Muscle changes in work-related chronic myalgia

Sven-Erik Larsson, Ann Bengtsson, Lars Bodegård, K. G. Henriksson and Jörgen Larsson

Muscle biopsies from the descending portion of the trapezius muscle were studied in 9 healthy subjects and in 10 patients with localized chronic myalgia related to static load during repetitive assembly work for 16 (10–31) years, with 10 (4–26) months of sick leave at the time of biopsy. Both categories showed isolated atrophic muscle fibers and occasional abnormal fibers with internally situated nuclei, some variation in fiber diameter, and fiber splitting. Fibers with a "moth-eaten" appearance due to a multifocal loss of oxidative enzyme activity were frequent both in the healthy and in the myalgic individuals. In contrast, isolated pathologic "ragged red" fibers were only found in the cases with myalgia (8 of 10), strongly suggesting mitochondrial damage. The phenomenon was confined to the Type 1 fibers. The frequency of Type 1 fibers was increased. Levels of adenosine triphosphate and adenosine diphosphate were reduced in myalgia patients, whereas lactate, pyruvate, and glycogen levels were normal, as well as phosphoryl creatine and total creatine.

Neck and shoulder complaints are common causes of long-term sick leave among industrial employees, and may show a poor prognosis (Kvarnström 1983). Trades with high risk are characterized by a small work place and a small working surface, short work cycle, little variation in work movements, posture and muscle load, and, finally, frequent precision movements. These circumstances may cause a static load in the shoulder-stabilizing muscles over excessively long periods of time. The condition has been recognized since antiquity and was described by Ramazinus in 1717. Yet, there is no acceptable clinical explanation for the occurrence of permanent, unspecific neck muscle complaints (Morgan-Hughes 1979).

Electromyography (EMG) and changes in the frequency spectrum have been used to examine work-related fatigue in the shoulder muscles (Jonsson 1979, Hagberg 1981). To our knowledge, there are no muscle biopsy studies of patients with work-related chronic myalgia. We have studied muscle tissue in individuals with persistent myalgia.

Departments of Orthopedics, Internal Medicine, and General Surgery, and the Neuromuscular Unit, University Hospital, Linköping, Sweden

Correspondence: Dr. Sven-Erik Larsson, Department of Orthopedics, University Hospital, S-581 85 Linköping, Sweden

Patients and methods

Ten patients with work-related chronic myalgia of the shoulder, specifically the trapezius muscle(s) were studied. They were all females and their mean age was 45 (30–58) years, and with symptoms of 10 (5–14) years. At the time of biopsy, their mean preceding sick leave was 10 (4–26) months. Two of the patients had been awarded a disability pension after sick leaves of 18 and 26 months. One improved patient had been working for 2 months using tackles, for unloading the weight of the arms.

The comprehensive clinical examination performed independently by specialists in orthopedics, rheumatology, neuromuscular diseases, and industrial medicine showed that all the patients had major complaints of pain and tenderness distinctly localized to the descending part of the

trapezius, preferentially on the side that had been most exposed to static load. Most patients also showed some tenderness in the levator scapulae and the insertions of the supraspinatus and infraspinatus muscles. None had complaints from the cervical spine and the shoulder joints, and the physical examination was normal in these respects. There was no evidence of generalized muscle pain or stiffness, nor inflammatory joint disease. None fulfilled criteria for primary fibromyalgia (Yunus et al. 1981 and Yunus 1983). General physical examination and laboratory tests were normal.

Nine healthy volunteers (previously reported by Bengtsson et al. 1986b). served as controls, 8 women and 1 man, mean age 40 (26–43) years. All of them were hospital employees and had no complaints whatsoever. Their work showed large variation in work movements with a minimum of static load on the shoulder muscles.

Blood samples were analyzed for erythrocyte sedimentation rate, hematology count, electrolytes, creatinine, liver enzymes, creatine kinase, thyroid function (thyroxine, triiodothyronine, T-3 uptake test, thyroid-stimulating hormone), rheumatoid factor (latex fixation test and Waaler-Rose test), and finally, antinuclear antibodies.

