Abnormalities of Cardiovascular Neural Control and Reduced Orthostatic Tolerance in Patients with Primary Fibromyalgia

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ABSTRACT. ***Objective.*** Fibromyalgia (FM) is a syndrome characterized by widespread musculoskeletal pain. Symptoms of orthostatic intolerance may also be present, suggesting underlying abnormalities of cardiovascular neural regulation. We tested the hypothesis that FM is characterized by sympathetic overactivity and alterations in cardiovascular autonomic response to gravitational stimulus.

Methods. Sixteen patients with primary FM and 16 healthy controls underwent electrocardiography examination, finger blood pressure, respiration, and muscle sympathetic nerve activity (MSNA) recordings at rest and during stepwise tilt test, up to 75°. The autonomic profile was assessed by MSNA, plasma catecholamine, and spectral indices of cardiac sympathetic (LF_{RR} in normalized units, NU) and vagal (HF_{RR} both in absolute and NU) modulation and of sympathetic vasomotor control (LF_{SAP}) computed by spectrum analysis of RR and systolic arterial pressure (SAP) variability. Arterial baroreflex function was evaluated by the SAP/RR spontaneous-sequences technique, the index α, and the gain of MSNA/diastolic pressure relationship during stepwise tilt test.

Results. At rest, patients showed higher values of heart rate, MSNA, LF_{RR} NU, LF/HF, LF_{SAP}, and reduced HF_{RR} than controls. During tilt test, lack of increase of MSNA, less decrease of HF_{RR}, and excessive rate (44%) of syncope were found in patients, suggesting reduced capability to enhance the sympathetic activity to vessels and withdraw the vagal modulation to sino-atrial node. Baroreflex function was similar in both groups.

Conclusion. Patients with FM have an overall enhancement of cardiovascular sympathetic activity while recumbent. Lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity characterize their autonomic profile during tilt test, and might account for the excessive rate of syncope. (J Rheumatol 2005;32:1787–93)

Key Indexing Terms:
FIBROMYALGIA SYNCOPE SYMPATHETIC NERVOUS SYSTEM
TILT TEST BARORECEPTORS

Fibromyalgia (FM) is a chronic disabling syndrome affecting 2%–6% of the general population[1], with higher prevalence in women. It is characterized by diffuse tenderness and musculoskeletal pain and discomfort on palpation of specific sites known as tender points[2,3].

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The mechanisms underlying pain in this syndrome are not fully understood. A potential role of an exaggerated neural sympathetic activation in generating and sustaining chronic pain has been postulated[4,5] on the basis of similarities of FM with other chronic pain syndromes, such as reflex sympathetic dystrophy[6] and causalgia[7], in which there is evidence of sympathetic overactivity.

Nonrheumatic disabling symptoms such as palpitations and dizziness on standing, occasional orthostatic hypotension, and syncope[8] are also present in primary FM[3]. These symptoms suggest a potential abnormality of cardiovascular autonomic regulation, and point to a remarkable comorbidity with other dysfunctions of orthostatic cardiovascular neural homeostasis[9], including chronic orthostatic intolerance[10] and neurally mediated syncope[11,12].

Attempts to quantify possible abnormalities of cardiovascular autonomic regulation in FM have furnished only partial and to some extent contradictory results. For instance, using the microneurographic technique, Elam and colleagues[13] found no differences in muscle sympathetic nerve activity (MSNA) of these patients compared with

healthy controls, in both the recumbent position and during cold pressor stimulation. In contrast, other studies indicate an increased sympathetic activity on the basis of the finding that selective sympathetic blockade by guanethidine reduced pain and the number of tender points[14]. Studies based on power spectrum analysis of heart rate variability showed increased sympathetic and decreased parasympathetic modulation of heartbeat[15] and signs of persistent nocturnal sympathetic activation[16] in these patients.

