Objective Measures of Disordered Sleep in Fibromyalgia

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ABSTRACT. Objective. Patients with fibromyalgia syndrome (FM) complain of inadequate sleep, which could contribute to common symptoms including sleepiness, fatigue, or pain. However, measures that consistently and objectively distinguish FM patients remain elusive.

Methods. Fifteen women with FM and 15 age- and gender-matched controls underwent 3 nights of polysomnography; Multiple Sleep Latency Tests to assess sleepiness; testing of auditory arousal thresholds during non-REM stage 2 and stage 4 sleep; overnight assessment of urinary free cortisol; and analysis of 24-hour heart rate variability.

Results. On the second night of polysomnography, women with FM in comparison to controls showed more stage shifts ($p = 0.04$) but did not differ significantly on any other standard polysomnographic measure or on the Multiple Sleep Latency Tests. Alpha EEG power during deep non-REM sleep, alone or as a proportion of alpha power during remaining sleep stages, also failed to distinguish the groups, as did auditory arousal thresholds. Urinary free cortisol did not differ between FM and control subjects in a consistent manner. However, decreased short-term heart rate variability (HRV) and especially ratio-based HRV among FM subjects suggested diminished parasympathetic and increased sympathetic activity, respectively. Other HRV measures suggested decreased complexity of HRV among the FM subjects.

Conclusion. Standard measures of sleep, a gold-standard measure of sleepiness, quantified alpha-delta EEG power, auditory arousal thresholds, and urinary free cortisol largely failed to distinguish FM and control subjects. However, HRV analyses showed more promise, as they suggested both increased sympathetic activity and decreased complexity of autonomic nervous system function in FM. (First Release Aug 15 2009; J Rheumatol 2009;36:2009–16; doi:10.3899/jrheum.090051)

Key Indexing Terms:
FIBROMYALGIA   SLEEP   ELECTROENCEPHALOGRAPHY   PAIN
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Some of the most prominent complaints of patients with fibromyalgia syndrome (FM) concern sleep, excessive daytime sleepiness, and fatigue rather than pain itself. Affected individuals frequently report light, easily-disturbed sleep, and daytime tiredness, fatigue, or sleepiness. The first objective evidence of any physiological abnormality in FM, reported nearly 3 decades ago, was the alpha-delta pattern recorded in the electroencephalogram (EEG) of FM patients studied during sleep[1]. The anomalous appearance of alpha EEG frequencies, which usually characterize wakefulness, overriding delta waves of deep non-rapid eye movement (non-REM) sleep, suggested a potential explanation for daytime fatigue. Subsequent research showed that patients with other pain syndromes often show alpha-delta sleep. The finding is no longer considered specific for FM, and may not be sensitive either[2-4]. Nevertheless, this or other non-specific polysomnographic measures of sleep disruption often distinguish FM patients from controls, and corre-

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late with pain and subjective daytime sleepiness[5]. In comparison to continuous alpha activity throughout the night or none at all, alpha-delta activity in the absence of alpha during other stages may predict sleep complaints and post-sleep worsening of pain particularly well[6].

Primary sleep disorders such as sleep-disordered breathing and restless legs syndrome also can occur among FM patients[7-9], and could exacerbate excessive daytime sleepiness[10]. However, most FM patients do not have these disorders, and most patients with these disorders do not develop FM[11].

Investigators have looked for other physiological distinguishing characteristics in FM. Affected patients sometimes complain of faintness, unsteadiness, palpitations, and blurred vision that could suggest autonomic dysfunction. One study of heart rate variability (HRV) found evidence of increased 24-hour sympathetic activity, and documented that this increase came from the night, when a decrease should normally accompany sleep[12]. However, another HRV study, published in abstract form, could not confirm abnormal regulation during sleep in FM patients[13]. FM may be associated with abnormalities of the hypothalamic-pituitary-adrenal system, the primary endocrine stress axis, but findings have not been consistent. Some but not all studies of FM patients suggest hyperactivity of the hypothalamic-pituitary-adrenal axis as reflected by elevated cortisol levels[14-16] and a diminished response to acute stressors[14,17,18]. In FM, cortisol levels on awakening and one hour later, but not at other circadian times, are associated with concurrent pain ratings[16].

