AN ABSTRACT OF THE DISSERTATION OF

Junggi Hong for the degree of Doctor of Philosophy in Exercise Sports Science presented on September 15th, 2008.

Title: The Effects of Whole Body Vibration on the Neuromuscular System.

Abstract Approved:

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Mark A. Hoffman

Recently, changes in human performance following whole-body vibration (WBV) training have been attributed to enhanced neuromuscular function. However, the exact neural and muscular mechanisms responsible for these changes remain less understood. The purpose of this study was to evaluate the acute and chronic effects of whole body vibration on the neural control of movement and muscle performance.

Twenty male and female subjects with no history of leg injury were randomly assigned to either an experimental or control group. To assess the acute effects of WBV, data was collected from subjects immediately before and following an exposure to WBV (3 bouts of 2 minute with one minute rest between bouts). During the vibration exposure, subjects stood quietly on the platform with a slight amount of knee flexion. Subjects in the control group performed trials of quiet standing on the laboratory floor. Trial length, rest periods and body positions were identical for both groups. The variables used to evaluate the acute effects were electromechanical delay and rate of force development. To assess the chronic effects, the experimental group received WBV training in the

laboratory over the course of 4 weeks. The training consisted of 3 sessions per week. During each session, the subjects performed 3 standing trials (2 minutes with one minute rest between bouts). The control group also reported to the laboratory for training consisting of trials of quiet standing. EMD and RFD were also used to assess chronic changes as well as two other measures on neural control, specifically presynaptic inhibition. The two measures of presynaptic inhibition were extrinsic presynaptic inhibition (EPI) and intrinsic presynaptic inhibition measured by paired reflex depression (PRD).

The analysis for an acute effect consisted of a 2×2 (Group × Test) ANOVA for the dependent measures EMD and RFD. The experimental (WBV) group demonstrated a significant group × test interaction for the electromechanical delay (p=0.02) and rate of force development (p=0.03). The experimental group decreased EMD by 16% (from 23.42 ms to 19.3 ms) and increased RFD by 15.6% (from 274N/sec to 323 N/sec). The analysis for the chronic effect consisted of 2×3×2 (Group × Test × Time) repeated measure ANOVAs for the dependent measures (EMD, RFD, EPI, and PRD). After a 4 week of WBV training, the experimental (WBV) group demonstrated a significant decrease in electromechanical delay (EMD). The results also showed a significant group × test interaction for the rate of force development (RFD), and paired reflex depression (PRD) over the course of the study. There were no changes in extrinsic presynaptic inhibition noted in any of the comparisons.

Through the use of these techniques and procedures, it is concluded that acute WBV has an effect on the EMD and RFD of the soleus muscle in young healthy subjects. Regarding chronic effects of WBV, our findings suggest that 4 weeks of WBV affects

intrinsic presynaptic inhibition as measured by paired reflex depression as well as well as EMD and RFD.

The Effects of Whole Body Vibration on the Neuromuscular System

By

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Doctor of Philosophy dissertation of Junggi Hong
Presented on September 15, 2008

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Junggi Hong, Author

CHAPTER 1: INTRODUCTION

The use of whole body vibration (WBV) to augment the function of the neuromuscular system has gained great popularity in the last several years. In some situations, WBV is used prior to athletic competition because of the perceived benefits to performance. It is also used in conjunction with traditional resistance training to enhance the benefits of the resistance training. More recently, some rehabilitation clinicians have started using WBV during the treatment of both orthopaedic and neurological conditions. The conclusions from the WBV literature are mixed in regard to the benefits gained from the vibration exposure. Two main challenges exist when interoperating the WBV literature: 1) there is a general lack of consistency in the protocols and equipment used for most studies and 2) there remains only speculation as to how WBV affects performance of the neuromuscular system. This study focused mainly on the second issue and was an exploration of the effects of WBV on neural mechanisms and neuromuscular performance after WBV exposure.

Although there is a lack of strictly controlled studies on the vibration training effect, current findings in this area suggest that vibration may have a beneficiary acute and/or chronic training effect on strength and power enhancement (Bosco 1998; Cardinale and Rittweger 2006; Delecluse et al. 2003). Researchers have speculated that increased muscle strength and power after WBV results from increased neuromuscular activation during WBV, which subsequently induces adaptations similar to resistance training (Bosco et al. 1999; Delecluse et al. 2003; Nordlund and Thorstensson 2007).

Neural adaptations are the first changes observed during the early stages of a strength training program that produce gains in muscle strength and power in the absence of increases in cross-sectional area of the muscle (Behm 1995). This same mechanism

has been speculated to be responsible for the muscle function changes seen in some WBV studies (Bosco 1998). The exact mechanism by which the WBV training can enhance neuromuscular activation is not known, but there are several possible explanations which could cause this enhancement. Specifically, one of the theoretical mechanisms for effects of WBV is neural adaptation related to increased muscle activation caused by increased excitability input from muscle spindles exposed to a vibration (Abercromby et al. 2007).

During WBV, skeletal muscles undergo small changes in muscle length, most likely since mechanical vibration is able to induce tonic excitatory influence on the muscles exposed to it (Seidel 1988). In other words, vibration elicits a response called "tonic vibration reflex," including activation of muscle spindles, mediation of the neural signals by Ia afferents (Hagbarth 1976), and finally, activation of muscle fibers via large alpha motoneurons. The tonic vibration reflex (TVR) is also able to cause an increase in recruitment of the motor units through activation of muscle spindles and polysynaptic pathways (De Gail et al. 1966). In addition, it has been proposed that the recruitment thresholds of the motor units during WBV are expected to be lower than during voluntary contractions resulting in a more rapid activation and training of high-threshold motor units (Delecluse et al. 2003; Roelants et al. 2004).

Recently, a possible connection between presynaptic inhibition and WBV has been speculated in an attempt to elucidate how the WBV induced neural adaptation occurs. For example, Bongiovanni et al. suggested that the contributing mechanism for the improvement in muscle function after WBV might be vibration induced presynaptic inhibition in the group Ia excitatory pathways (Bongiovanni et al. 1990). It has also been

reported that WBV exercise interacts with spinal reflex loops and possibly influencing these pathways (Rittweger et al. 2003).

The overall aim of the current study was to determine if WBV training changes select neural control mechanisms and muscular performance variables. In order to investigate the effects of WBV on these neural control mechanisms, extrinsic presynaptic inhibition (EPI), and paired reflex depression (PRD) of soleus muscle were assessed. For the muscular performance variables, electromechanical delay (EMD), rate of force development (RFD) of the soleus muscle in healthy subjects were assessed.

A brief explanation of the dependent measures included in this study as well as rational for their inclusion is presented here for the reader. Electromechanical delay (EMD) is the time interval between electrical activity and the mechanical responses of the muscle (Zhou et al. 1996). It has been reported that the magnitude of these delays in a given motor task may have some dependence on the structural differentiation of the neuromuscular system. The EMD, as a component of the stretch reflex, is thought to be vital for both the utilization of the stored energy in the series elastic component (SEC) of muscle stiffness and optimal sports performance (Nilsson et al. 1977). RFD, generally determined as the slope in the force time curve (Δforce/Δtime) assesses the explosive strength qualities of the neuromuscular system (Gruber and Gollhofer 2004). It has been shown that an increase in the rate of force development is closely related to improvement in efferent neural drive of the trained muscles, especially in a dynamic explosive type of strength training (Aagaard et al. 2002; Gruber and Gollhofer 2004). Presynaptic inhibition is a modulatory mechanism responsible for neurological changes seen with WBV. It has been suggested that the contributing intrinsic neural mechanism for the

improvement in muscle function after WBV training might be due to vibration induced presynaptic inhibition (Bongiovanni et al. 1990; Rittweger et al. 2000). Presynaptic inhibition can be either intrinsic or extrinsic based on the location of the inhibition to the synapse. Classical presynaptic inhibition is considered extrinsic inhibition (EPI) because of the involvement of the inhibitory interneurones effect on the synapse of the sensory and motor fibers. Conversely intrinsic presynaptic inhibition (IPI) is a regulatory mechanism of the synapse that is internal to the sensory and motor synaptic connection. To assess presynaptic inhibition in the present study, two conditioning protocols; 1) extrinsic presynaptic inhibition and 2) intrinsic presynaptic inhibition as measured with paired reflex depression (PRD) were measured. The EPI was measured by comparing conditioned and unconditioned H-reflexes of the soleus muscle (Iles 1996; Zehr and Stein 1999). To assess PRD, a paired-pulse technique was used to elicit paired soleus H-reflexes (Earles et al. 2002; Hye-Seon et al. 2007).

In order to investigate the acute effect of WBV, EMD and RFD were measured before and after WBV on the same day. To assess the chronic effects of WBV, EMD, RFD, and presynaptic inhibition (EPI and PRD) were measured at baseline, two week, and at four week intervals. The study consisted of a WBV group of 20 participants who received WBV 3 times per week for 4 weeks and a No-WBV group of 20 participants that didn't receive WBV.

The results of this study provide valuable insights regarding the responsiveness of the neuromuscular system after acute and short-term whole body vibration. This study is unique because it is the first study to examine how spinal mechanism is affected by WBV and how the changes in spinal mechanism induced by

WBV are related to the gains in functional muscular performances. This information will also help researchers involved in the health, fitness, and therapeutic sectors to better understand the neural aspects and therapeutic application of WBV to sports injury prevention and rehabilitation programs.

Although this study will contribute to the scientific literature base, it is not without limitations. A limitation to our methods is that our study recruited mostly healthy collegiate subjects who were relatively active and participating in various physical activities during the study period. It is not known that how their activity level might affect the outcome of the study. With a different population for example sedentary people, the outcomes might be different. Another limitation is that the present study doesn't measure the physiological variables such as muscle stiffness and stretch reflex. The present study will assume that the subjects in the control group will keep performing their intervention program throughout the study period.

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CHAPTER 2: MANUSCRIPT 1

Acute Effects of Whole Body Vibration on Electromechanical Delay and Rate of Force Development.

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ABSTRACT

Changes in muscular performance following whole-body vibration (WBV) have been attributed to adaptations in the neuromuscular system. However, due to a lack of standardization of WBV protocols and exposure time used in the literature, the responsiveness of the muscular system to acute exposure to WBV is still less understood. The present study solely examined the acute effect of WBV on two of the muscular functional variables [rate of force development (RFD) and electromechanical delay (EMD)]. For this purpose, forty young individuals with no leg injuries were randomly assigned to an experimental or control groups. The experimental group received acute WBV (3 bouts of 2 minute) while he/she stands on a vibration platform. The control group adopted the same position (squat position) for equal time but received no vibration. During each of the testing sessions (before and after acute WBV), rate of force development and electromechanical delay were measured while subjects were isometrically plantar flexing their ankle on the plate of an isokinetic dynamometer. After 3 bouts of 2 minute WBV, the experimental (WBV) group demonstrated a significant group × test interaction for the electromechanical delay (EMD). The results also showed a significant group × test interaction for rate of force development (RFD). Our findings suggest that acute WBV had an effect on the functional performance of the soleus muscle as measured with EMD and RFD in young healthy subjects.

Key words: whole body vibration, neurological adaptation, rate of force development, electromechanical delay

INTRODUCTION

Recently WBV has become increasingly popular among athletes and general population with the aim of improving strength and power performance. Several authors have reported functional changes in such as measures as vertical jump, and maximum strength, and joint position sense following exposure to WBV. However there remains little understanding as to the mechanisms responsible for these observed functional changes.

Prior to the development of WBV platforms, tendon and muscle vibration was studied from a neurological perspective to gain a better understanding of central nervous system function. Classic vibration paradigms have included direct stimulation of tendons or muscles followed by some assessment of neuromuscular function. The most common paradigm used was vibration application to a tendon followed by reflex assessment in both homonymous and heterogonous muscles as assessments of presynaptic inhibition. Additionally, this work leads to the understanding of the tonic vibration reflex (TVR). Tonic vibration reflex is a sustained contraction of a muscle subjected to vibration which is caused by vibratory activation of muscle spindles.

As noted previously, several authors have noted functional improvement in some individuals following WBV. In an attempt to better understand the effects of WBV on neuromuscular function, we designed this study to evaluate 2 specific function related variables before and after exposure to WBV.

Recently there have been efforts to investigate the effects of WBV particularly on certain functional muscular performance variables: rate of force development and electromechanical delay. Rate of force development represents the ability to rapidly contract the muscle [1] and is known to be closely related to an enhanced early neural

activation of the trained muscle [2]. Electromechanical delay has been investigated as another important neuromuscular related variable. EMD is the delay between the onset of electromyography (EMG) and the onset of mechanical response of the muscle. Recent studies suggested that EMD is closely related to muscle stiffness [3,4].

The present study was designed to investigate the acute effects of WBV on rate of force development (RFD) and electromechanical delay (EMD) of the soleus muscle in healthy subjects.

METHODS

Participants

A total of 40 individuals (24.2 ±5.9 yrs) participated in this study. Twenty women and twenty men with no history of lower leg injury were recruited through flyers posted on a university campus. Informed consent was obtained from each subject prior to participation in accordance with the university's Institutional Review Board. All subjects provided written consent after being fully informed of the nature of the study. Subjects were randomly assigned to one of the treatment groups (WBV or No-WBV).

Instruments and Protocols

Subjects in the WBV group stood, with knees flexed to approximately 20º, on the vibration platform (TurboSonic™ Seoul, Republic of Korea) (Figure 2-1). The experimental parameters for TurboSonic WBV device were set at a frequency of 20 Hz and 5 mm amplitude during each of the three 2-minute periods with one minute rest between vibration exposures. . Each training session lasted 10 min. The No-WBV group performed quiet standing trials in the same static semi squatting position on the floor. The difference between the WBV group and No-WBV group was that the WBV group

performed the standing position on the vibration machine and No-WBV group performed standing trials on the floor.

All subjects (WBV and No-WBV) were tested before and after their respective treatments (WBV or no-WBV). The outcome measures were that were assessed included: 1) electromechanical delay and, 2) the rate of force development. Both measurements were recorded in the soleus muscle of the dominant leg. It is important to note that rate of force development and electromechanical delay were variables calculated from the same trials. All testing procedures were performed on the dominant leg.

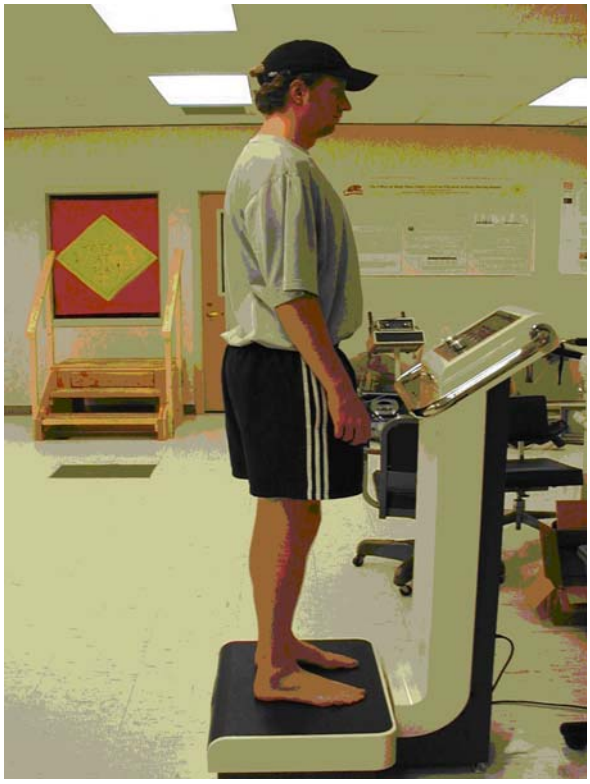

Figure 3-1 -– Whole Body Vibration

Testing procedures

For all subjects, isometric torque measurements were performed on the dominant ankle using an isokinetic dynamometer (Biodex System 3 Pro, Biodex Medical Systems Shirley, NY). The time required to prepare the subjects for the testing after their subjects' intervention was approximately 30 seconds. The subjects sat on the testing chair of the dynamometer and the leg was secured with body straps (Figure. 3-2), while the hip and the knee joints are flexed at 100 deg. Measurements of RFD and EMD were obtained during plantar flexion. All subjects were instructed to plantar flex the ankle as "hard and as fast as possible" after the light signal. The light was located on a wall approximately 5 feet from the subject. A verbal "ready" cue was given to the subjects about 1 to 3 seconds before the investigator triggered the light. Three trials were performed with 1 min rest between each trial.

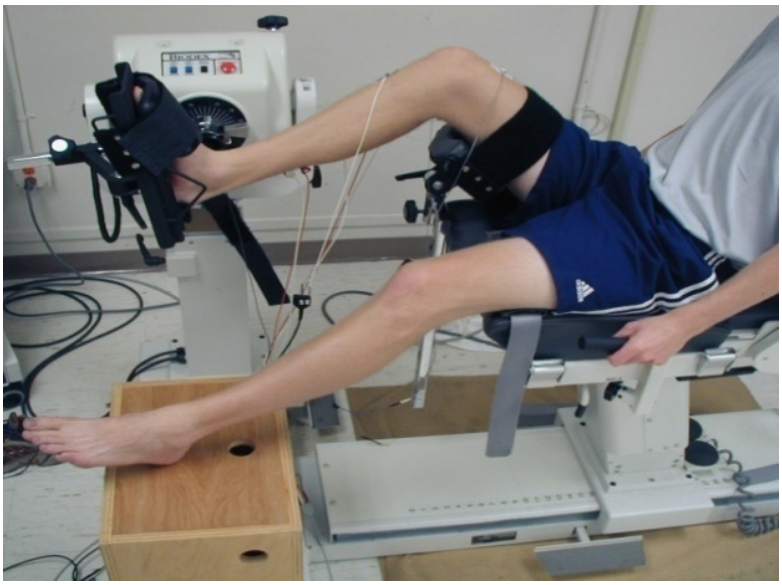

Figure 3-2 – RFD and EMD testing position

The torque and EMG signals were synchronously sampled at 2000 Hz. The raw unfiltered signals were analog-to-digital converted (Acqknowledge Software v.3.9.1, Biopac Systems, Goleta, CA) and stored on a PC. During the later process of analysis, the EMD and force signals were digitally high-pass filtered by using a fourth-order, zero lag Butterworth filter with a 10 Hz cutoff. The filtered force signal was then differentiated with the central-difference method to calculate the force's rage of change. Maximal rate of change was calculated as the maximal rate of force development. EMD was defined as the time interval between the onset of EMG signal and the onset of the torque applied to the footplate[5,6]. Onset of EMD and force was determined by the cumulative sum technique [7].

It can be seen in that a time plot of a single trial from the presentation of the stimulus (light signal) to the onset of the EMG signals and the time interval between the onset of the EMG signals to the force generation (electromechanical delay, EMD). RFD was calculated as the slope of the force time curve (Δforce/Δtime).

Statistical Analysis

Initially a 1 way ANOVA was applied to the baseline data to determine if differences between the groups (WBV, No-WBV) existed. Next, a 2 x 2 (group by test) mixed design ANOVA was applied to the EMD and RFD data. Descriptive data are reported as mean ± standard deviation (SD) All statistical analyses were performed using the SPSS 15 software (SPSS, Inc., Chicago, IL).

