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ORIGINAL RESEARCH

Exploratory Analysis of Respiratory Variability in Relation to Disease Impact, Affective Symptoms, and Pain Sensitivity in Fibromyalgia

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Purpose: Fibromyalgia is a complex multisystem disorder characterized by generalized chronic pain. While its etiology remains largely unclear, neuroinflammation, chronic stress, and autonomic dysregulation may play significant roles. Resultantly, respiratory patterns could serve as both a biomarker and a therapeutic target in fibromyalgia. We hypothesized that fibromyalgia impact, anxiety, depression, pain intensity, and pain sensitivity are associated with reduced respiratory variability.

Patients and methods: In this observational study, twenty-three female participants with fibromyalgia completed the Revised Fibromyalgia Impact Questionnaire (FIQR) and Hospital Anxiety and Depression Scale (HADS). Chronic pain intensity was assessed using a numerical rating scale. Pain sensitivity was measured using pain pressure thresholds, wind-up pain, and aftersensations. Respiratory rate, respiratory rate variability, and tidal volume variability were measured noninvasively using a thoracic bioimpedance electrode during restful waiting.

Results: No association was observed of respiratory variability with fibromyalgia impact, anxiety, chronic pain intensity, wind-up pain, and aftersensations. Higher depression scores were associated with lower tidal volume variability ($r = -0.45$, 95% CI: −0.04 to −0.73, $p = 0.033$). Additionally, higher pain pressure thresholds correlated with lower respiratory rate variability ($R = -0.43$, 95% CI: −0.02 to −0.72, $p = 0.039$) and tidal volume variability ($R = -0.47$, 95% CI: −0.07 to −0.74, $p = 0.023$).

Conclusion: While no direct association was found between respiratory variability and overall fibromyalgia impact, respiratory variability was associated with depression and pain sensitivity, both of which influence quality of life. These findings suggest that respiratory variability may have potential as a biomarker reflecting specific symptom dimensions of fibromyalgia. Further research is warranted.

Keywords: chronic pain, fibromyalgia, respiration, variability, pain sensitivity, biomarker

Introduction

Fibromyalgia is a complex disorder characterized by chronic, widespread nociplastic pain, with clinical features suggestive of central sensitization mechanisms.[1] While its etiology remains largely unclear, systemic factors such as neuroinflammation, chronic stress, and autonomic dysregulation have been proposed to play significant roles.[2] Despite its profound impact on quality of life, treatment options for fibromyalgia remain limited. Emerging therapeutic approaches are predominantly non-pharmacological, with breathing exercises showing particular promise.[3,4] The potential benefit of breathing exercises may be linked to the connection between respiration, inflammation, and autonomic dysregulation.[5–7] Consequently, respiratory patterns could serve as both a biomarker and a therapeutic target in fibromyalgia.

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The respiratory pattern in healthy subjects naturally varies over time, showing consistent fluctuations in rate, rhythm, and depth.[8,9] These fluctuations reflect the body's adjustment to changing needs in internal and external environments and result from various physiological inputs and chemical feedback loops.[10,11] More specifically, the respiratory centers receive and process multiple signals from different parts of the body, including central and peripheral chemoreceptors, pulmonary stretch receptors, and joint receptors, as well as from brain regions responsible for processing emotions. Notably, anxiety and depression are common in fibromyalgia patients and can influence their respiratory patterns.

Pain and breathing are closely linked bidirectionally. Acute pain typically triggers an increase in respiration, including an increase in inspiratory flow, respiratory rate, and tidal volume; however, the effects on respiratory variability are still not fully understood.[12] Chronic pain is associated with hyperventilation, which tends to decrease when pain is alleviated.[13] Conversely, voluntary control of breathing can significantly impact the perception of pain. For instance, slow, deep breathing has analgesic effects and enhances parasympathetic (vagal) activity;[14] however, this effect is less pronounced in individuals with chronic pain.[15]

Given the complex interplay between pain and breathing, we hypothesized that disease impact, anxiety, depression, and pain sensitivity are related to reduced spontaneous variability in respiratory parameters of patients with fibromyalgia. If such a relationship exists, respiratory variability analysis could be a promising diagnostic tool. Moreover, the application of specific breathing techniques might beneficially affect chronic pain-related symptoms. Our aim was to examine the relationships between respiratory variability and disease impact, anxiety, depression, and pain sensitivity in patients with fibromyalgia.

