Case Reports

Psychophysiological Fatigue Response of a Fibromyalgia Patient: A Case Control Report

Alejandro Rubio-Zarapuz
Universidad Europea de Madrid. Faculty of Sports Science. Spain

Jose Alberto Parraca*
Departamento de Desporto e Saúde, Escola de Saúde e Desenvolvimento Humano, Universidade de Évora, Portugal
Comprehensive Health Research Centre (CHRC), Universidade de Évora, Évora, Portugal

Pablo Tomas-Carus
Departamento de Desporto e Saúde, Escola de Saúde e Desenvolvimento Humano, Universidade de Évora, Portugal
Comprehensive Health Research Centre (CHRC), Universidade de Évora, Évora, Portugal

Santos Villafaina
Universidad de Extremadura, Facultad de Ciencias del Deporte, 10003 Cáceres, Spain
Departamento de Desporto e Saúde, Escola de Saúde e Desenvolvimento Humano, Universidade de Évora, Portugal

Vanda Lapao Silva
Family Health Unit – Lusitania, Rua do Ferragial do Poço Novo, Évora, Portugal

Vicente Javier Clemente-Suárez
Universidad Europea de Madrid. Faculty of Sports Science, Spain

ABSTRACT

Physical exercise is a useful model to assess the psychophysiological response of people with FM to fatigue. Thus, the present case-control report aimed to analyze the psychophysiological response of a young fibromyalgia patient and a control participant without fibromyalgia during a muscle fatigue protocol. With this aim, a 27-year-old female fibromyalgia patient with a 4-year diagnosis and a healthy 28-year-old female control participant were analyzed. The psychophysiological response of both participants was measured at 3 different points, baseline, right after the fatigue protocol (20 repetitions of knee flexion-extension of the dominant leg at 180º·s-1), and 6 min after ending the fatigue protocol. Results showed a more drastic cardiovascular response during the fatigue protocol with no increase in pain perception, and an increase in strength production in the fibromyalgia patient. Further on, differences were found on fatigue protocol recovery, not showing recovery at a subjective level (RPE), while showing it at an objective level (heart rate). On this line, we can conclude that the fibromyalgia patient analyzed presented differences in its psychophysiological response to a fatigue protocol compared to the control subject analyzed. Highlighting that after recovery, heart rate values indicate an objective recovery of the patient. While the rate of perceived exertion and pain visual scale increased showing how the patient's perception of recovery was not the same. Therefore, strategies to promote the recovery of people with FM are recommended considering the results of the present case control study.

As such, fibromyalgia patients' recovery and fatigue mechanisms should be further explored in future research.

Keywords: Fibromyalgia; case report; chronic pain; pain; fatigue; strength; exercise.

Introduction

Fibromyalgia is a chronic disorder mainly characterized by generalized musculoskeletal pain. With various health symptoms at social, mental, and physical level. Fatigue, stiffness, sleep disturbances and cognitive deterioration amongst the most common symptoms (Wolfe et al., 2010). On this line, fibromyalgia can also be associated with specific diseases such as rheumatic pathologies, psychiatric or neurological disorders, infections, and diabetes (Bellato et al., 2012). Further on, this syndrome´s etiology is still unknown, however, previous studies hypothesized genetics and/or stress to be related with the origin of fibromyalgia (Davis et al., 2014; Solak et al., 2014). Other authors mark various factors such as central and autonomous nervous system dysfunction, neurotransmitters, hormones, immunologic system, external stressors, and psychiatric aspects to have an influence on the development of this disease (Bellato et al., 2012). Further on, central sensitization is considered the main mechanism involved. Characterized by an increase in membrane excitability, synaptic efficacy, or a reduced inhibition of neuron's nociceptive pathways throughout the neural axis (Latremoliere & Woolf, 2009) increasing the response to central nervous system mediated stimulation(Meeus et al., 2013).

