Impact of Loading and Rest Intervals on Muscle Inflammation

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Abstract

The efficacy of many existing musculoskeletal disorders (MSDs) treatment and preventive approaches remains unclear in current literature. Instead of applying additional measures that generate additional costs, redesigning the job in a MSD preventive way in the first place could be a cost effective and health promoting alternative. Manipulating rest intervals and load-repetition combinations within the work time and workload capacity constraints could qualify one of the beneficial alternatives. The purpose of this study is to determine whether different load-repetition combinations and rest intervals with different frequencies and durations would have an impact on the inflammatory response of the muscle and the development of MSDs within certain constraints -- predetermined total work time, total rest time and total work volume.

In this study, a total of 24 healthy college men with homogenous anthropometry measures will be randomly assigned to a 19-minute bicep eccentric exercise task including a total of 4-minute rest time. The total workload for all eccentric exercise treatment combinations is 27 times the maximum voluntary isometric contraction (MIVC). Within the shift, the subjects will be randomly assigned to 90% MIVC or 30% MIVC workloads; each subject will also be assigned with 2 minutes or 0.5 minute rest intervals. This pilot study uses the recoverable short-term delayed onset muscle soreness (DOMS) analogous to the long-term MSDs to imitate muscle inflammation and healing processes in MSD cases. Three physical responses: serum CK level (a quantitative marker for skeletal muscle microtrauma), MIVC (a good measure of the degree of muscle recovery), and muscle soreness are measured before exercise and at days 1, 2, 4, 8 post-exercise of the human elbow flexor muscles. A two-factor (loading and rest interval) factorial regression model will be established for muscle inflammatory response.

The findings of the study would assist in understanding the effect of loading and rest on muscle inflammatory response and healing process as well as designing jobs with suitable rest intervals and load-repetition balance to prevent MSDs at manufacturing settings. The statistical regression model could provide guidance to implement ergonomic assessment tools.

Purpose and Benefit of the Proposed Research

Musculoskeletal disorders (MSDs) represent one of the leading causes of lost work days in industry, are associated with major economic costs (AAOS, 2009), and are a NORA research priority area (NIOSH, 2006). In 2004, 16.3 million strains/sprains were treated in the U.S. healthcare system, and the estimated cost of treating musculoskeletal injuries was $127.4 billion (AAOS, 2008). MSDs have shown to be more severe than the average nonfatal workplace injury or illness, to require longer recovery times, and to be responsible for millions of lost work days every year (AAOS, 2008). Several known MSD risks include high force demands, high repetition rates, awkward postures, and long durations (Bernard, 1997; Hoogendoorn et al., 1999). Several well advocated treatment approaches include thermotherapy (use ice or heat at the site of pain) (Wyss and Patel, 2013), massaging (Marcus, 1998), medications and dietary supplements such as protease enzyme that modulate the inflammatory response (PhRMA, 2011).

Preventive measures include stretching and warm-up programs (Choi and Woletz, 2010). However, the efficacy of these therapeutic and preventive approaches has not been convincingly validated (Marcus, 1998; Choi and Woletz, 2010; PhRMA, 2011; Wyss and Patel, 2013). In addition, to uniformly implement such programs at manufacturing occupational settings could be a costly engineering economic decision to make. Rather than pursuing the post hoc remedies, taking the concept of minimizing musculoskeletal injury when designing the tasks and jobs could be a less invasive, more cost effective and more worker-health-promoting approach.

This study chose eccentric muscle exercise as the experiment method because it provides a basis for examining the impact of load-repetition and rest frequency on muscle tissue fiber damage, inflammation, and repair in a situation where damaged muscle fibers are completely healed in approximately one week (Parasartwuth et al., 2005; Liao, 2010; Komi and Buskirk, 1972). Eccentric exercise also leads to muscle soreness and tenderness, often termed delayed-onset muscle soreness (Schwane et al., 1983; Ebbeling and Clarkson, 1989; Jones et al., 1989; Clarkson et. al., 1992; Cleak and Eston, 1992). The damaged fibers get repaired by fibers almost identical in nature to those damaged. And the repaired fibers actually become more resistant to eccentric damage experienced subsequently (Komi and Buskirk, 1972; Newham et al., 1987; Clarkson and Tremblay, 1988; Faulkner et al., 1992, 1993). This transient eccentric training effect provides the opportunity to assess damage to musculoskeletal tissues in manner where the damage produced is reversible and may even provide a training benefit to participants.

