CLINICAL STUDY

Autonomic nervous system dysfunction in multiple sclerosis patients

Brezinova M, Goldenberg Z, Kucera P

*1st Department of Neurology, University Hospital and Faculty of Medicine, Comenius University, Bratislava, Slovakia.***brezina.maria@zoznam.sk**

Abstract

We present the results of our study dealing with autonomic nervous system (ANS) function in multiple sclerosis (MS) patients. We performed a cardiovascular reflex examination (heart rate variation in deep breathing and active standing) and spectral analysis of heart rate variability in 36 MS patients who fulfilled the criteria for this diagnosis. We evaluated several various indexes used for the assessment of ANS function: I/E, I-E in deep breathing test; RRmax/RRmin in active standing, spectral analysis of heart rate variability in VLF, LF and HF bands were performed. We found a significant difference in I-E index values during deep breathing test in MS patients when compared to the healthy control group; we did not find any difference in I/E index (deep breathing test) and RRmax/RRmin (active standing) values. The spectral analysis of heart rate variability in the rest-tilt-rest test showed a significant difference in spectral powers in MS patients when compared to the healthy control group in all frequency bands. ***(Tab. 2, Fig. 7, Ref. 17.)***

Key words: autonomic nervous system, multiple sclerosis, cardiovascular reflex tests, spectral analysis of heart rate variability.

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) caused by autoimmune mechanisms.

Dysfunction of autonomic nervous system (ANS) causes a significant decline in performance in MS patients. It is assumed that it is caused by multiple demyelinating plaques localized in the brainstem and spinal cord. Autonomic symptoms are very frequent in MS patients, mainly disorders of micturition, impotence, sudomotor and gastrointestinal disorders; their frequency and severeness rises along with the degree of invalidization (1). Interactions between the immune system and ANS are multiple and have been proven by in vitro studies (2), on animal models (3) as well as by clinical trials (4). Autonomic dysfunction in MS can be not only a sign of the disease but also one of the many pathogenetic factors. For example, it has been shown that activation of the sympathetic NS has immunosuppressive effects whereas sympathetic blockades intensify the immune response (4).

Autonomic dysfunction in cardiovascular system can be detected using relatively simple noninvasive cardiovascular reflex tests and spectral analysis of heart rate variability. These tests have been commonly used for examination of diabetic autonomic neuropathy where they show sufficient sensitivity and specificity for the use in clinical practice (5).

The majority of so far published studies have confirmed abnormalities of cardiovascular tests in MS (6, 7, 8, 9, 10, 11, 12, 13), however the frequency of abnormalities as well as the results of individual tests show variable interpretations.

The aim of our study was to find a presence of ANS dysfunction in MS patients and to compare the values obtained by functional tests and the spectral power in MS patients with those of healthy volunteers.

Patients and methods

We have examined 36 patients, 11 men, 25 women, age 19–57 years (average 37.87 y), fulfilling criteria (14) of the definite diagnosis of multiple sclerosis; 29 patients with the relapsing –

1st Department of Neurology, University Hospital and Faculty of Medicine, Comenius University, Bratislava, Slovakia

Address for correspodence: M. Brezinova, MD, I. neurologická klinika FN a LFUK, Mickiewiczova 13, SK-813 69 Bratislava 1, Slovakia.
Phone: +421.2.57290406, Fax: +421.2.57290300

Tab. 1. Cardiovascular reflex tests in MS patients and healthy volunteers (mean value±standard deviation).

	I-E	I/E	RRmax/RRmin
MS	15.78±9.11	1.30±0.28	1.41±0.63
Control	22.33±8.83	1.40±0.17	1.47±0.28
Significance	p<0.05	NS	NS

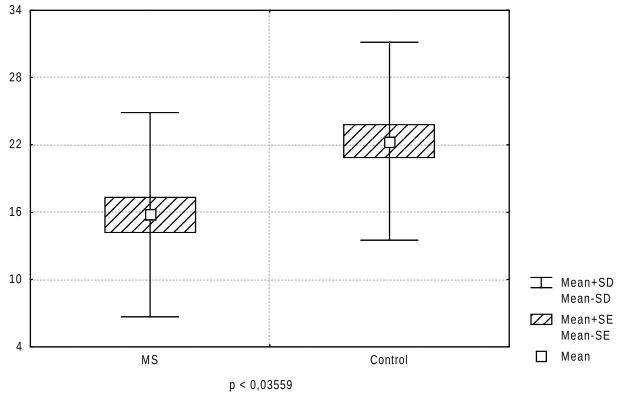

Fig. 1. I-E (difference between maximum and minimum heart rate).

