**Research Paper**

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# Is fatigue in patients with multiple sclerosis related to autonomic dysfunction?

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**Time-dependent frequency decomposition of fluctuations in cardiovascular signals (heart rate [HR], blood pressure, and blood flow) provides noninvasive and quantitative evaluation of autonomic activity during transient and steady-state conditions. This method was applied during a change of position from supine to standing in patients with multiple sclerosis (MS) who experienced unexplained fatigue and in age-matched control subjects.**

**No difference in response to standing, as reflected in the time domain parameters (mean HR, mean blood pressure, and mean blood flow), was observed between patients with MS and control subjects. Moreover, no difference was observed in very-low–frequency and low-frequency (related to sympathetic activity) content of HR, blood pressure, blood flow, or high-frequency content of HR (related to parasympathetic activity). The only spectral estimates that showed a significant difference between groups were the ratio of low-frequency to high-frequency content of HR and low-frequency content of HR normalized to total power. Both these parameters provide an estimate of the sympathovagal balance. A significant increase in these two estimates on standing was observed in control subjects only, indicating possible impairment of the sympathovagal balance response to standing in patients with MS who experienced fatigue. The authors observed a significant age dependence between close age subgroups, which occurred in the MS group only and was observed in some of the investigated spectral estimates that reflect vagal activity. Therefore, the authors assumed that age-related reduction in vagal activity occurred earlier in patients with MS who experienced fatigue. This reduction could also explain the lack of increase in the sympathovagal balance on standing. To validate this enhanced age dependence, further investigation should be performed in a larger group of subjects with a wider age range.**

*Key words:* multiple sclerosis, fatigue, heart rate variability, time-frequency analysis.

Autonomic dysfunction in patients with multiple sclerosis (MS) can be associated with many signs and symptoms. It is generally reflected by bladder, bowel, sexual, and sweating dysfunctions [1] and occasionally by abnormal response to autonomic tests. An abnormal response to standing, head-up tilt, cold-face test, the Valsalva maneuver, and deep breathing has been reported in various studies [1–6]. Diamond *et al.* [7] found that patients with MS had significantly lower vagal power, as measured by spectral peaks or area measures, during both unpaced and paced breathing conditions, as compared with control subjects. Anema *et al.* [5] found an abnormal mean heart rate (HR) response to standing in 28% of the 34 patients with MS who they analyzed and an abnormal mean blood pressure (BP) response in 13% of the patients.

Although the abnormalities of cardiovascular regulation always occur in a heterogeneous pattern that is consistent with scattered plaques [3], Vita *et al.* [1] first reported a significant correlation between autonomic dysfunction and both clinical evidence and magnetic resonance imaging evidence of brainstem lesions.

Analysis of fluctuations in cardiovascular signals, such as HR and BP, provides noninvasive and quantitative evaluation of autonomic functioning. In recent years, novel methods for time-frequency analysis have been applied to fluctuations in cardiovascular signals and have provided information regarding autonomic function, even in nonsteady conditions and during abrupt transitions or provocations [8,9]. Analysis of the autonomic system during transient conditions may reveal a malfunction hidden during steady state.

Applying standard spectral tools to analyze the short-term variability in R-R intervals at rest and after head-up tilting, Frontoni *et al.* [6] reported an impairment of cardiovascular reflexes in 25% of the patients with MS who they investigated. Moreover, they found no correlation between spectral parameters and lesion area or localization as detected by magnetic resonance imaging of the brain.

Fatigue is a common symptom in MS that frequently interferes with patients' daily activities. Its pathogenesis is unknown, and the question of whether there is a specific type of fatigue in MS is controversial. It is estimated that 75–90% of patients with MS experience fatigue at some point during the course of the disease and that, in approximately one half of these patients, subjective fatigue is a primary complaint [10]. MS fatigue has been shown to be

unrelated to depression or global impairment [11]. Although the involvement of autonomic dysfunction in fatigue in patients with chronic fatigue syndrome has been previously reported, such as during standing, the Valsalva maneuver, paced breathing, and performance of mental arithmetic [12–14], the cause of MS fatigue is poorly understood, and its relation to autonomic function has not been investigated.

Based on the observations of autonomic dysfunction in patients with chronic fatigue syndrome, we hypothesized that chronic fatigue in patients with MS could originate from an autonomic dysfunction, which may be shown by analysis of variability in cardiovascular signals. To test this hypothesis, we applied time-dependent spectral analysis on fluctuations in HR, BP, and blood flow (BF) during an active change of posture in patients with MS who had unexplained chronic fatigue and in control subjects.