This study aims to reduce the number and severity of

MSDs among manufacturing sector workers (Strategic Goal 3; Intermediate Goal 3.1, NORA Manufacturing Sector Council). This project will contribute to the NORA Manufacturing Sector Strategic Goals by determining the impact and potential benefit of certain rest frequencies when total work volume, total rest duration and shift duration are pre-determined (Intermediate Goal 3.3; Activity/Output Goals 3.3.1 and 3.3.2). Compared to some of the existing preventive and post-traumatic treatment programs such as massaging and anti-inflammatory medication, implementing suitable rest intervals and designing a load and repetition combination that contributes to lower injury rate could serve as a more cost-effective intervention approach (Activity/Output Goal 3.2.2, 3.2.3). The research findings could also present evidence for future ergonomic assessment tool design to incorporate rest interval considerations. (Intermediate Goal 3.2)

Specific Aims

The specific aims of this study are:

1. To randomly assign 24 subjects with relatively homogenous anthropometric features (in order to reduce nuisance factors) to non-dominant arm bicep eccentric exercises consisting low-force high-repetition or high-force low-repetition paired with frequent but short duration or infrequent but long duration rest intervals. There will be a total of four treatment combinations: high-load high-rest (HLHR), high-load low- rest (HLLR), low-load high-rest (LLHR), and low-load low-rest (LLLR);
2. To evaluate serum CK levels of the 24 subjects before exercise and 1, 2, 4, 8 days after exercise;
3. To evaluate the degree of MIVC force and muscle soreness before exercise, immediately after exercise and 1, 2, 4, 8 days after exercise;
4. To evaluate whether any or all of the dependent measures are influenced by the independent variables of load-repetition combination, rest interval choice and or their interaction.

Significance

One factor considered in this study is loading with different rates (different number of repetitions per minute). This factor is valuable to study on because force and repetition have long been recognized as key risk factors influencing the development of MSDs. However, no study has been conducted to explore the significance over different load-repetition combinations when total work volume and total work time are set as simultaneous constraints. According to the Palmgren-Miner Rule (Formula 1), variable loading may cause dramatically different mechanical tissue damage with the same total work volume when task completion time and rest time are unknown (Example 1) (Hashin, 1980).

The other factor considered in this study is rest intervals. Living tissues have the ability to heal themselves over time. It would be inaccurate to calculate the tissue damage without taking rest intervals in which they heal into consideration. For living tissues, total tissue damage experienced over time equals to the difference between damage due to mechanical stress and healing over time (Formula 2).

Cumulative Trauma Disorders (CTDs) including MSDs' symptoms increase over time with insufficient rest periods for muscle healing (Figure 1) (Thomas, 2013). It is yet unclear whether muscle healing follows linear, exponential or logarithmic patterns (Gallagher, 2013). Minimal research has been done to investigate how longer or shorter rest intervals within defined total rest duration would remedy or exacerbate the MSD risk factors (Gallagher, 2013). To the authors' knowledge, no currently existing ergonomic tool developed to assess MSDs appears to have taken rest interval duration and frequency into consideration.

Should the proposed study provide evidence that resting more frequently but of shorter duration, or less frequently but of longer duration given the total rest duration has influence on muscle tissue fiber disruption/inflammation, isometric force decrements, and muscle soreness when exercising with a specific load repetition combination at a certain total work volume, it would provide further evidence that rest frequency should be incorporated into future models and tools used to assess MSD risk. It is hoped that this study would provide guidance to suitable rest/break frequency implementation in manufacturing job design in order to prevent MSDs.

Research Strategy: Methods to Accomplish the Proposed Aims

Subjects

24 healthy men between the ages of 20 and 24 will be recruited to participate in this study. Qualified subjects do not currently use medical drugs, dietary supplements, or anabolic steroids, and are free of joint, muscular or cardiovascular diseases. Qualified subjects should not have performed eccentric exercise on the non-dominant arm bicep (to rule out any training effect) and will agree not to perform eccentric, concentric, isometric or other forms of weight training the week before, during and after the experiment. Each qualified subject will be given a written informed consent prior to participating in the study. The study protocol will require approval by the Auburn Institutional Review Board (IRB). Subjects will be randomly assigned to one of the four treatment combinations: HLHR, HLLR, LLHR, or LLLR. Subjects will be compensated for their participation in this study ($200 per subject).

Sample Size and Number of Replicates

The number of replicates for each treatment combination is determined with the assistance of the operating characteristic curve for a two-factor factorial design (Montgomery, 2012). The desirable power for this human-subject study is 0.70 or higher. This study uses 6 replicates per treatment combination because statistical power associated with 6 replicates is almost as high as 1.00 (Calculation 3).

