Research Article

Heart Rate and QT interval Variability in Multiple Sclerosis: Evidence for Decreased Sympathetic Activity

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Abstract

Decreased beat-to-beat heart rate variability (HR) and increased beat-to-beat QT interval variability are associated with significant cardiovascular mortality. The aim of this study was to compare beat-to-beat HR and QT variability among patients with multiple sclerosis (MS) and normal controls to investigate cardiac autonomic function. We investigated spectral measures of HR and QT interval variability in 13 patients with MS and 16 normal controls during sleep. Our results showed modest but significant decreases in HR total power (TP: 0-0.5 Hz), VLF power (very low frequency power: 0-0.04 Hz) and LF power (low frequency: 0.14-0.5 Hz) in patients with MS compared to normal controls. QT interval TP, VLF, LF and HF powers were all highly significantly lower ($p<0.00001$) in MS patients compared to normal controls. QTvi, a normalized index of QT variability corrected for mean QT interval divided by heart rate variability corrected for mean heart rate was significantly lower in MS patients. There was a significant inverse correlation between fatigue scores and QT TP, VLF and LF powers ($p=0.03$ to $0.01$). These findings suggest a decrease in cardiac sympathetic function more than a decrease in vagal function in some patients with multiple sclerosis, and decreased sympathetic function may be related to fatigue in these patients.

Keywords: Multiple Sclerosis, Sympathetic, Spectral, Heart Rate Variability, QT variability, Sleep, fatigue

Multipl Sklerozda Kalp Atımı ve QT Aralığı Değişkenliği: Azalma Sempatik Aktivite İcin Bir Kanıt

Özet

Kalp atımı aralari değişkenliklerinin(HR) azalması ve kalp atım aralari QT aralığı değişkenliklerinin artışı önemli ölçüde kardiovasküler mortalite ile birliktelik gösterir. Bu çalışmamın amacı, multipl sklerozlu hastalar ile normal kontroller arasında kardiak otonomik işlevi, kalp atım aralari HR ve QT değişkenliklerini karşılaştırmaktır. Normal kontrollere kıyasla MS hastalarında HR toplam gücü (TP:0-0,5 Hz), VLF gücü (çok düşük frekans gücü: 0-0,04 Hz) ve LF gücü (düşük frekans: 0,14-0,5 Hz) spektral ölçümlerini inceledik. QT aralığı TP, VLF, LF ve HF güçleri MS hastalarında normal kontrollere göre önemli ölçüde düşük bulundu ($p<0,00001$). QT değişkenliğinin bir normalize edilmiş göstergesi olan Qtvi ortalamada QT aralığı HR değişkenliğine bölündüğünde ve ortalama kalp atımı oranı MS hastalarında önemli ölçüde düşük bulundu. Yorgunluk skorları ile QT TP, VLF ve LF güçleri arasına önemli ölçüde ters bir ilişki saptandi ($p=0,03$ ten $0,01e$). Bu bulgular bazı MS hastalarında, vagal fonksiyon azalmasından ziyade kardiyak sempatik işlevde bir azalmayı düşündürdü, ve azalmış sempatik işlev bu hastalarda olasılıkla yorgunluğa bağlı idi.

Anahtar Kelimeler: Multipl Skleroz, Sempatik, Tayfıa ilgili, Kalp atım değişkenliği, QT değişkenliği, Uyku, yorgunluk
INTRODUCTION

Multiple Sclerosis is a progressive and disabling neurological condition associated with documented dysfunction of the autonomic nervous system (ANS). Studies have shown dysfunction of vagal as well as the sympathetic system (2,19,20,22,24,26,32,39,40,61). ANS dysfunction in MS has a known association with disorders of micturition, impotence, sleep, orthostatic intolerance, and may also have an association with excessive fatigue, and increased susceptibility to stress.

Decreased heart rate (HR) or heart period (HP) variability is an important noninvasive index of cardiac mortality (11,30). Several studies have shown the importance of HR variability to analyze normal and abnormal cardiovascular physiology (1,35,36,38,50). Linear measures such as spectral analysis decompose the human HR time series signal into very low frequency (VLF: 0-0.04Hz), low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.5 Hz) components. HF power is related to respiratory sinus arrhythmia (RSA) and thus to cardiac vagal function; LF power to baroreceptor mechanisms mediated dually by sympathetic and parasympathetic systems, and VLF power, to peripheral vascular and thermoregulatory mechanisms (1,33,44). It has been shown that HR variability increases during sleep, especially the HF component due to an increase in cardiac vagal function (58).

