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Impaired heart rate variability as a marker of cardiovascular autonomic dysfunction in multiple sclerosis

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Abstract

Multiple sclerosis (MS) can cause alterations in autonomic cardiovascular functions. We aimed to investigate the correlation of disease activity and disability with heart rate variability (HRV) of cardiovascular autonomic dysfunction (CAD) demonstrated by 24-h Holter monitorization. Thirty-four patients with clinically active relapsing-remitting MS, age 33.8 ± 7.6 years, were studied. Twenty healthy volunteers served as controls. The time domain long-term HRV parameters were recorded by a digicorder recorder calculated by ambulatory electrocardiograms.

Variabilities in time domain were lower in the MS patients: SDNN (standard deviation of all R-R intervals, p = 0,019), SDANN (standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recordings, p = 0,040), RMSSD (the square root of the mean of the sum of the squares of differences between adjacent R-R intervals, p = 0,026), HRVM (mean of the SDNN in all the 5-minute intervals, p = 0,029), HRVSD (standard deviation of the SDNN in all the 5-minute, p = 0,043).

These results suggest that MS causes CAD manifesting as long-term HRV abnormalities. This illness seems to cause a dysfunction in parasympathetic cardiovascular tone. Depressed HRV parameters are independent from the clinical findings, but the illness progression partially seems to provoke a decrease in such parameters.

Key words: Multiple sclerosis; heart rate variability; autonomic dysfunction; Holter monitoring, disability.

Introduction

Multiple sclerosis (MS) frequently causes disturbances of autonomic functions (Flachenecker *et al*., 1999; McDougall & McLeod, 2003). Cardiac autonomic dysfunction (CAD) is frequently observed in patients with MS, but the evolution over time and the relationship to clinical characteristics are not yet established (Flachenecker *et al*., 1999). Cardiovascular reflexes were extensively investigated in MS through classical cardiovascular autonomic tests (Senaratine *et al*, 1984; Sterman *et al*., 1985; Pentland & Ewing, 1987; Nordenbo *et al*., 1989; Anema *et al*., 1991; Vita *et al*., 1993) and, recently, by heart rate variability (HRV) analysis in some isolated periods (Monge-Argiles *et al*., 1998). The varied results of these works and their limited capacity to assess the respective role of the sympathetic and parasympathetic components have led to the search for other noninvasive tests (Monge-Argiles *et al*., 1998; Saari *et al*., 2004).

In MS, HRV analysis has been studied in the supine position (Frontoni *et al*., 1996) and during sleep (Giubilei *et al*., 1996), whereas many authors recommended the ambulatory 24-h ECG monitoring as the elected way of recording (Yotsukura *et al*., 1995; Yamasaki *et al*., 1996; Spallone *et al*., 1996). The variations in heart rate may be evaluated by a number of methods. Perhaps the simplest to perform are the time domain measures. In these methods, either the heart rate at any point in time or the intervals between successive normal complexes are determined (Malik, 1996). In recent years, Saari *et al*. (2004) noted that MS results in both reduced HRV and decreased blood pressure reactions indicating disturbed cardiovascular regulation. Mahovic and Lacusid (2006) suggested that autonomic control of heart rate depends on disease duration in MS patients and a longer duration of disease led to progressive impairment of cardiac autonomic balance in patients with MS.

Our aim was to investigate the correlation of disease activity and disability with composite scores of CAD in a cross-sectional study of patients with MS. HRV detected by ambulatory 24-h Holter

monitoring in experimental conditions, was used for assessment the time domain parameters.

Methods and Materials

We analyzed the long-term HRV in time domain in 34 patients MS (14 male and 20 female; mean ± SD age, 32 ± 8.12 years) with definite MS in a stable phase, and 20 age and sex-matched healthy control subjects (12 male and 8 female; mean 28.3 ± 11.2 years). The disability scores were calculated according to expanded disability status scale (EDSS) (Kurtzke, 1983). The mean number of attacks was 3.59 ± 1.88. Twenty-four-hour ambulatory electrocardiograms were recorded by a Del Mar Avionics 483 digicorder recorder (Irvine, CA). These recordings were analyzed with a PC by using special computer program provided by the manufacturer. Abnormal beats, significant pauses, and areas of artifact were automatically and, at later stage manually identified and discarded. Only normal-to normal beats were considered for analysis. After an overnight smoking, tea, coffee, and alcohol deprivation, each of the patients and controls underwent a neurological examination and the following ambulatory Holter monitoring. The tests started at 9.00 at a.m.

The following time domain parameters of HRV were calculated: 1) SDNN (standard deviation of all R-R intervals), 2) SDANN (standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recordings), 3) RMSSD (the square root of the mean of the sum of the squares of differences between adjacent R-R intervals), 4) HRVM (mean of the SDNN in all the 5-minute intervals), 5) HRVSD (standard deviation of the SDNN in all the 5-minute).