RESULTS

There was no baseline difference between the groups on either variable: EMD P=.371, RFD P=.329 **(Table 3-1).** The 2 × 2 ANOVA showed a significant group × test interaction (p=.001) for EMD (**Figure 3-3).**

Table 3-1: The mean and standard deviation of the neuromuscular parameters

	No-WBV (n=20)		**WBV(n=20)**	
	Pre	Post	Pre	Post
EMD (ms)	21.25 ± 7.63	21.11 ±6.49	23.42 ± 7.54	19.3 ± 8.08
RFD (N/sec)	318.41 ± 145.42	315.54 ± 137.99	274.13 ± 137.77	323.02 ± 161.98

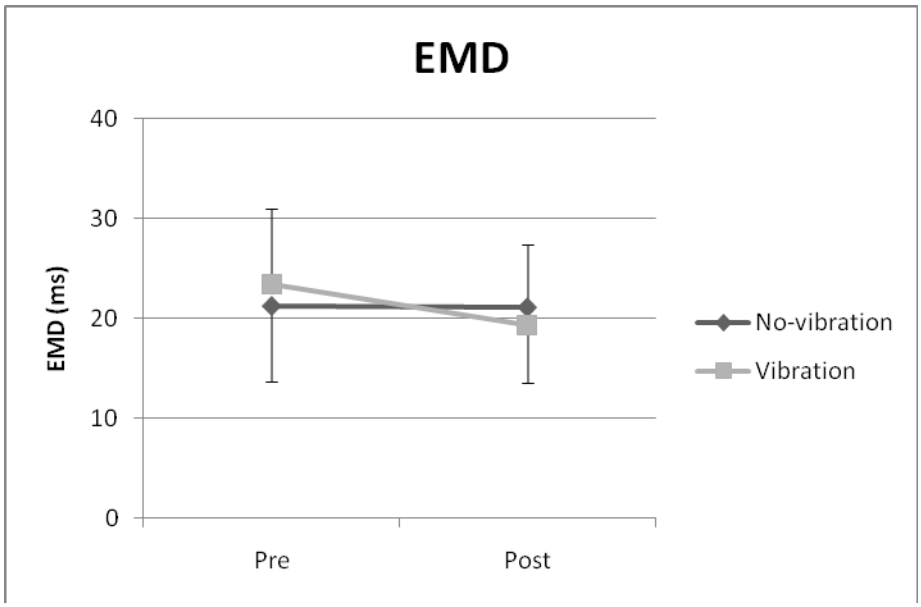

Figure 3-3: Group × Test interaction on EMD (p=.001)

The 2 × 2 ANOVA showed a significant group × test interaction (p=.003) for RFD. (**Figure 3-4**). RFD increased by 5.6% (from 274.13 N/sec to 323.03 N/sec) in the WBV group

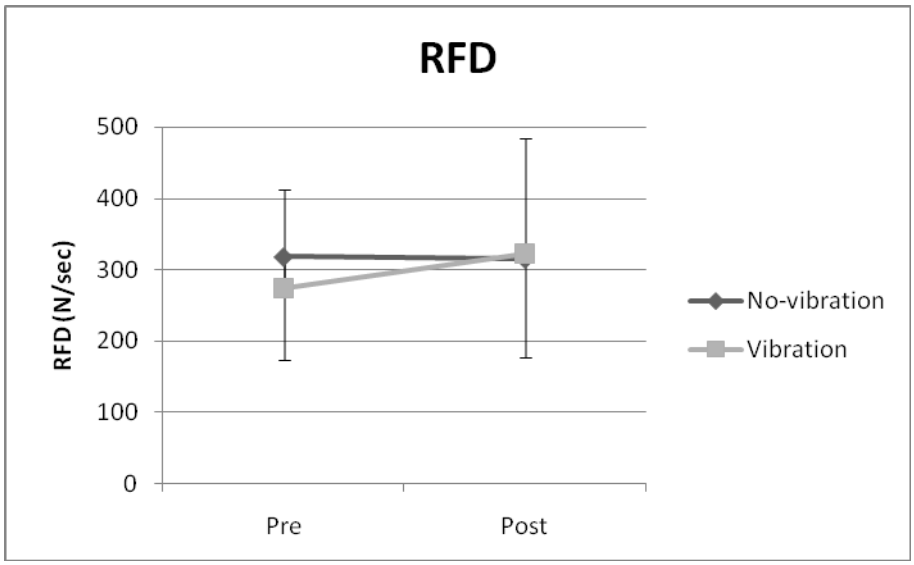

Figure 3-4: Group × Test interaction for RFD (p=.003)

DISCUSSION

The aim of this study was to examine changes in two functional variables (EMD and RFD) in of soleus muscle in young healthy individuals after three, two minute, bouts of WBV. The significance of our findings is that the pre and post EMD and RFD data in the No-WBV group were almost identical and that the pre and post data of the WBV group clearly showed the concurrent decreased in EMD and an increased in RFD during isometric contraction.

A shortened electromechanical delay with WBV

One of our primary findings was that after WBV, the soleus EMD was decreased. To date, we are aware of only 1 other investigation in which EMD after acute WBV was examined [3]. Hopkins et al in their recent study found no significant change in EMD after acute WBV [3]. The decreased EMD shown in our study is not in agreement with the previous study. However, in the previous experiment, five, 1 minute, bouts of WBV

with 26Hz was used as the acute WBV protocol and the EMD of peroneus longus muscle was measured [3]. Considering the fact that a different WBV protocols were used and the different muscles and testing protocols for EMD were used in our study and the previous study, comparison of our study with the previous study is limited.

Regarding possible contributing factors for EMD, the authors suggest that EMD is generally influenced by the maximal voluntary contraction force, rate of force development, muscle fiber types, muscle spindle sensitivity, and stiffness of series elastic components (SEC) of the muscle [3,8-10].

Among all these factors, the stiffness of SEC a neuromuscular based mechanism, we believe is the most likely to be influenced by an acute bout of WBV. It has also been reported that increased stiffness to the series elastic component would reduce the amount of slack taken up by cross-bridging and therefore reduce the amount of time necessary to produce force [9-11].

Concerning the effects of acute WBV on muscle stiffness, it has been reported that when muscles are vibrated, muscle spindle sensitivity and muscle stiffness increase to dampen the vibration [12]. It is also suggested that WBV causes fast joint rotation and muscle stretching which is likely to increase muscle stiffness through activation of both alpha and gamma sensory motoneuron [13]. In an attempt to better understand the mechanism of WBV on the muscle stiffness, the response of musculotendinous units to WBV has been reported [14]. Nigg and Wakening demonstrated that impact forces during running produce vibration, which are transmitted to the body at a frequency component between 10 and 20 Hz [14]. The study found that the soft tissues of the lower limb dampen the vibrations coming from heel contact changing their stiffness and the

adjustment of the stiffness of the lower limbs [14]. In our opinion, this mechanism called "muscle tuning" underlined by Nigg and Wakening could also be present during WBV.

Regarding the shortened EMD after acute WBV demonstrated in our study, we also suggest that pre-activated soleus muscle could have increased muscle stiffness. It has been suggested that the vibration effect is larger in the posture in which the receptor-bearing muscle is more pre-activated [15]. Rohmert et al have speculated that muscles with an increased muscle length or increased degree of pre-activation seemed to be most affected by vibration [16]. In addition, Burke et al [17] suggested that even a small increase in pre-activation may lead to increased muscle spindle sensitivity because of alpha-gamma co-activation which is known to increase the muscle stiffness [17]. In our study, WBV group performed a quiet standing with the knees slightly flexed (approximately 20 degree) on the WBV platform. Our hypothesis for decreased EMD after acute WBV is that while holding this flexed knee position during WBV, the tendon of the soleus muscle, which is the major representative of series elastic component, is slightly stretched. In addition, already pre-activated soleus muscle from holding flexed knee position further increases the stiffness of the SEC constantly contracting the muscle to maintain the posture against the vibration. Considering the fact that EMD is the time required to lengthen the SEC, we suggest that an increased stiffness of the soleus muscle following WBV decreased EMD by reducing the amount of time necessary to lengthen SEC. Although it has been demonstrated that EMD is shortened when muscle stiffness is increased by pretensioning the muscle [9-11], the findings of our study that No-WBV group didn't show any change in EMD after the quiet standing with the same position on

the floor suggest that only pre-activation of the muscle for a short period of time didn't correspond to the decreased EMD.

Increased rate of force development (RFD)

The findings of this study demonstrated that following WBV, maximal rate of force development (RFD) increased 15.6% in the WBV group whereas maximum RFD remained unchanged in the control group. To date, there are only two studies that investigated the acute effects of WBV on RFD [18,19]. However, the results of the studies are quite equivocal. The first study by de Ruiter et al found no change in RFD after acute WBV (5 bouts of 1 min with 30Hz, 8 mm). In contrast, Tihanyi et al. in their recent study showed a significant increase in RFD (19%). This increase in RFD is similar to the change observed in our study.

Possible explanations for the RFD changes after acute WBV in the present study can be sought from the better understanding of the characteristics of RFD and its possible connection with widely suggested mechanisms for WBV-induced changes in functional muscular performance. In our study, RFD was determined as the slope in the force time curve (Δforce/Δtime) [20]. The RFD has functional significance in fast and forceful muscle contraction [1]. Any increase in contractile RFD becomes highly important as it allows reaching a higher level of muscle force in the early phase of muscle contraction [1].

It has been documented that the effects of WBV on the functional muscular performance is similar to the effects of resistance training [21] and that the first adaptation mechanism of a skeletal muscle to resistance training is neural [21]. Previous studies suggested that WBV has been shown to improve power [22,23] and force

generating capacity in lower limbs [22-24]. It is hypothesized that the changes in RFD after acute WBV in the present study can be due to neural adaptation. To date since there is limited data available on the effects of acute WBV on the contractile rate of force development, the exact mechanism by which the acute exposure to WBV can enhance neuromuscular activation or muscular performance is not known, however there are several possible explanations which could cause these changes in RFD.

The literature suggests that changes in RFD has been often attributed to neural factors like increased doublet discharges [25], discharge rate [26], surface electromyographical (EMG) amplitude [2] , and decreased recruitment threshold [27]. Among all these physiological factors which are known to influence RFD, the decreased recruitment threshold of motor units after training seems to be connected to the possible factor for the RFD changes following the acute WBV in our study.

Since there is limited data available on the effects of WBV on RFD, the effects of tendon vibration on a single motor unit might provide meaningful insights regarding the changes seen with WBV. It has been demonstrated through a tendon vibration study that during vibration, skeletal muscles undergo small changes in muscle length, most likely because mechanical vibration is able to induce a tonic excitatory influence on the muscles exposed to it [28]. This excitatory influence is called tonic vibration reflex (TVR) and it includes activation of muscle spindles and mediation of the neural signals by Ia afferents [29]. Bongiovanni et al. in their muscle vibration study suggested that TVR affects the subjects' ability to generate high firing rates in high-threshold motor units [30]. Furthermore, several studies in which investigated the effects of tendon or muscle vibration on the single motor unit level have demonstrated that during vibration the

recruitment threshold of the motor units become lower [31-33]. Considering the fact that the lower leg muscles were also vibrated during WBV in our study, we suggest that during acute WBV, the motor unit recruitment threshold became lower possibly resulting in rapid muscle activation.

Another possible mechanism for the increased RFD following WBV can be found in other muscle vibration study. An experiment by Shinohara et al. demonstrated a significant increase in stretch reflex amplitude and motor unit discharge rate after prolonged muscle vibration [34]. The authors indicated that the increased stretch reflex depends on the sensitivity of the muscle spindles which is determined by the level of gamma motor neuron activity [34]. Considering that an attenuation of stretch reflex is a common finding after demanding exercise, the maintained or increased stretch reflex amplitude observed after muscle vibration seems most likely due to an enhanced central motor excitability, particularly with respect to the fast twitch fibers and motor units [35]. Although the stretch reflex was not assessed by the present study, based on the fact that increased efferent neural drive known to be closely related to the RFD [20], as a possible explanation for the changes in RFD observed in our study, enhancement of stretch reflex can be considered.

Since many different physiological factors are thought to contribute to the change in RFD, it is difficult to conclude which factor played major role in the RFD changes after acute WBV in the present study. However, there has been speculations that increased frequency, earlier recruitment as well as improved synchronization can be related to an excitatory modulation of the spinal motoneuron pool [20]. Holtermann et al. argued that the modulation of motor unit recruitment and discharge rate with training

involve an enhanced synaptic excitatory input to the motoneuron pool or increased motoneuron excitability [36]. It has been suggested that the contributing intrinsic neural mechanism for the improvement in muscle function after WBV training might be due to vibration induced presynaptic inhibition [30,37]. This view can be another important neural mechanism for the RFD changes after such an acute WBV in our study. It has been suggested that the neural modulation of presynaptic inhibition pathways is known to affect the recruitment of motor units for voluntary movements [38]. In addition, it is hypothesized that the enhanced excitatory synaptic input or motoneuron excitability with training causes high-threshold motor units to be recruited earlier in a maximal voluntary contraction (MVC) increasing RFD, whereas recruitment of additional motor units ends before maximal tension [39]. From the above findings, we speculate that the change in RFD after acute WBV observed in the present study may have occurred by neural modulation potentially involving alterations in recruitment threshold [1], stretch reflex, or presynaptic inhibition.

Although the present study did not include the measures of acute change in presynaptic inhibition after WBV training, we suggest that the contributing intrinsic neural mechanism for the improvement in muscle function after WBV training might be due to vibration induced presynaptic inhibition [30,37]. Furthermore, the neural modulation of presynaptic inhibition pathways is known to affect the recruitment of motor units for voluntary movements [38]. Further research is needed to test the hypothesis that WBV exercise interacts with spinal reflex loops and possibly influence these pathways, and examine how this spinal mechanism interacts with the improvement in muscle function caused by WBV.

A limitation to our methods is that our study recruited mostly healthy collegiate subjects who were relatively active and participating in various physical activities during the study period. It is not known that how their activity level might have affected the outcome of the study.

CONCLUSION

Recent studies have shown decreased EMD and increased RFD after acute WBV. Acute whole body vibration (WBV) has been suggested to elicit adaptive changes in the nervous system as well as in the muscular function performance. However, there is little information in the scientific literature in this regard. The present study was the first study to measure both of EMD and RFD after acute WBV exposure. The present study also confirmed logical effects on both of muscular function performance variables by a significant group × test interaction for each of those variables. Therefore it is indicated that these changes seen in the present study explain the functional performance s seen in the other WBV literature. This information may help researchers involved in the health, fitness, and therapeutic fields to better understand and determine the potential of WBV as an efficient intervention tool for rehabilitation and training. Further research is needed to investigate the effects of vibration exercise duration, vibration frequency, amplitude and load that are optimum to evoke an enhanced neuromuscular function in young adults, but also in athletes or elderly subjects and patients.

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CHAPTER 3: MANUSCRIPT 2

Effects of 4 Weeks Whole Body Vibration on Electromechanical Delay, Rate of Force Development, and Presynaptic Inhibition.

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ABSTRACT

Functional changes following the exposure to whole-body vibration (WBV) training has been attributed to adaptations in the neuromuscular system. The present study examined the effect of 4 weeks of WBV training on spinal control mechanisms (pre-synaptic inhibition) and muscle function [(rate of force development (RFD) and electromechanical delay (EMD)]. Forty young individuals with no history of lower leg injuries were randomly assigned to an experimental or control group. The experimental group received WBV training (3 bouts of 2 minute, 3 times a week) for 4 weeks. During each of the training sessions, the subjects stood on the vibration platform with the knees slightly flexed. The control group performed periods of standing in the same position as the experimental subjects. During each of the testing sessions, electromechanical delay and rate of force development were measured while subjects were isometrically plantar flexing their ankle on the plate of an isokinetic dynamometer. To assess presynaptic inhibition, subjects were tested in the prone position with the ankle positioned at 90º. A body pillow was used to standardize body, head, and hand position for each subject. After a 4 week of WBV training, the experimental (WBV) group demonstrated a significant improvement in electromechanical delay (EMD). The results also showed a significant group × test interaction for the rate of force development (RFD), and paired reflex depression (PRD) over the course of the study. Our findings suggest that 4 weeks of WBV appear to have an effect on the neurological variable (presynaptic inhibition) and also the functional variables (EMD and RFD).

Key words: whole body vibration, neurological adaptation, rate of force development, electromechanical delay, pre-synaptic inhibition

INTRODUCTION

Recently, whole-body vibration (WBV) has received a great deal of attention due to reports of enhanced physical performance (Cochrane et al. 2004a; Roelants et al. 2004). Researchers speculate that increased muscle strength and power following WBV training results from neuromuscular changes resulting in adaptations similar to those experienced with resistance training(Bosco et al. 1999; Delecluse et al. 2003; Nordlund and Thorstensson 2007).

There are several challenges associated with understanding the effects of WBV on physical performance because of the lack of standardization of WBV protocols in the literature. Additionally it remains difficult to gain a complete understanding of the time course of these effects due to the lack of standardization in protocols. Some authors have studies the acute or immediate effects while other has studied longer-term or chronic effects of WBV exposure. The main problem with comparing studies of such varied length of intervention is determining if observed changes are due to a neural or a muscular mechanism or a combination. The main focus of this study was to evaluate the neural aspects of WBV exposure through 4 weeks of WBV exposure.

The use of a vibratory stimulus to alter the function of the neuromuscular system is not a novel approach. Many early researchers stimulated muscle spindles by either directly stimulating the muscles containing the spindles or by vibrating the tendons attached to the muscles (Bosco et al. 1999; Desmedt 1983; Issurin et al. 1994; Issurin and Tenenbaum 1999). It is well accepted that when a muscle or a tendon is exposed to a vibratory stimulus that a tonic vibration reflex (TVR) is initiated where there is increased activation of the spindle afferents and enhanced neural drive (Cardinale and Pope 2003). Some authors speculate that TVR causes a mitigation of reflex levels due to a presynaptic

mechanism (Bongiovanni and Hagbarth 1990; Bongiovanni et al. 1990; Rittweger et al. 2003).

To date, we have been unable to identify any study that specifically measured the effect of WBV on presynaptic inhibition. However, there have been some efforts to determine the effect of WBV on more functional performance variables: rate of force development (RFD) and electromechanical delay (EMD). RFD describes the ability to rapidly develop muscular force (Gruber and Gollhofer 2004). Any increase in RFD is closely related to a higher level of muscle force in the early phase of muscle contraction (Aagaard et al. 2002). EMD is the delay between the onset of electromyographic activity (EMG) and the onset torque production. EMD, as a component of the stretch reflex, is vital for both the utilization of the stored energy in the series elastic component and optimal sports performance (Gleeson et al. 1998). It has been hypothesized that these two functional performance variables are both affected by a significant increase in muscle spindle sensitivity and efferent neural output, potentially induced by WBV (de Ruiter et al. 2003a; Hopkins et al. 2008). However, more studies are needed to determine the precise mechanism of WBV on these functional variables. The purpose of this study was to evaluate the training effect of a 4 week WBV program on 2 measures of presynaptic inhibition (intrinsic PI and extrinsic PI) as well as the its effect on 2 functional performance variables (EMD and RFD).

METHODS

A total of 40 subjects (24.2 yrs ± 5.9) were recruited to participate in this study. Twenty men and twenty women with no history of lower leg injury (specifically ankle or knee joint) were recruited through flyers posted on a university campus. All volunteers

were screened via an initial telephone interview to ensure they satisfied the inclusion criteria. A local Institutional Review Board approved the study. All subjects provided written consent after being fully informed of the nature of the study. Subjects were randomly assigned to one of the treatment groups (WBV or No-WBV).

The WBV group performed vibration training over a period of 4 weeks (3 times per week) for a total of twelve training sessions. Subjects in the WBV group stood, with knees flexed to approximately 20º, on the vibration platform (TurboSonic™ Seoul, Republic of Korea) (Figure 2-1). The experimental parameters for TurboSonic WBV device were set at a frequency of 20 Hz and maximal amplitude (5 mm) during each of the three 2-minute periods with one minute rest separated each period of vibration. Each training session lasted approximately 10 min. The No-WBV group performed the same static semi squatting position on the floor. Subjects in the No-WBV group performed the periods of quiet standing three times a week at their home. Both groups were asked to not to make any changes in their activity level during the study period. All subjects were informed and monitored for the training schedule by emails and phone conversation.

All subjects (WBV and No-WBV) were required to report to the laboratory on 3 occasions during a study period for data collection (Pre, Mid, Post). (Table 2-1).

Table 2-1: Testing / Training Schedule

Pre- Test	2 Weeks of WBV training	Mid-Test	2 Weeks of WBV training	Post-test

The outcome measures assessed were: 1) extrinsic presynaptic inhibition (EPI) and Paired reflex depression (PRD), 2) RFD, and 3) EMD. All testing procedures were performed on the dominant leg.

