

Muscle metabolism in fibromyalgia studied by P-31 magnetic resonance spectroscopy during aerobic and anaerobic exercise

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Objective: To investigate mechanisms underlying the reduced work capacity of fibromyalgia (FM) patients were compared to healthy controls at specified workloads, using P-31 magnetic resonance spectroscopy (MRS).

Methods: The forearm flexor muscle group was examined with MRS at rest, at sub maximal and at maximal controlled dynamic work as well as at maximal isometric contraction. Aerobic fitness was determined by bicycle ergometry.

Results: Metabolite concentrations and muscle pH were similar for patients and controls at lower workloads. At maximal dynamic and static contractions the concentration of inorganic phosphate was lower and at static contractions the pH decrease was smaller in patients. The performed work by patients was only 50% compared to controls and the patients experienced more pain. Maximal oxygen uptake was lower in the fibromyalgia group. Expired gas-analysis in this group showed ventilatory equivalents at similar relative levels of maximal work capacity.

Conclusion: Fibromyalgia patients seem to utilise less of the energy rich phosphorous metabolites at maximal work despite pH reduction. They seemed to be less aerobic fitted and reached the anaerobic threshold earlier than the controls.

Key words: fibromyalgia, MRS, phosphorous metabolites, intramuscular pH, anaerobic threshold

The main muscular symptoms in fibromyalgia (FM) are pain, stiffness and fatigue. Earlier studies have shown reduced voluntary muscular strength and exercise capacity (50–60% compared to normal), lower endurance and more muscular pain at a lower workload compared to healthy controls (1–3). This has been explained by a reduced ability to voluntarily recruit muscle fibres due to pain or an impaired muscle energy metabolism.

Studies of FM muscle metabolism have utilised biochemical analyses of muscle biopsies, or non-invasive examinations by means of ³¹P magnetic resonance spectrometry (MRS). Muscle biopsies taken at rest have shown reduced levels of phosphocreatine (PCr) and adenosin triphosphate (ATP) in painful muscle (m trapezius), but normal in the non-painful muscle (m tibialis anterior) (4, 5).

In the main studies using MRS, summarised in Table III below, some of the conclusions contradict the results from the biopsy studies. These studies are performed on small patient- and control groups, 8–15 members.

A fair comparison is difficult since these MRS-studies have been performed on different muscles and under a variety of experimental conditions. They

all elucidated a specific type of response but are together non-conclusive.

The aim of this study was to further test the hypothesis of reduced energy-rich substrates in painful muscles in FM. We therefore examined painful muscles by means of MRS in a well-defined female FM patient group at predetermined dynamic and isometric workloads. We related it to overall work capacity and compared with healthy matched volunteers.

Material and Methods

Participants

An exploratory study was conducted in order to ascertain the ability of participants to co-operate. The exclusions after the exploratory study were due to relative contraindications for examination in the MR tomograph such as claustrophobia, adipositas and difficulty in following instructions.

Nine female patients with diagnosed FM according to the American College of Rheumatology 1990 (6) participated. Nine matched female were recruited from the hospital staff. All were right-handed. No trained athletes were included. The Ethics Committee of Linköping University Hospital approved the study.

Patient group age was 45 years (34–52), height 165 cm (154–173) and weight 70.5 kg (57–79). Control group age was 45 years (25–59), height 167 cm (160–178) and weight 70 kg (60–80). (medians (ranges)). Permitted medication included

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estrogens (substitution or contraceptive pills), moderate doses of analgesics and low dosage tricyclic antidepressants at night.

Grip strength. Maximal handgrip strength of the right hand at rest was measured (strain gauge, Rank Stanley Cox, Great Britain). Pain before and after each test was recorded by Visual Analogue Pain Scale (VAS), length 10 cm anchored at "no pain" and "worst imaginable pain". Reported perceived effort (RPE) was recorded on a 6–20 Borg scale (7).