Open muscle biopsies from the patients were taken from the tender part of the upper part of the trapezius muscle. The biopsies from the controls were taken from the same part of the trapezius muscle as was done in the patients. With the subject in the prone position, the skin and the superficial subcutaneous fat were infiltrated with a local anesthetic; care was taken to avoid the muscle. No sedatives were given prior to the biopsy.

Routine histopathologic and histochemical methods were used. Serial sections of the formalin-fixed material were made at different levels of the biopsy. Formalin-fixed and paraffin-embedded specimens were stained with hematoxylin-eosin, Weigert-hematoxylin, van Gieson and Ladewig stains. Specimens frozen in liquid nitrogen were stained for ATP-ase, NADH-tetrazolium reductase, phosphorylase, and acid phosphatase. For fiber typing, staining for myofibrillar adenosinephosphatase (ATP-ase, preincubation at pH 9.4 and at pH 4.6) was used. The proportion of Types 1 and 2 fibers was determined by light or dark, respectively, staining for ATP-ase at pH 9.4. A modified Gomori-trichrome, hematoxylin-eosin, and van Gieson stains were also used on the frozen material. Periodic acid Schiff (PAS) was used for staining glycogen and Oil red-O for lipids.

The muscle samples removed for biochemical analyses were immediately frozen in liquid nitrogen and kept frozen until freeze dried. After powderization and removal of connective tissue, fat and blood, the specimens were extracted as described by Harris et al. (1974). Then, analyses were made for ATP, ADP, AMP, PC (phosphoryl creatine), Cr (creatine), lactate, pyruvate, and glycogen. Energy charge potential (ECP) was calculated from the formula ECP = 1/2 (ADP + 2 ATP) / (ATP + ADP + AMP), according to Atkinsson and Walton (1967). The total adenine nucleotide pool TA = ATP + ADP + AMP was calculated. ATP, PC, and glycogen were also referred to total creatine, TCr = PC + Cr.

The Student's two-tailed t-test $P < 0.05$ was considered significant.

Results

Occasionally, the biopsies showed slightly abnormal muscle fibers with internally situated nuclei, isolated atrophic fibers, a certain variation as to fiber diameter, and splitting. More clearly, "moth-eaten" fibers were seen evenly distributed over the cross section. In comparison with normal fibers, "moth-eaten" fibers were characterized by a multifocal loss of NADH tetrazolium-reductase activity (Figure 1). The findings were noted in patients and in healthy controls, as well, and did not lead us to classify the biopsy as pathologic.

On the other hand, "ragged red" fibers were observed only in biopsies from patients (Figure 2). These fibers were characterized by the existence of subsarcolemmal zones of bright red or reddish blue material when staining with Gomori-trichrome and an accumulation of formazan particles in the same area when staining for NADH tetrazolium reductase. These fibers also had a ragged appearance. Eight of 10 patients thus had evident pathologic muscle biopsy. Only a few "ragged red" fibers were seen in each biopsy, however. The phenomenon was apparently confined to the Type 1 fibers. Four patients were