Dependent Measures

A number of dependent measures will be collected before and after the prescribed eccentric exercise: serum CK levels obtained from 5-ml of dominant arm elbow flexor serum samples, MIVC and muscle soreness (collected immediately prior to exercise, 1, 2, 4, and 8 days after exercise).

Eccentric Exercise

Each subject will perform a bout of controlled eccentric exercise using the elbow flexors of the non-dominant arm according to their random assignment to the 4 treatment combinations. The arm will start with elbow flexed at approximately 60 degrees elbow excluded angle (Figure 2) and will end with the 180 degrees elbow excluded angle (elbow fully extended) (Figure 3). A computerized metronome will be used to assist subjects in performing a lengthening contraction lasting 30 seconds each if the subject performs high load exercise or 10 seconds each if the subject performs low load exercise. The total exercise period will last up to 19 minutes; however, subjects will be free to terminate the exercise period prior to this point due to discomfort associated with the eccentric exercise.

The total work volume for each individual subject will be 27 times his MIVC. High load conditions will be set at 90 % of the subject's MIVC with the elbow flexed at 90 degrees. Low load will be established at 1/3 of the high-force value. High rest conditions will be set to 2-minute rest intervals (a total of 2 rest intervals); low rest conditions will be set to 0.5-minute rest intervals (a total of 4 rest intervals). The rest intervals (4 minutes) are evenly distributed throughout the effective exercise time of the bout (15 minute). In addition, each subject will practice the timing of contractions with the dominant arm prior to the exercise. (See attachment for EAMC RehabWorks Sports Medicine Outreach Letter of Support.)

Maximum Isometric Voluntary Contraction

MIVC is considered to be the best method to quantify the degree and time-course of muscle injury and recovery after exposure to lengthening contractions (Warren et al. 1999). Subjects will perform three MIVCs with the elbow flexed at 90 degrees before the eccentric exercise, immediately after the exercise, and at days 1, 2, 4, and 8. This will permit assessment of any deficit in strength and recovery should certain loading and rest interval combinations lead to temporary decreases in isometric force capacity due to the temporary muscle fiber damage and subsequent fiber regeneration that occur with eccentric exercise.

Muscle Soreness

Before any contraction is performed in any session, a force transducer with a circular disc will be applied perpendicularly to the skin over four reference parts of the biceps to determine the amount of force at which subjects report any discomfort or pain. The reference spots will be on the medial and lateral aspects of the middle and distal portion of the muscle. Subjects will be asked to identify a spot of soreness 24 hours post- exercise, which will be used for subsequent assessments.

Serum Creatine Kinase Sample Collection and Analysis

A baseline 5-ml blood sample will be taken from the dominant arm anticubital vein immediately prior to exercise, and 1, 2, 4, and 8 days after exercise from each subject. The blood sampling and analysis will take place at the Auburn University Medical Clinic (AUMC). The serum sample data will be securely transferred to the Occupational Safety and Ergonomics (OSE) lab at Auburn University. The samples taken prior to the exercise will serve as the skeletal muscle microtrauma comparison baseline. (Chiang, 2009; Evangelista et al., 2011) The samples taken on the dates post-exercise will be used to analyze the possible trending of serum CK level over time. (See attachment for AUMC and Phlebotomist Training Letters of Support.)

Statistical Analysis and Regression Model

The data from this study will be analyzed using repeated measures ANOVA to examine the significance of load-repetition combination, rest intervals, and their interaction under high force conditions. Data will be analyzed using Minitab. A two-factor factorial regression model will be built for muscle inflammatory response with two variables: loading and rest intervals. (Formula 3)

Experiment Procedures

Step 1 Subjects will fill out a medical screening form to ensure that they are not experiencing any pain or discomfort in the non-dominant limb that would preclude participation in the study. Then the subjects will read and sign the informed consent and are allowed to raise any question or concern before signing the consent or starting the experiment.

Step 2 Subjects will be randomly assigned to one of the 4 task types. Subjects will report to the AU Medical clinic and EAMC RehabWorks for initial session (day 0). 5 ml blood will be drawn from each subject at the clinic to measure pre-exercise CK level. Initial muscle soreness will be tested. The subject will then perform three MIVCs using the non-dominant arm at an elbow flexion angle of 90 degrees. Each MIVC will be separated by a rest period of 2 minutes (Caldwell et al. 1974).

Step 3 Subjects will perform the prescribed bout of eccentric exercise. Each subject will practice the timing and precision of performance with the dominant arm prior to the exercise. Subjects will be free to terminate the exercise period prior to this point due to discomfort associated with the eccentric exercise.