Personal history of fitness

A self-report 10 item Activity Profile recorded the level of habitual physical activity (daily activities, means of travel and distance to work, gardening and sports) during the study period. Scoring for activity frequency: never=0, once a month=1, once a week=2, three times a week=3 and daily=4.

Aerobic capacity and bicycle ergometry

Maximal upright seated bicycle ergometry on an electrically braked bike with continuous oxygen-uptake (VO_2) measurement was performed within 2 months of the MRS. Starting with two steady state submaximal levels of 6 min each [20 and 40 Watts ($n=2$) or 30 and 60 Watts], participants were exercised with continual workload increments of 10–20 W/min until exhaustion [19–20 on the 6–20 RPE Borg scale (7) or maximal muscle pain (10 cm VAS scale)]. Each initial loading and increment rate were chosen after clinical estimate of the participant's aerobic capacity.

A 12 lead ECG (Case 12, Marquette Electronics Inc. Milwaukee, USA) continuously monitored the ECG and heart rate (HR) and Doppler derived non-invasive right arm systolic blood pressure was measured during steady-state loading and every 3rd minute during incremental loading together with the degree of perceived exertion and muscle pain. Minute ventilation, VO_2 and CO_2 -elimination were measured continuously 5 minutes before and during exercise using a mass spectrometer and employing an Argon dilution technique with on-line presentation of the respiratory data and calculation of an average every 15 s (Amis Innovision A/S, Odense, Denmark). The respiratory exchange ratio (RQ) was continuously calculated and the anaerobic threshold, visually identified and defined as the inflection point where the VCO_2 -production increased more than the VO_2 -uptake (8) and the ventilatory equivalents (VEQ , minute ventilation/ VO_2) were determined. For determination of maximal exercise data, the

last two observations before termination of exercise were averaged and maximal work capacity as well as maximal oxygen uptake ($\text{VO}_{2\text{max}}$) were obtained. The maximal work capacity of each participant was compared with reference values of continual incremental loading (9) and where 20 Watt increment was selected the reference value was corrected by a factor of 1.12 (10).

Magnetic Resonance Spectroscopy

Relative concentrations of muscle metabolites were measured by ^{31}P -spectroscopy using a GE Signa Advantage system and measurements obtained at 1.5 T in a 60 cm core. The examination was performed with the subject in a prone position with the arm stretched out in front of her and the belly of the flexor forearm muscles against a surface coil. This coil tuned for ^{31}P (25.8 MHz) is acting both as transmitter and an 8 cm-diameter receiver coil.

The magnetic field was adjusted by shimming for maximal resolution (7.5 Hz for the PCr peak), for each individual subject. The pulse sequence used was 90° hard pulses with a repetition time of 2500 ms. For every scan 2 excitations were averaged and spectra obtained for typically 40 averages during rest and moderate dynamic work. Fourier transformed spectra were processed and analysed using the SAGE peak analysis software. The areas for the resonance peaks of inorganic phosphorous (P_i), phosphocreatine (PCr) and β -ATP were recorded and the presence of phosphodiester (PDE) peaks noted when visible. The α - and γ -ATP peaks are not resolved from resonances from adenomono- and diphosphates AMP and ADP, therefore the total amount of ATP was calculated to be 3 times the concentration of β -ATP. The total MRS visible phosphorous was equal to the sum of P_i , PDE, PCr and $3x$ β -ATP and the concentrations of individual compounds were expressed as fractions of the total in order to increase the accuracy.

Intracellular pH values were derived from the chemical shift δ_{obs} between the P_i resonance (in ppm) and PCr according to Petroff et al (11).

Spectra were obtained from the right forearm flexors at rest, during submaximal and maximal dynamic contractions and from the left forearm flexors during isometric contraction. The performed work was quantified by means of squeezing a rubber bulb. The rubber bulb was connected to a sensor outside the examining room by a thin Teflon tube. The amount of air pressed out of the bulb registered by the sensor and integrated over time is linearly proportional to the performed work. This variable is given in arbitrary units.

