Clinical Pain Research

Kent Jonsson*, Andreas Pikwer, Erik M. G. Olsson, Magnus Peterson

Hypocapnia in women with fibromyalgia

https://doi.org/10.1515/sjpain-2024-0003
received January 12, 2024; accepted May 27, 2024

Abstract

Objectives – The purpose of this study was to investigate whether people with fibromyalgia (FM) have dysfunctional breathing by examining acid–base balance and comparing it with healthy controls.

Methods – Thirty-six women diagnosed with FM and 36 healthy controls matched for age and gender participated in this cross-sectional study. To evaluate acid–base balance, arterial blood was sampled from the radial artery. Carbon dioxide, oxygen, bicarbonate, base excess, pH and lactate were analysed for between-group differences. Blood gas analyses were performed stepwise on each individual to detect acid–base disturbance, which was categorized as primary respiratory and possible compensation indicating chronicity. A three-step approach was employed to evaluate pH, carbon dioxide and bicarbonate in this order.

Results – Women with FM had significantly lower carbon dioxide pressure (p = 0.013) and higher lactate (p = 0.038) compared to healthy controls at the group level. There were no significant differences in oxygen pressure, bicarbonate, pH and base excess. Employing a three-step acid–base analysis, 11 individuals in the FM group had a possible renally compensated mild chronic hyperventilation, compared to only 4 among the healthy controls (p = 0.042).

Conclusions – In this study, we could identify a subgroup of individuals with FM who may be characterized as mild chronic hyperventilators. The results might point to a plausible dysfunctional breathing in some women with FM.

Keywords: fibromyalgia, acid, base balance, hypocapnia, chronic hyperventilation

1 Introduction

Fibromyalgia (FM) is characterized by chronic widespread pain and symptoms such as general fatigue, anxiety, depression, cognitive dysfunction, muscle and joint stiffness [1,2]. The presence of these symptoms and their severity can vary, highlighting the heterogeneity within the FM population and suggesting the possible existence of subgroups or different phases of the disease. The clinical manifestations of FM have been suggested to result from microtrauma in muscles, neuroimmune dysfunction, dysregulation of neuroendocrine axes, disturbed sleep or the autonomic nervous system [3–5]. Reduced physical performance is common in FM, with a low peak rate of oxygen uptake and anaerobic threshold indicating reduced cardiorespiratory fitness [6,7]. Cardiorespiratory fitness reflects the capacity of the body's oxygen delivery system, including circulatory, respiratory and muscular systems, to deliver oxygen during sustained physical activity [8].

Previous research has reported disturbances in respiratory function in people with FM, including decreased thorax expansion, forced expiration and maximal inspiratory pressure [9,10]. The respiratory response to chronic pain is not completely understood and breathing may be influenced by multiple factors. The respiratory response can be initiated and perpetuated by biomechanical, biochemical or psychological stimuli, illness or the pain itself [11]. With the presence of, for example, pain, stiffness, anxiety and stress in FM, it is possible that several factors may affect the breathing of persons with this condition. Anxiety and stress can affect respiration by stimulating the sympathetic nervous system, probably due to the release of catecholamines increasing respiratory rate and causing hyperventilation [12,13]. Biomechanical restriction may change the breathing pattern towards shallow breathing, possibly to avoid dyspnoea due to the increased breathing effort required with restricted lung compliance. The

*** Corresponding author: Kent Jonsson,** Department of Rehabilitation Medicine, Nykoping Hospital, Nykoping, Sweden; Department of Public Health and Caring Sciences, Section of Family Medicine, Uppsala University, Box 564, SE-751 22, Uppsala, Sweden,
e-mail: kent.jonsson@uu.se, tel: +46 706 555 220, fax: +46 18 511 657
Andreas Pikwer: Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden; Department of Anesthesia, Eskilstuna County Hospital, Eskilstuna, Sweden, e-mail: andreas.pikwer@med.lu.se
Erik M. G. Olsson: Department of Women's and Children's Health, Healthcare Science and e-health, Uppsala University, Uppsala, Sweden, e-mail: erik.mg.olsson@uu.se
Magnus Peterson: Department of Public Health and Caring Sciences, Section of Family Medicine, Uppsala University, Box 564, SE-751 22, Uppsala, Sweden; Academic Primary Health Care, Region Uppsala, Uppsala, Sweden, e-mail: magnus.peterson@uu.se

restricted lung compliance is then compensated for by increased breathing frequency, especially during physical exertion [11,14]. Pain acts as a stressor that may trigger a stress response, resulting in increased breathing through a direct relationship between nociceptive afferents and respiratory networks [15,16].

