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Skeletal Muscle Recovery and Vibration

Garrett Collier Jones

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

Jonathan D. Blotter, Chair
J. Brent Feland
Mark B. Colton

Department of Mechanical Engineering
Brigham Young University

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ABSTRACT

Skeletal Muscle Recovery and Vibration

Garrett Collier Jones
Department of Mechanical Engineering, BYU
Master of Science

In the past decade there has been a significant increase in focus on the effect upper body vibration (UBV) has on the recovery of skeletal muscle after exercise-induced muscle damage. Recovery can be defined and investigated using a wide variety of methods. This study used three different measurements to track muscle recovery over 7 days following an exercise muscle damage protocol and applied vibration to a mathematical model. A visual analog scale (VAS) was used to measure muscle pain, a strain gauge was used to obtain maximum voluntary isometric contraction (MVIC) strength measurements, and shear wave elastography (SWE) represented muscle stiffness over the 7-day experiment. Thirty-three participants were divided into three groups. The first was a control group (C) that experienced no exercise and no therapy. The no vibration group (NV) performed the damage an exercise protocol but received no therapy. The vibration group (V) performed the same exercise protocol but also received vibration therapy. The exercise protocol consisted of 100 dumbbell curls at starting at 50% of their MVIC with one minute of rest after each set of ten. The data provided convincing evidence (27.2%, $p < 0.0001$) that group NV was not back to its normal stiffness after 7 days unlike group V, which was shown not to be any different from its baseline at the end of the week (9.15%, $p = 0.137$).

Three vibration factors (v_1, v_2, v_3) were added to a skeletal muscle regeneration model (SK) to simulate how vibration affects muscle regeneration. The three factors were determined by analyzing previous research to understand how vibration affects cells in the regeneration process. Adding these into SK decreased the time to recovery from about 13 days to about 7 days. Recovery was defined by reaching 10% of the original number of myofibers within the damaged muscle.

Keywords: skeletal muscle, shear-wave elastography, exercise-induce muscle damage, recovery

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1 INTRODUCTION

The time it takes for human muscle to recover after exercise-induced muscle damage can be a limiting factor in strength training. Aside from medications and rest, adjunctive therapies used to recover from such damage include massage, heat, and ice treatments. Research is being done on how effective vibration and these therapies are in helping the body recover from exercise-induced muscle damage as well as what physical changes they cause in the body [1–5].

One part of muscle recovery is the regeneration of the damaged muscle tissue. Mathematical models may be able to be used to effectively simulate skeletal muscle regeneration after exercise-induced muscle damage. To date, a few models have been previously created that simulate skeletal muscle regeneration of diseased muscles [6–8]. Recently a study used these previous models to create a basic simulation of the regeneration of healthy muscle after it has been damaged [8]. This model presents the regeneration process as a function of immune and myogenic responses. The effect vibration has on the cells in these responses conveys how upper body vibration affects muscle recovery.

One objective of this thesis is to determine whether upper body vibration (UBV) affects muscle recovery by conducting an UBV experiment. This experiment monitored muscle recovery over 7 days by measuring perceived pain of the muscle with a visual analog scale (VAS), muscle strength using a maximum voluntary isometric contraction test (MVIC), and muscle stiffness with shear wave elastography (SWE). Another objective of this thesis is to

propose what effect vibration has on the skeletal muscle regeneration process by researching how vibration changes the influx rates of specific cells in the current regeneration model. The final objective is to compare the results of the first two objectives.

The combination of the UBV experiment and adding vibration to the skeletal muscle regeneration model provided evidence for how effective UBV is as a recovery therapy. The experiment and the model were used to determine whether UBV has a direct impact on skeletal muscle recovery. Despite it being difficult to study the direct effect of vibration inside the human body, the indirect measurements used in this study were used to help decipher the acute effects UBV has on skeletal muscle recovery after exercise-induced muscle damage.

The second chapter of this thesis explores the consequences of using UBV therapy as a method of muscle recovery. This section discusses the setup of the experiment, the participants involved, the recovery measurements and analyses. This chapter is a journal paper being submitted to Journal of Sport Science and Medicine (JSSM). The third chapter introduces the current skeletal muscle recovery model. It reviews what research has been done on how vibration affects the cells in the regeneration process and proposes a new model that includes those effects. This chapter is a journal paper being submitted to the American Society of Mechanical Engineers (ASME). This thesis concludes by discussing the results of these studies and what further research should be performed.

2 SKELETAL MUSCLE AND VIBRATION RECOVERY

2.1 Abstract

This study investigated upper body vibration (UBV) as a therapy for effectively increasing the muscle recovery rate when applied after eccentric exercise. Thirty-three participants (25.8 ± 4.62 , 21), with no recent upper-body training (3 months), were divided into three groups: Control (C), and two exercise groups: No vibration (NV) and Vibration (V). Subjects in the exercise groups performed 100 bicep curls starting at 50% of their assessed maximum voluntary isometric contraction (MVIC) to induce muscle damage. Subjects in the V group received UBV therapy for 5 minutes, on days 1-4 after the exercise. All subjects completed a visual analog scale (VAS), MVIC, and shear wave elastography (SWE) of the bicep at baseline (pre-muscle damage protocol), 24 hours post damage, 48 hours post damage, and 7 days after the damage protocol. These variables of interest were used to measure muscle pain, strength, and stiffness respectively.

Groups NV and V experienced significantly more pain than group C two days after the exercise ($\alpha = 0.007$; 5.67 cm, $p < 0.0001$; 3.96 cm, $p < 0.0001$). There was no difference between the VAS of these two groups on day 2 (1.71 cm, $p = 0.039$) or day 7 (0.46 cm, $p = 0.572$). Groups V and C showed no difference in SWE between day 7 from their baseline (9.15%, $p = 0.137$; 9.45%, $p = 0.097$) in contrast to group NV (27.2%, $p < 0.0001$). The SWE of groups NV and C on day 7 (36.65%, $p < 0.0001$) were different, but not V and C (18.659, $p = 0.034$). There

were no significant differences in the MVIC of any of the groups on day 7 ($\alpha = 0.007$). These results show UBV increases the rate at which muscle stiffness returns to normal but has no significant effect on muscle pain or strength after damage.

2.2 Introduction

Exercise-induced muscle damage occurs after an individual performs a muscle training routine they are unaccustomed to or by overtraining. It results in various muscle damage symptoms such as delayed-onset-muscle-soreness (DOMS) [1–4], loss of muscle strength [1–4], and muscle stiffness [1–3]. Research into applicable methods to aid muscle recovery (i.e., massage, ice etc. [4,9,10]) has been investigated previously. Recently, whole body vibration (WBV) has been introduced as a potential way to decrease symptoms of DOMS [5,11–13]. Since limited studies currently exist, a method of vibration therapy will be investigated in this study to determine its efficacy at improving muscle recovery.

Research suggests that vibration positively affects muscle strength recovery [5,11,12] and recovery from DOMS [11,13], which are two factors in muscle recovery. Muscle recovery occurs as blood flowing through the muscle replaces dead immune cells with new cells that supply the skeletal muscle regeneration process [14–16]. Recent studies have shown that human body vibration increases blood flow and stimulates muscle and hormonal responses [13,17–22]. This study will focus on using UBV on the bicep at low frequency to determine how it affects muscle recovery.

Three different measurements were used to determine the effect UBV therapy has on muscle recovery. A visual analog scale (VAS) was used as a subjective measure of pain in response to the muscle damage protocol. A strength test was used as an indirect measure of

muscle damage [12]. Ultrasonic shear wave elastography (SWE) was used to track intrinsic muscle change and represent a measure of muscle stiffness. Recent studies have shown that SWE can be used to measure the stiffness of a muscle group [23–25]. The stiffness of the muscle is an objective measurement that can be used to suggest muscle recovery [26]. This is significant because some of the differences in previous results may originate from the fact that many measurements used for recovery are subjective rather than objective.