The volume of engaged muscles coincide with the

volume of the forearm from which signals are obtained by the surface receiver coil.

Exercise protocol

The subject was placed in prone position in the core of the magnet:

- At rest: 50 spectra were collected and added during 250 s while the right forearm rested on the spectroscopy coil.
- Dynamic contractions.:
 - Submaximal*: 50 spectra were collected and added during 250 s when the work consisted of squeezing a rubber bulb repetitively with the right hand at about half the maximal capacity. This level was reached by most of the participants after 250 s.
 - Maximal*: Squeezing the bulb repetitively as fast and as hard as possible until the limit of tolerable muscle-fatigue or pain was reached.
- Isometric contraction:
 - The bulb was kept pressed as hard as possible with the left hand at constant force until the limits of tolerable muscle-fatigue or pain were reached. During this compression the sensor signal was integrated over time.

After the dynamic and isometric maximal contractions the recovery was followed during 250 s in 50 averaged spectra. The intracellular pH was determined as the lowest value obtained during recovery.

Statistical analysis

Data are mainly reported as median values (ranges). Comparisons were performed using Mann-Whitney's U-test. A contingency Cell chi square test was applied to categorical data. Correlations was deduced by means of Spearman's test. A difference with a

p-value < 0.05 was considered significant. Analyses were performed in commercially available software programs (Statview 4.02, Abacus Concepts Inc., Berkeley, Cal, USA and STATISTICA 5.1, StatSoft Inc, Tulsa., OK, USA).

Results

The nine female patients and nine controls included in the main study did not significantly diverge from patients and controls in the exploratory study. Grip strength for patients was 24.0 (22.0–50.0) and controls 46.7 (32.2–51.5) N ($p < 0.05$). Activity score was 11(3–17) for patients and 10 (3–23) for controls. Maximum score to reach was 42.

Bicycle Ergometry

Results are shown in Table I. No difference was found in HR and systolic blood pressure at rest. All controls stopped exercise due to exhaustion but 6/9 of FM patients stopped due to muscle pain and 2/6 from dizziness and pain. Controls had a higher work capacity, a higher HR and a tendency to higher systolic blood pressure, SBP, at maximal workload. For the control group a correlation was found between change in SBP and change in P_i at maximum dynamic work measured with MRS. Anaerobic threshold was reached at lower absolute and relative work levels in FM than in controls, but at similar VEQ. No significant correlation was found between duration until the anaerobic threshold was reached and change in P_i . The FM patients performed 44% of the work above the anaerobic threshold, compared to 28% of controls ($p = 0.02$). Patients were less aerobically fit than controls but had a normal maximal work capacity compared to population-based reference values (9).

Table I. Results from the bicycle ergometry.

		Fibromyalgia		Healthy controls		Significance
		Median	Range	Median	Range	
Wmax (corr)	Watts	123	(75–194)	176	(143–229)	$p < 0.01$
Hrrest	bpm	73	(59–79)	71	(66–101)	NS
SBPrest	mmHg	115	(110–125)	130	(110–135)	NS
Hrmax	bpm	169	(120–179)	179	(151–197)	$p < 0.01$
SBPmax	mmHg	170	(160–190)	195	(150–230)	NS ($p = 0.06$)
VEQmax		33	(29–62)	35	(29–47)	NS
VO₂ max	l/min	1.8	(1.6–2.7)	2.3	(2.0–3.4)	$p < 0.05$
	ml/kg/min	24	(21–39)	36	(28–46)	$p < 0.01$
VE/VO₂	VO ₂ ml/kg/min	17	(11–24)	27	(20–34)	$p < 0.001$
inflection point	% of VO ₂ max	66	(43–84)	74	(69–78)	NS ($p = 0.06$)
	W _{AT} in % of W _{max}	56	(29–79)	72	(64–78)	$p < 0.05$

Abbreviations: HR, heart rate; SBP, systolic blood pressure; VEQmax, ventilatory equivalent at maximal load (minute ventilation /VO₂); VE/VO₂ inflection point, defines ventilatory threshold (8); VO₂ max: maximal oxygen uptake; W_{AT}, Watts at anaerobic threshold; Wmax, maximal work capacity corrected for differences in incremental load.