Furthermore, fibromyalgia also has a direct impact on patients' lives. As fatigue, and psychological and muscle symptoms limit patients from many normal activities such as cooking, cleaning the house, going for a walk. In fact, psychological disorders prevalence such as anxiety, somatization, dysthymia, panic disorders, PTSD, and depression have a higher prevalence in fibromyalgia patients compared to healthy population and patients with other rheumatic diseases (Clauw & Crofford, 2003; Giesecke et al., 2003). highlighting the possible impact of the inflammatory state in fibromyalgia symptomatology. Additionally, recent studies have found a link between inflammatory pathways and neurocircuitry in the brain. Showing the existence of interactions between inflammation and the brain which appear to promote the development of depression (Miller & Raison, 2016). On this line, previous authors have also found that patients with depression and fibromyalgia present an autonomic modulation disorder showing a higher sympathetic modulation compared to control sample (Clemente-Suárez, 2020; Villafaina et al., 2020). However, further research is necessary to better understand the involved mechanisms and implications.

Further on, as many factors contribute to the development of fibromyalgia, its treatment needs to be holistic with a multidisciplinary intervention (Giusti et al., 2017) based on patient education, exercise, and pharmacological and psychological treatments (Sarzi-Puttini et al., 2020). On this line, the most important factor for a successful treatment of Fibromyalgia is a prompt diagnosis and providing patients with information on the condition. Also, once the diagnosis has been done, a comprehensive assessment of pain, function and the psychosocial context should be carried out. With Fibromyalgia management taking the form of a comprehensive assessment of pain, function, and psychosocial context (Macfarlane et al., 2017). Therefore, non-pharmacological treatment options should be the first to consider based on availability, cost, safety issues and patient preference (Macfarlane et al., 2017). And, among non-pharmacological interventions, exercise is strongly recommended due to its effect on pain, physical function and well-being, availability, relatively low cost, and lack of safety concerns (Macfarlane et al., 2017). As with other diseases and disorders, exercise interventions should involve weight loss, aerobic and strength training accompanied by dietary modifications. Thus, reducing generalized inflammation characteristic of Fibromyalgia (Macfarlane et al., 2017). Weight loss will improve posture, wellbeing and reduce obesity-induced inflammation and peripheral nociceptive inputs (Schrepf et al., 2017). And aerobic exercise will improve pain and physical function in fibromyalgia patients. While resistance training will significantly improve pain (Macfarlane et al., 2017). However, care should be taken as these patients are usually deconditioned and affected by psychological factors (Busch et al., 2007). Furthermore, there is yet insufficient evidence to suggest superiority of one training modality over the other (Bidonde et al., 2014).

Therefore, subject Fibromyalgia patients to a strenuous fatigue protocol could help understand psychophysiological characteristics of fatigue and rest needs of Fibromyalgia patients. Allowing health care professionals to better structure exercise treatment for these patients by regulating the exercise rest ratio. Also, most of the scientific literature in people with FM and physical exercise interventions are focused on adults or older-adults (Carbonell-Baeza et al., 2011; Valkeinen et al., 2006; Villafaina et al., 2019). However, most of them were suffering from FM symptoms during decades without an official diagnose. Thus, it would be interesting to investigate young people with FM to better understand and manage this disease. In this regard, one of the non-pharmacological therapies with the highest level of evidence reducing FM symptoms is exercise (Busch et al., 2011). However, people with FM have fear or avoidance to physical exercise due to pain and fatigue (Leon-Llamas et al., 2022). For all these reasons, the present investigation was conducted with the objective of analyzing the psychophysiological response of a young fibromyalgia patient and a control participant without fibromyalgia in a muscle fatigue protocol. Results will allow to determine strategies to improve the recovery from exercise of people with FM.

Materials and Methods

Experimental approach to the problem

To reach the objectives of the study, we analyzed the psychophysiological response of a FM patient and a control participant before, after and 6 minutes after the completion of a standardized fatigue protocol. The CARE guidelines for clinical case report have been followed (Gagnier et al., 2014)

Participants

A FM female patient of 27 years of age and a 4-year diagnosis (169 cm, 99,8 kg, 34,9 Kg/m2, 41% adipose mass, 55,4% lean mass, and visceral adipose tissue index of 8) and a female, healthy control participant of 28 years of age (164 cm, 52,9 kg, 19,7 Kg/m2, 21,9% adipose mass, 75% lean mass and visceral adipose tissue index of 1). The patient manifested a level of 70 using a visual analogue scale, when 0 is no-pain and 100 the high level of pain that you can imagine. In addition, the participant manifested an 8 in the rate of perceived exertion (RPE), in a 6 to