## Methods

*Population and protocol*

We studied 10 patients (7 women, 3 men; age range, 22–58 y; mean age, 41 ± 13 y) with definite MS [15] and average disease duration of 9 ± 7 years. Inclusion criteria for participation in the study were a fatigue severity scale [11] score higher than 3.5, a visual analog scale (0–10) assessment of fatigue higher than 5, and a subjective report that fatigue interfered with at least 25% of the patient's daily activities. Exclusion criteria were cardiovascular illness, disorders with possible autonomic dysfunction, arrhythmia, or drugs with known autonomic effects. The control group included 10 healthy age-matched subjects (8 women, 2 men; age range, 25–50 y; mean age, 40 ± 9 y).

Patients and control subjects received a detailed explanation of the study protocol and gave informed consent for participation. The study was approved by the Ethical Committee of the Sheba Medical Center and by the Ethical Committee of the Israeli Ministry of Health.

None of the subjects experienced cardiovascular illness or pathologies with possible autonomic dysfunction or arrhythmia. All the recordings were taken in a quiet, warm room during the morning and early afternoon.

Subjects lay in the supine position for 10 minutes before recording began. Electrocardiograph activity (BIOPAC MP100 system; Biopac Systems, Goleta, CA, USA), continuous BP (Finapres; Ohmeda 2300, Madison, WI, USA), peripheral BF (Perimed Laser Doppler Flowmeter; Periflex 4001; Perimed, Sweden), and respiration (Respitrace; Ambulatory Monitoring, Ardsley, NY, USA) were continously monitored. After 10 minutes of supine rest, these signals were directly sampled to a personal computer during 10 minutes in the supine position and 5 minutes in the standing position, at a sampling rate of 500 Hz, using a Biopac MP100 system. The physical limitations of the patients with MS made it difficult to record their levels for more than 5 minutes in the standing position. Throughout recording, the subjects were asked to breathe freely and refrain from speaking or sleeping.

*Signal analysis*

R-R intervals were detected from the electrocardiograph signal using a predescribed algorithm [16]. They were smoothed and equally resampled to an effective rate of 10 Hz. The calibration interruptions of the Finapres were automatically corrected [17], and the signal was resampled to 10 Hz using a moving-average filter, to avoid aliasing. The BF and respiration signals were resampled to 10 Hz after using the same antialiasing, moving-average filter. All the signals were detrended using a nonlinear low-pass filter [8] and analyzed using the selective discrete Fourier transform algorithm (SDA) for time-frequency decomposition [8,9]. The nonlinear detrending filter removes very-low–frequency (VLF) information. Therefore, to obtain the evaluation of VLF content (only during steady-state supine position and standing), the SDA was applied to the unfiltered signals.

The SDA method calculates each spectral component from a specific portion of the signal, the length of which is inversely proportional to the frequency. As a result, the low-frequency (LF) components are calculated with a low time resolution and a high frequency resolution, whereas the high-frequency (HF) components are obtained with a high time resolution and a low frequency resolution. The SDA approach for time-dependent spectral analysis has been extensively verified on simulated and real signals, and applied to cardiovascular signals in various clinical situations and autonomic tests [9,18–20].

The results of the SDA analysis for each subject were displayed as three-dimensional time-dependent power spectra. Frequency ranges were selected according to three principal peaks, usually approximately 0.02–0.06 Hz for the VLF region, 0.06–0.2 Hz for the LF region, and 0.2–0.5 Hz for the HF region. One subject from the control group, whose respiration rate was approximately 0.13 Hz, was excluded from the study because of the overlap occurring between the LF and HF ranges. Integrals were calculated in absolute and in normalized units (divided by total autonomic power, e.g., 0.02–0.5 Hz).

The following parameters were calculated as functions of time: (1) mean HR, BP, and BF; (2) VLF region of HR, BP, and BF spectra, which mainly reflect vasomotor tone; (3) LF power of HR, which reflects both sympathetic and parasympathetic activities involved in the baroreflex; (4) HF power of HR, which reflects parasympathetic activity; (5) LF/HF ratio and normalized LF content of HR fluctuations, which are estimates of the sympathovagal balance; and (6) LF content of BP and BF fluctuations, which mainly reflects the sympathetic control of vasculature.