Dysfunctional breathing may affect acid–base balance and the analysis of blood gases can detect such a disturbance. Previous studies have suggested that altered blood gases may indicate respiratory dysfunction in chronic pain conditions [17,18]. Hypocapnia, i.e. low CO_2, has been observed in regional pain conditions, such as neck pain and low back pain [13,19]. In cases of regional neck pain, hypocapnia has been found to correlate with pain symptoms [13]. The presence of both neck and lower back pain is common in people with FM and similar findings would therefore be expected. The occurrence of hypocapnia has been suggested in at least a subgroup within an FM population [20], but the evidence for this is limited.

The primary aim of the present study was to compare blood gases in people with FM to those of healthy controls based on the hypothesis that people with FM may exhibit signs of mild chronic hyperventilation.

2 Method

2.1 Study design and study population

This was a cross-sectional case–control study that included 36 women diagnosed with FM according to the criteria defined by the American College of Rheumatology in 1990 (ACR 1990) [21]. A control group consisting of 36 age-matched healthy women was also included in the study. Women with FM were recruited consecutively from a pain clinic located in a medium-sized city in Sweden. The control group was composed of women employed in healthcare professions, mainly medical secretaries. The inclusion criterion for both groups was age between 20 and 65 years. The exclusion criteria encompassed the inability to attend a scheduled examination, physical trauma or surgery within the past 6 months, neurological or cardiorespiratory conditions, or psychiatric conditions affecting participation. Complaints related to the chest wall, neck and shoulder region were also considered exclusion criteria for the healthy controls. Smoking was not a criterion for exclusion. All participants were provided with both written and verbal information about the study, and written consent was obtained from each participant. The study received approval from the ethical committee in Stockholm (Dnr 2015/1147-31/4) and it was registered with ClinicalTrials.gov under identification number NCT0409873.

2.2 Procedure

Participants were recruited from March 2018 to January 2022. There was a temporary pause in recruitment in 2020 due to Covid-19. Eligibility was determined through interviews and a review of the medical records at the pain clinic where examinations had been conducted. Participants were allowed to take pain medication as needed. Smoking habits and drug use were recorded based on self-report. The duration of pain was also recorded for the participants with FM.

2.2.1 Pressure pain sensitivity

Sensitivity to mechanical pressure was assessed using a pressure pain threshold (PPT). An algometer (SBmedic Electronics, Schultzvagen 39, SE 17063 Solna, Sweden) was employed for this purpose. This device features a pressure-sensitive strain gauge at the tip. Pressure is indicated in kPa/s, and a scale is used to ensure the examiner maintains a constant pressure. Participants were positioned in a prone (face-down) posture on an examination table with support for their arms and ankles during the examination. A total of 14 paraspinal locations were examined, spanning from C7-Th7, aligned with the level of facet joints for each segment. The examination began on the right side and then proceeded to the left side. When a participant reported that the pressure induced pain, the pressure application was halted and recorded. Before the formal examination, a trial test was conducted on the subject's arm to acquaint the participant with the probe of the device. Each anatomical point was evaluated once to prevent temporal summation. An upper limit of 800 kPa was set for the algometer, and 800 kPa was recorded in the protocol. To assess differences in pain intensity, a PPT index was computed by summing the mean value of each segment and dividing by the number of segments.

