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Mindfulness-based intervention does not influence cardiac autonomic control or pattern of physical activity in fibromyalgia during daily life: An ambulatory, multi-measure randomized controlled trial*

Paul Grossman, PhD, Gunnar Deuring, MS, Harald Walach, PhD, Barbara Schwarzer, MD, and Stefan Schmidt, PhD

From the Department of Psychosomatic Medicine, Division of Internal Medicine, University Hospital Basel, Basel Switzerland (P.G., G.D); Institute of Transcultural Health Studies, European University Viadrina, Frankfurt (Oder), Germany (H.W., S.S.); Brain, Mind and Healing Program, Samueli Institute, Alexandria, VA, United States (H.W., S.S.); Institute of Environmental Health Sciences, University Medical Center, Freiburg, Germany (B.S.); Department of Psychosomatic Medicine, University Medical Center, Freiburg, Germany (S.S.).

Address correspondence and reprint request to Paul Grossman, Department of Psychosomatic Medicine, University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland. Email: Paul.Grossman@usb.ch .

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Fibromyalgia (FM) is a clinical functional disorder with major symptoms of chronic widespread pain, fatigue, stiffness and sleep disturbance. Predominantly afflicting women, high comorbidity exists with other functional somatic disorders, depression, chronic fatigue syndrome and history of emotional or physical trauma. To date, there is no clear-cut evidence of peripheral physiological abnormalities contributing to the etiology of fibromyalgia, the syndrome diagnosed on the basis of subjective report. Absence of clear evidence-based physiological abnormalities, together with fibromyalgia's high comorbidity with other functional disorders and depression, keep this diagnosis controversial. Additionally, patient complaints often correlate poorly with objective measures of function, e.g. sleep quality and extent of physical activity [1-4].

In the last decade, increasing evidence suggests that the syndrome is importantly related to central nervous system augmentation of somatosensory processing [5-8]. Additionally, impaired cardiovascular autonomic regulation, based on heart-rate variability (HRV) analysis, has been proposed to contribute to the etiology or maintenance of fibromyalgia [9-18]. To the extent that the relevant physiological measures can be made in daily life, it may be possible to discern whether putative physiological mechanisms are causally related to a syndrome. Thus if intervention-related improvements in fibromyalgia symptomatology are unrelated to alterations in cardiovascular autonomic regulation, the hypothesis of a causative link would be greatly weakened.

In this article, 1) we first report a comparison of female fibromyalgia patients with a matched control group of healthy women to evaluate differences in cardiac and respiratory functioning and in activity level during everyday functioning during awake hours. The purpose of these initial analyses is to show that our group of female fibromyalgia patients, in fact, exhibited different patterns of physical activity and cardiorespiratory functioning at baseline than age-matched healthy controls.

2) We next examine whether a mindfulness-based stress reduction (MBSR) was effective in producing changes in cardiovascular or respiratory functioning or altered patterns of daily physical activity, associated with fibromyalgia. Preliminary evidence suggests that mindfulness practice may influence respiratory and cardiovascular autonomic control [19-24], although this has only been shown during laboratory measurements. Additionally, another laboratory study suggests that altered breathing modulates pain responses in fibromyalgia [25].

This investigation was a three-armed randomized trial in which MBSR was compared to a no-treatment, wait-list group, as well as to an active comparison intervention attempting to control for the non-specific aspects of MBSR. An earlier publication of this investigation examined patient-reported clinical outcomes of health-related quality of life, depression, anxiety, pain experience and sleep quality [26]; see [26] for details and a review of the effects of MBSR upon fibromyalgia (as well as an additional recent review [27]). In the earlier report [26], the efficacy of MBSR for the primary, quality-of-life, outcome was not confirmed, although the MBSR group did manifest significant within-group differences in quality of life and many secondary measures. The results presented here represent planned secondary analyses of cardiac and respiratory autonomic measures, as well as accelometry-derived physical activity.

3) Finally, we investigate relations between objective physical changes and intervention-associated or spontaneous patient-reported benefits in fibromyalgia complaints. Namely, we examine the degree to which changes in fibromyalgia complaints during the study period were related to cardiorespiratory alterations and modified patterns of physical activity.

Methods

Participants

Fibromyalgia patients: 168 women, 18-70 years of age currently suffering from fibromyalgia (American College of Rheumatology (ACR) criteria [28]), were eligible for the trial. Exclusion criteria were life-threatening diseases, suppression of the immune system or participation in other clinical trials. Patients were recruited via patient self-help groups, news media and referrals from general practitioners, rheumatologists, and the University Medical Center Freiburg Interdisciplinary Pain Unit. During an intake examination at the hospital, patients were evaluated for all eligibility criteria and were examined by an experienced physician who employed ACR criteria to confirm diagnosis of fibromyalgia. Forty-six percent of the patients were taking antidepressants before intervention, but there were no differences between intervention groups. For further details regarding recruitment, see [26]. 140 patients completed pre- and post-intervention ambulatory monitoring, and 130 patients completed all 3 monitoring days.

Control participants. 33 healthy women were recruited from a gynecology clinic visit for a regular checkup and underwent a single 24-h ambulatory registration. Exclusion criteria were: 1) concomitant Axis I disorder not in remission (evaluated with a structured clinical interview for DSM-IV-R [53]); 2) presence of any of the following medical conditions: diabetes mellitus, previously diagnosed obstructive sleep apnea, pacemakers/defibrillators, atrial fibrillation, myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within 6 months of enrollment, congestive heart failure, uncorrected primary valvular disease, uncorrected thyroid heart disease, renal or hepatic dysfunction, dementia, multiple sclerosis, alcohol or drug abuse within 12 months, current pregnancy, primary sleep disorders including insomnia; 3) Medication use that would affect hormone levels or alter autonomic function or sleep including: hydrocortisone, anxiolytics,

oral contraceptives, hormone replacement therapy, benzodiazepines, non-benzodiazepine hypnotics, barbiturates, selective serotonin-reuptake inhibitors (SSRIs), MAO-inhibitors. These women were not paid for their participation. Data from this sample derive from a previous study recruited at approximately the same time and reported in detail elsewhere [29].

This study was approved by the University of Freiburg Ethics commission, and all patients completed informed consent prior to enrollment.

Design of Intervention Study

The design of the intervention study is detailed in an earlier publication, along with the CONSORT flow chart [26], and is here briefly reviewed. A three-armed trial was conducted, in which fibromyalgia patients were randomly assigned either to a) MBSR, b) an active control intervention aimed at equating the nonspecific features of MBSR (here termed relaxation intervention; RELAX) or c) a wait-list control group (WL). The MBSR was closely based upon the original program of mindfulness-based stress reduction [30] (the protocol adhered to the standard program, in terms of the number and duration of all sessions, and the week-to-week curriculum), whereas the active control intervention RELAX attempted to control for the nonspecific effects of MBSR by substituting the mindfulness and yoga exercises with progressive relaxation techniques and physical therapy procedures adapted to fibromyalgia patients [31]. Both interventions were eight-week group interventions with groups of 10-15 women that met once a week for 2.5 h. All women including the waitlist group were offered the active treatment of their choice at the conclusion of their follow-up measurements. Primary clinical endpoint was patient-reported health-related quality of life (Quality of Life Profile for the Chronically Ill [43]; also see [26]) at short-term follow-up after the end of the intervention.

We hypothesized the following regarding the objective physiological data presented here: 1) In contrast to control arms, MBSR would result in enhanced cardiac parasympathetic

control, as indexed by increased respiratory sinus arrhythmia (RSA; equivalent to, and the underlying phenomenon of, high-frequency HRV), and decreased heart rate (HR) after treatment and follow-up; secondarily, we examined whether patterns of cardiac measures during awake hours would differ between groups. 2) In comparison to other arms, MBSR participants would show increases in activity from pre-intervention to post-intervention and to follow-up, secondarily associated with different daytime patterns of these measures. 3) Improvement in clinical complaints would be associated with enhanced cardiac parasympathetic control of HR and increased daily physical activity.

Measures

Physiological Parameters

The following physiological signals were continuously registered via a multi-channel ambulatory monitoring system (LifeShirt System; Vivometrics, Ventura, CA) and stored on flashcards: One channel of ECG (sampled at 200 Hz), two channels of respiration via abdominal and thoracic inductance plethysmography band (50 Hz); and one three-dimensional accelerometer at chest level (50 Hz). We present here only data from awake hours (night-time data to be separately reported).

Respiratory, cardiac and accelerometry measures were analyzed by the Vivologic analysis software (Vivometrics, Ventura, CA), which is a full disclosure analysis system allowing validation of all parameters from the original raw signals.

The continuously sampled ECG signal was available for editing in the acquired data. Minute-by-minute heart rate (HR) and RSA, i.e. high-frequency HRV, were computed after all registrations of the original signal waveforms were manually screened for ECG arrhythmias, ectopic activity and movement artifact in the ECG signal. Minutes with excessive ectopic activity or other artifact in the remaining subjects were removed from all analyses and replaced with interpolated values. RSA was quantified in the time domain using

the peak-valley algorithm to estimate amplitude of RSA [32; 33]. This method has been previously validated as almost perfectly correlated with spectral analysis estimations [32; 33]. RSA values were transformed to natural logarithms in orders to normalize the distribution.