MRS

The main findings are shown in Table II

At rest and submaximal dynamic work no difference in the MRS measurements were found but the patients experienced more muscle pain and a higher perception of effort at work than controls.

At maximal dynamic workload patients and controls achieved the same decrease in intramuscular pH. However in spite of excellent co-operation, patients produced roughly half the work and obtained lower Pi values in half the endurance time compared to controls.

At maximal isometric work patients' continuation was inhibited by pain. The PCr levels decreased to the same extent as in controls. Patients did not reach the same decrease in pH as the controls and the production of Pi was lower, although patients and controls perceived the degree of effort similarly. A significant correlation between change in pH and change in Pi was found for the control group and the two groups taken together. The lack in correlation

for patients might depend on a large scatter in values for a small patient group (n=9). Typical spectra obtained at rest and at maximal dynamic work for a FM patient and a healthy control respectively are shown in Figure 1.

Discussion

The majority of MRS investigations have yielded results in contradiction to the biochemical analyses of muscle biopsies.(4) It is possible that these discrepancies are partly explained by methodological differences. In MRS, metabolites are measured in a much larger volume than in muscle biopsies, part of a muscle is compared to a mean of ca 100 fibres in a biopsy sample and MRS analyses may even include tissues other than the muscle.

The present study together with six others using MRS are summarised in Table III. There are important differences between these studies both in muscles chosen and in study conditions. De Blecourt et al. (12) and Jubrias et al.(13) only studied the

Table II. Results from the MRS study.

		Fibromyalgia median	Patients n=9 range	Healthy median	Controls n=9 range	sign. $p < 0.05$
At rest	PCr	0.51	(0.44–0.57)	0.55	(0.44–0.68)	NS
	P _i	0.06	(0.05–0.08)	0.06	(0.03–0.09)	NS
	ATP	0.43	(0.35–0.49)	0.39	(0.27–0.44)	NS
	PDE*	3/9		1/9		
	pH	7.09	(7.07–7.12)	7.10	(7.00–7.21)	NS
At sub- maximal dynamic work	PCr	0.35	(0.28–0.48)	0.35	(0.27–0.41)	NS
	P _i	0.22	(0.14–0.34)	0.23	(0.18–0.29)	NS
	ATP	0.40	(0.24–0.50)	0.40	(0.35–0.46)	NS
	PDE*	4/9		3/9		
	pH	7.04	(6.94–7.08)	7.01	(6.87–7.08)	NS
	work units	0.72	(0.28–1.02)	0.68	(0.48–1.27)	NS
	endurance (s)	250		250		
maximal dyn. work	VAS	7	(4–8)	0	(0–4)	0.001
	RPE	15	(13–18)	12	(8–17)	0.01
	PCr	0.24	(0.17–0.47)	0.23	(0.14–0.31)	NS
	P _i	0.27	(0.21–0.38)	0.40	(0.36–0.46)	0.001
	ATP	0.39	(0.32–0.59)	0.39	(0.26–0.42)	NS
	PDE*	6/9		2/9		
	pH	6.91	(6.73–6.93)	6.87	(6.49–6.94)	NS
	work units	0.38	(0.14–1.31)	1.06	(0.52–1.79)	0.01
	endurance (s)	75	(35–280)	300	(80–395)	0.05
	VAS	9.0	(7–10)	1.5	(0–5)	0.001
isometric work	RPE	18	(15–20)	18	(15–20)	NS
	PCr	0.39	(0.24–0.44)	0.37	(0.23–0.42)	NS
	P _i	0.17	(0.12–0.285)	0.19	(0.15–0.35)	0.05
	ATP	0.44	(0.40–0.52)	0.36	(0.30–0.48)	0.05
	PDE*	9/9		8/9		
	pH	6.99	(6.87–7.10)	6.89	(6.78–7.06)	0.01
	work units	0.96	(0.53–2.32)	1.32	(0.92–2.52)	NS
	endurance(s)	180	(90–415)	185	(65–285)	NS
	VAS	7	(1–10)	0	(0–6.5)	0.01
	RPE	19	(15–19)	17.5	(17–19)	NS

Values of PCr, Pi and ATP are expressed as fractions of total MRS visible peaks of P (i.e. PCr+Pi+3xβATP +PDE). *PDE given as frequency.