Assessment of the autonomic profile in patients with FM has major clinical relevance since a pharmacological rebalancing of a potentially altered cardiovascular neural regulation might positively influence both chronic pain and nonrheumatic symptoms, including orthostatic intolerance.

We tested the hypothesis that FM is characterized by chronic sympathetic overactivity. In addition, we evaluated whether a possible abnormal autonomic response to gravitational stimulus might account for the exaggerated rate of orthostatic intolerance reported in this population[8]. To rule out that possible hemodynamic and MSNA abnormalities might have been due to impaired arterial baroreflex inhibitory modulation of heartbeat and muscle sympathetic nerve activity, baroreflex function was also assessed by time and frequency domain analysis techniques.

MATERIALS AND METHODS

Thirty patients with primary FM who were consecutively referred to the rheumatology unit of the Sacco Hospital were initially evaluated for recruitment on the basis of the approved protocol. Five were excluded after the medical evaluation and 9 did not sign the consent form. We studied 16 patients with primary FM (15 women, one man; age 43.9 ± 3.2 yrs) who consecutively agreed to participate and 16 healthy control subjects (15 women, one man; age 37.2 ± 3.6 yrs). All subjects were nonsmokers (< 5 cigarettes/day). Diseases known to affect the autonomic nervous system such as hypertension, diabetes, and hypothyroidism and other relevant medical conditions including inflammatory and autoimmune diseases were excluded on the basis of complete medical evaluation, electrocardiogram (ECG), and routine laboratory tests. Adrenal dysfunction was ruled out by appropriate laboratory tests. FM was diagnosed according to the American College of Rheumatology classification criteria[3]. Every patient underwent an analytical interview to assess any signs or symptoms of orthostatic intolerance during the last 12 months.

Patients' clinical features are reported in Table 1. Presyncope was defined as the occasional occurrence of at least 3 of the following symptoms on standing: lightheadedness, tunnel vision, sweating, pallor, yawning, and nausea. Drug treatment was discontinued at least 5 half-lives before testing.

Controls were sedentary individuals who did not perform any regular physical activity and never experienced syncope or presyncope upon standing during the last year.

All subjects were studied after a light breakfast not containing alcohol or caffeine beverages, in a quiet room with a dim light and comfortable temperature. In every subject, we recorded the ECG, noninvasive blood pressure (Finapres; Ohmeda 2300, Atlanta, GA, USA), and respiratory activity by a thoracic bellows connected to a pressure transducer. MSNA was obtained from the right peroneal nerve by microneurography technique[17]. Briefly, a unipolar tungsten electrode was placed in the right peroneal nerve near the fibular head for multiunit postganglionic sympathetic nerve recording. The raw neural signal was amplified (1000-fold amplification), fed to a band pass filter (bandwidth between 700 and 2000 Hz), rectified, and integrated (time constant 0.1 s) by a nerve traffic analyzer system (Bioengineering Department, University of Iowa, Iowa City, IA, USA).

Table 1. Clinical features of patients with FM.

Characteristic	
Disease duration, yrs	7.2 ± 1.6
Pain visual analog scale (0–100)	69 ± 5
No. of tender points	14.5 ± 0.6
Health Assessment Questionnaire (0–3)	0.8 ± 0.2
Fatigue (0–100)	60 ± 6.3
Overall orthostatic intolerance signs and symptoms	**Percentage of Patients**
Presyncope	62.5
Syncope	12.5
Palpitations on standing	12.5
Dizziness	12.5

Integrated MSNA, ECG, arterial pressure, and respiratory activity signals were digitized at 300 samples/s by an analogical to digital board, and recorded for analysis.

Plasma epinephrine and norepinephrine were measured on venous blood samples.