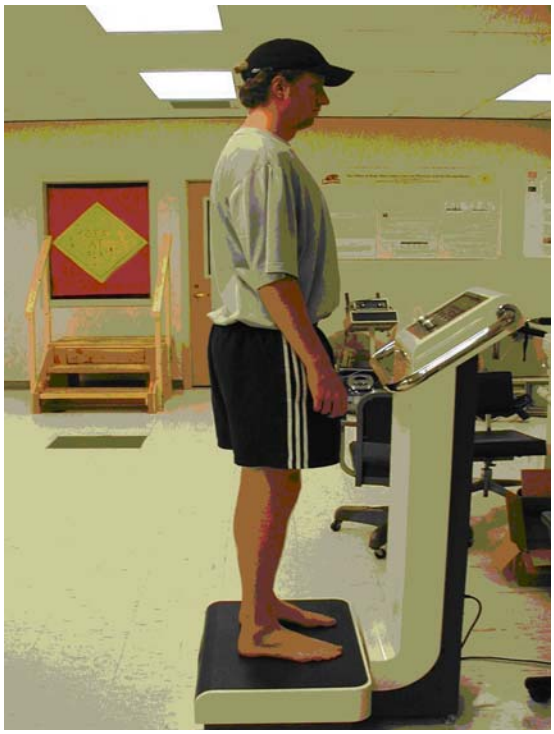

Figure 2-1: Whole Body Vibration

Two different conditioning protocols were used to assess presynaptic inhibition. Conditioning of the soleus motorneuron pool by stimulation the common peroneal nerve was used to assess extrinsic presynaptic inhibition while a paired reflex condition protocol (PRD) was used to assess intrinsic presynaptic inhibition. The protocols were randomly assigned to each subject. Subjects were tested lying prone on a padded table with the ankle positioned at 90º. A body pillow was used to standardize body, head, and hand position for each subject. Subjects remained in this same position for both presynaptic inhibition testing procedures. To elicit and record muscle responses and

stimulation intensity, an EMG channel with surface electrodes (MP 100, BIOPAC Systems Inc., Santa Barbara, California, USA) and a stimulating circuit (s88, Grass Instruments) was used. All areas of the skin where stimulating and recording electrodes were placed were shaven and cleaned with alcohol. Lubricated surface EMG-recording electrodes (Ag/AgCl) were placed over the main part of the muscle of the soleus and tibialis anterior muscle. The electrodes for the soleus were placed between 3 and 6 inches above the heel. The electrodes for the tibialis anterior were placed with the same distance on the muscle. A stimulating electrode (1 cm^2) was placed over the tibial nerve behind the knee to elicit a reflex of the soleus. A dispersal pad (3 cm^2) was placed above the distal thigh just above the patellar. An additional stimulating electrode was place over the head of the fibular for stimulation of the peroneal nerve (Figure. 2-2). Throughout the testing, EMG recordings of the soleus and tibialis anterior muscles were same for EPI and PRD.

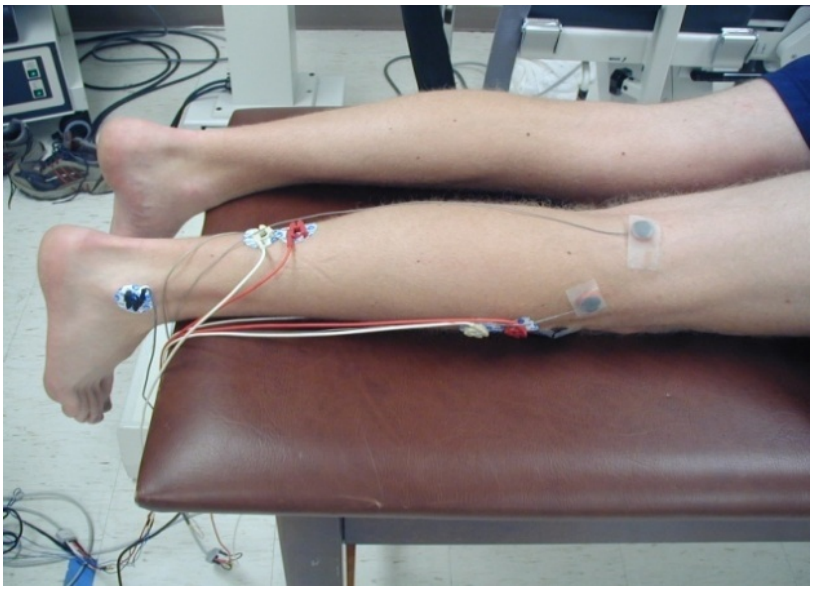

Figure 2-2: Electrodes placement for Spinal Reflex Testing

Once the recording electrodes, stimulating electrode, and the dispersal pad were applied to the skin and connected to the stimulating system, the muscle responses were measured by stimulating the tibial nerve (via 1 ms pulses). To capture peak-to-peak amplitude of the H-reflex and M-waves, EMG measurements were collected at a rate of 2000 samples per second. Acqknowledge waveform acquisition software for Microsoft Windows (Acqknowledge Software v.3.9.1, Biopac Systems, Inc. Goleta, California, USA) was used to determine the peak to peak amplitude of the H-reflex and M-wave to form the recruitment curves. Stimulus intensity was increased in small increments until the maximum H-reflex and M-wave amplitudes were obtained. For EPI testing, stimulating intensity for the tibial nerve was set up to elicit reflex of the soleus muscle 100 ms before stimulating intensity for the common peroneal nerve was triggered to elicit the reflex of tibialis anterior muscle. For the PRD testing, standardized H-reflex stimulating intensity was set up with 80 ms delay between first and second stimulation.

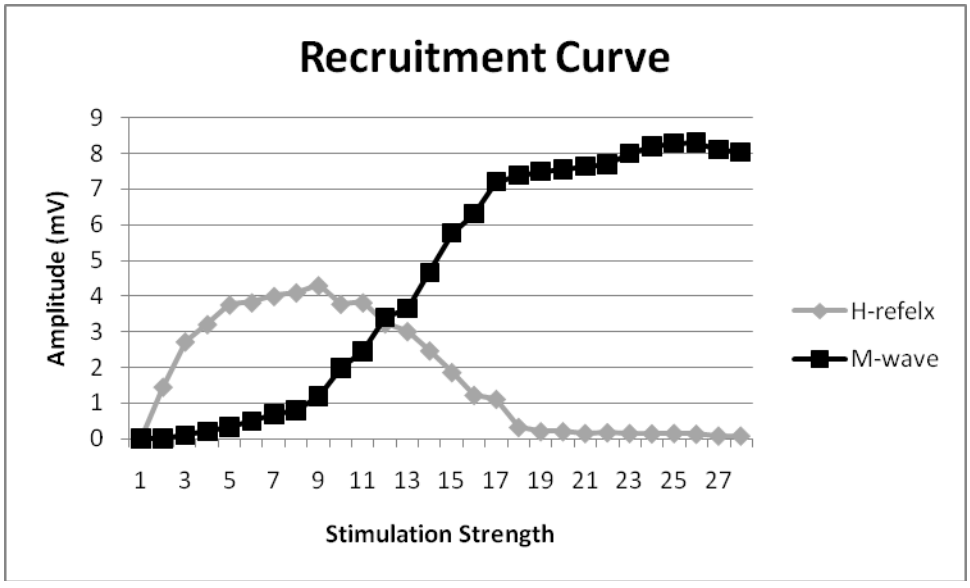

Figure 2-3: Recruitment Curve of the soleus muscle. The H-max and M-max were assessed to determine the stimulation intensity for pre-synaptic inhibition measurement.

The EPI was measured by comparing conditioned and unconditioned H-reflexes of the soleus muscle (Iles 1996; Zehr and Stein 1999). Following the determination of maximum H-reflex and a maximum M-wave, the intensity of the conditioning stimulation was set at 50% of max M-wave of the tibialis anterior and the intensity was maintained throughout testing. To condition the soleus motoneuron pool (MP), the stimulation of the tibial nerve preceded the soleus stimulation by 100 ms (Iles 1996; Zehr and Stein 1999). Unconditioned measures were assessed by stimulating the tibial nerve (25% of Mmax) with the same intensity and measuring the resulting reflex activity without the influence of a conditioning stimulus. For the assessment of EPI, conditioned (15 trials) and unconditioned (15 trials) H-reflexes were measured (Figure 2-4). At least 10 seconds passed between each of the stimulation pairs.

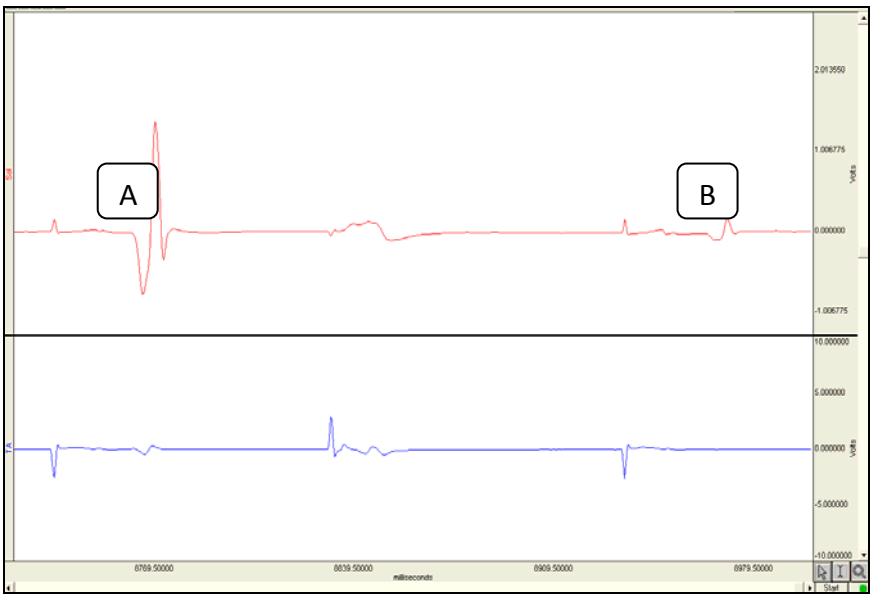

Figure 2-4: Modulation of the soleus H-reflexes from extrinsic pre-synaptic inhibition (EPI) protocol. A: Unconditioned S1 (tibial nerve) stimulus producing an H-reflex (2.10 volts). B: Conditioned S2 (common peroneal nerve) stimulus 100 ms prior to tibial nerve stimulation producing depressed H-reflex (0.270 volts). For the paired reflex depression protocol, conditioned S2 stimulus was tibial nerve stimulation. The degree of depression (% depression) of the second H-reflex produced relative to the first H-reflex was compared.

A paired-pulse technique was used to elicit paired soleus H-reflexes 80 ms apart (Earles et al. 2002; Hye-Seon et al. 2007). Both pulses stimulated the tibial nerve to elicit reflex of the soleus muscle. Stimulus intensity was adjusted to obtain an initial H-reflex of 25% of motoneuron pool (MP). Total 15 paired soleus H-reflexes were collected. To assess the PRD, the degree of depression (% depression) of the second H-reflex relative to the first was compared. At least 10 seconds passed between each of the stimulations.

For all subjects, isometric torque measurements were performed on the dominant ankle using an isokinetic dynamometer (Biodex System 3 Pro, Biodex Medical Systems Shirley, NY). The subjects sat on the testing chair of the dynamometer and the leg was secured with body straps (Figure.2 -5), while the hip and the knee joints are flexed at 100 deg. Measurements of RFD and EMD were obtained during plantar flexion. All subjects were instructed to "plantar flex the ankle as hard and as fast as possible" after the light signal. The light was located on a wall approximately 5 feet from the subject. A verbal "ready" cue was given to the subjects about 1 to 3 seconds before the investigator triggered the light. Three trials were performed with 1 min rest between each trial.

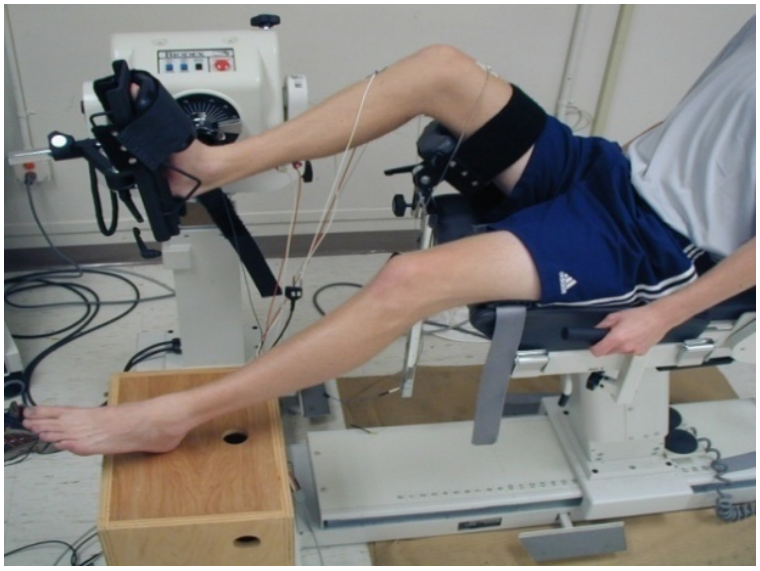

Figure 2-5: RFD and EMD testing position

The force signal and the EMG signals were synchronously sampled at 2000 Hz. The raw unfiltered signals were analog-to-digital converted (Acqknowledge Software v.3.9.1, Biopac Systems, Goleta, CA) and stored on a PC. During the later process of analysis, the EMD and force signals were digitally high-pass filtered by using a fourth-order, zero lag Butterworth filter with a 10 Hz cutoff. The filtered force signal was then differentiated with the central-difference method to calculate the force's rage of change. Maximal rate of change was calculated as the maximal rate of force development. EMD was defined as the time interval between the onset of EMG signal and the onset of the torque applied to the footplate (Aagaard et al. 2002). EMD was defined as the time interval between the start point of the light signal and the onset of the torque applied to the footplate (Muraoka et al. 2004; Zhou et al. 1995). Onset of EMD and force was determined by the cumulative sum technique (Scholz and Millford 1995)

Initially a 1 way ANOVA was applied to the baseline data to determine if differences between the groups (WBV, No-WBV) existed. Next a mixed design ANOVA

[2 (group) × 3 (time)] was used to determine if differences between the means existed. Alpha was set at 0.05. All statistical analyses were performed using the SPSS 15 software (SPSS, Inc., Chicago, IL). Data are reported as mean ± standard deviation (SD).

To confirm reliability of our data a test-retest reliability assessment was used on the data from the 20 control subjects across time. Retest reliability was determined for all parameters by an Intraclass Correlation Coefficient (ICC $_{2,1}$) method using linear regression analysis. The time period between the first and second measurement was 2 weeks. Reliability of EMD, RFD, EPI, and PRD were calculated as R= 0.87, 0.92, 0.94, and 0.84.

RESULTS

Subjects who received the WBV were similar to controls at baseline for all dependent measures; EMD, RFD, EPI, and PRD (Table 2-2). Two conditioning protocols were used to assess spinal pathways: 1) conditioning of the common peroneal nerve for extrinsic pre-synaptic inhibition and 2) paired reflex depression for intrinsic pre-synaptic inhibition. The 2 × 3 ANOVA for EPI showed no significant Group × Test interaction (p=.889), and test effect (p=.218) (Figure 2-6).

Table 2-2: The mean and standard deviation of the neuromuscular parameters

	No- WBV (n=20)			**WBV (n=20)**		
	Pre	Mid	Post	Pre	Mid	Post
EMD (ms)	21.25 ± 7.63	20.13 ± 6.20	20.92 ± 5.06	23.42 ± 7.54	20.62 ± 8.39	15.14 ± 7.13
RFD (N/sec)	318.41 ± 145.42	322.73 ± 142.03	321.58 ± 129.49	274.13 ± 137.77	320.41 ± 136.35	401.71 ± 176.
EPI (%)	75.13 ± 30.64	74.07 ± 32.38	73.48 ± 33.67	83.82 ± 22.78	88.87 ± 21.84	83.53 ± 24.05
PRD (%)	61.24 ± 27.12	63.15 ± 22.83	62.45 ± 24.69	71.97 ± 24.33	62.64 ± 22.76	45.74 ± 27.78

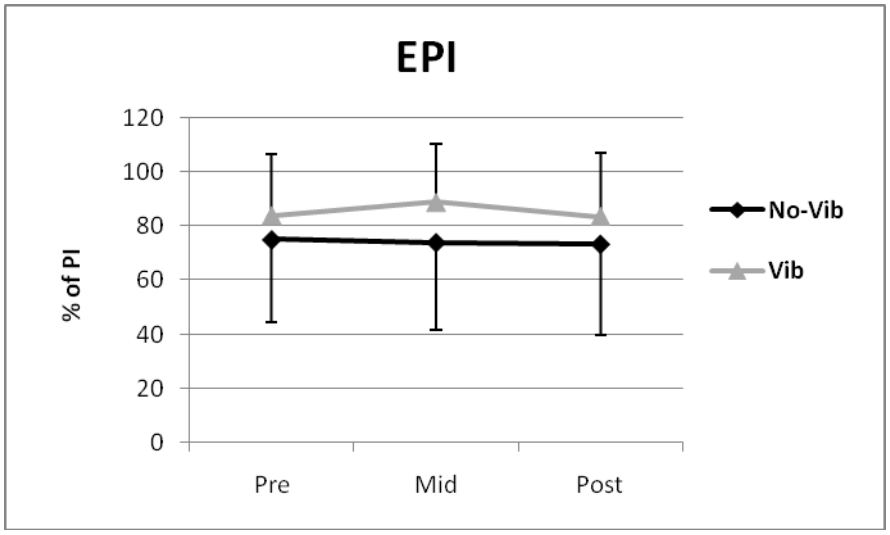

Figure 2-6: Mean and standard deviation (SD) of the EPI before (pre), after 2 weeks (mid), and after 4 weeks (post) in the WBV group and the No-WBV group. There was a no significant interaction, group, and test effect at $p<.05$. There was no significant difference in the means between groups at any of the testing sessions (pre, mid, post-test)

The 2 × 3 ANOVA showed a significant group × test interaction ($p<.001$) and test effects ($p=.001$) for PRD. However, the evaluation of the interaction revealed no significant differences between the means in the WBV group and the No-WBV group ($p=.052$)**.** After a 4 week of vibration training, PRD decreased by about 37% (from 71.9% to 45.7%) in the WBV group (Figure 2-7).

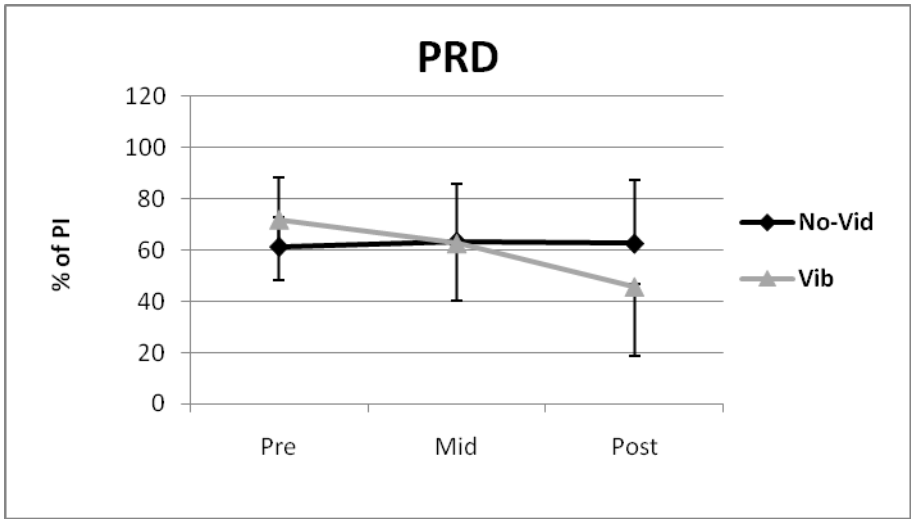

Figure 2-7: Mean and standard deviation (SD) of the PRD before (pre), after 2 weeks (mid), and after 4 weeks (post) in the WBV group and the No-WBV group. There was a significant interaction effect (group × test) and test effect at $p<.05$. However, no significant differences were shown between post-test values and either pre and mid-test values.

The 2 × 3 ANOVA showed a significant group × test interaction ($p=.001$) and test effect ($p=.617$) for EMD (Figure 2-8). The evaluation of the interaction revealed a significant differences between the means of the testing times in the WBV group ($p<.005$) but not in the No-WBV group ($p>.05$). EMD from pre-test to post-test decreased by about 35% (from 23.42 ms to 15.14 ms) in the WBV group, whereas it did not change significantly in the No-WBV group.

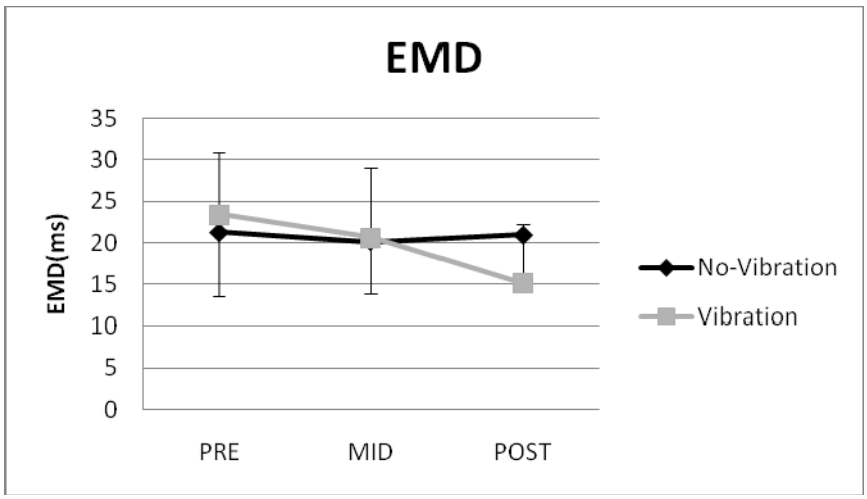

Figure 2-8: The 2 × 3 ANOVA showed a significant group × test interaction (p=.001) and test effect (p=.001) for EMD.