2.2.2 Arterial blood gases

Sampling was conducted by an experienced intensive care nurse using a standardized technique. The participants were positioned in a supine posture for approximately 5 min before sampling. They were instructed to breathe

normally to prevent hyperventilation or breath-holding during sampling. Arterial blood gases were obtained from the left radial artery; if this was not suitable (e.g. due to a covering tattoo or inability to locate the artery), then the right side was used. A heparinized syringe was employed for spontaneous filling and any air was meticulously removed before sealing the container. The collected samples were labelled with the patient's ID and promptly analysed for parameters, including $paCO_2$ (reference range: 4.7–6.0 kPa), paO_2 (reference range: 10–14 kPa), base excess (reference range: −3 to 3), pH (reference range: 7.35–7.45), standard bicarbonate (reference range: 22–27 mmol/l) and lactate (reference range: 0.5–2.2 mmol/l). The analysis was conducted using the Radiometer ABL825 device (Triolab AB, Radiometer ABL825, Mölndal, Sweden). A three-step approach was employed with each individual to identify hyperventilation (both acute and chronic) in participants of both groups and among those identify chronic hyperventilators [22]. In the first step, we assessed the pH level to determine the tendency towards either acidosis or alkalosis, using a pH of 7.4 as the cut-off point within the normal range. In the second step, we evaluated the possibility of a respiratory disorder by examining pCO_2. A value below the mean of the normal range, i.e. 5.3 kPa, was indicative of a tendency towards respiratory alkalosis. In the third step, we analysed compensatory responses. When a tendency towards respiratory alkalosis was identified, we looked for evidence of compensation, characterized by a reduction in standard bicarbonate levels. A value less than the mean of the normal range for standard bicarbonate, i.e. 24 mEq/l, was considered indicative of possible renal compensation (Figure 1).

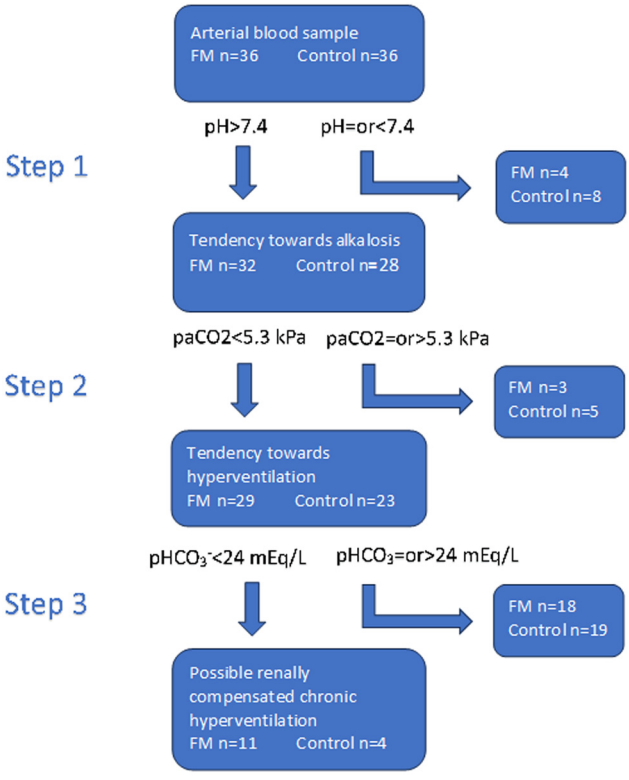

Figure 1: A stepwise analysis to determine respiratory acid–base disorder. $PaCO_2$, carbon dioxide tension; HCO_3^-, bicarbonate.

2.3 Statistical analysis

We used the Mann–Whitney *U* test, chi-square or Fisher's exact test to compare differences between the study groups. Median and range are reported for all parameters, except age and BMI, which are reported as mean values and standard deviations. The level of significance was set at $p < 0.05$. Data analyses were conducted using IBM SPSS Statistics version 28.0. *A priori* sample size calculation based on another report [23] indicated the need for 22 subjects per group considering a two-tailed hypothesis, $\alpha = 0.05$, $\beta = 0.8$ and an effect size (d) of 0.8.

3 Results

Baseline variables are presented in Table 1. The mean duration of generalized pain in the FM group was 10.3 years, and PPT was significantly lower compared to the control group. The analgesics used on a regular basis by persons in the FM group included the following: paracetamol ($n = 5$), non-steroidal anti-inflammatory drugs ($n = 2$), and gabapentin ($n = 1$). Some FM participants used analgesics occasionally, but none of these persons had taken any on the day of testing.

