Original Research

Relationship Between Exercise-induced Oxidative Stress Changes and Parasympathetic Activity in Chronic Fatigue Syndrome: An Observational Study in Patients and Healthy Subjects

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ABSTRACT

Purpose: Oxidative stress has been proposed as a contributor to pain in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). During incremental exercise in patients with ME/CFS, oxidative stress enhances sooner and antioxidant response is delayed. We explored whether oxidative stress is associated with pain symptoms or pain changes following exercise, and the possible relationships between oxidative stress and parasympathetic vagal nerve activity in patients with ME/CFS versus healthy, inactive controls.

Methods: The present study reports secondary outcomes from a previous work. Data from 36 participants were studied (women with ME/CFS and healthy controls). Subjects performed a submaximal exercise test with continuous cardiorespiratory monitoring. Levels of thiobarbituric acid–reactive substances (TBARSs) were used as a measure of oxidative stress, and heart rate variability was used to assess vagal activity. Before and after the exercise, subjects were asked to rate their pain using a visual analogic scale.

Findings: Significant between-group differences in pain at both baseline and following exercise were found (both, $P < 0.007$). In healthy controls, pain was significantly improved following exercise ($P = 0.002$). No change in oxidative stress level after exercise was found. Significant correlation between TBARS levels and pain was found at baseline ($r = 0.540$; $P = 0.021$) and after exercise ($r = 0.524$;

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$P = 0.024$) in patients only. No significant correlation between TBARS and heart rate variability at baseline or following exercise was found in either group. However, a significant correlation was found between exercise-induced changes in HRV and TBARS in healthy controls ($r = -0.720$; $P = 0.001$).

Implications: Oxidative stress showed an association with pain symptoms in people with ME/CFS, but no exercise-induced changes in oxidative stress were found. In addition, the change in parasympathetic activity following exercise partially accounted for the change in oxidative stress in healthy controls. More research is required to further explore this link. (*Clin Ther*. 2019;41:641–655) © 2019 Elsevier Inc. All rights reserved.

Key words: Autonomic nervous system, Chronic fatigue syndrome, Exercise, Oxidative stress, Pain.

INTRODUCTION

Oxidative stress is the imbalance between an increased production and/or reduced clearance of reactive oxygen species that potentially leads to damaged lipids, protein, and DNA.[1] Oxidative stress may induce deleterious changes, particularly to the CNS, given the intrinsic high vulnerability of neurons and glial cells to metabolic changes.[2,3] Oxidative stress covers an important role in synaptic plasticity and many other mechanisms involved in nociceptive modulation and central sensitization.[4,5] Elevated levels of spinal reactive oxygen species lead to peripheral and central sensitization and alter nociception,[6] resulting in hyperalgesia mediated by both local and spinal oxidant mechanisms. Nitric oxide also may induce peripheral and central sensitization by reducing receptor thresholds[7] and may reduce the inhibitory activity of the CNS, leading to central sensitization of dorsal horn neurons.[8] In line with these observations, oxidative stress has also been associated with chronic pain and proposed as a possible contributor to the maintenance of pain symptoms.[9]

Central sensitization—described as a state of generalized hyper-responsiveness of the CNS to a variety of stimuli—has been proposed as a key mechanism in many chronic pain conditions, including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[10–12] a chronic condition in which widespread pain is very common and often reported as more disabling than fatigue itself.[13] Indeed, patients with ME/CFS show hyper-responsiveness to different stimuli and hyperalgesia to electrical and mechanical stimulation when compared to healthy controls.[14]

In addition, a cardinal symptom of people with ME/CFS is postexertional malaise—a worsening of pain and other symptoms in response to exercise, lasting up to 48 h. While exercise normally induces hypoalgesic effects in healthy subjects, quickly increasing pain thresholds and improving subjective reports of pain symptoms,[15–17] people with ME/CFS actually show a decrease in pain thresholds following exercise.[18,19]

The exact mechanisms underlying this lack of exercise-induced hypoalgesia in ME/CFS are largely unknown, as ME/CFS is heterogeneous in nature and several mechanisms co-occur.[20–22] However, oxidative stress may reasonably be proposed as one of the underlying mechanisms. Higher levels of oxidative stress have been reported in people with ME/CFS,[23,24] and studies found that oxidative stress occurs earlier during exercise in people with ME/CFS compared to healthy controls.[25,26] In addition, people with ME/CFS present a delayed antioxidant response following exercise.[25,26]

A second important mechanism that has been proposed to explain the aforementioned exercise-induced hyperalgesia in people with ME/CFS is the alteration of the autonomic nervous system (ANS).[27] Following exercise, patients with ME/CFS show higher gene expression for receptors involved in ANS functions compared to those in healthy controls, and these gene concentrations are associated with pain symptoms.[28] A systematic review of the topic has shown that heart rate variability (HRV)—a commonly used and reliable measure of ANS parasympathetic (vagal) activity[29,30]—differs between people with ME/CFS and controls.[31] In another recent paper, we showed that exercise-induced hyperalgesia was associated with a reduced parasympathetic reactivation during the recovery phase following exercise.[32]

Interestingly, preliminary evidence suggests that a direct link might exist between ANS activity and oxidative stress responses.[33] Increased oxidative stress in the rostral ventrolateral medulla in turn causes excitation of the sympathetic branch.[34] Similarly, angiotensin-II receptor blockade induces both inhibition of the ANS sympathetic branch and a reduction in oxidative stress.[34] In addition,

experimentally induced increased levels of oxidative stress, in both animals and humans, will alter blood flow regulation and reduce muscle blood flow during exercise.[35] Although the link between ANS and oxidative stress appears to be clear, to the best of our knowledge this association has never been explored in patients with ME/CFS or—more generally—chronic pain.

