Do Inflammatory Responses to Eccentric Exercise Suggest a Fatigue Failure Process?

Sean Gallagher, PhD, CPE, Michael Porter, MISE,
Patrick Almas, MISE, Yousif Abulhassan
Department of Industrial Engineering
Auburn University

Recent evidence strongly suggests that force and repetition interact in a consistent manner to affect musculoskeletal disorder (MSD) risk, likely due to an underlying fatigue failure process in affected tissues. This pilot study evaluated whether a force-repetition interaction was present with respect to inflammatory responses of elbow flexor muscles after eccentric exercise. 24 subjects performed eccentric contractions with 6 assigned to each of 4 force and repetition combinations. Dependent measures included MRI data on edema in the muscle (day 2 versus day 0), relaxed elbow flexion angle, and isometric strength (both obtained days 0, 1, 2, 4, and 8 post-exercise). Significant force-repetition interactions were found for relaxed elbow angle at days 2 and 4 post-exercise ($p < 0.05$), and for days 2 and 4 for isometric strength ($p < 0.05$).

INTRODUCTION

Musculoskeletal disorders (MSDs) are widespread in the United States and throughout the world, and are associated with substantial financial and societal costs (Horton, 2010). MSDs are the second greatest cause of disability globally, having increased 45% worldwide according to the 2010 Global Burden of Disease Study (Horton, 2010). In 2011, MSDs accounted for 33% of workplace injuries and illnesses in the U.S. and a median of 11 days absence from work (BLS, 2012). MSDs constitute a major proportion of all compensable work-related diseases in many countries, including the United States (Hoogendoorn, et al., 1999). The estimated cost of treatment for patients with musculoskeletal conditions in 2004 was estimated at $510 billion, or the equivalent of 4.6 percent of the GDP (AAOS 2008). Indirect costs, primarily lost wages, were estimated to add another $339 billion resulting in total cost for musculoskeletal conditions of $849 billion, or 7.7 percent of the GDP (AAOS, 2008).

A recent systematic review of the MSD epidemiology literature examined studies that allowed assessment of an interaction between the two fundamental risk factors of force and repetition (Gallagher and Heberger, 2013). Twelve studies were identified that allowed assessment of the interaction between force and repetition and MSD risk. Of these, ten studies demonstrated a consistent pattern of interaction between these risk factors. This pattern of interaction was observed over a wide range of disorders, including LBDs (Zurada et al., 1997), carpal tunnel syndrome (Silverstein et al. 1987), hand/wrist tendinitis (Armstrong et al.,1987), lateral epicondylitis (Haahr and Andersen, 2003; Shiri et al., 2006), shoulder tendinitis (Frost et al., 2002), and nerve conduction signal latency - a diagnostic test for CTS (Nathan et al., 1988).

Authors of this systematic review noted that the pattern of the Force x Repetition interaction observed in these studies strongly suggests an underlying fatigue failure process in exposed tissues (Gallagher and Heberger, 2013). All known materials experience fatigue failure, and it would be surprising if biomaterials in vivo did not also share this inherent property of materials. However, none of the currently available ergonomics assessment tools have taken advantage of the insights of fatigue failure theory to assess MSD risk, nor have epidemiology reviews recognized the interaction between force and repetition as an expected consequence of a fatigue failure process in musculoskeletal tissues.

Additional evidence supporting the MSD fatigue failure hypothesis was recently demonstrated in a rat model of MSDs (Barbe et al. 2013). Specifically, tissue pathology of tendons, cartilage, and bone, as well as expression of inflammatory serum cytokines were all found to exhibit the same pattern of force and repetition interaction demonstrated in the epidemiology studies discussed above. Not only did the tissue pathology results appear to confirm a fatigue failure process at the tissue level, the cytokine response (usually indicative of the extent of tissue injury) demonstrated a Force x Repetition interaction.

The authors explored options for examining whether a fatigue failure process might be evaluated in human tissues *in vivo,* and determined that one available method would be to examine the inflammation responses associated with eccentric muscle contractions. Individuals who experience eccentric bouts of exercise will experience a short-term inflammatory response (peaking 2-4 days post-exercise) that is healed over the period of 1-2 weeks, and will subsequently enjoy a training benefit (a resistance to damage from similar eccentric exertions) that may last up to 6 months. Thus, the purpose of the current study was to examine whether inflammatory responses to various levels of force and repetition during eccentric exercise exhibit a force-repetition interaction.

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METHOD

Subjects

All experimental procedures were reviewed and approved by the Auburn University Institutional Review Board (IRB). Twenty-four subjects (18 males and 6 females) participated in this study. Demographics of the participants are shown in Table 1. Subjects were paid $200 for their participation in the study.

