Neuromuscular efficiency in fibromyalgia is improved by hyperbaric oxygen therapy: looking inside muscles by means of surface electromyography

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ABSTRACT

Objective. *Neuromuscular efficiency (NME) is impaired in fibromyalgia (FM). Hyperbaric oxygen therapy (HBOT) is a medical treatment using 100% of oxygen through an oxygen mask. HBOT in FM induces changes in cortical excitability and a secondary reduction in pain and muscle fatigue. However, there are still no direct data indicating changes in muscle fatigue. The aim of this study was to assess whether the reduction in muscle fatigue so far attributed to a central effect of HBOT can be directly detected by means of non-invasive sEMG as a change in NME.*

Methods. *The study was an observational longitudinal study on changes in NME induced by 20 sessions of HBOT at 2.4 atmosphere, in 22 patients with FM (3M; 19F) (age 49.8±9.5; height 164.7±7.5; weight 63.8±12.7). sEMG was recorded in single differential configuration from the biceps brachii muscle during the 30-second fatiguing contractions using linear arrays of eight adhesive electrodes.*

Results. *Evaluations made before and immediately after the first session showed that maximal strength did not change (T0 49±20 N, T1 49±19 N, p=0.792), thus suggesting that HBOT did not induce muscle fatigue or potentiation. After 20 sessions of HBOT, NME increased from 1.6±1.1 to 2.1±0.8 (p=0.050), whereas maximal strength, EMG amplitude and muscle fibre CV did not change.*

Conclusion. *HBOT did not improve muscle strength or change muscle fibre content, but improved the ability of the central motor command to generate the same effort (MVC) with fewer recruited fibres. Our sEMG findings underlined a modified central mechanism related to fibre type recruitment order, thus suggesting that muscle fatigue is not primarily a muscular problem, as also demonstrated by other authors with different methods.*

Introduction

Although its aetiology and efficacious treatment are still unclear, FM is a major problem for all National Health Services as many epidemiological studies have shown that affects a large number of people all over the world. A recent review of its prevalence in Europe has found that it affects 2.3% of the population as a whole and up to 3.9% of females, and the trend is similar in North America (1.9%, 2.9% of females), South America (1.12%, 2.45% of females), and Asia (1.64%, 3.24% of females) (1).

The main somatic symptoms of fibromyalgia are diffuse musculoskeletal pain, stiffness and fatigue, all of which are related to the muscle system and its functioning. Various attempts have been made to find specific alterations in muscle fibres using light microscopy, histochemistry, electron microscopy, and ultrastructural techniques, and the published results agree in suggesting local muscle hypoxia as a possible cause of the development of both specific and non-specific biopsy findings (for a short review see ref. 2).

Neuromuscular efficiency has been studied in conditions such as chronic heart failure (3) or hypoxia exposure (4) using multi-channel surface EMG (sEMG). Neuromuscular efficiency can be defined as the ability of the nervous system to recruit muscles and muscle fibres appropriately in order to produce a given effect, which is impaired in patients with fibromyalgia (5), thus raising the question as to whether fatigue is more centrally mediated than a clinical

epiphenomenon of local muscle hypoxia. The complexity of the syndrome is also reflected by the fact that pharmacological (6), non-pharmacological (7) and cognitive behavioural treatments (8) do not seem to be predictably efficacious.

Hyperbaric oxygen therapy (HBOT) is a medical treatment that enhances the body's natural healing process by means of the inhalation of 100% oxygen through an oxygen mask in which atmospheric pressure is increased and controlled. It has been used for a wide variety of conditions usually as part of planned overall medical care, and has led to promising results in the treatment of a number of painful orthopedic and rheumatological conditions (9), headache, complex regional pain syndrome, and FM (10, 11).

HOBT was proposed for FM on the hypothesis that it could act centrally by inducing changes in cortical excitability (12), on the basis of single-photon emission computed tomography (SPECT) findings that FM patients show abnormally high levels of activity in the somatosensory cortex, but reduced activity in the frontal, cingulate, medial temporal, and cerebellar cortices (13). Eftari *et al*. showed that HBOT normalised cortical excitability in a group of FM patients, and inferred a secondary reduction in pain and muscle fatigue on the grounds that the change temporally correlated with a clinical improvement on symptoms (12). However, there are still no direct data indicating changes in muscle fatigue.