In sum, however, no objective markers of sleep disturbance have been consistently specific for FM. Although fatigue and sleepiness have been studied using subjective questionnaires, the gold-standard laboratory measure of excessive daytime sleepiness, the Multiple Sleep Latency Test, has not been used to assess whether the complaints have physiological correlates. Similarly, although experimental sleep disruption may reduce pain thresholds and induce fatigue[19], the tendency for FM patients to arouse easily to external stimuli has not been assessed objectively. The aims of this pilot study, therefore, were to explore a range of potentially-novel physiologic differences, between FM patients and age-matched controls that might help to explain patient complaints of disturbed sleep, daytime sleepiness, fatigue, or pain. Preliminary reports and an ancillary, retrospective analysis of these data have been presented elsewhere[20-22].

MATERIALS AND METHODS

Participants. Patients were recruited from outpatient rheumatology referral clinics or through advertisements. Healthy control subjects were obtained through advertisements. This study was reviewed by the University of Michigan Institutional Review Board and was conducted according to principals of the Helsinki Declaration. Investigators interviewed and examined all subjects to determine that they met (or, for controls, failed to meet) criteria for FM as outlined by the American College of Rheumatology[23]. Testing included dolorimeter examination, complete blood count with differential, complete metabolic profiles, creatine phosphokinase, erythrocyte sedimentation rate, thyroid stimulating hormone, urine pregnancy test (if

necessary), and urine drug screening. Screening for psychiatric disorders employed the Mini-International Neuropsychiatric Interview, which identifies DSM-IV and ICD-10 psychiatric disorders[24].

Inclusion criteria were (1) age ≥ 18 and ≤ 65 years; (2) ability to discontinue psychotropic medications, hypnotics, analgesics, and herbal or over-the-counter supplements at least 2 weeks prior to the study (acetaminophen and diphenhydramine were allowed up to 3 days prior to the study); (3) American College of Rheumatology 1990 criteria for FM (for patients); and (4) signed informed consent. Exclusion criteria included (1) presence of an ongoing medical condition associated with pain or fatigue; (2) caffeine, cigarette, or alcohol use in excess of 500 mg/day, one-half pack/day, or 5 drinks/week, and unwillingness to discontinue this at least 3 days prior to the study; (3) recreational drug use confirmed on urine drug testing; (4) average time in bed of < 4 hours or regular bedtime later than 1:00 AM; (5) exogenous corticosteroids in any form for 3 months prior to study, or regular use of corticosteroids in the last 6 months; (6) pregnancy; (7) evidence of concurrent psychiatric illness in patients, or at any time in the past for controls; (8) known primary sleep disorder.

Daily diaries were used for 2 weeks prior to study and included information regarding the time in bed, sleep quality, and pain. The McGill Pain Questionnaire[25] was used as a measure of clinical pain. We also used a numerical rating scale, the Gracely Box Scale (GBS)[26-29] to assess present pain intensity. The Center for Epidemiological Studies Depression Scale (CES-D)[30] was used to assess mood. Group mean values were calculated for each measure.

Nocturnal polysomnograms and Multiple Sleep Latency Tests. Digital polysomnography (Telefactor DEEG/TWIN, W. Conshohocken PA, USA) on each of 3 consecutive nights included 6 EEG channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1, with sampling rates of 200 Hz); 2 electrooculogram channels; chin and bilateral anterior tibialis surface electromyography; 2 electrocardiographic (EKG) leads; nasal and oral airflow (thermocouples); thoracic and abdominal excursion (piezoelectric strain gauges); and finger oximetry.

The Multiple Sleep Latency Test was conducted on the day after the second nocturnal polysomnogram, following standard procedures[31]. Five nap attempts were scheduled 2 hours apart, usually at about 8:00, 10:00, 12:00, 2:00, and 4:00 pm. Subjective sleepiness was assessed before each nap attempt using the Stanford Sleepiness Scale[32].

Sleep studies were scored by a single registered polysomnographic technologist masked to subject group (FM vs control). Borderline polysomnographic features were arbitrated with an investigator board-certified in sleep medicine. Sleep and arousal scoring followed standard criteria[33,34]. Apnea was scored when nasal/oral airflow stopped for 10 seconds or more. An hypoponea was scored when airflow, chest excursion, or abdominal excursion diminished for at least 10 seconds, followed by an arousal, awakening, or oxygen desaturation $\geq 4\%$. Periodic leg movements were scored when they lasted 0.5 to 5.0 seconds, were separated by 5 to 90 seconds, and occurred in a series of at least 4 in a row. On the Multiple Sleep Latency Tests, the sleep latency of each nap was scored as the time between lights-out and the first epoch of stage 1 sleep[31]. The mean sleep latency on the 5 nap attempts was calculated.