Table 1. Subject demographics

	Male	Female
Age	25.5 (± 3.2 SD)	23.7 (± 2.8 SD)
Height (cm)	174.0 (± 6.1 SD)	162.2 (± 11.1)
Weight (kg)	83.0 (± 14.5 SD)	60.0 (± 11.8 SD)

Experimental Design

Subjects were randomly assigned to one of four force-repetition categories: low force, low repetition (LFLR), low force, high repetition (LFHR), high force, low repetition (HFLR) or high force, high repetition (HFHR). Each subject had a baseline MRI taken prior to the performance of the required exercise on day 0. Other baseline measures included relaxed elbow angle of the subject non-dominant arm, and isometric strength with the non-dominant arm at a 90-degree angle. MRI data acquisition procedures are detailed below. A follow-up MRI was obtained on day 2 post-exercise. In addition, measures of relaxed elbow angle and isometric strength were obtained during follow-up visits on days 1, 2, 4, and 8 post-exercise. It was hypothesized that these measures would demonstrate a specific pattern of interaction between force and repetition.

Eccentric Exercise

Peak isometric strength measures were used to set force levels for the eccentric trials. Subjects performed three tests of isometric maximum isometric elbow flexion strength at 90 degrees of elbow flexion, with each trial separated by 2 minutes. Participants were then asked to do the eccentric contraction regimen which involved eight sets of contractions at their prescribed force and repetition assignment using their non-dominant arm (Figure 1). High force eccentric contractions were set at 120% of the maximum isometric capacity, while low force contractions were set at 60% of the isometric max. Low repetition tasks were defined as two repetitions per set while high repetition tasks were eight reps per set. Each set of eccentric exercise lasted approximately 1 minute and was followed by a 30 second rest period. Subjects were given visual feedback on the amount of force they were producing on a video screen and were instructed to match the required torque for the condition as closely as possible. The duration of each eccentric contraction was 2 seconds and the dynamometer arm (see Figure 1) moved at a speed of 60 degrees per second.

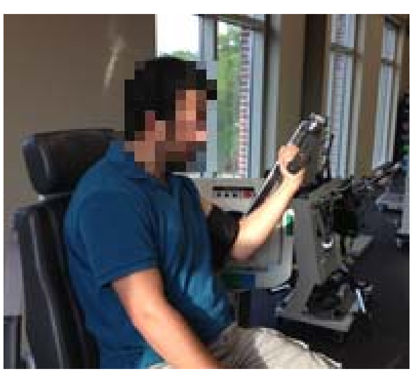

Figure 1. Subject performing eccentric exercise on Biodex.

MRI Data Acquisition

A 3 Tesla clinical scanner (Siemens AG, Erlangen, Germany) with a flexible RF coil wrapped loosely around the subject's arm and centered on the elbow joint was used to perform all magnetic resonance imaging. T2-weighted, turbo spin echo sequences were used in each MRI session to create multi-slice, two-dimensional structural images. A phantom filled with 0.05 molar copper sulfate solution was placed under the coil and next to the subject's arm to become a reference contrast region in each acquired image.

The T2-weighted images (useful for examining for evidence of edema) were evaluated for changes in signal due to edema related to the exercise. As can be seen in Figure 2, various regions were segmented for a contrast-noise ratio (CNR) analysis. These included the elbow flexor group in red (muscles affected by the eccentric exercise), the elbow extensor group in green (unaffected by exercise), the entire arm circumference (in pink), as well as the copper sulfate solution (blue) and a background region (yellow). The CNR ratio was calculated by comparing the CNR for the elbow flexors to the elbow extensors at Day 2 (post-exercise) versus the same comparison on Day 0 (pre-exercise).

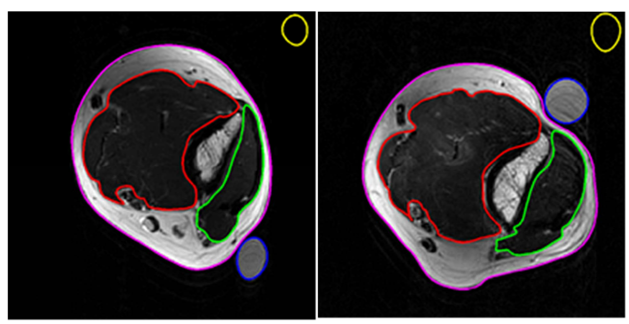

Figure 2. Baseline (left) and day 2 (right) MRI images for subject in HFHR condition. Elbow flexors are outlined in red and elbow extensors are outlined in green. Note increased signal intensity in elbow flexors on day 2 (indicative of inflammation).