On the surface electrocardiogram (ECG), QT interval reflects time for repolarization. Several studies have shown a relationship between prolonged QTc (QT interval corrected for heart rate) and life-threatening arrhythmias (27,48). Recent literature also implicated mental stress and abnormal repolarization in serious arrhythmias (10,47,49). Likewise increased QT variability in a single lead are associated with sudden cardiac death and increased cardiac morbidity (4,5,6,9,12,16,41).

We recently found that patients with panic disorder and depression are more sensitive to yohimbine (51) and have decreased HR variability and higher QT variability (54,55,60) and anxiety is reportedly associated with increased risk for cardiovascular mortality (15,28). Increased QT variability is reportedly associated with symptomatic patients with cardiomyopathy and sudden cardiac death (4,5,9). We have shown that there is an increase in beat-to-beat QT variability associated with intravenous isoproterenol and oral pemoline, a sympathomimetic agent (42,43,53). Therefore, these noninvasive measures may prove valuable to study cardiac vagal and sympathetic function and the effect of drugs on these measures.

Multiple sclerosis is quite frequently associated with various degrees of depression (3,25,34) and depression can be associated with increased QT variability and increased risk for cardiovascular mortality (14,23,60). In this preliminary study, we compared HR and QT variability measures of MS patients to those of age-matched normal controls. We hypothesized that sleep HR HF power will be significantly lower in the MS group. As some of the literature suggests that there may be decreased central sympathetic function in MS patients, we also hypothesized that QT variability measures, especially QT spectral powers and QTvi will be lower in these patients compared to controls.

METHODS

Subjects: These studies were approved by the Institutional Board at the Wright State University School of Medicine, Dayton, OH, USA.
Normal controls were healthy and had no significant history of any physical illness and the routine blood chemistry and urinary analyses were normal. The routine ECG (electrocardiogram) was also normal. Eighteen controls (5 males, 13 females) and 13 with MS (4 males, 9 females) were matched for age for HR and QT interval variability comparisons.

Subjects with MS: Table 1 shows the descriptive data on all these patients. This includes their height and weight, medications they were on, and their scores on the following scales.

1. Expanded Disability Status Scale (EDSS) (31): This documents the level of impairment related to signs and symptoms present, as well as for serial tracking of disease progression. However, this does not provide objective criteria to assess function.

2. Kurtzke Functional Systems Scores (31): This scale assigns a numerical value to the level of impairment during neurological examination to each of the systems.

3. Modified Fatigue Impact Scale (21,46): Subjects are asked to answer 21 questions regarding their fatigue during the 4 weeks prior to their evaluation. The maximal score is 84.

Medications that were received by MS patients: Table 1 lists all these medications and for some patients the list was not available. It should be noted that none of the patients were on any cardiac medications such as beta-blockers or anti-hypertensive drugs.

Recording of ECG: Electrocardiogram (ECG) was recorded in patients with multiple sclerosis during a standard nocturnal polysomnogram using Grass model 78 amplifier, interfaced with a Grass Braintree digital recording system using Grass Gamma Software (version 2). We used the average of first 4 epochs of 256 seconds of sleep data during a four-hour period for the analyses in this study so that it would be comparable among the two groups. We used a peak detection algorithm to identify the R-R intervals (in milliseconds) from the ECG.

Data from normal controls: These data were obtained form our previous studies on normal controls using 24-Holter ECG. The details of the data collection have been described in detail in our previous reports (56,57,58). We used the average of 4 epochs of 256-second segments during a four-hour sleep period.

Beat-to-beat variability of the QT interval: All these analyses were conducted on 4 epochs of 256-second segments of data sampled at 500 Hz. This QT variability algorithm has been described by Berger et al in detail and has been used by his and our groups in previous studies (5,6,9,53,56,60). This was performed on a PC using Solaris Desktop Unix software (Sunsoft, Mountainview, CA, USA). This uses a graphical interface of digitized ECG where the time of the ‘R’ wave is obtained using a peak detection algorithm. Then the operator provides the program with the beginning and the end of the QT wave template. This algorithm finds the QT interval for each beat using the time-stretch model. If the operator chooses a longer QT template, all the QT intervals will be biased accordingly. This algorithm’s purpose is mainly to study QT variability and not the mean QT. However, we also calculated QTc using Bazett’s formula to correct the mean QT for the R-R interval.