VLF estimates were evaluated only at baseline and in the standing position because the nonlinear detrending filter could not be used in evaluating this frequency range, and, without this filter, the results at the transition are not reliable [8]. All the other estimates were evaluated at five different times of interest: T1, 2 minutes averaged during baseline supine position; T2, at the onset of HR increase; T3, at maximal HR; T4, at minimal HR after the overshoot (Fig. 1); and T5, 2 minutes averaged in standing position. The

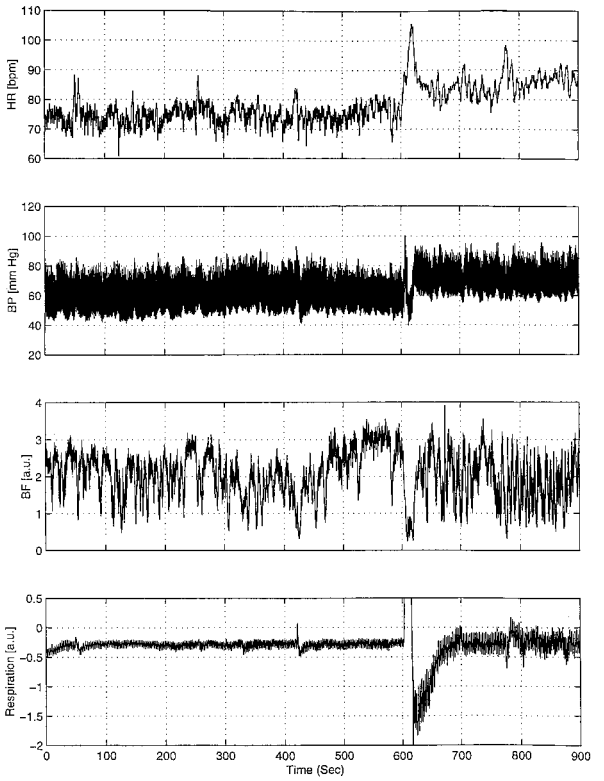


**Figure 1.** Instantaneous heart rate (HR), blood pressure (BP), blood flow (BF) and respiration signals of a patient with multiple sclerosis during 10 minutes in the supine position and 5 minutes standing. The transition from supine to standing position occurs at 600 seconds. At this time, a considerable increase in HR occurs, followed by an undershoot and stabilization at approximately 85 beats per minute. Simultaneously, a reduction in BP and BF occurs. bpm = beats per minute; au = arbitrary units.

times of interest are chosen according to the HR signal, not in absolute value, because the time of the transition varies slightly among subjects, and comparison of absolute times is not reliable [18].

The estimates were averaged in both groups. Age dependence was verified by separating each group into two subgroups: subjects aged less than and more than 45 years. Results were compared between patients with MS and control subjects, and between age groups with use of the Student $t$ test. Time evolution of the estimates was compared between patients with MS and control subjects by analysis of variance. The threshold for statistical significance was set at $p < 0.05$.

## Results

A typical example of the recorded signals of a patient during the entire procedure is shown in Figure 1. At the time of standing (600 seconds), a large increase in mean HR occurs, followed by an undershoot and an HR stabilization at a higher level. Simultaneously to the overshoot in HR, an overshoot in BP and an undershoot in BF occurs.

Measuring these signals at the times of interest previously specified and averaging them for the two groups of subjects, we obtained the data for the graphs in Figure 2. These graphs represent the changes in mean HR, BP, and BF in response to the change in posture, which were similar for both groups. Simultaneously, there was a significant decrease in BF and a significant increase in mean HR at time T3 in both groups. These changes were followed by a return toward baseline values and a stabilization at an intermediate level (significantly higher than baseline for HR only). On standing, mean BP reached a significantly higher level, as compared with the supine value.

The application of the SDA on the fluctuations in the recorded signals provides time-dependent power spectra