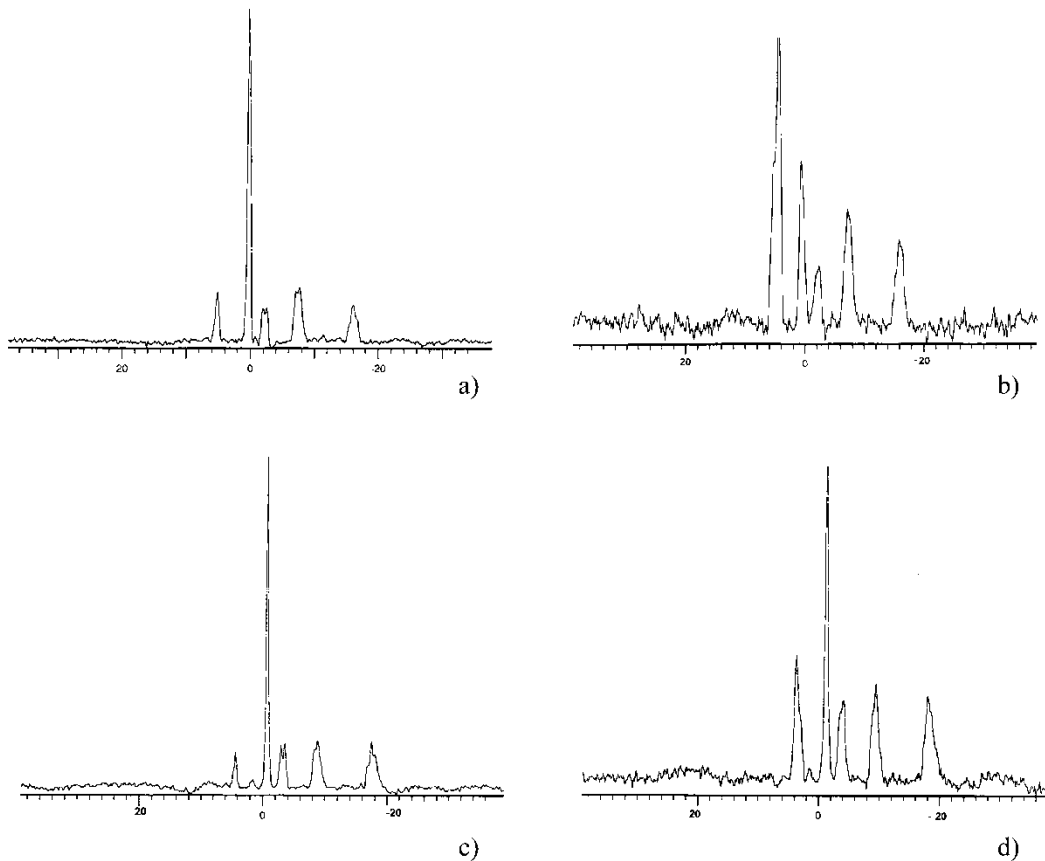


Fig. 1. Typical ^{31}P -spectra; a) at rest and b) during maximal dynamic work of a healthy control. c) at rest and d) at maximal dynamic work of a fibromyalgia patient. All spectra are normalized to the maximum peak and the intensity is given as a function of the chemical shift in ppm relative to PCr.

muscles at rest, and these results are in accordance with the present study. Submaximal dynamic work is defined as being an intensity of work not high enough to cause a significant decrease in intracellular pH. Simms (14) studied both painful and non painful muscles at submaximal level and found no differences between patients and controls at 60 % of MVC. The reported RPE values also indicated that maximal work was probably not performed. The results are in accordance with the present study in which no significant differences in the MRS results were recorded between patients and controls during and after submaximal dynamic work.