Isometric Strength

In addition to the baseline data, isometric strength assessments were performed on days 1, 2, 4, and 8 post-exercise. Isometric strength is considered one of the best measures of the degree of damage and subsequent recovery of the exposed muscle groups in the period after eccentric exercise (Prasartwuth et al., 2005). Three tests of isometric strength of the affected (non-dominant) arm were obtained on each of the follow-up days, with each trial being separated by 2 minutes as with the baseline isometric data collection. The percentage decrease in isometric strength for each follow-up day was calculated with respect to the baseline value.

Data Analysis
MRI data were analyzed using a custom MATLAB program, which permitted Contrast to Noise Ratio (CNR) analysis of muscles affected by the eccentric exercise (elbow flexors) versus those not affected by the exercise (elbow extensors). Edema in the inflamed muscle presented as increased signal in the MRI image (lighter color), and differences in the CNR was calculated at baseline and at day 2 in the same subject, with the former being subtracted from the latter to evaluate the inflammatory response. Subjects were requested to avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) for at least the first two days to avoid the inflammation reducing characteristics of these drugs, which could moderate the edema response. Subjects reported compliance with this request. Additional information for this study is reported in Gallagher et al. (2014).

RESULTS

MRI CNR results
While the expected pattern of response was generally observed (see Figure 3), the interaction between force and repetition was not statistically significant ($p > 0.05$) for the CNR analysis. Force was significant main effect ($p < 0.05$).

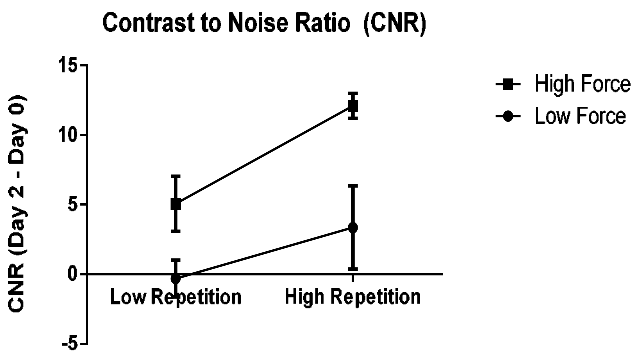

Figure 3. CNR responses for force-repetition categories. Force x repetition interaction was not significant ($p > 0.05$). Force was a significant main effect ($p < 0.05$)

Relaxed Elbow Angle
Figure 4 provides the data pertaining to resting elbow angle responses for the various force-repetition groups. Data on resting elbow angle was summed over the period of maximum inflammatory response. A significant force-repetition interaction was observed, with a high response among those experiencing the HFHR condition ($p < 0.001$).

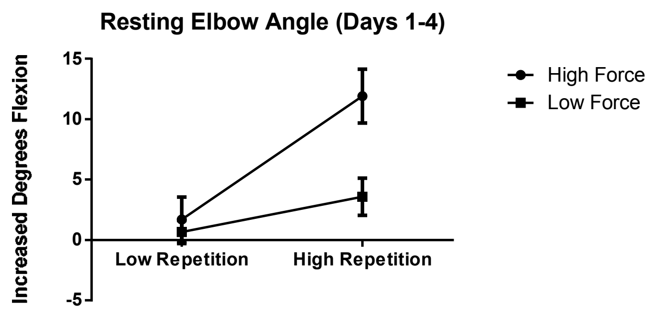

Figure 4. Sum of relaxed elbow angle values summed over days 1-4 post exercise. Force x repetition interaction significant at $p < 0.001$.

Isometric Strength
Figure 5 presents data regarding the average percentage decrease in isometric strength during the follow-up days after eccentric exercise compared to baseline values.

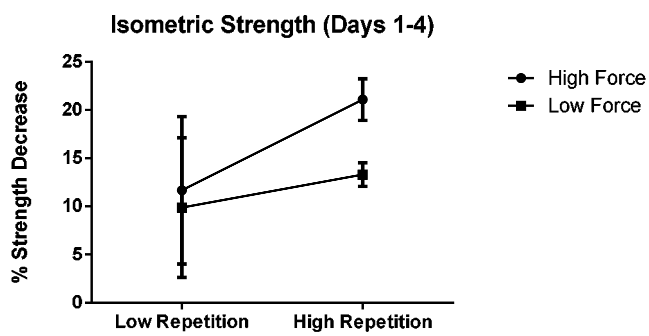

Figure 5. Isometric strength decrease averaged over days 1-4 post exercise. Force x repetition interaction significant at $p < 0.01$.