20 scale, her mother also has a diagnosis of fibromyalgia, and, at the time of the evaluation, she was taking antidepressants (duloxetine, sertraline, trazodone, and pregabalin), analgesics, and muscle relaxants (paracetamol + thiocolchicoside and cyclobenzaprine) and antipsychotics (quetiapine). Further on the participant presented 2.04 mU/L of the Thyroid stimulating hormone (TSH).

The whole procedure was carried out following the Declaration of Helsinki (revised in Brazil, 2013) and passed by the ethics committee of the University of Évora (GD/44902/2019). All data was anonymously collected. Before participation, all participants were informed about the experimental procedures, indicating the right to withdraw from the study at any moment and providing a written consent.

Procedure

First, participants signed an informed consent. Secondly, basal autonomous modulation was evaluated through heart rate variability (HRV) with the participants being seated for 3 minutes in a room without noise and with controlled temperature and humidity. Data collection was performed by a Kalenji chest band (Bluetooth and ant+) and the program Golden Cheetah. The Kubios HRV software (University of Kuopio, Kuopio, Finland) was used to analyze the next HRV parameters: mean, maximum and minimum heart rate; percentage of adjacent NN intervals that differ from each other by more than 50ms (pNN50) closely correlated with Parasympathetic nervous system activity. Root mean square of successive differences between normal heartbeats, which reflects the beat-to-beat variance in HR and is the primary time domain measure used to estimate the vagally mediated changes reflected in HRV (RMSSD); Low frequency band (LF); High Frequency band (HF); short term variability (SD1) which reflects parasympathetic activity and long-term variability (SD2) which reflects the long-term changes of RR intervals and is considered an inverse indicator of sympathetic activity.

Subsequently, the following parameters were measured in 3 different moments: basal, right after the fatigue protocol and after 6 minutes of recovery.

- Fatigue and pain subjective perception on a visual scale (scale 0-100).
- RPE by the Borg Scale (scale 6-20 RPE).
- Isometric strength of the dominant hand with a manual dynamometer (Takei Kiki Koyo, Japón).
- Mean, minimum and maximum heart rate.

Fatigue Protocol

The fatigue protocol was conducted with an isokinetic system Biodex System 3 (Biodex Corporation, Shirley, NY) (Costa et al., 2022). The protocol began with a gen-eral 3-minute bicycle warm up in a Monark 839E (Monark Exercise AB, Sweden) at 50-60 rpm without resistance to avoid fatigue prior to the fatigue protocol. After the general warm up, a specific warm up ensued that consisted of 3 repetitions of knee flexo-extension of the dominant leg at free speed (Tomas-Carus et al., 2015). Later, participants initiated the fatigue protocol performing 20 repetitions of knee flexo-extension of the dominant leg at 180º· s-1 at the highest possible intensity (Cla-mente-Suárez et al., 2021).

Results

Heart rate measurements are available in Figure 1. In basal conditions, the fi-bromyalgia patient had a higher mean and minimum heart rate value than the control participant while having a lower maximum heart rate value. Right after the fatigue protocol all heart rate variables increased in both patients. With variables being lower in the fibromyalgia patient compared to the control subject and after 6 minutes of re-covery mean and minimum hear rate values decreased in both patients with maxi-mum heart rate values being maintained in both patients. After 6 minutes of recovery mean and maximum values were still higher in the control subject compared to the fi-bromyalgia patient while the minimum heart rate value after recovery was higher in the Fibromyalgia patient compared to the control subject.

