Autonomic and Cardiac Testing in Multiple Sclerosis Patients Complaining Fatigue During Rehabilitative Treatment

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Abstract

In Multiple Sclerosis (MS) abnormalities of autonomic nervous system and cardiac parameters have been reported separately. Our objectives were to investigate whether MS patients with moderate disability and autonomic dysfunction presented alterations in cardiac function under stress and to see whether these changes contribute to MS fatigue. In 33 MS patients we examined the cardiovascular autonomic system and the echocardiographic parameters (stroke volume and ejection fraction) at rest and under stress. Fatigue has been assessed by a self-reported measure, the Fatigue Severity Scale. We have found a statistically significant correlation between the findings of cardiovagal tests and changes in cardiac parameters under stress with the degree of self-evaluated fatigue. Our results suggest that a relationship between the autonomic dysfunction and blunted cardiac response under stress might exist and can contribute to perception of fatigue. This physiopathological mechanism may be one aspect of the complex and multidimensional MS fatigue.

Key words: autonomic dysfunction, blunted cardiac response, fatigue, multiple sclerosis, under stress.

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Abnormalities of autonomic nervous system (ANS) function in Multiple Sclerosis (MS) have been reported in various studies [6, 9, 10, 17, 21, 28]. Some recent studies have also shown altered parameters of cardiac function at rest [20, 30]. However a possible relationship between these alterations has never been investigated.

During physical exercise ANS is responsible for compensating the haemodynamic cardiovascular responses to stress; this action is achieved mainly through a modulation of cardiac pump function. Autonomic dysfunction can therefore lead to limitation of exercise capacity and might contribute to not yet explained fatigue in MS patients. Fatigue is in fact still far to be understood especially because of its polymorphous presentation within MS patients.

Our objective was to investigate the occurrence of ANS dysfunction in MS patients with moderate disability and the eventual correlation with modifications in cardiac parameters after challenge with hyperventilation. We have tried to evaluate if these cardiovascular changes contributed to the perception of fatigue evaluated by a self-reported scale.

Materials and Methods

Patient group

We studied 33 MS patients, 20 males and 13 females (mean age 43 ± 10 years), admitted to our Department of Neurorehabilitation; these patients complained fatigue during rehabilitative treatment; MS disease duration ranged from 3 to 15 years (mean 8.3 ± 5.4).

Inclusion criteria were (1) age 20 - 55 years; (2) clinically definite MS, according to the Poser's criteria [23]; (3) classified as secondary progressive MS, clinically defined according to published criteria [15]; (4) no exacerbation in the four weeks preceding the enrollment; (5) able to gait (with o without bilateral assistance) and Expanded Disability Status Scale of Kurtzke (EDSS) [14] ranging from 3.0 to 6.5. Medication likely to influence autonomic nervous system and/or possibly affecting fatigue (antidepressants, amantadine) were withdrawn at least 48 h before testing. No patients taking immunosuppressive or immunomodulatory therapy were included. Cardiac and pulmonary diseases were excluded by means of clinical, ECG, chest X-ray, echocardiographic screening and spirometry.

The investigations were conducted with the understanding and the informed consent obtained from all the patients.

Autonomic and cardiac assessments

1) The autonomic cardiovascular activity has been explored with neuro-physiologic equipment (Medtronic Functional Diagnostics Keypoint software vs.3.01). We performed a non-invasive set of quantitative examinations to detect the involvement of the cardiovascular autonomic system. According to the most frequently used procedures in autonomic laboratories [16, 24], we performed the following series of tests: heart rate variability (HRV) during rest, deep breathing (HRV-Bre), Valsalva maneuver and active posture changes to investigate parasympathetic cardiac function; orthostatic blood pressure response (to tilt-table test) was used to investigate sympathetic cardiovascular function.

1a) Cardiovagal tests

The integrity of parasympathetic cholinergic (cardiovagal) function was investigated by assessing heart rate variability. Heart rate is inversely related to R-R interval and is easily calculated from it. Previous studies showed that heart rate variation to multiple tests is more reliable than a single test to detect a vagal dysfunction. The R-R interval changes have been analyzed during normal and deep breathing, standing and Valsalva test [19, 27].

Patients rested for 3 minutes in a supine position before the test.

The first run was obtained during baseline condition with normal breathing.