The purpose of this research was to further investigate the effects of vibration on muscle pain, strength and stiffness after exercise-induced damage. An upper body vibration experiment was performed, and its results are presented and analyzed in this paper. It is expected that upper body vibration will affect the symptoms of exercise-induced muscle damage.

2.3 Methods

2.3.1 Overview

The experiment performed in this study was created to investigate the effect of UBV on ratings of perceived pain, muscle strength and muscle stiffness. Each participant was randomly assigned to one of three groups: Control (C), and two exercise groups: No vibration (NV) and Vibration (V). A muscle-damaging protocol was performed by groups NV and V following baseline measurements. Subjects in the V group received vibration therapy to the upper extremities for four out of seven days following the protocol. Group NV did not receive any vibration therapy at any time after the protocol. The C group did not perform the muscle damage protocol or undergo any UBV, but had each measurement recorded. The independent variables were the three groups and the dependent variables for all groups were SWE, MVIC, and VAS

measurements performed at 4 different time points: 1) Baseline (prior to any interventions), 2) 24 hours post exercise, 3) 48 hours post exercise, 4) 1-week post exercise.

2.3.2 Participants

Twenty-four subjects (25.8 ± 4.62 , 21), volunteered to participate in this study. To reduce the amount of possible confounding variables, qualification criteria required that the participant had no current musculoskeletal joint pain or muscle pain related to DOMS, soreness, acute joint disease or history of arm or shoulder injury in the past 6 months. Participation also required that the volunteer had not regularly exercised their upper body in the past 3 months. Each participant was instructed to not participate in any strenuous activity that required the use of their biceps during the 1-week research period and to not use other adjunctive recovery therapies outside the experiment such as massage.

Prior to any measurements being taken, each subject was instructed on the study purpose and protocol. They were informed of the possible risks associated with the research and signed a university approved consent form. Approval for this study was received from the Institutional Review Board (IRB) at Brigham Young University. To prevent any type of placebo effect, they were not told the hypothesis of this study. Pre-exercise Testing

Each subject had their initial VAS, MVIC and SWE (baseline) measurements recorded on day 0. Groups V and NV then performed the damage protocol, and immediately after had their measurements recorded once more (POST). Group V then received UBV therapy. Group C did not perform the damage protocol and only had baseline measurements recorded.

2.3.3 Muscle Damage Protocol

Each participant completed ten sets of ten repetitions of bicep curl exercises using a dumbbell. Each repetition was performed at a rate of approximately one second concentrically raising the arm and three-seconds eccentrically lowering. More time was taken on lowering the arm to assure each participant would experience DOMS. The first two sets were completed using 50% of each participant's MVIC measurement. After these two sets, the weight was dropped by five lbs. for the final eight sets. Participants rested for one minute in between each set.

2.3.4 Vibration

Vibration therapy was induced using a vibration platform (Vibeplate 2424). The vibration was focused on the upper extremities by kneeling on a soft surface and then holding onto the outside edge of the platform (in a position similar to a push-up from the knees). The elbows were bent partially to mimic the frequency testing position (Figure 2-1). The subject was also instructed to lightly squeeze the platform while leaning on it to maintain contact and to facilitate some bicep contraction during vibration.

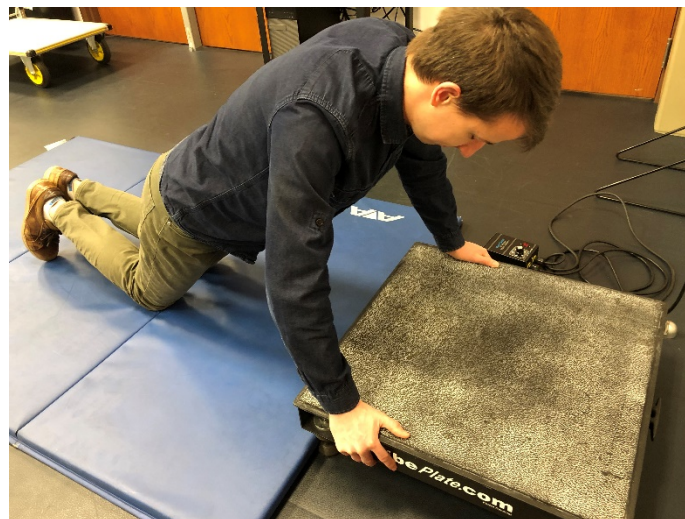


Figure 2-1: Vibration Therapy Setup

Since there is no standard for frequency when testing how vibration affects muscle recovery, the vibration frequency was determined by using the average bicep resonance frequency of participants in a pilot study. In the study, the bicep muscle was excited using pseudo-random noise using a vibration shaker. This noise excites an object with several different frequencies by sending a sequence of random pulses through an object. The object will naturally respond by filtering out most of the frequencies and vibrate at its resonance frequency. The muscle response was measured as seen in Figure 2-2 and Figure 2-3 using a Polytec PSV-500-3D scanning laser Doppler vibrometer (SLDV). The first resonance of the bicep was measured between 15 to 18 Hz. for all participants. Vibrating an object at its resonance frequency results in the largest amplitude response. It was assumed that exciting the muscle close to its resonance frequency would result in the greatest response by activating more motor units and would stimulate it more than other off-resonance frequencies. Therefore, the average of the resonance range (16 Hz.) was used as the frequency of the vibration therapy in this study.



Figure 2-2: Polytec PSV-500-3D Scanning Laser Doppler Vibrometer

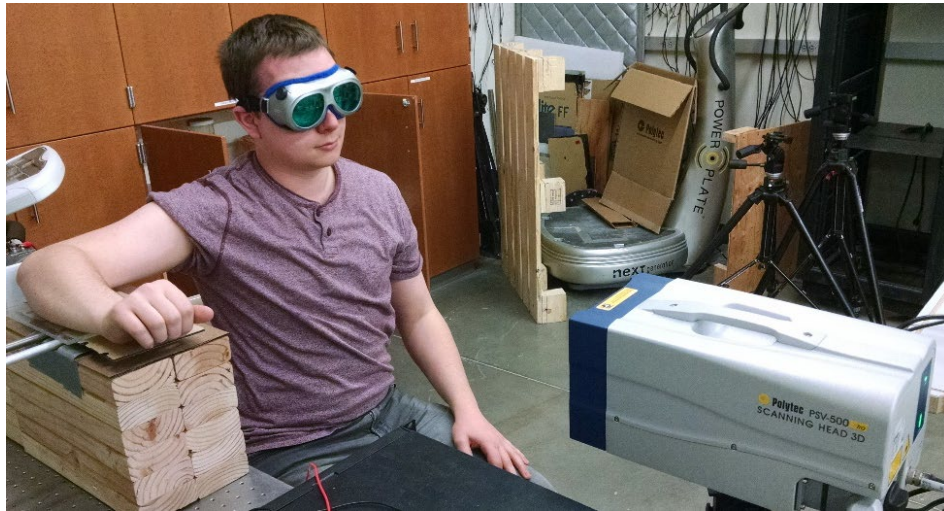


Figure 2-3: SLDV Obtaining Bicep Resonance

2.3.5 Soreness

Soreness was measured using a self-reported visual analog scale 100-mm line with “no pain at all” (0 mm) and “worst pain imaginable” (100 mm) at the two ends. The participant rated their pain by moving their right arm in the motion of a bicep curl. Starting from their arm at 180° the participant then bent their arm up to as close to 0° as possible while staying relatively relaxed and then straightening it out back to 180° again. The subjects then rated their perceived soreness by placing a single vertical line through the VAS, which has been shown to be a reliable measure that soreness is present (add reference: Jensen, MP, and Karoly, P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack, R. ed, Handbook of Pain. New York: Guilford Press; 2001: 135-151). The distance from no pain (mm) was used as the variable for data analysis.

2.3.6 Maximal Isometric Strength

Maximal voluntary isometric strength was measured using a strain gauge load cell. This measurement was performed by the participant pulling isometrically on a cable with their arm at a 45° angle from the vertical and against a wall (). The participant stood with heels, back, elbow and head against the wall each time the measurement was taken. The participant pulled three separate times for three seconds and the maximum value from the three attempts was recorded. We used LabVIEW to transform the voltage to a force (lbs.) for data analysis.



