J Neurol (1995) 242:639–643

ORIGINAL COMMUNICATION

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Cardiac autonomic function during sleep and wakefulness in multiple sclerosis

Received: 21 December 1994
Received in revised form: 23 February 1995
Accepted: 27 February 1995

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Abstract Some studies in multiple sclerosis (MS) patients have shown evidence of autonomic dysfunction involving the cardiovascular system. However, the findings in these studies have not been completely consistent. The discrepancy may be related to the limits of the traditional autonomic tests during wakefulness. In our study, after the investigation of the cardiovascular reflexes during wakefulness, heart rate (HR) variations were considered during sleep in order to avoid the limits of cooperation and the emotional state of the patient. We evaluated tonic (vagal activity) HR modifications in relation to the deepening of sleep, as well as phasic (sympathetic activity) HR modifications in relation to spontaneous body movements during sleep, in 25 MS patients and 25 age-matched controls. No difference was found between the two groups in autonomic function during wakefulness. A reduced parasympathetic activity was observed in MS subjects during both rapid eye movement (REM) and non-REM sleep, while no difference was found in sympathetic function between patients and controls. No significant correlation was found between cardiac autonomic data during sleep and MRI lesion load in the infratentorial areas and, in particular, of the brain stem. The findings of our study suggest that autonomic nervous system evaluation during sleep could show impairment earlier than the traditional autonomic tests during wakefulness.

Key words Multiple sclerosis · Sleep · Autonomic nervous system

Introduction

Autonomic nervous system (ANS) dysfunction is often present in multiple sclerosis (MS) [2]. Some studies on cardiovascular ANS functions have provided differing data about the frequency and significance of abnormalities in MS. It has been suggested that the cardiac ANS abnormalities are likely to involve central autonomic interconnections with brain stem centres [14, 21]. However, the findings on the relationship between cardiovascular ANS dysfunction and magnetic resonance imaging (MRI) brain stem lesions are debatable [1, 24]. An explanation for the discrepancies among the different observations might be the fact that small numbers of patients have been examined in some studies; there may also have been differences in methodology; or the limitation of the classical autonomic test during wakefulness may be the reason. In fact, the cardiovascular responses utilized in these tests (i.e. Valsalva manoeuvre, respiratory sinus arrhythmia, handgrip test) show great inter- and intraindividual variations [8]. A number of factors may contribute to this finding and they are greatly influenced by psychological factors, such as the attitude of the patient to the test. During sleep there are repetitive modifications of ANS that are very constant and not influenced by the patient's emotional status and the degree of cooperation. For this reason, we previously evaluated tonic (vagal activity) heart rate (HR) modifications in relation to the deepening of non-rapid eye movement (NREM) sleep, as well as phasic

(sympathetic activity) HR modifications in relation to spontaneous body movements during NREM and REM sleep, in healthy subjects and in patients with some neurological diseases [6, 19].

In the present study we applied the same methodology, comparing the findings of the traditional autonomic tests during wakefulness, in a selected group of MS patients. We also correlated the cardiac ANS data with the clinical findings and brain MRI results.

Subjects and methods

Subjects

The patients were recruited from the Multiple Sclerosis Centre of the Scientific Institute H San Raffaele in Milan and met the following criteria: (1) the diagnosis was of clinically definite MS [15]; (2) duration of the disease was longer than 2 years; (3) there were no concurrent medical diseases; (4) there was no history of psychiatric illness before the MS diagnosis and, in particular, no current or past history of DSM III-R major depression or bipolar disorder; (5) there was no history of alcohol or drug abuse; (6) the patient had been medication free for at least 2 weeks at the time of testing; (7) the patient was aged between 25 and 55 years; (8) the patient had a score of less than 6.0 on the Kurzke Extended Disability Scale (EDSS) [9].

The resulting sample consisted of 25 patients with MS (12 women and 13 men; mean age = 39.9 years; mean duration of the disease = 9.6 years; mean EDSS = 3.8). Twenty-five healthy subjects (12 women and 13 men; mean age = 38.5 years) served as controls.

