Abnormal muscle membrane function in fibromyalgia patients and its relationship to the number of tender points

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ABSTRACT

Objective. *Fibromyalgia (FM) is a disorder characterised by chronic widespread pain in soft tissues, especially in muscles. Previous research has demonstrated a higher muscle fibre conduction velocity (CV) in painful muscles of FM patients. The primary goal of this study was to investigate whether there is also a difference in CV in non-painful, non-tender point (TP) related muscles between FM patients and controls. The secondary goal was to explore associations between the CV, the number of TPs and the complaints in FM.*

Methods. *Surface electromyography (sEMG) was performed on the biceps brachii muscle of female FM patients (13) and matched healthy controls (13). Short static contractions were applied with the arm unloaded and loaded at 5% and 10% of maximum voluntary force. The CV was derived by cross-correlation method (CV-cc) and inter-peak latency method (CV-ipl). TP score and Fibromyalgia Impact Questionnaire (FIQ) were performed in all participants. Correlations were calculated between the CVs, TP score and items of the FIQ.*

Results. *In FM patients, the CV was higher than in the controls (CV-cc p=0.005; CV-ipl p=0.022). The CV was correlated with the number of TPs in FM patients (r=0.642 and 0.672 for CV-cc and CV-ipl, respectively). No correlations were found between the CV and any aspect of health status on the FIQ.*

Conclusion. *The results demonstrate abnormally high muscle membrane conduction velocity in FM, even in non-TP muscles. In addition, a relationship has been found between the high membrane velocity and the number of TPs.*

Introduction

Fibromyalgia (FM) is one of many unexplained disorders, with a high prevalence and large impact on the functioning of the patients. FM is characterised by chronic widespread pain, with painful spots known as tender points (TPs) (1-3). Although the causes are not clear, it is generally accepted that in FM and in its various related disorders dysregulation of control processes at several levels of the central nervous system plays an important role (4-8).

Since musculoskeletal pain is a major complaint, several studies have been dedicated to muscular physiopathology in FM. In biopsies of the painful muscles of FM patients only non-specific changes have been found (9, 10). Electromyographic examination has revealed that a *painful* trapezius muscle of FM patients (11), as well as a *painful* trapezius of patients with chronic neck pain (12) – which is considered a disorder related to FM – has higher muscle fibre conduction velocity (CV) than a muscle of healthy subjects. The investigators suggest that this difference might be due to local muscular changes in histopathology and microcirculation in FM (11).

The question arises whether the higher CV in FM patients could be a general rather than a local phenomenon, for example a property of muscle membrane. In the present study we tried to answer this question. Therefore we compared the CV of FM patients and healthy controls in a muscle that was clinically not painful and was not related to TP site (non-TP related). Such a muscle is the biceps brachii muscle (BB).

The primary goal of the present study was to investigate whether the CV in a non-TP related BB muscle of FM patients differs from that of healthy subjects. The second goal was to examine whether there is an association between CV and the symptoms and complaints, especially the number of TPs in FM patients.

Subjects and methods

Subjects

Thirteen female FM patients and 13 healthy women volunteered for the ex-

periment. All fulfilled the 1990 American College of Rheumatology (ACR) diagnostic criteria (1), and had been diagnosed by a rheumatologist. We chose to apply the 1990 ACR criteria because they are useful in identifying and strictly defining an FM group (2). Patients were recruited from the Association of Fibromyalgia Patients by personal contact and also through the Association website. Control subjects were healthy sedentary women, friends or neighbours of the patients. The groups were matched for age, height and body mass. The inclusion criteria for patients were: primary fibromyalgia (*i.e.* no concurrent rheumatologic disease was allowed) (13); female; aged between 25 and 55 years; complaint for at least two years; and the presence of at least 11 TPs (out of the 18 specific sites) (1). Exclusion criteria were: severe FM requiring the use of a wheelchair; the use of orthoses; pain in the shoulder, elbow or wrist of the dominant arm (because such devices and pain locations would have influenced the subject's performance during the sEMG procedure); obesity (defined as a body mass index >30); co-morbidity with diabetes mellitus, hypo- or hyperthyroidism, and polyneuropathy or myopathy (because these diseases can influence the CV results); and the use of medicines, drugs or tobacco (only sporadic use of paracetamol was allowed). Because we aimed to investigate clinically non-painful muscles, subjects were excluded when, on examination, palpation pain was stated at the insertions of the BB muscle. Subjects were also excluded when the thickness of their upper arm skin layer (at the spot where the electrodes were to be placed) exceeded 10.0 mm, because skin thickness influences the CV estimates (14). Patients involved in legal procedures concerning disability or employment were also excluded.