From the series of instantaneous heart rate sort cycle intervals, particularly those recorded over longer periods, traditionally 24 hours, more complex statistical time domain measures, can be calculated. These may be divided into two classes: (1) those derived from direct measurements of the NN intervals or instantaneous heart rate and (2) those derived from the differences between NN intervals. These variables may be derived from analyses of the total ECG recording or may be calculated using smaller segments of the recording period. The simple variable to calculate is the standard deviation of the NN intervals (SDNN), that is, the square root of variance. Since variance is mathematically equal to the total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. Other commonly used statistical variables calculated from segments of the total monitoring period include SDANN, the standard deviation of the average NN intervals calculated over short periods, usually 5 minutes, which is an estimate of the changes in the heart rate due to cycles longer than 5 minutes, and the SDNN index, the mean of the 5-minute standard deviations of NN intervals calculated over 24 hours, which measures the variability due to cycles shorter than 5 minutes. The most commonly used measures derived from interval differences include RMSSD the square root of the mean squared differences of successive NN intervals, NN50, the number of interval differences of successive NN intervals NN50, the number of interval differences of successive NN intervals greater than 50 ms, and pNN50 the total number of NN intervals. All of the measurements of short–term variation estimate high-frequency variations in heart rate and thus are highly correlated (Malik, 1996).

The relationship between CAD and disease-related parameters such as the, gender, age, EDSS, disease duration and the mean number of attacks were investigated. Patients with cardiac disorders, or any disease other than MS (in the patient group) were excluded. At the time of the study, no patients or controls were receiving drugs known to affect the autonomic nervous system. Pearson correlation analysis, Fisher's Exact Test ($\chi 2$) and student t test were used in statistical analysis. All tests were considered significant when $p < 0.05$.

Results

The demographic and clinical features of the patients are given in Table 1.

HRV parameters of the patients and controls are shown in Table 2. According to these results, all of the parameters of long-term HRV, the values of SDNN, RMSSD, HRVM, HRVSD, SDANN were much more decreased in the patient group than the controls. Variabilities in time domain were lower in most affected MS patients compared to controls. The differences in all parameters were more significant statistically in MS group: SDNN ($p = 0{,}019$), SDANN ($p = 0{,}040$), RMSSD ($p = 0{,}026$), HRVM ($p = 0{,}029$) and HRVSD ($p = 0{,}043$).

We did not find a significant difference between men and women among the different age groups. The correlation analysis did not show any correlation between duration of disease, the mean number of MS attacks, the age at onset of the disease and long-term HRV parameters. As regards the assessment of MS subgroups, as shown in Table 3, there was no significant difference between the groups of clinical types of MS patients ($p > 0.05$). However, the patients with RR MS have relatively higher mean values of SDNN, RMSSD, HRVM and HRVSD than

Table 1

Demographic and clinical features of the cases

	Value (n = 34)
Gender, n (%)	
Male	14 (41%)
Female	20 (59%)
Age (mean ± SD years)	32 ± 8.12
Duration of MS (mean ± SD years)	5.73 ± 4.78
Mean number of attacks ± SD	3.59 ± 1.88
EDSS (mean ± SD years)	3.6 ± 1.8
Clinical type of MS, n (%)	
RR	23 (68%)
PP-SP	11 (32%)

RR, relapsing-remitting; PP, primary progressive; SP, secondary progressive.

the primary progressive (PP) and secondary progressive (SP) types.

To study the effect of disability on HRV parameters and autonomic dysfunction in this study, the patients were divided into two subgroups based on EDSS score (≤ 3.5 versus > 3.5) and disease considered classification (RR vs. SP) based on the assumption that spasticity is much more likely to occur in patients with higher EDSS and/or SP disease course. In the patients whose disease disability was equally or less than 3.5, the mean value of SDNN, RMSSD, HRVM, HRVSD and SDANN were 17.14 ms, 65.06 ms, 68.08 ms, 33.05 ms and 112.43 ms respectively. Whereas, those mean values of HRV were 13.23 ms, 41.11 ms, 61.55 ms, 27.45 ms and 134.94 ms respectively in the patients, whose disease disability score more than 3.5.

As shown in the Table 3, there is, however, no significant difference with regard to the relationship between autonomic parameters and EDSS scores. Statistical significant differences were not found between the groups with mild/moderate or severe disability in terms of EDSS.

When we investigated whether the illness duration had any effect on HRV parameters, we could not detect any significant difference between the groups. On the other hand, there was no significant correlation between disease activity (relapse rate) and HRV parameters.