Procedure. Every subject was placed on a tilt table with a footrest and underwent instrumentation as described. Thirty minutes after instrumentation, baseline data acquisition was initiated and a blood sample was withdrawn for catecholamine evaluation. Recorded variables were analyzed during the last 5 min of supine rest. Then subjects were tilted at 15° intervals every 5 min until the 75° head-up position was reached. This position was maintained for 20 min. A second blood sample was obtained at minute 5 of the 75° tilt. For gravitational stimulus, recorded variables were analyzed in all subjects starting from minute 2 after the 75° upright position was obtained to the sixth minute of tilt, when all subjects, including those who would have developed syncope or presyncope, were still free of symptoms.

The experimental protocol was approved by the Sacco Hospital Institutional Review Board and all subjects provided written informed consent.

Data analysis. Microneurography was considered to reflect MSNA according to established criteria[18].

The methods used for signal processing, autoregressive spectrum and cross-spectrum analysis of RR interval and systolic arterial pressure variability, and respiration, have been described in detail[19,20]. There are 2 main oscillatory components, the amplitude of which is modulated by changes in cardiovascular neural control[19,21,22]. One is the high frequency (HF, ≈ 0.25 Hz). If obtained from RR variability, HF_{RR} provides an index of the vagal modulation of the sino-atrial node discharge[21]. The second oscillatory component is indicated as low frequency (LF, 0.1 Hz). In the case of systolic arterial pressure (SAP) variability, LF_{SAP} is a marker of the sympathetic vasomotor control[19,21-23]. The LF component of RR variability (LF_{RR}), expressed in normalized units (NU), may reflect the sympathetic efferent modulation to the sino-atrial node and its changes[19,21,22].

Normalization is achieved by dividing the absolute power of each component by total variance (minus the power of the very low frequency component) and multiplying by 100[19]. The LF_{RR}/HF_{RR} ratio may furnish a further index to evaluate the sympathovagal interaction to the sino-atrial node activity[19,22].

Arterial baroreflex control of heart rate was assessed by time and frequency domain analysis. The first method is based on the detection of spontaneous sequences of 3 or more SAP and RR values that simultaneously increase (positive sequences) or decrease (negative sequences)[24].

Sequences were considered to reflect baroreceptor activity if the following criteria had been matched: (1) RR interval variations were > 5 ms; (2) SAP changes were > 1 mm Hg; (3) sequences were longer than 4 beats. For each sequence, a linear regression between the 2 variables was computed, and the slope of the regression line calculated. In every subject, all the slopes with a correlation coefficient > 0.85 were averaged and the final value taken as the gain of arterial baroreflex control of heart rate (BRS).

Bivariate spectrum analysis of RR interval and SAP variability provided the index α, computed as the square root of the ratio between the powers of the spectral components of RR interval and SAP variability in the low frequency band[25].

Arterial barorefex modulation of MSNA in response to gravity was obtained by the gain of the regression line correlating changes of diastolic arterial pressure and corresponding modifications of MSNA during each level of the tilt procedure.

Data are expressed as mean ± SEM. One-way analysis of variance was used to evaluate differences between patients with FM and controls. Changes induced by the tilt maneuver were evaluated by Student t test for paired observations. Differences were considered significant at values of $p < 0.05$.

RESULTS

Baseline hemodynamic and neurohumoral variables. In recumbent position, HR, MSNA, and the indices of autonomic activity, LF_{SAP}, LF_{RR} in normalized units, and LF/HF were greater and HF_{RR} lower in patients than in healthy subjects (Figure 1, Tables 2 and 3), whereas arterial blood pressure and respiratory rate were similar in both groups (Figure 1 and Table 2).