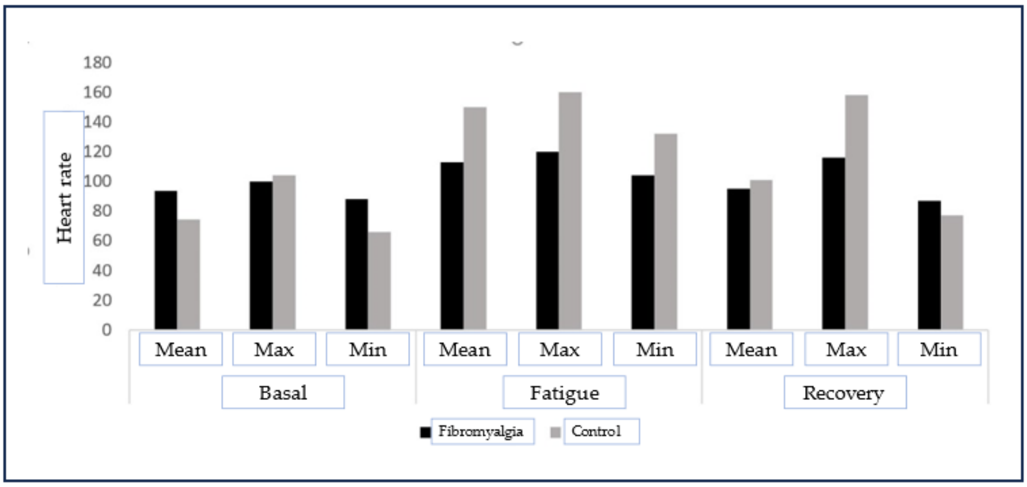

Figure 1. Heart rate values graphical representation measured in bpm. bpm: beats per minute. **RMSSD**: Square root of the mean of the sum of the squared differences between adjacent normal R-R intervals. **PNN50**: The percentage of differences between R-R in-tervals higher than 50 ms. **LF**: Low frequency. **HF**: High frequency. **n.u.**: Normalized unit. **SD1**: Poincaré Plot index of instantaneous recording of the variability. **SD2**: Poincaré plot index of overall variability.

Table 1 presents HRV basal data of participants, mean heart rate, maximum heart rate, RMSSD, pNN50, LF, HF, SD1 and SD2. With the fibromyalgia patient having higher mean heart rate, maximum heart rate, LF and lower RMSSD, pNN50, HF, SD1 and SD2 values than the control subject.

Table 1. Basal HRV of the participants.

	Fibromyalgia	Control
Mean heart rate (bpm)	93	73
Maximum heart rate (bpm)	101	88
RMSSD (ms)	11.6	71.5
PNN50 (%)	0	49.5
LF (n.u.)	90.8	31.1
HF (n.u.)	9.2	68.9
SD1 (ms)	8.2	50.7
SD2 (ms)	28	86.8

Table 2 presents participants' subjective perception and strength values. Values in the Fibromyalgia patient behaved as follows, fatigue visual scale increased from basal conditions to right after the fatigue protocol but did not increase nor decrease after recovery. Also, pain visual scale value was maintained from basal conditions to after the fatigue protocol but increased after recovery. On this line RPE value increased from basal conditions to right after the fatigue protocol and after recovery. And hand isometric value did not differ from basal to right after the fatigue protocol however, it increased after recovery. Further on the control patient fatigue visual scale increased from basal conditions to right after the fatigue protocol but decreased after recovery. While pain visual scale did not differ from 0 in any of the measurements. On this line, RPE values increased from basal conditions to right after the fatigue protocol but de-creased after recovery. And hand isometric strength values increased from basal con-ditions to right after the fatigue protocol but decreased after recovery respectively to both after the protocol and basal conditions.