Spectral analysis. One channel (C3-A2) of EEG, from lights-on to lights-out on the second laboratory night, was converted to ASCII text using Telefactor's built-in utility for spectral analysis. One-second segments (200 points) were used for Fourier power analysis implemented with MATLAB software. A Hanning window was applied to each segment before Fourier transformation. An average of powers derived from each of 30 one-second segments was used to characterize power for each 30-second epoch. Power was calculated separately for delta (1–4 Hz) and alpha (8–12 Hz) EEG frequency bands. The natural log transform of alpha power in slow-wave sleep (stages 3 and 4) was computed to normalize the distribution. The ratio of alpha power during slow-wave sleep to that power in all remaining sleep stages was also calculated[6].

Auditory arousal threshold (AAT). For the AAT evaluation[35], subjects were monitored for a third night. Real-time signal generation software was used for

precision control of an ordinary computer sound card (SoundMAX Digital Audio v5.0), the output of which was fed to inexpensive "ear bud"-style headphones (RadioShack). The system was calibrated using a B&K model 4134 condenser microphone, and found capable of delivering up to 88 dB sound pressure level to each ear. The signal generation software DaqGen (available as a free download from: http://www.daqarta.com) was used to calibrate the sound card to obtain resolution of better than 0.1 dB at all levels.

Prior to AAT testing, each subject had waking auditory threshold determined in the room where the sleep study was conducted. The AAT testing was conducted 4 times during the first 4 hours of sleep, during stage 2, stage 4, stage 2, and stage 4 sequentially. These stages were chosen because stage 2 generally represents the preponderant sleep stage each night, and stage 4 represents slow wave sleep previously reported to show abnormality in FM[1]. After 5 continuous minutes of the targeted stage, 988 Hz sinusoidal tone bursts of 2 s duration, at 10 s intervals, were generated starting at the subjects' awake auditory threshold and increasing in 10 dB steps until behavioral awakening occurred or a maximum of 80 dB was reached. The AAT was defined as the dB level that produced > 5 s wakefulness, or 80 dB if the maximum was reached without a behavioral awakening. Net stage-specific AAT was calculated for each subject by subtracting the awake auditory threshold from the awakening threshold during sleep. Results from the 2 trials within the given stage were averaged.

Urinary free cortisol (UFC). The first morning void was collected for measurement of free cortisol after each night.

Heart rate variability (HRV). A Holter monitor (DMS Holter, Stateside, NV, USA) was placed just prior to bedtime on the first night of study and was worn for the remainder of the study except during bathing. The sampling rate for the ECG signal was 128 Hz, which means that the absolute peak of the ECG signal was detected within ± 4 ms. Recordings were scanned using Cardioscan software (DMS Holter) at the Washington University School of Medicine Heart Rate Variability laboratory by experienced Holter technicians blinded to subjects' FM status. Each recording was overread by an investigator (PKS). Beat-stream files, representing the time and classification of each QRS complex, were transferred to a computer (Sun Microsystems, Mountain View, CA, USA) for time domain, frequency domain, and non-linear HRV analysis using standard methods[36-42]. Time domain indices of HRV are statistical calculations performed on the set of normal-normal (N-N) interbeat intervals. Frequency domain analysis partitioned the variance in the HR signal (actually heart period or N-N intervals) into its underlying frequency components using power spectral analysis. Non-linear HRV quantifies the structure of the HR time series.

The HRV indices were categorized according to the period over which they were assessed. Longer-term HRV indices quantify HRV cycles over periods of > 5 min (SDANN, ultra low frequency power). These indices are predominantly influenced by circadian rhythms and by sustained periods of activity. Intermediate-term indices quantify HRV over periods ≤ 5 min averaged over the entire recording period (SDNNIDX, very low frequency power, low frequency power). These quantify a combination of sympathetic and parasympathetic influences on heart rate and may include thermoregulation and baroreceptor activity as well as the effect of daily activities. Short-term HRV indices describe respiration-mediated beat-by-beat changes in heart rate and reflect primarily parasympathetic influences (e.g., pNN50, rMSSD, high frequency power). Ratio indices, such as normalized low frequency power or the low frequency power / high frequency power ratio, may reflect sympathovagal balance: low frequency power reflects a mixture of sympathetic and parasympathetic modulation of heart rate whereas high frequency power reflects parasympathetic control only[12,43].