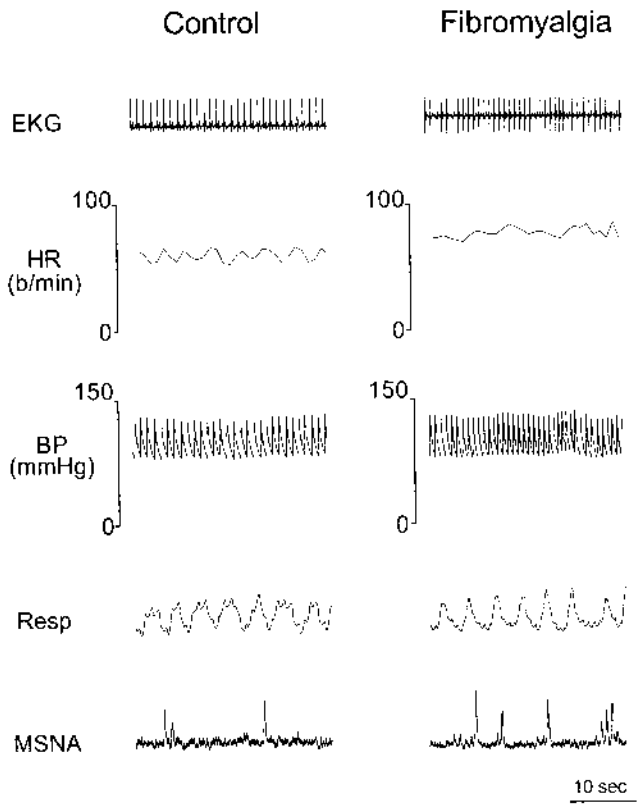

Figure 1. Examples of recorded variables in representative control and FM patient in recumbent position. Sympathetic modulatory activity to the heart and vessels, as suggested by greater heart rate (HR) and MSNA values, is increased in FM. Arterial pressure (BP) and respiratory rate (Resp) were similar in both subjects.

Table 2. Hemodynamic and respiratory measures of study subjects at rest and during passive orthostatism (tilt test).

	Rest		Tilt	
	Controls	FM	Controls	FM
HR, bpm	68 ± 2	74 ± 2*	89 ± 2	93 ± 3
RR, ms	896 ± 30	823 ± 24*	680 ± 19	656 ± 24
SAP, mm/Hg	118 ± 3	118 ± 4	118 ± 3	128 ± 6
DAP, mm/Hg	71 ± 2	76 ± 2	75 ± 3	78 ± 2
Resp, cycles/min	18 ± 1	16 ± 1	17 ± 1	16 ± 1

HR: heart rate (beats/min); SAP: systolic arterial pressure; DAP: diastolic arterial pressure; Resp: respiratory frequency. * $p < 0.05$, controls vs FM patients.

Plasma norepinephrine and epinephrine were similar in the 2 groups (Table 3).

Hemodynamic and neurohumoral response to 75° head-up tilt test. HR increased in both groups to a similar extent in response to 75° head-up tilt, while no changes could be observed for arterial pressure and respiratory rate compared with the resting position (Table 2).

Tilt increased MSNA and LF_{SAP} in controls, whereas in patients with FM MSNA and LF_{SAP} were unchanged compared with recumbent position (Table 3, Figure 2). The spectral index of cardiac sympathetic modulation LF_{RR} in NU, the LF/HF ratio, and plasma catecholamine values were enhanced similarly in the 2 groups (Table 3). The index of cardiac vagal modulation HF_{RR}, although reduced by tilt (Table 3, Figure 2), decreased to a lesser extent ($p < 0.05$) in patients (–16.2 ± 3.7 NU and –139.6 ± 50.0 ms^2) than in controls (–32.3 ± 4.6 NU and –901.4 ± 375.2 ms^2).

Baroreflex function. Table 4 summarizes the indices of arterial baroreflex modulation of heart rate as assessed by both time (BRS) and frequency (α_{LF}) domain analysis. Baroreflex control of heart rate was similar in the 2 groups both at rest and during tilt. The gain of the relationship between diastolic arterial pressure modifications and corresponding changes in MSNA during increasing levels of tilt was comparable in patients with FM and controls (Table 4).

Orthostatic tolerance. Stepwise tilt induced syncope or presyncope symptoms in 7 out of 16 (43.7%) FM patients (time of onset 7th minute ± 1) and in one out of 16 (6.2%) controls (time of onset 10th minute).