The HR (beats per minute: bpm) time series were sampled at 4 Hz using the technique of Berger et al (7). This signal maintains amplitude equal to the reciprocal of the current R-R interval, for the duration of that R-R interval. It also works as an antialiasing filter. It behaves as a low-pass filter, passes very little power beyond the Nyquist rate. It preserves all the frequencies up to ¼th of the sampling rate. It does not affect the information up to 1 Hz as we sample the signal at 4 Hz. We
used HR time series free of ventricular premature beats and noise. The data were then detrended by using the best-fit line prior to the computation of spectral analyses.

Spectral Analyses: Beat-to-beat HR time series of 256 seconds of data at 4 Hz (1024 points) was subjected to spectral analyses and the power spectrum was computed with the Blackman Tukey method \(^{(8,60)}\). The powers were integrated in the bands of VLF, LF and HF.

Statistical Analysis: We used BMDP statistical package (Berkley, California, U.S.A.) to perform all the analyses. We used student ‘t’ tests to compare the two groups for each of the HR and QT variables. We used a probability value of 0.05 for significance and all tests were two-tailed. We also performed correlational analyses between the MS disability scales and HR-HF power and QT powers, and QT\textsuperscript{vi}.

**RESULTS**

Table 1 shows the demographic data and the scores on K-P; K-C; K-S; K-B Kurtzke-Pyramidal, Cerebellar, Sensory and Bowel & Bladder Scores). Only subjects 3 and 8 had Brainstem Scores (2 and 1). These scores indicate the severity of autonomic dysfunction.

There was no significant difference in age among the groups. Table 2 shows the mean±SD for each variable and the significance of the difference between patients with MS and normal controls. Heart rate TP and VLF and LF powers were significantly lower in MS patients compared to controls. Heart rate LF/HF ratios were not significantly different between the two groups. QT variability measures were all significantly different between MS patients and the controls including a higher coherence of QT-HR-LF and QT-HR-HF in the patients with MS. Mean QTc was significantly lower in MS patients compared with normal controls.

**Table 1. Descriptive Data on Patients with Multiple Sclerosis**

<table>
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<tr>
<th>Subject</th>
<th>Ht. (Cm)</th>
<th>Wt. (Kg)</th>
<th>EDSS</th>
<th>MFIS</th>
<th>K-P</th>
<th>K-C</th>
<th>K-S</th>
<th>K-B</th>
<th>AH</th>
<th>AC</th>
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<td>3</td>
<td>2</td>
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<td>1</td>
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<td>Amitriptyline, Gabapentin</td>
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<tr>
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<td>193</td>
<td>87</td>
<td>2.5</td>
<td>69</td>
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<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Amantadine</td>
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</table>
Table 2. Sleep HR and QT variability Measures of Normal controls and Patients with Multiple Sclerosis

<table>
<thead>
<tr>
<th>Sclerosis</th>
<th>Normal Controls</th>
<th>Patients with MS</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>42.5±7.3</td>
<td>42.3±7.9</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>HRm (bpm)</td>
<td>63.5±6.8</td>
<td>70.2±18.6</td>
<td>1.7</td>
<td>NS</td>
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<td>HR-TP</td>
<td>3.2±0.5</td>
<td>2.6±0.9</td>
<td>2.4</td>
<td>0.03</td>
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<tr>
<td>HR-VLF</td>
<td>2.6±0.7</td>
<td>1.8±0.9</td>
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<td>0.01</td>
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<td>HR-LF</td>
<td>2.1±0.4</td>
<td>1.4±1.1</td>
<td>2.2</td>
<td>0.04</td>
</tr>
<tr>
<td>HR-HF</td>
<td>1.0±0.8</td>
<td>0.5±1.28</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>HR-LF/HF</td>
<td>3.3±2.2</td>
<td>3.2±1.9</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>452±23</td>
<td>436±22</td>
<td>3.1</td>
<td>0.05</td>
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<tr>
<td>QT-TP</td>
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<td>QT-VLF</td>
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<td>6.7</td>
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<td>QT-LF</td>
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<td>QT-HF</td>
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<td>COH-TP</td>
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<td>NS</td>
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<td>COH-LF</td>
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<td>0.66±0.14</td>
<td>8.5</td>
<td>0.00001</td>
</tr>
<tr>
<td>COH-HF</td>
<td>0.21±0.06</td>
<td>0.63±0.20</td>
<td>8.6</td>
<td>0.00001</td>
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<tr>
<td>QTvi</td>
<td>-1.43±0.24</td>
<td>-1.69±0.34</td>
<td>2.5</td>
<td>0.02</td>
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</table>

