BAROREFLEX SENSITIVITY IN MULTIPLE SCLEROSIS

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A b s t r a c t

Our study is aimed at finding out whether disturbed regulation of blood circulation is connected with the degree of clinical disability in a set of patients with disseminated cerebrospinal sclerosis. We evaluated the regulation of blood circulation by means of determination of baroreflex sensitivity (BRS); clinical disability of patients with SM was evaluated according to Kurtzke's Expanded Disability Status Scale, EDSS.

We examined 27 patients with clinically defined disseminated sclerosis in the remission stage (mean age 43.4 years, duration of SM 6.4 years, EDSS 3.25). The examination was carried out by means of non-invasive continuous recording of heart rate and blood pressure made by TASK FORCE MONITOR (CNS System, Graz, Austria), by the beat-by-beat measurement method. A 5-minute record was made in supine position with controlled breathing rate according to the metronome 0.33 Hz. By software processing of continuous recording of heart rate and blood pressure by means of sequential BRS analysis there were evaluated up-events, down-events, and total BRS for all events. On the basis of evaluation of the BRS examination we divided the set into two groups. Group A (13 patients, mean age 46.3 ± 8.7, duration of the disease 6.3 ± 7.6, EDSS 4.2 ± 1.2) consisted of patients with the number of up- or down-events ≤ 8. Group B (14 patients, mean age 40.5 ± 6.2, duration of the disease 6.5 ± 5.7, EDSS 2.1 ± 0.5) consisted of patients with the number of events ≥ 8.

Results: Sequential analysis of BRS in group B: up-events 13.7 ± 6.4 ms/mmHg, down-events 12.5 ± 4.6 ms/mmHg, all events 13.2 ± 5.4 ms/mmHg. In group A BRS could not be evaluated by sequential analysis because of a low number of recorded up- or down-events, which we regard as disturbed cardiovascular regulation.

Conclusion: Sequential analysis of baroreflex sensitivity of heart rate established in 14 patients (group B – mean age 40.5 ± 6.2 years, duration of the disease 6.5 ± 5.7 years, EDSS 2.1 ± 0.5) proved baroreflex regulation to be in compliance with the reference values. This method could not be evaluated in 13 SM patients (group A – mean age 46.3 ± 8.7 years, duration of the disease 6.3 ± 7.6 years, EDSS 4.2 ± 1.2) because of a low number of recorded up- or down-events indicating disturbed cardiovascular regulation of blood circulation.

INTRODUCTION

Disseminated multiple sclerosis (SM) is a chronic system autoimmunity disease causing, on the basis of dissemination of demyelination foci in the CNS region, a functional neurological deficit. The course is typically episodic, with acute attacks

of demyelination occurring in irregular intervals and bringing about often increasing motor deficit and loss of sensory functions (*1*).

Dysfunctions of the autonomic nervous system (ANS) are quite a frequent phenomenon in SM. They are characterised particularly by dysfunctions of the urinary bladder and disorders of sexual and sudomotor functions (*2-4*). Autonomic dysfunctions affecting the cardiovascular system regulation have, however, been also documented more and more frequently (*5-11*). The incidence of these dysfunctions varies as to frequency, importance of abnormities, and autonomic reflex tests being used (*5,6,10,12,13*). Alterations of cardiovascular system parameters were demonstrated in SM patients both at rest and during physical load when ANS is responsible for compensation of hemodynamic cardiovascular response to physical stress. Autonomic dysfunctions can therefore lead to a limitation of physical load capacity and can contribute to the fatigue of SM patients that has not yet been explained (*14-19*).

Cardiovascular autonomic functions in SM are most frequently monitored by means of conventional reflex tests (*5,6,20,21*). These methods are limited mainly by difficult interpretation and differentiation of the sympathetic or parasympathetic components of cardiovascular regulation by the autonomic nervous system.

A contemporary trend in testing of the autonomic nervous system is based on examination of heart rate variability (HRV), whose results we have already published (*22,23*). Monitoring of baroreflex sensitivity (BRS) is another possibility of evaluating cardiovascular regulation.