Methods

Study Setting

This exploratory study was a pre-planned sub-study of a larger randomized controlled trial which aimed to investigate the effects of pharmacological conditioning with s-ketamine on pain hypersensitivity in patients with fibromyalgia. The study was approved by the Medical Ethics Committee of Leiden University (The Netherlands) on 14 September 2022 (reference NL73444.058.21) and was prospectively registered in the EudraCT database (reference 2019-004812-73). The study complies with the Declaration of Helsinki. All participants provided written informed consent. This study was conducted between March 2023 and March 2024 and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology statement. The study was conducted at Amsterdam UMC, location VUmc, a university hospital in the Netherlands. Regarding data sharing, the deidentified participant data is available from the corresponding author upon reasonable request.

Funding

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Patient Population

Women (18–75 years) with chronic pain due to fibromyalgia, diagnosed by a rheumatologist, were eligible for inclusion in this study.[16] Participants were recruited via outpatient clinics, patient organizations, and online advertisements via social media. Potential participants were excluded if they had a medical diagnosis other than fibromyalgia that could explain their chronic pain symptoms. Severe psychiatric comorbidities unrelated to the symptoms of fibromyalgia, including current or previous dependence on strong analgesics, alcohol, or drugs, were exclusion criteria. Additional exclusion criteria included caffeine use within 12 hours before the trial, cardiac or respiratory comorbidity, a body mass index > 35 kg/m^2, and pregnancy or breastfeeding. Recorded patient characteristics included age, height, weight, educational level, and concomitant medical conditions.

Outcomes

The overall impact of fibromyalgia was assessed using the revised Fibromyalgia Impact Questionnaire (FIQR), which evaluates disease burden across three domains: function, overall impact, and symptoms.[17] The total score is calculated by summing individual item responses and is normalized to a 0–100 scale, where higher scores reflect a greater disease burden. The presence and severity of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). The two subscales for anxiety and depression both range from 0–23, where higher scores reflect more severe symptoms.

Baseline chronic pain intensity was quantified using a numerical rating scale (NRS; 0–10).

Pain sensitivity was assessed using three quantitative sensory tests: pain thresholds (PPTs), wind-up pain, and aftersensation.[18,19] The quantitative sensory tests were performed with a handheld analogue algometer capable of exerting a force of up to 10 kg (Force Dial; Wagner Instruments, Greenwich, CT, USA). Pressure stimuli were applied to the thenar muscles of the dominant hand and ipsilateral tibialis anterior. The PPTs were examined by applying three different pressure stimuli (kg force) to three neighboring sites on the hand and lower leg. The pressures required to elicit the first moment of pain were averaged to calculate the mean pressure threshold in kilograms force.[19] The mean pressure thresholds were calculated for each body site. Wind-up pain was measured using temporal summation, determined by applying pressure pain at the pain threshold level, while participants were asked to rate the first, fifth, and tenth stimuli on an NRS scale.[19] A single temporal summation (wind-up pain) score was obtained by subtracting the first from the tenth (last) stimulus. After-sensations were determined by asking participants to rate late pain (on the NRS) 15s after the tenth summation stimulus on the hand and lower leg and subtracting this pain score from the tenth stimulus.

Respiratory Variability

Respiratory measurements were performed using an impedance-based, non-invasive respiratory volume monitor (ExSpiron, Respiratory Motion, Waltham, MA, USA) with a thoracic electrode. This monitor continuously measures respiratory rate and changes in tidal volume with clinically appropriate accuracy.[20] The measured values were stored in internal memory as averages over 60-second periods. All baseline measurements were taken during 30 minutes of restful waiting. We calculated the quantitative variability of breathing parameters (ie, respiratory rate, tidal volume, and minute ventilation) over the 30-min period using the coefficient of variation, defined as the ratio between the standard deviation and mean of a time series.[10]

Statistical Analysis

As this was an exploratory study and no prior data were available in this specific context, no formal sample size calculation could be conducted. The findings may serve as a basis for estimating appropriate sample sizes in future, adequately powered studies. Data were analyzed using R software (2021, R Core Team, Vienna, Austria). Numerical data were assessed using histograms and Q-Q plots, and subsequently tested for non-normality using the Shapiro–Wilk test. Normally distributed data were described as mean (standard deviation), whereas non-normally distributed data were presented as medians (interquartile ranges). To examine correlations between respiratory variability and other variables, Spearman's rank correlation with a 95% confidence interval and significance level (p-value) were calculated.[21] Statistical significance was defined as $p < 0.05$.[22]