The 2 × 3 ANOVA showed a significant group × test interaction (p=.001) and test effect for RFD (p=.001). (Figure 2-9). However, the evaluation of the interaction revealed no significant differences between the means in the WBV group and the No-WBV group at any level of the testing sessions (pre, mid, post). After 4 weeks of WBV, RFD from pre-test to post-test increased by about 32% (from 274N/sec to 401 N/sec) in the vibration treatment group.

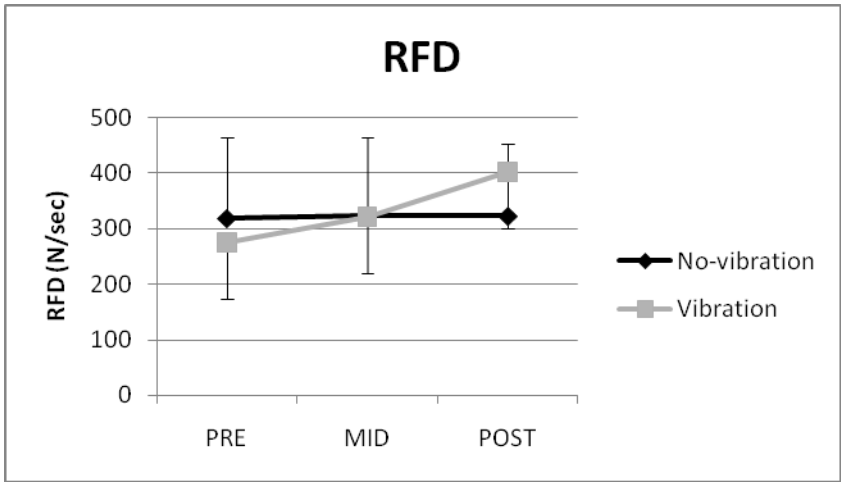

Figure 2-9: The 2 × 3 ANOVA showed a significant group × test interaction and test effect for RFD (p=.001)

DISCUSSION

The aim of this study was to determine if 4 weeks of WBV training affects the neuromuscular properties of the soleus. To our knowledge, this is the first study that has combined neurological and functional measures in the study of WBV. Our results demonstrated that 4 weeks of whole body vibration (WBV) training decreased EMD and increased RFD during isometric contractions in conjunction with a decrease in intrinsic presynaptic inhibition as measured by (paired reflex depression).

One of the main findings of our study is that 4 weeks of WBV training significantly shortened EMD by 35% over the course of the study. The EMD decrease of nearly 15% between the pre-test and mid-test however was not statistically significant. Interestingly the additional 20% decrease between the mid-test and post-test did result in the significant change. To date, we are unaware of any previous study in which investigated the chronic effects of WBV on EMD. In the present study, EMD was defined as the lag time between the beginning of the soleus muscle activation and the beginning of the plantar flexion force. The EMD includes the time courses of the propagation of action potential on the muscle membrane, the excitation-contraction coupling processes, and the stretching of the series elastic components (SEC) by the contractile component (Cavanagh and Komi 1979). Among the above mentioned components of EMD, it has been well accepted that the predominant component of EMD is the time required to lengthen the elastic components of the musculotendinous structures (Zhou et al. 1995). The musculotendinous unit possesses inherent series elastic slack (Svantesson 2004). It is

suggested that sufficient musculotendinous stiffness has to be present to compensate for this slack (Rack 1983). Muscle stiffness includes not only the passive tightness produced by tendon but also by other passive structures such as muscle fascia, skin, or joint capsule (Svantesson 2004). It has also been reported that increased stiffness to the series elastic component (SEC) would reduce the amount of slack taken up by cross-bridging and therefore reduce the amount of time necessary to produce force (Norman and Komi 1979; Vos et al. 1991; Zhou et al. 1995). Based on the fact that EMD is the time required to lengthen SEC of muscle and stiffness of SEC reduce the time of the slack present in SEC , we suggest that changes in EMD are primarily attributed to changes in the stiffness of the SEC of muscle (Granata et al. 2000).

With respect to the connection between muscle stiffness and WBV, it has been documented that when muscles are vibrated, muscle spindle sensitivity and muscle stiffness increase to dampen the vibration (Cardinale 2003). Vibration is also known to activate the joint mecahnoreceptors and stimulate the gamma efferents. As a result of the activation of the joint mechanoreceptors and gamma efferents by vibration, the muscle spindles become sensitized and muscle stiffness increases (Johansson 1991). Regarding the specific mechanism of how WBV increases muscle stiffness, Cardinale et al. also speculated that WBV causes fast joint rotation and muscle stretching which is likely to increase muscle stiffness following the purported neural potentiation of the stretch reflex pathway and motoneuron input (both alpha and gamma) (Cardinale and Pope 2003). It is our hypothesis that while subjects were being vibrated on the WBV platform, agonist and antagonist muscles of the lower leg were constantly being activated to maintain the

posture against the vibration, and it increased the stiffness of tendon, muscle fascia, and joint capsule around the ankle joint which might have shortened EMD.

Another possible explanation for the decreased EMD shown in the present study can be found in the connection between the roles of pre-activation and muscle stiffness (Riemann 2002). Pre-activation and muscle stiffness are often addressed at the knee and ankle joint (McNair 1992). It has been documented that as a result of pre-activation, muscle stiffness is believed to increase (Riemann 2002). In our study, the subjects in the WBV group held semi squatting position for 3 bouts of 2 minutes three times a week for 4 weeks. In our opinion, with the posture holding the knees flexed against the vibration, the soleus muscle became pre-activated and therefore the stiffness of already pre-activated soleus muscle with WBV seemed to be increased. This phenomenon has been documented by a recent study by Roelants et al. It has been shown that the WBV effect would be larger in the posture in which the receptor-bearing muscle is more pre-activated (Roelants et al. 2006). Another study by Rohmert has also speculated that muscles with an increased muscle length or increased degree of pre-activation seemed to be most affected by vibration (Rohmert 1989). In addition, Burke et al (Burke et al. 1976) suggested that even a small increase in pre-activation may lead to increased muscle spindle sensitivity because of alpha-gamma co-activation which is known to increase the muscle stiffness (Burke et al. 1976).

In this respect, we hypothesized that the semi squatting position held during WBV might have increased the level of pre-activation of the soleus muscle and resulted in increased muscle stiffness and decreased EMD.

Our results demonstrate that following 4 weeks of WBV training, rate of force development (RFD) increased by about 32% in the vibration group whereas maximum RFD remained unchanged in the No-WBV group. More specifically, in WBV group, RFD increased 15% from pre-test to mid-test (2 weeks) and 17% from mid-test to post-test (2 weeks). The increased RFD observed in our study was in line with a study by de Ruiter et al. In their study, de Ruiter et al showed that 11 weeks of WBV (30Hz, 8 mm) increased RFD by 7.5% (de Ruiter et al. 2003b). However due to the differences in WBV protocols and the muscles tested, direct comparison is limited.

In order to understand possible mechanisms of how WBV increases RFD, it is important to first identify what physiological factors contribute to the changes in RFD. First, Gruber et al. in their recent study suggested that by analyzing single motor unit recordings, they found motor units were activated earlier and showed increased firing frequencies after training (Gruber and Gollhofer 2004). According to Kukulka and Clamann, by an enhanced motoneuron excitability, high-threshold motor units can be recruited earlier in a maximal voluntary contraction and this early recruitment of motor units increases RFD (Paradisis 2007). Based on these single motor unit studies, we can find possible connection between WBV and factors affecting RFD. In a muscle vibration studies, it has been suggested that the tonic vibration reflex (TVR) affects primarily the participants' ability to generate high firing rates in high-threshold motor units (Bongiovanni et al. 1990). It has been also documented that the tonic vibration reflex (TVR) is able to cause an increase in recruitment of the motor units through activation of muscle spindles and polysynaptic pathways (De Gail et al. 1966). Based on the findings from muscle or tendon vibration studies, Romaiguere et al. suggested that the recruitment

thresholds of the motor units during WBV are expected to be lower compared with voluntary contractions, probably resulting in a more rapid activation (Romaiguere et al. 1993). In our opinion, the mechanism of tendon or muscle vibration affecting the motor units might be similar to the mechanism of WBV affecting the motor unit threshold. However, since there is limited data available on the effects of WBV on this particular functional variable (RFD), more research is recommended.

With respect to other potential effect of WBV on RFD, the findings of a recent muscle vibration study by Shinohara et al can be considered. Shinohara et al. in their recent study demonstrated a significant increase in stretch reflex amplitude and motor unit discharge rate after prolonged muscle vibration. The authors indicated that the increased stretch reflex depends on the sensitivity of the muscle spindles which is determined by the level of gamma motor neuron activity (Shinohara 2005). Cochrane et al. also suggested that muscle length change during WBV causes activation of gamma fusimotor input that enhances the discharge of primary afferents to increase motoneuron activation, thereby causing powerful and rapid contractions (Cochrane et al. 2004b). Although it is assumed that WBV causes rapid contraction by enhancing the discharge rate, we do not have enough evidence to suggest that RFD may have changed by the above mentioned mechanism (increase in motor unit discharge rate). The more research should focus on investigating isolated effects of WBV on these purported neural adaptation mechanisms.

Recently, presynaptic inhibition has been suggested as a modulatory mechanism responsible for neurological changes seen with WBV(Abercromby et al. 2007; Rittweger et al. 2003). However, no study to date has looked at how WBV affects this spinal

mechanism. In this regard, the present study is unique in the fact that it utilized 2 different presynaptic inhibition protocols to assess how WBV affects spinal level control. Our results showed a significant interaction between group and time for the measurement of paired reflex depression (PRD). PRD measures the relative influence of the reflex activation history on reflex excitability (Mendell 1984; Trimble et al. 2000) and represents another means by which reflex excitability is controlled (Mendell 1984; Trimble et al. 2000). It has been proposed that the reduced PRD of the H-reflex would represent a decrease in the depression associated with the reflex activation history and would effectively allow spindle afferent feedback to contribute to the neural drive of the muscle (Trimble et al. 2000). Concerning the relationship between WBV and presynpatic inhibition, the classic tendon vibration protocols have already been shown to cause inhibition due to this gating of spindle afferent feedback which can be achieved through presynaptic control mechanisms(Eccles et al. 1962).

Regarding a possible mechanism for an increased RFD by presynaptic inhibition, it has been suggested that the neural modulation of presynaptic inhibition pathway is affected by the recruitment of motor units for voluntary movements (Gruber and Gollhofer 2004). In addition, it is hypothesized that the enhanced excitatory synaptic input or motoneuron excitability with training causes high-threshold motor units to be recruited earlier in a maximal voluntary contraction (MVC) increasing RFD (Gruber and Gollhofer 2004). This finding can be a supporting evidence for the speculation that main neural adaptation occur in supraspinal structures caused by an enhanced neural drive in descending corticospinal pathway. Based on these findings and mechanisms documented in the previous studies, the change in RFD following WBV in our study indicates that

WBV appears to have an effect on RFD. However more studies should look at the effects of WBV on each of these possible factors for the increased RFD, i.e., potentially involving alterations in motor unit recruitment, motor unit discharge rate, and possibly presynaptic mechanism.

The present study assessed not only the PRD (intrinsic presynaptic inhibition) but also classical presynaptic inhibition (extrinsic presynaptic inhibition). Classical presynaptic inhibition is considered extrinsic inhibition (EPI) because of the involvement of the inhibitory interneurones effect on the synapse of the sensory and motor fibers.

In this study, the EPI remained unchanged after 4 weeks of WBV training but IPI as measured with paired reflex depression of soleus H-reflex decreased by 37% in the WBV group. These findings support the hypothesis that changes seen with WBV may have been due to presynaptic inhibition (Bongiovanni et al. 1990; Rittweger et al. 2000), and that WBV interacts with the spinal reflex loops, potentially influencing these pathways (Rittweger et al. 2000). Theoretically, it has been shown that in the spinal cord, the preferentially activation of Ia afferents by muscle vibration initiates impulses in a polysynaptic excitatory pathway and a presynaptic inhibitory pathway (Romaiguere et al. 1993). The spinal polysynaptic excitatory pathway evokes the tonic vibration reflex (TVR), whereas the spinal presynaptic inhibitory pathway is responsible for the vibration-induced reflex inhibition (Romaiguere et al. 1993). Furthermore, it has been shown that the depression of the soleus H-reflex during vibration of the achilles tendon is less pronounced (Pierrot-Deseilligny 2005).

Another possible explanation for this phenomena has been addressed by Hultborn et al. Hultbron et al suggest that due to alpha-gamma co-activation, more I afferents will

be active and already active Ia afferents will increase their firing when the subject voluntarily activates the muscle (Hultborn et al. 1987). They also suggest that during the voluntary contraction the H-reflex will consequently be influenced by this Ia afferents firing (Hultborn et al. 1987). Based on these previous findings, we suggest that a possible mechanism for the changes in presynaptic inhibition after WBV observed in our study can be associated with mechanism suggested by Hultborn et al. It has been already well known that co-activation of muscles increase and the activity of Ia afferernts increases during WBV (Romaiguere et al. 1993). Therefore, during WBV subjects' holding the semi squat position against vibration may have increased co-activation of the lower leg muscles and increase the activity of more I a afferents. Also, since IPI as measured with PRD is known to be affected by spindle and reflex activation history (Romaiguere et al. 1993), the status of already active Ia afferents and their firing during WBV may have been a factor that caused reduction of inhibition. Considering the fact that there has been no data available regarding the effects of WBV on presynaptic inhibition until this present study was conducted and the possible mechanism for the change in presynaptic inhibition discussed here is based on the tendon vibration study, more research should investigate effects of this WBV on presynaptic mechanisms.

It has been proposed that modulation of the reflex depression associated with the frequency of reflex activation would allow the facilitation provided by the spindle afferents to temporarily summate and contribute to the neural drive when loads are resisted during voluntary movements (Trimble et al. 2000). Earles et al. in their recent study reported that the power-trained group demonstrated less PRD than the endurance-trained group. They suggest that the decrease in the inhibition associated with presynaptic

control (PRD) in power-trained athletes should intuitively increases the gain of the monosynaptic stretch reflex. This may in turn provide functional importance during the onset of a movement (particularly a ballistic movement) (Earles et al. 2002). It has been also suggested that this high gain may allow the monosynaptic stretch reflex to assist in the high-force movement. Moreover, Meunier and Pierrot-Deseilligny state that functionally, increased reflex gains are important to meet appropriate loading during muscular action and this facilitation of reflex gains has been mainly attributed to reduced presynaptic inhibition of Ia afferents (Meunier and Pierrot-Deseilligny 1989). Taking all these postulates into context, it is suggested that WBV training has a great impact on peripheral presynaptic inhibition of Ia termainals on motoneurons of the acting muscle (Vallbo and Hulliger 1982).

CONCLUSION

The present study indicates that 4 weeks of WBV appear to have an effect on the neuromuscular properties of soleus muscles and spinal mechanisms (presynaptic inhibition). This is demonstrated by a decreased electromechanical delay in line with a significant group × test interaction for the rate of force development and the presynpatic inhibition (PRD) of the soleus muscle. The results of our study suggest that changes in the spinal mechanism after 4 weeks of WBV might be associated with the changes seen not only in the muscular performance variables from the present study, but also the changes seen in recent WBV studies. The findings here may provide a means of isolating effect of WBV on the neuromuscular system and perhaps may give important insights about the role of training on human nervous system. Further research is needed to investigate other mechanisms that may underlie the physiological responses and

adaptation to WBV, and how these responses may occur among individuals with abnormal muscle function or soft-tissue injury.

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CHAPTER 4: CONCLUSION

The use of whole body vibration (WBV) to enhance performance of the neuromuscular system has drastically increased over the past several years (Bosco 1998; Cochrane et al. 2004). One of the main reasons for the increased popularity of WBV is the belief that strength and performance gains can be achieved in a relatively short period of time (Cardinale and Pope 2003). Recent study by Bosco et al. showed that a single session of acute WBV enhanced muscular performance of well trained athletes (Bosco et al. 2000). In addition, recently, more scientific publications report positive effects from WBV exercise, also among people with the neuromuscular impairments (Rittweger et al. 2002; Tihanyi et al. 2007). Although WBV is being employed from athletes and patients in their training and rehabilitation regimes, it is still unclear how WBV induces such an enhancement of muscular function.

Although it is challenging to explain how these adaptive muscle responses occur with WBV or what intrinsic neural mechanism is responsible for these changes, several investigators have tried to find a possible mechanism for the positive acute effects of WBV training. One of the theoretical mechanisms for acute and chronic effects of WBV is neural adaptation related to increased muscle activation caused by increased excitability input from muscle spindles exposed to a vibration (Abercromby et al. 2007). It has been hypothesized that the enhanced muscle power observed following vibration occurs via potentiation of the neuromuscular system whereby stimulation of muscle spindles (Ia afferents) results in reflex activation of motoneurones with increased spatial recruitment (Komi 2000; Romaiguere et al. 1993). It has been also shown that the continued enhancement of the stretch-reflex pathway can be attributed to the gamma motoneurone input causing an increase in sensitivity of the primary endings (Issurin and

Tenenbaum 1999; Rittweger et al. 2000). Furthermore, tonic vibration reflex (TVR) can recruit additional motor units via the activation of muscle spindle afferents resulting in increased discharge and enhanced neural drive (Burke et al. 1976; Gillies et al. 1971; Issurin et al. 1994). In addition, it has been proposed that the recruitment thresholds of the motor units during WBV are expected to be lower than during voluntary contractions, possibly resulting in a more rapid activation and training of high-threshold motor units.

As an another possible mechanism, effects of WBV on the properties of spinal pathways has been theorized by several researchers (Bongiovanni and Hagbarth 1990; Bongiovanni et al. 1990; Rittweger et al. 2000). Bongiovanni et al. suggested that the contributing mechanism for the improvement in muscle function after WBV might be vibration induced presynaptic inhibition in the group Ia excitatory pathways (Bongiovanni et al. 1990). It has also been reported that vibration exercise interacts with spinal reflex loops and possibly influencing these pathways (Rittweger et al. 2003).

Despite the above possible explanations for neuromuscular enhancement after WBV, the presynaptic inhibition after WBV training had not yet been studied. Furthermore, to date, there is only limited data on the effect of WBV training on functional muscular performances. To better understand the effects of WBV on the neuromuscular system and functional muscular performance, the present study set out to investigate the acute and short-term (4 weeks) effects of WBV on electromechanical delay, rate of force development, and presynaptic inhibition.

Interpretation of data from the current study suggests that 4 weeks of WBV has an effect on the neuromuscular properties of soleus muscles and spinal mechanisms (presynaptic inhibition). This is demonstrated by a decreased electromechanical delay

with a significant group × test interaction for the rate of force development and the presynpatic inhibition (PRD) of the soleus muscle. It is therefore concluded that 4 weeks of WBV appear to have an effect on the functional performance of the soleus muscle and spinal mechanisms (presynaptic inhibition).

In the second aspect of the study, we evaluated acute effects of WBV on specifically functional muscular performance. As muscular performance related variables, electromechanical delay (EMD) and rate of force development (RFD) were measured before and after 6 minutes of WBV. After acute WBV training, the experimental (WBV) group demonstrated a significant interaction for the electromechanical delay (EMD) and rate of force development (RFD) indicating that acute WBV appear to have an effect on these functional performance variables.

The findings here will help researchers involved in the health, fitness, and therapeutic fields to understand more about the potential of WBV as an efficient intervention tool for rehabilitation and training. Further research is needed to investigate the effects of vibration exercise duration, vibration frequency, amplitude and load that are optimum to evoke an enhanced neuromuscular function in young adults, but also in athletes or elderly subjects and patients.

Although this study will contribute to the scientific literature base, it is not without limitations. A limitation to our methods is that our study recruited mostly healthy collegiate subjects who were relatively active and participating in various physical activities during the study period. It is not known that how their activity level might have affected the outcome of the study. With a different population for example sedentary people, the outcomes might have been different. Another limitation is that the present

study didn't measure the physiological variables such as muscle stiffness and stretch reflex. Additionally, the adaptation of the neural mechanisms demonstrated by tendon and muscle vibration studies to explain the possible mechanisms for the changes seen in the present study might be another limitation.

The present study assIt should be considered that the present observations have been made in healthy young adults of moderate levels of physical fitness. We recommend future research investigate the effects of acute and chronic WBV not only in young adults, but also in athletes or elderly subjects and patients.