AIM

Our study is aimed at finding out whether disturbed regulation of blood circulation is connected with the degree of clinical disability in a set of patients with disseminated cerebrospinal sclerosis. We evaluated the regulation of blood circulation by means of determination of baroreflex sensitivity (BRS); clinical disability of patients with SM was evaluated according to Kurtzke's Expanded Disability Status Scale, EDSS.

METHODS

The set of patients examined consisted of patients with diagnoses from the neurological outpatient ward for SM of 1st Dept. of Neurology of the Faculty of Medicine, Masaryk University, St. Anne's Faculty Hospital, and from the team of the "Unie ROSKA Brno-město" association. The patients with internal, metabolic and other diseases that could influence the validity of the results of autonomic testing were excluded from the study. The patients were tested in a clinically stabilised state of the disease. They confirmed their participation in the study by signing "Informed consent of the patient"; the study was accepted by the relevant ethical committee of St. Anne's Faculty Hospital in Brno. Clinical evaluation of disability by means of the EDSS scale was performed before the examination of the autonomic nervous system.

EDSS (Kurtzke's Expanded Disability Status Scale) (*26*) is a standard scale for evaluation of disability of SM patients. It is a neurological examination with evaluation by 0.5 point, in the interval

from 0 (no functional disorder or impairment) to 10 (death because of SM), impact of SM disease being on 8 basic functional systems.

BRS (baroreflex heart rate sensitivity) characterises the function of baroreceptors participating in maintaining blood pressure and heart rate and expresses the level of activity of the autonomic nervous system. Extension of the heartbeat interval R – R (CI) in milliseconds at increase of SBP by 1 mm Hg is an indicator of BRS. The BRS value (ms. mmHg[1]) is the function expressing the relation between spontaneous fluctuation of SBP and R – R intervals.

The examination was carried out by means of non-invasive continuous recording of heart rate and blood pressure made by TASK FORCE MONITOR (CNS System, Graz, Austria) (*25*), by the beat-by-beat measurement method. A 5-minute record was made in supine position with controlled breathing rate according to the metronome 0.33 Hz, for comparison of the results among the patients. By software processing of a continuous recording of heart rate and blood pressure (BP) by sequential analysis there are found events of at least three or more consecutive monotonous changes of SBP with a minimal deviation of 1 mmHg/1 heartbeat and, at the same time, at least three consecutive monotonous changes of RR intervals with a minimal change of 4 ms/1 heart beat. The events of SBP changes can thus have BP up-events or BP down-events. Then the regression terms for all up-events and all down-events and mean values for both types of events are calculated. The results are given separately for up- and down-events and further as the total BRS for all events in ms/mmHg. The values are given as mean ± SD. The impossibility of a reliable measurement of BRS because of the low number of events (less than 8) was considered to be a disturbed cardiovascular regulation.

Heart rate variability (HRV) was also examined by the instrument TASK FORCE MONITOR (CNS System, Graz, Austria) (25). By means of spectral analysis we evaluated the very low-frequency component of HRV (0.02 – 0.05Hz, VLF-RRI), the low-frequency component of HRV (0.05–0.15Hz, LF-RRI), the high-frequency component of HRV (0.15–0.50Hz, HF-RRI), the total spectral power (HRV TP), the index of sympathovagal balance (LF/HF), the length of cardiac interval (RRI), and heart rate SF.

Statistical analysis of the data (program STATISTICA for Windows – version 7.7) was made by means of a t-test for independent specimens and the Wilcoxon test.

RESULTS

Twenty-seven patients with verified SM disease, in the remission stage (mean age 43.4 years, duration of SM disease 6.4 years, EDSS 3.25) were examined.

On the basis of evaluation of the BRS examination we divided the set into two groups according to the number of down- or up-events of blood pressure. Group A with disturbed cardiovascular regulation consisted of patients with BP up-events or BP-down events ≤ 8. Group B consisted of patients with the number of events ≥ 8.

The characteristics of anthropometric data and characteristics of SM disease in both groups are shown in *Table 1*.