Sample size. Since sEMG studies are usually performed using very small samples and there are no criteria available for defining clinically relevant differences, sample size was calculated based on the ability to detect at least a strong correlation between the CV and the symptoms and complaints of FM patients (r=0.6, power=80%, α=0.05, one-sided, required n=13).

Ethics

The protocol was conducted according to the Declaration of Helsinki and was approved by the local ethics committee (Medisch Spectrum Twente, Enschede, the Netherlands). All participants gave their written informed consent.

Experimental set-up

In our protocol, we applied static contractions, also called position tasks (15). We used low force levels because in the previously mentioned two studies on the painful muscles (see introduction), the higher CV in FM was found at low force levels (11, 12). In addition, low forces are more usual in daily living.

The method used has been described in detail in previous studies (16, 17). Maximum voluntary contraction force (MVC) of elbow flexors was measured with a hand-held dynamometer (Lameris Instruments, Utrecht, The Netherlands). During the experiment, the subjects were seated in a chair. The upper arm was slightly abducted and comfortably supported at 45° of shoulder flexion; the forearm was free and supinated. Subjects were asked to hold the forearm horizontally (elbow angle 135°). An individually adjustable horizontal bar was used showing the subjects the position at which the lower arm was really horizontal. The position was held for 6–7 seconds; the measurements were performed during 4 seconds. Three levels of force were applied: unloaded, 5% and 10% of MVC. Every test was repeated three times for each force level. In the loaded tests a bag filled with lead and sand was placed in the palm.

EMG recording and data processing

Measurements were performed on the short head of the BB of a dominant arm (17). A surface electrode array consisted of three gold-coated electrodes (Harwin, P25-3526), diameter 1.5 mm, with a 15 mm distance between the electrodes. The electrode array was placed parallel to the muscle fibres (18). Bipolar derivation was made from the proximal to distal direction, producing two differential signals. A correlation coefficient between the signals was accepted at r>0.7 (18, 19). The signals were amplified (gain 2,000 to 10,000 times) and band-pass filtered at 2-250 Hz by EMG apparatus (Viking IV, US). The signals were digitised and stored on a personal computer (sampling 10 kHz, 12 bits acquisition). Data were analysed with LabVIEW version 6.1. In order to strengthen confidence in the results, the CV was measured using two methods, the CC method (20) and the IPL method (17, 21), CV-cc and CV-ipl, respectively. The peak selection algorithm has been described previously (17). In both CC and IPL methods, the CV calculations were performed over 2.0 s signal epochs.

The skin temperature was measured with an electronic thermometer (NTC type, Viking, US), the sensor was placed ~ 5 cm proximally from the derivation electrode. The skin thickness was measured with callipers, on the spot where the electrodes were placed.

Tender points

The same experienced observer (physiotherapist) examined each participant by manual palpation of the 18 body sites defined in the 1990 ACR criteria for FM (1). The TP palpation is considered positive at a pressure of 4 kg/cmq (see the 1990 ACR criteria). The TP score was calculated as the number of sites where the patient stated that the palpation was painful (range 0 to 18).

Fibromyalgia impact questionnaire (FIQ)

All participants completed a validated Dutch version of the FIQ (22, 23). The FIQ is a ten-item questionnaire specifically designed to assess the current health status of people with FM. The first item contains ten sub-items with 4-point rating scales about physical function. Items 2 and 3 ask for the number of days the individual felt well, and the number of days off work, during the past week. Further, the questionnaire contains seven visual analogue scales (VASs) for inability to do job, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. The scores for each item were standardised so as to range from 0 to 10, with higher scores indicating greater impairment.