Figure 3 depicts the Kaplan-Meier curves of vasovagal reaction-free tilt time (gravitational survival) observed in the control group and in patients with FM. Note that the FM population had an increased risk of vasovagal reactions compared with age and sex matched controls.

DISCUSSION

Our results suggest that patients with FM had an overall increase of sympathetic activity and a reduction of cardiac

Table 3. Indices of autonomic activity in study subjects at rest and during tilt test. Due to reduced RR variance, LF_{RR} in ms^2 is unchanged during tilt test, whereas it increases in NU[35].

	Rest		Tilt	
	Controls	FM	Controls	FM
MSNA, bursts/min	12 ± 2	22 ± 2*	27 ± 3†	26 ± 3
Bursts/100 beats	19 ± 2	31 ± 4*	32 ± 3†	34 ± 5
NE, pg/ml	266 ± 25	264 ± 32	496 ± 36†	590 ± 90†
E, pg/ml	31 ± 7	34 ± 7	64 ± 11†	75 ± 13†
RR σ^2, ms^2	2390 ± 601	1186 ± 268	1292 ± 267†	786 ± 166†
LF_{RR}, ms^2	579 ± 111	573 ± 139	499 ± 119	476 ± 130
NU	49.5 ± 4.6	66.5 ± 4.5*	81.8 ± 2.6†	87.8 ± 1.9†
HF_{RR}, ms^2	939 ± 365	198 ± 51*	82.6 ± 21.9†	52 ± 15†
NU	46.0 ± 4.4	25.4 ± 3.8*	14.1 ± 2.8†	8.6 ± 1.6†
LF/HF	1.46 ± 0.3	3.7 ± 0.7*	10.0 ± 1.9†	16.3 ± 2.5†
SAP σ^2, mm/Hg^2	11.9 ± 3	12.6 ± 3.6	21.6 ± 4.9	21.4 ± 3.8
LF_{SAP}, mm/Hg^2	2.2 ± 0.5	6.3 ± 2*	12.3 ± 3.8†	10.2 ± 1.7

MSNA: muscle sympathetic nerve activity, NE: norepinephrine, E: epinephrine, σ^2: variance, LF_{RR}: low frequency component of RR variability, HF_{RR}: high frequency component of RR variability, NU: normalized units, LF_{SAP}: low frequency component of systolic arterial pressure, variability. * $p < 0.05$, controls vs FM patients. † $p < 0.05$ rest vs tilt.

vagal modulation in recumbent position, compared with healthy controls. That the indices of baroreflex modulation of heart rate and muscle sympathetic nerve activity were similar in patients and controls at rest suggests that the enhanced sympathetic activity of the heart and vessels observed in FM is unlikely to be due to a failure of the inhibitory modulation exerted by arterial baroreceptors, but rather it seems to be the result of a primary increase of central sympathetic drive. Finally, the lack of enhancement of MSNA and LF_{SAP} in response to the gravitational stimulus in the presence of reduced decrease of the vagal related spectral component HF_{RR} compared with controls might increase the susceptibility to vasovagal episodes, thus accounting for the exaggerated rate of syncope observed in patients with FM in this study.

Autonomic profile and baroreflex function at rest. In our study, the increased values of heart rate, MSNA, and spectral indices of cardiac (LF_{RR} NU) and vascular (LF_{SAP}) sympathetic modulation, and the reduced levels of HF_{RR}, at rest indicate an alteration of the autonomic profile of patients with FM consistent with an exaggerated sympathetic drive to the heart and vessels and a reduced vagal modulation of heartbeat. Accordingly, the LF/HF ratio, an index of sympathovagal balance, was increased.