Results

We recruited 54 participants; 14 declined participation, 12 did not meet eligibility criteria, and respiratory data were incompletely captured or stored in 5 cases. Consequently, data from 23 patients with chronic pain due to fibromyalgia were included in the final analysis. The patient characteristics and baseline pain assessments are presented in Table 1. We analyzed 1,380 measurements of respiratory rate and tidal volume.

The mean respiratory rate was 15.5 ± 2.3 breaths/min (mean ± SD), mean variability of the respiratory rate was 0.201 ± 0.039 (mean ± SD), and mean variability of tidal volume was 0.233 ± 0.081 (mean ± SD). The median fibromyalgia disease impact score (FIQR) was 42 (interquartile range: 34–59; range: 13–77), indicating a mild to severe disease

Table 1 Baseline Characteristics

	n = 23
Age, years	50.2 ± 12.0
Weight, kg	75.6 ± 12.9
BMI, kg/m^2	26.7 ± 4.72
Educational level	
Secondary school	3 (13.0)
Lower vocational education	5 (21.7)
Higher vocational education	13 (56.5)
University	2 (8.7)
Pulmonary comorbidity	
Asthma/COPD	4 (17.4)
Obstructive Sleep Apnea Syndrome	3 (13.0)
Smoking	5 (21.7)
Pain characteristics	
Fibromyalgia disease impact, FIQR	42 (13 to 77)
Anxiety, HADS	6 (1 to 14)
Depression, HADS	6 (1 to 15)
Chronic pain intensity, NRS	4 (1 to 8)
Pain pressure threshold, kg force	3.21 ± 1.28
Wind up, Δ NRS	2 (0 to 6)
Aftersensations, Δ NRS	2 (0 to 6)

Notes: Data are shown as mean ± SD, median (interquartile range), or n (%).
Abbreviations: NRS, numerical rating scale; SD, standard deviation; FIQR, Revised Fibromyalgia Impact Questionnaire; HADS, Hospital Anxiety and Depression Scale.

impact. The median anxiety score (HADS) was 6 (interquartile range: 6–8; range: 1–14), indicating normal to borderline abnormal (mild) anxiety. The median depression score (HADS) was 6 (interquartile range: 4.5 to 10.5; range: 1–15), indicating normal to borderline abnormal (mild) depression. The median chronic pain intensity (NRS) was 4 (interquartile range: 2.5 to 5.0; range, 1–8), indicating mild to moderate chronic pain intensity. Fibromyalgia disease impact (FIQR score) correlated with pain intensity (r = 0.48, 95% confidence interval: 0.04–0.76, p = 0.034) but not with anxiety or depression scores.

No association was found between the respiratory variability parameters and the impact of fibromyalgia (Figure 1A–C).

The associations between anxiety and depression (HADS scores) and respiratory variability are shown in Figures 2A–C and 3A–C. We observed a negative association between the HADS score for depression and variability in tidal volume (r = −0.45, 95% confidence interval: −0.04 to −0.73, p = 0.033) but not the variability in respiratory rate. We found no association between anxiety and respiratory variability.

The associations between chronic pain intensity and respiratory variability are shown in Figure 4A–C. No association was observed between pain intensity and respiratory variability.

The associations between pain sensitivity, measured by PPTs, and respiratory variability are shown in Figure 5A–C. We observed a negative association between the PPT and variability in both respiratory rate (r = −0.43, 95% confidence interval: −0.03 to −0.72, p = 0.039) and tidal volume (r = −0.47, 95% confidence interval: −0.07 to −0.74, p = 0.023). We found no associations of respiratory variability with the other pain sensitivity measures.