The primary aim of this study was to assess whether the reduction in muscle fatigue so far attributed to a central effect of HOBT can be directly detected by means of non-invasive sEMG of the biceps brachii muscle as a change in neuromuscular efficiency before and after treatments repeated over time in a group of patients with fibromyalgia.

Methods

Patients

Twelve of an initially unselected group of 40 female patients with a confirmed diagnosis of fibromyalgia made by two experts (SP, FA) on the basis of the 1990 and 2010 American College of Rheumatology (ACR) criteria at the Department of Rheumatology, University Hospital Luigi Sacco, Milan, did not consent to participate in the study mainly because the length of the protocol and logistical problems (distance from the hospital).

Patients with 1) inflammatory causes of pain; or muscle pain caused by conditions such as vitamin D deficiency 2) alcohol/drug abuse or dependence; 3) significant difficulty in maintaining attention or understanding clinimetric evaluation instructions; 4) any clinical condition that may interfere with the assessment; 5) pregnant women or potentially childbearing women not using an adequate method of birth control; and 6) any of the following medical conditions that preclude safe HBOT treatment: a) severe cognitive impairment; b) current mood episodes, claustrophobia or seizure disorder; c) active or severe pulmonary disease, previous thoracic surgery or pneumothorax; d) a history of severe heart disease; e) chronic or acute sinusitis/otitis media or major eardrum trauma; and f) a history of bleomycin-including chemotherapy or current chemotherapy were excluded from the study.

The remaining 28 were sent to the Hyperbaric Unit, Habilita Hospitals & Research, Zingonia (Bergamo) to be assessed by an expert for their eligibility for HBOT, and three were considered ineligible because of the presence of a clinical contraindication to the treatment (14).

Finally, of the 25 patients enrolled in the study, two dropped out because of the side effects of HBOT (15, 16), and one who was unwilling to continue the study because of unforeseen family problems. The study was therefore completed by 22 patients (3 males and 19 females) (mean age 50.6, min 28 max 64 years; mean height 164.7, min 164 max 175 cm; mean weight 66.9, mean 45 max 95 kg). All the patients received analgesic treatment (paracetamol, tramadol) at stable doses before the enrollment in the study protocol. All the patients were in controlled rehabilitation therapy, but no one was practicing heavy physical activity at the moment of enrollment. Ten patients were receiving duloxetine (mean dose 30 mg/daily), five patients were treated with pregabalin (mean dose 75 mg/daily), four patients were treated with amitriptyline (mean dose 50 mg/daily).

The sEMG experimental protocol was carried out by two neurophysiology technicians supervised by a trained neurologist (RC) who was blinded to the treatment. The data were analysed by AR,GB. All of the participants gave their written informed consent before taking part in the study, and the protocol was approved by the Scientific Technical Committee of Habilita (no. 6/2016).

EMG protocol

The subjects were familiarised with the sEMG device by being asked to make ten sub-maximal isometric contractions at 90° of elbow flexion (0°=full extension), and were then asked to make two maximal voluntary contraction (MVCs) separated by three minutes rest in order to avoid any cumulative effects. If the MVCs differed from each other by more than 5%, a third MVC was required. Each attempted MVC lasted 3–5 seconds, during which the subjects were given strong verbal encouragement to maximise their effort, and received visual feedback generated by signal acquisition software. The greatest MVC was used to calculate submaximal loads.

Three minutes after the last MVC, the subjects were involved in two isometric contractions at respectively 30% and 60% of the torque exerted during the MVC separated by a 5-minute interval. They received visual feedback about the actual torque exerted, and were instructed to maintain constant the target elbow flexion torque at 90° for 30 seconds. They were also provided with standardised encouragement to keep the exerted torque as stable as possible.

EMG measurements

The myoelectrical signals were recorded in single differential configuration from the long head of the biceps brachii muscle during the 30-second fatiguing contractions using linear arrays of eight adhesive electrodes separated by an inter-electrode distance of 5 mm (OT Bioelettronica, Turin, Italy). Before the arrays were positioned, the

skin was slightly abraded with paste and cleaned with water in accordance with the skin preparation recommendations of the Surface Electromyography for the Non-invasive Assessment of Muscles (SENIAM) project (17).