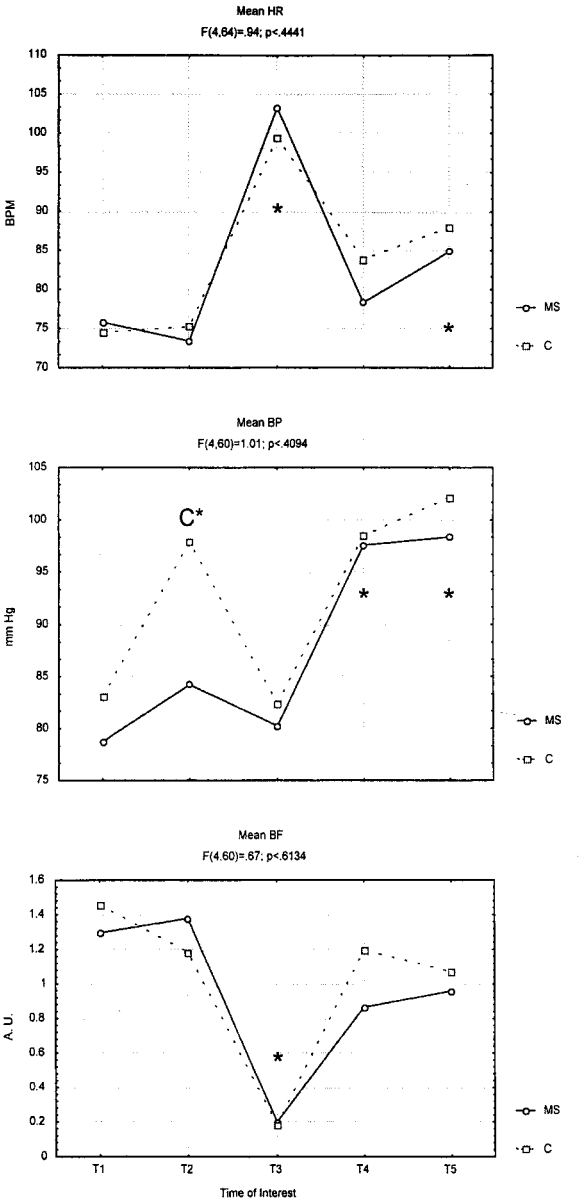


**Figure 2.** Comparison between the average values of mean heart rate (HR), blood pressure (BP), and blood flow (BF) for the multiple sclerosis group (MS; solid line and circles) and the control group (C; dashed line and squares). Significant difference for both groups, as compared with baseline, is indicated by *, and significant difference for the control group only is indicated by C*. Times of interest are at supine position, the onset of HR increase, maximal HR, minimal HR, and stable standing position. In both groups, there is a significant increase in HR at the time of the transition and stabilization to a level higher than the supine level. Both groups also stabilize at a higher level of mean BP. The reduction in BF at the instant of standing also is significant, as compared with the supine level in both groups. BPM = beats per minute.

that can be displayed as three-dimensional graphs (Fig. 3) and as contour plots (Fig. 4). These figures display an example of the application of the time-dependent analysis of patients. The power spectra of HR, BP, and BF show peaks in the same region of power. The HF peak, located at the respiratory frequency (Fig. 4, right panel), is clearly observed in the HR and BP spectra. The reduction in this peak, obvious in the spectrum of HR fluctuations (Fig. 3, top panel), reflects the decrease in vagal tone on standing. It has been reported previously that the effects of this vagal reduction on the HF peak of BP power is blurred by changes in type of respiration, from mainly abdominal breathing while in the supine position to mainly chest breathing while in the standing position [21]. Indeed, in the time-dependent power spectrum of BP fluctuations, a slight increase in HF peak is evident (Fig. 3, middle panel).

The LF peaks of the three spectra show a considerable and long-lasting enhancement on standing. It is interesting to note the almost total reduction of power in BF fluctuations at the instant of the change of posture, followed by a smooth increase. The time-frequency contour plots (Fig. 4) similarly support these results. Such a display allows one to determine more precisely the frequency ranges for the calculations of the integrals than in the three-dimensional graphs.

When analyzing the VLF content of fluctuations in HR, BP, and BF, we observed that patients with MS and control subjects present a similar behavior (Table 1). The VLF content of BF fluctuations was smaller for patients with MS, both for supine and standing positions. However, the high standard deviation of the results causes this difference to be nonsignificant.

Also in LF and HF contents of HR fluctuations, no significant difference was found between patients with MS and control subjects (Fig. 5). The differences observed, especially at times T2 and T5 in the LF content, were nonsignificant because of large standard deviations, and there was no difference (with analysis of variance) in the time