In the present study, we aimed to explore whether oxidative stress is associated with pain or with changes in pain after exercise, and whether a possible relationship exists between oxidative stress and ANS functions in people with ME/CFS and healthy controls. We believe that unravelling the mechanisms associated with symptoms worsening following exercise will help to identify the targets for future treatments, therefore improving patients' care.

We hypothesized that oxidative stress is associated with higher pain levels, and that the change in pain symptoms induced by exercise is associated with the change in oxidative stress in response to exercise. In addition, we expected that oxidative stress and ANS functions are also associated; that is, the higher the level of oxidative stress, the lower the parasympathetic activity in patients with ME/CFS.

METHODS

The present study reports additional analysis of a subset of participants from a previous experimental study[32] from which oxidative stress measures were available. While the previous work focused on postexertional malaise and ANS responses, the present work reports oxidative stress changes and their relationship to pain.

Subjects

Eighteen patients with ME/CFS and 18 healthy inactive (sedentary) controls participated in the study. Patients' diagnosis, based on the criteria from the 1994 Centers for Disease Control and Prevention,[36] was established by 2 physicians specializing in internal medicine and with expertise regarding the diagnosis and treatment of ME/CFS. Patients were excluded if they reported any evidence of other known neurologic, endocrine, immune, or cardiovascular pathology.

Healthy controls were friends of either patients or professionals involved in the research project and volunteers who responded to advertisements. They were included if they had no known significant pathology and had an inactive (sedentary) lifestyle. *Inactivity* was defined as having a seated occupation and performing a maximum of 3 h/wk of moderate physical activity.[37]

All participants were women aged between 18 and 65 years, Dutch speaking, and not pregnant, breastfeeding, or <1 year postpartum. Only women were included, as sex is an important source of bias in exercise physiology and pain studies,[38–40] and because ME/CFS is predominantly prevalent in women.[41] Participants were asked to refrain from consuming caffeine, alcohol, and nicotine and to avoid physical exertion on the day of the experiments. If possible, patients were also asked to abstain from medication that acts on the cardiovascular system, the CNS, and the endocrine system in the 48 h prior to the experiments.

The experiment protocol was approved by the ethics committee at the University Hospital Brussels. All participants provided written informed consent before the start of the assessment.

Procedure

An initial familiarization session was scheduled for at least 1 week before the start of the experimental session, to inform participants about the procedures and devices used during the experiment. Demographic and clinical information was also collected during this first meeting.

Experiments took place in a quiet room with a constant temperature between 21 °C and 23 °C. Pain symptoms were assessed using self-reports. Prior to exercise testing (10 min at rest) and during the subsequent recovery period (again 10 min), physiologic measures of autonomic function were obtained. Measures of autonomic functions were measured through ECG recording during 10 min of quite supine lying. The Nexus-10 wireless and portable telemetry data acquisition system (Mind Media BV, Herten, the Netherlands) was used to calculate the root mean square of successive differences between NN intervals (RMSSD). Patients wore an elastic belt around the chest, in which a stretch-sensitive piezoelectric sensor was placed to record respiratory peaks and respiratory rate.

A submaximal bicycle exercise test, known as the aerobic power index, with continuous

cardiorespiratory monitoring was then performed. The aerobic power index is a standardized test shown to be valid and reliable in both patients with ME/CFS and healthy people.[42] The detailed procedure for the aerobic power index test can be found elsewhere.[19] In summary, cycling started at a workload of 25 Watt/min, increased by 25 Watt/min until the patient reached 75% of his or her age-predicted maximal heart rate. Cycling rate was kept constant at 70 cycles/min.[43] After the test, subjects were asked the same self-reported measures of pain, which were taken as the baseline measurements. Finally, subjects were asked to lie down for 10 min, after which a second blood sample was collected for measuring oxidative stress responses to exercise.

Outcomes Measures

Self-Reported Measures of Pain

Pain was assessed with 2 different tools. The first is the Bodily Pain Subscale of the 36-item Short Form Health Survey (SF-36). It consists of 2 items that assess pain intensity and the influence that pain had on one's life during the previous 4 weeks.[44] The 2 items give a general score ranging from 0 to 100, with higher scores indicating more bodily pain. While the previous study administered SF-36 postexercise as well, we decided to not include that measure: SF-36 is specifically designed for assessing different health domains in the previous 4 weeks, and it is not able to detect quick symptom changes, such as pre–post 1 bout of exercise. For this purpose, we indeed preferred to use a visual analog scale (VAS) for assessing bodily-pain intensity. The VAS comprised 100-mm horizontal lines, with the outer points labeled as "no pain" and "unbearable pain." In order to control for clinical features that might have influenced our results, depression and anxiety were assessed using the Hospital Anxiety and Depression Scale,[45] a validated and reliable tool for assessing psychological distress in both patients and healthy subjects.[46]

Determination of Oxidative Stress

Two tubes of blood were collected 10 min before and following the exercise test. Samples were stored at ambient temperature for 1 h and were then centrifuged for 10 min at 4000 rpm. The resulting serum was stored at −80 °C. Each sample was labeled with a code so that the researcher in charge of the analysis was blinded to the group allocation. Biochemical analysis was performed at RED Laboratories (Asse, Belgium). *Oxidative stress* was evaluated by measurements of thiobarbituric acid–reactive substances (TBARSs) (OxiSelect TBARS Assay Kit for malondialdehyde [MDA] quantitation; Cell Biolabs, San Diego, California). TBARS is a well-established assay for screening and monitoring lipid peroxidation—a generally accepted marker of oxidative stress.[47] The TBARS assay provides relevant information concerning free–radical activity in disease states and measurement of the characteristics of many antioxidant compounds.[48,49]