Figure 2-4: Maximum Voluntary Isometric Contraction

2.3.7 Stiffness

Subjects were evaluated for “stiffness” of the lower $\frac{1}{4}$ of the bicep muscle via ultrasound SWE. The positioning of the ultrasound head was longitudinal with the muscle belly of the biceps in the lower $\frac{1}{4}$ of the bicep, and permanent marker spots for the ultrasound head positioning were made to improve reliability of positioning the ultrasound head. Subjects were

instructed to maintain these marks between measurement days and the marks were darkened on all subsequent visits. All elastography measurements were made using a GE Logiq S8 and a 9L head (Figure 2-5 and Figure 2-6). A region of interest within the confines of the bicep muscle was positioned by the ultrasonographer and once the elastogram reading appeared consistent the recording was stopped, and the stiffness rating was recorded from 4 separate screen shot samples taken from the cineloop recording. The software provides the stiffness rating of the muscle in kilopascals. The overall stiffness for each measurement was recorded from the average of four samples taken in the selected area.



Figure 2-5: GE Logiq S8 Ultrasound Machine



Figure 2-6: Ultrasound 9L Head

Samples of the SWE results can be seen in Figure 2-7 and Figure 2-8. The 4 circles in each figure are the samples recorded and averaged from the muscle. The scale on the left shows the colors in the samples relative to stiffness using kilopascals. For our settings, the scale ranged from 0-150, with red being 0 and dark blue at 150. The numbers on the bottom left are the average stiffnesses from each of the 4 sampling circles taken within the region of interest. The samples in Figure 2-7 have an average of 40.53 kPa, while the average of the samples in Figure 2-8 is 111.8 kPa. Figure 2-7 shows the SWE of a participant from the control group that did not experience any exercise-induced muscle damage. The difference between the stiffness of the two participants can be seen in the color of the muscle. The samples with higher stiffness are dark blue in color compared to the green color of the less stiff samples.

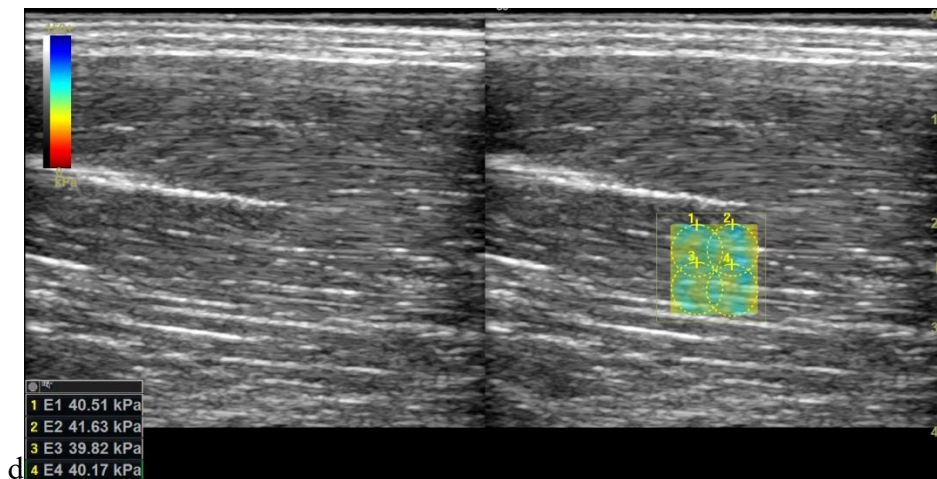


Figure 2-7: SWE Day 1 Group C Sample

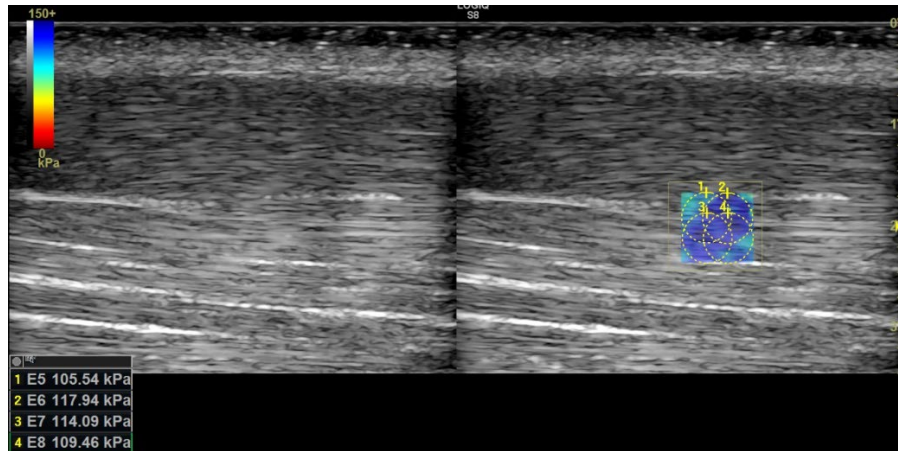


Figure 2-8: SWE Day 1 Group V Sample

2.3.8 Statistical Analysis

The variance and normality of the measurements of three groups were analyzed for each day. The results for each group were shown to be normally distributed but the variance between each day was inconsistent. To avoid error due to inconsistent variance, the data from these measurements were analyzed using least square means studentized t-test. This test compares data without adjusting for multiple comparisons. A Bonferroni multiplier was used to adjust for the increased likelihood of falsely rejecting the null hypothesis that results from doing multiple comparisons. Significance was measured using 95% confidence intervals ($\alpha = 0.05$) but with the Bonferroni multiplier, the strictness of significance increased ($\alpha = 0.007$).

Since stiffness and strength are subject to each participant's unique characteristics, the data for muscle strength and stiffness were normalized using their percent changes from the baseline measurements. Each measurement, for each participant, each day was subtracted from and divided by the baseline value. This allowed for an objective comparison between the results of all participants and groups. The soreness was normalized simply by taking the difference between each measurement each day and the baseline measurement. This was done since

normalizing using percent change would result in dividing by zero. The least square mean of the final measurement was used to analyze the difference between the final and baseline measurements. The least square mean adjusts the actual means based on other factors such as the mean group size.

2.4 Results

2.4.1 VAS

An effects test was done to evaluate the interaction between the groups and days. This provided statistical evidence ($p < 0.0001$) that there was an interaction with the VAS each day. Figure 2-9 shows from the results of this measurement that most of the participants did not feel any pain after 7 days. Table 2-2 shows there was a difference of 1.71 cm (17.1 mm) between the means of group V and group NV on Day 2, the day pain was greatest for both exercise groups. This suggests ($p = 0.039$) there was a significant difference between the pain rating of V and NV groups 2 days after exercise, with the V group reporting lower perceived pain. Both V and NV groups demonstrated significantly greater pain ratings at day 2 as compared to the control group ($p < 0.001$) (See Figure 2-7). Table 2-1 and Table 2-3 show that there was no significant difference between the means of each group on day 7 and their baseline values nor any significant difference between any of the groups on day 7 ($\alpha = 0.007$).