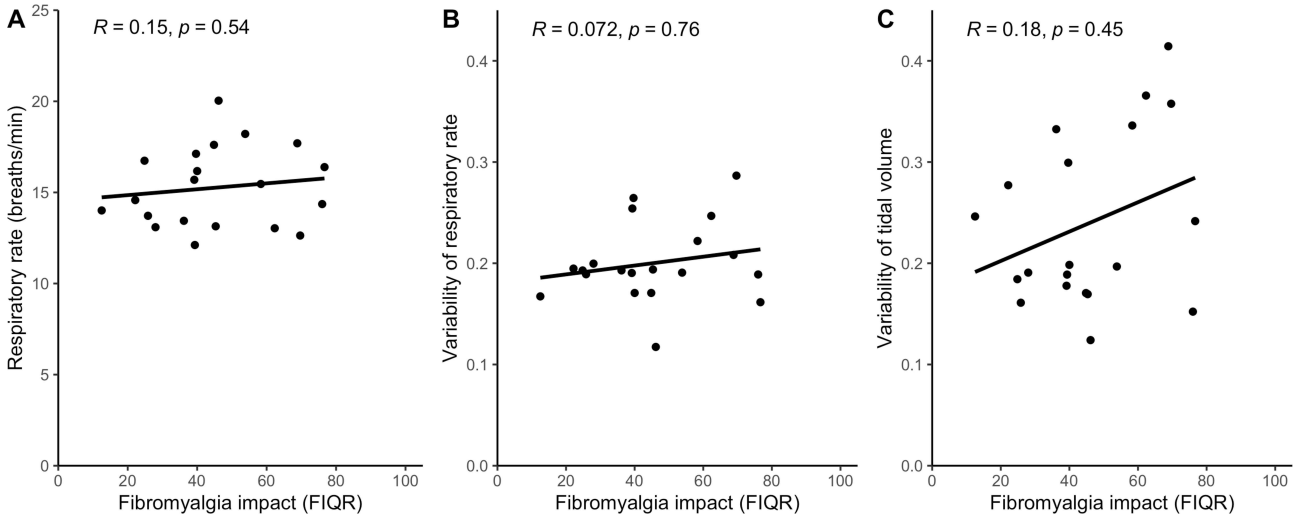

Figure 1 Correlations between respiratory variability and fibromyalgia impact in women with fibromyalgia syndrome. Respiratory parameters were measured during 30 min of restful waiting. Variabilities in the respiratory rate and tidal volume were calculated as coefficients of variation. The fibromyalgia impact was measured using the Revised Fibromyalgia Impact Questionnaire (FIQR). (**A**) Mean respiratory rate, (**B**) Variability of respiratory rate, (**C**) Variability of tidal volume. R: Spearman's rank correlation coefficient.