Physiologic Measures of Autonomic Function

Data from the ECG recording were analyzed offline with the BioSig toolbox in MatLab software (The MathWorks, Natick, Massachusetts). The mean of measurements over the 10-min periods were then used for further analysis. From these measures, heart rate, HRV, and the high-frequency (HF) component of HRV (power range, 0.15–0.40 Hz) were calculated after fast Fourier transformation. Further details regarding raw data handling, artefact removal, and analysis have been described in a previous article.[32]

Although international guidelines (1996) recommend reporting the low-frequency (LF) component of HRV and the LF/HF ratio,[50] more recent work questions the validity and reliability of these measures.[51–53] For this reason, we are not reporting these parameters in the present article; however, a detailed report of all autonomic measures from this study—including both LF-HRV and the LF/HF ratio—has appeared previously.[32] Here we report measures of heart rate, HRV, and HF-HRV, expressed as RMSSD, in order to link parasympathetic activity with changes in oxidative stress.

Statistical Analysis

We explored our data using between- and within-group comparisons. Normality of the variables in each group (patients and healthy controls) was tested with the Shapiro–Wilk test, and appropriate descriptive statistics were calculated. Group comparisons at baseline and following the exercise test were examined using the independent-samples *t* test or the Mann–Whitney *U* test, according to the

results-of-normality analysis. The χ^2 test was used to analyze categorical data. The paired-samples *t* test or Wilcoxon signed rank test was performed to analyze the effects of exercise in each group. The Pearson or Spearman correlation analysis was used to examine the relationship between self-reported pain and TBARS measures. Correlation analyses were also performed to identify associations between ANS function and oxidative stress, as well as between changes in parasympathetic activity (Δ-HRV) and changes in oxidative stress levels (Δ-MDA-TBARS). The significance level was set at 0.05. All data were analyzed using SPSS version 23.0 (IBM, Armonk, NY).

RESULTS

Subjects' Characteristics

Thirty-six subjects (18 patients with ME/CFS and 18 healthy inactive controls) completed the assessment. Table I summarizes the demographic and clinical characteristics of the groups. No statistically significant differences in age, body mass index, anxiety, or depression at baseline were found. Pain was scored significantly higher on the SF-36 subscale in patients with ME/CFS ($P < 0.001$). Patients with ME/CFS also reported significantly more pain than did controls, as expressed on the VAS ($P < 0.001$). No differences in either the level of oxidative stress or the measures of ANS activity (ie, heart rate, respiratory rate, HRV, and HF-HRV) at baseline were found.

Effect of the Exercise Challenge

Within-group analysis revealed that pain (VAS) improved following exercise only in healthy controls ($P = 0.002$), while it did not change in patients with ME/CFS ($P = 0.393$). Oxidative stress, measured using MDA-TBARS level, did not change in response to exercise in either group. In comparison, HRV and HF-HRV (measured through RMSSD calculation) decreased significantly only in patients ($P = 0.039$ and $P = 0.035$, respectively). On exercise testing, similar changes in the other measures (eg, heart rate and respiratory rate), were found in both groups. The effects of exercise on ANS measures (heart rate, HRV, and HF-HRV) in ME/CFS were presented in a recent article[32] and are reported here only to provide a clearer general picture of the results. Data are summarized in Table II. Figures. 1 and 2 pair pain and MDA-TBARS values, respectively, before and after exercise in both healthy controls and in patients with ME/CFS.

Associations Between Pain and Oxidative Stress

No correlations between MDA-TBARS and pain symptoms were found in healthy subjects. On the contrary, in patients with ME/CFS, MDA-TBARS levels were related to VAS bodily pain, both at baseline and after exercise (Table III). Figure 3 summarizes visually the most relevant correlations between MDA-TBARS levels and bodily pain in ME/CFS (baseline, $r = 0.540$ [$P = 0.021$]; postexercise, $r = 0.524$ [$P = 0.026$]). Linear regression analysis revealed that MDA-TBARS significantly explained pain symptoms

Table I. Descriptive demographic and clinical characteristics at baseline in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and in healthy controls.

Characteristic	ME/CF ($n = 18$)	Controls ($n = 18$)	*P*
Age, y	40.9 (9.9)	32.8 (14.2)	0.680
BMI, kg/m^2	26.7 (6.1)	23.8 (4.5)	0.111
Time since ME/CFS diagnosis, mo	75.7 (57.1)	—	—
HADS—Anxiety	10.8 (5.6)	8.6 (7.1)	0.323
HADS—Depression	10.2 (5.4)	8.4 (12.2)	0.143
SF-36 bodily pain[†]	53.4 (19.3)	18.8 (20.4)	<0.001*

BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; SF-36 = 36-item Short-Form Health Survey.
*Statistical significance at $P < 0.05$ (Mann—Whitney nonparametric test).
[†] Assessed using a visual analog scale: 0 = no pain to 100 = worst pain imaginable.

Table II. Effects of submaximal aerobic exercise on pain, oxidative stress (Δ MDA-TBARS), and physiologic hart function before (pre) and after (post) submaximal aerobic exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and in healthy controls. Data are given as mean (SD) unless otherwise noted.