Step 4 On days 1, 2, 4, and 8 post-exercise, the subjects will report to AUMC for follow-up blood sample in order to have their post-exercise serum CK level measured. They will report to the EAMC RehabWorks for MIVCs measurements. Subjects' muscle soreness will also be assessed on these days with the force transducer.

Step 5 Two-way ANOVA method will be used to assess differences in response among different assigned task types. Two-factor factorial regression model for muscle inflammatory response with two coded variables (loading and rest interval) will be built as future ergonomic assessment tool design guidelines.

If the statistical analysis concludes that certain loading level and rest interval demonstrate a significant decrease in MSD risk, in terms of decrease in serum CK level, in isometric strength, and in muscle soreness, it will be the first time for rest interval to be taken into consideration when assessing human tissue inflammation *in vivo* with different load-repetition combinations and when total work volume, total effective work time and total rest time are predetermined in the work scenario.

These findings would provide support for additional and larger research grants to examine rest intervals, loading and their interaction in a wide range of disciplines. These may include (but are not limited to) the design implementation of manufacturing jobs, research in the animal models, tolerance of cadaveric tendons, ligaments, and spinal motion segments focusing on tissue fatigue life, and the development of ergonomic assessment tools that incorporate rest intervals, load-repetition combination within the above-mentioned constraints that may better diagnose MSD risk in the occupational setting.

Appendix

*30 N * 80 Repetitions = 80 N * 30 Repetitions = 2400 N*

Calculation 1. Different % UTS and Number of Repetitions Could Share the Same Total Work Volume yet Pose Drastically Different Musculoskeletal Injury Risks

*90% * MIVC * 2 repetition/minute * 15 minutes = 30% * MIVC * 6 repetition/minute * 15 minutes = 27MIVC*

Calculation 2. All subjects' total work volume is 27MIVC

Number of Replicates (n)	ϕ^2	Φ	V1	V2	Power
4	7.26	2.69	1	12	0.65
5	9.05	3.01	1	16	0.71
6	10.86	3.30	1	20	~1.00

Calculation 3. Sample Size and Number of Replicates Determination

Assume UTS (Ultimate Tissue Strength) to be 100 N. The cumulative loads for lifting 30 N for 80 repetitions and lifting 80 N for 30 repetitions appear to be identical: 2400 N (Calculation 1). The estimated cycles to failure at 30 N (30% UTS) and 80 N (80% UTS) are 51,383 and 37 respectively; the estimated % Cycles to Tissue Failure are 0.15% and 81.1% respectively. In both cases, the tissue experience a total of 2400 N load, but the effects in terms of mechanical tissue failure are dramatically different (Gallagher, 2013). In this study, the total work volume for all subjects is 27 times their individual MIVC (Calculation 2).

Example 1. Variable loading may cause dramatically different mechanical tissue damage with the same total work volume

$$c = \sum_{i=1}^{n} \frac{n_i}{N_i} = \frac{n_1}{N_1} + \frac{n_2}{N_2} + \frac{n_3}{N_3} + ... + \frac{n_k}{N_k}$$

Formula 1. Pulmgren-Miner Rule: Fatigue Failure Model with Various Loading

$$D(t) = D_S(t) - H(t)$$

Formula 2. Muscle Damage over Time Taking Living Tissue Healing Ability into Consideration

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \epsilon$$

Formula 3. Two-factor Factorial Regression Model. x_1: Loading; x_2: Rest Interval.

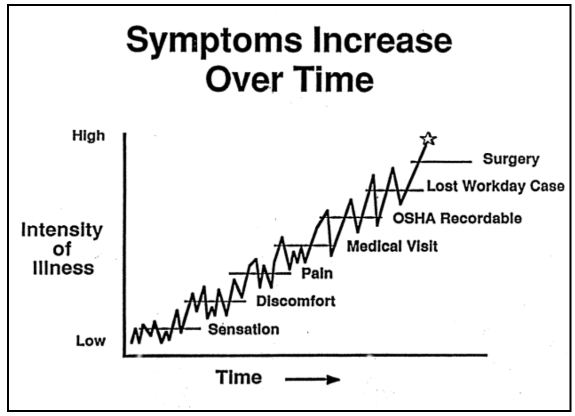

Figure 1. Cumulative Trauma Disorder (CTD) Symptoms Increase Over time

Figure 1. Bicep Eccentric Exercise: Flexed Posture

Figure 2. Bicep Eccentric Exercise: Extended Posture

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