Acta Orthop Scand 1988;59(5):552–556

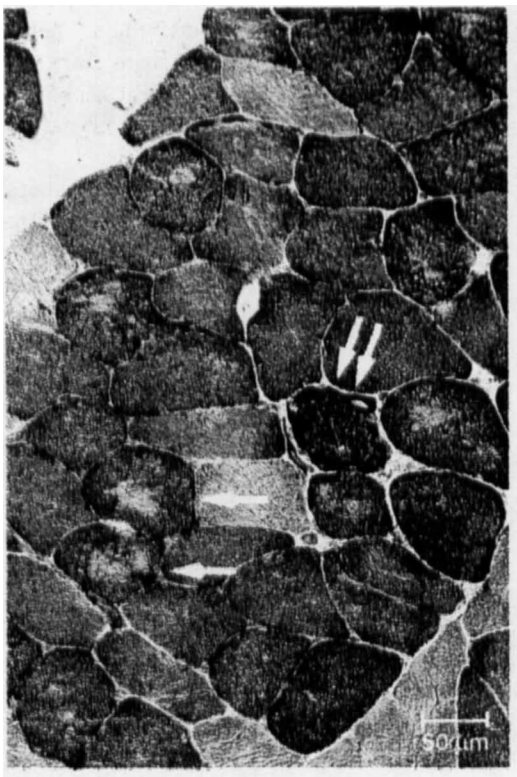

Figure 1

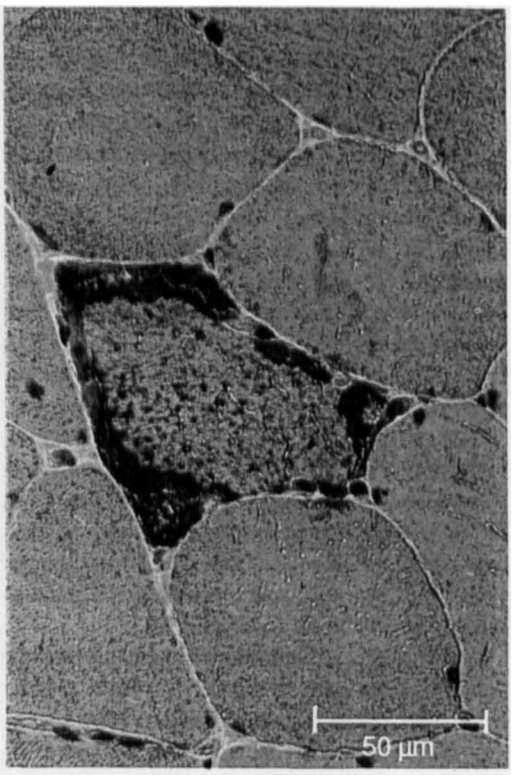

Figure 2

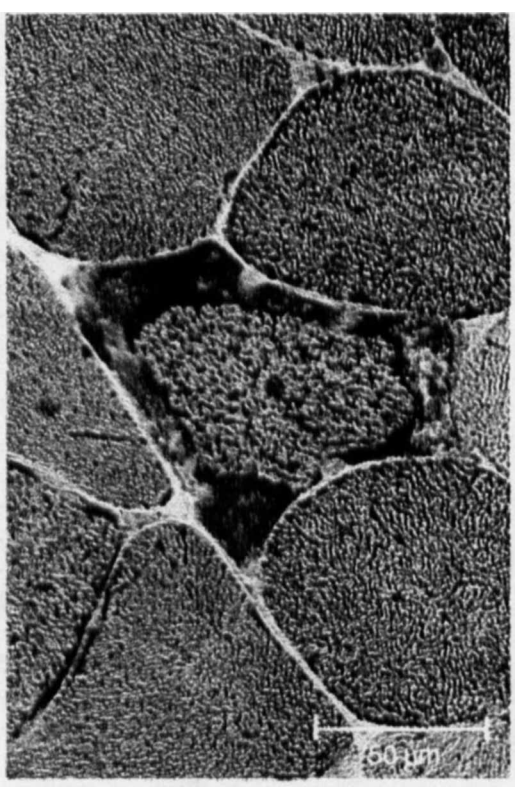

Figure 3

Figure 1. Trapezius muscle from a healthy 34-year-old woman. Staining for NADH-tetrazolium reductase. The interfibrillary network is normal.

Figure 2. Trapezius muscle from a healthy 35-year-old man. Staining for NADH-tetrazolium reductase. "Moth-eaten" fibers are seen at arrows.

Figure 3. Trapezius muscle from a 51-year-old woman with shoulder pain. Staining for NADH-tetrazolium reductase. "Ragged red" fibers at arrow.