Parameter	ME/CFS ($n = 18$)				Controls ($n = 18$)				$P^{\ddagger}$
	Pre	Post	Δ	$P^{\dagger}$	Pre	Post	Δ	$P^{\dagger}$	
Pain[§]	50.11 (33.03)	51.03 (32.02)	0.917 (15.07)	0.393	15.80 (21.56)	5.16 (7.55)	−10.64 (17.19)	0.002**	0.007*
Heart rate, bpm	71.20 (7.70)	73.90 (8.80)	3.06 (5.47)	0.053	73.74 (8.11)	73.84 (7.78)	0.35 (6.42)	0.983	0.191
Respiratory rate, breaths/min	16.11 (4.27)	18.43 (3.74)	1.68 (2.06)	0.006*	15.63 (3.75)	16.67 (2.82)	1.03 (1.33)	0.001**	0.287
MDA-TBARS, μM/L	11.22 (2.66)	11.11 (2.69)	−0.11 (2.02)	0.879	10.29 (2.30)	10.52 (2.07)	0.24 (1.67)	0.586	0.580
HRV, RMSSD[‖]	28.04 (14.99)	21.70 (9.88)	−6.34 (14.06)	0.039*	43.33 (31.93)	45.20 (29.93)	1.87 (26.44)	0.811	0.308
HF-HRV	178.69 (171.7)	97.11 (81.9)	−81.58 (154.8)	0.035*	547.53 (810.8)	541.71 (600.2)	−5.81 (539.6)	0.711	0.521

HF-HRV = high frequency component of heart rate variability; MDA-TBARS = malondialdehyde—thiobarbituric acid reactive substances (this is a standardized method to measure lipid peroxidation, a measure thought to reflect oxidative stress).
Statistically significant differences: *$P < 0.05$, **$P < 0.01$.
[†] Wilcoxon signed rank test for within-group analysis.
[‡] Mann—Whitney *U* for between-group comparisons.
[§] Assessed using a visual analog scale: 0 = no pain to 100 = worst pain imaginable.
[‖] Expressed as root mean square of successive differences.

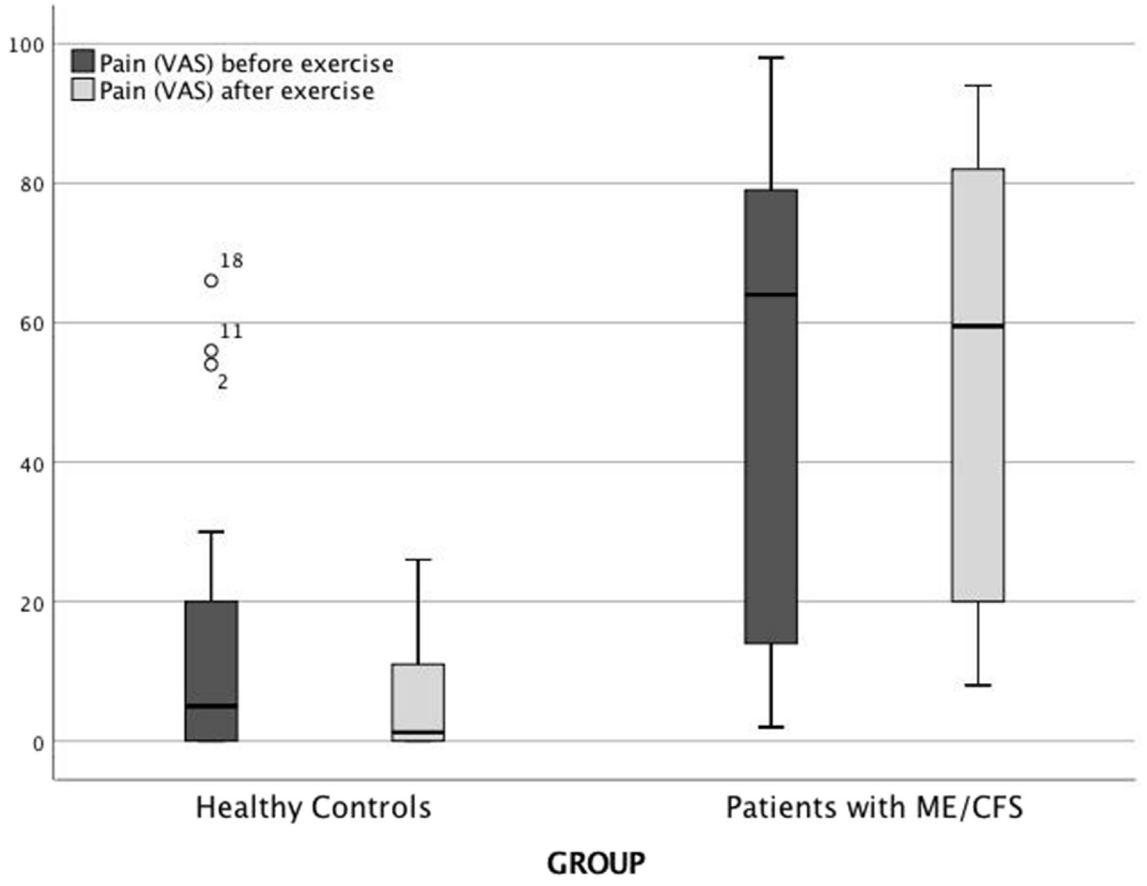

Figure 1. Mean (SD) pain scores before and after submaximal aerobic exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and healthy controls.

in MC/CFS (before exercise, $R^2 = 0.259$ [$P = 0.03$]; after exercise, $R^2 = 0.254$ [$P = 0.03$]).