Table 1

Basic anthropometric data and data characterising SM disease in examined groups (the values are expressed as mean ± SD)

In total 27 SM patients	Group A (BRS ≤ 8 events)	Group B (BRS ≥ 8 events)
	n= 13	N=14
Gender	2M/11F	3M/11F
Age	46.3 ± 8.7	40.5 ± 6.2
Height [m]	1.7 ± 0.1	1.7 ± 0.1
Mass [kg]	67.7 ± 12.6	69.0 ± 12.6
BMI	23.8 ± 4.3	23.8 ± 4.1
Body surface area [m^2]	1.80 ± 0.13	1.81 ± 0.14
EDSS	4.2 ± 1.2	2.1 ± 0.5 *
Duration of SM	6.3 ± 7.6	6.5 ± 5.7
RR form	8	9
SP form	4	3
PP form	1	2

RR form – relapsing remitting form of SM disease, SP – secondary progressive form, PP – primary progressive form, BMI – body mass index, * p < 0.05

The examined indicators of baroreflex sensitivity are in *Table 2*.

Table 2

Results of baroreflex sensitivity (BRS) in monitored groups

Controlled breathing 0.33Hz	Group A	Group B
R-R interval [ms]	826.3 ± 102.0	837.0 ± 115.9
HR [heartbeat/min]	74.0 ± 9.0	73.4 ± 10.3
SBP [mmHg]	115.0 ± 13.7	114.2 ± 5.4
DBP [mmHg]	78.2 ± 9.8	74.9 ± 4.3
n (number of up-events)	Not evaluated *	12.9 ± 5.3
BRS up-events [ms/mmHg]	Not evaluated *	13.7 ± 6.4
N (number of down-events)	Not evaluated *	15.4 ± 8.8
BRS down-events [ms/mmHg]	Not evaluated *	12.5 ± 4.6
N (number of all events)	Not evaluated *	28.3 ± 13.3
BRS all events [ms/mmHg]	Not evaluated *	13.2 ± 5.4

HR – heart rate, SBP, DBP – systolic, diastolic BP, BRS up-events – absolute value of baroreflex sensitivity for up-events, BRS down-events – absolute value of BRS for down-events, BRS all events – absolute value BRS all events, n – number of recorded events, * not evaluated by sequential analysis of BRS because of insufficient number of recorded events

Additional examined values of heart rate variability (HRV) are given in *Table 3* with statistical significance of comparison between the groups.

Table 3
Results of heart rate variability (HRV)

HRV controlled breathing 0.33Hz		Group A	Group B	P
VLF-RRI	[ms^2]	357.8 ± 878.5	112.3 ± 93.1	NS
LF-RRI	[ms^2]	178.7 ± 312.2	475.4 ± 1070.5	NS
HF-RRI	[ms^2]	298.6 ± 551.3	551.1 ± 1356.8	NS
TP-RRI	[ms^2]	835.0 ± 1205.3	1138.8 ± 2440.5	NS
LF/HF	[1]	1.4 ± 1.5	1.6 ± 1.3	NS
R-R interval	[ms]	826.3 ± 102.0	837.0 ± 115.9	NS
HR	[bpm]	74.0 ± 9.0	73.4 ± 10.3	NS

VLF-RRI – very low-frequency component of HRV (0.02–0.05Hz), LF-RRI - low-frequency component of HRV (0.05–0.15Hz), HF-RRI – high-frequency component of HRV (0.15–0.50Hz), TP – total power of HRV, LF/HF – index of sympathovagal balance, RRI – interval of RR, HR – heart rate, NS – low statistical significance

DISCUSSION

A disorder of regulation of the cardiovascular functions in SM is clinically less frequent, but potentially dangerous (*35*). These abnormalities were studied in the past on the basis of a number of examinations of cardiovascular reflexes with a different measure of informative value. That is why the results and interpretation of disorders of cardiovascular functions often diverge in the published papers. Abnormalities of cardiovascular reflexes were proved controversially in both branches of sympathetic and parasympathetic nervous supply (*3,5,6,9–11,29*). *Saari et al.* (*27*) documented that the measure of disability in SM correlates with reduction of cardiovascular response and also with the volume of lesions of the central nervous system, verified by means of magnetic resonance examination. According to the authors it can be supposed that particularly lesions of midbrain, but also, even if with a lesser impact, lesions of the hemispheres are responsible for most cardiovascular abnormalities. This hypothesis was indicated already by the results of *Acevedo et al.* (*5*), who established a connection of cardiovascular dysfunctions in SM with affection of the reflex paths in the brainstem. A partial answer to the question whether autonomic cardiovascular regulation in SM is affected by a direct mechanism was given by the study of authors *Sanya et al. (28),* who investigated carotid baroreflexes in patients with SM separately for parasympathetic and sympathetic cardiovascular regulation. The baroreflex function was reduced not only in cardiac regulation of the baroreflex, also sympathetic regulation of the tonus of arterial bed was affected. The authors think that indirect impairment of sympathetic vasomotor regulation