Table 2-1: VAS Percent Change at 1-Week

Therapy Group	Percent Change (cm)	<i>p</i> -value	Confidence Interval
Vibration	-.089	0.890	(-1.27, 1.09)
No vibration	0.374	0.512	(-0.734, 1.48)
Control	0.146	0.786	(-0.866, 1.16)

Table 2-2: Difference between mean soreness values on Day 2

Therapy Groups	Difference (cm)	<i>p</i> -value	Confidence Interval
No Vibration - Vibration	1.71	0.039	(0.089, 3.34)
Vibration - Control	3.96	< 0.001	(2.40, 5.52)
No Vibration - Control	5.67	< 0.001	(4.17, 7.17)

Table 2-3: VAS Difference Between Each Therapy at 1-Week

Therapy Groups	Difference (cm)	<i>p</i> -value	Confidence Interval
No Vibration - Vibration	0.463	0.5722	(-1.16, 2.09)
Control - Vibration	0.235	0.7655	(-1.33, 1.80)
No Vibration - Control	0.228	0.7624	(-1.27, 1.73)

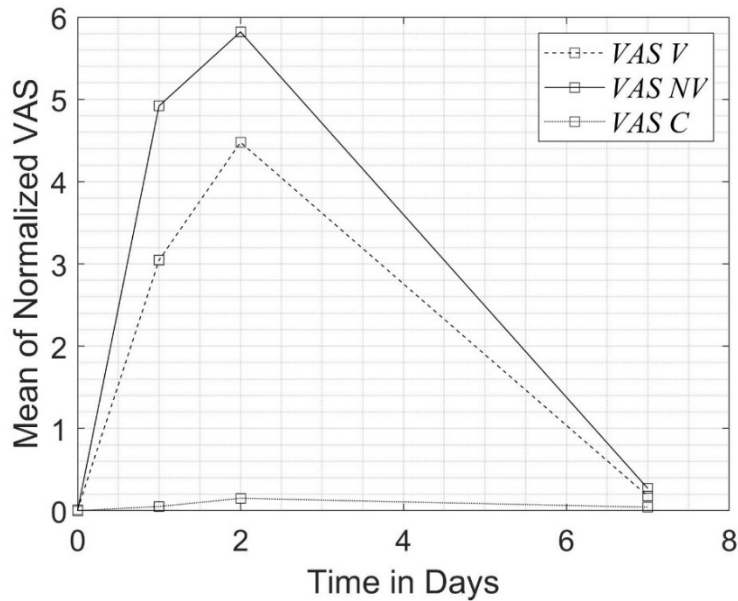


Figure 2-9: Mean of Normalized VAS Values

2.4.2 Muscular Strength

The effect test suggests the therapy influenced the measured strength of the participants ($p = 0.047$). The maximum isometric strength test did not show any distinction between the two exercise groups throughout the week. Table 2-4 shows there is no significant statistical evidence

($\alpha = 0.007$) of any difference between any of the individual groups and their baseline measurement. Table 2-5 likewise shows no statistical significance between the values of any of the three groups at 1-week. Figure 2-10 shows the strength of the exercise groups drops immediately after the exercise but no significant separation between the groups occurs throughout the week.

Table 2-4: MVIC Percent Change at 1-Week

Therapy Group	1-Week Percent Change (%)	<i>p</i> -value	Confidence Interval
Vibration	0.832	0.913	(-0.131, 0.147)
No vibration	5.69	0.370	(-0.068, 0.181)
Control	-2.77	0.640	(-0.141, 0.086)

Table 2-5: MIVC Difference Between Each Therapy at 1-Week

Therapy Groups	Difference Between Groups (%)	<i>p</i> -value	Confidence Interval
No Vibration - Vibration	4.86	0.606	(-0.138, 0.235)
Vibration - Control	3.61	0.561	(-0.144, 0.216)
Control - No Vibration	8.46	0.321	(-0.084, 0.253)

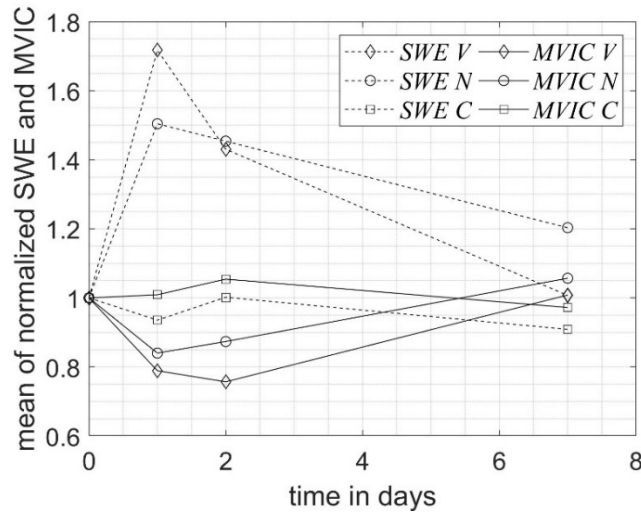


Figure 2-10: Mean of normalized SWE and MVIC values

2.4.3 Stiffness

The SWE measurements provided evidence that the mean bicep stiffness of group V and group C were no different at 1 week from their baseline measurements (Figure 2-10). The confidence intervals for the C and V groups (-0.031, 0.214 and -0.208, 0.019 respectively) both contain zero. This shows that it is possible there was no difference between mean 1-week stiffness and baseline measurements. Their two-tailed p -values are high (0.137 and 0.097 respectively) and provide no evidence ($\alpha = 0.007$) that there is any difference between their mean 1-week and baseline measurements. Group NV does not have zero in its confidence interval (0.156, 0.387) and its p -value is statistically significant ($p < 0.0001$). There is convincing evidence that the null hypothesis, that there is no difference between the 1-week mean of NV and its baseline values, should be rejected. Figure 2-10 shows practical evidence that the mean stiffness measurements of the exercise groups increased by at least 50% the day after the exercise protocol.

The comparison between the three groups 1-week measurement was completed using the least square means student's t test. The results suggest there is a difference between the stiffness of participants in group NV and V as well as groups V and C. There is convincing evidence ($p < 0.0001$) that there is a difference between groups NV and C.

Table 2-6: SWE Percent Change at 1-Week

Therapy Group	1-Week Percent Change (%)	p -value	Confidence Interval
Vibration	9.15	0.137	(-0.031, 0.214)
No vibration	27.2	< 0.001	(0.156, 0.387)
Control	9.45	0.097	(-0.208, 0.019)

Table 2-7: SWE Difference Between Each Therapy at 1-Week

Therapy Groups	Difference Between Groups (%)	<i>p</i> -value	Confidence Interval
No Vibration - Vibration	18.05	0.033	(0.015, 0.346)
Vibration - Control	18.59	0.034	(0.015, 0.357)
No Vibration - Control	36.65	< 0.0001	(0.201, 0.532)

2.5 Discussion

UBV is currently used as an exercise therapy to help muscle recover from exercise-induced muscle damage. Research has presented evidence for [12] and against vibration therapy increasing the muscle recovery rate [23]. The methods for obtaining data for analysis are sometimes dependent on the mindset of the participant and do not measure the objective properties of the damaged muscle. There is a need to obtain objective results to determine the physical effect UBV has on the muscle recovery rate. SWE is a method that measures the stiffness of muscle tissue. This study investigated UBV therapy using a visual analog scale, maximum voluntary isometric contraction and shear wave elastography.

2.5.1 Soreness

The test results in Table 2-3 show that bicep DOMS (VAS) was not significantly lower for participants in group V than those in group NV ($p = 0.5722$) on Day 7. This result contrasts other studies that have shown vibration therapy does decrease or prevent muscle soreness [27–29]. In this study, the lack of statistically significant evidence could be a result of not directly applying UBV to the bicep. The difference may also stem from a more intense damage protocol than other studies. It is possible that the subjects experienced more soreness than those in other studies.

The mean of the group NV is 17.1 cm higher than group V on Day 2 and the p-value (0.039) suggests this difference has some significance. Practically, the difference of 17.1 cm between the means of these two groups would be significant enough to show the therapy had some influence on muscle soreness after two days. However, more evidence is needed to determine if the difference is statistically significant.

2.5.2 Muscle Strength

The MVIC test did not show a significant difference between the strength of the therapy groups. Our results show the strength returned to the baseline values for each group after 1 week of recovery. There is no evidence that our use of vibration therapy had any effect on the recovery rate of muscle strength (Figure 2-10). These results match those from other studies which also showed vibration therapy had no effect on muscle strength recovery [30–32].

The reason MVIC did not show any difference between group V and group NV might be because of the influence of confounding variables. In other words, outside factors such as pain and motivation, may have minimized any influence the vibration had on the actual recovery of the muscle [33]. If this is the case the results would be affected, and it would be beneficial to measure motor recruitment instead.