Regarding the SF-36 bodily pain score and MDA-TBARS levels, no significant correlations were found. The Δ-MDA-TBARS from baseline to postexercise did not correlate with the changes in pain measures (Table III).

Associations Between Oxidative Stress and ANS Activity

No association between MDA-TBARS and ANS activity was found in either group at baseline or after the exercise challenge. In the healthy-controls group, strong associations were found between Δ-MDA-TBARS levels and Δ-HRV. More specifically, the exercise-induced decrease in MDA-TBARS level was strongly associated with the increases in HRV ($r = -0.720$; $P = 0.001$) and HF-HRV ($r = -0.674$; $P = 0.002$). Linear regression analysis demonstrated that the change in parasympathetic activity may explain over 36% of the change in MDA-TBARS levels ($R^2 = 0.366$; $P = 0.008$). Also, Δ-MDA-TBARS was correlated with Δ-HRV ($r = -0.522$; $P = 0.026$). No such correlations were found in the ME/CFS group. Table III shows the aforementioned correlations. The most relevant associations are presented in Figure 4.

DISCUSSION

In the present study, we aimed to investigate possible associations between oxidative stress and pain symptoms in healthy subjects and patients with ME/CFS, and to assess whether oxidative stress levels and ANS parasympathetic (vagal) activity are linked. We

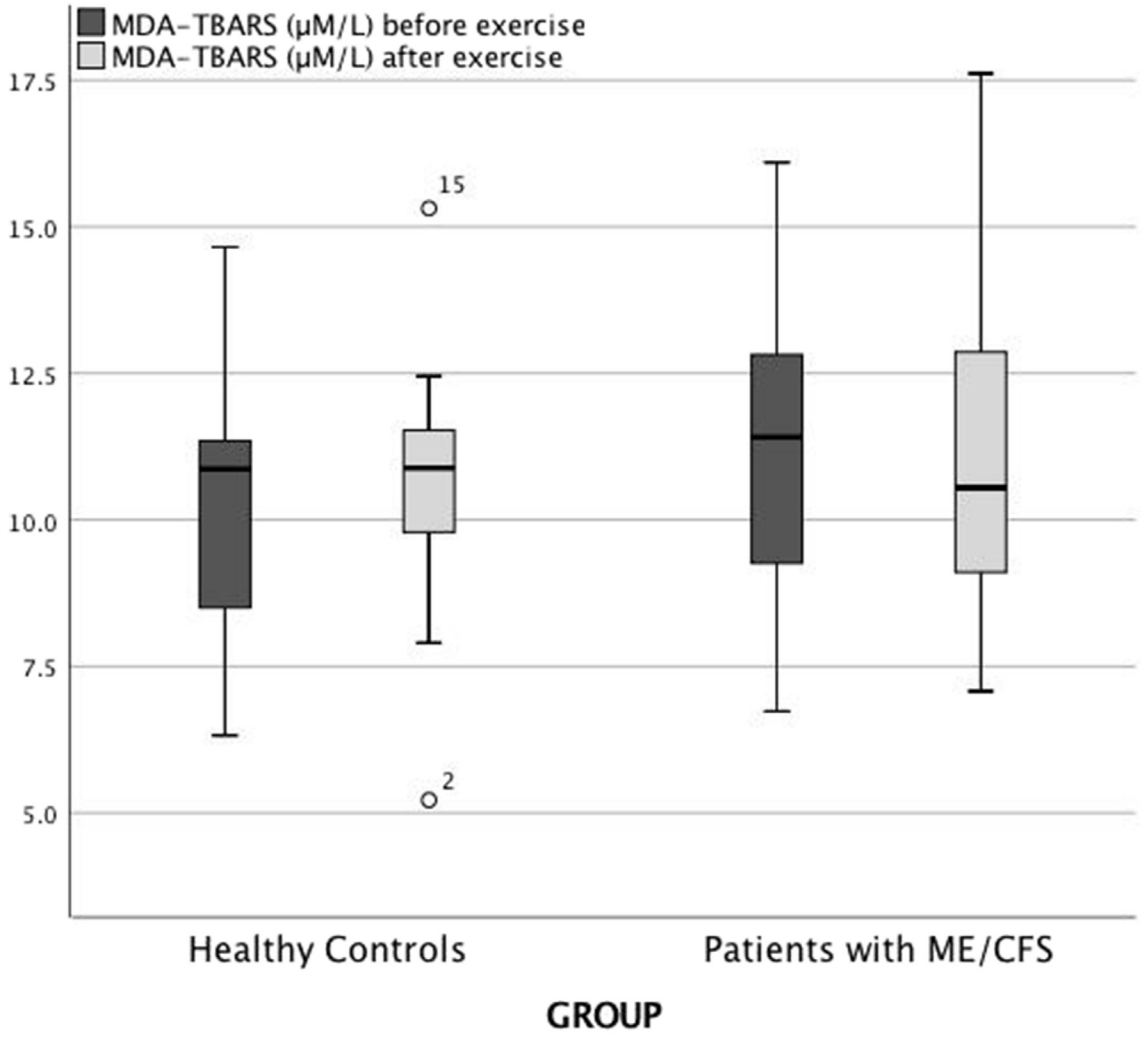

Figure 2. Mean (SD) levels of malondialdehyde—thiobarbituric acid reactive substances (MDA-TBARS) before and after submaximal aerobic exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and healthy controls.

set up a design in which subjects underwent a submaximal exercise test and we recorded pain symptoms, oxidative stress level, and ANS activity before and after the test.