Detrended fluctuation analysis quantifies the fractal scaling properties of the short-term R-R interval time series[44,45]. Normal values for the short-term detrended fractal scaling exponent (DFA1) are about 1.1. Higher values indicate less complexity and more periodicity in the HR time series, whereas lower values indicate more random fluctuations. The other non-linear measure used in this study was the Poincaré plot ratio (SD12) which is the ratio of the axis of an ellipse fitted to a scatterplot of each N-N interval versus the next[44]. A higher SD12 indicates a relative predominance of

beat-to-beat changes in HRV. Definitions for these indices are found in Table 4. At least 18 hours of usable 5-min segments were required for the 24-hour HRV data and 4.5 hours of usable segments were required for nighttime (00:00–06:00) HRV data reported here. Usable 5-min segments were defined as those in which at least 80% of intervals were scored as normal-to-normal intervals.

Sample size. Sample size for this pilot study was estimated from anticipated Multiple Sleep Latency Test and AAT results. To have 90% power in a paired t test with α = 0.05 to detect a 5-min sleep latency difference between FM and control subjects, with a standard deviation no larger than 5.5 min, both thought reasonable based on previous research (see example[46]), a sample size of 15 subjects per group was required. An expected mean AAT for normal individuals of 58 ± 10 dB suggested that 15 subjects per group would be needed to detect a 12 dB difference (SD ≥ 13.3 dB) between groups with 90% power.

Analysis. The main explanatory variable was group (FM vs control). Data were summarized as mean ± standard deviation and compared using Student's T test or Wilcoxon's rank sum test. Primary outcome variables were the natural log transform of alpha power during slow-wave sleep, mean sleep latency on the Multiple Sleep Latency Test, and AAT. Secondary outcome variables included the ratio of alpha power during slow-wave sleep to that during remaining sleep stages, UFC, and HRV. Correlations were performed using Spearman's rho.

RESULTS

Participants. Demographic, menopausal, and body mass index data for FM and control subjects are presented in Table 1. Subjects were matched individually by age and menopausal status. Body mass index did not differ between groups. FM subjects in comparison to controls reported more symptoms of fatigue, depression, and sleep problems. FM patients expressed significantly more pain on the 2-week pain diary (5.0 ± 1.6 vs 0.0 ± 0.1, p < 0.0001), the GBS (12.6 ± 4.0, vs 0.4 ± 1.1, p < 0.0001), and the McGill Pain Questionnaire (10.5 ± 4.8 vs 0.5 ± 0.8, p < 0.0001). Patients with FM scored higher on the CES-D (11.1 ± 5.6 vs 2.5 ± 3.2, p < 0.0001) and 3 met CES-D criteria for depression (> 16), but did not meet criteria for major depressive disorder when assessed by structured clinical interview.

Polysomnography. No standard polysomnographic measure (Table 2) showed a significant difference between FM and controls except for the number of stage shifts (p = 0.04). The amount of slow-wave sleep obtained ranged from 23 minutes (5.0% of sleep time) to 127 minutes (27.4%). Spectral analysis of these periods and other sleep stages (Table 3) showed that alpha power during slow-wave sleep was not

Table 1. Characteristics of study subjects.

	Control, n = 15	Fibromyalgia, n = 15
Age, yrs, mean ± SEM	42.5 ± 3.3	43.7 ± 3.5
Race		
Caucasian	9	15
Asian	2	
Black/African American	4	
Menopausal status		
Pre	10	10
Post	5	5
Body mass index	26.2 ± 1.5	26.5 ± 0.7

significantly greater among FM subjects versus controls; nor was the ratio of alpha power during slow wave sleep divided by alpha power during other stages.