The next cardiovascular reflex test was obtained following instructions from the operator and the second run included recording during deep breathing at a frequency of 6 cycles for one minute (5 sec for inspiration and 5 sec for expiration). A plot of R-R intervals versus time was displayed online on the computer screen. Positive and negative peaks (*maxima* and *minima*) were defined by means of a three-point search algorithm. The normal and deep breathing R-R interval were analyzed using the following algorithm: the difference between the shortest and the longest RR intervals given in percent of the mean of all maximal and minimal peaks [(RRmax - RRmin) x 100/RRmean]. Pathologic values, corrected for age, were those exceeding 2 SD (standard deviation).

The third test was the heart rate variability to the Valsalva maneuver (HRV-Val) expressed as the Valsalva ratio, which is the ratio of the longest R-R shortly after the maneuver to the shortest R-R during the respiratory effort; a ratio of less than 1.20 was classified as a pathologic [19, 24, 27].

The last test was the heart rate variability to standing (active change of posture, HRV-Post) expressed as the 30:15 ratio, which is the longest R-R interval around the 30^{th} beat after standing divided by the shortest R-R around the 15^{th} beat; ratios lower than 1.03 were classified as a pathologic [19, 24, 27].

Parasympathetic autonomic score (PAS) [16]

Because HR variability during normal breathing is often minimal, slight reductions are difficult to be detected. A score for parasympathetic dysfunction was obtained from three cardiovagal tests by scoring each test, giving 0 for abnormal and 1 point for a normal result, according to age-dependent reference values [27].

1b) Sympathetic cardiovascular (adrenergic) test

Tilt-table testing by achieving changes in blood pressure (BP) in patients with motor disorders is able to reveal the integrity of the autonomic cardiovascular reflexes (early responses occurring within 30-60 sec). After 10 min of supine rest, patients are positioned at 70° of inclination from the horizontal on a tilt-table with a foot board for weight bearing; blood pressure and heart rate are measured at baseline and at minute 1 and every 3 min thereafter.

Orthostatic hypotension is a reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min [24].

Maximal heart rate increase after standing has been included as a marker of cardiovagal integrity.

2) Functional echocardiographic parameters changes

Since patients with motor disabilities cannot be exercised to achieve maximal o submaximal heart rate, we used ventilation as a possible alternative. Hyperventilation performed under echocardiographic monitoring has been already proposed as a screening test to unmask vasospastic myocardial ischaemia [18]. Patients underwent hyperventilation (approximately 24 cycles/min for at least 3 min). The resulting changes of cardiac function have been assessed by the following echocardiographic parameters:

stroke volume (SV) [ml] = (End diastolic Volume - End Sistolic Volume)

ejection fraction (EF) [%] = [(End diastolic Volume - End Sistolic Volume) / (End Diastolic Volume)] * 100

These parameters have been taken by color flow Doppler two-dimensional (method of area-length) transthoracic echocardiography, at rest and following hyperventilation.

MS self-evaluated fatigue

We have chosen Fatigue Severity Scale (FSS) [12], as a self-evaluated measure with a reported physical focus [7].

Fatigue was described as an increased weakness during exercise or lack of energy out of proportion to the degree of effort or an abnormal sense of tiredness that limits daily activities and interferes with work, family or social life.

FSS is based on a nine-items questionnaire assessing the fatigue reported during the preceding 2 months (e.g., exercise brings on my fatigue; fatigue interferes with my physical functioning; my fatigue prevents sustained physical functioning). Each item is scored between 1 and 7 indicating strong disagreement and strong agreement, respectively. The FSS score was the mean value from all nine items. This scale shows sensitivity and reliability in the assessment of fatigue; the authors of FSS reported no significant correlation between the degree of fatigue and the depression scale scores.

Statistical analysis

For statistical analysis, the SPSS package was used.

Correlations between age, EDSS, PAS, FSS, ΔEF (EF after hyperventilation – EF at rest) and ΔSV (SV after hyperventilation – SV at rest) were determined using Pearson Correlation. A P value of < 0.01 was considered statistically significant.