Table 1. Contents of high-energy phosphates, Cr, TCr, lactate, pyruvate, and glycogen in the trapezius muscle of healthy individuals (n 8) and patients (n 10). Mean (SD)

	Controls		Patients		
ATP	23.9	(1.0)	18.6	(2.3)	$P < 0.001$
ADP	3.3	(0.30)	2.7	(0.24)	$P < 0.001$
AMP	0.12	(0.03)	0.15	(0.05)	NS
TA	27.3	(1.16)	21.4	(2.45)	$P < 0.001$
ECP	0.935	(0.0045)	0.929	(0.0079)	NS
PC	69.5	(3.9)	64.0	(8.1)	NS
Cr	50.4	(4.2)	46.9	(8.0)	NS
TCr	120	(5.3)	111	(12.2)	NS
Lactate	5.0	(1.7)	4.3	(2.0)	NS
Pyruvate	0.46	(0.14)	0.45	(0.13)	NS
Glycogen	277	(39)	245	(29)	NS
ATP/TCr	199	(8.7)	168	(16.4)	$P < 0.001$
Glycogen/TCr	2.3	(0.25)	2.2	(0.41)	NS

ATP adenosine triphosphate, ADP adenosine diphosphate, AMP adenosine monophosphate, TA total adenine nucleotide pool, ECP energy charge potential, PC phosphoryl creatine, Cr creatine, TCr total creatine.
All values are given in mmoles/kg of dry muscle except glycogen where, the value is mmoles of glycosyl units/kg of dry muscle.

found to have discrete perivascular infiltration of lymphocytes. The findings were not classified as pathologic. Selective atrophy of Type 2 fibers was noted in 4 patients. Patients showed an increased frequency ($P < 0.01$) of Type 1 fibers (72 ± 6 percent, mean ± SD) compared with controls (54 ± 13 percent, mean ± SD). Stainings for glycogen, phosphorylase, and lipids were normal in all the biopsies.

As to the biochemical analyses, lower values were obtained for ATP and ADP in the patients ($P < 0.001$) compared with the controls, as well as TA, whereas AMP showed a tendency at higher values (Table 1). PC showed somewhat low values, but the difference was not significant, as was the case also for total creatine (TCr). The values for lactate, pyruvate, and glycogen were within normal limits. The quotient ATP/TCr was reduced in the patients while PC/TCr showed no difference.

Discussion

The morphologic findings of "ragged red" fibers indicating myopathy in myalgic patients have not, to our knowledge, been reported earlier. This is an indication of a pathologic condition of the muscle, in particular of the mitochondriae, not prevailing in the normal state. Experimentally, "ragged red" fibers have been found to appear after induced muscle ischemia causing early changes of the mitochondria (Heffner and Barron 1978); "moth-eaten" fibers appeared before the occurrence of "ragged red" fibers in ischemic rat muscle. In humans, "moth-eaten" muscle fibers are often found in chronic neuropathy and myopathy. In the trapezius muscles, "moth-eaten" appearance of slow oxidative Type 1 muscle fibers are frequently found also in individuals without muscle pain (Bengtsson et al. 1986a). The common denominator for "moth-eaten" fibers may be localized hypoxia, possibly secondary to overload. "Ragged red" fibers indicate mitochondrial damage and are found in mitochondrial myopathies, but also sometimes in other myopathies (Swash et al. 1978, Sengers et al. 1986). We have recently found that "ragged red" fibers can also be found in nonpainful trapezius muscle. The occurrence of "moth-eaten" and "ragged red" fibers may show a gradual increase dependent upon the degree of exposure to static muscle load. The muscle may show pathology even before lasting pain occurs. In patients with work-related chronic myalgia muscle pathology appears to be a regular finding.

In our patients the demonstrated morphologic changes and local muscle pain might be due to very local, temporary hypoxia causing a limited energy crisis within the fiber. This explanation gets support from our findings of reduced contents of ATP and ADP within the muscle. The force to keep the arm in a position of 45° abduction and 45° flexion with the elbow at a straight angle has recently been calculated at 18 percent of the

maximum muscle strength in the average female assembly worker (Kvarnström 1985). The increased frequency of Type 1 fibers in our patients and the morphologic evidence of atrophy of Type 2 fibers may be regarded as a response of the muscle to these work conditions. At this contraction level, there is most likely a local impairment of the capillary blood circulation regionally in the muscle. This may cause a drop in energy substrates in the involved muscle fiber. Our biochemical analyses reflect mean values of all fibers in the biopsy representing a mixture of normal and pathologic fibers. Nevertheless, a drop in ATP and ADP was found. On the other hand, lactate values were normal. This does not exclude focal changes in lactate. The changes in lactate may not be great enough to give pathologic total values.