Discussion

In our study, all of the HRV domain parameters were on a decrease in MS patients than those of the controls. The present study shows that both relapsing-remitting and progressive MS patients had HRV abnormalities. This result was confirmed when we compared the controls with several clinical MS subgroups. The most important finding in the present series was that parasympathetic cardiovascular tone significantly was lower in MS, in relation to control group. There are conflicting reports on the presence and the extent of CAD in patients with MS (Sterman *et al*., 1985; Pentland & Ewing, 1987; Anema *et al*., 1991; Thomadies *et al*., 1993; Vita *et al*., 1993; Giubilei *et al*., 1996). This discordance might be the result from differences in patient selection, methodology and the clinical status of the patients. In fact, most of the previous studies were designed without considering the phase of the disease in the RR MS form.

In accordance with previous reports (Pentland and Ewing, 1987; Anema *et al*., 1991; Giubilei *et al*., 1996) we observed a relative but not a statistically significant association between HRV parameters and disability of the patients. Some authors (Lachenecker *et al*., 2001) reported that parasympathetic dysfunction was closely related to the progression of disability, in contrast, sympathetic dysfunction was associated to the clinical activity of disease in MS patients. They claimed that this was in line with previous observations suggesting that the autonomic nervous system may be intimately linked with the disordered immune regulation in MS. Saari *et al*. (2004) found that cardiovascular autonomic dysfunction correlates with brain magnetic resonance imaging lesion

Table 2

Values of HRV variables in MS patients and controls

		SDNN (ms)	RMSSD (ms)	HRVM (ms)	HRVSD (ms)	SDANN (ms)
Patients	Mean	9.05	33.81	53.99	23.78	101.79
	SD	7.24	14.78	16.91	6.78	26.32
Controls	Mean	19.78	50.16	65.96	27.4	134.71
	SD	9.00	16.16	11.10	3.27	32.95
	P	0.019	0.026	0.029	0.043	0.040

SDNN, standard deviation of all R-R intervals; SDANN, standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recordings; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent R-R intervals; HRVM, mean of the SDNN in all the 5-minute intervals; HRVSD, standard deviation of the SDNN in all the 5-minute.

Table 3

Values of HRV variables according to disease parameters

		n	SDNN (ms)	RMSSD (ms)	HRVM (ms)	HRVSD (ms)	SDANN (ms)	*P*
MS Type	RRMS PP-SPMS	23 11	16.22 12.73	58.01 40.61	68.86 55.75	32.38 25.28	118.95 135.63	NS
Disability	(EDSS: ≤ 3.5) (EDSS: > 3.5)	16 18	17.14 13.23	65.06 41.11	68.08 61.55	33.05 27.45	112.43 134.94	NS
Number of attacks	< 5 ≥ 5	21 6	16.22 12.73	62.15 37.95	70.03 61.56	33.62 27.01	123.61 114.66	NS
Duration	sort: < 5 years long: ≥ 5 years	19 15	17.59 11.88	62.58 39.46	69.40 58.58	32.51 27.02	125.63 122.73	NS

SDNN, standard deviation of all R-R intervals; SDANN, standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recordings; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent R-R intervals; HRVM, mean of the SDNN in all the 5-minute intervals; HRVSD, standard deviation of the SDNN in all the 5-minute; NS Statistically not significant.

load. In particular, the midbrain lesions found in MS are associated with cardiovascular dysfunction.

Because serious cardiovascular disorders are seldom encountered clinically in MS, the possibility of sympathetic hypofunction providing protection for cardiac involvement can be hypothesized. Other authors, however, claim that MS causes an increase in sympathetic cardiovascular tone; the parasympathetic tone is variable and depends on clinical and paraclinical findings, but it seems to decrease with illness progression (Monge-Argiles *et al*., 1998; Flachenecker *et al*., 2001). Gunal *et al*., (2002) considered that autonomic function testing is necessary in order to detect subclinical changes in MS patients.

Flachenecker *et al*. (1999) investigated cardiovascular reflex tests and their association with orthostatic dizziness in patients with MS in order to examine the hypothesis that the sympathetic nervous system is specifically involved in these patients. Abnormal responses on at least one cardiovascular reflex test were observed in 40% of MS patients, compared to 17% of the control group, with a statistically significant involvement of the sympathetic vasomotor system. These results provided further evidence that the sympathetic nervous system is involved in patients with MS. McDougall and McLeod (2003) reported that parasympathetic cardiovascular autonomic abnormalities occurred in 16% of patients and were associated with increased MS severity, however, sympathetic cardiovascular abnormalities were present in 13% of patients and showed no significant association with MS severity. A progressive decrease of total HRV parameters has been correlated with age according their study. Our population composed of young subjects did not show such a correlation.