Our results only partially confirm results from the available literature. First, we did not find higher levels of oxidative stress in ME/CFS and chronic pain when compared to healthy subjects at baseline, as previously reported.[6,14,23] A possible explanation might be that, in the present study, we controlled for physical activity levels, enrolling only sedentary healthy controls. Studies focusing on oxidative stress in patients with chronic pain rarely account for physical activity. However, patients are likely less active than healthy subjects.[54–56] Our results suggest that lower physical activity may account for higher oxidative stress levels and should be assessed in patients with chronic pain. Our results are in line with those shown by Jammes et al,[26] who did not find any increase in oxidative stress at baseline in patients without acute infection or a high level of physical stress.

Second, exercise did not induce any change in oxidative stress levels. However, oxidative stress

Table III. Correlation analysis between pain, oxidative stress (MDA-TBARS), and parasympathetic activity (HRV) before (pre) and after (post) submaximal aerobic exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and healthy controls. The table reports nonparametric correlation both before and after exercise, and between the pre–post changes (Δ).

Parameter	Pre		Post		Δ	
	r	*P*	*r*	*P*	*r*	*P*
ME/CFS						
Pain†						
MDA-TBARS, μM/L	0.540*	0.021*	0.524*	0.026*	0.026	0.917
HRV	0.443	0.065	0.116	0.648	0.351	0.154
HF-HRV	0.314	0.204	0.046	0.855	0.260	0.298
MDA-TBARS, μM/L						
HRV	0.251	0.315	0.253	0.311	0.107	0.671
HF-HRV	0.173	0.491	0.349	0.156	−0.080	0.754
HRV‡						
HF-HRV	0.917**	0.001**	0.922**	0.001**	0.901**	0.001**
Controls						
Pain†						
MDA-TBARS, μM/L	0.179	0.476	0.119	0.638	0.076	0.765
HRV, RMSSD	0.070	0.783	0.065	0.798	0.001	0.997
HF-HRV	−0.061	0.811	0.010	0.970	−0.078	0.759
MDA-TBARS, μM/L						
HRV, RMSSD	0.073	0.773	0.401	0.099	−0.720**	0.001**
HF-HRV	0.145	0.570	0.443	0.066	−0.674**	0.002**
HRV‡						
HF-HRV	0.975**	0.001**	0.957**	0.001**	0.973**	0.001**

HF-HRV = high-frequency component of HRV; MDA-TBARS = malondialdehyde–thiobarbituric acid reactive substances (this is a standardized method to measure lipid peroxidation, a measure thought to reflect oxidative stress); HRV = heart rate variability.
Statistically significant differences: *$P < 0.05$, **$P < 0.005$.
† Assessed using a visual analog scale: 0 = no pain to 100 = worst pain imaginable.
‡ Expressed as root mean square of successive differences.

responses to exercise might be mediated by exercise intensity. A maximal exercise test seems to induce clear changes in TBARS level in patients with ME/CFS.[9] It is possible that the submaximal exercise test we used was not sufficiently intense to induce an oxidative stress response.

However, exercise was intense enough to exert a hypoalgesic effect in healthy subjects, confirming findings from the existing literature.[15,19,32,57,58] Patients with ME/CFS, in contrast, did not show hypoalgesia following exercise.[19,22,34,59] Oxidative stress was consistently associated with patients' pain symptoms both prior to and following exercise in our study, explaining >25% of patients' pain.

The mechanisms underlying this exercise-induced hypoalgesia have been explored but are still not fully understood.[22,25,58,59] We found very interesting results when exploring the association between parasympathetic activity and oxidative stress and we therefore propose that exercise-induced oxidative stress responses might be finely regulated by parasympathetic activity. We have already shown that HRV is lower in patients with ME/CFS[31] and that it is further decreased in patients with ME/CFS but not in healthy subjects.[32]