Figure 1: Shows the inverse correlations between Modified Fatigue Impact Scale and QT spectral powers (Total: 0-0.5 Hz; VLF: 0-0.04 Hz and LF: 0.04-0.15 Hz). TP was used with and without correction for the mean QT interval. VLF and LF were corrected for mean QT interval. The correction for mean QT interval did not make any difference at all in the results. Correction was made by Power divided by square of mean QT interval.
Correlations: There were strong inverse correlations between MFIS and QT TP, QT VLF and QT LF powers (corrected and uncorrected for mean QT) (-0.6 to −0.7) (Figure 1). Figure 2 shows a significant inverse correlation between QTvi and bowel and bladder involvement on Kurtzke neurological impairment scale. QT total power and LF power also correlated inversely with EDSS (R=0.48; P=0.07), with a trend toward significance. There were no significant correlations between HR HF power and any of the disability scales.

DISCUSSION

Our study did not show a decrease of sleep HF power in MS patients, which suggests the decrease in cardiac vagal function might depend up on several factors associated with this illness including the site of the lesions. On the other hand, a highly significant decrease in QT variability measures suggests a decrease in sympathetic function as we have shown that QTV increases during standing and increases during intravenous isoproterenol administration, and also with pemoline (42,43,53). This finding is in line with several studies on multiple sclerosis showing impaired sympathetic skin response, orthostatic dizziness and decreased rise of BP during handgrip (2,19,20,22,24,32,40,61). The association of fatigue with MS may also be due to the impaired orthostatic BP regulation due to decreased sympathetic function (29). One study suggests that the autonomic dysfunction may be of spinal cord origin (18). In comparison to our previous studies on patients with anxiety, it appears that there is a more significant difference between patients with panic disorder and MS patient in regards to the QT variability measures. This is due to the fact that this group is associated with an increased QT variability compared to controls in our studies.

Even though this is a small sample, the strong inverse association between MFIS and the QT powers suggests that the lower the sympathetic function the more severe the fatigue. Likewise, QTvi, which also increases during sympathetic challenges (42,43,53,60), is inversely related to the impairment of bowel and bladder function. We speculate that this most likely is due to the relatively predominant peripheral cholinergic function as there is a profound decrease in sympathetic function. Likewise EDSS was also negatively related to QT variability (a trend toward significance) and this clearly deserves further systematic investigation correlating these measures with MRI (magnetic resonance imaging) studies of the brain. However, due to the small sample size, all these interpretations should be viewed with caution.

Effect of medications on HR and QT variability measures: It is possible that antihistamines, anticholinergics and benzodiazepines can decrease HR variability, especially the HF power but may in fact, increase QTvi and not decrease it. Even sympathomimetic drugs should only increase QTvi and thus the profound decrease in QT variability measures in these patients may not be explained by any medications they were taking. Beta-blockers can decrease QTvi but to our knowledge none of these patients were receiving any beta-blockers.
There is substantial evidence suggesting that MS is associated with different degrees of autonomic dysfunction and our findings support a decrease in cardiovascular sympathetic function in patients with MS. This may make these patients more supersensitive to any sympathetic stimulus and exacerbate the illness process (37). This also may lead to some new interventions to make these patients less vulnerable to sympathetically mediated stress if these novel indices are studied systematically and correlated with the site of the lesion and progress of the disease. Finally this relationship suggests that cardiovascular mortality and serious ventricular arrhythmias need to be studied further in these patients both in the lab during supine and standing postures and with 24-hour Holter ECG along with MRI of the brain.

There are some negative studies also in regards to the sympathetic skin response (13). In this study, we found a decreased QTc in patients with multiple sclerosis compared to controls and this is not in agreement with a recent report by de Seze et al (17), showing prolonged QTc. In their study, QTc correlated with a reduction in spinal cord area. These differences should be addressed in well-designed studies with data on various degrees of severity of lesions in multiple sclerosis. Future studies should be designed to relate cardiovascular abnormalities to CNS lesions. In addition, several new nonlinear analyses of heart rate and other ECG interval time series should be applied in future studies, which may be more sensitive indicators of disease progression (45,52,53,59).

Limitations: It would have been more ideal to have supine and standing or tilt data to examine the effects of postural challenge on HR and QT variability measures. It may also have been important to have all 24-hours of ECG so that sleep and wake data could have been compared. We did not have ratings on depression and this may be an important factor in relation to the measures studied.

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