Additionally, this study is limited by the lack of various WBV parameters (frequency, amplitude, and duration). As indicated in the previous studies, the vibration frequency, amplitude, and duration play in important role. The present study only used relatively low frequency (20Hz) and high amplitude (5 mm). However, future studies should investigate the effects of various exercise duration, vibration frequency, amplitude and load that are optimum to evoke the neuromuscular enhancement.

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APPEDICES

APPENDIX ONE: DATA ANALYSIS SUMMARY

GR*TEST*TIME on EMD

Within-Subjects Factors

Measure: EMD

test	time	Dependent Variable
1	1	emd1pr
	2	emd1po
2	1	emd2pr
	2	emd2po
3	1	emd3pr
	2	emd3po

Between-Subjects Factors

		Value Label	N
Group	1	control	20
	2	experiment	20

Descriptive Statistics

	Group	Mean	Std. Deviation	N
emd1pr	control	.021252	.0076373	20
	experiment	.023424	.0075431	20
	Total	.022338	.0075727	40
emd1po	control	.021118	.0064946	20
	experiment	.019302	.0080840	20
	Total	.020210	.0072960	40
emd2pr	control	.020131	.0062042	20
	experiment	.020624	.0083957	20
	Total	.020378	.0072907	40
emd2po	control	.020338	.0049853	20
	experiment	.016096	.0081512	20
	Total	.018217	.0070065	40
emd3pr	control	.020925	.0050699	20
	experiment	.015144	.0071357	20
	Total	.018035	.0067749	40
emd3po	control	.020372	.0058801	20
	experiment	.011752	.0053252	20
	Total	.016062	.0070507	40

Tests of Within-Subjects Effects

Measure: EMD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
	Sphericity Assumed	.001	2	.000	15.608	.000
	Greenhouse-Geisser	.001	1.715	.000	15.608	.000
	Huynh-Feldt	.001	1.836	.000	15.608	.000
	Lower-bound	.001	1.000	.001	15.608	.000
test * Group	Sphericity Assumed	.001	2	.000	12.661	.000
	Greenhouse-Geisser	.001	1.715	.000	12.661	.000
	Huynh-Feldt	.001	1.836	.000	12.661	.000
	Lower-bound	.001	1.000	.001	12.661	.001
Error(test)	Sphericity Assumed	.002	76	2.29E-005		
	Greenhouse-Geisser	.002	65.178	2.67E-005		
	Huynh-Feldt	.002	69.758	2.50E-005		
	Lower-bound	.002	38.000	4.58E-005		
time	Sphericity Assumed	.000	1	.000	31.209	.000
	Greenhouse-Geisser	.000	1.000	.000	31.209	.000
	Huynh-Feldt	.000	1.000	.000	31.209	.000
	Lower-bound	.000	1.000	.000	31.209	.000
time * Group	Sphericity Assumed	.000	1	.000	26.600	.000
	Greenhouse-Geisser	.000	1.000	.000	26.600	.000
	Huynh-Feldt	.000	1.000	.000	26.600	.000
	Lower-bound	.000	1.000	.000	26.600	.000
Error(time)	Sphericity Assumed	.000	38	8.38E-006		
	Greenhouse-Geisser	.000	38.000	8.38E-006		
	Huynh-Feldt	.000	38.000	8.38E-006		
	Lower-bound	.000	38.000	8.38E-006		
test * time	Sphericity Assumed	4.02E-007	2	2.01E-007	.028	.973
	Greenhouse-Geisser	4.02E-007	1.592	2.52E-007	.028	.949
	Huynh-Feldt	4.02E-007	1.694	2.37E-007	.028	.957
	Lower-bound	4.02E-007	1.000	4.02E-007	.028	.869
test * time * Group	Sphericity Assumed	9.13E-006	2	4.56E-006	.626	.537
	Greenhouse-Geisser	9.13E-006	1.592	5.73E-006	.626	.503
	Huynh-Feldt	9.13E-006	1.694	5.39E-006	.626	.512
	Lower-bound	9.13E-006	1.000	9.13E-006	.626	.434
Error(test*time)	Sphericity Assumed	.001	76	7.29E-006		
	Greenhouse-Geisser	.001	60.500	9.16E-006		
	Huynh-Feldt	.001	64.381	8.60E-006		
	Lower-bound	.001	38.000	1.46E-005		

GR*TEST on PRE EMD

Within-Subjects Factors

Measure: EMD

test	Dependent Variable
1	emd1pr
2	emd2pr
3	emd3pr

Between-Subjects Factors

		Value Label	N
Group	1	control	20
	2	experiment	20

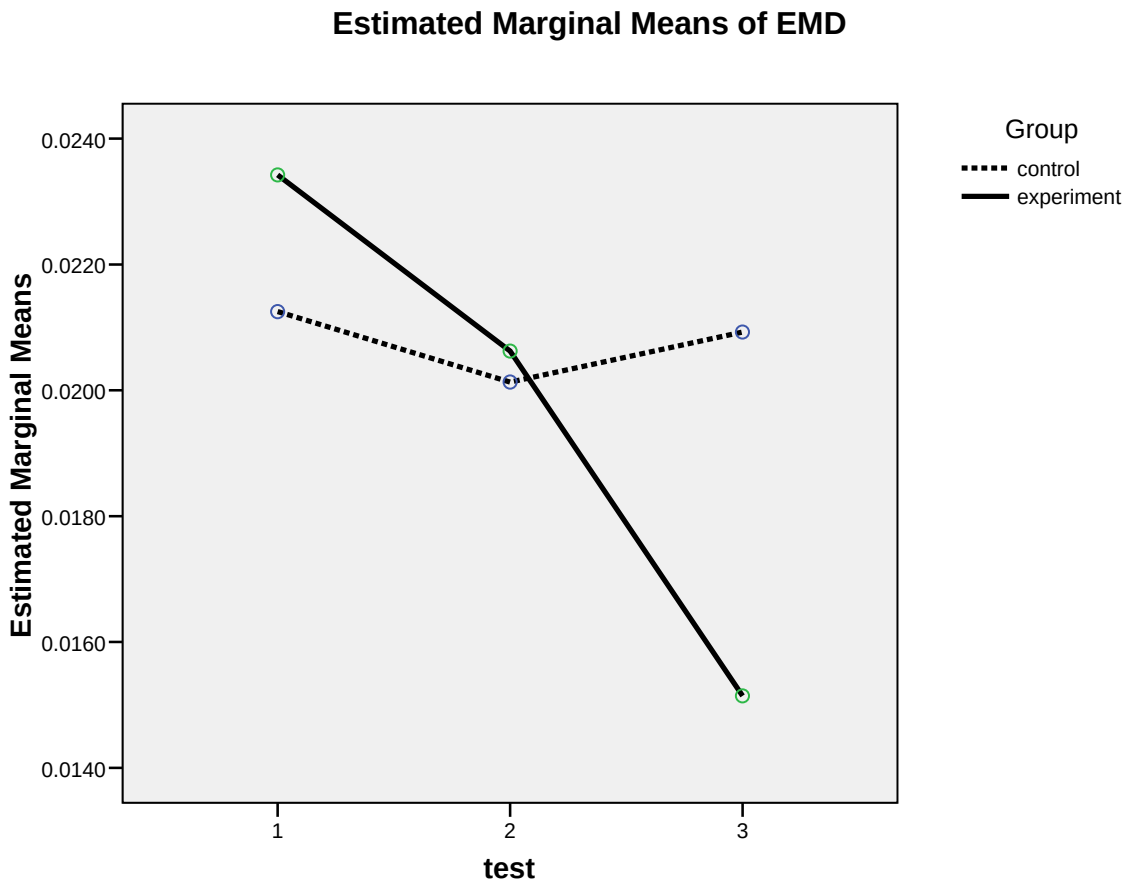
Descriptive Statistics

	Group	Mean	Std. Deviation	N
emd1pr	control	.021252	.0076373	20
	experiment	.023424	.0075431	20
	Total	.022338	.0075727	40
emd2pr	control	.020131	.0062042	20
	experiment	.020624	.0083957	20
	Total	.020378	.0072907	40
emd3pr	control	.020925	.0050699	20
	experiment	.015144	.0071357	20
	Total	.018035	.0067749	40

Tests of Within-Subjects Effects

Measure: EMD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	.000	2	.000	15.909	.000
	Greenhouse-Geisser	.000	1.767	.000	15.909	.000
	Huynh-Feldt	.000	1.895	.000	15.909	.000
	Lower-bound	.000	1.000	.000	15.909	.000
test * Group	Sphericity Assumed	.000	2	.000	15.061	.000
	Greenhouse-Geisser	.000	1.767	.000	15.061	.000
	Huynh-Feldt	.000	1.895	.000	15.061	.000
	Lower-bound	.000	1.000	.000	15.061	.000
Error(test)	Sphericity Assumed	.001	76	1.17E-005		
	Greenhouse-Geisser	.001	67.131	1.32E-005		
	Huynh-Feldt	.001	72.012	1.23E-005		
	Lower-bound	.001	38.000	2.33E-005		



One-way ANOVA for the test effect on PRE EMDs

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
emd1pr	Between Groups	.000	1	.000	.819	.371
	Within Groups	.002	38	.000		
	Total	.002	39			
emd2pr	Between Groups	.000	1	.000	.045	.834
	Within Groups	.002	38	.000		
	Total	.002	39			
emd3pr	Between Groups	.000	1	.000	8.725	.005
	Within Groups	.001	38	.000		
	Total	.002	39			

GR*TEST on POST EMDs

Within-Subjects Factors

Measure: EMD

test	Dependent Variable
1	emd1po
2	emd2po
3	emd3po

Between-Subjects Factors

		Value Label	N
Group	1	control	20
	2	experiment	20

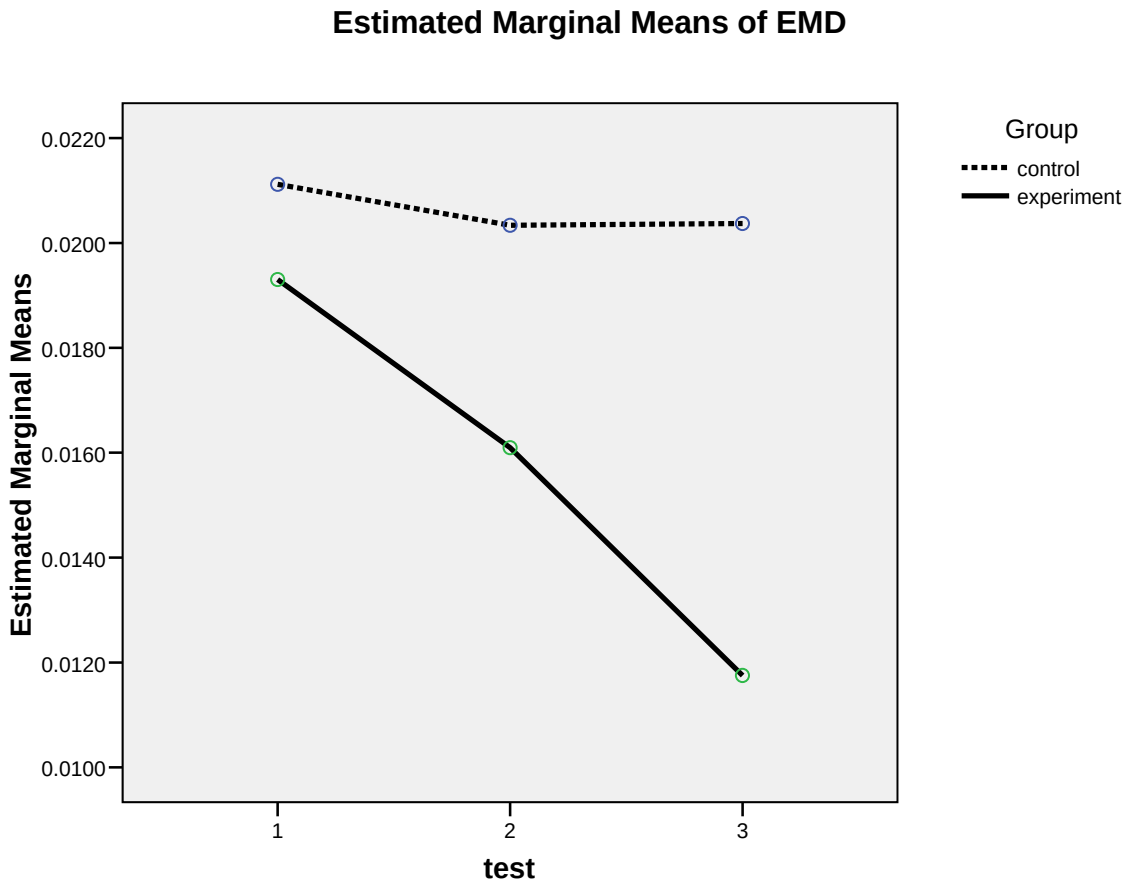
Descriptive Statistics

	Group	Mean	Std. Deviation	N
emd1po	control	.021118	.0064946	20
	experiment	.019302	.0080840	20
	Total	.020210	.0072960	40
emd2po	control	.020338	.0049853	20
	experiment	.016096	.0081512	20
	Total	.018217	.0070065	40
emd3po	control	.020372	.0058801	20
	experiment	.011752	.0053252	20
	Total	.016062	.0070507	40

Tests of Within-Subjects Effects

Measure: EMD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	.000	2	.000	9.291	.000
	Greenhouse-Geisser	.000	1.788	.000	9.291	.000
	Huynh-Feldt	.000	1.920	.000	9.291	.000
	Lower-bound	.000	1.000	.000	9.291	.004
test * Group	Sphericity Assumed	.000	2	.000	6.416	.003
	Greenhouse-Geisser	.000	1.788	.000	6.416	.004
	Huynh-Feldt	.000	1.920	.000	6.416	.003
	Lower-bound	.000	1.000	.000	6.416	.016
Error(test)	Sphericity Assumed	.001	76	1.85E-005		
	Greenhouse-Geisser	.001	67.955	2.07E-005		
	Huynh-Feldt	.001	72.965	1.93E-005		
	Lower-bound	.001	38.000	3.71E-005		



One-way ANOVA for the test effect on POST EMDs

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
emd1po	Between Groups	.000	1	.000	.613	.438
	Within Groups	.002	38	.000		
	Total	.002	39			
emd2po	Between Groups	.000	1	.000	3.943	.054
	Within Groups	.002	38	.000		
	Total	.002	39			
emd3po	Between Groups	.001	1	.001	23.614	.000
	Within Groups	.001	38	.000		
	Total	.002	39			

GR*TIME on EMD TEST 1

Within-Subjects Factors

Measure: EMD

time	Dependent Variable
1	emd1pr
2	emd1po

Between-Subjects Factors

		Value Label	N
Group	1	control	20
	2	experiment	20

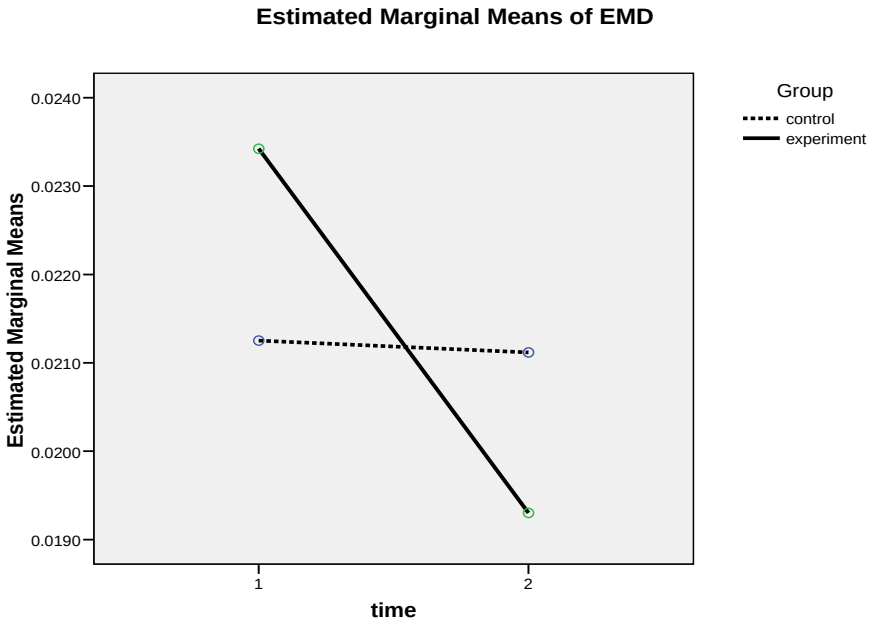
Descriptive Statistics

	Group	Mean	Std. Deviation	N
emd1pr	control	.021252	.0076373	20
	experiment	.023424	.0075431	20
	Total	.022338	.0075727	40
emd1po	control	.021118	.0064946	20
	experiment	.019302	.0080840	20
	Total	.020210	.0072960	40

Tests of Within-Subjects Effects

Measure: EMD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	9.05E-005	1	9.05E-005	13.171	.001
	Greenhouse-Geisser	9.05E-005	1.000	9.05E-005	13.171	.001
	Huynh-Feldt	9.05E-005	1.000	9.05E-005	13.171	.001
	Lower-bound	9.05E-005	1.000	9.05E-005	13.171	.001
time * Group	Sphericity Assumed	7.95E-005	1	7.95E-005	11.570	.002
	Greenhouse-Geisser	7.95E-005	1.000	7.95E-005	11.570	.002
	Huynh-Feldt	7.95E-005	1.000	7.95E-005	11.570	.002
	Lower-bound	7.95E-005	1.000	7.95E-005	11.570	.002
Error(time)	Sphericity Assumed	.000	38	6.87E-006		
	Greenhouse-Geisser	.000	38.000	6.87E-006		
	Huynh-Feldt	.000	38.000	6.87E-006		
	Lower-bound	.000	38.000	6.87E-006		



One-way- ANOVA for EMD test 1

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
		Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
emd1pr	control	20	.021252	.0076373	.0017077	.017677	.024826	.0100	.0370
	experiment	20	.023424	.0075431	.0016867	.019893	.026954	.0122	.0387
	Total	40	.022338	.0075727	.0011973	.019916	.024759	.0100	.0387
emd1po	control	20	.021118	.0064946	.0014522	.018078	.024158	.0120	.0340
	experiment	20	.019302	.0080840	.0018076	.015519	.023085	.0060	.0370
	Total	40	.020210	.0072960	.0011536	.017877	.022543	.0060	.0370

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
emd1pr	Between Groups	.000	1	.000	.819	.371
	Within Groups	.002	38	.000		
	Total	.002	39			
emd1po	Between Groups	.000	1	.000	.613	.438
	Within Groups	.002	38	.000		
	Total	.002	39			

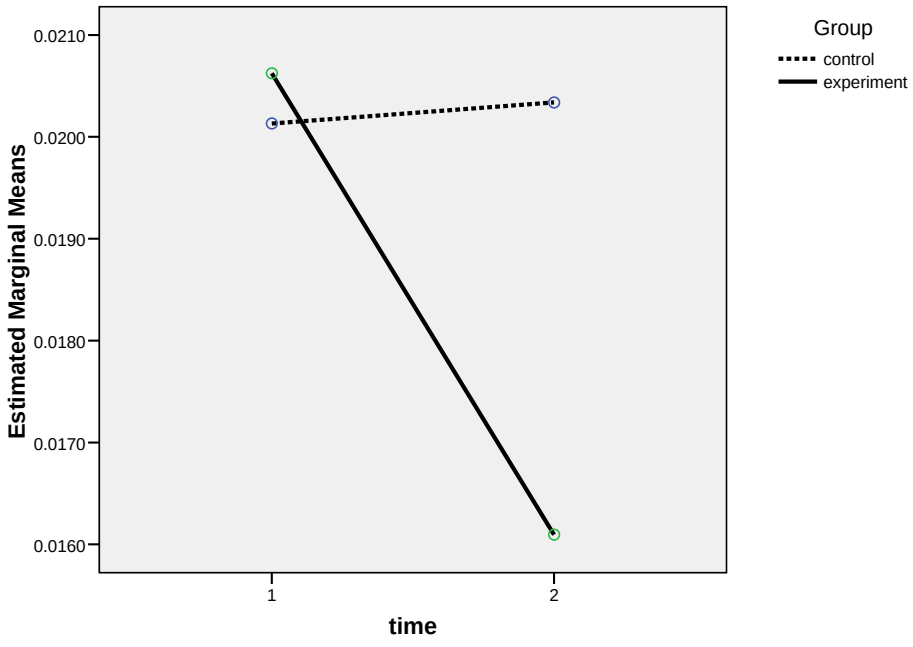
GR*TIME on EMD TEST 2

Tests of Within-Subjects Effects

Measure: EMD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	9.34E-005	1	9.34E-005	9.790	.003
	Greenhouse-Geisser	9.34E-005	1.000	9.34E-005	9.790	.003
	Huynh-Feldt	9.34E-005	1.000	9.34E-005	9.790	.003
	Lower-bound	9.34E-005	1.000	9.34E-005	9.790	.003
time * Group	Sphericity Assumed	.000	1	.000	11.750	.001
	Greenhouse-Geisser	.000	1.000	.000	11.750	.001
	Huynh-Feldt	.000	1.000	.000	11.750	.001
	Lower-bound	.000	1.000	.000	11.750	.001
Error(time)	Sphericity Assumed	.000	38	9.54E-006		
	Greenhouse-Geisser	.000	38.000	9.54E-006		
	Huynh-Feldt	.000	38.000	9.54E-006		
	Lower-bound	.000	38.000	9.54E-006		