Another reason this test may not have shown any difference between the two groups is a lack of significant UBV therapy. As previously mentioned, the vibration was not applied directly to the bicep. Several other variables such as the vibration duration, frequency, amplitude and when treatment was applied may have influenced the data. For example, the UBV was not applied immediately after exercise and participants were only treated 4 of the 7 days between the

baseline and day 7 measurements. Increasing the number of days UBV therapy was applied could affect the results of this test.

2.5.3 Stiffness

After muscle damage occurs, the immune system sends pro-inflammatory macrophage cells to the damaged region to boost the myogenic response [14,15]. It has been suggested that the stiffness of the muscle is related to its secondary acute inflammation and swelling caused by the immune response [25]. Our research showed that UBV does affect the stiffness of the bicep after damage-inducing exercise.

No difference was discovered between the baseline and day 7 mean bicep stiffness for both V and C. In contrast, the mean bicep stiffness of NV participants was 27.2% higher on day 7 compared to their baseline mean. UBV did affect the muscle recovery by causing V to obtain normal stiffness one week after exercise. This recovery of muscle stiffness might relate to the immune response of the muscle [25]. Vibration may affect muscle inflammation, and therefore muscle stiffness. Future research that investigate the cell population inside the muscle after vibration should be done to validate this theory. This is the first study we are aware of that measured the effects of UBV therapy using SWE over 7 days after an exercise.

Figure 2-10 shows that bicep stiffness increased after exercise and peaked after one day. Niitsu et al. used a similar bicep curl exercise to induce muscle damage and found the peak stiffness occurred 2 days after the exercise [34]. The difference between these results might simply be the difference in the damage protocol. Niitsu's participants completed 45 bicep curls whereas participants in this study completed 100. It would be interesting to learn if the magnitude of the exercise protocol affected when the peak stiffness occurs.

The muscle recovery process is very intricate and results in the formation of new myofibers. The six main cells involved in this process are interdependent and the rate at which they function in the recovery process is related to the rate at which muscle recovery occurs [14,35]. Vibration on the bicep turns into a biophysical force on these cells which they transduce into a cellular response. This biochemical signal is transmitted to the nucleus or effector cells. When these components are stimulated in this manner they respond by activating mechanosensitive signaling pathways [36]. This process needs further research but might result in the effect vibration has on the differentiation and proliferation of these cells.

The significance of these results is in its potential to help individuals recover faster. This is extremely important for athletes who must compete multiple times in one week. Since the stiffness of the V group returned to its baseline value faster than the NV group, UBV seems to increase the rate at which the muscle regeneration process occurs. Faster recovery also allows athletes to spend more time on other things that will help them prepare for their next competition. UBV could in the future also be used by doctors to target specific molecular processes.

2.5.4 Limitations

Although this experiment successfully showed UBV affected muscle stiffness, there are a few limitations to these results. First, the group sizes were small and only represent a non-trained population. These results may not apply to trained or highly trained athletes who have undergone significant resistance training. Second, the effect of using a different vibration frequency more consistent with previous literature was not compared, and the use of the resonance frequency of a muscle group should be further investigated in future studies. The predictions made are limited

to the values used in this experiment. However, those values were selected based on previous research and it was predicted that they would have the greatest impact on skeletal muscle recovery. It would be beneficial for research to investigate the significance changing these variables has on muscle recovery.

2.5.5 Conclusion

There is no evidence from this research that UBV has any significant effect on the pain and strength of skeletal muscle after exercise-induced muscle damage. The pain and strength of damaged muscles increase until they peak two days after exercise but UBV has no measurable effect on the rate at which these values return to normal. The stiffness of skeletal muscle measured by SWE returns to the baseline value after 7 days when UBV is used as a muscle recovery therapy. This shows that UBV therapy at resonance frequency helped the skeletal muscle return to baseline stiffness values as compared to no vibration. This research could be implemented by athletes and physical trainers to use vibration to increase the recovery rate of the stiffness of skeletal muscle.

3 A MATHEMATICAL MODEL OF SKELETAL MUSCLE REGENERATION AND VIBRATION

3.1 Abstract

A recent surge of vibration-based muscle recovery methods and products has encouraged the investigation of the effects of upper body vibration (UBV) on skeletal muscle regeneration. Few mathematical models have been created to simulate the normal functions in the body. This study investigates the effect UBV has on the muscle recovery rate by adapting vibration factors into the Stephenson and Kojourahov skeletal muscle regeneration mathematical model (SK).

An adaptation to SK has been proposed in this study which includes the physiological effects of vibration. Three additional vibration factors have been added to SK. The first term, (v_1) , accounts for the increase in the influx rate of type 1 macrophages (P_1). These cells are part of the body's immune response to muscle damage. They control the proliferation rate of satellite cells (S) and phagocytize dead myofiber cells. The second term, (v_2) , increases the rate of the phenotype change of P_1 to type 2 macrophages (P_2). P_2 are used to support S differentiation and prevent apoptosis of myoblasts (M_b). The final term, (v_3) , increases the fusion rate of M_b . M_b fuse with each other to create myotubes which align to create myofibers (M). The addition of these three factors decreases the overall skeletal muscle regeneration time by 47%.

3.2 Introduction

Muscle recovery can play a significant role in training for athletes and everyday levels of activity for the general population. Strengthening a muscle through exercise requires repeatedly damaging and repairing the skeletal muscle tissue. The recovery process requires time, rest, and proper nutrition. Research into applicable methods to aid muscle recovery (i.e., massage, ice, heat, anti-inflammatory medication, etc.) has been investigated for years but new methods are still being explored to discover how to effectively increase the rate at which this recovery process occurs.

UBV is used to apply vibration to specific muscles and limits vibration to surrounding tissue and organs. Research suggests that UBV affects muscle recovery [5,11,13,30,37]. UBV encourages recovery by stimulating cells involved in the muscle regeneration process and increasing blood flow [17,18].

The ability to model and predict muscle recovery would be a significant benefit to athletes in preparation for competition, physical therapists, and rehabilitating patients. Muscle recovery models have been developed that investigate Duchenne muscular dystrophy [6,7], idiopathic pulmonary fibrosis [8], and acute recovery from fatigue [38,39]. Stephenson and Kojourahov adapted the two former models to create one that simulates skeletal muscle regeneration of healthy muscle after it has been damaged [14]. This model, (SK), includes immune and myogenic responses. The immune response involves macrophage cells that monitor the replacement of dead skeletal muscle cells which occurs in the myogenic response. This chapter discusses the results of introducing UBV into SK based on the results from the UBV experiment previously analyzed in Chapter 2. It specifically demonstrates how UBV modifies the influx of each cell in the regeneration process and therefore the overall rate of recovery.

3.3 Biological Background and Assumptions

Skeletal muscle regeneration is the process by which the cells in the human body work together to heal skeletal muscle tissue. The process replaces dead skeletal muscle cells at the end of their life cycle, as well as those destroyed from skeletal muscle damage. Muscle damage is defined as the necrosis of cells and can result from skeletal muscle burn, freeze, crush and tear injuries. Once necrosis occurs, the muscle's immune system adjusts the skeletal muscle regeneration process to appropriately account for the damage that has been done.

Before the muscle experiences any damage, the muscle regeneration process ensures the cells that undergo apoptosis are replenished and that the muscle has a community of necessary immune and myogenic cells to maintain the skeletal muscle. The immune cells consist of type 1 and 2 macrophages that monitor the myogenic response. Satellite cells are a stem cell that act as the building block for the rest of the myogenic cells.

3.3.1 Immune Response

Type 1 macrophages, (P_1), are inflammatory cells that phagocytize dead myofiber cells, (M_d), in damaged skeletal muscle, promote satellite cell (S) proliferation and reduce S differentiation [14,15,40]. P_1 cells maintain a small population until stimulated by sudden damage. Once stimulated by skeletal muscle damage, there is an influx of P_1 in proportion to the skeletal muscle necrosis that increases the population of resident macrophages in the muscle. As part of its role in balancing the muscle repair immune response, this cell changes phenotype and becomes a type 2 macrophage, (P_2). The rate at which this occurs is an important factor in how long it takes the muscle to recover [14]. P_2 are anti-inflammatory cells that use a growth factor (TGF- β) to stimulate S differentiation and cell-to-cell contact to hinder apoptosis of myoblasts.