Autonomic evaluation during wakefulness

The following cardiovascular autonomic tests were performed.

R-R interval variation during deep breathing

The R-R intervals during maximal deep breathing at a rate of 6 cycles/min were recorded during 1 min with the subject in a supine position. The result was expressed as the mean difference between the maximum HR during inspiration and minimum HR during expiration (IE_{diff}). This test reflects parasympathetic function.

Valsalva ratio

A Valsalva manoeuvre was performed for 15 s in the supine position during continuous electrocardiographic (ECG) monitoring. Three recordings were made in each subject. The maximum HR during the manoeuvre divided by the minimum HR after release for each recording, and the mean of the three recordings were calculated. The ratio reflects parasympathetic function.

Blood pressure and HR response to standing (orthostatic test)

Blood pressure (BP) at rest in the supine position was measured as the mean of three recordings. The subjects were tilted to 80°, and BPs were recorded at 30-s intervals for 3 min. The response was expressed as the difference between the mean systolic BP in the supine position and the mean of the two lowest systolic BPs after tilting.

Using the R-R interval recordings we determined the HR 30:15 ratio, defined as the ratio of the R-R intervals corresponding to the longest and the shortest R-R intervals around beat 15 and 30 after standing.

The BP response reflects sympathetic function. The HR response reflects parasympathetic function.

Autonomic evaluation during sleep

Standard 8-h polysomnography was performed for two consecutive nights and included electroencephalograms, electro-oculograms, submental electromyograms (EMGs) and bilateral anterior tibial EMGs. Nasal/oral airflow recorded with a thermistor, ear oximetry, respiratory activity recorded with a thoracic and abdominal strain gauges and continuous ECG monitoring were also obtained. Subjects were under continuous videographic monitoring by a trained sleep technician in an adjacent room.

Sleep stages were scored according to the guidelines of Rechtschaffen and Kales [16] and the second-night data were analysed.

Tonic and phasic HR variability was evaluated in relation to spontaneous body movements during sleep, according to the procedure and the method published elsewhere [4, 6]. Apnoea- or hypopnoea-related body movements, as well as periodic leg movement-related body movements, were excluded. During 20 seconds of quiet wakefulness we measured the mean R-R interval before sleep onset. During sleep, we measured the shortest R-R interval during the 20 s after the onset of body movements and the longest and the mean R-R intervals between 30 and 10 s before body movements (Fig. 1). The 10 s immediately preceding body movements were excluded as the movement-related tachycardia has been shown to commence 8 seconds before body movements [22]. The following indexes were calculated as the average of at least three measurements randomly selected, either during rapid eye movement (REM) or non-REM (NREM) sleep:

(1) the ratio of the mean R-R interval before body movements to the mean R-R interval during wakefulness (sleep/wakefulness ratio = $R_{s/w}$);

(2) the ratio of the longest R-R interval before body movements to the shortest one after body movement (body movement ratio = R_{bm}).

$R_{s/w}$ was considered to be an index of tonic HR decrease, induced by sleep (mainly vagal activity). R_{bm} was considered to be an index of phasic HR increase, induced by body movements (mainly sympathetic activity).