Respiratory parameters included respiration rate, or breathing frequency ($F_{b,}$ breaths/m), as well as calibrated tidal volume (V_t, ml) and minute ventilation (V, l/m; [34; 35]. Previous research has validated this method of ambulatory monitoring of respiratory timing and volumetric parameters [34; 35]. Respiratory parameters were primarily included to evaluate whether differences in RSA could be accounted for by variation in F_b or V_t , well known to exert large within-individual effects upon RSA that are independent of cardiac vagal variations [36].

Motion activity, also termed physical activity here, was the sum of the three axes of integrated accelerometer signal. On the instrumentation day, accelerometers were calibrated during a walking test (see below).

Questionnaire Data

Patient-reported, standardized clinical questionnaire data were gathered at all three time-points: before intervention, after the 8-week intervention, and after an additional 8-week post-intervention follow-up; for detailed results, see [26]. These included measures of health-related quality of life, fibromyalgia impact, depression, sleep quality, anxiety, pain perception and physical complaints [37-43].

Procedures

Participants came to the laboratory on a weekday morning. They were connected to the LifeShirt ambulatory monitoring device, and a respiratory calibration of tidal volume was made by having subjects breathe a known volume of air into a closed system for several breaths [34; 35]. Subsequently, the accelerometer physical activity sensor was calibrated by having subjects walk on a measured course at three speeds, slow, medium and fast. Times and

distances reached were recorded and the accelerometry data was later individually calibrated to speed. Training was then given on how to use the ambulatory electronic diary during awake hours.

Participants were requested to go about normal daily life as best as possible but to refrain from bathing while they were being monitored. Participants returned the next day and were disconnected from the ambulatory monitor.

Data Analysis

We performed both intention-to-treat (ITT) and per-protocol (PP; i.e. completer) analyses on all data that examined intervention group X time effects. One hundred and sixty-eight patients were included in the ITT analyses, and 130 in the PP results. Twenty-eight patients refused to participate in the ambulatory part of this study, and 10 patients were excluded due to equipment failure. Before pursuing the ITT analyses, we performed independent t-tests on all demographic measures and standardized patient report outcomes at each time point, comparing those completing (n=130) *vs.* those not completing (n=38) ambulatory assessment. This was done to evaluate whether these two groups were different from each other among any of the salient characteristics of our study. We found no significant differences on any variable. Therefore, within-group mean values replaced all missing data for the ITT analyses. This resulted in very similar mean values for each of the dependent variables, but often higher levels of statistical significance, due to the larger sample size. Figures and tables depict original PP data.

Descriptive statistics were used to describe central tendency (mean, median), and variation (SD, range) of the biological measures in each group. Any values that were significantly skewed were transformed appropriately. Multivariate Wilks' lambda analyses were performed for the repeated measures in order to determine significance. *Post hoc* comparisons were performed with Tukey Tests of Honestly Significant Differences.

Based on a significance value of $p<0.05$, we calculated and employed the Benjamini-Hochberg adjustment [44] for multiple comparisons: ITT results with p's <0.0225 and PP results with p's<0.0125 were considered significant (Bonferroni corrected significance level, p's <0.0025).

Physiological data: Median values of parameters as described in the data analysis section were calculated for each consecutive minute of daytime and evening hours.

These data were then classified into four times of day: 9:00-11:59, 12:00-14:59, 15:00-17:59, and 19:00-21:59 (we later employ the nearest hour, e.g. 12:00-15:00, for ease of presentation).We decided *a priori* to have four equal periods for time-of-day, and chose to start the evening period at 19:00. We presumed that rhythms in specific physiological parameters would occur, and we were also interested in whether fibromyalgia patients manifested different patterns of physiological activity than controls across the day.

Comparisons between patients and control participants. The pre-intervention registrations were used for the patient sample in these analyses. Repeated-measures multivariate analyses of variance (RM-MANOVAs) for each physiological parameter were performed, with a Fibromyalgia vs. Control Grouping factor. Time-of-day (morning, early afternoon, late afternoon and evening) was the repeated measure.

Effects of intervention in the patient sample. To assess reliability of measurement, test-retest correlations were first computed for outcome measures comparing time-points (pre-intervention, post-intervention and follow-up) for the wait-list (no treatment) group. RM-MANOVAs for each physiological parameter were performed, with a grouping factor of "Intervention Arm." There were two repeated measures: Time-point (pre-intervention, post-intervention and follow-up), and time-of-day (morning, early afternoon, late afternoon and evening). Wilks' lambda was again used for multivariate comparisons. Post hoc comparisons were performed with the same tests as mentioned above.

Relations between clinical improvements based upon questionnaire data and physiological / accelerometry findings. Measures from the patient self-report data were highly correlated with each other [26]. Therefore we created a single composite measure of clinical change at post-intervention and at follow-up based on the sums of the standardized scores of the individual measures. The average of post-intervention and follow-up standardized scores were then computed as a measure of overall change after intervention; however, findings were not different when only post-intervention or follow change scores were employed. To ascertain whether clinical change moderated physical effects on interventions, we repeated all analyses of intervention effects using this measure of clinical improvement as a covariate. We assumed that this would control for the heterogeneity of patient-.reported clinical responses.

Additionally, groups of responders and nonresponders were formed, based upon those participants who reported clear overall improvement in health-related quality of life (HRQoL; see [26] for details) after treatment *vs.* those participants who showed no or negative change. Our rationale was to compare participants who demonstrated at least moderately strong change-score effect sizes (which are equivalent to standardized change scores). Therefore, an average standardized change score ≥.65 (corresponding to at least a moderately large effect size of improvement) was chosen at the lower cutoff of the improved (responder) group; change scores < 0.05 (corresponding to no or negative effect size of change) were chosen for the no-to-negative-change (nonresponder) group. It should be noted that when other criteria were employed (e.g. scores ≥0.50 *vs.* ≤ 0.00), results did not change. This procedure was, furthermore, performed irrespective of group membership in order to investigate whether perceived clinical changes in HRQoL were related to objective physical measures, independent of type of intervention. Therefore, all analyses were then repeated with this clinical change as sole grouping factor with Time-point and Time-of-day as repeated

measures. Once again, these analyses were performed to assess whether differences in clinical patient-reported outcomes were associated with autonomic or physical activity outcomes.

Power Analysis. Using GPower Version 3.1.2 with an ANOVA test of within-between factor interactions (Group [3] X Time-point [2]; power [1-β] =.8, N=130) for PP analyses (adjusted for three dependent measures with an average correlation among repeated measures of 0.7) showed sensitivity to minimally detect a small effect size f =0.13 (eta^2=.04).

Results

Comparisons between fibromyalgia patients and healthy control females

Demographic variables. Average age between groups was similar (52.9 y ± 9.4 SD vs. 53.4 y ± 6.0 SD, see Table 1). In comparison with the control sample, fibromyalgia patients were less educated (31% vs. 67 % completing at least some college education, $p<0.01$) and were less frequently married (57% vs. 81 %; $p<0.01$).

Ambulatory findings. Fibromyalgia patients exhibited markedly higher mean HRs than controls (86.0 vs. 77.5 beats/m; SD's, 9.8 and 9.5 beats/m) and lower RSA (4.1 vs 4.7 ln ms^2; SD's =9.8 and 9.5 ln ms^2) across awake hours ($p's \leq 0.0001$; see Table 2 and Fig. 1a-b). There was an overall time-of-day effect ($p<10^{-15}$), indicating increasing HR from morning to early afternoon, then a decline to evening. Additionally a Group X Time-of-Day interaction for HR ($p<0.02$) was found, which indicated less dynamic HR responsiveness over awake hours among fibromyalgia patients (see Fig. 1a).

No main effects for Group or interaction effects of Group X Time-of-day were found for any respiratory measure (e.g. see Fig. 1c).

Calibrated activity did not exhibit an overall effect of Group ($p = 0.33$). However, there was a Group X Time-of-Day interaction ($p<0.001$), such that patients showed a linear decline in activity across awake hours, whereas controls' overall level of activity increased from morning to afternoon, then decreased only slightly during evening (Fig 1d and Table 2).

Intervention effects among fibromyalgia patients

In order to evaluate reliability, test-retest correlations were calculated for the three main outcome measures of the wait-list group (i.e. the group with no active intervention) by time-of-day for each time-point, i.e. between-subject correlations were performed comparing mean levels for times-of-day with each respective variable across time-points. Therefore, three correlation coefficients derived for each time of day: pre-intervention vs. post-intervention, pre-intervention vs. follow-up, and post-intervention vs. follow-up. The correlation coefficients were than averaged across the three time-point comparisons. For each time of day, the averaged correlation coefficients over times-of-day were 0.70, HR; 0.74, RSA; 0.83, respiration rate; and 0.70 for accelerometry activity (p's<0.0001; similar r's for all groups, pooled).

Grouping Factor (Intervention Arm) X Repeated Measures (Time-point [3 levels] and Time-of-day [4 levels]) RM-MANOVAs were performed on all physiological and accelerometry measures for the PP completer sample of 130 patients (see Table 3) and for the ITT analyses (n=168). There were no differences in outcome for RSA or HR: Group X time-point interaction effects for the three measures did not even indicate any tendency toward significance for either ITT or PP results ($p>0.35$). There were also no effects when secondary analyses were performed for a) pre-intervention to post-intervention and pre-intervention to short-term follow-up; or b) comparing different arms of the study, i.e. WL *vs.* MBSR, or WL *vs.* RELAX. Additionally analysis of the respiratory data indicated no differences in F_b, V_t or $\dot{V}$.

