Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients

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ABSTRACT

Objective. *Fibromyalgia (FM) is characterised by chronic musculoskeletal pain, autonomic nervous system (ANS) dysfunction, and disturbed sleep. The aim of this study was to evaluate the influence of ANS dysfunction on the genesis of sleep disorders.*

Methods. *Fifty female FM patients and 45 healthy subjects matched for age, gender and body mass index underwent a clinical, polysomnographic and autonomic profile evaluation at rest and during a tilt test in order to determine muscle sympathetic nerve activity (MSNA), plasma catecholamine levels, and the spectral indices of cardiac sympathetic (LF_{RR}) and vagal (HF_{RR}) modulation computed by means of the spectrum analysis of RR during sleep.*

Results. *The FM patients had a higher heart rate (HR), more MSNA and a higher LF/HF ratio, and lower HF_{RR} values at rest ($p<0.05$), and showed no increase in MSNA, a smaller decrease in HF_{RR}, and an excessive rate of syncope (46%) during the tilt test. Their sleep was less efficient ($p<0.01$), and they had a higher proportion of stage 1 non-REM sleep ($p<0.001$), experienced many arousals and periodic limb movements (PLMs) per hour of sleep ($p<0.001$) and a high proportion of periodic breathing (PB%) ($p<0.0001$). Their cyclic alternating pattern (CAP) rate was significantly increased ($p<0.001$). During sleep, they had a higher HR and LF/HF ratio, and a lower HF_{RR} ($p<0.001$). The number of tender points, CAP rate, PB% and PLMI correlated positively with HR and the LF/HF ratio, and negatively with HF_{RR} during sleep.*

Conclusion. *Our findings seem to show that sleep causes the same effects as a stressful test in FM patients. A vicious circle is created during sleep: pain increases sympathetic cardiovascular activation and reduces sleep efficiency, thus causing lighter sleep, a higher CAP rate, more arousals, a higher PLMI, and increasing the occurrence of PB, which gives rise to abnormal cardiovascular neural control and exaggerated pain sensitivity.*

Introduction

Fibromyalgia (FM) is a chronic pain disorder of unknown aetiology that is characterised by symptoms of morning stiffness, fatigue, depression, non-restorative sleep, and reduced cognitive performance (1), some of which are worsened by emotional distress, meteorological changes, insomnia and strenuous activity (2, 3).

Some of the symptoms, and the patients' physical and psychological characteristics can be attributed to autonomic nervous system (ANS) dysfunction (4-7), which is frequent because their sympathetic nervous system is persistently hyperactive, but hypoactive in response to stress (8, 9). This paradox is in line with the principle that the continuous over-stimulation of β-adrenergic receptors causes desensitisation and down-regulation (10). Neurotransmitter abnormalities may increase pain perception, fatigue, sleep/mood dysfunction, and memory problems (11). The idea that FM patients suffer from ANS dysfunction has been supported by both reductionist and holistic hypotheses (12).

A large percentage of FM patients report sleep disturbance, including difficulties in falling or staying asleep, early morning awakenings, and non-restorative sleep (13-15), and it is clear that unrefreshing or non-restorative sleep is directly related to pain and the other common symptoms of FM patients. In 2009, the OMERACT group (originally the Outcome Measures in Rheumatoid Arthritis Clinical Trials, but now Outcome Measures in Rheumatology group) established that FM is a multi-symptom

syndrome, and included fatigue and sleep disturbances in the inner core set of disease domains to be assessed in all clinical trials of FM (16). In the following year, the American College of Rheumatology (ACR) included patient-reported measure of unrefreshing sleep in its Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity (17).

The ANS plays an important role in coordinating many bodily functions during sleep. It is not unusual for patients with untreated sleep disorders to describe symptoms of ANS impairment, and the majority of patients with autonomic impairment have some form of sleep disorder (18). As the cause of sleep disorders in FM patients is still unclear, the aim of this study was to evaluate the influence of ANS dysfunction on the genesis of their sleep disorders.