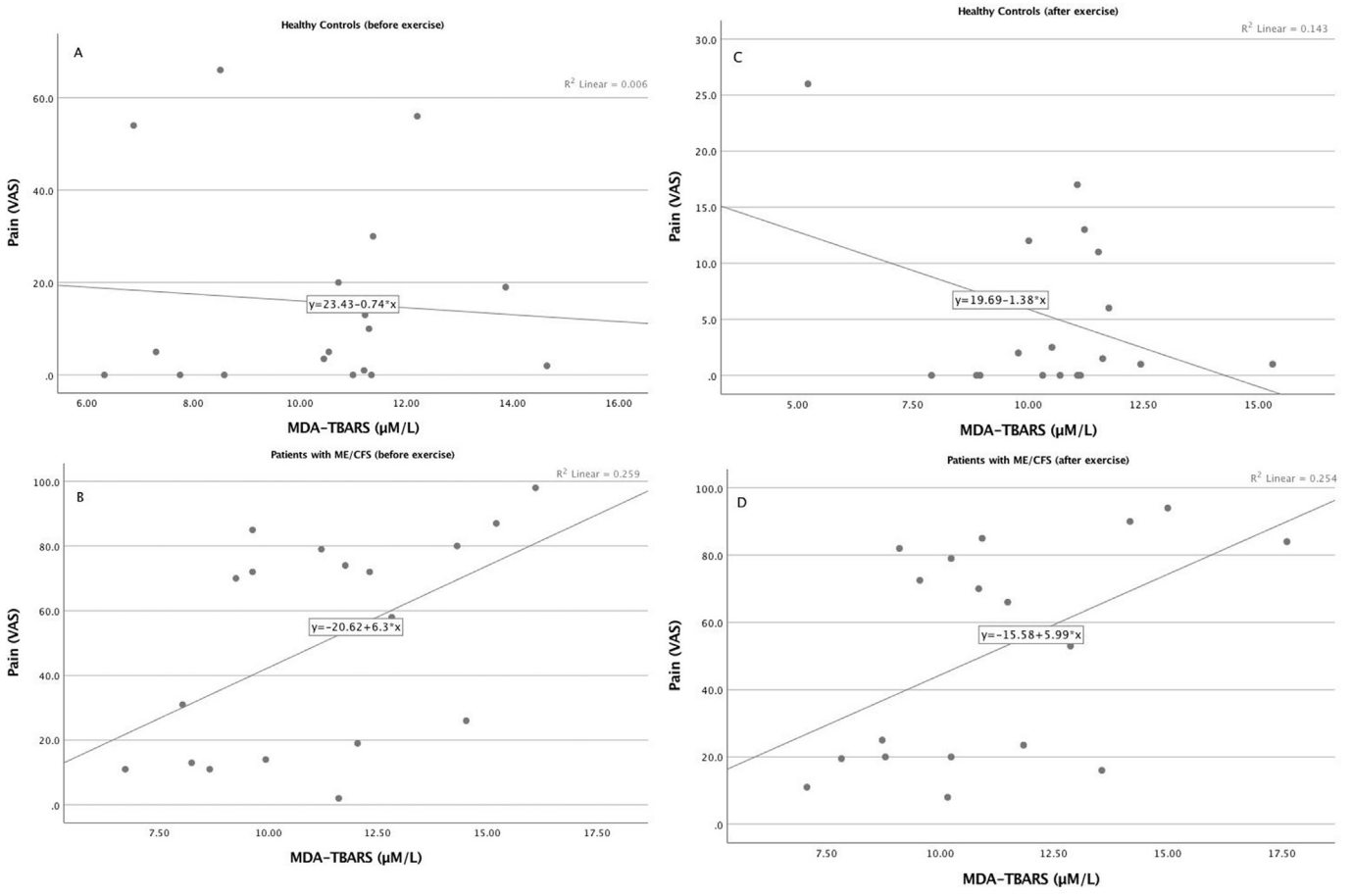

Figure 3. Associations between pain symptoms (assessed using a visual analog scale: 0 = no pain to 100 = worst pain imaginable) and oxidative stress levels before and after submaximal aerobic exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and healthy controls. Only patients showed statistically significant correlations (B and D).