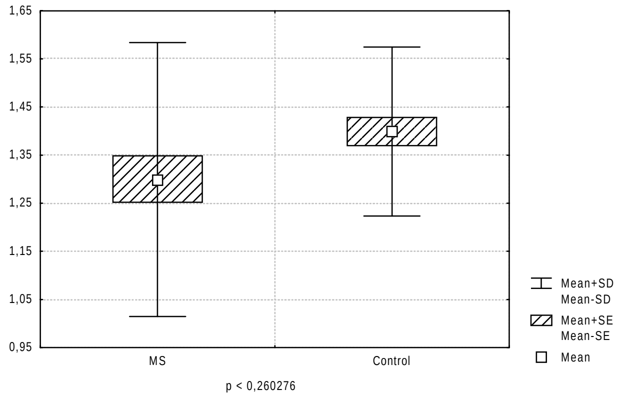

Fig. 2. I/E (maximum R-R interval minimum R-R interval ratio).

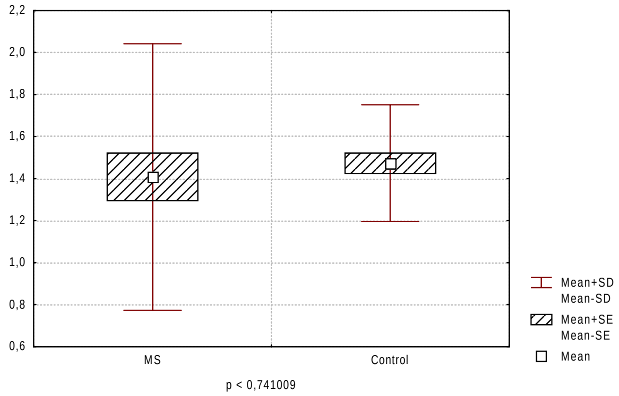

Fig. 3. RRmax/RRmin (maximum R-R interval minimum R-R interval ratio after stand up).

remitting form, 3 patients with the primary progressive form and 4 patients with the secondary progressive form; the duration of the disease was 0.5–30 y (average 6.9 y), EDSS (Expanded Disability Status Scale) score was 1–6 (average 3). Patients with other systemic or neurological diseases that could have caused the autonomic dysfunction were excluded. We have performed all tests for ANS in 13 healthy age- and sex-matched volunteers. Cardiovascular reflex tests and spectral analysis of heart rate variability were performed using VarCor PF6 system in the standardized conditions – before the test a person to be examined had been laid comfortably on the examination bed till the heart rate values have stabilized; room temperature was 20–22 °C; all sources of possible perturbing influence have been removed; no entrance of other persons in to the room was permitted. The inter-test intervals have been so long as to stabilize the heart rate closely to the baseline values.

The cardiovascular reflex tests comprised of the monitoring of *heart rate variation in deep breathing* – four consecutive deep inspiration cycles, each lasting 10 seconds, in supine position (I/E index – maximum R-R interval minimum R-R interval ratio and I-E index – difference between maximum and minimum heart rate were evaluated) and that of *heart rate variation after active standing* – continuous stand up from supine position (RRmax/RRmin index - maximum R-R interval to minimum R-R interval ratio after standing up was evaluated). Spectral power (ms^2) was evaluated by *spectral analysis of heart rate variability* in low-frequency and high-frequency bands (VLF 0.020–0.050 Hz, LF 0.050–0.150 Hz, HF 0.150–0.500 Hz) in the rest-tilt-rest test, when the first lying position (330 pulses) is followed by an active stand up and still standing (approximately the same time period) when the activation of the sympathetic NS and a decrease in vagal activity occur barroreflexively. During the following change to a supine position a compensative increase in vagal activity occurs. The 3rd interval, i.e. the second supine position, was evaluated; assuming a physiological reactivity of the vagus this interval represents the best functional status of the vagus (15).

The evaluated indexes and spectral powers in individual frequency bands obtained from MS patients and healthy subjects were compared using t-test for independent values.

Results

Performing cardiovascular reflex tests we found out a significant difference in I-E index values in deep breathing test in MS patients compared to the healthy control group, the differences in I/E index in deep breathing test and RRmax/RRmin index in active standing were not significant (Tab. 1, Figs 1, 2, 3).

In the MS patients group the spectral analysis of heart rate variability in rest-tilt-rest test showed a decrease in spectral pow-

Tab. 2. Spectral power in individual frequency bands (ms²) in MS patient and healthy volunteers (mean value±standard deviation).