Statistics

For analyses of the CV, a repeated measures model of ANOVA was used (24) that included the within-subjects factor 'force' with 3 levels (unloaded, 5% and 10% of MVC) and the between-subjects factor 'group' with two levels (FM group and controls). If significant interactions appeared between the factors force and group, then *post-hoc* analyses were applied for every group using the factor 'force'. To evaluate associations between variables, Pearson's correlation coefficients were calculated. If required, Student *t*-tests or Mann-Whitney U-tests were applied. The analyses were performed using SPSS 13.0 statistical software. $p<0.05$, two-tailed, was used to identify statistical significance.

Results

Participant characteristics

Characteristics of the subjects are summarised in Table I. The strength was significantly lower in the FM group than in controls ($t(24)=2.8$, $p=0.011$). As it was expected, the number of TPs was higher in the FM group than in controls ($p<0.001$) and FM patients scored significantly worse on all relevant FIQ items (Table II). The distribution of TP sites in FM group and controls is shown in Table III.

Muscle fibre conduction velocity (CV)

The CV, as obtained by both the CC and IPL methods, was significantly higher in the FM group than in controls (between-subjects effects: CV-cc $p=0.005$; CV-ipl $p=0.022$). The results are shown in Fig. 1. When measured by the IPL method, the CV changes on forces differed between groups: the CVs of the FM group did not alter whereas those of controls increased with increasing forces (interaction force x group $p=0.049$; effect of force in FM group $p=0.41$; in controls $p=0.05$). This indicates that the FM patients tended to produce a high CV still at the lowest force levels, *i.e.* when the arm was unloaded.

CVs measured by the CC and IPL methods were highly correlated ($r=0.83$, $p<0.001$). However, the CVs measured by the CC method were higher than those measured by the IPL method; this applied to both groups (Fig. 1a and 1b) (paired samples *t*-test for all $p<0.001$; FM group $p<0.001$; controls $p<0.001$).

Correlations between sEMG and clinical signs and complaints

A positive association was found between the number of TPs and the CV in the FM group (CV obtained cumulatively from 3 force levels: CV-cc $r=0.642$, $p=0.018$; CV-ipl $r=0.672$, $p=0.012$) (Fig. 2). No correlation was found between the duration of complaints and the CV or between the duration of complaints and the number of TPs (Table IV). Neither was a correlation found between the strength and the CV in FM group ($r=-0.103$, $p=0.74$). No significant correlation was found between the number of TPs in the FM group and the

Table I. Characteristics of the subjects.

	FM* patients (n=13)	Controls (n=13)	*p*-values
Age (years)	43 (5)	42 (7)	0.83
Height (cm)	168.1 (7.0)	171.8 (5.9)	0.15
Body mass (kg)	69.3 (13.1)	67.2 (7.1)	0.62
Voluntary maximum strength (N)	92.9 (20)	113.7 (18.6)	0.011
Duration of complaints (years)	9.1 (5.1)	N.A.	N.A.
Number of tender points	14 (3)	2 (2)	<0.001
Skin thickness (mm)	7.8 (0.8)	5.5 (0.8)	0.057
Skin temperature (°C)	30.3 (1.0)	30.2 (0.8)	0.69

Values are mean (SD). All subjects are women. *Fibromyalgia.

Table II. Fibromyalgia impact questionnaire

	FM* patients (n=13)	Controls (n=13)	*p*-values
Physical function	3.7 (2.6)	0.1 (0.2)	<0.001
Days felt good	5.8 (3.4)	0.1 (0.4)	<0.001
Work days missed [a]	4.0 (5.5)	0.0 (0.0)	N.A.
Job ability	5.7 (2.5)	N.A.	N.A.
Pain	5.6 (2.0)	0.0 (0.0)	<0.001
Fatigue	5.3 (3.6)	0.4 (0.9)	<0.001
Morning tiredness	6.5 (2.9)	0.8 (1.8)	<0.001
Stiffness	5.2 (3.1)	0.1 (0.3)	<0.001
Anxiety	2.7 (2.2)	0.3 (0.7)	0.002
Depression	2.1 (2.2)	0.0 (0.0)	0.001

Values are mean (SD). All subjects are women. *Fibromyalgia. [a]n=5 for FM.

Table III. Frequency of occurrence of the tender points (TPs) in the fibromyalgia (FM) patients and controls.