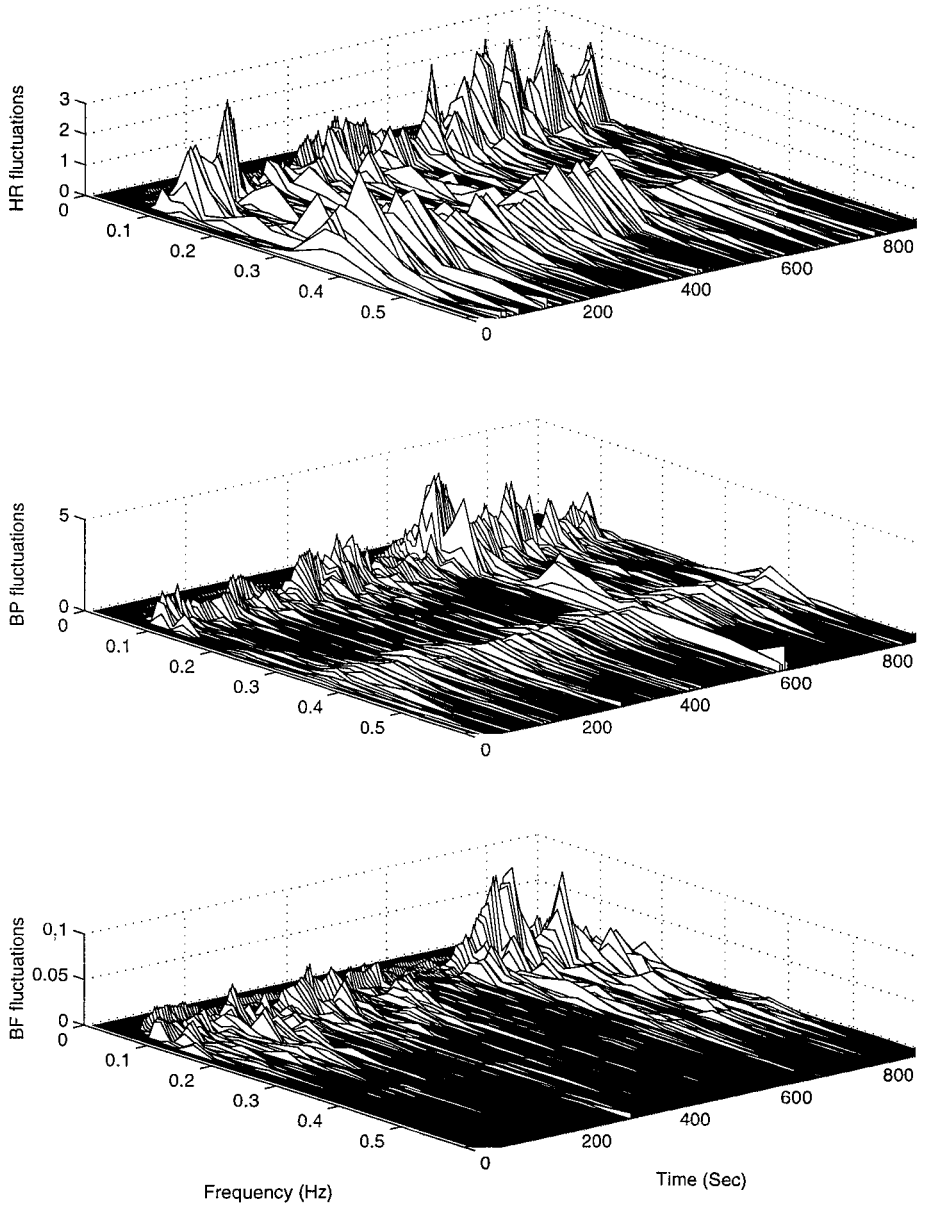


**Figure 3.** Time-dependent power spectra of heart rate (HR; **Top**), blood pressure (BP; **Middle**), and blood flow (BF; **Bottom**) fluctuations. The x-axis is the frequency axis, the y-axis is the time axis, and the z-axis is the power axis. Two distinct peaks of power (at approximately 0.1 and 0.4 Hz) are observed in HR and BP spectra. A reduction in the high-frequency peak (HF) of HR fluctuations occurs on standing (600 seconds), accompanied by a slight increase in the HF peak of BP fluctuations. The low-frequency peaks (LF) of the three signals increase at the standing position.

