomic neuropathy diabetic patients.⁴⁵

EFFECT OF SCI ON INDICES OF THE CARDIAC AUTONOMIC FUNCTION

Heart rate variability

HRV analysis has been used in the SCI population to estimate cardiac autonomic integrity and, to a lesser extent, cardiovascular risk. Although HRV has been shown to be reliable and reproducible in individuals with SCI,⁷⁴ the physiological basis of this measure remains somewhat equivocal, especially pertaining to the interpretation of the LF component. For example, earlier work by Inoue *et al.*⁷⁵ suggested that LF power corresponds to cardiac sympathetic outflow, as individuals with complete tetraplegia failed to show any sign of it. Contradicting work by Koh *et al.*⁷⁶ demonstrated that LF power reflects cardiac vagal outflow, as atropine administration abolished LF power in individuals with SCI. Guzzetti and colleagues showed that half of their cohort with complete tetraplegia exhibited a detectable LF component, suggesting that, in some individuals, LF power corresponds to sympathetic spinal rhythmicity.⁷⁷ Moreover, Inoue *et al.*⁷⁸ reported that the physiological correlates of LF power in individuals with tetraplegia may be different from those in able-bodied individuals and that LF power in individuals with SCI is simply a reflection of reflex sympathetic outflow caused by stimuli from the periphery (bladder or bowel distension or spasms from the limbs). In conclusion, these conflicting results suggest that the LF power in individuals with SCI reflects cardiac sympathetic innervation,⁷⁵ cardiac vagal innervation,⁷⁶ spinal rhythmicity⁷⁷ or reflexive sympathetic outflow.⁷⁸

Without doubt it is difficult to discern the physiological correlates of the LF component of HRV in individuals with SCI. Some of the confusion in this area may be attributed to the early assumptions that individuals with complete sensorimotor injuries are also autonomically complete, which have since been shown as incorrect.⁷⁹ In addition, the studies described above demonstrate a wide range of inter-participant variability that may obscure mean findings. Therefore, the physiological basis of LF power cannot be determined by these previous studies.

Notwithstanding the limitations of the LF:HF ratio as a measure of sympathovagal balance,¹³ the concomitant reduction in HF power alongside LF power following SCI has been suggested to be a result of the body's attempt to maintain cardiac sympathovagal modulation.^{80,81} Other investigations have suggested that the reduced HF power may be due to altered cardiac cholinergic receptor response to vagal outflow. For example, Wecht *et al.*⁸² reported comparable degrees of HF withdrawal among individuals with tetraplegia, paraplegia and able-bodied controls in response to head-up tilt. However,

the subsequent increase in HR was blunted in the group with tetraplegia, which may be due to altered sino-atrial node response to vagal withdrawal. Further, Wecht *et al.*⁸³ examined cardio-autonomic response to the cold face test, a stimulus that increases vagal activity, in young able-bodied participants, older able-bodied participants and individuals with SCI.⁸⁴ Individuals with SCI and older adults demonstrated a similar attenuation in HF response to the cold face test compared with young participants, suggesting accelerated cardiac vagal aging in young healthy individuals with SCI. Although both younger and older participants showed an expected bradycardia during the test, those with SCI presented a paradoxical increase in HR, which was attributed to either the SCI *per se* or the profound physical inactivity associated with SCI.⁸³ Alternatively, this paradoxical increase in HR could also be attributed to a potential impairment in the accentuated antagonism response,⁸⁵ in which there is a reduction in the normal parasympathetic dominance over the effects produced by the simultaneous increase in sympathetic outflow during the cold face test.⁸⁶

These observations suggest that a possible alteration in sino-atrial nodal response to vagal activity could be accountable for the reduced HF power reported following SCI. However, another possible explanation for the reduced HF power following SCI is the profound physical inactivity associated with this population. This is evidenced by studies demonstrating increased HF power following a period of exercise⁸⁷ and better HF dynamics in physically fit SCI individuals compared with their sedentary counterparts.^{88,89} These reports strongly suggest that the previously observed reduction in HF power^{90,81} is not a compensatory mechanism to maintain sympathovagal balance but may be a reflection of the severe physical inactivity in this population.⁹¹

One of the conditions for the validity of HRV as a measure of the cardiac autonomic function is that it should change significantly after administration of autonomic blockade.⁹¹ Results from our laboratory⁹² showed that, during cardiovascular stress, metoprolol administration resulted in variable amounts of reduction in the LF:HF ratio (40–73%), whereas atropine completely abolished HF power during rest. These results confirm that, in individuals with SCI, the HF power corresponds to cardiac vagal outflow; however, because of the variable and incomplete reduction in the LF:HF ratio in response to metoprolol, its association with cardiac sympathetic regulation is unclear.

Taken together, two conclusions can be drawn from the aforementioned investigations. First, the HF component of HRV seems to be a valid measure of cardiac vagal activity in individuals with SCI. Second, it is still unclear what the LF component of HRV corresponds to in individuals with SCI due to conflicting results.^{75–78} Likewise, the most recent investigation regarding the physiological correlates of HRV after SCI showed that the LF:HF response to sympathetic blockade is considerably variable within individuals with incomplete SCI.⁹² This lack of consensus on the validity of the LF power in individuals with SCI makes it difficult to delineate what it truly represents, and using it in research or clinical investigations may lead to spurious conclusions.