Materials and methods

Study population

Fifty consecutive Caucasian women (age 51.2±7.3 years) whose FM had been diagnosed on the basis of the 2010 ACR classification criteria were compared with 45 healthy female controls matched for age and body mass index. All of the subjects were enrolled between 1 May 2014 and 1 May 2016.

The patients were required to stop any FM-related pharmacological treatment and benzodiazepines (6 patients) for two weeks before study entry in order to avoid any rebound effect or withdrawal symptom. Furthermore, no patients were treated with drugs able to modify the stress response (*i.e.* corticosteroids).

After a light breakfast not containing alcohol or caffeine beverages, all of the enrolled subjects underwent a clinical evaluation and autonomic test in a quiet, dimly lighted room kept at a comfortable temperature. During the night of the same day, they underwent a polysomnography examination in a sound-attenuated, temperature-controlled sleep laboratory.

The study was approved by our local Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all of the subjects before they underwent any study procedure.

Clinical evaluation

All of the subjects underwent an 18 tender point examination (16) and described the intensity of somatic pain using a 100 mm visual analogue scale (VAS) before being administered a sleep questionnaire to evaluate sleeping complaints (19) and the Epworth Sleepiness Scale (ESS) (20), an 8-item questionnaire designed to measure the general level of daytime sleepiness. Total ESS scores can range from 0 to 24; the clinically normal range is 2-10 with a normal statistical distribution and a model score of 6.

Autonomic testing

All of the subjects underwent an electrocardiography examination, had their blood pressure non-invasively measured (Finapress; Ohmeda 2300, Atlanta, GA, USA), and their respiratory activity measured by means of thoracic bellows connected to a pressure transducer.

Muscle sympathetic nerve activity (MSNA) was measured from the right peroneal nerve using a microneurography technique (21). Briefly: a unipolar tungsten electrode was placed in the right peroneal nerve near the fibular head in order to make a multiunit post-ganglionic sympathetic nerve recording. The raw signal was amplified 1000-fold, fed to a band pass filter (bandwidth 700-2000 Hz), rectified, and integrated (time constant 0.1 second) using a nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City, IA, USA).

The integrated MSNA, ECG, arterial pressure and respiratory activity signals were digitised at 300 samples/second using an analogical to digital board, and recorded for analysis.

Plasma epinephrine and norepinephrine levels were measured in venous blood.

Each subject was placed on a tilt table with a footrest and underwent instrumentation as described above. Data acquisition was started 30 minutes after baseline, and a blood sample was withdrawn for catecholamine evaluation. The recorded variables were analysed during the last five minutes of supine rest, after which the subjects were tilted at 15° intervals every five minutes until the 75° head-up position was reached and maintained for 20 minutes. A second blood sample was obtained after five minutes of the 75° tilt.

The recorded variables were analysed in all subjects from the second to the sixth minute after reaching the 75° upright position, during which time all of the subjects were still free of symptoms, including those who subsequently developed syncope or pre-syncope. Pre-syncope was defined as the occurrence of at least three of the following symptoms upon standing: light-headedness, tunnel vision, sweating, pallor, yawning, and nausea.

Polysomnography

Polysomnography was carried out using a computer-assisted device (Alice 5, Healthdyne, Marietta, OH, USA). An electroencephalogram, 6-channel ECG, electro-oculogram, and submental, and right and left tibialis anterior muscle electromyograms were recorded using surface electrodes and standard techniques (22).

Naso-oral thermocouples and thoracic and abdominal belts with attached piezo-electrodes were used to record airflow and ventilatory effort. Oxyhaemoglobin saturation was recorded by means of finger pulse oximetry (Nonin 9600, Plymouth, MN, USA). Overnight EEG activity was recorded using 10 bipolar leads (Fp2-F4, F4-C4, C4-P4, P4-O2, Fpl-F3, F3-C3, C3-P3, P3-O1, FZ-CZ, and CZ-PZ) and a classic unipolar C3-A2. The transducer and lead wires allowed normal positional changes during sleep. Bedtime and awakening time were left to each subject's discretion: the polysomnography was terminated after final awakening. The sleep, cardiological and breathing variables were stored on an optical disc, and then manually scored by two blinded physicians in 30-second epochs according to standard criteria (22).