Autonomic abnormalities in keeping with our findings have been inferred indirectly on the basis of similarities of FM with other neurological disorders likely to be characterized by sympathetic overactivity, such as reflex sympathetic dystrophy[6] and causalgia[7], or by pharmacological probes. Indeed, systemic sympathetic blockade by guanethidine[14] reduced tender points, and stellate ganglion blockade by local bupivacaine[4] decreased regional tender points and diminished pain in subjects with primary FM at rest.

Other studies sought to define the cardiovascular autonomic profile of patients with primary FM by addressing disjointedly the neural control of heart rate and arterial vessels, without assessing arterial baroreflex function[15]. In accord with our results, studies based on power spectrum analysis of heart rate variability pointed to an increased sympathetic activity to the heart at rest[15] and at night time[16], and a decreased 24-hour heart rate variability[16].

In contrast to our findings, similar levels of postganglionic sympathetic activity have been recorded in healthy controls and FM patients at rest, by means of microneurography techniques[13]. We do not have a clear explanation for this discrepancy. Differences in the severity of the syndrome between the 2 populations might account for the different results.

In our study plasma norepinephrine was similar in the 2 groups of subjects, in spite of higher MSNA observed in FM patients. However, it must be noted that norepinephrine may not reflect the state of the central sympathetic activity. Indeed, norepinephrine plasma concentrations are likely to be influenced not only by the spillover into the blood but also by its systemic clearance[26] and norepinephrine transporter efficiency[27], neither of which we could measure in this study.

That FM shares with chronic orthostatic intolerance[10] and neurally mediated syncope[11] a number of autonomic related signs and symptoms, including fatigue, palpitations, lightheadedness, and loss of consciousness upon standing[12] may suggest a comparable underlying autonomic profile. Indeed, this is the case in patients with chronic orthostatic intolerance, in whom increased values of HR, MSNA, LF/HF ratio, and LF_{SAP} have been observed while recumbent[10]. In contrast, at rest, subjects with both recurrent[12] and occasional[11] neurally mediated syncope showed hemodynamic and autonomic profiles analogous to those in healthy