	Power VLF	Power LF	Power HF	Total power
MS	200.87±172.62	327.84±399.48	594.16±722.89	1137.92±1112.06
Control	214.84±159.64	962.67±1747.71	1200.35±1281.55	2472.48±2446.31
Significance	p<0.001	p<0.001	p<0.001	p<0.001

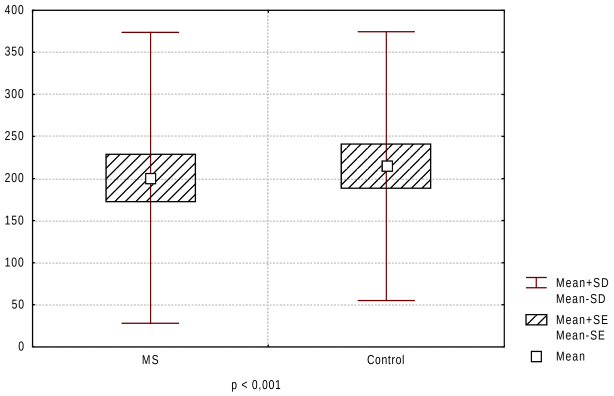

Fig. 4. Spectral analysis of heart rate variability – power VLF (ms²).

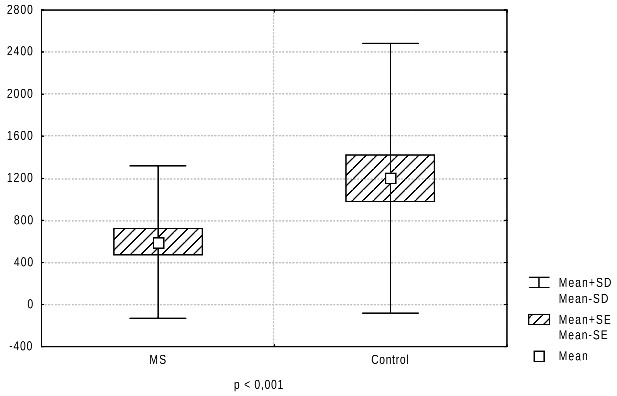

Fig. 6. Spectral analysis of heart rate variability – power HF (ms²).

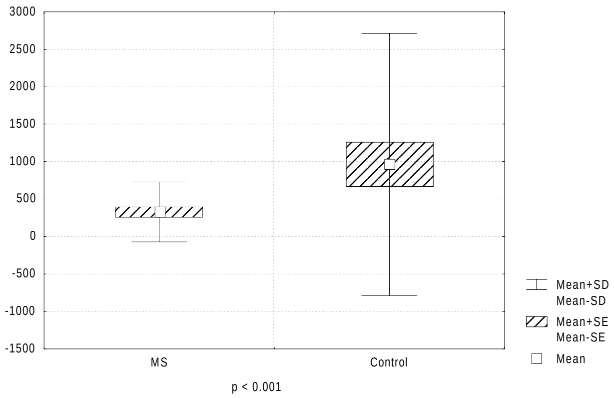

Fig. 5. Spectral analysis of heart rate variability – power LF (ms²).

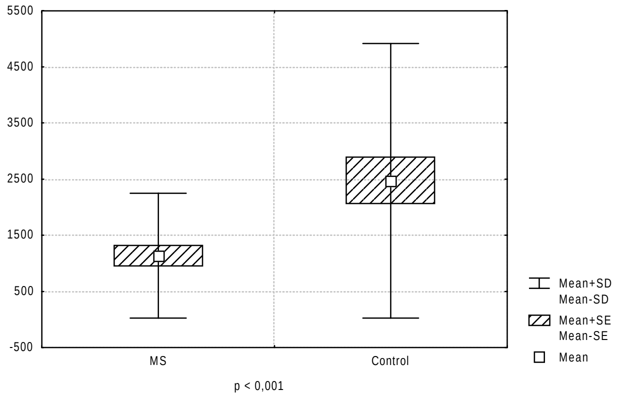

Fig. 7. Spectral analysis of heart rate variability – total power (ms²).

ers in all spectral bands when compared to healthy volunteers (Tab. 2, Figs 4, 5, 6, 7).

Discussion

In the MS patients group we performed cardiovascular reflex tests as follows: heart rate reaction to deep breathing and active standing. In deep breathing test we evaluated I-E and I/E indexes that are regarded as indirect markers of parasympathetic activity in particular. In active standing we evaluated RRmax/RRmin index indicating the functional status of both subsystems. According to our results the I-E index seems to be the most sensitive as it was the only one to show a significant difference compared to healthy control group. In line with our results, Flachenecker et al (8), who repeatedly examined his patient group during a 24 months period, found a progression of parasympathetic dysfunction predominantly in deep breathing test. Nasseri et al (13) report that this index together with 30:15 index (RR interval at 30th heart beat after the stand-up to RR interval at the 15th heart beat after the stand-up ratio) showed a significant worsening at the examination repeated after 2 years. The same authors, however, in their previous study (12) observed a tendency toward a decrease in the values in all tests at the examination repeated after 1 year. Acevedo et al (6) actually found significant changes in all tests.