Apnea was defined as a reduction in airflow lasting for at least 10 seconds, and hypopnea as a reduction in airflow of ≥30% accompanied by a 4% decrease in oxygen saturation and/or followed by an arousal with continued chest and

abdominal movement. The respiratory disturbance index (RDI) was defined as the average number of episodes of apnea and hypopnea per hour of sleep, and the desaturation event frequency (DEF) as the number of episodes of a ≥4% decrease in oxyhaemoglobin saturation per hour of sleep. Periodic breathing (PB) was defined as a series of at least three successive cycles of waxing and waning ventilation with apneas or hypopnea. Arousals were scored in accordance with the criteria of the American Sleep Disorders Association (ASDA) (22).

To qualify as a periodic limb movement (PLM) during sleep, the movement had to last 0.5-1 second, recur every 5-90 seconds, and occur in a series of at least four successive movements with an amplitude of at least 8 μV (22); periodic movements with a close temporal relationship to apnea or hypopnea were not interpreted as PLMs. A PLM index (PLMI, the number of PLMs per hour of sleep) of >5 throughout the entire night of sleep was considered to be pathological.

An alpha-delta intrusion was defined as the spontaneous occurrence of alpha waves in delta wave sleep (23).

The cyclic alternating pattern (CAP) parameters were identified on the basis of the scoring rules (24). All CAP sequences include at least two consecutive CAP cycles and always begin with a phase A and a phase B. The absence of a phase A for >60 consecutive seconds creates a prolonged stationary condition of arousal stability, and is scored as non-CAP. The CAP rate referring to non-REM sleep is the percentage ratio between total CAP time and total non-REM time. We also calculated the mean duration of B phases, and the number and mean duration of subtypes A1, A2 and A3.

Data analysis

Computer analysis was used to determine the sleep histograms of each patient and identify the sequences of periods of a CAP, PB, and PLMs. Microneurography was considered to reflect MSNA on the basis of established criteria (25).

The methods used for signal processing, and autoregressive spectrum and cross-spectrum analysis of the RR interval, systolic arterial pressure variability and respiration have been described in detail elsewhere (26). In brief, the ECG signal was digitised at a sampling rate of 500 per second, and respiration was monitored by recording chest movements. A fast Fourier transform (FFT)-based algorithm was used for the spectral analysis of heart rate variability (HRV). The RR intervals were converted to 4 Hz, and an exact Hamming window was used for the FFT. The data concerning HRV during sleep were detected using the ECG signals: for each hour of sleep, 5-minute segments of artefact-free ECG data during stage 2 sleep, rapid eye movement sleep, and slow-wave non-REM sleep were selected for analysis. All of the ECG lines were visually controlled for artefacts and extrasystoles. HRV was automatically analysed at a sampling rate of 500 Hz in accordance with the recommendations of the International Federation of Clinical physiology for the practice of clinical neurophysiology (26).

There are two main oscillatory components, the amplitude of which is modulated by changes in cardiovascular neural control. If the high-frequency component (HF, 0.15-0.40 Hz) is obtained from RR variability, HF_{RR} provides an index of the vagal modulation of the sino-atrial node discharge (7). If the low-frequency component (LF, 0.04-0.15 Hz) is obtained from the variability of systolic arterial pressure (SAP), LF_{SAP} is a marker of sympathetic vasomotor control (7). The LF component of RR variability (LF_{RR}), which is expressed in normalised units (NU), may reflect the modulation of the sympathetic efferent to the sino-atrial node and its changes (7). Normalisation involves dividing the absolute power of each component by total variance (minus the power of the very low frequency component), and multiplying by 100 (27).

The LF_{RR}/HR_{RR} ratio can provide a further index for evaluating the sympathovagal interactions with sino-atrial node activity (7).

Statistical analysis

The data were analysed using SPSS v. 6.1 software (SPSS, Chicago, IL, USA), and are expressed as mean values and standard deviations. A *p*-value of <0.05 was considered significant.