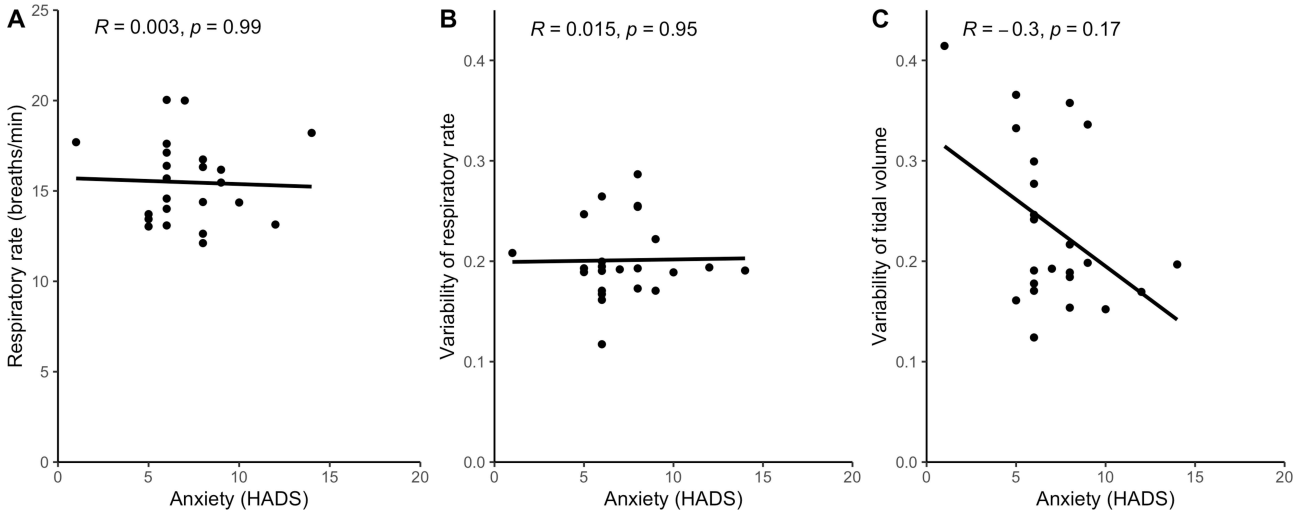

Figure 2 Correlations between anxiety and respiratory variability in women with fibromyalgia syndrome. Anxiety was assessed using the Hospital Anxiety and Depression Scale (Hads). Respiratory parameters were measured during 30 min of restful waiting. Variabilities in the respiratory rate and tidal volume were calculated as coefficients of variation. (**A**) Mean respiratory rate, (**B**) Variability of respiratory rate, (**C**) Variability of tidal volume. R: Spearman's rank correlation coefficient.

Discussion

This is the first exploratory study to quantify respiratory variability in patients with fibromyalgia. We tested the hypothesis that variability in respiratory parameters, specifically respiratory rate and tidal volume, is associated with the impact of fibromyalgia on quality of life, anxiety, depression, pain intensity, and pain sensitivity. We found no association of respiratory parameters with fibromyalgia disease impact (FIQR), anxiety, chronic pain intensity, wind-up pain, and aftersensations; however, we observed an association between depression and respiratory variability, as well as between PPTs and variability in both respiratory rate and tidal volume. Patients with a decreased pain threshold, which may indicate central sensitization, exhibited higher variability in both respiratory rate and tidal volume. While the exact pathophysiology of increased pain sensitivity in fibromyalgia remains unknown,[23,24] emerging evidence suggests a central rather than peripheral nervous system origin.[25–28] Because of this likely central origin, we believe that fibromyalgia may affect breathing variability.

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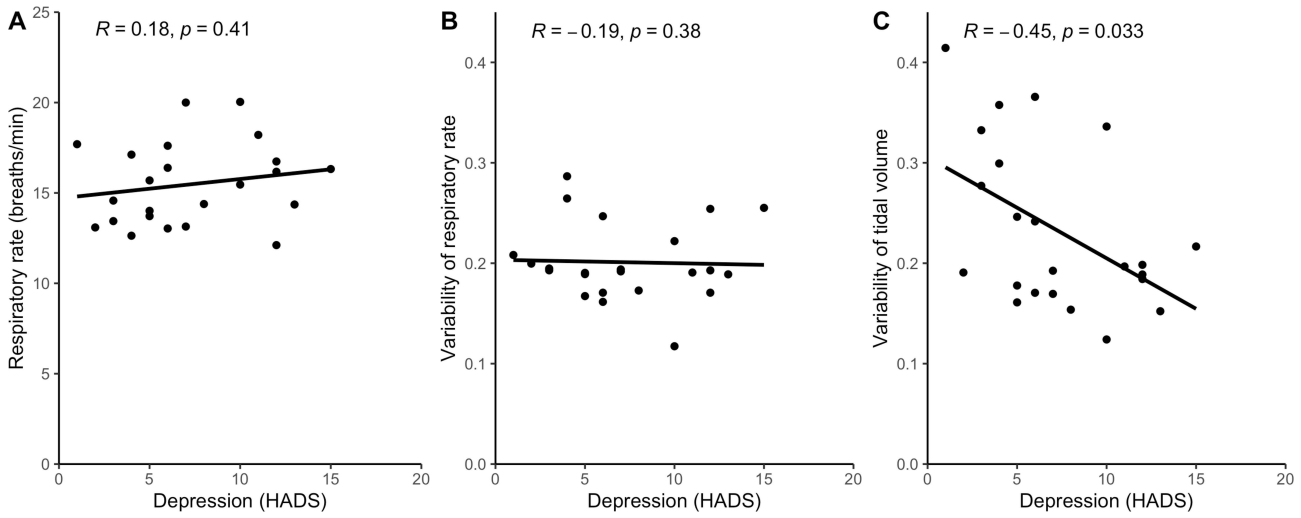

Figure 3 Correlations between depression and respiratory variability in women with fibromyalgia syndrome. Depression was assessed using the Hospital Anxiety and Depression Scale (Hads). Respiratory parameters were measured during 30 min of restful waiting. Variabilities in the respiratory rate and tidal volume were calculated as coefficients of variation. (**A**) Mean respiratory rate, (**B**) Variability of respiratory rate, (**C**) Variability of tidal volume. R: Spearman's rank correlation coefficient.