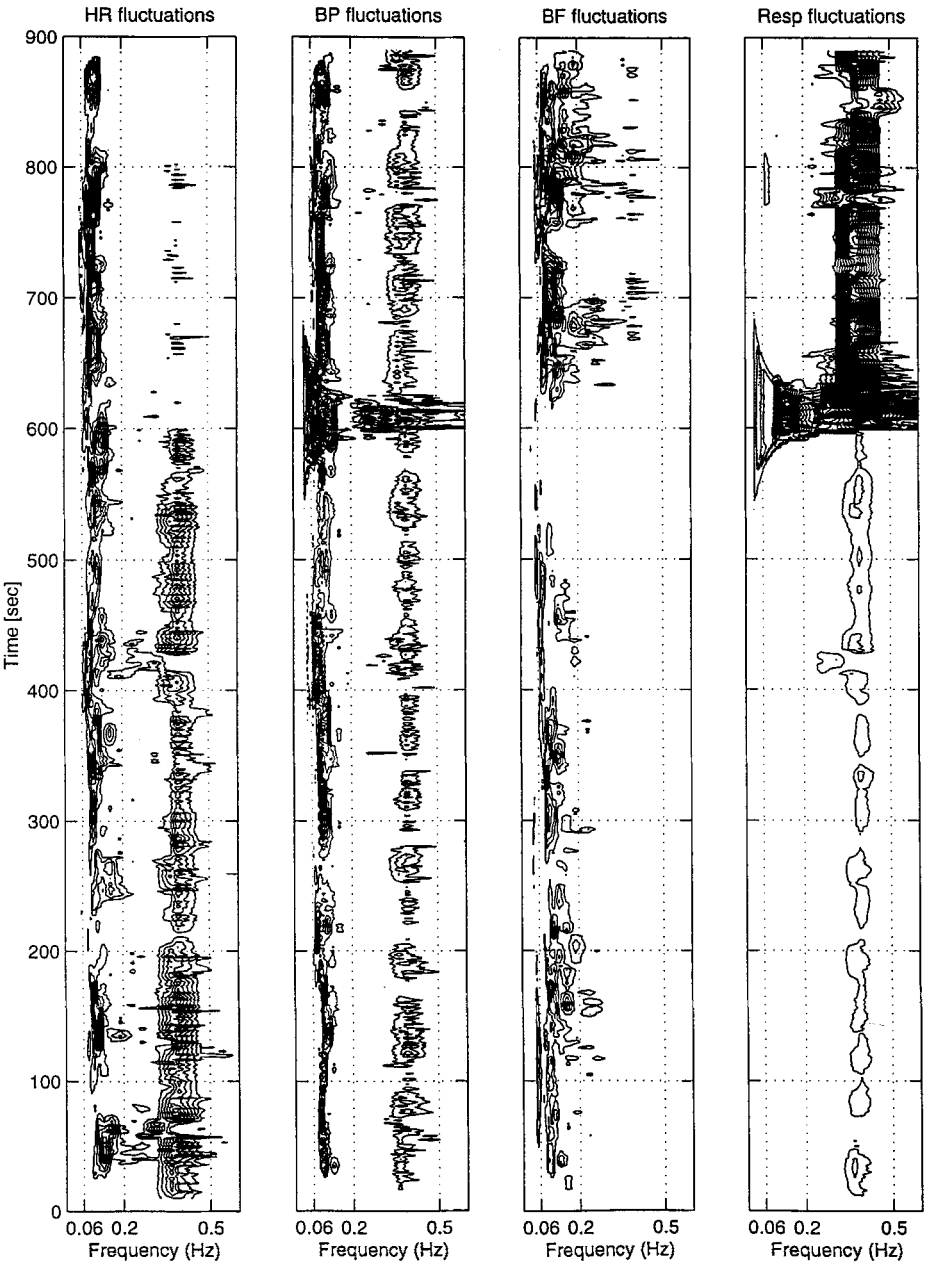


**Figure 4.** The same time-dependent power spectra as in Figure 3, displayed as contour plots. The right panel presents the respiratory power spectrum, which is essentially used to determine the limits of the high-frequency peak. HR = heart rate; BP = blood pressure; BF = blood flow; Resp = respiration.

evolution in these two estimates. The LF/HF ratio, which reflects the sympathovagal balance, revealed significant differences between the two groups at times T2 and T5 (Fig. 6). When comparing the time evolution of the LF/HF ratio of HR fluctuations with analysis of variance, an almost significant difference ($p < 0.056$) was obtained. A significant increase in LF/HF ratio at time T3, as compared with baseline T1, was observed only in patients with MS (Fig. 6, top panel). On the other hand, a significant enhancement on standing, at time T5, was observed only in control subjects. The same significant differences were observed when analyzing the normalized LF content of HR fluctuations (Fig. 6, bottom panel).

LF content of BP fluctuations increased and remained significantly higher than supine baseline, similarly for both groups (Fig. 7, top panel). LF content of BF fluctuations did not present any significant time evolution, and the slight enhancement for patients with MS, as compared with control subjects, was nonsignificant throughout the entire experiment.

Only patients with MS showed an age-dependence in some of the estimated parameters. All these significant estimates are summarized in Table 2. Mean HR and VLF, LF, and HF contents of HR fluctuations showed significant age-dependence at some of the times of interest. In the control group, no difference was observed.