We examined the relationship between the abnormalities of HRV parameters and duration of illness, degree of disability and number of attacks. The patients with high disability scores, those with EDSS scores ≥ 4, had numerically lower HRV parameters, but this difference was not statistically significant. This suggests that illness duration rather than age may influence the HRV parameters, though there was no significant correlation between the parameters and illness duration. Mahovic and Lakusic (2007) reported that the main finding in their study was that patients with more than five years from the diagnosis of MS had lower parasympathetic activity than patients within five years from the diagnosis of MS. Therefore, they hypothesized that longer duration of the disease, because of more widespread plaques throughout the brain, leads to more lesions of CNS pathways, that influence cardiovascular reflexes and autonomic control of heart rate.

In conclusion, cardiac autonomic function is partially impaired in MS patients. Our study tends to suggest that this autonomic impairment is related to clinical parameters such as disability, duration of illness, number of relapses of MS, but we found no statistically significant correlations, probably because of the small sample size. Further studies on larger MS cohorts are warranted.

REFERENCES

Anema JR, Heijenbrok MW, Faes, TJC, Heimans JJ, Lanting P. *et al*. Cardiovascular autonomic function in multiple sclerosis. Journal of Neurological Sciences. 1991;104:129-134.

Flachenecker P, Wolf A, Krauser M., Hartung HP, Reiners K. Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic

intolerance. Journal of Neurology. 1999;246:578-586.

Frontoni M, Fiorini M, Strano S, Cerutti S, Giubilei F. *et al*. Power spectrum analysis contribution to the detection of cardiovascular dysautonomia in multiple sclerosis. Acta Neurologica Scandinavia. 1996;93:241-245.

Giubilei F, Vitale A, Urani C, Frontoni M, Fiorini M, Millefiorini E. *et al*. Cardiac autonomic dysfunction in relapsing remitting multiple sclerosis during a stable phasis. European Neurology. 1996;36:211-214.

Gunal DI, Afsar N, Tanridag T, Aktan S. Autonomic dysfunction in multiple sclerosis: correlation with disease-related parameters. European Neurology. 2002;48:1-5.

Kurtzke, J. Rating neurologic impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). Neurology. 1983;33:1444-1452.

Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Multiple Sclerosis. 2001;7:327-334.

Malik M. Task force of the European Society of Cardiology and the North American Society of the Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93:1043-1065.

Mahovic D, Lakusic N. Progressive Impairment of Autonomic Control of Heart Rate in Patients with Multiple Sclerosis. Archives of Medical Research, 2007;38:322-325.

McDougall AJ, McLeod JG. Autonomic Nervous System Function In Multiple Sclerosis. Journal of Neurological Sciences. 2003;15:79-85.

Monge-Argiles JA, Palacious-Ortega F, Vila-Sobrino JA, Matias-Guiu J. Heart rate variability in multiple sclerosis during a stable phase. Acta Neurologica Scandinavia. 1998;97:86-92.

Nordenbo AM, Boesen F, Andersen EB. Cardiovascular autonomic function in multiple sclerosis. Journal of Autonomic Nervous System. 1989;26:77-84.

Pentland B, Ewing DJ. Cardiovascular reflexes in multiple sclerosis. European Neurology. 1987;26:46-50.

Thomadies TN, Zoukos Y, Chaudira KP, Mahtias CJ. Physiological assessment of aspects of aoutonomic function in patients with secondary progressive multiple sclerosis. Journal of Neurology. 1993;240:139-143.

Saari A, Tolonenb U, Pääkkö C, Suominenb EK, Pyhtinenc J, Sotaniemia K. *et al*. Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. Clinical Neurophysiology. 2004;115:1473-1478.

Senaratine MPJ, Carrol D, Warren KG, Kappagoda T. Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. Journal of Neurology Neurosurgery and Psychiatry. 1984;47:947-952.

Spallone V, Bernardi L, Maiello MR. Twenty-four-hour blood pressure and spectral analysis of heart rate variability in diabetic patients with various degrees of autonomic neurpathy. Comparison to standart cardiovascular test. Clinical Sciences (Colch). 1996;91:Suppl:105-107.

Sterman AB, Coyle PK, Panasci MS, Grimson R. Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. Neurology. 1985;35:1665-1668.

Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesinos. Journal of Neurological Sciences. 1993;120:82-86.

Yamasaki Y, Kodoma M, Matsuhisa M. Diurnal heart rate variability in health subject: effects of aging and sex difference. American Journal of Physiology. 1996;271:303-310.

Yotsukura M, Sasaki K, Kachi E, Sasski A, Ishihakara T, Ishıkawa K. Circadian rhythm and variability of heart rate in Duchenne-type progreeive dystrophy. American Journal of Cardiology. 1995;76:947-951.

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