The relationship between the two types of macrophages is essential in maintaining and balancing the rest of the muscle regeneration process.

3.3.2 Myogenic Response

S cells are a special type of stem cell located in skeletal muscle fibers and are the initial myogenic cell used to build and rebuild muscle tissue. Before the muscle experiences any damage, this group of cells will maintain its own dormant population to support normal muscle regeneration. Proliferation of these stem cells occurs after the muscle is damaged. This rapid influx in S is increased by approximately 40% if P_1 are involved in the process [41]. S continues the recovery process by differentiating into myoblasts, (M_b), and contributing cells to myofibers, (M).

M_b are specialized cells that can fuse with each other to create myotubes, which then align with and fuse to myofibers [15]. The rate of myoblast fusion can occur quickly, and correct timing is important to prevent permanent damage to muscle tissue.

Each of the six cells in the skeletal muscle regeneration process (P_1 , P_2 , S , M_b , M , M_d), has a significant effect on the recovery of damaged skeletal muscle. If any individual cell population is unable to perform its required function, the rest of the process suffers, and the muscle will not heal properly [35]. The process is balanced so that an influx of one cell population affects the recovery rate of the damaged muscle.

Figure 3-1 is a depiction of the SK model. The immune response is portrayed by the two macrophage types regulating S and M_b . The myogenic response is represented by the S directly contributing to the creation of M_b and M , which are used to create new muscle fibers. The

responses continue as the M_d are phagocytized by P_1 until the muscle is rebuilt and the immune response stops.

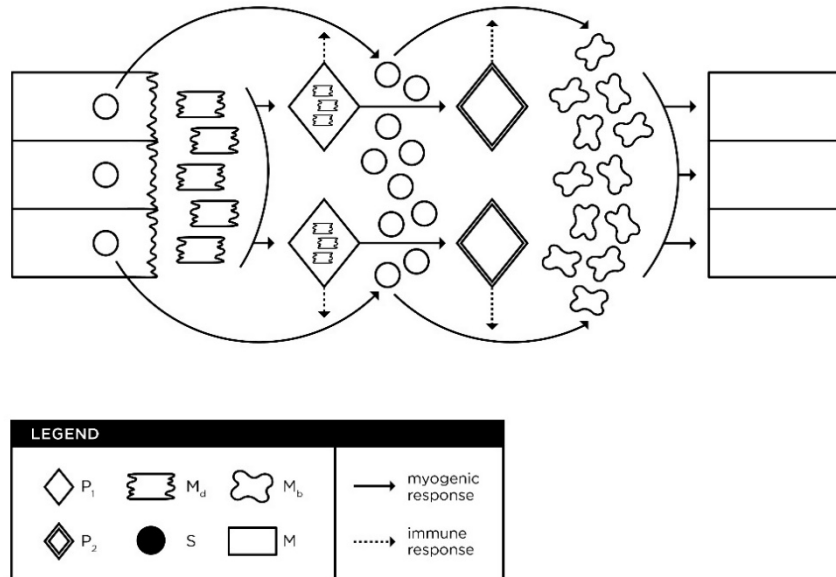


Figure 3-1: Skeletal Muscle Regeneration Process

3.4 Mathematical Model Background and Assumptions

3.4.1 Skeletal Muscle Regeneration Model

The SK model was created to simulate skeletal muscle recovery in mammals [14]. Six ordinary differential equations (ODE) were used to model the biological process and the rate of change of the six major cells described in the previous section. The cells are modeled as variables P_1 , P_2 , S , M_b , M and M_d . Table 3-1 provides the values for each of the variables in the ODE's. The variables a_i , d_i , f_i , and r_i represent constant rates of cell influx (regardless of any damage), cell death, cell fusion and cell differentiation respectively. The variable b_1 represents

the rate at which P_1 that prevent S differentiation. Variable b_2 represents the cell-to-cell contact between P_2 and M_b which restricts the apoptosis of the latter. The c_i values are constants that define the relationship between the immune response cells and the myogenic system. The combination of these rates and variables results in Equations 3-1 through 3-6,

$$\frac{dP_1}{dt} = a_1 + a_2M_dP_1 - r_1M_dP_1 - d_1P_1 \quad (3-1)$$

$$\frac{dP_2}{dt} = r_1M_dP_1 - d_2P_2 \quad (3-2)$$

$$\frac{dS}{dt} = a_3S \left(1 - \frac{S}{k}\right) + a_4M_dP_1S + a_5M_dS - r_2S - \frac{r_3P_2S}{b_1P_1+c_1} \quad (3-3)$$

$$\frac{dM_b}{dt} = \frac{r_3P_2S}{b_1P_1+c_1} - f_1M_b^2 - f_2M_bM - \frac{d_3M_b}{b_2M_bP_2+c_2} \quad (3-4)$$

$$\frac{dM}{dt} = r_2S + f_1M_b^2 + f_2M_bM - d_4M - n\Delta M \quad (3-5)$$

$$\frac{dM_d}{dt} = -d_5P_1M_d + n\Delta M \quad (3-6).$$

3.4.2 Macrophage Rate of Change

The rate of change of P_1 as defined by Equation 3-1, is determined by its normal influx rate a_1 , its death rate d_1 , the influx a_2 caused by the current number of M_d , and by r_1 , the rate of the phenotype change from P_1 to P_2 . This rate of change is also directly affected by the number of M_d . Equation 3-2 shows the number of P_2 increases depending on the rate of the phenotype change from P_1 and decreases due to its death rate, d_2 .

3.4.3 Satellite Cell Rate of Change

The myogenic cellular portion of the skeletal muscle regeneration process begins with S . Its cell count increases naturally at the rate a_3 until its capacity of 2100 is reached [14]. This S ODE is

setup using the term $a_3S \left(1 - \frac{S}{k}\right)$, so that the natural influx gradually slows to a stop as S approaches its maximum from a lower value. Once dead myofibers have been sensed the

Table 3-1: Values for ODE coefficients

Variable	Value	Units	Variable	Value	Units
a_1	1.0000	$\frac{cells}{(day)(mm^3)}$	d_3	2.0000×10^{-5}	$\frac{1}{day}$
a_2	0.4000	$\frac{mm^3}{(cells)(day)}$	d_4	1.5300	$\frac{1}{day}$
a_3	0.0140	$\frac{1}{day}$	d_5	2.7000×10^{-4}	$\frac{mm^3}{(cells)(day)}$
a_4	0.0040	$\frac{(mm^3)^2}{(cells)^2(day)}$	r_1	3.0000×10^{-5}	$\frac{mm^3}{(cells)(day)}$
a_5	0.1155	$\frac{(cells)(day)}{mm^3}$	r_2	0.9900	$\frac{1}{day}$
b_1	0.0020	$\frac{mm^3}{cells}$	r_3	6.0000×10^{-5}	$\frac{mm^3}{(cells)(day)}$
b_2	2100	$\frac{(mm^3)^2}{(cells)^2}$	f_1	0.0100	$\frac{mm^3}{(cells)(day)}$
c_1	2.465×10^{-7}	dimensionless	f_2	1.8000×10^{-4}	$\frac{mm^3}{(cells)(day)}$
c_2	1.000×10^{-8}	dimensionless	k	3.5600×10^{-4}	$\frac{cells}{mm^3}$
d_1	1.6000×10^{-4}	$\frac{1}{day}$	n	4.5000	dimensionless
d_2	1.2000×10^{-5}	$\frac{1}{day}$			

immune system, S grows at a rate of a_4 in proportion to M_d and P_1 , as seen in the term $a_4M_dP_1S$. The increase in S is also determined by a_5M_dS at the rate a_5 , which occurs in proportion to the number of dead myofiber cells regardless of the number of P_1 . A portion of the S population is donated directly to help create myofibers at the rate r_2 . The rate r_3 , affects how quickly S differentiate into myoblasts as seen in $\frac{r_3P_2S}{b_1P_1+c_1}$. This differentiation is also affected by the P_1 secretion factor b_1 . This relationship displays how the influx of P_1 decreases the rate of S

differentiation in proportion to its secretion factor b_1 , while an increase of P_2 will increase the rate.