Results

Autonomic cardiovascular tests

Baseline measurements resulted in a mean supine blood pressure of 122±12 / 75±11 mm Hg. Mean supine heart rate was 68±9 beats per minute (bpm). All patients performed all five test. Autonomic tests resulted to be normal in 15 patients: no subject showed orthostatic hypotension, the maximal heart rate increase after tilt-table was 18±5 bpm and all the cardiovagal tests were in the normal range (PAS = 3). Also the 18 others patients had no orthostatic hypotension but had no variation of heart rate during Tilt Table Test; besides in these patients, at least one cardiovagal test was found to be pathologic. In particular, 4 patients had PAS = 0, 10 PAS = 1 and 4 PAS = 2. The most frequently altered test was the HRV-Val (all 18 pt) followed by HRV-Post (14 pt) and HRV-Bre (4 pt). We did not observe any significant difference between these last patients and the others 15 in the baseline parameters.

Functional cardiac parameters changes under stress

At rest, all 33 patients showed a normal EF (60% ± 8).

Mean SV resulted 42,3 ml ± 6. After the respiratory effort, significant abnormal sense of tiredness or lack of energy were reported. Neither chest pain nor ST-T changes were detected during hyperventilation in any patient.

After maximal hyperventilation 15 pt showed an increased SV, with a mean SV change of 9 ml ± 5 (18%) (ranging from 0 to 26 ml) and an increased EF, with a mean change of 9.5 ± 5 (15%) (ranging from 0 to 25); 18 pt showed a decreased SV, with a mean decrease of -9.7 ml ± 4 (-18%) (ranging from -2 to -29 ml) and a decreased EF, with a mean decrease of - 7.4 ± 3 (-13%) (ranging from -1 to -28).

Correlation between cardiac parameters changes under stress and autonomic tests

Autonomic scores (PAS) and changes in cardiac parameters (ΔEF and ΔSV) showed a statistically significant correlation (PAS vs ΔEF: $r_{(33)}$=0.626, p<0,01; PAS vs ΔSV: $r_{(33)}$=0.752, p<0.01). Neither autonomic tests nor changes in cardiac parameters correlated with age and EDSS score (PAS vs age: $r_{(33)}$=-0.261, p=0.143; PAS vs EDSS:
$r_{(33)}$=-0.158 p=0,38; ΔSV vs age: $r_{(33)}$ =0.118, p=0.514; ΔSV vs EDSS: $r_{(33)}$=-0.027, p=0.880; ΔEF vs age: $r_{(33)}$=0.231, p=0.195; ΔEF vs EDSS: $r_{(33)}$=-0.147; p=0.414).

Correlation between cardiac parameters changes, autonomic and fatigue scores

Autonomic findings and changes in cardiac parameters were significantly associated with fatigue scores (FSS).

PAS, ΔEF, ΔSV and FSS showed a statistically significant correlation (FSS vs ΔEF: $r_{(33)}$=-0.832, p<0,01; FSS vs ΔSV: $r_{(33)}$=-0.668, p<0.01; FSS vs PAS: $r_{(33)}$=-0.760, p<0.01). FSS scores was not correlated with age and EDSS (FSS vs age: $r_{(33)}$=0.177, p=0.324; FSS vs EDSS: $r_{(33)}$=0.053, p=0,771).

Discussion

Autonomic pathological tests were observed, in various percentages, from 20-40% [6, 17, 21] to more than 50% [1, 10, 28] of MS patients. All these studies showed a variable impairment of the two cardiovascular autonomic components.

In our study, we observed a reduced parasympathetic activity in over 50% of tested patients. The test that most often resulted pathological is HRV-Val, that it is considered after HRV-Bre the second best cardiovagal test [24]. The heart rate variability during Valsalva maneuver and in particularly during active change of posture is influenced by both divisions of ANS but is mainly mediated by parasympathetic pathways. In these patients with pathologic cardiovagal tests, a prevailing parasympathetic abnormality is suggested also by the absence of heart rate variation during Tilt Table Test.

Moreover the cardiovascular sympathetic component, assessed by tilt-table BP response, resulted to be normal. The discrepancies between the results of other studies and the present findings might be related to several factors: our patients presented a moderate disability with an ability to assisted gait, and none of them was compelled to use wheelchair only; in some studies BP modifications have been assessed during active standing while in others, sympathetic tests, such as BP response to sustained handgrip or to mental stress, that are not been well validated [24], have been employed; no study has assessed BP changes by continuous perfusion controlled volume-clamp measurement (Finapres, Portapres); furthermore, neither patients suffered of syncope during daily life nor of orthostatic hypotension [9, 28, 29].