Discussion

Clear differences can be appreciated in heart rate values measured in both pa-tients with heart rate being higher in basal conditions in the fibromyalgia patient compared to the control participant which could be explained by fibromyalgia patients more sedentary behavior decreasing cardiovascular function with a smaller heart producing a smaller cardiac output and thus, needing to be compensated by a higher heart rate. However, autonomic modulation also has a role to play and heart rate values correlate with the autonomous response in the fibromyalgia patient as a low RMSSD, pNN50 and high LF values among other parameters indicate a high sympa-thetic autonomous modulation contrary to the control participant who had lower heart rate values in basal conditions and as such his HRV parameters indicated a much more parasympathetic modulation of the autonomous nervous system. On this line, previous studies have shown how FM patients present an autonomic dysregulation in comparison to healthy control subjects (Villafaina et al., 2020). This autonomic dysregulation is marked by a higher sympathetic tone in basal conditions. Which can be one of the causes of a higher central temperature, blood microcirculation anomalies and disorders on the blood capillary level (Albrecht et al., 2013; Choi & Kim, 2015). Furthermore, autonomous nervous system modulation of the fibromyalgia patient concords with previous literature, showing an hyperactivation of the sympathetic branch as shown by the low values of RMSSD, PNN50, HF, SD1 y SD2 and the high values of LF (Table 1). This autonomic dysregulation with a marked sympathetic basal modulation has also been described in other pathologies of psychological base such as anxiety and depression (Clemente-Suárez, 2020). Both psychological conditions are normally identified in fibromyalgia patients (Ramiro et al., 2014). Further on, previous studies have shown that a sympathetic nervous system hyperactivity can have direct effects in different cortical regions, decreasing information processing and negatively affecting subject's subjective perception (Beltrán-Velasco et al., 2019; Delgado-Moreno et al., 2017, 2019). This autonomic

	Fibromyalgia			Control		
	Basal	Fatigue	Recovery	Basal	Fatigue	Recovery
Fatigue visual scale (0-100)	10	30	30	0	6	2
Pain visual scale (0-100)	70	70	80	0	0	0
Rate of per-ceived exertion (6-20)	8	10	12	6	10	6
Hand isometric strenght (N)	11	11	15	24	27	22,5

Table 2. Participants' Subjective perception and strength values.

dysregulation of the patient maintained in time could be another area to explore as a new approach for a more efficient pain treat-ment, taking into consideration the subjective character of this sensorial and emotional experience. Moreover, fatigue and pain visual scale and rate of perceived exertion were higher on the fibromyalgia patient in basal conditions in line with the higher heart rate parameters of the patient in basal conditions showing how psychological and subjective variables are intertwined with physiological parameters and allowing us to see how the pain caused by fibromyalgia can affect the patient and even in basal conditions the rate of perceived exertion is higher than a control participant. However, things differ after the fatigue protocol.

Moreover, TSH normal values range from 0.4 to 4.5 mU/L. As a rule, routinely and without clinical suspicion of thyroid pathology, only TSH is requested. When this is altered, then a further study with T3, T4, antibodies and eventually thyroid ultra-sound is requested. Therefore, as our patient had a value of 2.04 mU/L for TSH (inside normality) no further testing was requested as there was no suspicion of thyroid pa-thology (Sheehan, 2016).

Further on, right after the fatigue protocol, the fibromyalgia patient shows a di-minished cardiovascular response compared to the control subject which could be ex-plained by the decreased cardiovascular fitness of the fibromyalgia patient. On this line, analyzing the perceptive response of the fibromyalgia patient, we can see that the carry out of a high intensity activity did not produce an increase in the perception of pain. It only produced a light increase in fatigue and rate of perceived exertion. This is an important result as the connection between muscle quality and pain perception it's known. Showing how pain perception is higher when muscle weakness is high and muscle size is low (Latey et al., 2017). Additionally, body composition of the fibrom-yalgia patient shows a decreased muscle mass and high quantity of adipose tissue. This last fact could also be a determinant factor in pain perception as the negative effect of inflammation has been demonstrated in pain perception (Ji et al., 2016) and it has been shown that adipose tissue increases body inflammation parameters (Festa et al., 2001). Moreover, analyzing the rate of perceived exertion of the fibromyalgia patient and the control subject, we can see how the fatigue protocol produced the same rate of per-ceived exertion on both subjects through intense exercise (Figure 1). This response is important as it displays how the fibromyalgia patient even with a high pain perception can perform high intensity exercise with the same rate of perceived exertion as the healthy participant.