Both cardiovascular parameters did show effects of time-of-day (p's$<.0002$; see Fig. 2a-b) for ITT and PP analyses. These effects were characterized by a curvilinear increase in HR and decrease in RSA from morning to afternoon, followed by an evening return toward the

morning levels. Increases in activity did not show parallel increasing HRs and decreasing RSA. Additionally HR showed a significant effect of time-point ($p<0.002$, PP; $p<0.00001$, ITT) that was unrelated to group assignment; HR was about 2 beats/m higher at pre-intervention than at either post-intervention or follow-up. RSA exhibited this effect only for ITT analyses ($p<0.01$) with higher levels at both later time-points, also unrelated to intervention.

Multivariate analyses of physical activity revealed main effects for time-of-day ($p's < 10^{-15}$ for ITT and PP results). There was a linear decrease in activity over the day. Additionally, there was an effect of time-point upon activity ($p<.006$) only for ITT analysis, indicating a slight decrease from pre-intervention to both post-intervention and follow-up, the latter two time-points being very similar. There were no effects of treatment.

Respiratory parameters also did not show effects of treatment in any analyses (e.g. see Fig 2c). There was an effect of time-point upon breathing frequency ($p<.006$) only for ITT analysis, indicating a slight decrease from pre-intervention to follow-up (0.4 breaths/m). Also unrelated to treatment arm, there were effects of time-of-day for each of the respiratory measures for ITT and PP analyses ($p's <.0001$); a small increase in breathing frequency from morning to late afternoon (0.6 bpm) that remained constant during evening hours (see Fig 2c). There were also small decrease in V_t from morning to evening of 30 ml, and a similarly small linear decrease in V of 0.6 l/m from morning to evening ($p<10^{-6}$).

Relations between intervention-related clinical improvement and changes in physical function

When standardized change score of clinical patient-reported outcome was used as a covariate for the Group (Intervention Arm) by repeated-measures analyses, results were not altered in any way, and the effects of the covariate were consistently insignificant. Additionally when intervention arms were pooled, there were no significant correlations between any objective measure and self-reported clinical benefits. Analyses were repeated for each individual

patient-reported outcome (i.e.health-related quality of life, fibromyalgia impact, depression, sleep quality, anxiety, pain perception and physical complaints), and the lack of effects remained the same as for the single, composite, clinical measure of patient-reported outcome.

Two groups were subsequently defined on the basis of Cohen's d effect sizes of change scores of patient-reported HRQoL, averaged across subscales, from baseline to post-intervention and baseline to follow-up time-points. Twenty participants showed effect sizes > 0.65, based on averaged standardized change scores; 92 participants showed almost no change or clinically worsened based on patient-reported outcomes (PRO), with change scores ≤0.05 (the remainder fell between the effect-size cutoffs). Effect sizes for the improved group vs. no improvement/worsening group were 1.07(SD=0.38) *vs.* -0.38 (SD=0.43) at post-intervention compared to pre-intervention; 0.88 (SD=0.50) *vs.* -.42 (SD=0.44) at follow-up compared to pre-intervention; and 0.97 (SD=0.36) *vs.* -0.40 (SD=0.34) averaged over these two time intervals.

Group (Improved *vs.* Not) X Time-point X Time-of-day analyses revealed no main or interaction effects related to improvement. Additional exploratory analyses with individual self-report measures as covariates also indicated no effects. Therefore, these results indicate that reported clinical improvement was unrelated to changes in daily physical activity or cardiac or respiratory function.

Discussion

Comparisons between fibromyalgia patients and healthy women. The first analyses compared fibromyalgia female patients with a cohort of healthy, similarly aged women under conditions of everyday living using ambulatory monitoring. Findings confirmed depressed parasympathetic regulation of HR among women with fibromyalgia; RSA was substantially lower, and HR higher, among patients throughout the day. Importantly, these effects could not be accounted for by differences among groups in concurrent physical activity or respiratory

functioning: Decreases in activity will ordinarily be accompanied by reductions in HR and elevations in RSA [33]. In fact, a Group X Time-of-day interaction effect indicated that both groups started the day with similar levels of activity, but patients progressively ***reduced*** their activity as the day wore on. On the other hand, patients did not manifest expected concordant decreases in HR and increases in RSA across the day (see Fig. 2). Changes in RSA could also not be explained by concurrent alterations in breathing (by which within-individual changes in F_b and V_t can alter RSA independent of changes in cardiac vagal tone; see [36]). These findings may, therefore, reflect a specific pattern of cardiac autonomic control over the day among women with fibromyalgia, namely decreases in cardiac vagal tone across the day, despite a corresponding decrease in physical activity. The fact that HR remained rather constant over the measurement period may also suggest compensatory sympathetic reduction across awake hours (since HR should otherwise increase in response to vagal withdrawal).

These results consequently indicate atypical levels of autonomic cardiovascular regulation. Whether this is a consequence of some specific disorder-related abnormality or is secondary to reduced aerobic fitness [45] remains to be clarified, since we unfortunately did not collect exercise data. Nevertheless, the pattern of progressively reduced activity among the patient group across the day may suggest a reduced level of physical fitness in this disorder. Additionally, a pattern among women with fibromyalgia of systematically decreasing levels of physical activity across day and evening has not been previously reported and is consistent with common complaints of fatigue and exhaustion among those suffering from fibromyalgia.

Effects of intervention upon cardiac autonomic regulation or respiratory function. No effects of intervention or tendencies could be found for any physiological measure during the day (Group X Time-point or 3-way interactions: p's>0.20), although there does seem to have been an adaptation effect for HR and breathing frequency from the first time-point to the

subsequent ones. Particularly, HR was higher before intervention across groups, suggesting a habituation effect to the measurement procedure. However, these results indicate that neither cardiac autonomic regulation nor respiration was affected by MBSR.

Effects of intervention upon pattern of physical activity. A highly reliable, quasi-linear reduction in physical activity over awake hours was observed among patients, but was not influenced by intervention. Activity also decreased from pre-intervention to post-intervention and follow-up across groups for ITT analyses.

Relations between reported clinical improvement and changes in objective physical parameters. Although many exploratory analyses were performed, we could find no relationships, whatsoever, between patient-reported clinical improvement and either changes in physical activity or alterations in physiological parameters. Thus, our findings suggest that women with fibromyalgia may alter their experience of disorder-related complaints with no discernable covariation of either their pattern of daily activity or their autonomic control of HR. This lack of association between subjective and objective parameters may be particularly noteworthy given claims in the literature that aberrant cardiovascular regulation is closely related to the etiology or maintenance of fibromyalgia, e.g. [9-18; 46; 47]. Indeed, absence of any relationship between cardiac measures and symptomatic improvement may indicate that altered cardiac autonomic tone in fibromyalgia is merely epiphenomenal to physical deconditioning.

The dissociation between symptom improvement and alterations in objective physical functioning appears consistent with the hypothesis that central nervous system augmentation of somatosensory processing may be a primary feature of fibromyalgia. Alterations in CNS amplification of somatosensory stimulation over time may induce changed perception of experiences, such as sleep quality and extent of physical activity, with no corresponding changes in objectively measured parameters. Interventions that aim, directly or indirectly, at

modifying central somatosensory and/or perceptual processing may possibly be more effective than treatments mainly focusing upon altering peripheral physiological function or overt behaviors. This hypothesis is also consistent with the moderate within-group effects we earlier reported for many of the patient-reported outcomes [26].

Our study provides important evidence that an eight-week MBSR does not influence patterns of cardiovascular or respiratory autonomic activity in fibromyalgia patients. Despite the fact that measurements were sensitive enough to detect effects of time-of-day and adaptation to measurement for most parameters, there was not a hint of effects of intervention on cardiorespiratory variables or motor activity. These ambulatory data weigh against laboratory findings of improved autonomic functioning after MBSR among fibromyalgia patients or other populations [19; 48; 20; 49; 50]. Such differences in results might be explained by the fact that experimental demand characteristics in laboratory studies lead participants consciously to behave in a certain manner during brief laboratory measurements, and this may entail practicing the mindfulness skills that they have learned. This, in turn, can influence autonomic activation and then might lead to only temporarily improved autonomic control. Enduring changes in physiological functioning during everyday life are probably substantially more difficult to achieve and may require substantially more than an eight-week mindfulness course. However, we cannot rule out the possibility that skills learned in meditation practice may be more selectively employed under specific circumstances of daily life, something that we did not attempt to measure. Nevertheless, our results point, once again (e.g. [51; 52]), to possible dangers of generalizing from the laboratory to the real world and underscore the importance of ecologically valid data collection procedures such as achieved by our ambulatory monitoring.