One-way analysis of variance was used to evaluate the differences between the FM patients and controls. The changes induced by the tilt manoeuvre were evaluated using Student's *t*-test for paired observations, and Pearson's chi-squared was used for the other comparisons of mean values and proportions. Pearson's product was used to assess the correlations between the cardiac automonic profle indices (HR, LF_{RR}, HF_{RR} and the LF/HF ratio) during sleep and the number of tender points, the pain VAS, the CAP rate, PB as a percentage of sleeping time, and the PLMI.

Table I. Clinical features and signs and symptoms of orthostatic intolerance in fibromyalgia patients and healthy controls.

	FM (n=50)	Controls (n=45)	*p*
Disease duration (years)	7.6 ± 3.2		
Age (years)	53.6 ± 8.4	54.4 ± 8	n.s.
BMI (kg/m^2)	26 ± 3	25.7 ± 3	n.s.
ESS score	15 ± 4	4 ± 3	0.0001
Tender points (No.)	15 ± 2	3 ± 1	0.0001
Pain VAS (mm)	71 ± 16	14 ± 3	0.0001
Presyncope (%)	61	10	0.001
Syncope (%)	13	1	0.001
Palpitations on standing (%)	13	1	0.001
Dizziness (%)	13	1	0.001

BMI: body mass index; VAS: visual analogue scale.
Data expressed as Mean ± SD; significance threshold $p<0.05$.

Results

Table I shows the anthropometric and clinical characteristics of the study

population. FM patients had more tender points (p<0.001), a higher ESS score (p<0.001), and more signs and symptoms of orthostatic intolerance (p<0.001) than the controls. They also had a higher heart rate (HR), more MSNA and a higher LF/HF ratio, and lower HF_{RR} values at rest (Table II). The increase in tilting-induced MSNA was less in the FM patients (2±1 *vs*. 16±3.1 bursts/min, p<0.05; 2±1 *vs*. 12±2.8 bursts/100 p<0.05), whereas the trend in the spectral indices of the cardiac autonomic profile (LF_{RR} and the LF/HF ratio) and plasma catecholamine levels were similar in the two groups; furthermore, the decrease in the index of cardiac vagal modulation (HF_{RR}) was also less in the patients (HF_{RR}NU -17.3±3.2 *vs*. -32.4±4.8, p<0.05; $HF_{RR}ms^2$ -148±50 *vs*. -857±374, p<0.05). The stepwise tilt induced syncope or pre-syncope in 23 of the 50 patients (46%) and two of the 45 controls (5%) (p<0.001),

The sleep values (Table III) show that that the patients experienced less efficient sleep (p<0.01), twice as many arousals per hour of sleep (p<0.001), and many more PLMs per hour of sleep (p<0.0001). The percentage of stage 1 non-REM sleep was markedly increased in the patients, causing a reduction in slow-wave sleep (p<0.001); stage 2 non-REM and REM sleep were not increased. Alpha intrusions during delta sleep were identified in 16 patients (32%) and two control subjects (5%) (p<0.001).

DEF per hour of sleep was higher in the FM patients (p<0.01). There were no differences in the RDI or average SaO_2% between the patients and controls. Periodic breathing was observed in 45 FM patients (90%) and only two controls (5%), and occurred for a mean 15% of sleeping time, mainly during the light stages of non-REM sleep.

Table IV shows that the CAP rate was significantly increased in the patients (69±6% *vs*. 44±11%, p<0.001), as was the mean duration of CAP (46±3 *vs*. 27±2 seconds, p<0.001), phase A (20±4 *vs* 10±1 seconds, p<0.001) and phase B (25±2.8 s. *vs*. 16±3 seconds, p<0.001). The FM patients also experienced more episodes of A phase subtype A1 (151±13 *vs*. 75±13, p<0.001)

Table II. Autonomic nerve system tests in fibromyalgia patients and healthy controls.