TP location	FM patients (n=13)		Controls (n=13)	
	Right	Left	Right	Left
Suboccipital insertion	10 (77)	9 (69)	0	0
Mid-upper trapezius	13 (100)	9 (69)	3 (23)	3 (23)
Lower sternocleidomastoid	10 (77)	11 (92)	2 (15)	2 (15)
Origin of the supraspinatus	11 (85)	8 (61)	2 (15)	1 (8)
Near the second costochondral junction	12 (92)	12 (92)	2 (15)	3 (23)
Upper outer quadrant of the buttock	9 (69)	8 (61)	2 (15)	3 (23)
Prominence of the greater trochanter	1 (92)	9 (69)	1 (8)	1 (8)
Lateral epicondyle	10 (77)	9 (69)	0	0
Medial fat pad of the knee	8 (61)	12 (92)	1 (8)	2 (15)
Mean number of TPs in a subject	7	7	1	1

Values are number (%) unless indicated otherwise. Number: a number out of 13 subjects in whom a given TP location occurred; %: percentage of the subjects in whom a given TP location occurred. All subjects are women.

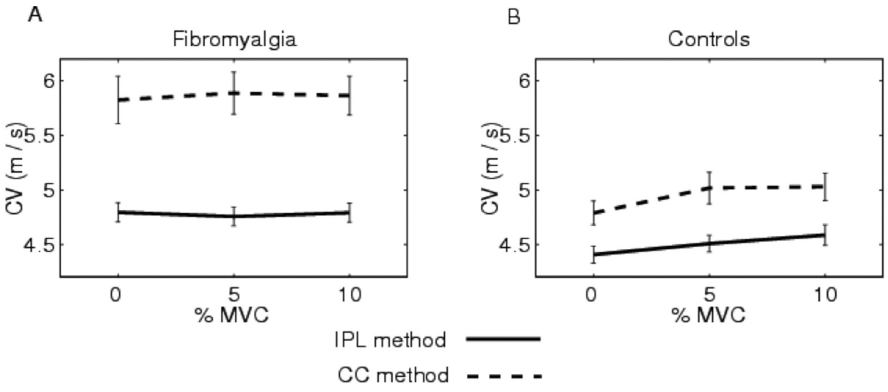

Fig. 1. Muscle fibre conduction velocity (CV) in fibromyalgia patients and healthy controls. The CV was obtained from the biceps brachii muscle using surface electromyography, the cross-correlation (CC) and the inter-peak latency (IPL) methods. Short (four-second) static contractions were applied at three force levels: with unloaded arm, and with 5% and 10% of maximum voluntary contraction strength (MVC). (**A**) Fibromyalgia female patients (13) and (**B**) matched controls (13). Means and standard errors are shown. In FM patients, the CV is higher than in controls, as measured by both methods.