The optimal position and orientation of the array was sought on the basis of visual inspection of the sEMG signals. The sites showing the clear propagation of muscle fibre action potentials and the main innervation zones were identified using a dry linear array of 16 electrodes separated by an inter-electrode distance of 5 mm (OT Bioelettronica). The adhesive electrode arrays were then placed parallel to the muscle fibres proximal to the innervation zone in which the unidirectional propagation of the motor units (MU) action potentials was detected. In order to ensure correct electrode-skin contact, the electrode cavities were filled with 20-30 μl of conductive paste (Spes-Medica, Battipaglia, Italy), and the arrays were fixed using an extensible dressing (Fixomull®, Beiersdorf, *D*).

The sEMG signals were amplified, sampled at 2048 Hz, bandpass filtered (3 dB bandwidth, 20-450 Hz, 12 dB/oct slope on each side), and converted to digital data using a 16-bit A/D converter (EMG-USB2+, OT Bioelettronica). Samples were visualised during acquisition, and then stored on a personal computer using OT BioLab software (v. 1.8, OT Bioelettronica) for further analysis.

HBOT

Treatments were done using a hyperbaric chamber GAMMA, GALEAZZI S.p.A. n° 510/88, ISPESL n° SP 78-88. capacity: 16 places (15 patients + 1 doctor).

Type of delivery of O2: the oxygen, stored in liquid form in a specific cryogenic tank, is gasified, normalised (ambient temperature and pressure 10 bar approx.) and supplied 100% pure to patients by means of individual breathing systems. The breathing system consists of a silicone oronasal mask with oxygen delivered by a strigger system (average resistance 20–25 mm water column) which reduces the pressure at the environmental levels. Redundant systems of analysis of the percentage of oxygen present in the hyperbaric environment are present to ensure that the safety parameters are not exceeded (< 22%).

Delivery times: therapies are normally divided into 3 periods of oxygen breathing of 20–25 minutes. Taking into account the times necessary for compression, decompression, oxygen respiration and pauses between the aforementioned periods, the indicative duration of an ordinary therapy was 91 minutes.

O2 dispensation control: the mask is provided of a specific analysis system able to measure the percentage of oxygen present in the mask and available for the patient.

Although oxygen is delivered to the patient in pure 100% form, there are always minimum leakages in the contact between the mask and the face of the patient (the oxygen comes out and the ambient air enters) with a real percentage of oxygen in the mask reduced to an average of 95%. Below this percentage signals are activated, alerting the personnel within the chamber to check the current situation (mask not positioned, uncooperative patient, etc.) This monitoring takes place in real time and with each patient's control step every 3–4 minutes.

Data analysis

The sEMG signals were visually inspected in order to select the best channels to use for variable estimates. The muscle fibre conduction velocity (CV) of the sEMG signals were computed off-line among all the selected channels using numerical algorithms (18) and non-overlapping signal epochs of 0.5 seconds. CV was computed as e/d, where e is the inter-electrode distance and d the delay between the signals obtained from the two double differential arrays positioned 5 mm apart (the value of d was obtained by identifying the time-shift required to minimise the mean square error between the Fourier transforms of the two double differential signals). The correlation coefficient between the two adjacent double differential signals was calculated and, if it was less than 0.8, the recorded signals were excluded from the analysis.

The fractal dimension (FD) was calculated using the box-counting method (19) (20). The mean power spectral frequency (MNF) and FD estimates were computed using non-overlapping signal epochs of 0.5 seconds and were averaged among all of the accepted channels. The data were analysed using custom-written software in MATLAB R2014a (Mathworks, Natick, MA, USA).

The maximum torque of each MVC was determined, and the instant at which it occurred was used to calculate the EMG variables. In the case of fatiguing contractions, it has been demonstrated that linear regression is the best model for fitting EMG data during sub-maximal isometric contractions (21), and so linear regressions were used to calculate the rate of change in the EMG variables (calculated as the percentage ratio between the change in the EMG estimate in one second and the initial value, and expressed as %/s). Neuromuscolar efficency (NME) was calculated as the ratio between force and muscle fibre CV (22).

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of data distribution and, if the data were not normally distributed, they were log-transformed before statistical analysis and back-transformed to obtain descriptive statistics. Student's *t*-tests for independent samples were used to compare maximal force and the EMG values at T0 *vs*. T1 (acute effects) and pre- *vs*. post HBOT treatment (cumulative effects). The statistical analyses were made using SPSS statistics software (version 20.0, IBM Corporation, Somers, NY, USA), and a p-value of <0.05 was considered statistically significant. The data are all expressed as mean values ± SD.