	Rest		Tilt	
	Controls (n=45)	FM (n=50)	Controls (n=45)	FM (n=50)
HR (bpm)	70 ± 2	76 ± 3*	90 ± 3	93 ± 3
RR(ms)	901 ± 33	831 ± 24*	689 ± 21	673 ± 24
SAP (mmHg)	120 ± 4	121 ± 5	119 ± 3	124 ± 6
DAP (mmHg)	73 ± 2	76 ± 3	76 ± 3	78 ± 2
Respiratory rate (cycles/min)	18 ± 1	17 ± 1	18 ± 2	16 ± 1
MSNA (bursts/min)	12 ± 2	23 ± 2*	28 ± 3+	25 ± 3
Bursts/100 beats	19 ± 2	32 ± 4*	31 ± 3+	34 ± 5
NE (pg/mL)	271 ± 26	261 ± 32	501 ± 40+	598 ± 86+
E (pg/mL)	33 ± 7	34 ± 8	65 ± 11+	75 ± 13+
LF_{RR} (ms^2)	578 ± 111	574 ± 139	500 ± 118	503 ± 130
LF_{RR} NU	50.1 ± 4.5	67.5 ± 5.2*	82.3 ± 3.1+	88.9 ± 2+
$HF_{RR}(ms^2)$	940 ± 366	198 ± 51*	82.8 ± 22+	53 ± 15+
HF_{RR}NU	46 ± 4.4	26 ± 3.8*	14.3 ± 2.8+	8.7 ± 1.8+
LF/HF	1.47 ± 0.3	3.8 ± 0.8*	14 ± 2+	17 ± 2.5+

HR: heart rate (beats/min); SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MSNA: muscle sympathetic nerve activity; NE: norepinephrine; E: epinephrine; LF_{RR}: low frequency component of RR variability; HF_{RR}: high frequency component of RR variability; NU: normalised units. Data expressed as Mean ± SD; significance threshold p<0.05.
*p<0.05 control subjects *vs*. FMS patients; +p<0.05 Rest *vs*. Tilt.

Table III. Sleep parameters in fibromyalgia patients and healthy controls.

	FM (n=50)	Controls (n=45)	p
Sleep time (min)	293 ± 45	393 ± 40	0.001
Sleep efficiency (% of sleep time)	78 ± 10	89 ± 6	0.01
Stage1 non-REM sleep (% of sleep time)	20 ± 5	12 ± 5	0.001
Stage 2 non-REM sleep (% of sleep time)	36 ± 10	36 ± 3	n.s.
Slow-wave non-REM sleep (% of sleep time)	6 ± 2	18 ± 3	0.001
REM sleep (% of sleep time)	17 ± 9	18 ± 8	n.s.
Average SaO_2% during sleep (%)	94.8 ± 1.6	95 ± 1.7	n.s.
RDI (events/hour)	3 ± 1	3 ± 0.7	n.s.
DEF (events/hour)	9 ± 6	3.2 ± 2	0.01
PB (% of sleep time)	15.3 ± 8	1 ± 2	0.0001
Arousal/index (events/hour)	10 ± 3	4 ± 2	0.001
Alpha intrusions (no.)	16	2	0.001
PLMI (events/hour)	22 ± 7	5 ± 1	0.0001

REM: rapid eye movement; SaO_2%: oxygen saturation; RDI: respiratory disturbance index; DEF: desaturation event frequency; PB: periodic breathing; PLMI: periodic limb movement index.
Data expressed as mean ± SD; significance threshold p<0.05.

Table IV. The cyclic alternating pattern (CAP) parameters in fibromyalgia patients and healthy controls.

	FM (n=50)	Controls (n=45)	p
CAP rate	69 ± 6	44 ± 11	0.001
CAP cycle duration (secs)	46 ± 3	27 ± 2	0.001
Phase A duration (secs)	20 ± 4	10 ± 1	0.001
Phase B duration (secs)	25 ± 2.8	16 ± 3	0.001
Subtype A1 (no.)	150 ± 13	75 ± 13	0.001
Subtype A2+A3 (no.)	116 ± 20	64 ± 18	0.001

Phases A and B are components of the cyclic alternating pattern (CAP). Variations during CAP involve different degrees of muscle tone, heart rate and respiratory activity, which increase during phase A and decrease during phase B. Phase A subtype A1: a slow high-voltage EEG pattern generally associated with mild or trivial polygraphic variations. Phase A subtype A2: a rapid low-amplitude EEG pattern preceded by or mixed with slow high-voltage waves and associated with a moderate increase in muscle tone and/or cardiorespiratory rate. Phase A subtype A3: a fast low-voltage EEG pattern alone for more than two-thirds of the duration of phase A, coupled with markedly increased muscle tone and/or cardiorespiratory rate. Data expressed as Mean ± SD; significance threshold p<0.05.