It is of clinical importance to note that pain, tenderness, and sense of fatigue, as well as the morphologic and biochemical changes, persisted in our patients despite long-term sick leave.

Clinically, the condition appears as a maintained local, mainly static hyperactivity of the muscle. This might be primary as a more or less pronounced habitual neuromuscular hyperactivation, or secondary due to the occurrence of muscle tissue changes that may elicit local pain that, in turn, might lead to maintained hyperactivation of the muscle. Interestingly, similar changes of myopathology have recently been demonstrated in biopsies taken from painful trigger points not only from the trapezius muscle, but also from the deltoid muscle in patients with defined primary fibromyalgia (Bengtsson et al. 1986a and b). A causative factor in common for these local muscle changes might be reduced muscle oxygenation as demonstrated in fibromyalgia patients by Lund et al. (1986).

References

Atkinson D E, Walton G M. Adenosine triphosphate conservation in metabolic regulation. Rat liver citrate cleavage enzyme. J Biol Chem 1967;242(13):3239–41.

Bengtsson A, Henriksson K G, Larsson J. Muscle biopsy in primary fibromyalgia. Light microscopical and histochemical findings. Scand J Rheumatol 1986; 15(1):1–6.

Bengtsson A, Henriksson K G, Larsson J. Reduced high energy phosphate levels in the painful muscles of patients with primary fibromyalgia. Arthritis Rheum 1986;29(7):817–21.

Hagberg M. Electromyographic signs of shoulder muscular fatigue in two elevated arm positions. Am J Phys Med 1981;60(3):111–21.

Harris R C, Hultman E, Nordesjö LO. Glycogen, glycolytic intermediates and high energy phosphates determined in biopsy samples of musculus quadriceps femoris of man at rest. Methods and variance of values. Scand J Clin Lab Invest 1974;33(2):109–20.

Heffner R R, Barron S A. The early effects of ischemia upon skeletal muscle mitochondria. J Neurol Sci 1978;38(3):295–315.

Jonsson B. Electromyography and muscular over exertion Methodological aspects. Acta Neurol Scand 1979;73(Suppl. 60):159.

Kvarnström S. Occurrence of musculoskeletal, disorders in a manufacturing industry with special attention to occupational shoulder disorders. Scand J Rehabil Med 1983; (Suppl 8):1–114.

Kvarnström S Arbetsrelaterade problem i halsrygg och skuldra utgör ett växande problem i företagshälsovården. Läkartidningen 1985;82(17):1590–2

Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. Scand J Rheumatol 1986;15(2):165–73.

Morgan-Hughes J A. Painful disorders of muscle. Br J Hosp Med 1979;22(4):360, 362–5.

Ramazinus B. De Morbis Artificium. Padua 1717.

Sengers R, Stadhouders A, Bastiaensen L. "Ragged red" fibre pathology due to micro angiopathy? Muscle Nerve 1986;9(Suppl 5):184.

Swash M, Schwartz M S, Sargeant M K. The significance of ragged red fibres in neuromuscular disease. J Neurol Sci 1978;38(3):347–55.

Yunus M, Masi A T, Calabro J J, Miller K A, Feigenbaum S L. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 1981;11(1):151–71.

Yunus M B. Fibromyalgia syndrome: a need for uniform classification (Editorial). J Rheumatol 1983;10(6): 841–4.

Acknowledgements

This work was supported by grants from AFA (Arbetsmarknadens Försäkringsaktiebolag, Stockholm, and King Gustaf the Fifth's Eightieth Birthday Fund.