A number of comments and reservations, nevertheless, require mention. First, given the scale of the study and the demands on participants, we were only able to monitor for a single

day at each time-point. It is possible that a longer period of monitoring time may be necessary to achieve sufficient reliability of measurement. Nevertheless, within-group patterns of ambulatory parameters were similar across the three measurement time-points, and test-retest correlations were reasonably high (r's=0.7-0.8). We also performed many exploratory analyses, and none of the results showed even any tendency toward significance in terms of group effects nor relations between objective measures and reported clinical improvements. Therefore it seems unlikely that more extensive monitoring would substantially alter our conclusions. On the other hand, this issue of limited reliability is likely to be a far greater problem for brief laboratory assessments than for ambulatory measurements based upon many hours of data acquisition.

Reliability of measurement, of course, also relates to aspects of both participant and researcher burden. Even with modern technological advances, 24-h monitoring of multiple physical functions remains to some extent intrusive, and monitoring may influence behavior and be found somewhat aversive. Although we did not directly assess the degree of perceived burden, it became clear during debriefing that a number of fibromyalgia patients found the procedure somewhat uncomfortable. This may have affected our results. Indeed, about 15% of the patients refused to participate in this part of the investigation, which, of course, somewhat impairs representativeness of our fibromyalgia sample (although there were no differences between "refusers" and ambulatory participants on any measured variable). Additionally, almost half the patients were taking psychopharmacological medication, and results may have been different among a sample without drugs.

In conclusion, our investigation provides evidence that real-life patterns of cardiovascular autonomic tone and daytime physical activity are not influenced by mindfulness training. Furthermore, neither spontaneous nor treatment-related improvements in fibromyalgia symptoms were associated with objective physical measures. Nevertheless, these negative

findings are interesting in their own right, and this study demonstrates the feasibility and utility of multi-measure physiological monitoring in clinical trials. Assessing autonomic functioning concurrently with measurement of physical activity allows evaluation of the behavioral and metabolic context of physiological functioning. This seems a promising approach to ecologically valid clinical trial assessment of interventions for psychosomatic disorders. Finally, our investigation should, perhaps, be considered an initial, exploratory step toward integrating contextually sophisticated, "real-life" ambulatory assessment into relevant clinical trial research.

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References

[1]Landis CA, Frey CA, Lentz MJ, Rothermel J, Buchwald D, Shaver JL. Self-reported sleep quality and fatigue correlates with actigraphy in midlife women with fibromyalgia. Nurs Res 2003;52(3):140-147.

[2]McLoughlin MJ, Colbert LH, Stegner AJ, Cook DB. Are Women with Fibromyalgia Less Physically Active than Healthy Women? Med Sci Sports Exerc 2010.

[3]Okifuji A, Hare BD. Nightly Analyses of Subjective and Objective (Actigraphy) Measures of Sleep in Fibromyalgia Syndrome: What Accounts for the Discrepancy? Clin J Pain 2010.

[4]Stuifbergen AK, Phillips L, Carter P, Morrison J, Todd A. Subjective and objective sleep difficulties in women with fibromyalgia syndrome. J Am Acad Nurse Pract 2010;22(10):548-556.

[5]Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46(5):1333-1343.

[6]Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10(9):895-926.

[7]Robinson ME, Craggs JG, Price DD, Perlstein WM, Staud R. Gray Matter Volumes of Pain-Related Brain Areas are Decreased in Fibromyalgia Syndrome. J Pain 2010.

[8]Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2010.

[9]Martinez-Lavin M, Hermosillo AG, Rosas M, Soto ME. Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. Arthritis Rheum 1998;41(11):1966-1971.

[10]Stein PK, Domitrovich PP, Ambrose K, Lyden A, Fine M, Gracely RH, Clauw DJ. Sex effects on heart rate variability in fibromyalgia and Gulf War illness. Arthritis Rheum 2004;51(5):700-708.

[11]Staud R. Heart rate variability as a biomarker of fibromyalgia syndrome. Fut Rheumatol 2008;3(5):475-483.

[12]Di Franco M, Iannuccelli C, Alessandri C, Paradiso M, Riccieri V, Libri F, Valesini G. Autonomic dysfunction and neuropeptide Y in fibromyalgia. Clin Exp Rheumatol 2009;27(5 Suppl 56):S75-78.

[13]Reyes Del Paso GA, Garrido S, Pulgar A, Martin-Vazquez M, Duschek S. Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. Psychosom Med 2010;72(5):462-470.

[14]Solberg Nes L, Carlson CR, Crofford LJ, de Leeuw R, Segerstrom SC. Self-regulatory deficits in fibromyalgia and temporomandibular disorders. Pain 2010;151(1):37-44.

[15]Reyes del Paso GA, Garrido S, Pulgar A, Duschek S. Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. J Psychosom Res 2011;70(2):125-134.

[16]Kulshreshtha P, Gupta R, Yadav RK, Bijlani RL, Deepak KK. A comprehensive study of autonomic dysfunction in the fibromyalgia patients. Clin Auton Res 2012;22(3):117-122.

[17]Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, De Wandele I, Da Silva H, Calders P. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: a systematic review. Seminars in arthritis and rheumatism 2013;43(2):279-287.

[18]Martinez-Martinez LA, Mora T, Vargas A, Fuentes-Iniestra M, Martinez-Lavin M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol 2014;20(3):146-150.

[19]Ditto B, Eclache M, Goldman N. Short-term autonomic and cardiovascular effects of mindfulness body scan meditation. Ann Behav Med 2006;32(3):227-234.

[20]Bauer-Wu S, Sullivan AM, Rosenbaum E, Ott MJ, Powell M, McLoughlin M, Healey MW. Facing the challenges of hematopoietic stem cell transplantation with mindfulness meditation: a pilot study. Integr Cancer Ther 2008;7(2):62-69.

[21]Kodituwakku S, Lazar SW, Indic P, Brown EN, Barbieri R. Point process time-frequency analysis of respiratory sinus arrhythmia under altered respiration dynamics. Conf Proc IEEE Eng Med Biol Soc 2010;2010:1622-1625.

[22]Krygier JR, Heathers JA, Shahrestani S, Abbott M, Gross JJ, Kemp AH. Mindfulness meditation, well-being, and heart rate variability: a preliminary investigation into the impact of intensive Vipassana meditation. Int J Psychophysiol 2013;89(3):305-313.

[23]Ahani A, Wahbeh H, Nezamfar H, Miller M, Erdogmus D, Oken B. Quantitative change of EEG and respiration signals during mindfulness meditation. J Neuroeng Rehabil 2014;11:87.

[24]Park J, Lyles RH, Bauer-Wu S. Mindfulness meditation lowers muscle sympathetic nerve activity and blood pressure in African-American males with chronic kidney disease. Am J Physiol Regul Integr Comp Physiol 2014;307(1):R93-R101.

[25]Zautra AJ, Fasman R, Davis MC, Craig AD. The effects of slow breathing on affective responses to pain stimuli: an experimental study. Pain 2010;149(1):12-18.

[26]Schmidt S, Grossman P, Schwarzer B, Jena S, Naumann J, Walach H. Treating fibromyalgia with mindfulness-based stress reduction: Results from a 3-armed randomized controlled trial. Pain 2010;152(2):361-369.

[27]Lauche R, Cramer H, Dobos G, Langhorst J, Schmidt S. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. J Psychosom Res 2013;75(6):500-510.

[28]Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33(2):160-172.

[29]Grossman P, Deuring G, Garland SN, Campbell TS, Carlson LE. Patterns of objective physical functioning and perception of mood and fatigue in posttreatment breast cancer patients and healthy controls: an ambulatory psychophysiological investigation. Psychosom Med 2008;70(7):819-828.

[30]Kabat-Zinn J. Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain and Illness. New York: Delacorte, 1990.

[31]Grossman P, Tiefenthaler-Gilmer U, Raysz A, Kesper U. Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being. Psychother Psychosom 2007;76(4):226-233.

[32]Grossman P, van Beek J, Wientjes C. A comparison of three quantification methods for estimation of respiratory sinus arrhythmia. Psychophysiology 1990;27(6):702-714.

[33]Grossman P, Wilhelm FH, Spoerle M. Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. Am J Physiol Heart Circ Physiol 2004;287(2):29.

[34]Grossman P, Spoerle M, Wilhelm FH. Reliability of respiratory tidal volume estimation by means of ambulatory inductive plethysmography. Biomed Sci Instrum 2006;42:193-198.

[35]Grossman P, Wilhelm FH, Brutsche M. Accuracy of ventilatory measurement employing ambulatory inductive plethysmography during tasks of everyday life. Biol Psychol 2010.

[36]Grossman P, Taylor EW. Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. Biol Psychol 2007;74(2):263-285.

[37]Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. . Applied Psychological Measurement 1977;1:385-401.

[38]Brähler E, Scheer J. Der Gießener Beschwerdebogen (GBB). Bern: Hans Huber, 1983.

[39]Spielberger CD. Manual for the State-Trait Anxiety Inventory: STAI (Form Y). Palo Alto, CA: Consulting Psychologists Press 1983.

[40]Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research 1989;28:193-213.

[41]Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: Development and validation. Journal of Rheumatology 1991;18:728-733.

[42]Geissner E. Die Schmerzempfindungsskala (SES). Handanweisung. Göttingen: Hogrefe, 1996.

[43]Siegrist J, M. B, Junge A. Profil der Lebensqualität chronischer Kranker. Manual Göttingen: Beltz Test, 1996.

[44]Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society B 1995;57(1):289-300.