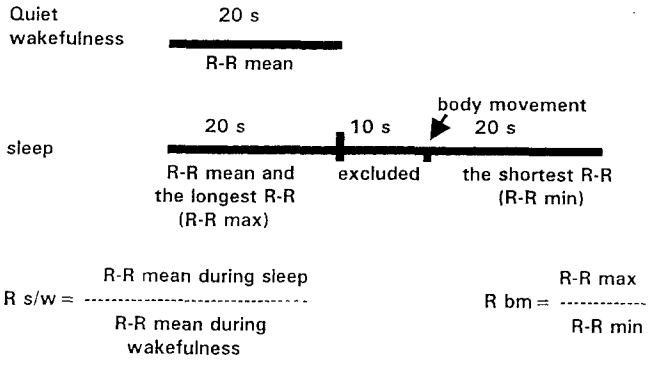

Fig. 1 Heart rate parameters measured during quiet wakefulness and sleep

Magnetic resonance imaging

Brain MRI was performed in each MS patient. T2-weighted MRI was performed with a Siemens system operating at 1.5 T (SE 2400/25–90, 5-mm contiguous axial and 4-mm sagittal slices, 256 × 256 image matrix). Scans were examined by one of us, who was unaware of patients' disease pattern. Lesions were counted and sized for 16 anatomically defined locations (7 periventricular and 9 separate from the ventricles). An arbitrary scoring system weighted for lesion size was used to estimate total and regional lesion loads: 1 point was given for each lesion with a diameter 1–5 mm, 2 points for 6–10 mm, and 3 points for over 10 mm.

Statistical analysis

The results of cardiac autonomic data of MS patients and controls were analysed with the Mann-Whitney test. The relationship between cardiac autonomic variables and clinical or MRI findings in MS patients was explored by means of the Spearman correlation test.

Results

The polysomnographic results we obtained in MS patients and controls were reported in our previous paper [5]. MS patients had significantly reduced sleep efficiency and experienced more awakenings during sleep. No difference was found in sleep architecture parameters between MS patients and controls. Periodic leg movements during sleep were found in 9 patients (36%) and 2 controls (8%).

The results of the cardiovascular autonomic tests during wakefulness are reported in Table 1. No difference was found in these tests between patients and controls. Regarding the individual values, no abnormality was found among the MS patients in the deep breathing, Valsalva and BP response to standing tests. Only 2 MS patients (8%) had abnormal results in the HR response to standing.

The cardiac ANS indices are reported in Table 2. The $R_{s/w}$ during both NREM and REM sleep was significantly reduced in MS patients compared with controls. This finding in patients could be related to a decreased vagal tone during sleep or, inversely, to an increased HR during wakefulness. The mean R-R interval during wakefulness was not significantly different between MS patients and controls (0.86, SD 0.09 vs 0.83, SD 0.10), while the mean R-R interval during sleep was significantly different between MS patients and controls (NREM sleep: 0.90, SD 0.07 vs 0.96, SD 0.08, $P = 0.007$; REM sleep: 0.89, SD 0.08 vs 0.95, SD 0.07, $P = 0.011$). In other words, in MS patients HR decreased to a lesser degree during both types of sleep, suggesting a parasympathetic dysfunction.

The values of R_{bm} in the MS group were not different from those of controls during both NREM and REM sleep. This finding indicated a similar body movement-related tachycardia during sleep in MS patients and controls.

Table 3 shows the distribution of MRI lesion load in MS patients. The correlation analysis between autonomic indices and clinical parameters showed that there was no statistically significant correlation with duration of disease, Kurtzke EDSS score, or single Kurtzke FSS score including that of brain stem function. No significant correlation was found between cardiac autonomic indices and MRI lesion load of periventricular and non-periventricular areas and, in particular, of the brain stem.

Table 1 Autonomic cardiovascular functions during wakefulness. Values are expressed as mean (SD)

Test	MS Patients ($n = 25$)	Controls ($n = 25$)	P
Deep breathing:			
$IE_{diff.}$	24.9 (8.5)	25.8 (6.9)	NS
Valsalva ratio	2.1 (0.4)	1.7 (0.4)	NS
Orthostatic test:			
Blood pressure	−2.5 (8.1)	−1.3 (7.6)	NS
Heart rate 30:15 ratio	1.4 (0.2)	1.3 (0.1)	NS

Table 2 Heart rate variability during sleep. Values are expressed as Mean (SD)

		MS Patients ($n = 25$)	Controls ($n = 25$)	P
$R_{s/w}$	NREM sleep	1.04 (0.09)	1.15 (0.07)	001
	REM sleep	1.03 (0.09)	1.14 (0.08)	001
R_{bm}	NREM sleep	1.52 (0.16)	1.57 (0.18)	NS
	REM sleep	1.53 (0.18)	1.56 (0.16)	NS