Force-repetition interaction estimates
In a 2 x 2 analysis of the sort depicted here (involving two levels each for force and repetition), the estimate of the interaction effect is represented by the "difference of the differences". Specifically, the estimate of the interaction effect (L) in our specific case may be given by:

$$L = (HFHR-HFLR)-(LFHR-LFLR)$$

If we examine the estimate of this interaction effect for each of the dependent measures reported in this paper, we can test the consistency of the responses to the eccentric exercise. Table 2 provides the estimates for the CNR comparisons between day 2 versus day 0 as well as individual estimates for change in relaxed elbow angle and % isometric strength decrease for days 1, 2 and 4. As can be seen from this table, the interaction effects was always found to have a positive value, indicating that the difference between HFHR-HFLR was always greater than LFLR-LFLR.

Table 2. Estimates of the force –repetition interaction effect (L) for dependent measures.

Measure	HFHR	HFLR	LFHR	LFLR	L
MRI CNR (D2-D0)	12.3	5.1	3.4	-0.3	3.5
Δ relaxed elbow angle(°), (D1-D0)	11.6	3.8	2.8	1.7	6.7
Δ relaxed elbow angle (°) (D2-D0)	9.8	0.7	2.6	-0.2	6.3
Δ relaxed elbow angle (°) (D4-D0)	14.3	0.5	5.3	0.5	9.0
% decr. isometric strength (D1-D0)	20.5	19.1	13.8	16.9	4.6
% decr. isometric strength (D2-D0)	23.5	12.1	14.2	10.3	7.6
% decr. isometric strength (D4-D0)	19.3	3.8	11.9	2.4	6.0

DISCUSSION

The purpose of the current pilot study was to investigate whether force-repetition interactions were evident with respect to various measures related to muscle damage and inflammation after exposing subjects to various force and repetition levels in eccentric exercise. This was considered a method of investigating whether a fatigue failure process is responsible for tissue damage *in vivo*.

Results of this pilot study provide partial support for the hypothesis that a fatigue failure process may be responsible for the damage experienced by muscle tissue subjected to eccentric exercise. The strongest support came from the data on relaxed elbow angle and isometric strength decrease. The change in the resting elbow angle after intense eccentric exercise is thought to involve an increased influx of calcium ions into the muscle, thought to be due to a defect in the sarcoplasmic reticulum (SR) that occurs in concert with the muscle damage associated with eccentric contraction (Cleak and Easton, 1992). In this study, a clear force x repetition interaction in the elbow angle indicated that the damage to the SR follows what would be anticipated with fatigue failure in the muscle tissues.

Isometric strength is another measure that demonstrated a force-repetition interaction of the expected form. Measures of isometric strength are considered to be the best overall indicator of the health of the muscle and/or damage thereto following eccentric exercise (Prasartwuth et al. 2005). The isometric strength findings echo those of the relaxed angle analysis that suggest that HFHR conditions generate considerably more damage than other force-repetition combinations, congruent with the fatigue failure hypothesis.

The CNR analysis from the MRI images showed the general pattern anticipated, but significant between subjects variability was present and did not result in a significant force-repetition interaction from being detected. Several issues may have interfered with the MRI analyses. For one thing, some subjects had difficulty remaining still throughout the time required for MRI data acquisition, resulting in movement artifacts. This could be addressed in the future by reducing the time of the MRI data collection by reducing the number of slices obtained.

In summary, all of the dependent measures described in this paper demonstrated a pattern of response suggestive of an interaction between force and repetition. Some of these achieved statistical significance while others did not. The fact that some measures did not achieve statistical significance may have been due in part to a lack of statistical power. The "between subjects" nature of the experimental design is not ideal in terms of statistical power due to the considerable between-subjects variability. However, in this case a within-subjects design is not feasible since exposure to eccentric exercise provides a training effect that makes within-subjects comparisons unreliable. This represents a limitation to the current pilot study that can be addressed with larger sample sizes in future studies.

CONCLUSIONS

Based on the findings of this study, the following conclusions are drawn:

1. Changes in relaxed elbow angle and isometric strength after eccentric exercise exhibited force-repetition interactions congruent with what would be expected if muscle damage were due to fatigue failure of the affected tissues.
2. Results of MRI analysis on edema in the muscles after eccentric exercise showed the general pattern of force-repetition interaction anticipated from fatigue failure theory, but did not achieve statistical significance.
3. The results of this study provide support for the theory that MSDs are the result of a fatigue failure process.
4. Use of eccentric exercise as a method of examining fatigue failure of muscle tissues in vivo appears fruitful as a research technique and further research may incorporate measures such as creatine phosphokinase and inflammatory cytokines.
5. Future studies using this technique may need to incorporate a larger number of subjects due to the significant between-subjects variability observed with certain dependent measures.

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