[45]Jones KD, Burckhardt CS, Deodhar AA, Perrin NA, Hanson GC, Bennett RM. A six-month randomized controlled trial of exercise and pyridostigmine in the treatment of fibromyalgia. Arthritis Rheum 2008;58(2):612-622.

[46]Petzke F, Clauw DJ. Sympathetic nervous system function in fibromyalgia. Curr Rheumatol Rep 2000;2(2):116-123.

[47]Martinez-Lavin M. Is fibromyalgia a generalized reflex sympathetic dystrophy? Clin Exp Rheumatol 2001;19(1):1-3.

[48]Carlson LE, Speca M, Faris P, Patel KD. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav Immun 2007;21(8):1038-1049.

[49]Lush E, Salmon P, Floyd A, Studts JL, Weissbecker I, Sephton SE. Mindfulness meditation for symptom reduction in fibromyalgia: psychophysiological correlates. J Clin Psychol Med Settings 2009;16(2):200-207.

[50]Delgado LC, Guerra P, Perakakis P, Vera MN, Reyes del Paso G, Vila J. Treating chronic worry: Psychological and physiological effects of a training programme based on mindfulness. Behav Res Ther 2010;48(9):873-882.

[51]Pfaltz MC, Michael T, Grossman P, Blechert J, Wilhelm FH. Respiratory pathophysiology of panic disorder: an ambulatory monitoring study. Psychosom Med 2009;71(8):869-876.

[52]Pfaltz MC, Grossman P, Michael T, Margraf J, Wilhelm FH. Physical activity and respiratory behavior in daily life of patients with panic disorder and healthy controls. Int J Psychophysiol 2010;78(1):42-49.

[53] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC.

Figure Legend

Figure 1a-d. Comparisons between 130 female fibromyalgia patients and healthy controls across time-of day. Darkened circles, fibromyalgia patients; open squares, controls. Whiskers, 95% confidence intervals. Scale breaks on y-axes emphasize the restricted range of variation.

Figure 2a-d. Effects of time-of-day over the three time points for heart rate, respiratory sinus arrhythmia, breathing frequency and activity. . Scale breaks on y-axes emphasize the restricted range of variation.

Table 1. Demographic Data of Fibromyalgia Patients and Controls

Variable	Fibromyalgia N=130 *Mean (SD)*	Control N=33 *Mean (SD)*
Age	54.1 (9.1)	53.41 (5.98)
Ethnicity (*Percent)*		
Caucasian	100%	97%
Other		3%
Education (*Percent)*		
College+	32%	67%
High School	35%	35%
<High School	33%	0%
Marital Status (*Percent married*)	58%	82%

Table 2. Comparison of fibromyalgia patients (time-point 1) and healthy female controls on physiological and activity

measures during awake hours related to time-of-day.

	Breathing Frequency Means ± (S.D.)		**RSA Means ± (S.D.)**		**Heart Rate Means ± (S.D.)**		**Activity Means ± (S.D.)**	
Time-of-Day	**Fibro**	**Control**	**Fibro**	**Control**	**Fibro**	**Control**	**Fibro**	**Control**
9:00-12:00	21.85 (3.45)	20.60 (3.07)	4.24 (0.82)	4.97 (0.87)	85.52 (10.76)	74.13 (9.28)	0.87 (0.25)	0.85 (0.23)
12:00-15:00	22.29 (3.63)	21.81 (3.82)	4.11 (0.82)	4.65 (0.80)	87.18 (10.75)	79.38 (10.78)	0.83 (0.26)	0.87 (0.30)
15:00-18:00	22.61 (3.51)	21.74 (3.54)	4.12 (0.85)	4.63 (0.94)	85.85 (10.63)	78.57 (10.92)	0.82 (0.25)	0.87 (0.33)
19:00-22:00	22.31 (3.49)	21.27 (2.60)	4.05 (0.86)	4.64 (0.87)	85.33 (10.29)	77.96 (10.30)	0.79 (0.26)	0.87 (0.28)

Table 3. Means for physiological and activity measures by time point (pre-intervention, post-intervention; short-term follow-up) and time-of-day. W, wait-list; MBI, mindfulness-based intervention; RELAX, active control. Breathing frequency, breaths/m; respiratory sinus arrhythmia, ln ms^2; heart rate, beats/m; activity, arbitrary units.

Repeated Measure	Breathing Frequency Means ± (S.D.)				Respiratory Sinus Arrhythmia Means ± (S.D.)				Heart Rate Means ± (S.D.)				Activity Means ± (S.D.)			
	Pooled	WL	MBSR	RELAX	Pooled	WL	MBSR	RELAX	Pooled	WL	MBSR	RELAX	Pooled	WL	MBSR	RELAX
Time-Point 1 9:00-12:00	22.40 (3.42)	23.32 (3.81)	21.93 (2.89)	21.86 (3.31)	4.24 (0.82)	4.10 (0.82)	4.20 (0.89)	4.39 (0.75)	86.88 (10.54)	87.71 (10.06)	87.04 (11.75)	85.84 (10.05)	0.87 (0.25)	0.91 (0.26)	0.88 (0.30)	0.82 (0.16)
12:00-15:00	22.60 (3.49)	23.79 (3.89)	22.02 (3.09)	21.92 (3.14)	4.11 (0.82)	3.98 (0.86)	4.20 (0.82)	4.14 (0.78)	88.33 (10.79)	89.85 (11.29)	87.26 (11.47)	87.69 (9.63)	0.83 (0.25)	0.83 (0.25)	0.87 (0.31)	0.80 (0.19)
15:00-18:00	22.39 (3.34)	23.30 (3.90)	21.90 (3.00)	21.89 (2.84)	4.12 (0.85)	3.94 (0.88)	4.19 (0.87)	4.20 (0.80)	87.01 (10.59)	87.92 (10.88)	86.08 (11.33)	86.88 (9.73)	0.82 (0.25)	0.85 (0.28)	0.84 (0.27)	0.79 (0.19)
19:00-21:00	21.55 (3.15)	22.48 (3.44)	21.01 (2.92)	21.07 (2.86)	4.05 (0.86)	3.97 (0.86)	4.07 (0.85)	4.10 (0.89)	86.31 (10.47)	87.48 (9.92)	85.12 (12.40)	86.13 (9.17)	0.79 (0.27)	0.81 (0.29)	0.81 (0.32)	0.76 (0.19)
Time-Point 2 9:00-12:00	21.94 (3.43)	22.50 (3.71)	21.73 (3.22)	21.55 (3.31)	4.35 (0.91)	4.12 (0.97)	4.37 (0.81)	4.52 (0.90)	85.44 (10.57)	87.07 (9.72)	83.50 (11.09)	85.45 (10.88)	0.81 (0.22)	0.82 (0.25)	0.79 (0.22)	0.82 (0.20)
12:00-15:00	22.17 (3.21)	22.98 (3.77)	21.52 (2.85)	21.91 (2.76)	4.16 (0.89)	4.01 (0.98)	4.13 (0.76)	4.32 (0.90)	86.40 (10.63)	87.24 (10.83)	85.89 (10.94)	85.95 (10.33)	0.79 (0.22)	0.80 (0.25)	0.77 (0.21)	0.79 (0.18)
15:00-18:00	21.98 (3.24)	22.67 (3.71)	21.27 (2.94)	21.91 (2.87)	4.23 (0.91)	4.05 (1.07)	4.29 (0.68)	4.32 (0.93)	85.26 (10.93)	86.61 (12.08)	83.56 (10.35)	85.37 (10.17)	0.78 (0.23)	0.77 (0.27)	0.79 (0.22)	0.78 (0.19)
19:00-21:00	22.00 (3.23)	23.36 (3.65)	21.51 (3.21)	21.01 (2.15)	4.22 (0.97)	4.08 (1.11)	4.26 (0.74)	4.32 (1.02)	83.81 (10.17)	84.96 (10.78)	81.92 (9.71)	84.28 (9.92)	0.73 (0.24)	0.73 (0.29)	0.69 (0.21)	0.76 (0.20)
Time-Point 3 9:00-12:00	22.06 (3.40)	23.50 (4.04)	21.47 (3.11)	21.07 (2.29)	4.26 (0.87)	4.00 (0.83)	4.28 (0.80)	4.46 (0.93)	85.00 (10.75)	87.28 (11.00)	82.98 (9.11)	84.39 (11.61)	0.82 (0.29)	0.85 (0.18)	0.84 (0.43)	0.75 (0.21)
12:00-15:00	22.23 (3.42)	23.36 (3.78)	21.58 (3.63)	21.65 (2.40)	4.09 (0.85)	3.93 (0.85)	4.12 (0.74)	4.19 (0.93)	85.83 (10.12)	87.49 (10.17)	84.51 (9.29)	85.23 (10.77)	0.79 (0.30)	0.84 (0.22)	0.81 (0.44)	0.72 (0.17)
15:00-18:00	21.96 (3.33)	23.21 (3.71)	21.10 (3.27)	21.44 (2.54)	4.04 (0.89)	3.79 (0.95)	4.14 (0.80)	4.17 (0.89)	85.64 (11.24)	87.70 (12.01)	83.36 (10.08)	85.50 (11.24)	0.79 (0.32)	0.80 (0.23)	0.83 (0.50)	0.73 (0.15)
19:00-21:00	22.40 (3.42)	23.32 (3.81)	21.93 (2.89)	21.86 (3.31)	4.19 (0.89)	4.02 (0.92)	4.27 (0.82)	4.27 (0.91)	82.82 (10.63)	83.31 (10.46)	80.87 (10.00)	84.07 (11.35)	0.73 (0.31)	0.76 (0.20)	0.76 (0.47)	0.66 (0.18)