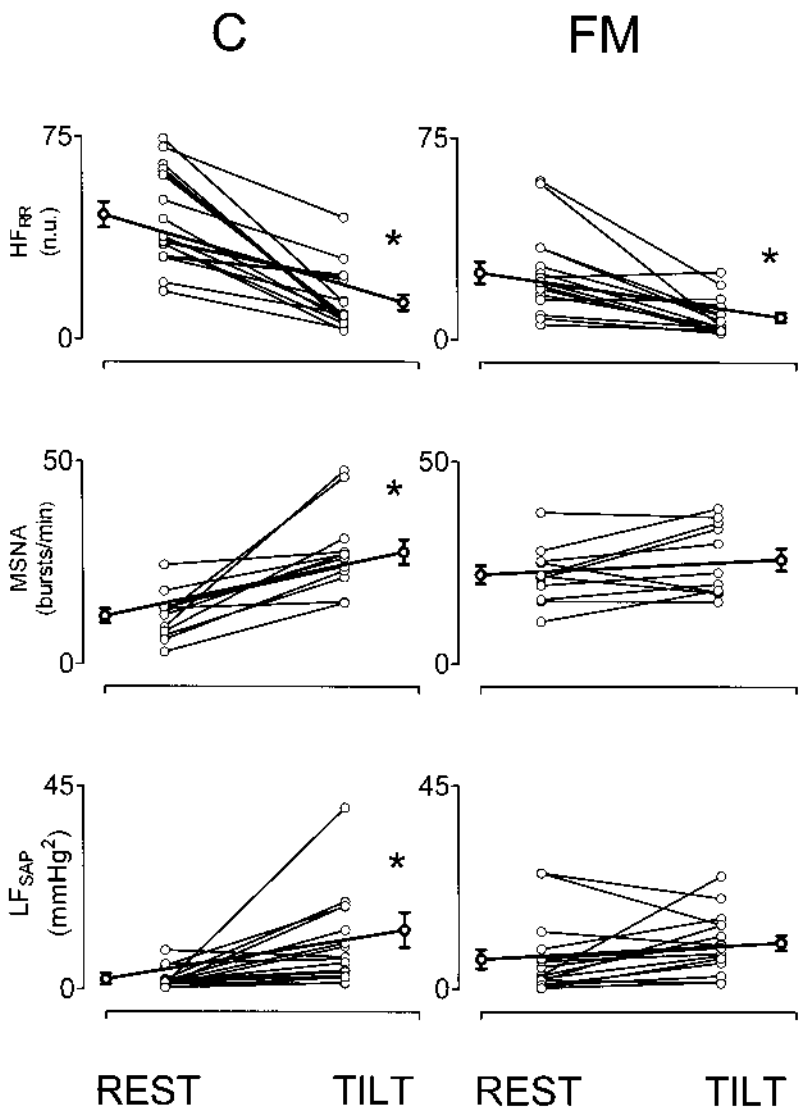

Figure 2. Modifications induced by the 75° head-up tilt maneuver in cardiac vagal modulatory activity (HF_{RR}) and in the sympathetic vasomotor control (MSNA and LF_{SAP}) in controls (C) and FM patients. Individual values and mean group values (thicker lines) are shown. Adequate MSNA recordings were obtained in the 2 conditions in 12 controls and 11 patients. HF_{RR} and LF_{SAP} values refer to all 16 controls and 16 FM subjects. During tilt, the amount of decrease of the spectral index of cardiac vagal control HF_{RR} is lower in FM patients than in controls. In addition, the expected increase of the indices of sympathetic modulation to the vessels is blunted in patients compared with controls. *$p < 0.05$ tilt versus rest.

controls. These dissimilarities have potential clinical implications, since they may result in different therapeutic approaches.

It is likely that the overall increase of sympathetic activity we observed in FM patients may take part in the central nervous system sensitization process[28], thus playing a crucial role in generating and sustaining chronic pain[5].

Autonomic profile during tilt test and orthostatic tolerance in FM. An important finding of our study is the lack of increase of MSNA and LF_{SAP} in response to the tilt maneuver observed in patients with FM. The abnormality of the response of sympathetic vasomotor control during the gravitational stimulus was associated with a reduced decrease of the HF_{RR} component of RR variability compared to controls, suggesting a concomitant insufficient cardiac vagal withdrawal. Indeed, during tilt test, the heart rate increased in patients as in controls, in spite of an absent rise in sympathetic drive to the vessels that would have been required as a compensatory mechanism. On the basis of these observations, FM seems to share a similar autonomic profile with

Table 4. Indices of baroreflex function in controls and patients with FM at rest and during tilt test.

	Rest		Tilt	
	Controls	FM	Controls	FM
BRS, ms mm Hg	24.1 ± 3.7	16.7 ± 3.2	7.8 ± 1.3*	6.5 ± 1.6*
α_{LF}, ms mm Hg	19.4 ± 3.0	13.6 ± 2.6	7.3 ± 1.1*	6.7 ± 1.2*
$Slope_{MSNA/DAP}$, bursts/min/mm Hg			0.63 ± 0.2	0.49 ± 0.1

BRS: gain of SAP-RR relationship of spontaneous sequences, α_{LF}: alpha index assessed in the low frequency band, $Slope_{MSNA/DAP}$: gain of DAP-MSNA relationship during progressive tilt. * $p < 0.05$ rest vs tilt test.