Table 3 Distribution of MRI lesion load[a] in multiple sclerosis patients

Brain regions	Median	Range
Periventricular	24	0–76
Body of lateral ventricles	12	0–46
Frontal horn	2	0–15
Trigone	6	0–12
Occipital horn	3	0–12
Temporal horn	0	0– 6
Third ventricle	0	0– 3
Fourth ventricle	0	0– 5
Non-periventricular	14	2–74
Brainstem	1	0– 7
Cerebellum	0	0– 7
Internal capsule	2	0– 8
Basal ganglia	0	0– 8
Frontal lobe	7	0–33
Parietal lobe	2	0–15
Temporal lobe	1	0– 9
Occipital lobe	0	0– 6
Corpus callosum	2	0– 7

[a] Arbitrary score; see text for details

Discussion

Cardiovascular ANS function in MS has been investigated by several studies and abnormalities have been detected in a variable percentage of patients, from 10% up to 55% [1, 13, 14, 20, 24]. Abnormality was most frequently found in the deep breathing test (parasympathetic test) and in those tests assessing sympathetic function. The discrepancies in the results obtained from the different studies might be related to the fact that patients over 60 years of age were sometimes included. It is known that in subjects older than 60, there is a "physiological" reduction of HR variability [3, 18]. For this reason, we only included subjects aged between 25 and 55 years.

The discrepancies among the studies that evaluated ANS function in MS may be also related to the limits of the classical autonomic tests during wakefulness. These tests are greatly influenced by psychological factors and it is known that MS patients can undergo mood alterations or experience anxiety.

Concerning the autonomic cardiovascular reflexes during wakefulness we found no significant difference between MS patients and controls. Only 2 MS patients had abnormal value in a parasympathetic test, such as the HR response to standing. There is general agreement that a diagnosis of ANS dysfunction cannot be substantiated on the basis of the result of a single test, and that the presence of at least two abnormal tests indicates ANS dysfunction [12]. According to this criterion none of our MS patients should have been affected by ANS impairment. On the other hand, not all MS patients were able to complete all autonomic tests during wakefulness in some other studies [1, 14].

Sleep serves as a model for studying the neural modulation of the cardiovascular system under circumstances that are natural and repeatable [11]. For this reason, we evaluated in our patients, as well as the autonomic cardiovascular reflexes during wakefulness, tonic and phasic HR variations during sleep in relation to spontaneous body movements. No significant difference in R_{bm}, (a mainly sympathetic index) was observed between the two groups during sleep. In contrast, $R_{s/w}$ (a mainly vagal index) was significantly reduced in MS patients. It has been suggested that plaques of demyelination may disrupt the vasomotor centre in the medulla or interfere with the descending ANS pathways during their course in the brain stem. In our study the functional system score of the EDSS indicative of brain stem lesions was not associated with abnormal cardiac ANS findings, in agreement with the study of Anema et al. [1]. Based on MRI findings these authors found, like us, no indication for localization of the autonomic disturbances in the brain stem. In contrast, Vita et al. [24] found a significant association between the presence of autonomic dysfunction and MRI evidence of brain stem lesions. The discrepancy may be related to the different evaluation of MRI findings. In fact, we did not perform a qualitative evaluation but utilized a quantitative scoring system. However, our results of a parasympathetic involvement in MS patients are in agreement with the study of Vita et al. [24]. These authors found that the patients with at least two abnormal autonomic tests showed mainly a parasympathetic dysfunction.

Our data suggest that the ANS impairment in MS may have its origin in supramedullary reflex pathways or in the spinal cord. Another possibility is that the damage to peripheral afferent or efferent pathways may contribute to ANS impairment. Consistent abnormalities in peripheral nerve sensory conduction have been demonstrated in MS, probably due a defect in peripheral nervous system myelin [17].

In conclusion, our study has demonstrated more rigid and thus less adaptive dynamics of the parasympathetic cardiac activity in MS patients during sleep. This ANS dysfunction appears to be unrelated to MRI lesion loads for infratentorial regions, particularly in the brain stem. Follow-up studies that could clarify whether cardiac autonomic dysfunction is associated with the progressive course of MS should include the evaluation of ANS during sleep by using our method, as well as HR spectral analysis [23].