On the Multiple Sleep Latency Test, daytime sleepiness showed no significant difference between groups: the mean sleep latency was 11.8 ± 4.8 in the FM patients and 13.1 ± 5.2 in controls (p = 0.55). However, FM patients reported more subjective sleepiness on the Stanford Sleepiness Scale prior to their nap attempts (2.9 ± 0.3 vs 2.0 ± 0.3, p < 0.005). The FM patients, in comparison to controls, also showed significantly higher scores on the Profile of Mood States prior to each nap (all p < 0.001).

Auditory arousal threshold. There were no significant differences (p = 0.39) between awake auditory thresholds for FM patients (11.1 ± 6.4) and control subjects (11.8 ± 6.7). Similarly, there were no significant differences on net AAT in either stage 2 (34.3 ± 11.5 vs 34.0 ± 15.5, p = 0.48) or stage 4 (43.6 ± 13.8 vs 49.7 ± 11.1, p = 0.10) sleep, although the AAT for FM patients during stage 4 sleep was numerically lower.

Urinary free cortisol. Overnight UFC was significantly lower in FM patients than control subjects for the first night (10.4 ± 8.4 vs 18.1 ± 9.1, p = 0.02), but not the second night (13.7 ± 13.6 vs 19.4 ± 13.5, p = 0.14) or the third night, after the stress of the AAT testing (15.7 ± 13.8 vs 15.8 ± 5.0).

Heart rate variability. There were significant group differences in nighttime HRV between FM and control subjects (Table 4). Longer-term HRV (SDANN, ultra low frequency), ratio HRV (normalized low frequency power), and the short-term fractal scaling exponent were increased in FM, while normalized HF power and SD12 were decreased. The trend toward higher mean nighttime heart rates in FM (by 5 bpm) did not reach significance (p = 0.160).

Twenty-four-hour recordings (Table 5) suggested similar mean heart rates between groups. However, in contrast to nighttime findings, mean 24-hour SDANN and ultra low frequency power showed non-significant decreases in FM. Other HRV measures were virtually the same for 24-hour and nighttime recordings, except that the higher low frequency / high frequency ratio in FM became statistically significant (p = 0.019).

DISCUSSION

Our study of women with FM and age-matched female controls assessed the ability of several promising physiologic measures to discriminate between groups. Standard nocturnal polysomnographic measures showed only nonspecific evidence of mild sleep disruption in FM subjects. Further, FM and control subjects showed no difference in objectively quantified alpha-delta sleep, even when considered in relation to alpha power during all remaining sleep stages. The common FM complaint of excessive daytime sleepiness could not be confirmed by a gold-standard sleep laboratory measure. The frequent FM complaint of easy awakening from sleep could not be corroborated by increased sensitivity, in comparison to controls, to titrated auditory stimuli. Overnight UFC also did not show consistent differences between FM subjects and controls. In contrast, evidence of altered physiologic arousal was obtained from longer-term HRV, and ratio-based and non-linear HRV measures that capture relationships between sympathetic and parasympathetic activity.

Our findings demonstrate that FM subjects were not clearly sleepier than controls: the discrepancy did not approach statistical significance, and the clinical significance of a one-minute difference in mean sleep latency on a Multiple Sleep Latency Test is questionable (the score ranges from 0 to 20 min). At the same time that participants made their nap attempts, FM subjects' self-ratings in comparison to those of controls suggested considerably more subjective sleepiness.

Table 2. Polysomnographic measures*. Values are expressed as mean (SD).

	Control, n = 15	Fibromyalgia, n = 15	p**
Total recording time, min	478.5 (4.1)	481.2 (6.4)	0.097
Total sleep time, min	419.1 (29.7)	420.9 (32.0)	0.756
Sleep efficacy, %	87.6 (5.8)	87.5 (7.0)	0.967
Stage shifts, no.	107 (22)	126 (27)	0.042
Arousals, no.	43.3 (16.1)	64.9 (39.4)	0.089
Wake after sleep onset, min	49.3 (27.6)	50.0 (35.4)	0.820
% Stage 1	6.8 (3.9)	6.4 (3.3)	0.917
% Stage 2	55.8 (6.6)	51.6 (7.0)	0.115
% Stage 3–4	15.7 (7.3)	19.0 (8.5)	0.340
% REM	21.7 (5.0)	22.9 (4.3)	0.590
Apnea/hypopnea index	0.4 (0.6)	1.2 (2.4)	0.488
Minimum oxygen saturation, %	92.0 (3.7)	93.4 (2.7)	0.271
Periodic leg movement index	5.1 (10.1)	7.8 (8.8)	0.449

* Sleep efficacy: (total sleep time/total recording time) × 100; % Stage 1: stage 1 time (over the entire night) * 100/total recording time; Apnea/hypopnea index: total number of apneas and hypopneas/total sleep time in hours. ** Wilcoxon rank sum test. REM: rapid eye movement sleep.