Results

EMG results (acute effects: T0-T1)

An evaluation was made before and immediately after the first session. Maximal strength did not change after one session of HBOT (T0 49±20 N, T1 49±19 N; $p=0.792$), thus suggesting that it did not induce muscle fatigue or potentiation. There was also no change in conduction velocity (CV: T0 3.97±0.97 m/sec, T1 4.13±0.45 m/sec; $p=0.4557$) or neuromuscular efficiency (NME: T0 1.4±0.6, T1 1.3±0.8;

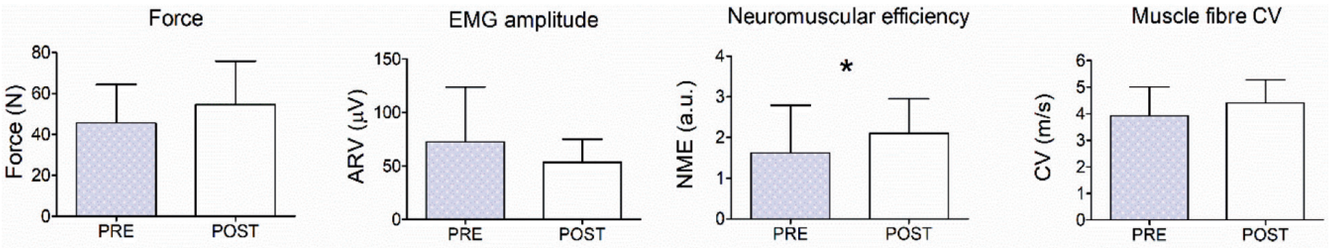

Fig. 1. Mean mechanical and electromyographical (EMG) values recorded during MVC (Maximum Voluntary Contractor); average rectified EMG amplitude; NME (*i.e.* the ratio between force and ARV); and muscle fibre CV. *p=0.050.

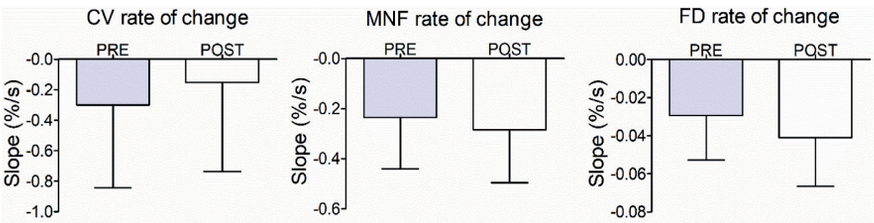

Fig. 2. Mean (SD) rate of change in EMG variables during the fatiguing contraction (30 seconds at 60% of maximal force): muscle fibre CV; mean power spectra frequency of the EMG signal (MNF); fractal dimension of the EMG signal (FD). There were not statistically significant differences between PRE *vs*. POST.

p=0.695), but average rectified value (ARV) decreased from 77±48 μV to 72±51 μV (p=0.024).

EMG results pre- vs. post-MCV (cumulative effects: T1-T20)

The mechanical and EMG variables recorded during the MVC are shown in Figure 1. There was no difference in maximal strength, EMG amplitude or muscle fibre CV before and after the intervention (p>0.3), but NME (*i.e.* the ratio between EMG amplitude and force) increased from 1.6±1.1 to 2.1±0.8 (p=0.050).

The rate of change in the EMG variables (used as indices of the myoelectric manifestation of fatigue) are shown in Figure 2. None of these variables were affected by the intervention (p>0.3).

Discussion

FM is a major cause of chronic widespread pain, and its general population prevalence of 2.3% makes it a considerable burden on National Health Services because of the delays in making a correct diagnosis (23) and very late referrals for rehabilitation. The most disabling aspects of the syndrome are pain and fatigue, but there may also be various combinations of other symptoms, the most frequent of which are non-refreshing sleep, mood disturbances, cognitive impairment, and a sense of memory loss. All of these symptoms and signs are related to region-specific anatomical changes in grey matter volume, central sensitisation with decreased functional connectivity in the descending pain-modulating system, and increased activity in the so-called pain matrix (24). It is therefore a complex and heterogeneous clinical condition that always reduced the patients' quality of life and leads to increasing physical, functional and emotional disability.