At the group level, the FM participants demonstrated significantly lower $paCO_2$ levels ($p = 0.019$) and higher lactate levels ($p = 0.034$) compared to the control group when the acid–base balance was not taken into account (Figure 2). There were no significant differences between the two groups for the other blood gas parameters (Table 1).

Employing the three-step acid–base analysis, 11 participants in the FM group had pH, $paCO_2$ and standard bicarbonate deviations suggesting possible renally compensated mild chronic hyperventilation compared to only 4 of the healthy controls ($p = 0.042$). When comparing this subgroup to all others within the FM population, significant differences were found in $paCO_2$, base excess and standard bicarbonate, but not in paO_2, pH and lactate. There were no significant differences in PPT between the subgroups (Table 2 and Figure 3).

Table 1: Comparison of background variables between people with FM (n = 36) and a control group (n = 36). Differences were assessed using the Mann–Whitney U test, chi-square test, or Fisher's exact test

Background variables	FM, n = 36	Control group, n = 36	P-value
Age, mean, years	43.8 [10.0]	41.8 [10.2]	0.388
BMI, mean, kg/m^2	26.8 [4.6]	25.1 [4.1]	0.134
Smokers, n	5	1	0.088
Education, n University/Gymnasium	8/28	12/24	0.293
PPT, median [range] kPa	169 [75.8–376.7]	472.5 [231–726.1]	0.001
$paCO_2$, median [range], kPa	4.7 [3.4–5.6]	4.9 [3.8–5.8]	**0.019**
paO_2, median [range], kPa	13.6 [9–17.7]	12.8 [10.2–15.5]	0.106
S-bicarbonate, median [range], mmol/l	24.0 [19–30]	24.0 [22–30]	0.500
Base excess, median [range], mmol/l	−0.85 [−7.2–6.0]	−0.4 [−2.8–3.5]	0.267
pH median [range]	7.43 [7.37–7.60]	7.43 [7.38–7.48]	0.141
Lactate, median [range], mmol/l	1.2 [0.5–2.0]	1.0 [0.6–2.2]	**0.034**

Data are presented as numbers, mean, median, and range. BMI = body mass index; PPT = pressure pain threshold; $paCO_2$ = arterial carbon dioxide tension; paO_2 = arterial oxygen tension; S-bicarbonate = standard bicarbonate. Significant differences are marked in bold.