Table V. Autonomic nerve system parameters variations during non-REM and REM sleep in fibromyalgia patients and in controls.

	FM (n=50)	Controls (n=45)	*p*
HR (bpm) non-REM	70 ± 3	58 ± 3	0.001
HR (bpm) REM	63 ± 3	62 ± 3	n.s.
LF_{RR} (ms^2) non-REM	368 ± 130	348 ± 129	n.s.
LF_{RR} (ms^2) REM	342 ± 140	345 ± 148	n.s.
LF_{RR} NU non-REM	50 ± 12	46 ± 6	n.s.
LF_{RR} NU REM	46 ± 8	44 ± 4	n.s.
HF_{RR}(ms^2) non-REM	138 ± 40	648 ± 316	0.00001
HF_{RR}(ms^2) REM	313 ± 140	393 ± 320	0.01
HF_{RR}NU non-REM	10 ± 6	31 ± 8	0.0001
HF_{RR}NU REM	15 ± 8	27 ± 7	0.001
LF/HF non-REM	3.0 ± 0.6	1.58 ± 0.5	0.0001
LF/HF REM	1.7 ± 0.6	1.68 ± 0.8	n.s.

HR: Heart rate (beats/min); LF_{RR}: low frequency component of RR variability; HF_{RR}: high frequency component of RR variability; NU: normalised units.
Data expressed as mean ± SD; significance threshold $p<0.05$.

Table VI. Correlations between heart rate (HR), the low frequency component of RR variability (LF_{RR}), the ratio between the low- and high-frequency component of RR variability (LF/HF), and clinical features, cyclic alternating pattern (CAP), periodic breathing (PB), and the periodic limb movements index (PMLI).

		r	*p*
HR bpm during sleep *vs.*	Tender points (n)	0.68	0.001
	Pain VAS (mm)	0.65	0.001
	CAP rate	0.78	0.0001
	PB (% of sleeping time)	0.76	0.0001
	PLMI (events/hour)	0.76	0.0001
HF_{RR} during sleep *vs.*	Tender points (n)	-0.58	0.01
	Pain VAS (mm)	-0.59	0.01
	CAP rate	-0.77	0.0001
	PB (% of sleeping time)	-0.84	0.0001
	PLMI (events/hour)	-0.79	0.0001
LF/HF ratio during sleep *vs.*	Tender points (n)	0.60	0.01
	Pain VAS (mm)	0.57	0.01
	CAP rate	0.78	0.0001
	PB (% of sleeping time)	0.80	0.0001
	PLMI (events/hour)	0.84	0.0001

Significance threshold $p<0.05$.

and subtype A2+A3 (116±20 *vs.* 64±18, $p<0.001$).

During sleep, the patients had a higher HR, and LF/HF ratio, and lower HF_{RR}, differences that were more marked during non-REM sleep (Table V), as were the presence of CAP, PB and PLMs. PLMs were mainly observed during CAP subtype A2 and A3. As in the tilt test, there was also a decrease in the index of cardiac vagal modulation during sleep: the decrease in HR_{RR} during sleep and in comparison when awake was less in the FMS patients than the controls (11.6±4.2 *vs.* 31.1±5.3 NUs, $p<0.01$; 45±38 *vs.* 403±281 ms^2, $p<0.0001$).

The number of tender points, pain VAS, the CAP rate, the PB% of sleeping time and the PLMI all seemed to correlate positively with HR and the LF/HF ratio, and negatively with HF_{RR} during sleep (Table VI).