References

1. Anema JR, Heijenbrok MW, Faes TJC, et al (1989) Cardiovascular autonomic function in multiple sclerosis. J Neurol Sci 104: 129–134
2. Benarroch EE, Chang FLF (1993) Central autonomic disorders. J Clin Neurophysiol 10: 39–50
3. Ewing DJ, Neilson JMM, Shapiro CM, Stewart JA, Reid W (1991) Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients. Br Heart J 65: 239–244
4. Ferini-Strambi L, Zucconi M, Oldani A, et al (1992) Heart rate variability during sleep in snorers with and without obstructive sleep apnea. Chest 102: 1023–1027
5. Ferini-Strambi L, Filippi M, Martinelli V, et al (1994) Nocturnal sleep study in multiple sclerosis: correlations with clinical and brain magnetic resonance imaging findings. J Neurol Sci 125: 194–197
6. Franceschi M, Ferini-Strambi L, Minicucci F, et al (1986) Signs of cardiac autonomic dysfunction during sleep in patients with Alzheimer's disease. Gerontology 32: 327–334

7. Gutrecht JA, Suarez GA, Denny BE (1993) Sympathetic skin response in multiple sclerosis. J Neurol Sci 118: 88–91
8. Kaijser L, Sachs C (1988) Autonomic nerve function as evaluated from cardiovascular responses and regulation of lung ventilation in sleep apnea syndrome and narcolepsy. In: Kulbertus HE, Franck G (eds) Neurocardiology. Futura, New York, pp 327–343
9. Kurtzke J (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33: 1444–1452
10. Malpas SC, Purdie GL (1990) Circadian variation of heart rate variability. Cardiovasc Res 24: 210–213
11. Mancia G (1993) Autonomic modulation of the cardiovascular system during sleep. N Engl J Med 328: 347–349
12. McLoed SG, Tusk RR (1987) Disorders of the autonomic nervous system. 2. Investigation and treatment. Ann Neurol 21: 519–529
13. Nordenbo AM, Boesen F, Andersen EB (1989) Cardiovascular autonomic function in multiple sclerosis. J Auton Nerv Syst 26: 77–84
14. Pentland B, Ewing DJ (1987) Cardiovascular reflexes in multiple sclerosis. Eur Neurol 26: 46–50
15. Poser CM, Paty DW, Scheinberg L, et al (1983) New diagnostic criteria for multiple sclerosis: guideline for research protocol. Ann Neurol 13: 227–231
16. Rechtschaffen A, Kales A (eds) (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Brain Information Service/Brain Research Institute, University of California at Los Angeles
17. Shefner JM, Carter JL, Krarup C (1992) Peripheral sensory abnormalities in patients with multiple sclerosis. Muscle Nerve 15: 73–76
18. Smirne S, Montanari C, Pinto P, Ferini-Strambi L (1988) Cardiac autonomic dysfunction during sleep in diabetic patients. In: Smirne S, Franceschi M, Ferini-Strambi L (eds) Sleep in medical and neuropsychiatric disorders. Masson, Milan, pp 3–12
19. Smirne S, Ferini-Strambi L, Zucconi M, et al (1990) Cardiac autonomic dysfunction during sleep in some neurological disease. Neurophysiol Clin 20: 131–136
20. Sterman AB, Coyle PK, Panasci DJ, et al (1985) Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. Neurology 35: 1665–1668
21. Thomaides TN, Zoukos Y, Chaudhury KR, et al (1993) Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. J Neurol 240: 139–143
22. Townsend RE, Johnson LC, Naitoh P, et al (1975) Heart rate preceding motility in sleep. Psychophysiology 12: 217–219
23. Van de Borne P, Nguyen H, Biston P, Linkowski P, Degaute JP (1994) Effects of wake and sleep stages on the 24-h autonomic control of blood pressure and heart rate in recumbent men. Am J Physiol 266: H 548–H 554
24. Vita G, Fazio MC, Milone S, et al (1993) Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brain stem lesions. J Neurol Sci 120: 82–86