A method less frequently used in the evaluation of autonomic nervous system is that of spectral analysis of heart rate variability. This method is based on the knowledge that reciprocal efferent activity of sympathetic and parasympathetic NSs is modulated at the level of sinoatrial node during every heart cycle by central as well as peripheral oscillators (16) and with the analysis of those oscillations it is possible to evaluate the status and function of these oscillators. According to Stejskal (17) with certain allowance it is possible to consider the spectral output with frequency higher than 150 mHz as an indicator of the parasympathetic tone. The region under this limit accounts for sympathetic oscillations and the middle region about 100 MHz reflects specifically the sympathetic activity of barroreceptors.

According to our results, where we found a significant decrease in spectral powers in all spectral bands compared to healthy volunteers, this method appears to be more sensitive than conventional cardiovascular reflex tests. Similar results have been reported by Linden et al (10) who showed statistical significant changes in their group of patients compared to the healthy control group. Frontoni et al (9) found changes mainly in the frequency bands, that according to our current knowledge represent the sympathetic part of the spectrum – VLF, LF. Such a result can be expected and is in line with the knowledge about interactions between the autonomic NS and immune system (4), as well as with the study results of Flachenecker et al (8), where catecholamine levels correlated well with the clinical activity of the disease.

We can state that the symptoms of autonomic nervous system dysfunction can be confirmed by objective measurements, whereas the spectral analysis of heart rate variability is more sensitive method than conventional cardiovascular reflex tests. The changes in the variability of heart rate could be used in the prospect of the estimation of progression of the disease as well as in that of the evaluation of treatment effectiveness (while accepting the limits of the test).

References

1. Krahulec B. Možnosti využitia kardiovaskulárnych reflexov v diagnostike porúch autonómneho nervového systému u nediabetikov. Časť 2. Noninvas Cardiol 1995; 4 (3): 165—173.

2. Karaszewski JW, Reder AT, Anlar B, Arnason GW. Increased high affinity beta-adrenergic receptor densities and cyclic AMP responses of CD8 cells in multiple sclerosis. J Neuroimmunol 1993; 43 (1—2): 1—7.

3. Kuroda Y, Mori T, Hori T. Restraint stress suppresses experimental allergic encephalomyelitis in Lewis rats. Brain Res Bull 1994; 34 (1): 15—17.

4. Chelmicka -Schorr E, Arnason BG. Nervous system-immune system interactions and their role in multiple sclerosis. Ann Neurol 1994; 36 (Suppl): S29—32.

5. Pfeifer MA, Cook D, Brodsky J, Tice D, Reenan A, Swedine S, Halter JB, Porte Jr D. Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. Diabetes 1982; 31 (4 Pt 1): 339—345.

6. Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. Acta Neurol Scand 2000; 101 (2): 85-88.

7. Flachenecker P, Wolf A, Krauser M, Harting HP, Reiners K. Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. J Neurol 1999; 246 (7): 578—586.

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

9. Frontoni M, Fiorini M, Strano S, Cerutti S, Giubilei F, Urani C, Bastianello S, Pozzilli C: Power spectrum analysis contribution to the detection of cardiovascular dysautonomia in multiple sclerosis. Acta Neurol Scand 1996; 93 (4): 241—245.

10. Linden D, Diehl RR, Kretzschmar A, Berlit P. Autonomic evaluation by means of standard tests and power spectral analysis in multiple sclerosis. Muscle Nerve 1997; 20 (7): 809—814.

11. McDougall AJ, McLeod JG. Autonomic nervous system function in multiple sclerosis. J Neurol Sci 2003; 215 (1—2): 79—85.

12. Nasseri K, TenVoorde BJ, Ader HJ, Uitdehaag BM, Polman CH. Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. J Neurol Sci 1998; 155 (1): 50—54.

13. Nasseri K, Uitdehaag BM, van Walderveen MA, Ader HJ, Polman CH. Cardiovascular autonomic function in patients with relapsing remitting multiple sclerosis: a new surrogate marker of disease evolution? Europ J Neurol 1999; 6 (1): 29—33.

14. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13 (3): 227—231.

15. Opavský J. Autonomní nervový systém a diabetická autonomní neuropatie. Klinické aspekty a diagnostika. Praha, Galén 2002, 303 s.

16. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991; 84 (2): 482—492.

17. Stejskal P, Salinger J. Spektrální analýza variability srdeční frekvencie. Základy metodiky a literární přehled o jejím klinickém využití. Med Sport Boh Slov 1996; 2: 33—42.

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