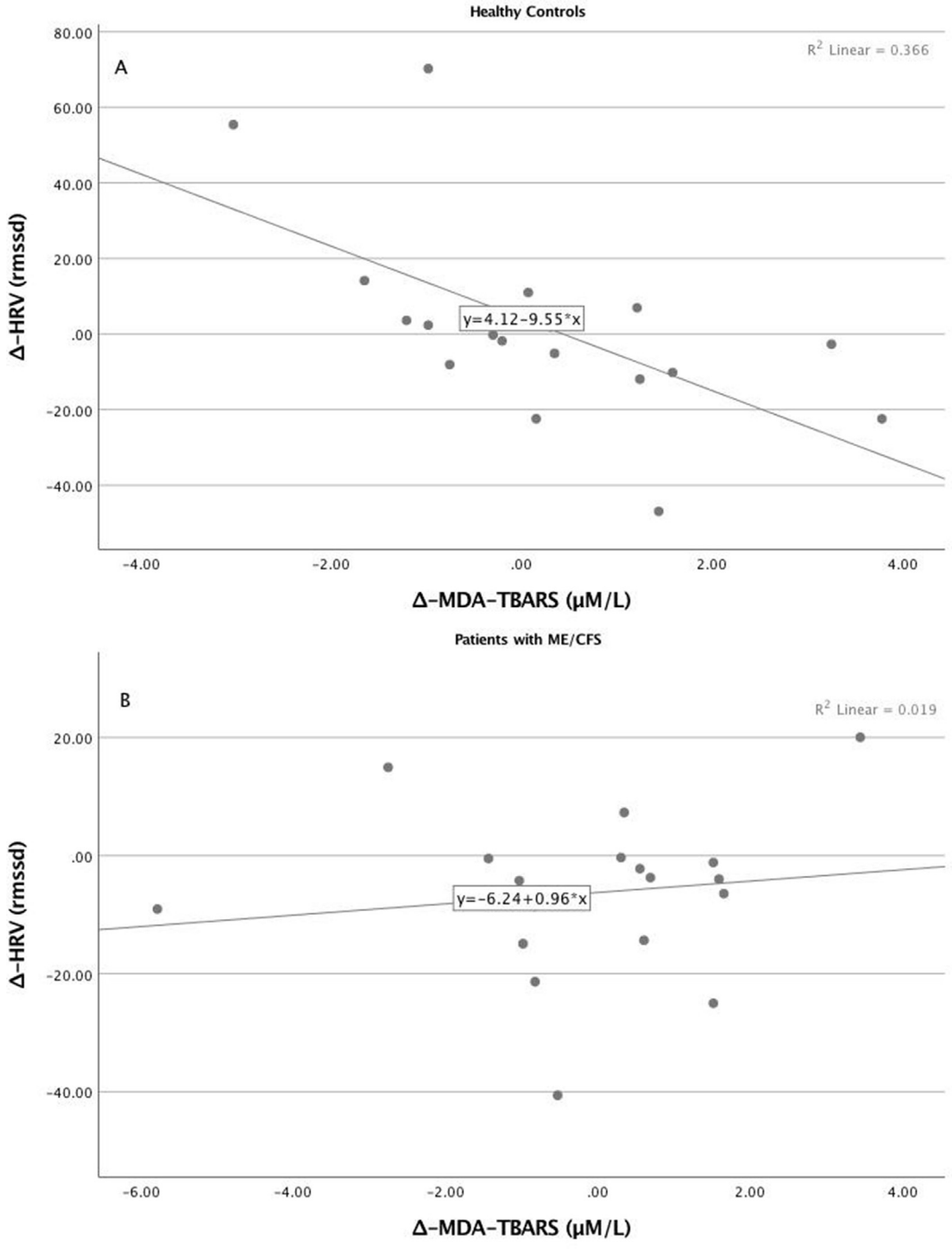

Figure 4. Associations between exercise-induced changes in parasympathetic activity (Δ HRV) and changes in Oxidative stress levels (Δ MDA-TBARS) in patients with chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS) and healthy controls. HRV = heart rate variability; MDA-TBARS = malondialdehyde—thiobarbituric acid reactive substances (this is a standardized method to measure lipid peroxidation, a measure thought to reflect oxidative stress); RMSSD = root mean square of successive differences.

Now we have found that exercise-induced changes in parasympathetic activity were strongly associated with changes in oxidative stress in healthy people, and that changes in the vagal activity can explain up to 36% of the change in oxidative stress level. In particular, the decrease in oxidative stress was associated with increases in both HRV and HF-HRV following exercise. Increased HRV reflects an increase in parasympathetic (vagal) activity.[60] That is, the more the increase in parasympathetic activity during exercise, the more the reduction in oxidative stress levels. This finding supports those from animal and preliminary human studies, suggesting an interplay between oxidative stress and the ANS,[34,35] and calls for further research on this potentially very relevant link. This association was found only in healthy controls, suggesting that it might be a normal physiologic response that may be disrupted in patients. Unfortunately, we failed to find an association between pain reduction and oxidative stress changes—which would have made our results more coherent. However, we did not take any measure of antioxidant capacity, which might be more relevant than pro-oxidant products when moderate exercise is employed.[61]

Our data should be interpreted with caution. First, oxidative stress was associated with pain in patients with ME/CFS, but exercise did not induce a significant change in oxidative levels. Second, the association between oxidative stress and parasympathetic activity does not refer to postexertional values, but rather the (pre−post) changes induced by the exercise bout. However, it is also true that symptoms worsening in people with ME/CFS are specifically related to physical exertion, so that exploring exercise-induced changes is potentially crucial to understanding their condition. Finally, we included measures of parasympathetic activity only: HF-HRV and RMSSD. HRV measures reflecting sympathetic activity such as LF-HRV and the LF/HF ratio, have been extensively criticized and deemed unreliable,[51−53] and we decided not to include them. Other measures have been recently proposed to assess sympathetic activity, in particular blood pressure variability.[62−64] A link between blood pressure and pain sensitivity has been found in patients with chronic pain.[65] Blood pressure changes have been linked to exercise-induced hypoalgesia[66]—suggesting a relevant role for the baroreceptor reflex.[67] However, beat-to-beat blood pressure registration is required to assess this relationship,[68] something that our devices could not measure.

In addition, other mechanisms could play a role in the pathophysiology of ME/CFS. Immune system alteration and inflammation are definitely major ones. Evidence shows that elevated levels of inflammatory cytokines released by degenerative peripheral tissues and immune cells can be part of the pathophysiology of ME/CFS as well as other persistent and widespread pain syndromes, such as fibromyalgia.[69−72] However, whether these mechanisms play a role in exercise-induced fatigue or hyperalgesia has yet to be investigated in detail. To date, available data on the link between immune system changes and postexertional malaise are inconclusive.[22] Future research exploring the immune system response is warranted, as it might be of outstanding clinical interest.

CONCLUSIONS

Trying to translate basic knowledge into clinical research is always challenging, especially when using indirect measures of complex phenomena such as ANS activity and oxidative stress. However, we believe our results are interesting and exciting insights into the as-yet underexplored link. While we found no exercise-induced changes in oxidative stress, we found consistent associations between pain symptoms and oxidative stress in patients with ME/CFS. On the contrary, there was a strong association between exercise-induced changes in ANS and oxidative stress changes in healthy controls. The more that parasympathetic activity increases following exercise, the greater the reduction in oxidative stress. We suggest that vagal activity exerts regulatory actions on oxidative stress during exercise. Patients with ME/CFS and other chronic pain conditions might lack this control, and that might account for the lack of exercise-induced hypoalgesia that is often found in these patients. Exploring these mechanisms could potentially lead to helpful and innovative treatments for chronic pain.

Conflicts of Interest

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J. Van Oosterwijck, J. Nijs, M. Meeus, I. De Wandele, and G. Moorkens contributed to conceptualization; J. Van Oosterwijck, M. Meeus, and G. Moorkens to data curation; A. Polli and K. Ickmans to formal analysis; J. Nijs, J. Van Oosterwijck, K. Ickmans and L. Paul to funding acquisition; A. Polli, J. Van Oosterwijck and L. Lambrecht to the investigation; J. Nijs, J. Van Oosterwijck, K. Ickmans, M. Meeus, and I. De Wandele to the methodology; J. Van Oosterwijck, M. Meeus, and G. Moorkens to project administration; U. Marusic, M. Meeus, G. Moorkens and L. Lambrecht to resources; J. Van Oosterwijck, K. Ickmans, U. Marusic, and L. Paul to supervision; J. Nijs, J. Van Oosterwijck, A. Polli, and I. De Wandele to validation; A. Polli, J. Van Oosterwijck and K. Ickmans to visualization; A. Polli wrote the original draft; and all of the authors contributed to reviewing and editing the manuscript.

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