Jacobsen (15) studied the patients and controls both during aerobic and anaerobic exercise and found a similar pH decrease in patients and controls at maximal power output, despite the fact that patients performed only half the work. Their explanation was that the patients had a reduced voluntary capacity of work but normal biochemical response to work and recovery. Vestergaard-Poulsen (16) also showed that the patients achieved a significantly lower MVC than the sedentary and energetic controls. They concluded that the findings in FM could be a result of lower

levels of daily physical activity. The lower motor unit recruitment and weak metabolic changes during exercise were explained as a result of lower central activation, due to lower muscle pain tolerance.

Our study support these studies but our hypothesis is different. We also found that at maximal dynamic contractions the decrease in pH at exhaustion was the same in patients and controls. The patients reached the point at which they were unable to carry on after having performed only half the work units and after half the endurance time, compared to controls. This means that muscle exhaustion and a similar decrease in pH appear after a lower muscle work output in FM. The increase in Pi is lower in patients and a lower production of lactic acid is assumed. The similar pH decrease can not therefore have the same cause as in controls. An impaired outwash of the lactic acid generated by muscle contractions in FM could explain this finding. An impaired outwash in general might explain the higher frequency of diesterpeaks in patients in dynamic work. This in turn could be explained by an impaired microcirculation and/or an incomplete relaxation between contractions as found in the trapezius muscle of FM patients (17, 18). A lower

Table III. Summary of six main MRS studies together with the present investigation.

Authors	Patients/controls	Examined muscle	Circumstances	Observations patients – controls	Conclusions	Remarks
Blecourt 91	10 patients, 9 female 6 controls, 5 female	trapezius	at rest	no differences between patients and controls	No differences	
S Jacobsen 92	12 patients, 8 female 7 controls, 3 female	calf muscles	at rest, during aerobic and anaerobic exercise and during recovery	pH=6.89–6.80 Pi/PCr=1.00–1.60 MPO=8.6–17.3 figures from max work	Differences found, probably due to differences in MPO	MPO = maximum power output
Simms 94	13 patients, all female 13 controls, all female	upper trapezius anterior tibial	at rest, during repeated isometric contractions and during recovery. 60% of MVC	pH=7.08–7.07 7.12–7.20 PCr/Pi=10.21–9.17 9.10–8.98 Borg=15.2–15.8	No differences between patients and controls	Measurements probably made during medium work
Jubrias 94	11 patients, all female 10 controls, all female	forearm muscles, wrist flexors	all measurements done at rest after concentric and eccentric exercise	Frequent occurrence of phosphodiesterases in patients.	No other differences between patients and controls	
Vestergaard-Poulsen 95	10 patients, all female 8 controls, all female	anterior tibial muscle	isometric contraction, 10 % of MVC until exhaustion	pH=6.85–6.73 PCr/Pi=1.73–1.02 MVC=19.8–25.5	MVC significantly lower in patients. differences in MRS probably due to lower physical activity	
Park 98	12 patients, all female 11 controls, 10 women	quadriceps	repeated isometric muscle contractions 25.50% of MVC for 6 minutes	PCr=18.6–21.1 ATP=4.8–5.5 pH not given increased PDE	values in patients lower than controls	
Lund Bengtsson present work	9 patients 9 controls all female	Forearm flexors	At rest, moderate and max dynamic work and at static work	Increased PDE. No changes at rest or moderate work. At max dynamic patients produced less work despite the same decrease in pH	Differences found	

relaxation rate might also contribute (19). The effects of both may be expected to be more pronounced at maximal work loads.