234

can be responsible for postural disorders and vertigo that are described in as many as 49 % of SM patients (*29*). The finding of sympathetic vasomotor disorder of the function and its correlation with general fatigue in SM was also established in the study of authors *Flachenecker et al.* (*31*).

The results of our study indicate that the mechanisms of baroreflex control in group B with EDSS 2.9 with a clearly expressed BRS in the values corresponding to the average age of a healthy population seem to be in the range of reference standard values (36,37,38). In this group, values of BRS of BP up-events 13.7 ± 6.4 ms/mmHg, BP down-events 12.5 ± 4.6 ms/mmHg, and mean BRS for BP total events 13.2 ± 5.4 ms/mmHg were measured.

On the other hand, in the second group of SM patients (group A) for BRS determination by the sequential method in 13 patients there was not found a sufficient number of BP up-events or BP down-events. This difference between groups A and B can be hypothetically explained by a dissimilarity of the autonomic regulation of BRS, and an increase of the sympathetic tonus in group A can be supposed. Group A does not differ statistically significantly from group B either in anthropometric values or in duration of the disease (6.3 ± 7.6 vs. 6.5 ± 5.7 years). The groups do not differ in proportional representation of the forms of SM disease, either. This can be explained by the significant difference of the extent of clinical disability of the autonomic nervous system. In group A there is a larger measure of disability according to EDSS (3.6 ± 1.4) than in group B (2.9 ± 1.4). We have not found, however, any correlation between the indicators of BRS and EDSS. HRV indicators show a generally lower total power (TP) in group A (835.0 ± 1205.3 ms^2) than in group B (1138.8 ± 2440.5 ms^2) and a decrease of LF and HF of the HRV component as against group B (178.7 ± 312.2 vs. 475.4 ± 1070.5ms^2; 298.6 ± 551.3 vs. 551.1 ± 1356.8 ms^2); it was not statistically significant, however.

On the basis of our results we can conclude that a lower degree of clinical disability need not be connected with cardiovascular regulation impairment, and a higher degree can mean its impairment at the level of baroreceptors. The question arises whether a reduced baroreflex sensitivity of the heart rate will increase the risk of occurrence of cardiovascular diseases in SM patients. *Fleming et al.* (*34*) found out that elderly SM patients have a lower probability of falling ill with such diseases as acute IM, heart failure, hypertension, angina pectoris, and cerebrovascular diseases than have their contemporaries of the same age. *Slawta et al.* (*33*) documented on a group of 123 women with SM that the risk of heart diseases is approximately the same as in a normal population. Even if we meet serious cardiovascular diseases in connection with SM relatively rarely in our department, there exists a possibility of lesion of cardiovascular functions in SM patients. Verification of our results requires, however, further examination of SM patients.

CONCLUSION

Sequential analysis of baroreflex sensitivity of heart rate established in 14 patients (group B – mean age 40.5 ± 6.2, duration of the disease 6.5 ± 5.7, EDSS 2.9 ± 1.4) proved baroreflex regulation to be in compliance with the reference values. This method could not be evaluated in 13 patients (group A – mean age 46.3 ± 8.7, duration of the disease 6.3 ± 7.6, EDSS 3.6 ± 1.4) because of a low number of recorded up- or down-events. We regard the difference between groups A and B as a dissimilarity of autonomic regulation of BRS. The results indicate that a lower degree of clinical disability need not be connected with cardiovascular regulation impairment and a higher degree can mean its impairment at the level of baroreceptors.

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