3.4.4 Myoblast Rate of Change

M_b increases at the rate of the differentiation of S . M_b decreases at the rate they fuse with each other and M , (f_1 and f_2 respectively). M_b reduction also occurs due to apoptosis defined by $\frac{d_3 M_b}{b_2 M_b P_2 + c_2}$. This natural cell death occurs at the rate of d_3 and relative to the cell-to-cell contact, b_2 , between M_b and P_2 cells.

3.4.5 Myofiber Rate of Change

The apex of the skeletal muscle regeneration process is the formation of new muscle fibers. The creation of M is dependent on the rates previously described in relation to the S and M_b . M increases with M_b fusion and as S donate themselves to become M . Muscle damage is the only cause of M death in the regeneration model. Damage is modeled using a lognormal probability density function. This mimics M damage by a sharp initial increase followed by a gradual decrease [42].

3.4.6 Dead Myofiber Rate of Change

The regeneration process completes its full cycle as M die and become M_d . The number of M_d increases simply based on damage done to the muscle and decreases as the cells are phagocytized by P_1 at the rate of d_5 .

3.5 Biological Effects of Vibration

3.5.1 Vibration and Myogenic Cells

Several studies have been conducted on the effects of using vibration to reduce the muscle recovery time after exercise-induced muscle damage. The experiment in chapter 2 was conducted to measure the effect of vibration on the skeletal muscle. The results showed muscle stiffness returned to normal when vibration was used for five days following an exercise protocol but did not for N.

A review of research has been done on how vibration affects each cell in the skeletal muscle regeneration process. Some experimentation has been done on rodents or blood samples that has discovered some of the cells fluctuate due to vibration. Ceccarelli et al. did a preliminary investigation that showed vibration promotes *S* terminal differentiation and M_b fusion [20]. Weinheimer-Haus and Pongkitwitoon et al. performed an experiment that showed vibration increased P_1 and P_2 accumulation [22,43]. Pongkitwitoon et al. also suggested that vibration promoted the phenotype change from the inflammatory inducing P_1 , to the inflammatory reducing P_2 . Wang et al. tested vibration on blood cells to show that it increases myotube formation from M_b [44]. Myotubes are created by M_b fusion and fuse with each other to create M . Finally, Corbiere et al. conducted research on mice to show that vibration affects M size on injured mice [21].

Although the testing procedures and participants used in these experiments are different from each other and the UBV therapy study, their results can be used to propose changes in SK. The unique effect vibration has on the individual cells in the regeneration process should not be significantly different whether they are a culture in a dish or in the body. Both cell populations

experience mechanotransduction, which is the transformation of a physical force into a molecular response [36]. These studies have been used to provide evidence of how vibration might affect the skeletal muscle regeneration process.

3.5.2 Skeletal Muscle Regeneration Model and Vibration

To model the effect vibration has on each of these cell types and the overall effect on the skeletal muscle regeneration process, three coefficients were added to SK. The first term, v_1 , represents the percent increase in the influx of P_1 . This has been given the value 0.82, which is how much macrophages increased in the results of Pongkitwitoon et al. vibrating macrophages at low-intensity vibrations [43]. The value for v_1 was estimated using the average percent-change of P_1 cells.

The second vibration term, v_2 , was determined to be 0.46 based on the up regulation of TGF- β from the results of Pongkitwitoon et al. [43]. The increase of this growth factor indicates a faster phenotype change from P_1 to P_2 cells, since it used by P_2 to stimulate S differentiation. This is also supported by the results also showing a reduction in pro-inflammatory cytokines.

The effect vibration has on M_b fusion in the skeletal muscle regeneration process is defined by v_3 . Ceccarelli et al. performed an analysis on the S and discovered the gene dysferlin, which is involved in M_b fusion, expressed itself more when vibration for 4 days at 30 Hz. was applied [20]. Wang et al. discovered through a study on cell culture vibration increased the number of myotubes 2.5 times [44]. For this experiment they used a frequency of 10 Hz. for 10 minutes on three consecutive days with 3 days of observation afterwards. The results from these experiments was averaged to give v_3 the value of 2.5 to represent the results of this study. The term $\left(1 - \frac{M}{M_0}\right)$ was added to decrease the effect v_3 has on the fusion rate M approaches its original value.

The combination of these factors has been adapted into Equations 3-1 to 3-6 produce Equations 3-7 through 3-12,

$$\frac{dP_1}{dt} = (1 + v_1)a_1 + a_2M_dP_1 - (1 + v_2)r_1M_dP_1 - d_1P_1 \quad (3-7)$$

$$\frac{dP_2}{dt} = (1 + v_2)r_1M_dP_1 - d_2P_2 \quad (3-8)$$

$$\frac{dS}{dt} = a_3S \left(1 - \frac{S}{k}\right) + a_4M_dP_1S + a_5M_dS - r_2S - \frac{r_3P_2S}{b_1P_1+c_1} \quad (3-9)$$

$$\frac{dM_b}{dt} = \frac{r_3P_2S}{b_1P_1+c_1} - (1 + v_3(1 - \frac{M}{M_0})) (f_1M_b^2 + f_2M_bM) - \frac{d_3M_b}{b_2M_bP_2+c_2} \quad (3-10)$$

$$\frac{dM}{dt} = r_2S + (1 + v_3(1 - \frac{M}{M_0})) (f_1M_b^2 + f_2M_bM) - d_4M - n\Delta M \quad (3-11)$$

$$\frac{dM_d}{dt} = -d_5P_1M_d + n\Delta M \quad (3-12).$$

3.6 Results

3.6.1 Skeletal Muscle Regeneration Model

The simulation of Equations 3-1 to 3-6 using ode45 in MATLAB, results in Figure 3-2, which displays the volumetric number of each of the six cells and the day the muscle healed.

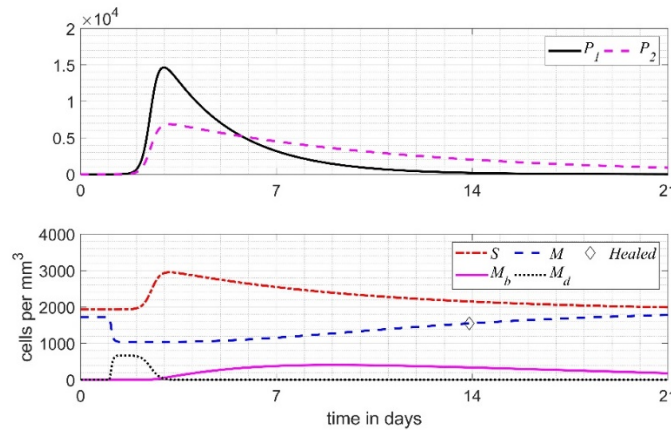


Figure 3-2: Simulation of Equation 1

The figure shows the progression of the recovery of M . The normal recovery of the muscle occurs at approximately 13 days. Recovery is defined as the point in time at which M returns to 10% of its initial amount.

3.6.2 Skeletal Muscle Regeneration Model with Vibration

Table 3-2 shows the values given to the vibration terms in Equations 3-7 through 3-12. These values have been qualitatively taken from the previously mentioned studies [20,22,43]. The results from adding these values into the skeletal muscle regeneration process are seen in Figure 3-3. The dotted lines represent the results of the changes made due to vibration. The recovery time for the cells that experienced vibration is approximately 8.5 days.