Its complexity is also reflected in the substantial lack of efficacious pharmacological and non-pharmacological treatments, whether they are used alone or in combination (6, 23). A wide range of non-pharmacological treatments have been tried, including various types of exercise, cognitive-behavioural therapy, physiotherapy, physical therapy including transcutaneous electrical nerve stimulation, LASER treatment of trigger points, heat and cold, balneotherapy and acupuncture (7, 25). HBOT has also been suggested because, under normal circumstances, oxygen is transported throughout the body only by red blood cells, whereas HBOT allows oxygen to be carried into all body fluids, plasma, lymph, bone and central nervous system fluids, and areas where blood circulation is diminished or blocked (26). *In vitro,* HBOT increases cell metabolism, reduces apoptosis, alleviates oxidative stress, and increases neurotrophin and nitric oxide levels by enhancing mitochondrial function in neurons and glial cells, and it may even promote the neurogenesis of endogenous neural stem cells (27, 28).

On the basis of these premises and MNF findings of altered cortical activity in FM patients, two Israeli groups (10-12) have evaluated the efficacy of HBOT in improving fibromyalgia symptoms by rectifying the typically altered brain functions. Both groups suggest that the clinical improvement is due to a primary improvement in central functions that is only secondarily reflected on muscle fatigue and pain.

The aim of this study was to look directly at muscle in order to assess whether the rearranged cortical activity induced by HBOT can really improve neuromuscular efficiency and therefore muscle function. To this end, sEMG was used as a widely accepted and reproducible means of evaluating muscle fatigue because its variables correlate with acute alterations in motor unit recruitment strategies and/or chronic changes in the number or size of muscle fibre types that reflect muscle biopsy findings and can be used to foresee the mechanical and functional impairments observed in biomechanical and clinical studies, including neuromuscular efficiency and the early development of fatigue (18, 22).

We have previously used sEMG to observe altered neuromuscular efficiency in FM patients (5), whose muscles simply work inefficiently rather than showing any specific alteration capable of explaining pain and muscle fatigue, and these seems to be related to a failure in central control due to an alteration in suprasegmental control. These conclusions are supported by the find-

ings of the present study showing the same sEMG picture in the pre- HBOT tests: *i.e*. patients with FM are affected by neuromuscular inefficiency that is mainly due to altered central motor drive. As there were no changes in muscle fibres, these findings suggest that HBOT acted at central level by inducing a change in adopted strategies, optimising mechanical output, and reducing the myoelectrical manifestations of fatigue. This possibility has previously been demonstrated in healthy subjects using a different conditioning treatment (29-31).

In terms of the acute effects of HBOT on sEMG parameters, evaluations were made before and immediately after the first session showing that maximal strength had not changed (T0 49±20 N, T1 49±19 N, p=0.792), thus suggesting that HBOT did not induce muscle fatigue or potentiation. However, after 20 sessions of HBOT, neuromuscular efficiency (*i.e*. the ratio between EMG amplitude and force) increased from 1.6±1.1 to 2.1±0.8 (p=0.050), whereas maximal strength, EMG amplitude and muscle fibre CV did not change.

In other words, HBOT did not improve muscle strength or change muscle fibre content, but improved the ability of the central motor command to generate the same effort (MVC) with fewer recruited fibres. Our sEMG findings underlined a modified central mechanism related to fibre type recruitment order, thus suggesting that muscle fatigue is not primarily a muscular problem, as also demonstrated by other authors with different methods.

This study has some limitations: it was not a double-blind RCT, and it used different HBOT parameters from those used by the Israeli groups. However, a double-blind RCT did not seem to be practical because of the high risk of dropouts due the length of the treatment (20 sessions of approximately 90 minutes). Moreover, all of the enrolled patients were in controlled rehabilitation and had undergone a long list of previous physical therapies: the introduction of another control would have led to a substantial bias.

In relation to the HBOT parameters used, there was a general agreement among the authors that a treatment duration of 40 sessions was not realistic in our local situation because the patients attending the recruiting centre came from all over Italy. We therefore decided to reduce the number of sessions from 40 to 20, and to increase chamber pressure to 2.4 atm instead of using the 2 atm used in the other experiments. We are aware that the statistical significance of the improvement in NME observed in our study may have been due to the reduction in the number of sessions, which raises the question of the right HBOT dose for FM. This is fundamentally important not only because the length of the treatment may be difficult for the patients to cope with, but also (and more importantly) because HBOT is a recognised pharmacological treatment (30) and the appropriate dose has to be carefully assessed. There is therefore a need to develop HBOT protocols and establish the intensity (O_2 atm) and duration and number of individual sessions for patients with this specific pathology, all of which will require more research and a shared consensus concerning the best treatment/dose.

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