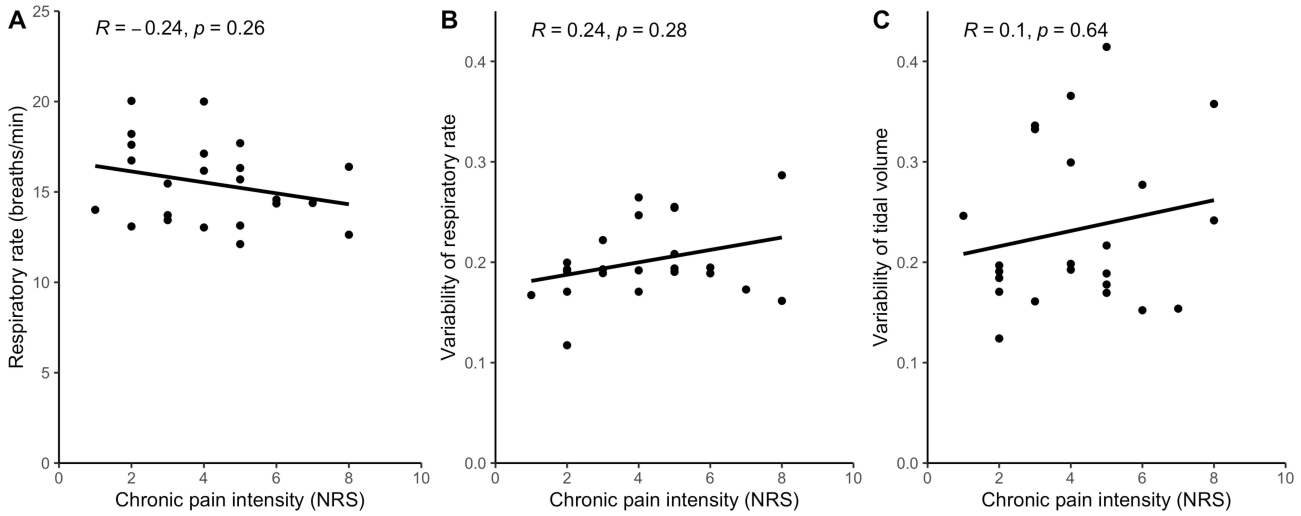

Figure 4 Correlations between chronic pain intensity and respiratory variability in women with fibromyalgia syndrome. Chronic pain intensity was measured using the Numerical Rating Scale (NRS). Respiratory parameters were measured during 30 min of restful waiting. Variabilities in the respiratory rate and tidal volume were calculated as coefficients of variation. (**A**) Mean respiratory rate, (**B**) Variability of respiratory rate, (**C**) Variability of tidal volume. R: Spearman's rank correlation coefficient.

Previous studies have examined spontaneous breath-to-breath variations in breathing parameters of healthy individuals, using similar non-invasive respiratory monitoring during restful waiting and expressing respiratory variability as the coefficient of variation.[29,30] However, differences in the duration of respiratory measurements across studies limit direct comparisons. Despite these methodological differences, respiratory rate variability was lower in healthy individuals studied by Vlemincx et al[29] (0.164 ± 0.072) than in fibromyalgia patients in the present study (0.201 ± 0.039). Although this comparison remains speculative, it suggests that respiratory rate variability is elevated in chronic pain conditions and may be further increased in patients with heightened pain sensitivity.

Consistent with broader fibromyalgia studies,[31,32] our cohort showed mild-moderate symptom burden, though respiratory variability patterns did not align with disease impact scores. Regarding the mechanisms explaining the association between fibromyalgia, pain sensitivity, and respiratory variability, we believe that neuroinflammation and autonomic dysregulation are two potential pathways. Recent evidence indicates that inflammation plays a significant role in the etiology of fibromyalgia.[2] Pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-17, and TNF-a are elevated in