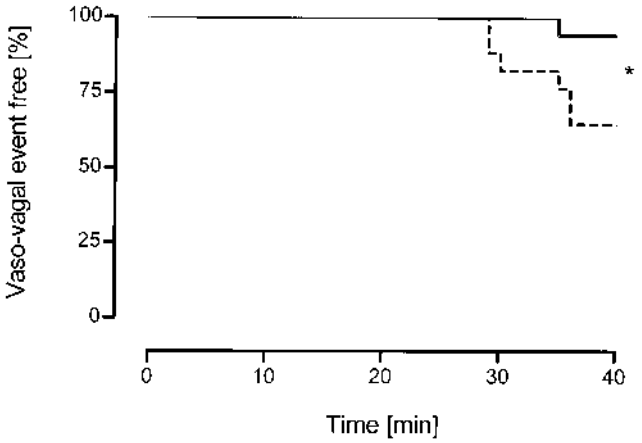

Figure 3. Kaplan-Meier curves of tilt time without vasovagal events (tilt survival) in FM patients (broken line) and controls (solid line). Patients with FM were at higher risk for vasovagal reactions. *$p < 0.05$.

habitual neurally mediated syncope[12] during orthostatic stress. Not surprisingly, patients showed higher rates of syncope than the control group, a finding that is in keeping with reports pointing to a reduced orthostatic tolerance in FM[8].

Of interest, although the autonomic profiles of patients with FM and chronic orthostatic intolerance were alike in the recumbent position, important dissimilarities in cardiovascular neural regulation were observed during the gravitational stimulus. Indeed, in subjects with chronic orthostatic intolerance[10] the lack of increase of MSNA in response to tilt test was associated with a remarkable, possibly compensatory, increase of cardiac sympathetic drive, leading to excessive tachycardia and high levels of LF/HF ratio, whereas in FM patients HR and LF/HF did not show such a marked enhancement. Of note, a clinical model based on norepinephrine reuptake inhibition[29] was able to reproduce the changes in heartbeat observed in patients with chronic orthostatic intolerance during the tilt test, but not those found in patients with FM. From a clinical standpoint, in chronic orthostatic intolerance the discordant cardiac and vascular sympathetic control was paralleled by the rareness of episodes of syncope during standing. This differs markedly from the 44% rate of loss of consciousness found during orthostatic stress in patients with FM in our study.

The blunted enhancement of sympathetic activity to vessels and the reduced cardiac vagal withdrawal during tilt test in patients with FM are in keeping with findings suggesting reduced sympathetic responsiveness to stressors such as auditory stimulation[30], cold pressor challenge[13,30], standing[31], and tilt test[16,31], although an excessive increase of heart rate consistent with enhanced cardiac sympathetic sensitivity has been also reported during orthostatic stress[32].

Limitations. Increased heart rate at rest, fatigue, and reduced orthostatic tolerance with presyncope signs and symptoms were found in healthy subjects after prolonged bed rest[33,34], and may even be present after 48 hours of supine position[35]. Patients with FM might progressively reduce their daily physical activity due to muscle soreness and symptoms of orthostatic intolerance. We were not able to assess the potential role of physical deconditioning that might have affected the autonomic profiles, particularly on standing, compared to the healthy sedentary controls. In addition, it is important to point out that we found a discernible overlap of individual values between patients with FM and controls in most of the indices of cardiovascular autonomic control (Figure 2). Due to the low number of study patients, we could not further compare the autonomic profiles of patients with normal versus those with abnormal orthostatic tolerance. However, a remarkable increase of the index of sympathetic vasomotor control LF_{SAP}, similar to or even higher than that observed in most of the controls, was found in only one patient (Figure 2). Interestingly, that patient had a normal orthostatic tolerance and did not faint. Similarly, the only control subject who fainted had a paradoxical decrease of LF_{SAP} in response to tilt test (Figure 2). These considerations support the hypothesis that a blunted increase of vascular sympathetic modulation might be a mechanism promoting orthostatic intolerance.

In conclusion, patients with fibromyalgia seemed to be characterized by a global increase of central cardiovascular sympathetic activity while recumbent. A blunted enhancement of sympathetic modulation to the vessels and impaired cardiac vagal withdrawal characterized their autonomic profiles during a gravitational stress, and may account for the excessive rate of syncope observed in that population upon standing.

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