Figure 1a

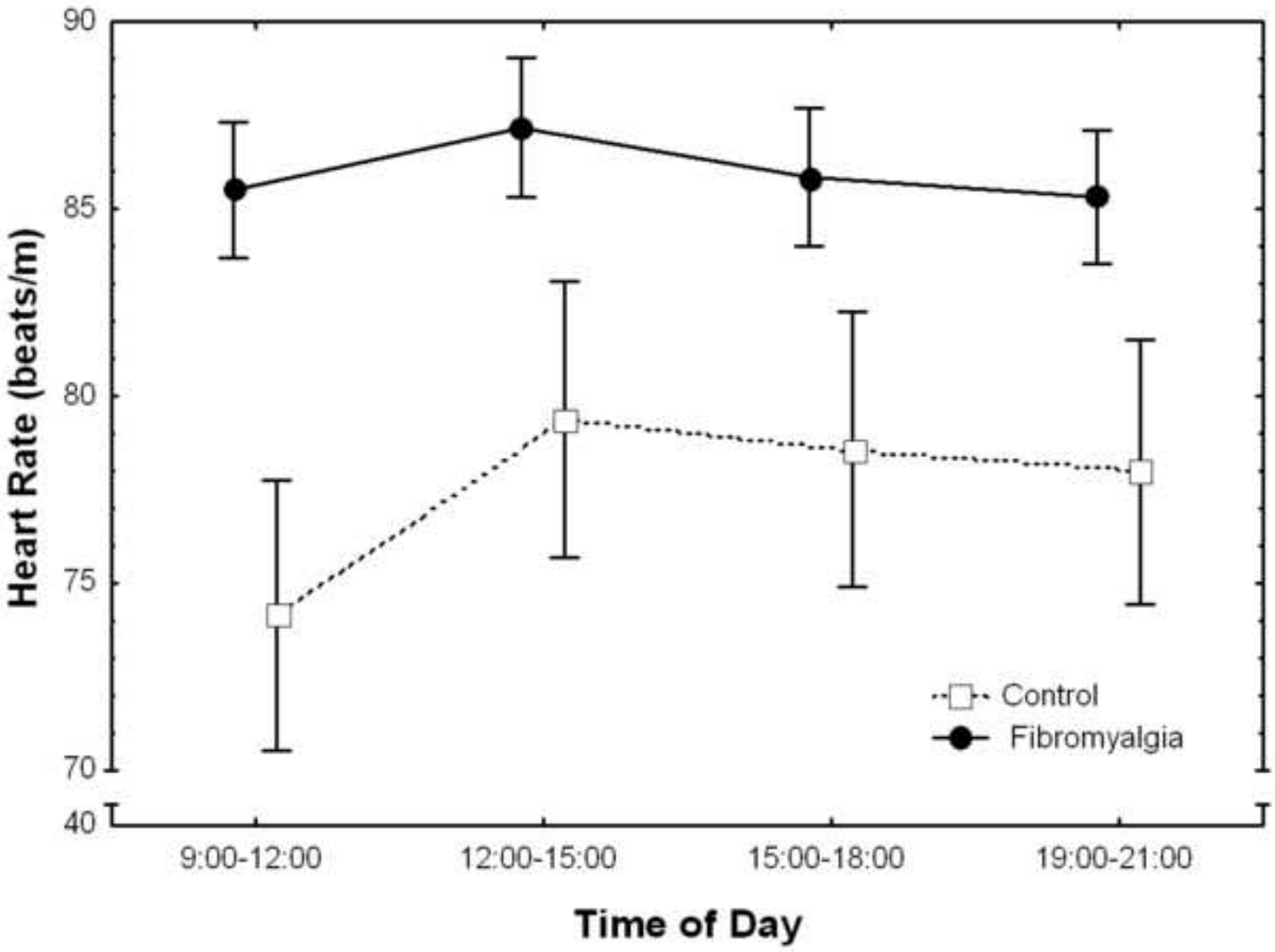


Figure 1b

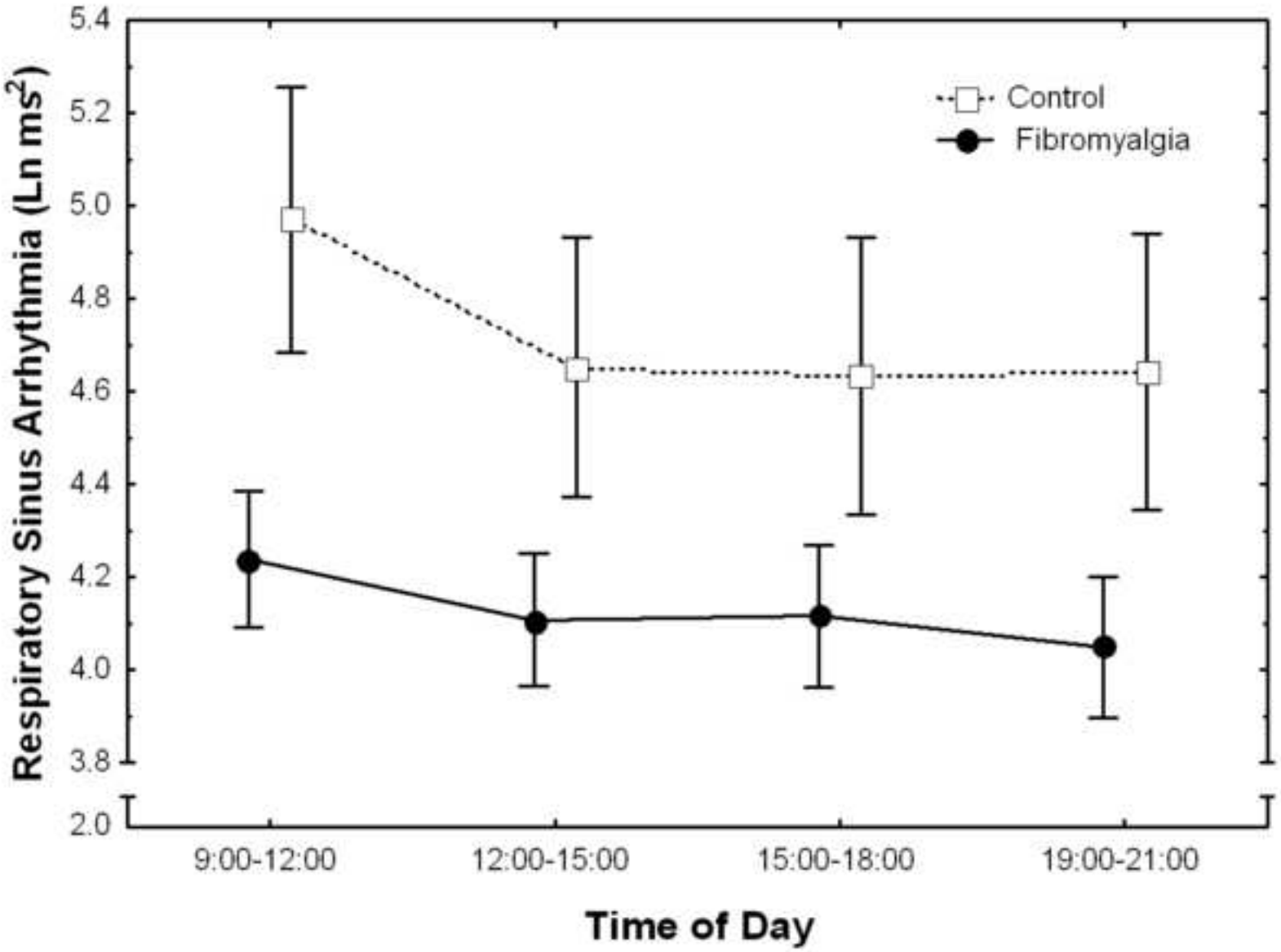


Figure 1c

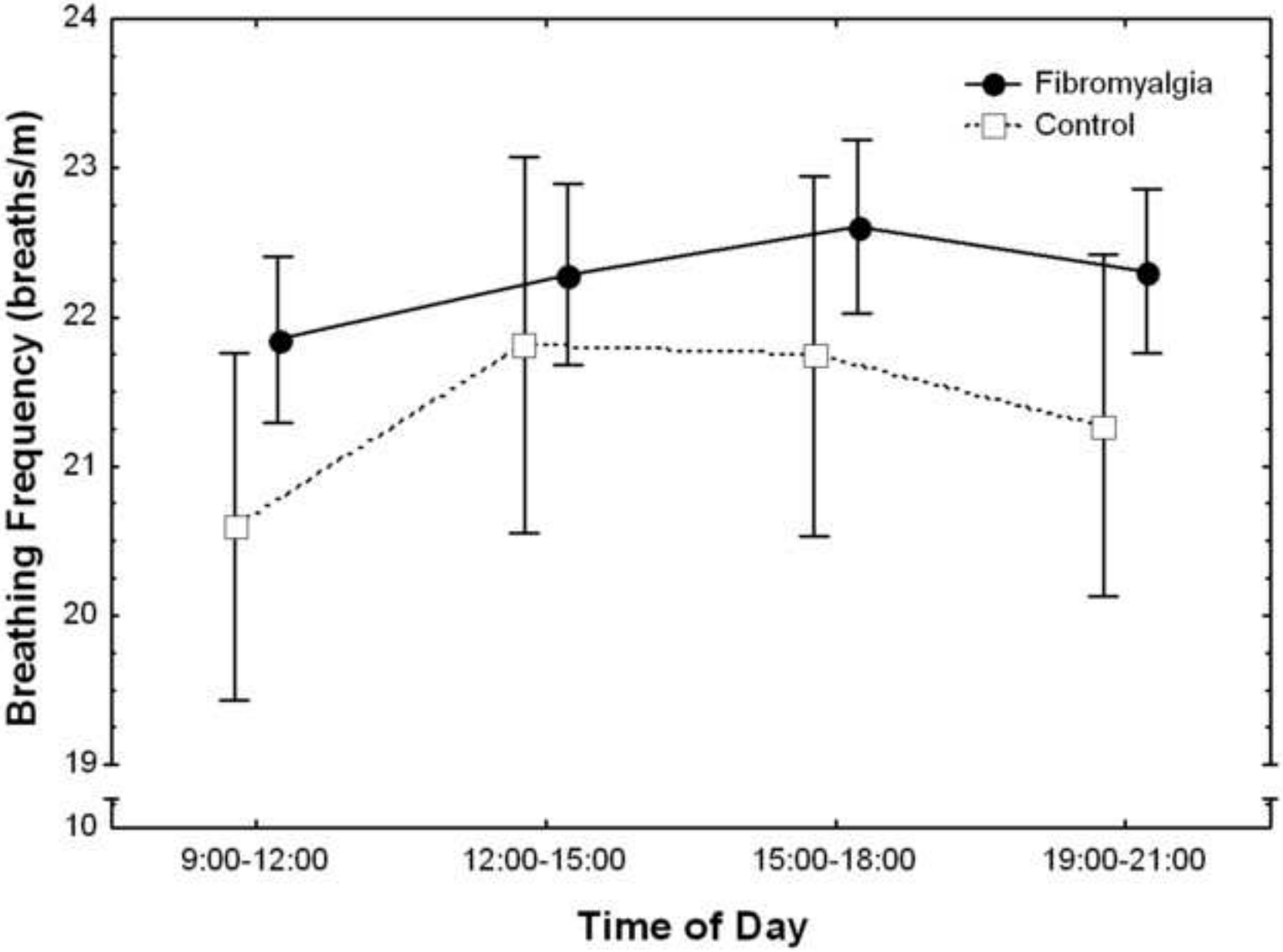