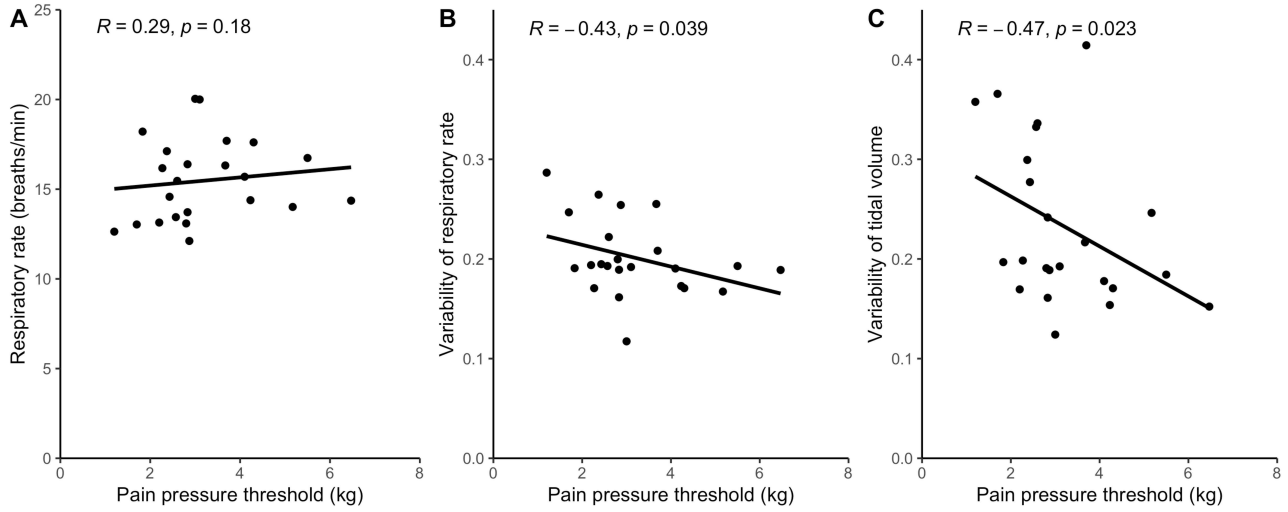

Figure 5 Correlations between pain pressure thresholds and respiratory variability in women with fibromyalgia syndrome. The pain pressure threshold (kg) was defined as the mean pressure needed to evoke pain in three tests at the thenar muscle of the dominant hand and ipsilateral tibialis anterior muscle. Respiratory parameters were measured during 30 min of restful waiting. Variabilities in the respiratory rate and tidal volume were calculated as coefficients of variation. (**A**) Mean respiratory rate, (**B**) Variability of respiratory rate, (**C**) Variability of tidal volume. R: Spearman's rank correlation coefficient.

patients with fibromyalgia compared to healthy controls and have also been associated in some studies with symptoms such as pain, anxiety, and fatigue.[33–35] Furthermore, positron emission tomography (PET) scans reveal increased activation of glial cells in the brains of patients with fibromyalgia, indicating ongoing neuroinflammation.[36] Inflammation may influence respiratory plasticity as it reduces the adaptive capabilities of respiratory control.[5] The second proposed mechanism is autonomic dysregulation, as there is a disruption in the balance between the sympathetic and parasympathetic nervous systems in fibromyalgia patients.[37] This disruption could also be reflected in altered respiratory variability.[7] Conversely, modifying respiratory variability through targeted breathing exercises may, in turn, influence fibromyalgia symptoms, presenting a potential therapeutic approach.

These findings show that patients with heightened somatic symptom burden and pain sensitivity displayed greater respiratory rate variability, which may reflect altered central control of respiration. In general, low or absent respiratory variability implies a rigid regulation of breathing, reflecting poorer reactivity to input into the respiratory center. By contrast, increased respiratory variability associated with heightened pain sensitivity may indicate a dysregulated respiratory system characterized by an exaggerated response to stimuli.

Our findings on respiratory variability contribute to the body of research on the relation between pain and respiration. We demonstrated that pain sensitivity and chronic pain intensity have different associations with respiration, as pain pressure thresholds but not chronic pain intensity were inversely correlated with variability of respiratory rate and tidal volume. Prior studies have consistently shown an increase in minute ventilation in response to tonic sustained pain stimuli.[38–42] This increase in total ventilatory output is a result of increased tidal volume,[38,39,41] respiratory rate,[42] or both.[40] Sudden, short-lasting pain stimuli result in increased inspiratory flow.[43–45] Chronic pain also causes hyperventilation, but this could partly be attributed to the influence of anxiety, panic, and a sense of uncontrollability rather than the direct effect of actual painful stimuli.[46,47]