Discussion

Our findings seem to show that sleep causes the same effects as a stressful test in FM patients. A vicious circle is created during sleep: pain increases sympathetic cardiovascular activation and reduces sleep efficiency, thus causing lighter sleep, a higher CAP rate, more arousals, a higher PLMI, and increasing the occurrence of PB, which gives rise to abnormal cardiovascular neural control and exaggerated pain sensitivity.

It is known that the intensity of the chronic pain felt by FM patients is related to their sympathetic cardiovascular activity: the greater the sympathetic drive to the heart and vessels, the greater the entity of the chronic pain (28). The magnitude of the pain is not due to circadian rhythm abnormalities and its 24-hour distribution can vary widely from person to person (29).

FM patients show abnormal CAP and PB rates when sleeping that may be generated by the exacerbation of chronic pain (19). The relationship between the autonomic network and CAP is well known (30); furthermore, PB increases baroceptor gain, and sympathetic outflow causes an oscillatory respiration pattern as a result of barorespiratory coupling (31). FM patients also show PLMs (32-34), the genesis of which is due to an increased excitatory nociceptive imput (35). Previous studies have shown that CAP is frequently observed in FM patients with PLMs, and may appear just before or at the same time as the emergence of PLMs (36).

At baseline all of the patients have a positive ESS score, suggesting disturbed sleep, consequently we did not evaluate the presence of anxiety, insomnia or depression because we believe that these symptoms are derived from the sleep alterations.

Our data confirm that, at rest, FM patients have a higher HR, greater MSNA, a higher LF/HF ratio, lower HF_{RR} values than controls. The behaviour of these parameters and the excessive rate of syncope (46%) during tilting suggests that FM patients are characterised by an overall increase in resting sympathetic cardiovascular activity, and that their autonomic profile during tilting is characterised the absence of increased sympathetic discharge to vessels and decreased cardiac vagal activity.

The non-restorative sleep of patients with FM is not related to a marked disruption in sleep architecture, although they may be more easily aroused because of the presence of PLMs and have less slow-wave sleep because of

the exacerbation of pain. However, it is closely related to a serious alteration of the microstructure of sleep, as shown by their 25% higher CAP rate.

This study is the first to evaluate the behaviour of the autonomic nervous system during sleep, and showed that sleep causes the same effects as those of a stressful tilt test in FM patients. During sleep, they show increased sympathetic activity and reduced cardiac vagal modulation in comparison with healthy controls. The increased values of HR and the spectral indices of cardiovascular sympathetic modulation (LF_{RR}), and the reduced level of HF_{RR}, indicate an interaction with their autonomic profile, and this is consistent with an exaggerated sympathetic drive to the heart and vessels, and a reduction in the vagal modulation of heart beats. Accordingly, the LF/HF ratio (an index of sympatovagal balance) is increased.

The correlations between the parameters of the autonomic nervous system network and pain intensity and the presence of CAP, PB and PLMs reveal a vicious circle: the painful exacerbation increases sympathetic cardiovascular activation and reduces sleep efficiency, thus increasing light sleep, the CAP rate, arousals, PLMs and PB. Increased PB alters cardiovascular neural control and, as suggested by Reyes del Paso *et al*., the deficient ascending pain inhibition arising from the cardiovascular system may contribute to exaggerated pain sensitivity (37).

Conclusions

Our data confirm that the FM patients have an autonomic nervous system dysfunction that is consistent with sympathetic over-activity due to the intensity of chronic pain when awake and during sleep. These findings explain the excessive rate of syncope observed in the FM population during wakefulness, and the increased presence of CAP, PB and PLMs during sleep.

As PB increases baroceptor gain and sympathetic outflow, it creates a vicious circle: the painful exacerbation increased sympathetic cardiovascular activation and reduces sleep efficiency, thus increasing light sleep, the CAP rate, arousals, PLMs and the occurrence of PB, which in its turn causes abnormalities in cardiovascular neural control and exaggerated pain sensitivity. Pain is the trigger of this vicious circle, consequently to control it can improve the quality of life and stop the process as it has been pointed out by Ghini *et al*. (38). Further studies focused on pain control will be suggested in order to verify this hypothesis.

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