An inadequate increase in bloodflow in response to increasing load might be another contributing factor to a relatively lower intracellular pH. In dynamic contractions by patients with chronic shoulder pain an increase in bloodflow on the painfree side but not on the pain side after dynamic contractions has been shown (20). Lund et al studied oxygen pressure in trapezius and brachioradial muscles at rest in FM patients and found changes compatible with a disturbed regulation of microcirculation (21). Local blood flow at the capillary level is regulated by endothelial cells. Lindman et al found morphological aberrations in endothelial cells in muscle capillaries both in FM and trapezius myalgia patients (22). No reduction in capillary density has been found in FM (23).

Given that FM patients experience and report a generalised muscle pain, stiffness and fatigue, these changes could be the morphological correlate to a disturbance in blood flow regulation that leads to a decreased response on demand for increased blood flow during muscle work. A reduced blood flow during work, with accumulation of metabolites and with a predisposition to ischemia, could in turn mean pain in the muscle during exercise, reduced endurance and premature exhaustion. It can not be excluded that dysautonomia found in FM can be of importance for the disturbance in the regulation of microcirculation (24). The frequency of occurrence of PDE peaks is interesting (13). For the majority of the patients (6 out of 9) diester peaks appeared in the spectrum during maximal dynamic work. The corresponding figures for the control group was 2. During maximal static work (in which ischaemic conditions are expected) with the tested muscle group on the nondominant side, all patients and controls showed increased PDE levels. This is in agreement with the findings of both Parks (25, 26) and Jubrias (13). A more frequent appearance of PDE peaks in FM patients during maximum dynamic work indirectly supports the hypothesis of incomplete relaxation between contractions and/or an impaired outwash.

In all reported MRS studies except that by Park et al (25) the concentrations are given as relative to the amount of phosphorous in the individual sample. Park et al report the metabolite levels in muscles as relative to the β -ATP level for healthy individuals i. e. normalised to the standard value 5.5 mmol ATP per kg (wet weight of muscle) (26) Their quantitative MRS analysis showed that patients at rest had significantly lower PCr and ATP levels and lower PCr/Pi ratios compared to

controls. This is in agreement with the results from the analysis of biopsies taken from the trapezius muscle at rest (4, 5). In the present MRS study the metabolites are given as fractions of the total amount of phosphorous for every individual and not normalised to any standard value. (Recalculating the results from Park's study (25) in the same way, values from the two studies are fully consistent). The relative concentrations of the phosphorous metabolites seem to be the same in healthy individuals and FM patients while the absolute concentrations of the metabolites differ according to Park's findings.

Self reported levels of aerobic fitness in the present study were similar for patients and controls. At bicycle ergometry patients had a higher anaerobic capacity than controls but work capacity was normal according to population derived reference values (9). Furthermore, patients reached the anaerobic threshold at a lower relative work level but at similar ventilatory equivalencies as the controls. All but one patient stopped exercising due to pain and dizziness but the anaerobic threshold, minute ventilation etc. indicate that they were hemodynamically loaded similarly to controls.

Even though bicycle ergometry reflects total cardiovascular fitness and not performance or endurance in individual muscle groups it is dependant on muscular blood flow (capillarisation), and the number or amount of mitochondria and their enzymes. The results from the ergometry suggest that the patient group worked relatively longer time after reaching the anaerobic threshold than did the controls. Jacobsen et al reported a similar finding (15). Possible explanations include a higher tolerance for anaerobic work or an earlier anaerobic contribution to the metabolism in exercising FM patients.

The ergometry finding of relatively longer work capacity above anaerobic threshold indicates that neither lower aerobic fitness nor poorer co-operation or motivation in FM can explain the lower muscular work capacity.

In summary our study showed that FM patients despite excellent co-operation at maximal dynamic workload reached the same decrease in pH after performing half the work compared to healthy controls and in cycle ergometry reached the anaerobic threshold earlier. Reduced physical activity or central cardiovascular performance may only partly explain the finding. The results of the present study do not contradict previous work but we propose another interpretation than previously. The results of the present study suggest that impaired muscle metabolism and/or microcirculatory disorder contribute to impaired muscular performance in FM.

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