Regarding the relation between chronic pain and variability of other vital functions, recent studies have reported that chronic pain in fibromyalgia is also associated with heart rate variability (HRV). This association is likely influenced by the relation between the low- and high-frequency components of HRV and the sympathetic and parasympathetic branches of the autonomic nervous system. Chronic pain may affect the autonomic nervous system in general and the sympathetic nervous system activity in particular.[48,49] Elevated sympathetic and reduced parasympathetic cardiac modulation have been observed in patients with fibromyalgia.[50] Consistent with these findings, HRV has been associated with quality of life, physical function, and perceived stress.[51] Regarding the underlying mechanism, the observed decrease in HRV in fibromyalgia is unlikely to be due to deconditioning alone, as reduced HRV is less evident in patients with chronic fatigue

syndrome, who are presumably less active and fit than patients with fibromyalgia.[52] Instead, it is speculated that the lack of an autonomic response to stressors may contribute to deficits in pain inhibition in fibromyalgia.[52,53] Further studies are needed to explore whether the relationship between pain sensitivity and respiratory variability is mediated by the autonomic nervous system.

This study raises the question of whether respiratory variability could aid in the diagnosis, classification, and follow-up of chronic pain. A recent study addressed the potential applications of machine learning algorithms to automatically detect and monitor pain using respiratory and cardiovascular measurements.[54] Another intriguing question for future studies is whether therapeutic interventions aimed at decreasing breathing variability may also decrease pain sensitivity and thus potentially improve chronic pain states. Two previous studies have shown favorable results of hyperventilatory breathing exercises on pain thresholds. In the first study, participants engaged in deep, forceful breathing while receiving electrical stimuli. Those who performed the breathing exercises exhibited higher pain thresholds than those in the control group who did not receive such instructions.[4] In the second study, participants performed a series of thirty deep, forceful breaths. Similarly, using standardized electrical stimuli, the authors observed significantly higher pain thresholds in participants who performed the breathing exercises compared to the control group.[3] These findings suggest that targeted breathing interventions may modulate pain sensitivity, and we propose that respiratory variability is a specific topic of interest. Future key experiments include longitudinal follow-up of respiratory measurements in patients with fibromyalgia to explore whether changes in symptom load over time are consistently associated with alterations in respiratory variability.

Regarding the limitations of our study, we focused exclusively on patients with fibromyalgia, a condition in which identifying a clear biological substrate is complex. Therefore, our results relate to this specific pain syndrome. However, we expect similar effects on respiratory patterns in other patients with central sensitization due to chronic pain. In addition, participants with high PPTs were exposed to more intense pressure stimuli, which - theoretically - could have independently contributed to the observed decrease in respiratory variability. However, this seems unlikely as respiratory variability was assessed over a longer period of 30 minutes. Of note, participants in this study had normal to borderline abnormal scores on the HADS anxiety and depression subscales, which limits the ability to extrapolate our findings to individuals with clinically significant affective symptoms. The HADS is a screening tool rather than a diagnostic instrument. Nonetheless, our results suggest that respiratory patterns may be sensitive to subtle affective states, even in the absence of overt psychopathology. The sample size was relatively small (n = 23), and no formal power analysis was conducted, as this was an exploratory investigation. As such, the findings should be interpreted with caution and considered hypothesis-generating rather than confirmatory. While the risk of type I error from multiple comparisons exists, this is generally considered acceptable within the context of exploratory research.[22] It should be noted that PPT is not a specific marker of central pain sensitivity, as it may also be influenced by peripheral nociceptive mechanisms. Lastly, concomitant medications (eg, antidepressants, analgesics) were not controlled for and may confound respiratory or symptom measures.

Conclusion

In conclusion, this exploratory study aimed to investigate the association between fibromyalgia and respiratory variability. Contrary to our hypothesis, we found no association between fibromyalgia disease impact and chronic pain intensity on respiratory variability. However, in patients with fibromyalgia, respiratory variability decreases with mildly increased depression scores, but not with anxiety. Also, respiratory variability increases with decreasing patient's pain pressure threshold, which may be a surrogate marker for central sensitization, suggesting a possible link between central sensitization and respiratory variability. Further studies should examine the potential benefits of respiratory variability for the diagnosis, monitoring, and treatment of fibromyalgia.

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Disclosure

The author(s) report no conflicts of interest in this work.

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