Table 3. Results of spectral analysis. Values are expressed as mean ± SD.

	Fibromyalgia, N = 15	Control, N = 15	p*
Natural log (alpha power during slow-wave sleep)	11.9 ± 1.09	11.5 ± 1.03	0.29
Alpha power during slow-wave sleep/ alpha power during remaining sleep stages	0.37 ± 0.32	0.25 ± 0.20	0.22

* Student's T-test.

Table 4. Nighttime (00:00–06:00) heart rate variability (HRV).

	Fibromyalgia, n = 13	Control, n = 11	p
Longer-term HRV			
Heart rate (beats per minute)	73 ± 11	67 ± 9	0.160
SDNN [SD of N-N intervals (ms)]	80 ± 22	93 ± 21	0.141
SDANN [SD of 5-min averaged N-N intervals (ms)]	67 ± 21	47 ± 19	0.021
Ln (ultra low frequency power)	8.46 ± 0.60*	7.75 ± 0.77	0.021
Intermediate-term HRV			
SDNNIDX [average of 5-min SDs of N-N intervals (ms)]	58 ± 17	60 ± 19	0.849
Ln (very low frequency power)	7.49 ± 0.60*	7.37 ± 0.50	0.596
Ln (low frequency power)	6.79 ± 0.73*	6.68 ± 0.57	0.679
Short-term HRV			
pNN50 [percent of N-N intervals > 50 ms different from previous]	11.4 ± 10.8	18.0 ± 19.2	0.304
rMSSD [root mean square of successive differences of N-N intervals (ms)]	35 ± 17	43 + 25	0.359
Coefficient of variance (%)	11.4 ± 3.7	8.7 ± 1.7	0.038
Ln (high frequency power)	5.82 ± 1.07*	6.21 ± 0.91	0.360
Ratio-based HRV			
Normalized low frequency power (%)	66 ± 9*	54 ± 17	0.033
Normalized high frequency power (%)	27 ± 10*	41 ± 17	0.025
Low frequency/high frequency ratio	3.9 ± 2.0*	2.4 ± 2.1	0.121
Nonlinear HRV			
DFA1	1.27 ± 0.17*	1.05 ± 0.28	0.033
SD12	0.27 ± 0.08*	0.38 ± 0.13	0.029

* N = 12 FM. Ln: natural log. N-N intervals: times between heartbeats with normal morphology and correct beat onset time. Ultra low frequency power: variance in heart rate explained by underlying cycles from once in 5 min to once in 24 h. Very low frequency power: variance in heart rate explained by underlying cycles from once in 20 s to once in 5 min. Low frequency power: variance in heart rate explained by underlying cycles of 3–9 per min (based on averages of 5-min determinations). High frequency power: variance in heart rate explained by underlying cycles respiratory frequencies (9–24/min), based on averaged 5-min determinations. Normalized high frequency power: the average proportion of variance in heart rate explained by low frequency power (based on averaged 5-min determinations). LF/HF ratio: the numerical ratio of low to high frequency power (based on average 5-min determinations). DFA1: the short-term fractal scaling exponent, expressing the degree of randomness or correlation of 4–11 beat sequences. SD12: the Poincaré ratio, the ratio of the axes of an ellipse drawn to fit the scatterplot of each N-N interval vs the next.

The FM subjects in comparison to controls also simultaneously rated their mood state as lower. These uniquely time-paired results highlight differences between subjective perception and objective measures in FM subjects.