Previous Ziaber's study [30] reported, in MS patients with EDSS ranging 5-7, abnormalities of cardiac parameters at rest (EF and cardiac output) investigated by color flow Doppler transthoracic echocardiography. A recent study of Olindo et al. [20], based on radionuclide angiocardiography has confirmed these findings without correlating them with the degree of disability.

In our patients, echocardiographic assessment at rest showed normal EF and SV values [4]. Differences with other studies may well be accounted for the patient selection.

Some authors proposed that in MS patients autonomic impairment may account for a decreased cardiac response. Ziaber et al. [30] reported impaired VEF, SV and cardiac output after tilt to erect position. Senartane et al [25]. found attenuated heart rate and systolic blood pressure in response to exercise.

Our objective was to evaluate in MS patients with moderate disability changes in cardiac function under stress and correlate them with ANS dysfunction. We have found a statistically significant correlation between the results of cardiovagal tests and changes in cardiac parameters, evaluated by ΔEF and ΔSV. Therefore patients with cardiovagal dysfunction didn't appear to show a proper response to stress. Besides, the absence of heart rate variation after hyperventilation and during Tilt Table Test might sustains the hypothesis that the parasympathetic abnormalities might be closely correlated with the depressed cardiovascular responses.

ANS regulates cardiac pump function throughout either a modulation of both heart rate and myocardial contractility. However our results showing a decrease response after stress even for those parameters such as SV and EF that are the less heart rate- dependent might suggest a reduced myocardial efficiency, too. A subclinical involvement of the heart, probably secondary to MS, has been proposed by previous echocardiographic, metabolic and functional studies [3, 20, 30] but we believe that further studies are needed to understand its clinical relevance.

We have found a statistically significant correlation between the results of cardiovagal tests and the cardiovascular responses under stress with degree of self-evaluated fatigue. The chosen self-report measure (FSS) has been recognized to be helpful in the assessment of physical fatigue. Neither cardiovagal tests nor changes in cardiac parameters nor FSS scores correlated with age and neurologic disability.

In different neurological disorders, as Multiple System Atrophy or Chronic Fatigue Syndrome (CFS), "fatigue" symptom has been discussed to be consequence of autonomic dysfunction [8]. Particularly, reduction of the vagal tone has been suggested as a possible explanation of fatigue in CSF patients [26]. Recently, a spectral analysis of heart rate variability has identified an age-related reduction of vagal activity that occurs earlier in MS patients complaining fatigue [11]. Our study seems to confirm that a parasympathetic dysfunction might be one of the possible factors influencing fatigue perception in MS patients.

ANS response represents a compensatory mechanism to exercise-induced stress. ANS dysfunction can lead to physical intolerance by blunting cardiac responses. In fact, ANS provides two different types of responses during exercise: initially prevails the parasympathetic withdrawal, followed, as duration and intensity of exercise increase, by a prevailing sympathetic activation. Moreover alteration of modification of vagal tone for increasing levels of exercise might contribute to the early onset of fatigue [22].

This physiopathological mechanism may be one aspect of the complex and multidimensional MS fatigue [2, 5, 6, 10, 13, 29, 30].

Conclusion

Our results suggest that in MS patients might exist a relationship between parasympathetic dysfunction and blunted cardiovascular responses under stress. Besides these modifications can contribute to perception fatigue in MS patients.

The impact of fatigue on patients function and quality of life clearly warrants intervention.

A further validation of the etiology is important because in addition to pharmacological measures, such as caution in prescribing medication likely to influence autonomic nervous system, rehabilitative treatment, such as physical exercise strategies, can be effective to prevent or delay the occurrence of fatigue in MS patients.

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Supplier

Neuro-physiologic equipment: Medtronic Functional Diagnostics Keypoint software vs.3.01

Abbreviations

ANS autonomic nervous system
BP blood pressure
CFS Chronic Fatigue Syndrome
EDSS Expanded Disability Status Scale of Kurtzke
EF ejection fraction
ΔEF (EF after hyperventilation – EF at rest)
FSS Fatigue Severity Scale
HRV-Bre heart rate variability during deep breathing
HRV-Post heart rate variability during active change of posture
HRV-Val heart rate variability during Valsalva maneuver
MS Multiple Sclerosis
PAS parasymphatetic autonomic score
SV stroke volume
ΔSV (SV after hyperventilation – SV at rest)