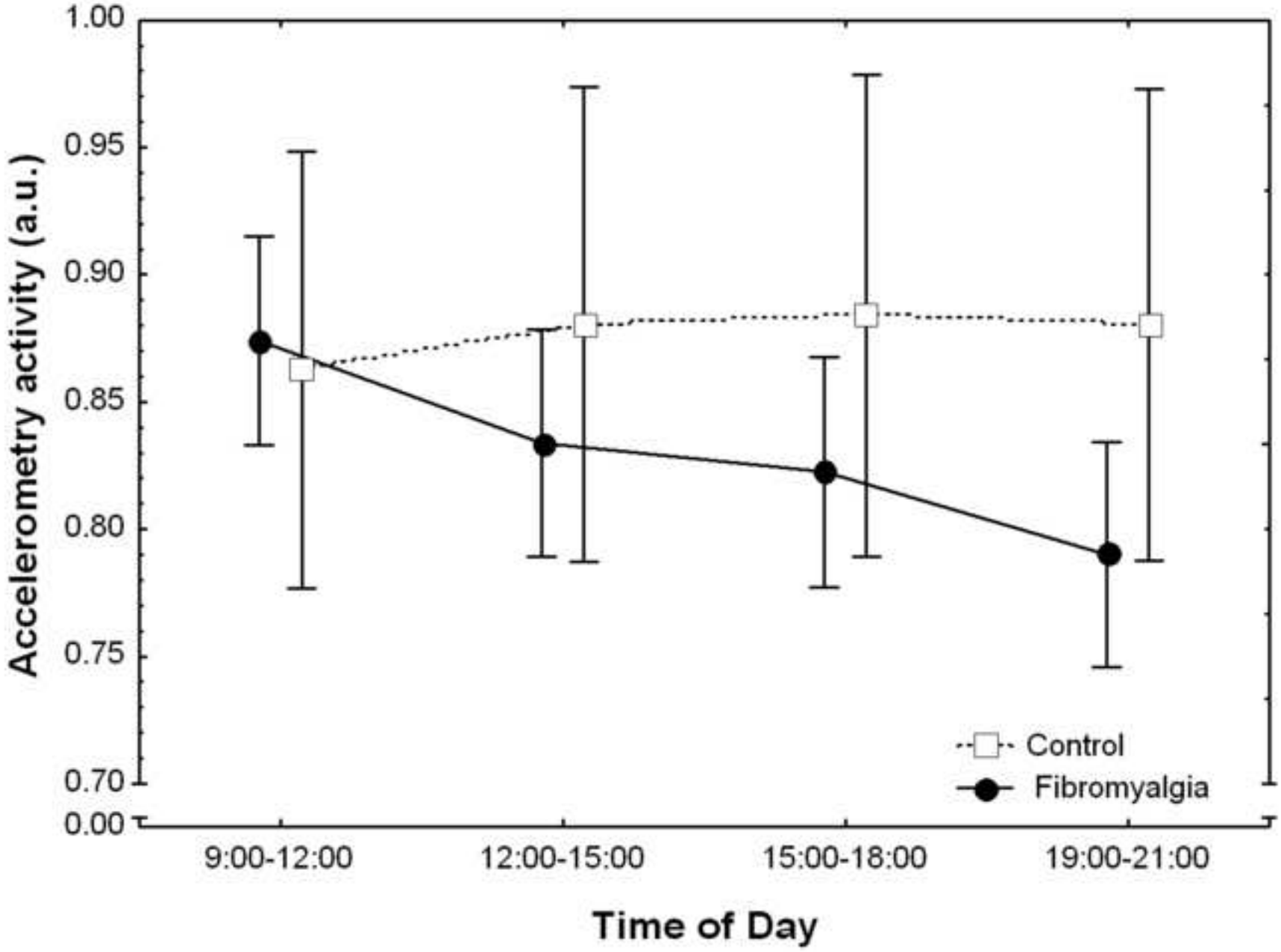


Figure 1d



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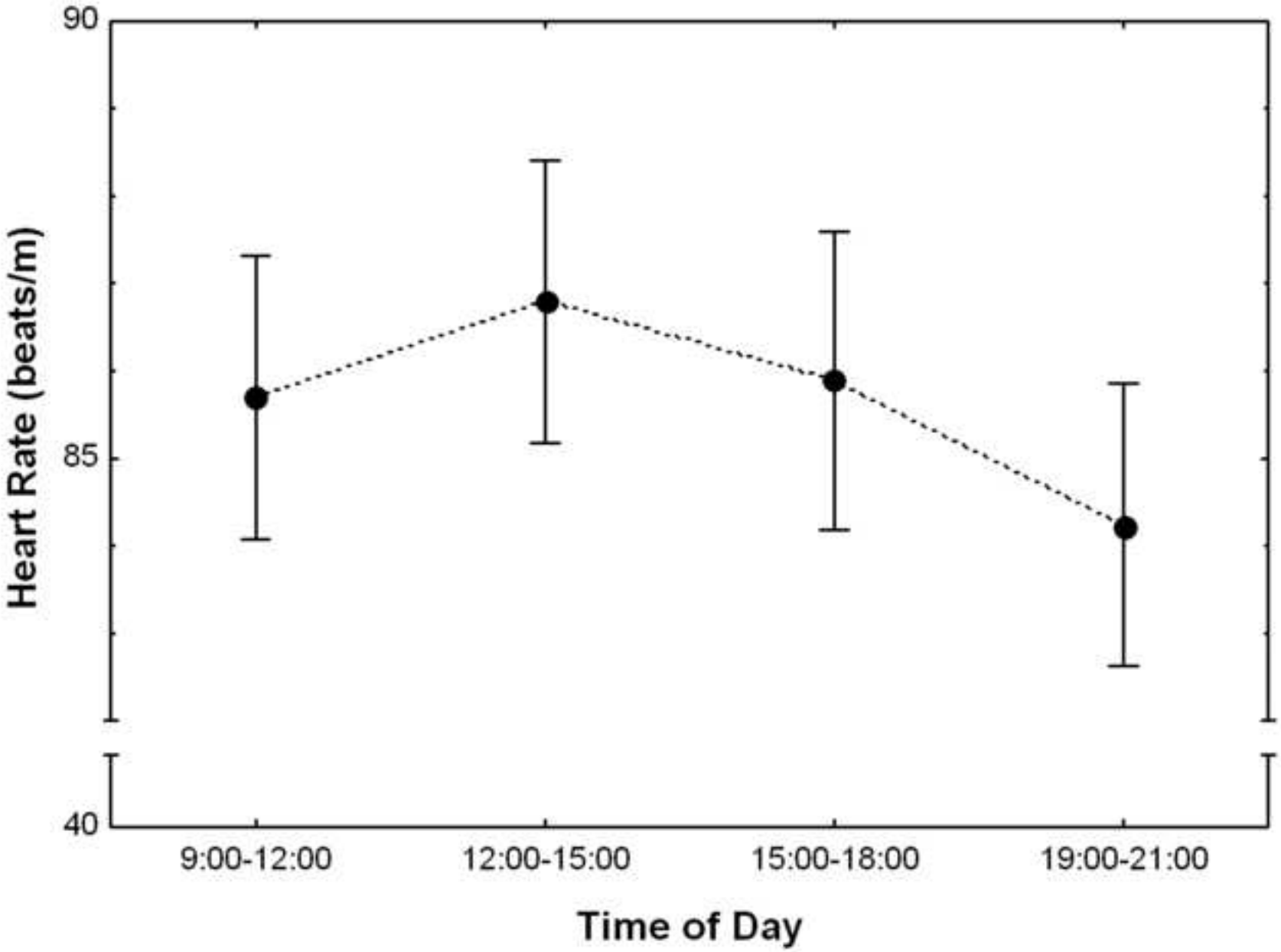