Similarly, although FM patients do not have physical abnormalities associated with ear disease[47], awake subjects do show increased sensitivity to sounds of all magnitudes including those encountered in everyday activities[48]. Our results of auditory arousal threshold testing during sleep remain somewhat ambiguous. Arousal from stage 4 sleep trended towards a lower auditory threshold for FM subjects compared to controls, and the lack of significance could well have arisen from the sample size. In this case, a difference of 6 dB could potentially suggest clinical significance. We are not aware of any similar data, obtained during sleep, with which to compare to our results. However, experimental disruption of deep non-REM sleep can reduce pain threshold and induce fatigue in FM[19]. Medications that augment slow wave sleep may improve FM symptoms[49]. Such data combine with our findings to suggest that a larger and more definitive assessment of arousal thresholds during deep non-REM sleep would be worthwhile.

Although severe nocturnal sleep disruption might have been expected to increase overnight UFC, the only significant difference we found between FM and control subjects occurred during the first night, and in the opposite direction. We hesitate to draw strong conclusions from this observation because it was not replicated on the next 2 nights. However, we can speculate that the initial difference could have reflected differences in established circadian rhythms between the groups, one that perhaps began to ameliorate after the first night with a continued stay in a parallel environment.

Of the objective measures we chose to explore, HRV measures that reflect psychophysiologic arousal seemed to be the most sensitive discriminators between FM and control subjects. HRV was assessed over 24 hours and also separately during usual nocturnal sleep hours. Significant and consistent between-group differences were seen for 24-hour and nighttime ratio HRV measures, and for non-linear HRV measures. Ratio measures, while not quantifying sympathet-

Table 5. Twenty-four-hour heart rate variability (HRV).

	Fibromyalgia, n = 11	Control, n = 10	p
Longer-term HRV			
Heart rate (beats per minute)	75 ± 8	74 ± 9	0.682
SDNN [SD of N-N intervals (ms)]	105 ± 22	119 ± 33	0.267
SDANN [SD of 5-min averaged N-N intervals (ms)]	86 ± 21	101 ± 32	0.209
Ln (ultra low frequency power)	8.91 ± 0.47	9.19 ± 0.64	0.274
Intermediate-term HRV			
SDNNIDX [average of 5-min SD of N-N intervals (ms)]	57 ± 13	56 ± 14	0.209
Ln (very low frequency power)	7.37 ± 0.45	7.24 ± 0.43	0.523
Ln (low frequency power)	6.76 ± 0.38	6.53 ± 0.36	0.182
Short-term HRV			
pNN50 [percent of N-N intervals > 50 ms different from previous]	9.3 ± 8.8	14.7 ± 13.7	0.343
rMSSD [root mean square of successive differences of N-N intervals (ms)]	32 ± 12	38 ± 19	0.343
Coefficient of variance (%)	13.1 ± 2.7	14.3 ± 3.3	0.348
Ln (high frequency power)	5.54 ± 0.78	5.97 ± 0.78	0.223
Ratio-based HRV			
Normalized low frequency power (%)	70.4 ± 9.1	56.6 ± 10.3	0.004
Normalized high frequency power (%)	22.9 ± 9.1	35.0 ± 10.1	0.009
Low frequency/high frequency ratio	4.8 + 2.3	2.7 ± 1.33	0.019
Non-linear HRV			
DFA1	1.31 ± 0.16	1.11 ± 0.18	0.016
SD12	0.26 ± 0.06	0.32 ± 0.09	0.098

For definitions see legend to Table 4.

ic activity per se can be interpreted as reflecting sympathetic and parasympathetic balance. Measures that reflect intermediate-term HRV, like SDNNIDX, the average variability over 5 min, were not different between groups. This suggests that total autonomic activity was similar in FM and control subjects. However, the marked increase in normalized low frequency power combined with the marked decrease in normalized high frequency power (each of which quantifies the relative contribution of oscillations in these bands to intermediate-term HRV) are consistent with a shift towards greater sympathetic control of heart rate, both during the nighttime and over the 24-hour cycle in FM patients. Relative increases in sympathetic activity during sleep would be consistent with our observation of a trend toward more frequent arousals in FM subjects as compared to controls. Sympathetic surges are known to occur during and after EEG-defined arousals triggered by sleep apnea or artificial tones[50,51], and before arousals associated with periodic leg movements[52]. Sleep apneas and periodic limb movements most typically occur at frequencies between every 20 seconds to every 2 minutes, resulting in increased power in the very low frequency HRV band, which measures underlying HRV changes at these frequencies. However, no such difference between FM and control subjects was observed in our study.