When we analyze the variables after six minutes of recovery, we observe how heart rate mean values of both participants are quite close however it does not trans-late on an equal effect of recovery on both subjects. As the control subject comes from a higher heart rate value right after the fatigue protocol which indicates a better recov-ery capacity than the fibromyalgia patient and if another measure was made after this one, we would probably observe that heart rate values would keep lowering until reaching baseline values. However, the fibromyalgia patient has already reached base-line values in only six minutes of recovery as the cardiovascular response wasn´t as great and baseline values were already high in this patient. Further on, looking at the maximum and minimum heart rate value we can discern that the control participant's heart rate fluctuates more than that of the fibromyalgia patient, again showing the autonomic dysregulation in comparison to healthy control subjects (Villafaina et al., 2020). Further on, the subjective perception of the fibromyalgia patient also fluctuates after this recovery, the fatigue visual perception scale is maintained from before the recovery period. However, the pain and the rate of perceived exertion both increased after the recovery period which illustrates how even if heart rate values indicate re-covery for this patient, the person does not perceive it that way. This could show an impaired recovery for fibromyalgia patients after fatigue. However, further research should be carried out focused on monitoring recovery for longer periods of time for fi-bromyalgia patients. Additionally, these findings also show how psychological and physiological factors should be considered when treating fibromyalgia patients.

On this line, isometric strength values also suffered variations throughout the study with values increasing after the fatigue protocol due to the activation that oc-curs after a high intensity exercise which normally produces an increase in force pro-duction values(Torres Piraua et al., 2017). In the control subject, this increase in force production happened right after the protocol and then it decreased after recovery. However, for the fibromyalgia patient the increase in strength values was delayed un-til after the recovery period which could be related to muscle activation and muscle function being impaired in fibromyalgia patients (Góes et al., 2016). On this line, strength values are lower in fibromyalgia patients which could be due to the afore-mentioned muscle function impairment or to more control mechanisms and muscle activity limitations than those solely of the organism (Thomas & Segal, 2004) that the patient may have developed during the disease. This way limiting the patient from performing activities at a real maximum volitive intensity.

Furthermore, the results obtained in this case control report open the door for fu-ture research on the psychophysiological response caused by programs based on in-tense physical activity in fibromyalgia patients with a wider sample than the one used in this study. However, it is true that getting a wider sample is not always easy when researching diseases as having access to patients can be hazardous.

Further on, the main limitations of this study would have been to not have moni-tored heart rate variability throughout the whole protocol as it could have yielded im-portant information regarding autonomic modulation in fibromyalgia patients during high intensity exercise which should be noted for future studies. And the difference between the BMI of the patient with fibromyalgia and the healthy control, this situa-tion can have a direct implication, as it can affect the physiological regulation and the psychometric profile of the subjects. This is something that will consider for future re-search where both the patient and the control individual should have similar charac-teristics apart from the disease. Additionally, fibromyalgia patients' recovery should be further studied as we observed a delayed post activation in force production and because RPE and pain perception were higher after recovery rather than right after the protocol. Further exploring the psychophysiological response of fibromyalgia patients to high intensity exercise could help physicians and exercise professional to better un-derstand this disease and to determine how high intensity physical activity could be beneficial for this condition.

Conclusions

We can conclude that the fibromyalgia patient analyzed presented differences in its psychophysiological response to a fatigue protocol compared to the control subject analyzed. Highlighting that after recovery, heart rate values indicate an objective recovery of the patient. While rate of perceived exertion and pain visual scale increased showing how the patient's perception of recovery was not the same. As such, fibrom-yalgia patients' recovery and fatigue mechanisms should be further explored in future research.

Author Contributions

Conceptualization, V.J.C.-S. and PTC; methodology, V.J.C.-S. and JAP.; investigation, V.J.C.-S. and VLS.; writing - original draft preparation, all authors; writing- review and editing, all authors; supervision, SV and JAP. All authors have read and agreed to the published version of the man-uscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki (revised in Brazil, 2013) and approved by the Institutional Review Board of the University of Évora (GD/44902/2019).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

All data are in the manuscript.

Conflicting of Interests

The authors declare no conflict of interest.

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ADDRESS FOR CORRESPONDENCE:

Jose Alberto Parraca, Departamento de Desporto e Saúde, Escola de Saúde e Desenvolvimento Humano, Universidade de Évora, Portugal, E-mail: jparraca@uevora.pt