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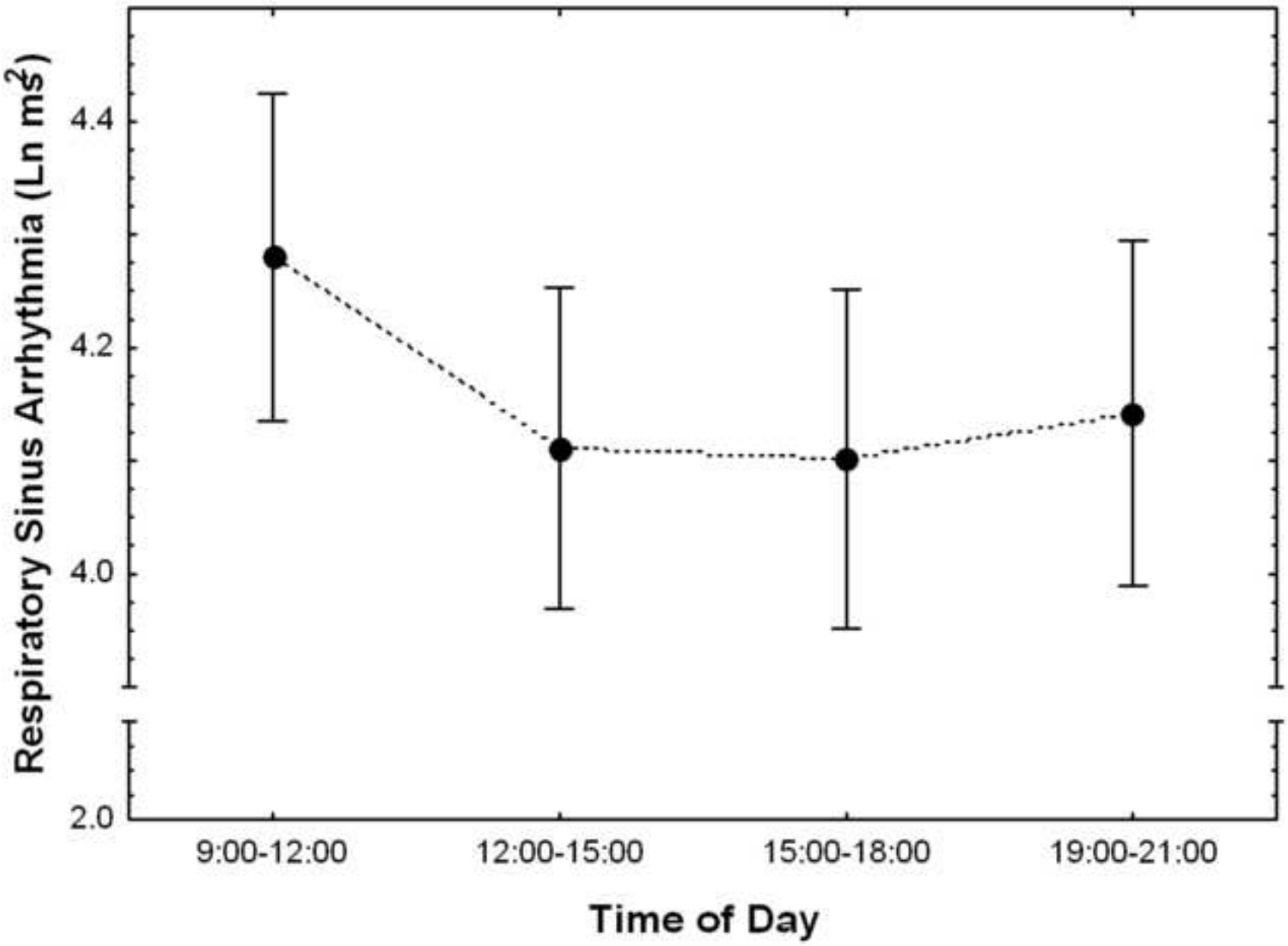

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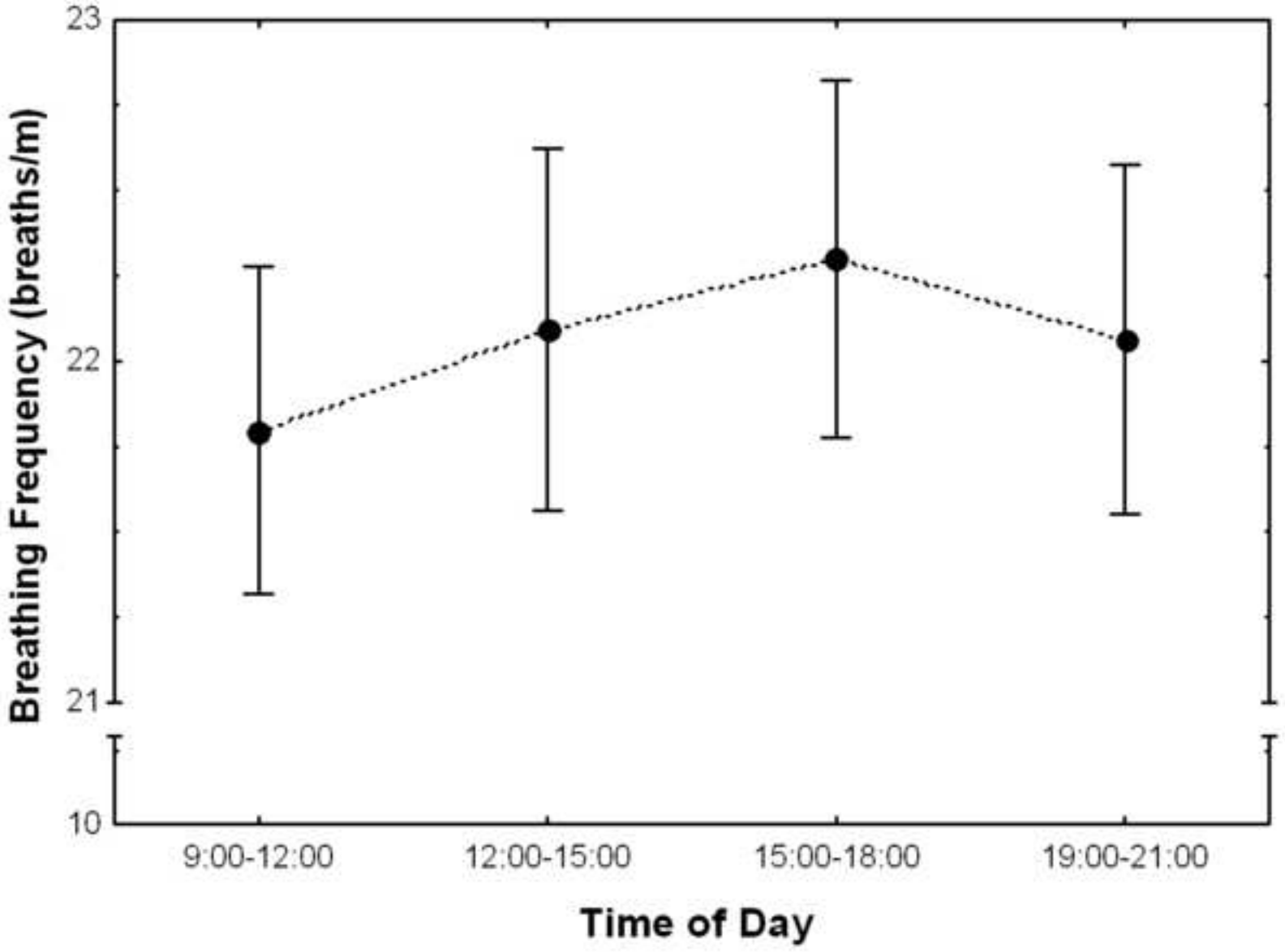

Figure 2d