Estimated Marginal Means of EMD



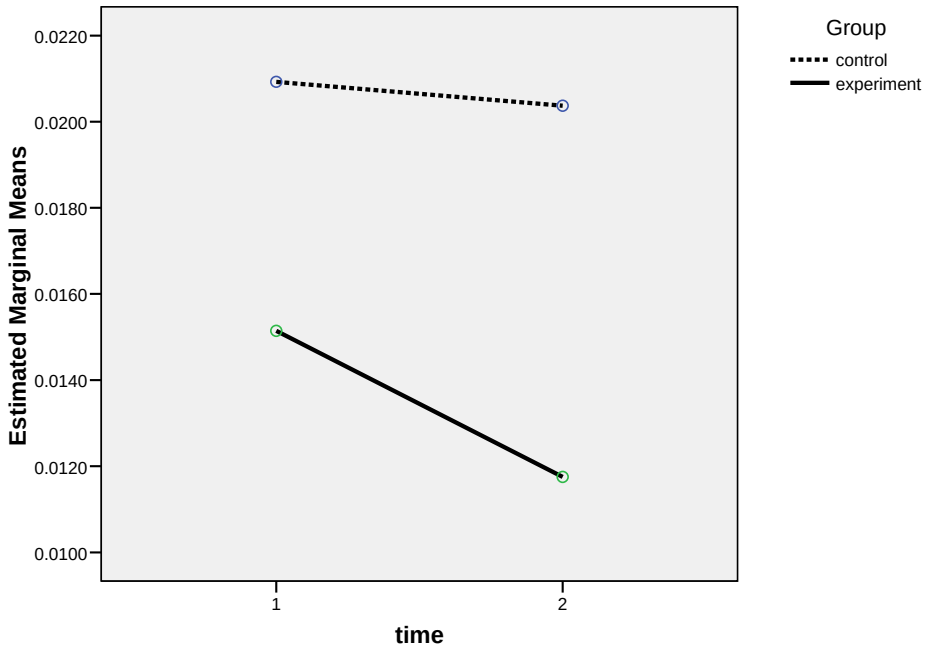
GR*TIME on EMD TEST 3

Tests of Within-Subjects Effects

Measure: EMD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	7.79E-005	1	7.79E-005	11.907	.001
	Greenhouse-Geisser	7.79E-005	1.000	7.79E-005	11.907	.001
	Huynh-Feldt	7.79E-005	1.000	7.79E-005	11.907	.001
	Lower-bound	7.79E-005	1.000	7.79E-005	11.907	.001
time * Group	Sphericity Assumed	4.03E-005	1	4.03E-005	6.160	.018
	Greenhouse-Geisser	4.03E-005	1.000	4.03E-005	6.160	.018
	Huynh-Feldt	4.03E-005	1.000	4.03E-005	6.160	.018
	Lower-bound	4.03E-005	1.000	4.03E-005	6.160	.018
Error(time)	Sphericity Assumed	.000	38	6.54E-006		
	Greenhouse-Geisser	.000	38.000	6.54E-006		
	Huynh-Feldt	.000	38.000	6.54E-006		
	Lower-bound	.000	38.000	6.54E-006		

Estimated Marginal Means of EMD



GR*TEST*TIME FOR RFD

Tests of Within-Subjects Effects

Measure: RFD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	182523.627	2	91261.814	13.277	.000
	Greenhouse-Geisser	182523.627	1.697	107585.022	13.277	.000
	Huynh-Feldt	182523.627	1.814	100607.745	13.277	.000
	Lower-bound	182523.627	1.000	182523.627	13.277	.001
test * Group	Sphericity Assumed	126788.256	2	63394.128	9.223	.000
	Greenhouse-Geisser	126788.256	1.697	74732.886	9.223	.001
	Huynh-Feldt	126788.256	1.814	69886.188	9.223	.000
	Lower-bound	126788.256	1.000	126788.256	9.223	.004
Error(test)	Sphericity Assumed	522403.001	76	6873.724		
	Greenhouse-Geisser	522403.001	64.469	8103.167		
	Huynh-Feldt	522403.001	68.940	7577.647		
	Lower-bound	522403.001	38.000	13747.447		
time	Sphericity Assumed	42379.853	1	42379.853	16.546	.000
	Greenhouse-Geisser	42379.853	1.000	42379.853	16.546	.000
	Huynh-Feldt	42379.853	1.000	42379.853	16.546	.000
	Lower-bound	42379.853	1.000	42379.853	16.546	.000
time * Group	Sphericity Assumed	31908.222	1	31908.222	12.458	.001
	Greenhouse-Geisser	31908.222	1.000	31908.222	12.458	.001
	Huynh-Feldt	31908.222	1.000	31908.222	12.458	.001
	Lower-bound	31908.222	1.000	31908.222	12.458	.001
Error(time)	Sphericity Assumed	97330.005	38	2561.316		
	Greenhouse-Geisser	97330.005	38.000	2561.316		
	Huynh-Feldt	97330.005	38.000	2561.316		
	Lower-bound	97330.005	38.000	2561.316		
test * time	Sphericity Assumed	468.137	2	234.068	.229	.796
	Greenhouse-Geisser	468.137	1.719	272.325	.229	.763
	Huynh-Feldt	468.137	1.840	254.405	.229	.778
	Lower-bound	468.137	1.000	468.137	.229	.635
test * time * Group	Sphericity Assumed	2915.868	2	1457.934	1.426	.247
	Greenhouse-Geisser	2915.868	1.719	1696.224	1.426	.247
	Huynh-Feldt	2915.868	1.840	1584.606	1.426	.247
	Lower-bound	2915.868	1.000	2915.868	1.426	.240
Error(test*time)	Sphericity Assumed	77699.340	76	1022.360		
	Greenhouse-Geisser	77699.340	65.323	1189.458		
	Huynh-Feldt	77699.340	69.925	1111.187		
	Lower-bound	77699.340	38.000	2044.719		

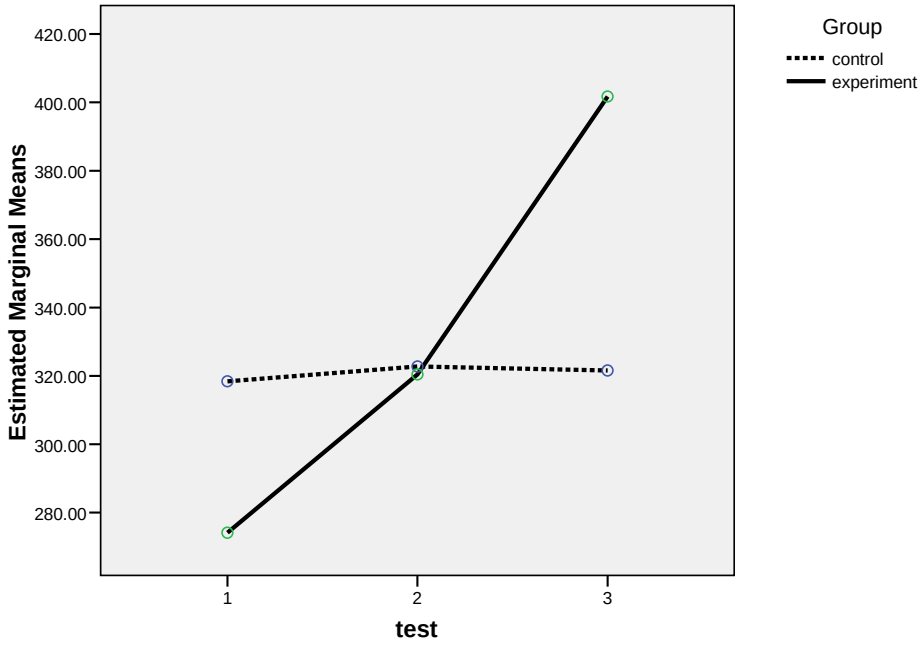
GR*TEST on PRE RFDs

Tests of Within-Subjects Effects

Measure: RFD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	86939.413	2	43469.707	13.028	.000
	Greenhouse-Geisser	86939.413	1.775	48973.361	13.028	.000
	Huynh-Feldt	86939.413	1.905	45636.572	13.028	.000
	Lower-bound	86939.413	1.000	86939.413	13.028	.001
test * Group	Sphericity Assumed	80121.074	2	40060.537	12.007	.000
	Greenhouse-Geisser	80121.074	1.775	45132.560	12.007	.000
	Huynh-Feldt	80121.074	1.905	42057.463	12.007	.000
	Lower-bound	80121.074	1.000	80121.074	12.007	.001
Error(test)	Sphericity Assumed	253576.656	76	3336.535		
	Greenhouse-Geisser	253576.656	67.459	3758.970		
	Huynh-Feldt	253576.656	72.391	3502.854		
	Lower-bound	253576.656	38.000	6673.070		

Estimated Marginal Means of RFD



One-way ANOVA for the test effect on PRE RFDs

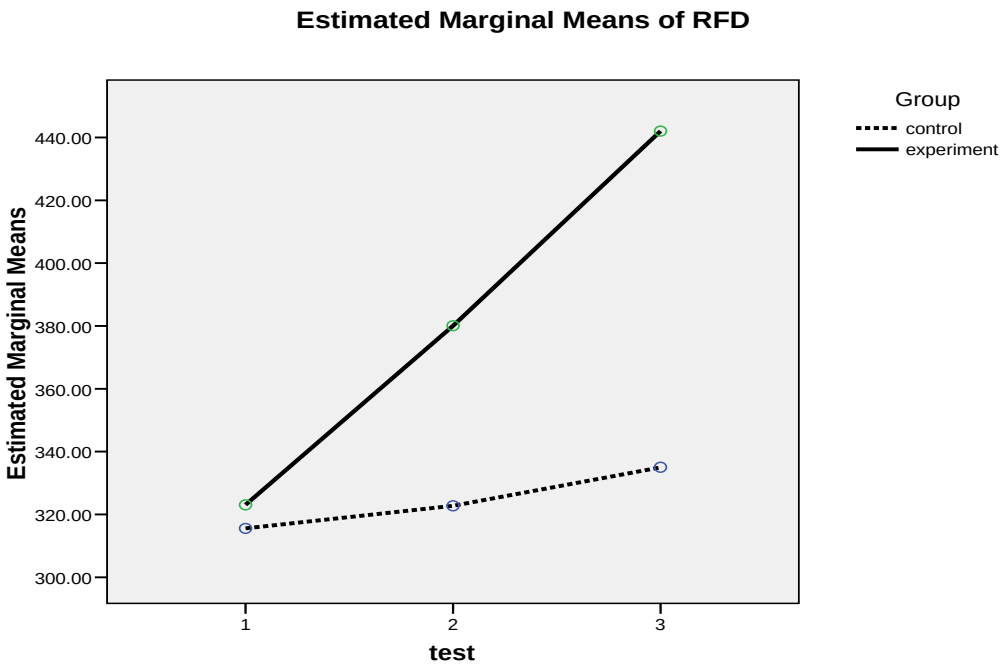
		Sum of Squares	df	Mean Square	F	Sig.
rfd1pr	Between Groups	19610.576	1	19610.576	.977	.329
	Within Groups	762491.391	38	20065.563		
	Total	782101.967	39			
rfd2pr	Between Groups	54.009	1	54.009	.003	.958
	Within Groups	736567.693	38	19383.360		
	Total	736621.702	39			
rfd3pr	Between Groups	64201.326	1	64201.326	2.677	.110
	Within Groups	911453.231	38	23985.611		
	Total	975654.557	39			

GR*TEST on POST RFDs

Tests of Within-Subjects Effects

Measure: RFD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	96052.350	2	48026.175	10.533	.000
	Greenhouse-Geisser	96052.350	1.653	58114.025	10.533	.000
	Huynh-Feldt	96052.350	1.764	54454.325	10.533	.000
	Lower-bound	96052.350	1.000	96052.350	10.533	.002
test * Group	Sphericity Assumed	49583.049	2	24791.525	5.437	.006
	Greenhouse-Geisser	49583.049	1.653	29998.960	5.437	.010
	Huynh-Feldt	49583.049	1.764	28109.791	5.437	.009
	Lower-bound	49583.049	1.000	49583.049	5.437	.025
Error(test)	Sphericity Assumed	346525.686	76	4559.548		
	Greenhouse-Geisser	346525.686	62.807	5517.277		
	Huynh-Feldt	346525.686	67.028	5169.829		
	Lower-bound	346525.686	38.000	9119.097		



One-way ANOVA for the test effect on POST RFDs

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
rfd1po	Between Groups	559.790	1	559.790	.025	.876
	Within Groups	860326.873	38	22640.181		
	Total	860886.662	39			
rfd2po	Between Groups	32875.507	1	32875.507	1.426	.240
	Within Groups	875985.259	38	23052.244		
	Total	908860.766	39			
rfd3po	Between Groups	114627.127	1	114627.127	4.169	.048
	Within Groups	1044733.235	38	27492.980		
	Total	1159360.362	39			

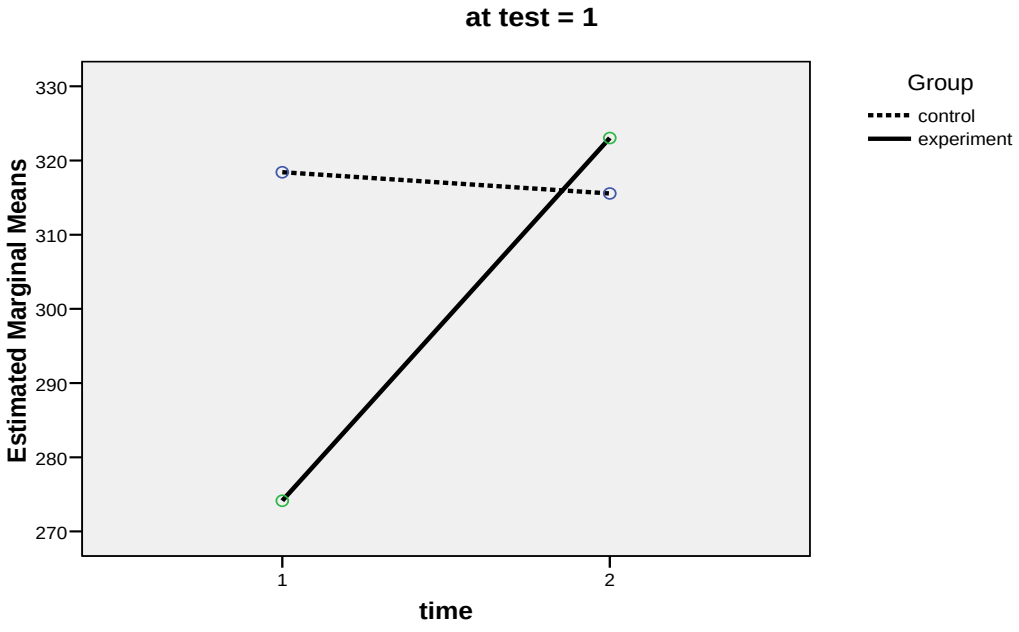
GR*TIME on RFD TEST 1

Tests of Within-Subjects Effects

Measure: RFD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	10593.756	1	10593.756	7.752	.008
	Greenhouse-Geisser	10593.756	1.000	10593.756	7.752	.008
	Huynh-Feldt	10593.756	1.000	10593.756	7.752	.008
	Lower-bound	10593.756	1.000	10593.756	7.752	.008
time * Group	Sphericity Assumed	13398.459	1	13398.459	9.804	.003
	Greenhouse-Geisser	13398.459	1.000	13398.459	9.804	.003
	Huynh-Feldt	13398.459	1.000	13398.459	9.804	.003
	Lower-bound	13398.459	1.000	13398.459	9.804	.003
Error(time)	Sphericity Assumed	51933.284	38	1366.665		
	Greenhouse-Geisser	51933.284	38.000	1366.665		
	Huynh-Feldt	51933.284	38.000	1366.665		
	Lower-bound	51933.284	38.000	1366.665		

Estimated Marginal Means of RFD



One-way ANOVA for the RFD test 1

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
		Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
rfd1pr	control	20	318.4159	145.42851	32.51880	250.3533	386.4786	119.42	672.79
	experiment	20	274.1321	137.77400	30.80720	209.6519	338.6123	122.79	615.16
	Total	40	296.2740	141.61178	22.39079	250.9844	341.5637	119.42	672.79
rfd1po	control	20	315.5480	137.99329	30.85624	250.9652	380.1308	128.03	614.86
	experiment	20	323.0299	161.98214	36.22031	247.2199	398.8399	110.38	645.21
	Total	40	319.2890	148.57327	23.49150	271.7729	366.8050	110.38	645.21

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
rfd1pr	Between Groups	19610.576	1	19610.576	.977	.329
	Within Groups	762491.391	38	20065.563		
	Total	782101.967	39			
rfd1po	Between Groups	559.790	1	559.790	.025	.876
	Within Groups	860326.873	38	22640.181		
	Total	860886.662	39			

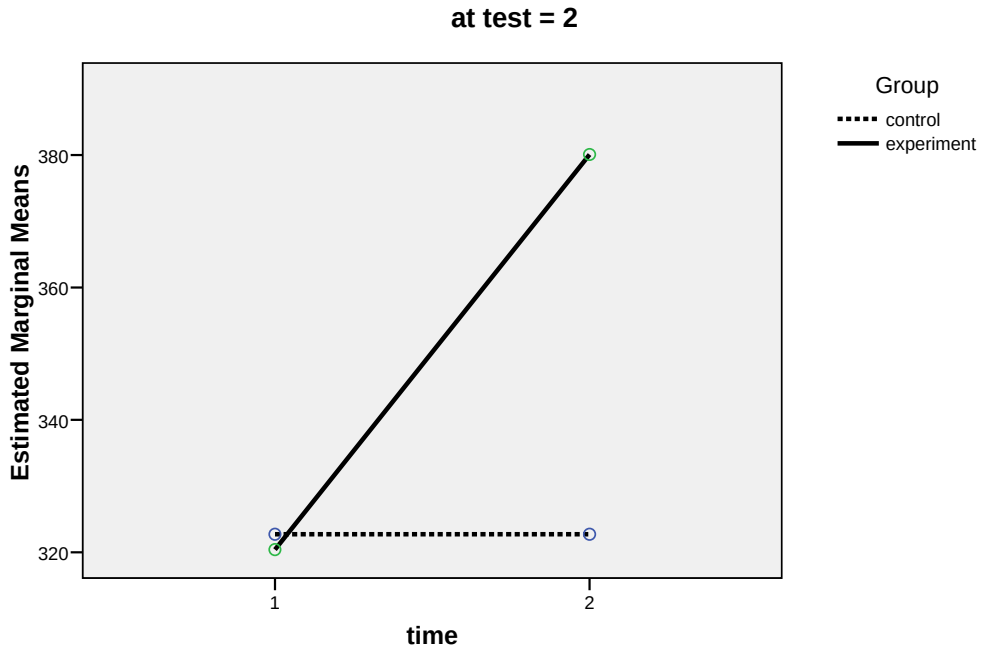
GR*TIME on RFD TEST 2

Tests of Within-Subjects Effects

Measure: RFD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	17804.928	1	17804.928	10.902	.002
	Greenhouse-Geisser	17804.928	1.000	17804.928	10.902	.002
	Huynh-Feldt	17804.928	1.000	17804.928	10.902	.002
	Lower-bound	17804.928	1.000	17804.928	10.902	.002
time * Group	Sphericity Assumed	17797.262	1	17797.262	10.897	.002
	Greenhouse-Geisser	17797.262	1.000	17797.262	10.897	.002
	Huynh-Feldt	17797.262	1.000	17797.262	10.897	.002
	Lower-bound	17797.262	1.000	17797.262	10.897	.002
Error(time)	Sphericity Assumed	62062.914	38	1633.235		
	Greenhouse-Geisser	62062.914	38.000	1633.235		
	Huynh-Feldt	62062.914	38.000	1633.235		
	Lower-bound	62062.914	38.000	1633.235		