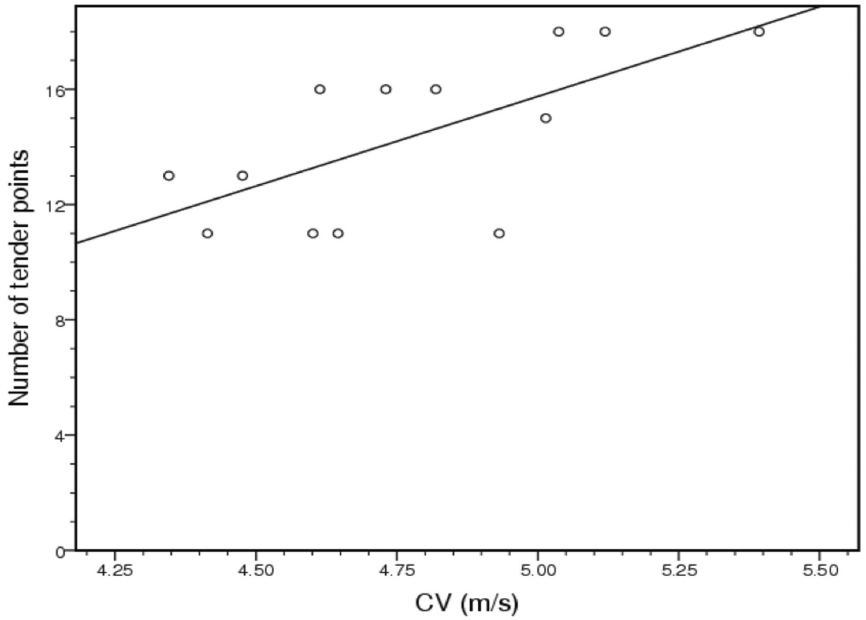

Fig. 2. Correlation between the number of tender points and the muscle fibre conduction velocity (CV) in fibromyalgia patients. The CV was obtained from a non-painful biceps brachii muscle of fibromyalgia patients (n=13) during short (four-second) contractions at three force levels: the arm unloaded, and loaded with 5% and 10% of maximum voluntary contraction strength. The CV was measured by the inter-peak latency method. The CV values are cumulative over the three force levels. There is a positive correlation between the number of tender points and CV.

self-reported pain, as measured by the VAS-pain of the FIQ (r=0.395, p=0.18). Finally, no significant correlations were found between the CV and any other aspect of health status on the FIQ (r's between -0.335 for physical functioning and 0.137 for stiffness) (Table IV).

Discussion

In a non-painful and non-TP site related muscle of FM patients we found a higher muscle fibre conduction velocity than in that of healthy subjects. A second notable finding was that there was a clear positive correlation between the muscle conduction velocity and the number of TPs in the FM patients.

Higher muscle fibre conduction velocity in FM

In earlier studies, a higher CV was observed in TP related muscles of FM patients and of patients with related disorders as compared with controls. These findings were explained by supposed local muscle changes in histopathology and microcirculation (11, 12). Our results show, however, that a non-painful, non-TP related muscle of FM patients also exhibits a higher CV. This can no longer be ascribed to local phenomena, but rather seems to point to a general feature of the musculature. CV measurements in non-TP related muscles of FM patients have rarely been performed. As far as we know, only a study by Casale *et al*. showed a larger proportion of fast propagating motor unit potentials in FM patients compared with controls, and the CVs of the patients tended to be higher, which is in line with our findings (25).

Several factors can influence CV. One of them is the type of motor units (MUs) participating in muscular activity: larger MUs with their fast twitch, fast propagating type II muscle fibres would produce higher CVs (26). Following the size principle, large MUs are in particular activated at higher force levels (27). Since our study on non-TP related muscle, as well as the two studies discussed above on TP related muscle (11, 12), involved low force levels, it seems unlikely that the activation of large MUs would have played a role. Another factor which the CV is dependent on is the muscle fibre diameter: thicker fibres propagate the action potential faster (14). However, the diameter of muscle fibres would not seem to play a part in explaining the present findings since there is no evidence of thicker fibres in FM (9, 10).

A more plausible explanation for the higher CV in FM could be functional alterations of the muscular membrane. It has been demonstrated that, in FM patients, there is an increased muscular activity between intended contractions; *i.e*. FM patients are unable to relax between contractions (28). Physiologically, after having produced an action potential, the muscle membrane develops a short after-depolarisation (AD), a period during which the membrane is hyper-excitable and the membrane conduction (the CV) is increased (29, 30). Following a prolonged stimulation or voluntary contraction, the AD becomes longer and may last for several minutes

Table IV. Pearson inter-correlations between study variables in the fibromyalgia patients.

	1	2	3	4	5	6	7	8	9	10	11	12
1. CV*												
2. Number tender points	0.672											
3. Duration complaints	-0.126	0.153										
4. Physical function	-0.335	0.159	0.045									
5. Days felt good	0.077	0.467	0.045	0.692								
6. Work days missed	0.080	0.381	0.953	0.499	0.088							
7. Job ability	0.091	0.468	-0.115	0.481	0.612	0.842						
8. Pain	0.156	0.395	0.309	0.531	0.849	0.315	0.762					
9. Fatigue	0.192	0.627	-0.023	0.692	0.655	0.714	0.637	0.499				
10. Morning tiredness	-0.093	0.264	-0.017	0.592	0.652	0.668	0.848	0.757	0.516			
11. Stiffness	0.137	0.284	0.183	0.452	0.696	0.316	0.491	0.545	0.533	0.718		
12. Anxiety	-0.115	-0.129	-0.006	0.183	0.020	0.657	0.294	-0.025	0.294	0.164	-0.021	
13. Depression	-0.090	0.117	0.095	0.655	0.708	0.458	0.599	0.560	0.677	0.567	0.561	0.643

*muscle fibre conduction velocity.

or even hours (31, 32). In FM patients, the inability to relax may induce such a prolonged AD, with a higher CV as a result.