Non-linear heart rate dynamics

A limited number of investigations have used non-linear HRV methods to investigate the effects of SCI on cardiac autonomic modulation. Millar *et al.*³⁵ confirmed a similar role for cardiac vagal modulation in the genesis of HR complexity in individuals with incomplete tetraplegia and able-bodied controls. Measures of non-linear heart rate dynamics were similar between individuals with SCI and able-bodied controls at baseline and in response to sympathetic blockade with metoprolol and vagal blockade with atropine.

In response to a cardiovascular stress, baseline HR complexity was lower in those with SCI, but vagal blockade again reduced overall complexity in both groups and ameliorated these group baseline differences. These results suggest that HR complexity is similarly modulated primarily by cardiac parasympathetic activity in both SCI and AB populations. Non-linear measures of HR complexity also demonstrate excellent intra- and inter-visit reproducibility (greater than frequency parameters) in individuals with tetraplegia.²⁹

Non-linear measures of HR dynamics have shown a unique ability to uncover novel information not obtained by traditional linear HRV methods. Merati *et al.* demonstrated that non-linear measures were sensitive to differences in the SCI lesion level, with complexity lower in individuals with SCI lesions between T5-L4 than able-bodied controls and measures of self-similarity higher in those with SCI (T5-L4 or C6-T4) than able-bodied controls. These differences were not detected using traditional time- or frequency-domain measures of HRV.⁹³ More recently, Zamuner *et al.* reported that only non-linear measures of complexity were able to discriminate between those with paraplegia who are sedentary and those who are active or able-bodied controls.⁸⁸

Two studies have employed non-linear measures of HR dynamics to examine the acute or chronic response to a stressor in individuals with SCI. Agiovlasitis *et al.*⁹⁴ reported that collegiate athletes with paraplegia had lower HR complexity at baseline and in response to a 2-min bout of static handgrip than similarly active able-bodied controls, with no differences in HRV between groups. Millar *et al.* found alterations in non-linear measures of HR dynamics following 4 weeks of body-weight supported treadmill training, but not head-up tilt training, in individuals with SCI, whereas HRV measures were unchanged with both interventions.⁹⁵ Collectively, these results demonstrate that non-linear measures of HR dynamics are sensitive to smaller changes in heart rate behaviour and/or detect unique information not quantified by linear methodologies. These methods may be useful in detecting dysfunction of the autonomic nervous system present in individuals with SCI. It also seems that non-linear measures of HR dynamics mainly reflect cardiac parasympathetic activity in individuals with SCI, as shown by studies employing autonomic blockade³⁵ and exercise training.⁹⁵ However, similar to linear HRV, the ability of non-linear measures to assess cardiac sympathetic activity in individuals with SCI has yet to be validated.

QT-variability index

Because of the QTVI being a relatively novel method for assessing the cardiac autonomic function, literature regarding its use after SCI is relatively scarce. In the first study to investigate the QTVI in individuals with SCI, La Fountaine *et al.* compared resting QTVI values between able-bodied controls and individuals with tetraplegia, high paraplegia and low paraplegia. Results showed that all SCI groups had significantly elevated QTVI values compared with the able-bodied group, whereas there were no difference between any of the SCI groups. In addition, QTVI showed a negative correlation with HF power in all SCI groups, whereas LF power was negatively correlated with the QTVI only in the groups with sympathetic dysfunction (tetraplegia and high paraplegia).⁹⁶ A possible explanation for the comparable QTVI values among the SCI groups is that the SCI participants were not compared based on the amount of autonomic function. This was addressed by Ravensbergen *et al.*, who showed that the elevated QTVI in individuals with SCI was related to both the level of injury and autonomic completeness, as those with injuries above T5 and/or autonomically complete injuries exhibit higher QTVI values compared with able-bodied controls.⁹⁷

Although these cross-sectional studies^{96,97} provide evidence for elevated QTVI in individuals SCI, they do not specifically discern the physiological basis of the QTVI following SCI. Accordingly, a recent study conducted by our group⁴³ investigated the contribution of cardiac autonomic activity to the QTVI in individuals with incomplete tetraplegia in response to cardiovascular stress and autonomic blockade. Results showed that, in both the able-bodied and SCI groups, the QTVI significantly increased during cardiovascular stress and subsequently decreased after Metoprolol infusion during the cardiovascular stress. Further, atropine significantly increased the QTVI during resting supine conditions. These results suggest that, in autonomically incomplete injuries, the QTVI may reflect cardiac sympathetic activity during times of sympathetic arousal and inversely reflects cardiac vagal activity during vagal dominance. Although it is clear that the QTVI reflects cardiac autonomic activity and may hold value as a valid index of cardiac autonomic function in individuals with SCI, all of the knowledge obtained about this measure is from cross-sectional studies^{96,97} or experimental studies with small sample sizes.⁴³ Therefore, further large-scale, longitudinal studies are warranted to confirm these results, as this method may hold clinical and physiological importance.

CONCLUSION

The physiological basis of these non-invasive measures must be well understood by investigators and clinicians who wish to employ them for assessing the cardiac autonomic function in individuals with SCI. Measures such as HF power, time-domain HRV, non-linear HRV (complexity) and QTVI may be used to assess the cardiac vagal function in SCI. In contrast, with the potential exception of the QTVI, the electrocardiogram-based measures discussed in this review are limited in their ability to assess the cardiac sympathetic function in individuals with SCI. Accordingly, researchers should refrain from using LF power and the LF:HF to gauge cardiac sympathetic activity in this population. Furthermore, the QTVI may hold promise as an index of both cardiac sympathetic and parasympathetic activity after SCI, but further research is required to confirm the efficacy of this tool.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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