Estimated Marginal Means of RFD



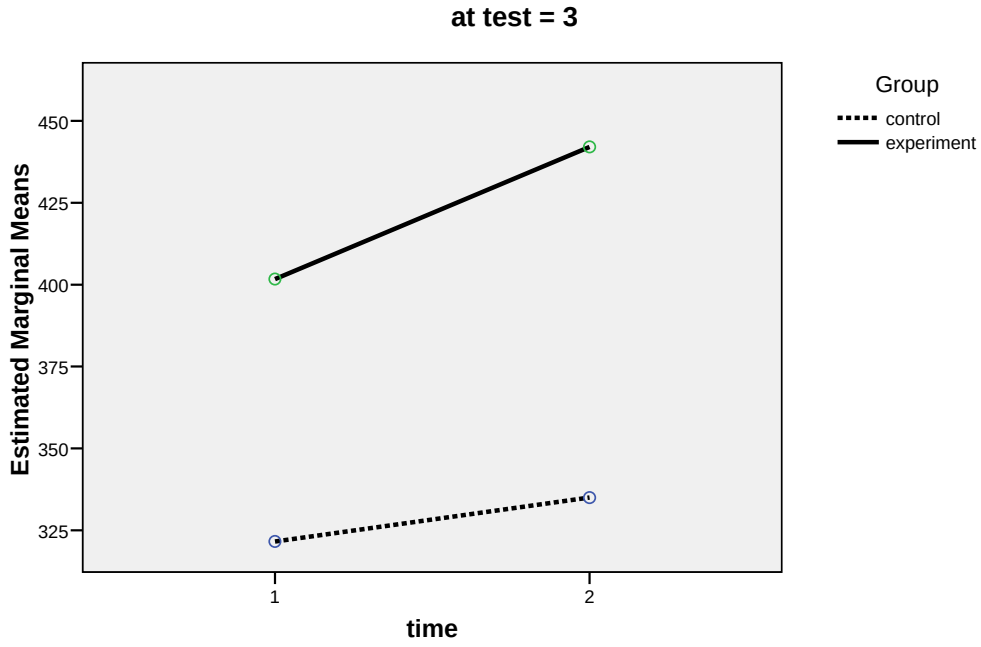
GR*TIME on RFD TEST 3

Tests of Within-Subjects Effects

Measure: RFD

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
time	Sphericity Assumed	14449.305	1	14449.305	8.996	.005
	Greenhouse-Geisser	14449.305	1.000	14449.305	8.996	.005
	Huynh-Feldt	14449.305	1.000	14449.305	8.996	.005
	Lower-bound	14449.305	1.000	14449.305	8.996	.005
time * Group	Sphericity Assumed	3628.368	1	3628.368	2.259	.141
	Greenhouse-Geisser	3628.368	1.000	3628.368	2.259	.141
	Huynh-Feldt	3628.368	1.000	3628.368	2.259	.141
	Lower-bound	3628.368	1.000	3628.368	2.259	.141
Error(time)	Sphericity Assumed	61033.147	38	1606.135		
	Greenhouse-Geisser	61033.147	38.000	1606.135		
	Huynh-Feldt	61033.147	38.000	1606.135		
	Lower-bound	61033.147	38.000	1606.135		

Estimated Marginal Means of RFD



GR*TEST on EPI

Multivariate Tests(b)

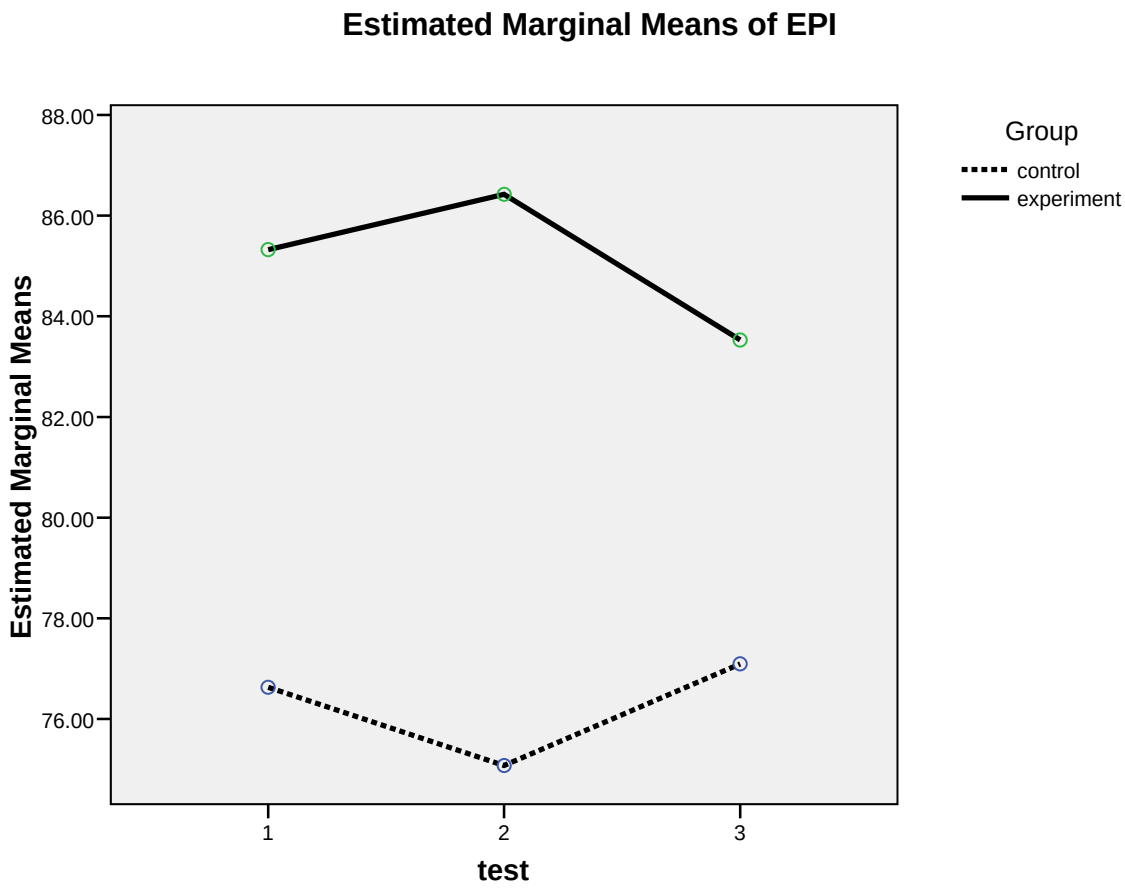
Effect		Value	F	Hypothesis df	Error df	Sig.
test	Pillai's Trace	.009	.165(a)	2.000	37.000	.848
	Wilks' Lambda	.991	.165(a)	2.000	37.000	.848
	Hotelling's Trace	.009	.165(a)	2.000	37.000	.848
	Roy's Largest Root	.009	.165(a)	2.000	37.000	.848
test * Group	Pillai's Trace	.052	1.024(a)	2.000	37.000	.369
	Wilks' Lambda	.948	1.024(a)	2.000	37.000	.369
	Hotelling's Trace	.055	1.024(a)	2.000	37.000	.369
	Roy's Largest Root	.055	1.024(a)	2.000	37.000	.369

a Exact statistic
b Design: Intercept+Group
Within Subjects Design: test

Tests of Within-Subjects Effects

Measure: EPI

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	9.132	2	4.566	.117	.889
	Greenhouse-Geisser	9.132	1.630	5.603	.117	.849
	Huynh-Feldt	9.132	1.738	5.255	.117	.862
	Lower-bound	9.132	1.000	9.132	.117	.734
test * Group	Sphericity Assumed	120.920	2	60.460	1.553	.218
	Greenhouse-Geisser	120.920	1.630	74.190	1.553	.222
	Huynh-Feldt	120.920	1.738	69.593	1.553	.221
	Lower-bound	120.920	1.000	120.920	1.553	.220
Error(test)	Sphericity Assumed	2958.030	76	38.921		
	Greenhouse-Geisser	2958.030	61.935	47.761		
	Huynh-Feldt	2958.030	66.026	44.801		
	Lower-bound	2958.030	38.000	77.843		



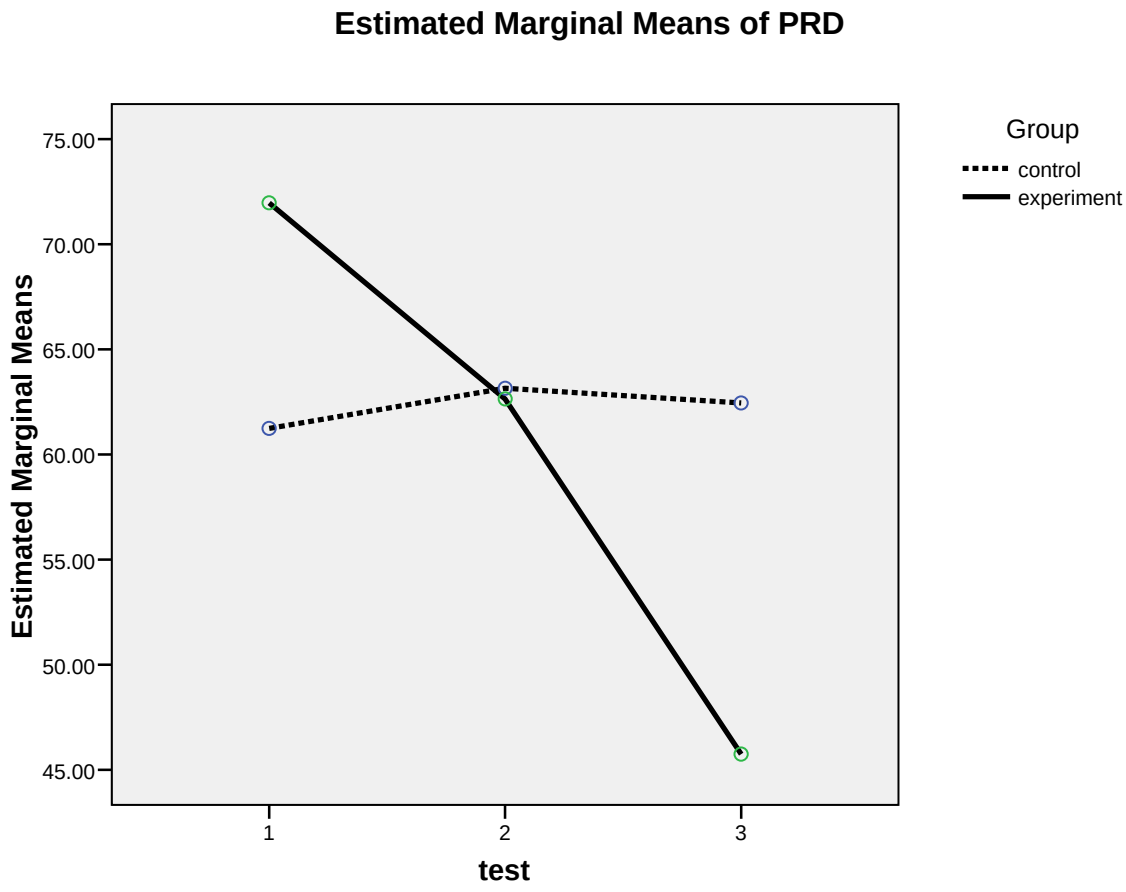
GR*TEST on PRD

Multivariate Tests(b)

Effect		Value	F	Hypothesis df	Error df	Sig.
test	Pillai's Trace	.428	13.841(a)	2.000	37.000	.000
	Wilks' Lambda	.572	13.841(a)	2.000	37.000	.000
	Hotelling's Trace	.748	13.841(a)	2.000	37.000	.000
	Roy's Largest Root	.748	13.841(a)	2.000	37.000	.000
test * Group	Pillai's Trace	.421	13.457(a)	2.000	37.000	.000
	Wilks' Lambda	.579	13.457(a)	2.000	37.000	.000
	Hotelling's Trace	.727	13.457(a)	2.000	37.000	.000
	Roy's Largest Root	.727	13.457(a)	2.000	37.000	.000

Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
test	Sphericity Assumed	3301.642	2	1650.821	13.082	.000
	Greenhouse-Geisser	3301.642	1.525	2164.952	13.082	.000
	Huynh-Feldt	3301.642	1.618	2041.082	13.082	.000
	Lower-bound	3301.642	1.000	3301.642	13.082	.001
test * Group	Sphericity Assumed	3804.482	2	1902.241	15.074	.000
	Greenhouse-Geisser	3804.482	1.525	2494.674	15.074	.000
	Huynh-Feldt	3804.482	1.618	2351.939	15.074	.000
	Lower-bound	3804.482	1.000	3804.482	15.074	.000
Error(test)	Sphericity Assumed	9590.824	76	126.195		
	Greenhouse-Geisser	9590.824	57.952	165.497		
	Huynh-Feldt	9590.824	61.469	156.028		
	Lower-bound	9590.824	38.000	252.390		



One-way ANOVA for the test effect on PRDs

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
prd1	Between Groups	1151.329	1	1151.329	1.734	.196
	Within Groups	25235.030	38	664.080		
	Total	26386.359	39			
prd2	Between Groups	2.550	1	2.550	.005	.945
	Within Groups	19748.880	38	519.707		
	Total	19751.430	39			
prd3	Between Groups	2790.570	1	2790.570	4.040	.052
	Within Groups	26249.920	38	690.787		
	Total	29040.490	39			

APPEDIX TWO: OVERALL TRIAL DATA

Overall Trial Data

	01C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.033	0.015	0.038	140.33	105.96	159.29
	Trial 2	0.036	0.042	0.033	124.48	91.64	174.59
	Trial 3	0.031	0.027	0.030	150.05	126.35	170.40
	PreAvg	**0.033**	**0.028**	**0.033**	**138.28**	**107.98**	**168.09**
	PreStDev	0.003	0.014	0.004	12.907	17.444	7.903
Post	Trial 4	0.024	0.026	0.04	156.78	147.66	182.10
	Trial 5	0.029	0.027	0.024	107.34	152.11	165.40
	Trial 6	0.027	0.016	0.036	119.96	147.20	153.82
	PostAvg	**0.027**	**0.023**	**0.034**	**128.03**	**148.99**	**167.11**
	PostStDev	0.003	0.006	0.009	25.689	2.713	14.220

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.364	0.208	0.894	1.897	2.304	0.996	2.278	3.804	0.503
	1.617	0.586	0.361	1.831	2.006	0.363	1.944	3.77	0.217
	1.477	0.32	0.411	1.855	2.083	0.541	1.989	2.415	0.365
	1.648	0.55	0.561	1.494	1.83	0.414	2.546	3.284	0.221
	1.638	0.149	0.148	1.83	1.802	0.419	2.121	2.924	0.184
	1.575	0.399	0.474	1.85	2.062	0.014	2.523	1.478	0.201
	1.862	0.249	0.354	1.825	1.36	0.98	2.693	2.368	0.235
	1.831	0.274	0.249	1.73	1.956	0.575	2.237	2.648	0.517
	1.685	0.468	0.217	1.409	2.102	0.309	2.336	1.305	0.261
	1.679	0.241	0.392	1.856	2.112	0.126	2.432	0.882	0.145
	1.41	0.188	0.582	1.659	1.895	0.012	2.605	1.716	0.243
	1.97	0.122	0.717	1.962	2.355	0.869	2.009	2.101	0.15
	1.582	0.659	0.221	1.701	1.716	0.525	2.321	2.79	0.219
	1.858	0.183	0.458	1.797	1.156	0.867	2.592	1.238	0.303
				1.428	1.574	0.276	2.162	0.956	0.23
Avg	1.656857	0.328286	0.431357	1.7416	1.887533	0.485733	2.3192	2.245267	0.266267
StDev	0.176633	0.174607	0.206491	0.172199	0.33032	0.325768	0.242058	0.967542	0.113021
% of Inhibition	**81.2**		**74**	**-10**		**72.2**	**0.02**		**88.6**

Overall Trial Data

	02C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.022	0.024	0.028	192.40	245.52	278.44
	Trial 2	0.021	0.026	0.024	329.94	328.10	230.02
	Trial 3	0.024	0.018	0.026	269.96	278.44	407.36
	PreAvg	**0.022**	**0.023**	**0.026**	**264.10**	**284.02**	**305.27**
	PreStDev	0.002	0.004	0.002	68.955	41.574	91.668
Post	Trial 4	0.021	0.052	0.02	262.18	239.10	312.31
	Trial 5	0.019	0.008	0.025	245.59	278.33	253.46
	Trial 6	0.023	0.008	0.023	216.67	279.33	241.85
	PostAvg	**0.021**	**0.022**	**0.023**	**241.48**	**265.59**	**269.21**
	PostStDev	0.002	0.025	0.002	23.032	22.940	37.775

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.269	0.019	0.778	2.516	0.008	0.867	2.646	0.004	0.69
	2.022	0.013	0.772	2.424	0.006	1.102	2.619	0.006	0.746
	2.221	0.008	0.988	2.12	0.007	0.785	2.559	0.006	1.147
	2.068	0.033	0.734	2.356	0.008	0.556	3.022	0.004	0.504
	2.183	0.017	1.163	2.456	0.006	0.696	2.231	0.007	0.609
	2.045	0.033	0.927	2.022	0.009	0.544	3.255	0.007	0.648
	2.046	0.035	0.747	2.535	0.01	0.532	3.026	0.005	1.653
	2.256	0.034	0.492	2.746	0.006	0.895	2.735	0.006	0.58
	1.586	0.031	0.374	2.593	0.006	0.859	2.986	0.007	1.181
	1.938	0.029	0.752	2.026	0.01	0.932	2.597	0.006	0.437
	1.62	0.021	0.408	2.431	0.005	0.968	2.218	0.005	0.538
	2.215	0.013	0.347	2.143	0.008	0.8	2.807	0.006	0.786
	2.368	0.037	0.464	2.362	0.006	0.652	2.487	0.006	0.7
	1.688	0.015	0.937	2.159	0.008	0.729	2.868	0.006	1.813
	2.155	0.032	0.853	2.363	0.008	0.928	2.804	0.004	0.652
Avg	2.045333	0.024667	0.715733	2.350133	0.0074	0.789667	2.724	0.005667	0.8456
StDev	0.242208	0.009803	0.247437	0.214818	0.001549	0.169771	0.290379	0.001047	0.416729
% of Inhibition	**98.8**		**65.1**	**99.7**		**67.4**	**99.8**		**69**

Overall Trial Data

	03C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.021	0.022	0.017	296.36	334.47	305.63
	Trial 2	0.018	0.022	0.012	258.96	280.58	291.67
	Trial 3	0.013	0.014	0.023	267.56	282.59	294.51
	PreAvg	**0.017**	**0.019**	**0.017**	**275.36**	**299.22**	**297.27**
	PreStDev	0.004	0.005	0.005	19.588	30.550	7.374
Post	Trial 4	0.015	0.020	0.02	199.96	362.02	288.56
	Trial 5	0.012	0.024	0.014	320.45	330.78	275.43
	Trial 6	0.022	0.014	0.021	243.88	339.19	264.75
	PostAvg	**0.016**	**0.019**	**0.019**	**289.75**	**344.00**	**276.25**
	PostStDev	0.005	0.005	0.005	60.976	16.168	11.927

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.234	0.009	0.921	1.01	0.009	0.523	1.087	0.002	0.365
	0.919	0.027	0.361	0.9	0.009	0.222	1.194	0.016	0.471
	1.395	0.006	0.476	0.952	0.015	0.341	1.114	0.005	0.474
	1.394	0.007	0.616	0.935	0.052	0.277	0.823	0.006	0.217
	1.235	0.006	0.8	1.072	0.036	0.128	0.962	0.007	0.511
	1.113	0.006	0.351	1.189	0.021	0.148	1.299	0.006	0.62
	1.103	0.009	0.647	0.994	0.008	0.733	0.928	0.003	0.452
	1.015	0.006	0.517	1.306	0.022	1.104	1.16	0.006	0.805
	1.367	0.007	0.265	1.201	0.018	0.204	1.192	0.004	0.32
	1.025	0.008	0.652	1.249	0.01	0.123	1.16	0.005	0.649
	1.192	0.004	0.29	0.909	0.013	1.141	0.967	0.005	0.76
	1.085	0.005	0.13	1.086	0.021	0.713	0.863	0.009	0.258
	1.218	0.009	0.203	1.299	0.02	0.372	1.122	0.005	0.376
	1.414	0.011	0.672	0.981	0.095	0.793	0.87	0.012	0.411
	1.316	0.007	0.604	1.044	0.099	0.577	1.088	0.007	0.506
Avg	1.201667	0.008467	0.500333	1.075133	0.029867	0.493267	1.055267	0.006533	0.479667
StDev	0.155734	0.005436	0.228759	0.140486	0.029587	0.340975	0.143226	0.003543	0.170624
% of Inhibition	**99.3**		**58.4**	**97.3**		**54.2**	**99.4**		**54.6**