Table 3-2: Values for vibration coefficients

Variable	Value
v_1	0.82
v_2	0.5
v_3	2.5

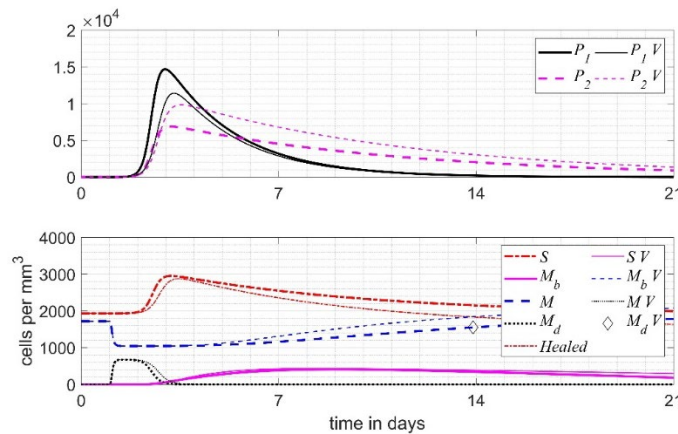


Figure 3-3: The Skeletal Muscle Regeneration Process Including the Effect of vibration

The results found in Figure 3-3 show that although v_1 increases the rate at which P_1 naturally increases, the number of P_1 is not higher in the vibration simulation than the original simulation. This is because v_2 has increased enough so that P_1 switches to P_2 faster than P_1 can accumulate. Thus, the vibration model results in a larger number of P_2 cells throughout the entire recovery process.

The number of P_1 cells has decreased in the vibration model. As a result, the time it takes M_d to be phagocytized by P_1 increased. The delay in the reduction of M_d directly effects the number of S and causes it to take more time for these cells to reach their maximum amount. The maximum amount of S is lower as well because there are fewer P_1 cells.

Finally, v_3 has a significant effect on the number of M_b throughout the regeneration process. The larger supply of P_2 allows for an increase in the number of M_b . With the increase of both M_b cells and their fusion rate because of v_3 , there is a higher demand of S . This results in S decreasing at a faster rate than in the original model. The overall rate of influx of M increases as well because of the faster fusion rate of M_b .

3.6.3 Skeletal Muscle Recovery and Vibration Experiment

Figure 3-4 is the simulation of the M from the SK model with and without the effects of vibration. The dotted line represents the M that have experienced vibration while the solid line is the M that has not. The M from the vibration cells increase back to their original value after about 8.5 days compared to the 13 days for the regular M group. The day each group recovers is marked by a diamond.

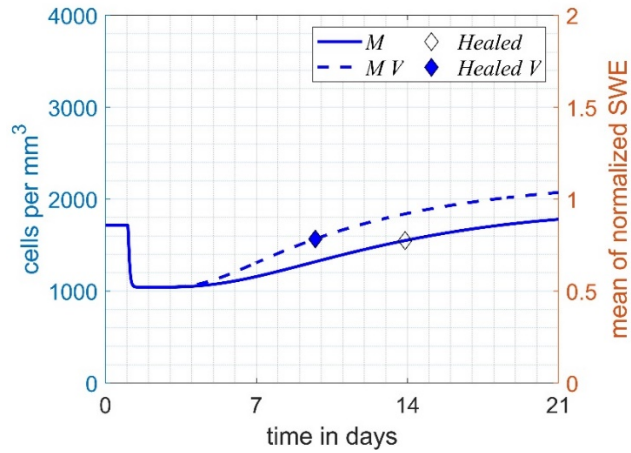


Figure 3-4: Myofiber recovery for the Vibration and No Vibration cells

The results of the vibration therapy study have been plotted in Figure 3-5 with the *M* simulation to show the similarities in time to recovery. The SWE shows recovery time for the vibration cells is about 7 days, similar to the *M* simulation. The SWE results follow a similar but inverted slope as the slope of *M*.

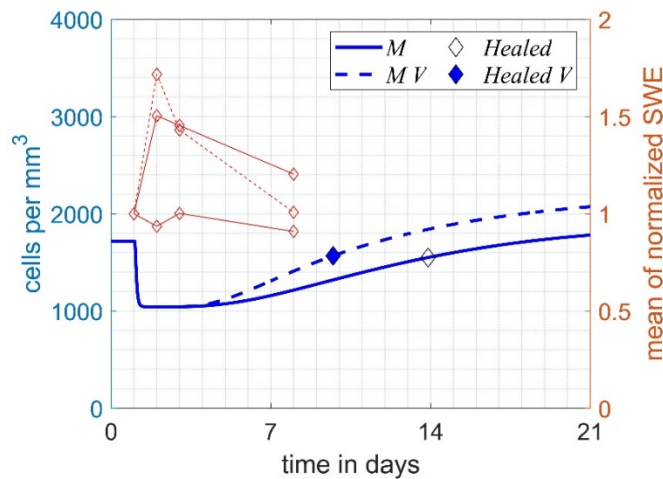


Figure 3-5: SWE results plotted with myofiber recovery simulations

3.7 Discussion

There are several factors that affect the recovery of a muscle. The regeneration process is one specific cycle that shows the recovery of some of the cells in the process. Vibration has been adapted into the skeletal muscle regeneration process based on the results of previous research. The results show that the regeneration rate of the skeletal muscle is almost twice as fast than normal regeneration. The three vibration factors work harmoniously to increase the rate at which M recovers. The first two factors, v_1 and v_2 , cause an influx in the P_2 and S cells that are needed for the formation of M_b . The increase of M_b along with the increase of its fusion due to v_3 results in the increase of M .

There is a similarity between vibration-adapted regeneration process and the results of the UBV experiment. They both show recovery occurs close to 7 days after skeletal muscle damage. The study on UBV suggests there is a physical change within the muscle that changes its stiffness. This change occurs after human body vibration helps it return to the original stiffness after seven days, whereas no vibration therapy does not return to normal within this time. The change in muscle stiffness could be directly related to the number of M after the muscle is damaged and their regeneration over the following days.

This is the first study to propose a mathematical model to show any effect vibration has on skeletal muscle regeneration. These results show the positive effect UBV has on muscle regeneration. The results are significant because vibration is a common therapy in sports and medicine. Understanding the effect vibration has on the muscle recovery process could be utilized to create products that could be tuned to the need of an individual athlete to optimize their recovery. The more that is understood about the mechanical effect vibration has on the body, the more effective vibration therapy will become.

Further research should be done to validate the proposed model. Research could be done to discover how to use vibration therapy to control the value of each of the three vibration factors. This would likely be accomplished by changing the vibration therapy parameters (frequency, amplitude, duration and when vibration therapy is applied during the exercise protocol). An optimization study could then be performed to determine which values for each factor would produce the optimal vibration therapy.

3.8 Conclusion

A mathematical model for skeletal muscle regeneration that accounts for vibration therapy has been presented. This model seems to validate the concept of decreased recovery time due to vibration therapy. The model proposes physical changes within skeletal muscles as a result of vibration therapy. Ultrasound muscle stiffness measurement verified the decreased muscle recovery time due to vibration. These results can be used to predict the results of various vibration therapies by discovering how changing therapy or damage parameters affect the recovery time.

Further research is needed to discover whether other vibration factors should be included in the regeneration model and to validate the values selected to represent the three factors currently used in the model. Physiological and biomedical research is needed to better understand the effect vibration has on individual cells and what their molecular response is.

4 CONCLUSION

Exercise-induced muscle damage is experienced after overworking skeletal muscle and results in pain, loss in strength and stiffness. There is no evidence from this study that using UBV affects the pain or strength of individuals when applied on damaged muscle. However, it is apparent that the stiffness of the muscle returns to its baseline value earlier than when no therapy is used. This could affect the treatment individuals and trainers use after exercise to increase the rate and effectiveness of recovery. Applying the effects of vibration to the SK model provided supporting evidence that vibration does improve skeletal muscle regeneration by decreasing the time it takes for muscle to regenerate. Further research should be done to combine the skeletal regeneration model with the acute effects of vibration recorded through experimentation by taking measurements of the cells inside the muscle during the experiment. This could be used to improve the regeneration model, so it more accurately simulates vibrational effects.

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