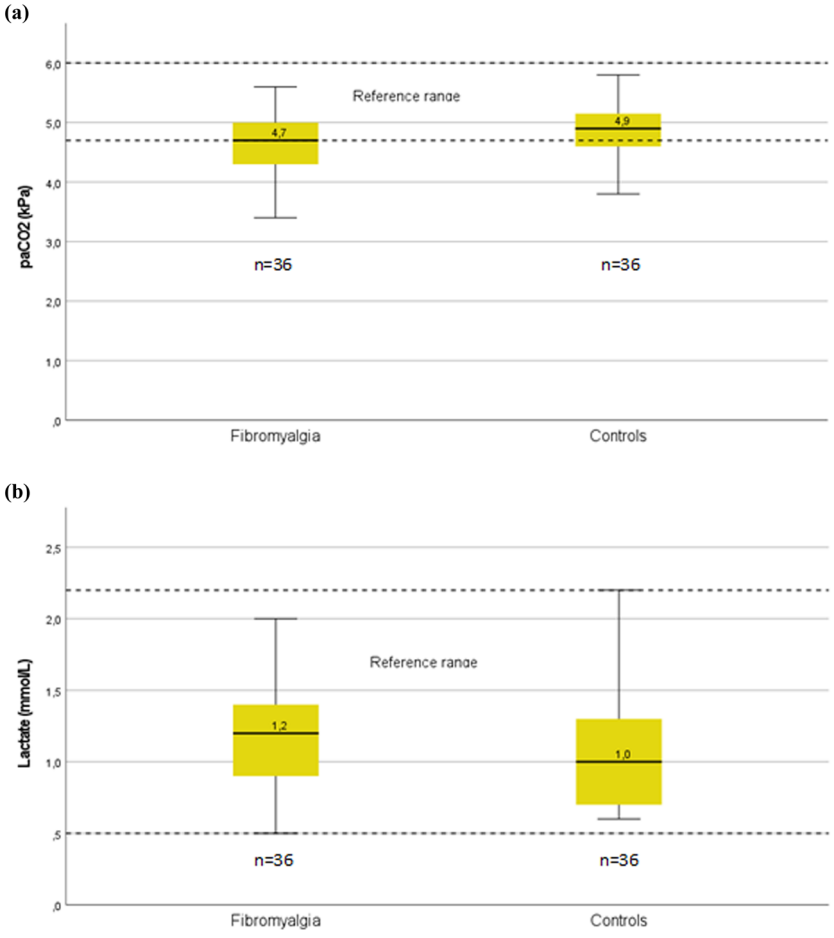

Figure 2: Arterial blood gases in cases and controls: (a) carbon dioxide tension ($paCO_2$) and (b) lactate. The dashed lines show the reference range. Numbers and median are presented for each group.

Table 2: Comparison of blood gases between possible renally compensated (n = 11) and all others (n = 25) within the FM population and between possible renally compensated (n = 4) and all others (n = 32) within the control group. Differences were evaluated using the Mann–Whitney U test

	FM			Controls		
	Compensated respiratory alkalosis, n = 11	**All others*, n = 25**	***P*-value**	**Compensated respiratory alkalosis, n = 4**	**All others*, n = 32**	***P*-value**
$paCO_2$, median [range], kPa	4.4 [3.5–4.8]	4.8 [3.4–5.6]	**0.004**	4.6 [4.2–4.8]	5.0 [3.8–5.8]	0.055
paO_2, median [range], kPa	12.9 [9–17.7]	13.6 [10.2–16.8]	0.612	13.3 [11.1–15.5]	12.8 [10.2–15.1]	0.545
S-bicarbonate, median [range], mmol/l	23.0 [22–23]	25.0 [19–30]	**0.001**	22.5 [22–23]	24.0 [22–30]	**0.010**
Base excess, median [range], mmol/l	−2.7 [−3.7 to −1.8]	−0.2 [−7.2 to 6.0]	**0.001**	−2.4 [−2.8 to 3.5]	−0.3 [−2.7 to 2.9]	0.383
pH, median [range]	7.43 [7.41–7.60]	7.43 [7.37–7.56]	0.892	7.43 [7.41–7.46]	7.43 [7.38–7.48]	0.437
Lactate, median [range], mmol/l	1.0 [0.5–1.7]	1.3 [0.6–2.0]	0.456	1.3 [0.7–2.2]	1.0 [0.6–1.5]	**0.035**
PPT, median [range], kPa	193.9 [81.3–366.4]	143.4 [75.8–376.7]	0.588	316.0 [307.6–512.3]	478.6 [231.9–726.1]	0.142

Data are presented as median and range. BMI = body mass index; $paCO_2$ = arterial carbon dioxide tension; paO_2 = arterial oxygen tension; S-bicarbonate = standard bicarbonate; PPT = pressure pain threshold. *pH ≤ 7.4 or $paCO_2$ ≥ 5.3 kPa or $pHCO_3^-$ ≥ 24 mEq/l. Significant differences are marked in bold.

In the FM group, 17 participants had $paCO_2$ below the reference range (i.e. below 4.7 kPa). Out of these, nine had possible renally compensated mild chronic hyperventilation and eight had possible acute hyperventilation. Blood gas values for this subgroup are presented in Table 3.

4 Discussion

In this study, we could identify a subgroup among individuals with FM and with possible renally compensated mild chronic hyperventilation. This finding supports the hypothesis that chronic dysfunctional breathing may be a factor to consider in some individuals with FM. This subgroup could be identified using an arterial blood gas sample followed by a simple acid–base analysis. However, we do not know if this is a phenomenon in some individuals that influences the FM syndrome or vice versa, i.e. if respiratory disturbance is an outcome that depends on the severity of a painful condition. It is important to note that the severity of symptoms in individuals with FM can vary considerably and not everyone experiences all the symptoms associated with the condition. This variability in symptoms may also extend to respiratory dysfunction.