Of interest was the finding, for the first time, of markedly increased DFA1 (short-term fractal scaling exponent) and concomitantly decreased SD12 in FM patients. The DFA1 reflects the degree to which heart rate patterns are correlated (higher DFA1) vs random (lower DFA1) on a scale of 4 to 11 beats. Normal DFA1, as found in the controls in this study, is about 1.1. Decreased SD12 in FM subjects was consistent with increased DFA1 and also suggests a difference in the underlying structure of heart rate patterns in FM. Both results suggest a lack of normal complexity in the regulation of heart rate patterns in FM. Decreased heart rate variability has been reported in FM[53,54]. These observations combine with ours to support the recent hypothesis that "decomplexification" of the autonomic nervous system, with persistent and inflexible sympathetic predominance across the circadian cycle, may play a key role in FM, as well as related conditions such as irritable bowel, chronic fatigue, and Gulf War syndrome[55]. Sympathetic hyperactivity could potentially explain not only HRV changes in FM, but also important features of the syndrome, and chronic pain or allodynia in particular[56], to the extent that the sympathetic nervous system can activate primary afferent nociceptors[57].

The most promising sleep-specific measures in our study for physiological discrimination between FM and control subjects were the longer-term nighttime heart rate variability (SDANN and ultra low frequency) measures. A significant increase in SDANN and ultra low frequency was found in FM subjects versus controls during the nighttime, in contrast to a trend towards relatively decreased values in FM subjects for the same variables over the 24-hour cycle. This surprising result suggests a difference in the strength of

underlying autonomically-mediated ultradian rhythms of heart rate, perhaps reflecting more disturbed sleep not measured by standard variables or an abnormality of neurocardiac integration in FM.

Both these changes suggest higher levels of sympathetic activity in FM versus control subjects and confirm findings of a previous investigation[12]. However, in that study the difference in 24-hour HRV arose mainly at midnight and 3:00 AM measurement points. In contrast, our data showed no significant difference between daytime and nighttime, suggesting that the increased physiological arousal represented by this measure may permeate both sleep and wakefulness.

Among the limitations of our study was small sample size; therefore, failure to find more sleep-related differences between FM and control subjects cannot be taken as proof that those relationships do not exist. Multiple tests in a limited sample, without adjustment for simultaneous comparisons, were performed because the priority was to explore a range of physiologic measures for a potentially robust approach. This means, however, that identified associations, especially those with marginal p values, deserve prospective replication. Finally, stringent inclusion and exclusion criteria also limit, to some extent, applicability of the findings to clinical practice, where comorbid psychopathology, medication use, and primary sleep disorders are common and potentially influential. In particular, HRV changes, reflecting increased sympathetic and decreased parasympathetic activity, have been reported in a range of psychiatric conditions, including major depression[58]. Although none of our subjects met criteria for major depression, we cannot exclude the possibility that differences between FM and control subjects could have been influenced by more subtle levels of psychiatric comorbidity. However, the increase in nighttime values for longer-term HRV and the marked increase in the short-term fractal scaling exponent have not been reported in depression, and therefore may be more specific to FM.

In short, our comparison of carefully selected FM and control subjects failed to show many differences in standard polysomnographic measures, an objective measure of daytime sleepiness, sensitivity to an auditory stimulus, or overnight cortisol levels. However, FM subjects did show HRV changes consistent with decreased parasympathetic control of heart rate and relatively high sympathetic activity during both daytime and nighttime hours. Whereas the HRV changes themselves seem unlikely to mediate the symptoms of fibromyalgia, the underlying autonomic dysfunction potentially could affect pain. To assess whether specifically nocturnal HRV differences between FM subjects and controls reflect abnormalities of sleep, as opposed to other pathophysiology in FM, will require longitudinal or interventional study designs. Our present results more broadly suggest that efforts to distinguish sleep of FM and non-FM subjects may benefit from newer, non-standard approaches to analysis of polysomnographic data. In particular, one largely unexplored analytic approach[59], while not part of our original prospective protocol, demonstrated retrospectively the potential value of focus on durations of uninterrupted, specified sleep stages[22]. Beyond manipulations of traditionally scored sleep patterns, however, analyses of HRV and other autonomic measures may offer the most immediate promise for consistent physiologic measures that will distinguish sleep of patients with FM with reasonable sensitivity and specificity.

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