Alternatively, the muscle membrane in FM may be facilitated by the direct effect of the excitatory transmitter adrenaline (or noradrenaline) on it. Adrenergic hormones are being released in situations of stress and physical exercise (29). Apart from the well-known adrenergic effects on the sarcolemma resulting in stronger contractions (33, 34), adrenergic activity stimulates the K^+/Na^+ pump of the skeletal membrane (35, 36). Activation of the K^+/Na^+ pump leads to higher membrane excitability (37) and increased CV (38). A muscle in FM seems to be over-activated; it resembles a muscle under adrenergic conditions. Little is known about the production of adrenergic hormones in FM. However, one study has found relatively high plasma levels of noradrenalin in FM while the levels of adrenalin were relatively low (39).

In FM and related disorders, the overall neural processes are often over-activated and the central regulation is misbalanced. Examples are the mechanism of sensitisation of pain processes in FM (40), and the presentation of complaints in the fibromyalgia-related disorders such as irritable bowel syndrome (41), tension headache, migraine (42) or hyperventilation syndrome (43, 44). The over-activated muscle membrane in FM might be regarded as part of the overall neural hyperactivity in the central and peripheral nervous system (45).

Tender points

TPs are painful spots not specific for FM (1, 13). They are found to occur on a continuous spectrum throughout the population (in particular female). However, the number of TPs is clearly higher in FM patients than in healthy women (46). In our study, the FM patients had on average 13 to 15 out of the potential 18 TPs whereas healthy women had 2 to 3 TPs. According to another study by Jacobs *et al*. (47), we found no correlation between the number of TPs in the FM patients and their experienced pain. This finding suggests that there are other factors than only an increased pain experience or a higher sensitivity to pain (48) that contribute to the development of TPs. In addition, previous studies have shown that the number of TPs is not stable. In the same person, the number of TPs may vary over time (46, 49).

The variability in the number of TPs in the same subject (49), the presence of TPs across the population (46) and the lack of evidence for pathology in muscle biopsy (9, 10) suggest that TPs may have a functional character. We found a strong positive correlation between the number of TPs and the degree of muscle membrane disturbance (CV) in the FM patients. As far as we know, it is the first time that a relationship has been found between an objective physiological finding in a muscle (CV) and the number of TPs, *i.e*. the extent of peripheral signs in FM. A possible underlying cause of this relationship could be that the long-working muscles (*i.e*. especially the postural muscles) would - on the basis of the overactive, hyper-excitable membranes – contract continuously, excessively, and would thus become overworked. With those TPs which are located in muscles, an accumulation of metabolite substances, such as lactate, and changes in microcirculation would lead to pain (50, 51).

On the methods

In this study, we deliberately applied very strict exclusion criteria for FM patients, such as: no other illnesses, no obesity, no medication, and no wheelchair use. Since FM patients often use medication and self-help devices, one can argue that our patients' sample may not have been representative of the FM population as a whole. We applied these strict criteria because we were interested in pure fibromyalgia and not in the effects of medication or bodily immobility.

The study groups were relatively small, which can be regarded as a limitation of the study. However, the groups were sufficiently large to show a significant difference in membrane function between patients and controls in sEMG, and a significant correlation between the sEMG finding and the number of TPs. For calculating mutual relationships between items of the FIQ, the patients' group was too small.

CVs obtained by the CC method were higher than those obtained by the IPL method (Fig. 1a-b). Such a difference was also found in a previous study (16). The CVs in the CC method are

probably biased towards higher values because in this method especially larger MUPs determine the CV (52).

Conclusions

1. In the non-TP related muscles of FM patients, functional muscle membrane disturbances have been found, suggesting an overall muscular membrane disorder.
2. The degree of membrane disturbances is correlated with the number of TPs; many of them are localised in muscles.
3. We suggest that both membrane disturbances and muscular signs might be caused by increased adrenergic excitatory action on the muscle membrane in FM.

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