## Discussion

In the current study, we analyzed the time evolution of autonomic control during an autonomic stimulus to verify whether patients with MS who have significant fatigue also have autonomic dysfunction. We observed that these patients present an almost normal autonomic functioning during the entire change of posture. They show a reduction

**Table 1.** VLF content of HR, BP, and BF fluctuations during supine and standing positions for MS and control groups

| | VLF HR supine | VLF HR standing | VLF BP supine | VLF BP standing | VLF BF supine | VLF BF standing |
|---|---|---|---|---|---|---|
| MS | 6.2 ± 5.6 | 11 ± 8.6 | 6.8 ± 5.1 | 11 ± 9 | 0.06 ± 0.10 | 0.047 ± 0.051 |
| Control | 6.2 ± 3.5 | 17 ± 13 | 15 ± 12 | 15 ± 9 | 0.29 ± 0.29 | 0.4 ± 0.8 |

The increases at standing, as compared with supine position, are not statistically significant because of the large standard deviations. VLF = very low frequency, HR = heart rate, BP = blood pressure; BF = blood flow; MS = multiple sclerosis.

in the HF peak of HR fluctuations, proving a vagal reduction on standing. Simultaneously, the LF of HR and BP fluctuations is enhanced. Even though the LF peak is mediated both by the sympathetic and by the parasympathetic limbs, the observed reduction of vagal activity on standing proves that the LF enhancement must be related to an increase in sympathetic activity.

This finding of normal autonomic response to standing concurs with the report of Frontoni *et al.* [6]. Still, they have shown an impairment in cardiovascular reflexes, mostly of mild degree, only in 4 of 16 patients with MS who were studied, in whom lower VLF and LF power in supine rest was reported as compared with their aged-matched controls.

The only difference we observed when comparing patients with MS who experienced fatigue with control subjects occurred in the time evolution of the sympathovagal balance (Fig. 6). Patients with MS presented an exaggerated increase at time T3 of the balance, as compared with control subjects. On the other hand, on standing, they stabilize at a level similar to supine level, whereas normal subjects reach a higher level of the balance, with a sympathetic prevalence. Moreover, we found a significant age dependence in the HF content of HR fluctuations (Table 2), presumably indicating that patients with MS present reduced vagal activity as early as age 45, as opposed to control subjects. This reduction in vagal activity may also be reflected in the VLF and LF contents of HR fluctuations.

The reduction in vagal activity as function of age has been well-established previously [22]. However, it seems that for patients with MS who experience fatigue, this decrease is more marked than in control subjects and occurs even in the relatively small age range we analyzed. This reduction in vagal activity might explain the difference in the sympathovagal balance during the change of posture, especially its lack of enhancement on standing (Fig. 6). This difference could be blurred when considering the HF con-

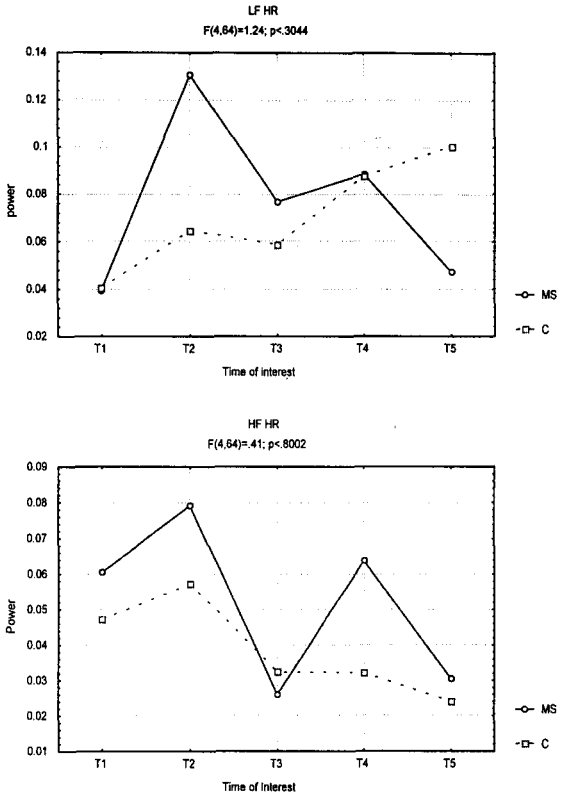


**Figure 5.** Low-frequency (LF) and high-frequency (HF) content of heart rate (HR) fluctuations as a function of times of interest in patients with multiple sclerosis (MS; solid line and circles) and control subjects (C; dashed line and squares). We found no significant difference between groups or when comparing with supine baseline.

