Effects of Arthritis on Muscle Bioenergetic Reserve Determined by In-Vivo 31P Magnetic Resonance Spectroscopy

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Abstract:

It is unclear whether muscle dysfunction in arthritis is secondary to disuse-induced atrophy or to specific correlates of the arthritis process. We hypothesized that, in fact, the biochemical and bioenergetic sequelae of arthritis would differ significantly from those of pure atrophy. We investigated muscle function, muscle bioenergetics, cytokine expression, and muscle fiber type in the rat secondary to atrophy, adjuvant-induced arthritis, and a combination of these. Our results suggest that muscle dysfunction secondary to arthritis and to atrophy are distinct.

Introduction:

Arthritis is a disabling chronic condition that rises in prevalence in late-life. Loss of muscle strength accompanies arthritis and appears to be an important mediator of poor mobility function in arthritic patients and in older adults in general. In humans, skeletal muscle dysfunction that accompanies arthritis has been assumed to develop as a consequence of disuse of the muscle. We hypothesize that skeletal muscle function in the setting of arthritis is distinct from atrophy, and conducted the following experiment to determine the individual and combined effects of arthritis and hind-limb unloading on contractile force and bioenergetics measured by ^{31}P NMR spectroscopy.

Methods and Materials:

Animal models: Three to four month old Fisher 344 rats were treated to either develop arthritis (CIA: n= 5), muscle atrophy from hind-limb unloading (HU: n= 6) or both (CH: n=9) and compared to control animals (CTL: n=6). Arthritis was induced by subcutaneous injection into the tail base of bovine type II collagen. Rats were given injections on days 0 and 7. Atrophy was induced by placing animals in a tail-suspension harness for 7 days. Combined arthritis and atrophy animals were induced with collagen as described above and unloaded by tail suspension from day 8 to 14.

^{31}P NMR spectroscopy: NMR spectroscopy was performed on the 15th day following arthritis induction, and on the 8th day of hind-limb unloading. ^{31}P NMR of rat quadriceps muscle was performed on a 1.9 T, 31 cm Bruker ABX Biospec. Spectra were recorded with an interpulse delay of 1 s and flip angle of 90^{o} for a period of 1 min. A total of 25 spectra were acquired: 2 for baseline, 8 during electrically stimulated exercise, and 15 during recovery to baseline. The muscle was stimulated using a pair of rectangular pulses each of duration 5 ms, with an interval between the pulses of 200 ms and an interval between the pulse pairs of 2 s. Contractile force was measure with a force transducer. Force levels were expressed relative to initial force. Muscle bioenergetic status was expressed as the ratio of phosphocreatine and the sum of phosphocreatine and inorganic phosphate [PCr/(PCr+Pi)].

Immediately after the NMR experiment, blood samples were taken and the gastrocnemius was removed for measurement of serum and muscle cytokine levels. The quadriceps, soleus, and plantaris muscles were also removed and flash frozen for muscle fiber type staining.

Data Analyses: Two-way repeated-measures ANOVA (Statview; Abacus Concepts) was used to compare the values of relative metabolite ratios and force across the exercise and early recovery periods. Statistical significance was assessed at $P<0.05$. Data are shown as mean ± SEM

Results:

PCr/(PCr+Pi) data by stimulation for all groups are depicted in Figure 1. Through most of the exercise period the mean PCr/(PCr+Pi) values were highest in the HU group and lowest in the CIA group. The CH group differed from HU ($P<0.02$) but not from CIA during exercise. During early recovery, HU and CH differed from CTL ($P<0.01$). The CH group showed the slowest recovery rate of the groups. Consistent with the trends observed during exercise, CH differed from HU but not from CIA during early recovery.

Relative force data are plotted against time in Figure 2 for all groups. CIA and CH groups exhibited lower force than CTL throughout the stimulated exercise. Mean force was indistinguishable between CIA and CH, but both were lower than HU ($P<0.01$).

Discussion:

The present study demonstrates that bioenergetic and force characteristics of muscle in the presence of induced arthritis differ from that of atrophy. The greatest depletion of energy substrate secondary to muscle stimulation was seen in the animals with arthritis. The combination of arthritis and HU resulted in an attenuated rate of bioenergetic recovery to baseline. These results imply that arthritis-associated muscle dysfunction cannot be attributed solely to atrophy. Mechanisms for the trends observed are under investigation.

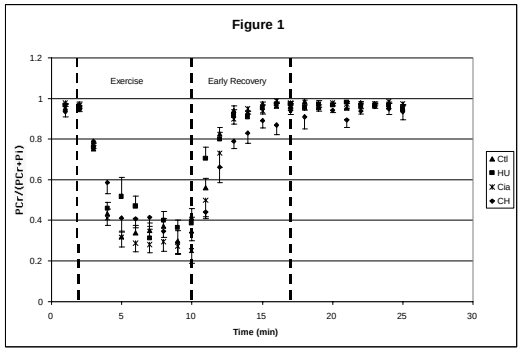

Figure 1: Bioenergetic analysis of rat quadriceps for all pathological groups during exercise and recovery from exercise.

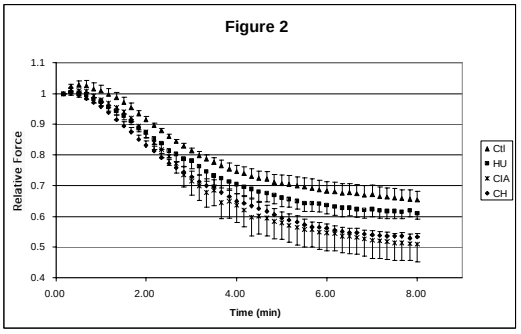

Figure 2: Relative force of rat quadriceps for all pathological groups during exercise.