In the present study, women with FM exhibited significantly lower $paCO_2$ at the group level. This observation aligns with findings from other studies related to painful conditions [13,19,24]. Low $paCO_2$ levels in the blood can result from various factors, including high altitude, pulmonary disorders, cardiovascular disorders, metabolic disorders, some medications, central nervous system disorders, or miscellaneous causes such as pain [25]. Except for pain, none of our study participants had medical disorders known to impact respiration. Since the subgroup categorized as possible renally compensated chronic hyperventilation appeared to have a tendency towards higher PPT, it may indicate that there are causes other than pain that influence dysfunctional breathing.

During blood gas sampling, procedural discomfort might influence $paCO_2$ and pH by causing faster breathing or breath-holding. This risk could be greater in the FM group due to their heightened sensitivity to pain. However, when evaluating for non-compensated (i.e. acute) versus compensated (i.e. chronic) changes, the presence of acute hyperventilation appeared to be similar between the groups (Figure 1). The identification of individuals at risk could possibly be further simplified by initial transcutaneous measurements of $paCO_2$, even though this was not employed in this study. A physiological reference range for $paCO_2$ between 4.7 and 6.0 kPa was used. Nearly half of the FM group (47%) had

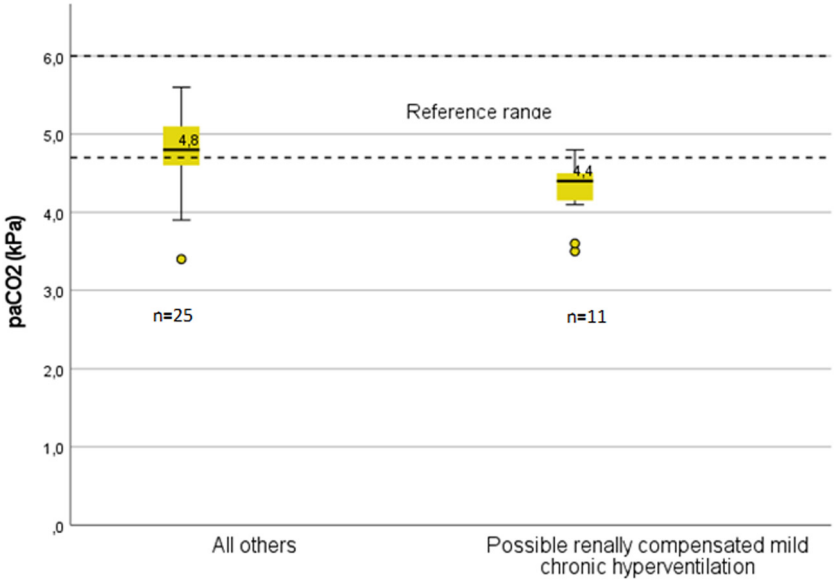

Figure 3: Arterial carbon dioxide tension ($paCO_2$) in women with FM, subgrouped by possible renally compensated mild chronic hyperventilation and all others. The dashed lines show the reference range. Numbers and median are presented for each group.

Table 3: Blood gas variables presented for women with FM (*n* = 17) and with $paCO_2$ below the reference range (i.e. 4.7 kPa)

Blood gas variables	Fibromylagia *n* = 17
$paCO_2$, median [range], kPa	4.2 [3.4–4.6]
PaO_2, median [range], kPa	14.2 [11.9–17.7]
S-bicarbonate, median [range], mmol/l	23.0 [19–26]
Base excess, median [range], mmol/l	−2.4 [−7.2 to 0.2]
pH median [range]	7.43 [7.37–7.60]
Lactate, median [range], mmol/l	1.2 [0.5–1.9]

Data are presented as median and range. $paCO_2$ = arterial carbon dioxide tension; paO_2 = arterial oxygen tension; S-bicarbonate = standard bicarbonate.

values below the reference range, similar to findings in persons with chronic neck pain (42%) [13]. This suggests the presence of hypocapnia in a subgroup of individuals with either localized or generalized pain. In this study, we found four controls who were categorized as having possible renally compensated chronic hyperventilation and somehow reminded of cases within the same category. They had significantly higher lactate and lower standard bicarbonate compared to other controls. They also had lower base excess and $paCO_2$ below the reference range, indicating hypocapnia. Interestingly, they exhibited lower PPT compare to other controls, however, it was not significant (Table 2).