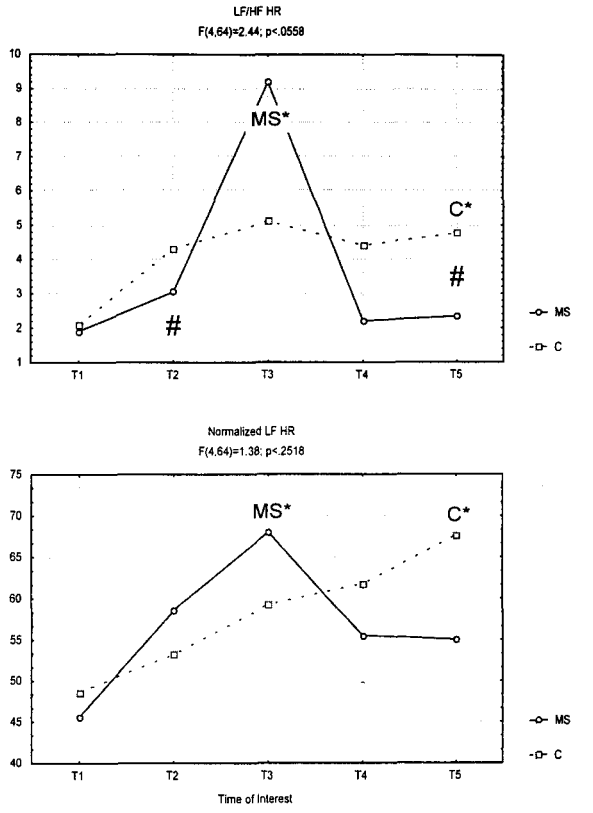


**Figure 6.** Low-frequency (LF)/high-frequency (HF) ratio and LF content normalized to total power of heart rate (HR) fluctuations as a function of times of interest. The # symbol indicates a significant difference between patients with multiple sclerosis (MS) and control subjects (C). The increase at T3 is significant (*) only in patients with MS, whereas only control subjects stabilize at a higher level on standing (T5).

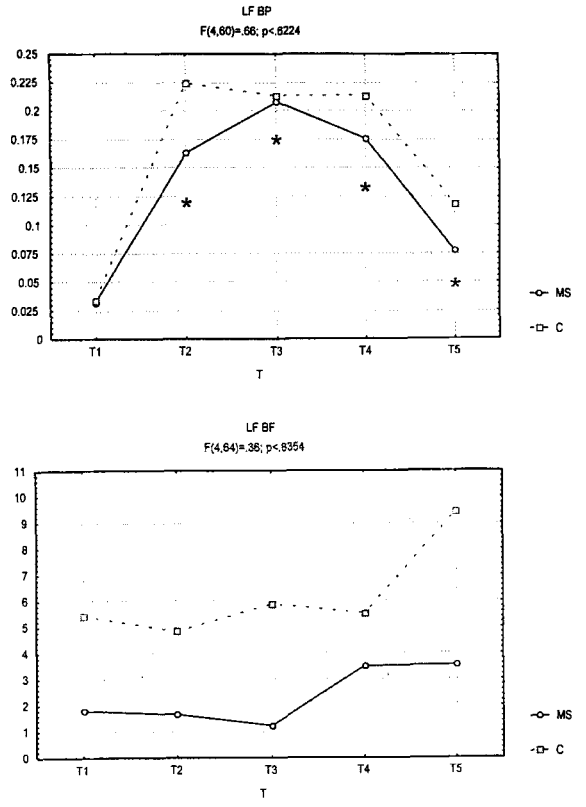


**Figure 7.** Low-frequency (LF) power of blood pressure (BP) and blood flow (BF) fluctuations as a function of times of interest. LF content of BP fluctuations is significantly higher as compared with baseline for both groups at all times of interest. There is no significance in the differences of the LF content of BF fluctuations when compared with supine levels or between groups. MS = multiple sclerosis; C = control.

tent of HR fluctuations because of the large individual variability, which results in a large standard deviation (Fig. 5, bottom panel), and be unmasked by the autonomic povocation achieved by the change in position. It is of interest to note that the same decrease in vagal power has been observed during paced breathing in patients with chronic fatigue syndrome [13].

We conclude that patients with MS who have chronic fatigue present normal sympathetic activity and possibly slightly reduced vagal activity, as compared with control subjects. This study also shows a more significant age-dependent decrease in vagal activity in patients with MS, as compared with control subjects. A larger population with a wider age range has to be investigated before ascribing clinical relevance to these findings. The same analysis should also be applied to patients with MS who do not have chronic fatigue, before relating fatigue to a possible vagal reduction.

**Table 2.** Parameters with a significant age dependence for patients with MS

| Age dependence | <45 | >45 |
|---|---|---|
| HR T3 | 111 | 95 |
| HF HR T1 | 0.063 | 0.012 |
| HF HR T5 | 0.032 | 0.01 |
| LF HR T1 | 0.046 | 0.015 |
| LF HR T4 | 0.14 | 0.036 |
| LF HR T5 | 0.072 | 0.023 |
| VLF HR T5 | 0.016 | 0.0057 |

Control subjects showed no significant differences.
MS = multiple sclerosis; HR = heart rate; HF = high frequency; LF = low frequency; VLF = very low frequency.

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