An explanation for the decreased $paCO_2$ may be that hyperventilation is secondary to a primary metabolic disturbance, such as lactatemia. While the FM group did have significantly higher lactate levels compared to the healthy controls, none of the FM subjects had hyperlactatemia (lactate greater than 2 mmol/l), and there was no significant difference between compensated and uncompensated cases within the FM population. Individual analyses suggest that respiratory changes were primarily and not secondary to metabolic acidosis, and biochemical factors, as well as psychological and biomechanical factors, may also be considered. Since our study population was healthy, except for the chronic pain condition, severe hypocapnia was not expected. However, hypocapnia can propagate or initiate physiological dysfunctions [25]. Hyperventilation involves excessive breathing, which leads to decreased $paCO_2$ levels and subsequent alkalosis. Respiratory alkalosis can impact various functions, including those in smooth muscles (e.g. spasm, vasoconstriction), skeletal muscles (e.g. weakness, fatigue), the nervous system (e.g. tingling, numbness) and psychological aspects (e.g. restlessness, catastrophic thinking) [26]. In this study, a subgroup of individuals appeared to exhibit a chronic respiratory condition. They had a mean close to the lower limit of normal for standard bicarbonate but also base excess, thus defining the metabolic component of the acid–base disorder. Persistent or chronic alterations in breathing patterns may lead to the development of compensatory mechanisms in the body. In such cases, the body may compensate by excreting bicarbonate and retaining acid in response to chronic hyperventilation, leading to compensatory metabolic acidosis. Even low-grade metabolic acidosis can induce a variety of symptoms despite blood gases being within the normal range [27]. Metabolic acidosis may lead to

hindered mitochondrial function, resulting in reduced energy production and decreased muscle contractile capacity, which is of particular interest. Clinically, this can manifest as decreased endurance during exercise, difficulty relaxing muscles, muscle pain, or increased exhaustion with effort [28], which are all common features seen in people with FM.

5 Strengths and limitations

In this study, we used blood gas sampling as the gold standard for measuring CO_2 compared to other methods, such as end-tidal or transcutaneous measurement. In addition to CO_2, we also examined several other variables relevant to blood gas analysis (e.g. base excess) to gain insight into both respiratory and metabolic components. While we employed a simple approach to analyse acid–base disturbances, a more comprehensive analysis, incorporating factors such as anion gap, strong ion differences, and phosphate and albumin levels, would be necessary to confidently determine the mechanism behind any potential disturbances. However, this level of analysis was beyond the scope of our study. Both groups received the same instructions before blood sampling, but there is still a possibility that the groups were influenced differently, especially patients having a risk of hypervigilance affecting ventilation, particularly in a stressful situation. It is important to note that this is a cross-sectional study. Therefore, we cannot draw conclusions as to how respiration may vary over time in the FM population. Nor can causality be determined as to whether chronic hyperventilation is a consequence of pain or if chronic hyperventilation can be the cause of various symptoms, including pain. In addition, the moderate number of participants warrants some precautions when considering the results of the study.

6 Conclusions and implications

In this study, we have identified a subgroup of individuals with FM who may be characterized as having mild chronic hyperventilation. This result suggests that dysfunctional breathing may be present in certain individuals with FM. Respiratory rate and tidal volume are two key components of ventilation that influence CO_2 elimination. Hypocapnia may result from any condition that increases respiratory rate or tidal volume. Future research should focus on investigating respiratory function in individuals with FM, as well as potential mechanisms that could affect ventilation in this population.

Research ethics: This research involved human subjects and complied with all relevant national regulations and institutional policies; it was carried out in accordance with the tenets of the Helsinki Declaration (amended in 2013). It has been approved by the ethical committee in Stockholm, Sweden, Dnr 2015/1147-31/4. The trial was registered with ClinicalTrials.gov identification number: NCT04098731.

Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission. KJ and MP contributed to the study conception and design, and KJ with the acquisition of data and drafting of the work. KJ, AP, EO and MP contributed to the analysis and interpretation of data and co-authored and revised the manuscript.

Competing interests: The authors state no conflicts of interest.

Research funding: The study was funded by the Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden.

Data availability: The raw data can be obtained on request from the corresponding author.

Artificial intelligence/Machine learning tools: Not applicable.

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