Overall Trial Data

	04C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.016	0.015	0.017	566.62	407.17	505.39
	Trial 2	0.019	0.012	0.012	464.63	372.07	464.63
	Trial 3	0.015	0.011	0.020	367.56	454.22	294.51
	PreAvg	**0.017**	**0.013**	**0.016**	**415.33**	**411.15**	**421.51**
	PreStDev	0.002	0.002	0.004	99.541	41.220	111.856
Post	Trial 4	0.014	0.020	0.01	462.92	388.52	485.22
	Trial 5	0.012	0.013	0.014	392.36	387.53	415.66
	Trial 6	0.023	0.023	0.012	404.71	437.05	425.43
	PostAvg	**0.016**	**0.019**	**0.013**	**420.00**	**398.75**	**425.01**
	PostStDev	0.006	0.005	0.001	37.683	28.311	37.658

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.615	0.97	1.461	2.198	1.723	0.461	2.543	4.434	0.593
	2.409	1.076	1.334	2.278	1.629	0.705	1.912	5.718	0.496
	1.758	1.333	0.845	2.411	0.827	0.508	2.262	4.848	0.53
	2.057	0.927	1.487	2.209	2.483	0.522	2.189	5.322	0.351
	2.507	0.898	1.396	2.176	1.508	0.377	2.53	5.717	0.567
	2.155	1.463	0.829	2.099	2.699	1.073	2.49	4.987	0.797
	2.433	1.303	0.546	2.144	1.602	0.504	1.996	5.132	0.728
	2.361	0.736	1.573	1.772	1.992	0.513	1.975	5.318	0.595
	2.012	1.123	1.003	2.229	2.189	0.295	2.162	5.308	0.508
	1.741	1.495	0.784	2.393	2.003	0.334	2.324	4.263	0.2
	2.566	0.956	1.511	2.419	1.814	0.343	2.285	5.172	0.343
	2.169	0.648	1.664	2.198	1.918	0.468	2.661	5.194	0.335
	1.822	1.021	1.009	2.342	1.89	0.152	2.209	3.98	0.286
	2.296	1.014	0.954	2.061	0.816	0.171	2.267	4.611	0.494
	1.667	1.298	1.471	1.847	1.767	0.285	2.456	5.233	0.339
Avg	2.104533	1.084067	1.191133	2.185067	1.790667	0.4474	2.284067	5.0158	0.477467
StDev	0.322781	0.250514	0.351579	0.187957	0.507143	0.226315	0.222078	0.503062	0.167235
% of Inhibition	**48.5**		**41.5**	**18.1**		**79.6**	**20**		**79.1**

Overall Trial Data

	05C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.029	0.027	0.027	242.60	269.85	266.46
	Trial 2	0.037	0.027	0.030	302.01	276.31	280.14
	Trial 3	0.017	0.026	0.030	303.68	384.32	217.68
	PreAvg	**0.028**	**0.027**	**0.029**	**282.76**	**310.16**	**254.76**
	PreStDev	0.010	0.001	0.002	34.790	64.307	32.835
Post	Trial 4	0.016	0.026	0.04	316.83	277.59	276.06
	Trial 5	0.032	0.020	0.024	320.72	287.54	250.44
	Trial 6	0.023	0.023	0.024	325.94	287.54	206.47
	PostAvg	**0.024**	**0.023**	**0.029**	**321.16**	**284.23**	**244.32**
	PostStDev	0.008	0.003	0.008	4.572	5.744	35.198

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	0.729	0.135	0.044	1.385	1.013	1.077	1.271	0.119	0.544
	0.586	0.168	0.07	1.621	0.723	0.826	1.535	0.071	0.338
	0.587	0.081	0.065	1.315	0.357	0.811	1.363	0.158	0.46
	0.74	0.058	0.111	1.516	0.336	0.482	1.555	0.096	0.457
	0.53	0.008	0.104	1.569	0.44	0.178	1.197	0.04	0.586
	0.675	0.029	0.049	1.711	0.282	0.716	1.205	0.007	0.522
	0.53	0.032	0.089	1.509	0.705	0.427	1.475	0.039	0.469
	0.569	0.009	0.021	1.393	0.322	0.153	1.517	0.058	0.281
	0.66	0.095	0.021	1.733	0.526	0.358	1.178	0.014	0.218
	0.789	0.057	0.107	1.438	0.305	0.277	1.5	0.016	0.276
	0.757	0.025	0.071	1.542	0.011	0.915	1.099	0.015	0.327
	0.757	0.039	0.052	1.631	0.577	0.345	1.433	0.056	0.441
	0.617	0.029	0.064	1.646	0.401	0.666	1.216	0.307	0.355
	0.538	0.007	0.161	1.983	0.493	0.593	1.233	0.357	0.42
	0.623	0.099	0.043	1.667	0.208	0.176	1.354	0.455	0.461
Avg	0.6458	0.058067	0.071467	1.577267	0.4466	0.533333	1.342067	0.120533	0.410333
StDev	0.090557	0.048491	0.037654	0.167579	0.242188	0.293134	0.151963	0.140033	0.106866
% of Inhibition	**91.1**		**89**	**71.7**		**66.2**	**20**		**69.2**

Overall Trial Data

	06C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.018	0.019	0.017	168.15	184.49	237.46
	Trial 2	0.018	0.016	0.022	189.03	186.46	213.57
	Trial 3	0.016	0.020	0.028	209.71	209.05	221.03
	PreAvg	**0.017**	**0.018**	**0.022**	**188.97**	**193.33**	**224.02**
	PreStDev	0.001	0.002	0.006	20.781	13.650	12.223
Post	Trial 4	0.016	0.015	0.02	191.66	222.67	268.12
	Trial 5	0.019	0.023	0.027	207.17	169.33	238.11
	Trial 6	0.023	0.016	0.024	202.87	195.55	234.12
	PostAvg	**0.019**	**0.018**	**0.024**	**200.57**	**195.85**	**246.79**
	PostStDev	0.004	0.004	0.003	8.004	26.675	18.587

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	0.981	0.06	0.209	1.244	0.008	0.837	1.355	0.004	0.575
	0.984	0.079	0.359	1.055	0.009	0.286	1.365	0.005	0.621
	1.465	0.038	0.195	1.255	0.009	0.545	1.165	0.007	0.288
	1.523	0.034	0.155	1.304	0.01	0.982	1.087	0.008	0.148
	1.426	0.168	0.114	1.281	0.008	0.395	1.108	0.003	0.229
	1.361	0.024	0.335	1.33	0.005	0.343	1.394	0.005	0.243
	1.472	0.042	0.208	1.163	0.008	0.413	1.455	0.004	0.708
	1.263	0.048	0.256	0.892	0.009	0.573	1.131	0.009	0.568
	1.337	0.037	0.227	1.325	0.005	0.223	1.068	0.005	0.697
	1.232	0.081	0.276	1.155	0.006	0.19	1.466	0.004	0.292
	1.199	0.068	0.121	1.158	0.005	0.57	1.16	0.005	0.762
	0.953	0.043	0.297	1.248	0.004	0.44	1.371	0.003	0.798
	1.306	0.052	0.401	1.079	0.006	0.527	1.337	0.004	0.779
	1.14	0.035	0.423	1.362	0.005	0.335	0.946	0.006	0.32
	1.379	0.043	0.66	1.151	0.01	0.28	1.143	0.007	0.252
Avg	1.268067	0.0568	0.2824	1.200133	0.007133	0.4626	1.236733	0.005267	0.485333
StDev	0.185608	0.034945	0.140984	0.125783	0.002066	0.220225	0.161786	0.001792	0.236723
% of Inhibition	**95.6**		**77.3**	**99.5**		**61.5**	**99.6**		**60.8**

Overall Trial Data

	07C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.018	0.016	0.017	410.45	412.35	419.45
	Trial 2	0.015	0.016	0.022	372.10	329.53	371.08
	Trial 3	0.016	0.020	0.022	390.23	345.76	389.65
	PreAvg	**0.016**	**0.017**	**0.020**	**390.97**	**350.13**	**393.68**
	PreStDev	0.002	0.002	0.003	19.184	43.888	24.401
Post	Trial 4	0.013	0.015	0.01	430.34	412.35	388.32
	Trial 5	0.016	0.021	0.012	420.46	333.75	376.45
	Trial 6	0.013	0.016	0.013	408.87	360.81	385.99
	PostAvg	**0.014**	**0.017**	**0.013**	**419.02**	**368.87**	**382.06**
	PostStDev	0.002	0.003	0.001	10.746	39.930	6.289

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.297	0.032	0.011	3.558	0.169	0.221	2.318	0.19	0.086
	2.851	0.261	0.025	3.183	0.043	0.167	1.888	0.186	0.088
	2.64	0.065	0.056	3.589	0.148	0.078	2.018	0.143	0.007
	2.674	0.092	0.052	3.067	0.111	0.025	2.663	0.198	0.025
	3.135	0.486	0.242	3.025	0.107	0.008	2.537	0.146	0.048
	3.148	0.242	1.042	3.586	0.096	0.013	1.953	0.196	0.028
	2.394	0.101	0.456	3.462	0.187	0.058	1.994	0.075	0.025
	3.366	0.18	0.228	3.298	0.094	0.005	2.647	0.279	0.064
	1.639	0.089	0.052	3.545	0.157	0.006	2.457	0.153	0.115
	2.84	0.05	1.137	3.28	0.059	0.122	2.469	0.191	0.045
	2.42	0.137	0.05	3.733	0.265	0.059	1.959	0.155	0.071
	2.058	0.079	0.68	2.371	0.191	0.029	2.352	0.374	0.123
	3.026	0.351	0.115	2.555	0.025	0.015	2.643	0.14	0.036
	2.353	0.393	0.836	3.778	0.051	0.334	1.789	0.158	0.073
	2.028	0.209	0.45	3.188	0.082	0.136	1.913	0.192	0.051
Avg	2.591267	0.184467	0.362133	3.2812	0.119	0.085067	2.24	0.185067	0.059
StDev	0.482065	0.137721	0.389021	0.405625	0.066266	0.095631	0.318335	0.068149	0.033863
% of Inhibition	**92.9**		**86.1**	**96.4**		**97.5**	**73.7**		**97.4**

Overall Trial Data

	08C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.024	0.018	0.017	117.98	145.78	170.36
	Trial 2	0.025	0.029	0.022	120.76	150.23	171.65
	Trial 3	0.024	0.023	0.022	119.78	142.21	160.32
	PreAvg	**0.024**	**0.023**	**0.020**	**119.42**	**142.07**	**168.28**
	PreStDev	0.001	0.006	0.003	1.410	4.018	6.203
Post	Trial 4	0.028	0.020	0.01	163.55	170.37	138.57
	Trial 5	0.028	0.025	0.012	138.36	163.20	142.76
	Trial 6	0.026	0.029	0.013	179.76	152.93	105.49
	PostAvg	**0.027**	**0.025**	**0.013**	**161.78**	**160.38**	**121.50**
	PostStDev	0.001	0.005	0.001	20.862	8.766	20.416

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.054	0.236	2.045	2.957	0.552	1.685	2.31	0.591	1.425
	2.027	0.295	2.181	2.366	0.36	1.999	2.301	0.574	1.645
	2.174	0.942	1.703	2.413	0.264	1.571	3.027	0.406	1.697
	1.682	0.962	1.558	2.509	0.52	1.869	2.773	0.422	1.87
	1.848	0.249	1.939	3.107	0.165	1.881	2.398	0.245	2.022
	2.297	0.307	1.487	2.691	0.276	1.01	2.356	0.446	1.502
	2.038	0.245	1.944	2.612	0.092	1.82	2.879	0.36	2.529
	2.258	0.176	1.847	2.625	0.144	1.975	3.186	0.919	2.33
	2.221	0.363	2.069	2.867	0.51	1.025	3.114	0.496	2.179
	1.873	0.318	1.956	2.311	0.234	0.599	3.048	0.557	1.92
	1.6	0.241	1.986	2.353	0.111	0.748	2.626	0.536	2.353
	2.234	0.368	2.097	2.661	0.315	0.849	3.326	0.488	2.469
	1.844	0.15	2.01	2.523	0.15	0.314	2.859	0.833	2.054
	2.039	0.305	1.656	3.171	0.181	0.705	2.647	0.547	2.449
	1.786	0.344	2.203	3.264	0.781	0.627	3.161	0.971	2.616
Avg	1.998333	0.366733	1.912067	2.695333	0.310333	1.245133	2.800733	0.5594	2.070667
StDev	0.21806	0.24577	0.219049	0.310257	0.19893	0.597067	0.346368	0.203276	0.386806
% of Inhibition	**81.7**		**4.4**	**88.5**		**53.9**	**80.1**		**26.1**

Overall Trial Data

	09C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.033	0.022	0.030	295.48	340.16	228.10
	Trial 2	0.031	0.025	0.025	297.68	329.43	275.98
	Trial 3	0.030	0.039	0.021	308.97	255.58	272.41
	PreAvg	**0.031**	**0.029**	**0.025**	**300.71**	**308.39**	**252.51**
	PreStDev	0.002	0.009	0.005	7.235	46.045	26.675
Post	Trial 4	0.030	0.025	0.02	246.58	228.36	210.27
	Trial 5	0.027	0.020	0.025	282.60	238.21	355.32
	Trial 6	0.038	0.041	0.029	273.19	272.53	302.89
	PostAvg	**0.032**	**0.029**	**0.025**	**267.46**	**246.37**	**282.21**
	PostStDev	0.006	0.011	0.004	18.680	23.188	73.450

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.645	0.161	1.725	2.185	0.308	1.805	2.44	0.517	1.68
	2.185	0.3	1.046	1.982	0.315	1.245	2.339	0.651	1.837
	1.745	0.248	1.272	2.489	0.352	1.734	2.31	0.525	1.823
	2.493	0.135	1.783	2.144	0.206	1.764	2.409	0.399	1.429
	2.237	0.305	1.364	2.332	0.164	0.805	2.481	0.63	1.896
	1.922	0.146	0.775	2.097	0.195	1.603	2.234	0.687	1.838
	2.21	0.188	1.019	2.195	0.32	1.564	2.63	0.631	1.421
	2.037	0.208	1.198	2.266	0.514	1.447	2.231	0.545	1.312
	1.906	0.105	1.365	1.98	0.302	1.516	2.47	0.653	1.415
	1.717	0.139	1.451	2.31	0.444	1.031	2.338	0.58	1.772
	2.07	0.245	1.046	1.913	0.289	1.783	1.955	0.749	1.5
	1.923	0.397	1.157	2.693	0.166	1.681	2.574	0.647	1.696
	1.945	0.153	0.862	2.862	0.443	1.752	2.127	0.538	2.09
	1.92	0.1	0.775	2.198	0.192	1.55	2.29	0.66	1.808
	1.87	0.243	1.321	2.416	0.318	1.896	2.093	0.611	1.695
Avg	1.988333	0.204867	1.2106	2.2708	0.301867	1.545067	2.328067	0.601533	1.6808
StDev	0.22362	0.084296	0.305698	0.262196	0.106485	0.305715	0.183106	0.085824	0.220108
% of Inhibition	**92.9**		**86.1**	**96.4**		**97.5**	**91.8**		**97.4**

Overall Trial Data

	10C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.040	0.022	0.030	339.05	340.16	375.88
	Trial 2	0.033	0.028	0.025	302.65	389.43	358.32
	Trial 3	0.038	0.039	0.021	324.76	243.58	272.41
	PreAvg	**0.037**	**0.030**	**0.025**	**322.15**	**324.39**	**335.54**
	PreStDev	0.004	0.009	0.005	18.339	74.193	55.370
Post	Trial 4	0.032	0.025	0.02	416.68	323.04	310.22
	Trial 5	0.032	0.020	0.019	282.60	310.78	355.32
	Trial 6	0.038	0.041	0.019	243.19	325.33	299.89
	PostAvg	**0.034**	**0.029**	**0.019**	**314.16**	**319.72**	**321.81**
	PostStDev	0.003	0.011	0.001	90.948	7.824	29.478

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.645	0.161	1.725	2.185	0.308	1.805	2.44	0.517	1.68
	2.185	0.3	1.046	1.982	0.315	1.245	2.339	0.651	1.837
	1.745	0.248	1.272	2.489	0.352	1.734	2.31	0.525	1.823
	2.493	0.135	1.783	2.144	0.206	1.764	2.409	0.399	1.429
	2.237	0.305	1.364	2.332	0.164	0.805	2.481	0.63	1.896
	1.922	0.146	0.775	2.097	0.195	1.603	2.234	0.687	1.838
	2.21	0.188	1.019	2.195	0.32	1.564	2.63	0.631	1.421
	2.037	0.208	1.198	2.266	0.514	1.447	2.231	0.545	1.312
	1.906	0.105	1.365	1.98	0.302	1.516	2.47	0.653	1.415
	1.717	0.139	1.451	2.31	0.444	1.031	2.338	0.58	1.772
	2.07	0.245	1.046	1.913	0.289	1.783	1.955	0.749	1.5
	1.923	0.397	1.157	2.693	0.166	1.681	2.574	0.647	1.696
	1.945	0.153	0.862	2.862	0.443	1.752	2.127	0.538	2.09
	1.92	0.1	0.775	2.198	0.192	1.55	2.29	0.66	1.808
	1.87	0.243	1.321	2.416	0.318	1.896	2.093	0.611	1.695
Avg	1.988333	0.204867	1.2106	2.2708	0.301867	1.545067	2.328067	0.601533	1.6808
StDev	0.22362	0.084296	0.305698	0.262196	0.106485	0.305715	0.183106	0.085824	0.220108
% of Inhibition	**89.7**		**39.2**	**86.8**		**32**	**74.2**		**27.9**

Overall Trial Data

	11C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.021	0.018	0.030	504.46	592.67	375.88
	Trial 2	0.019	0.005	0.025	583.90	630.06	358.32
	Trial 3	0.012	0.010	0.021	649.10	756.39	272.41
	PreAvg	**0.017**	**0.011**	**0.025**	**579.15**	**659.70**	**335.54**
	PreStDev	0.005	0.006	0.005	72.434	85.794	55.370
Post	Trial 4	0.021	0.002	0.02	598.60	642.81	310.22
	Trial 5	0.022	0.007	0.019	416.53	596.10	355.32
	Trial 6	0.014	0.016	0.019	687.32	732.57	299.89
	PostAvg	**0.019**	**0.008**	**0.019**	**567.48**	**657.16**	**321.81**
	PostStDev	0.004	0.007	0.001	138.048	69.360	29.478

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	0.746	0.112	0.182	2.331	0.524	1.017	1.674	0.304	0.649
	0.769	0.191	0.146	2.253	0.973	0.659	1.371	0.123	0.295
	0.661	0.146	0.267	2.142	0.5	0.567	1.393	0.182	0.393
	0.761	0.189	0.27	2.201	0.457	0.948	1.804	0.407	0.422
	0.815	0.134	0.209	2.322	1.288	0.868	1.526	0.369	0.443
	0.823	0.184	0.197	2.033	0.705	1.079	1.449	0.288	0.477
	0.729	0.112	0.323	2.241	0.552	0.267	1.552	0.353	0.226
	0.826	0.172	0.152	2.063	0.928	1.048	1.773	0.187	0.555
	0.817	0.234	0.209	2.154	0.465	0.496	1.584	0.308	0.254
	0.752	0.149	0.125	1.97	0.538	0.719	1.616	0.156	0.287
	0.694	0.118	0.161	1.755	0.317	0.422	1.689	0.106	0.409
	0.644	0.086	0.121	2.111	0.686	0.333	1.711	0.2	0.49
	0.703	0.059	0.185	1.897	0.623	0.678	1.635	0.186	0.386
	0.789	0.1	0.163	2.308	0.673	0.468	1.24	0.114	0.356
	0.686	0.049	0.269	2.249	0.639	0.361	1.341	0.059	0.395
Avg	0.747667	0.135667	0.1986	2.135333	0.657867	0.662	1.5572	0.2228	0.402467
StDev	0.060237	0.052153	0.059729	0.167047	0.244411	0.275595	0.167774	0.107541	0.11338
% of Inhibition	**81.9**		**73.5**	**69.2**		**69**	**85.7**		**74.2**

Overall Trial Data

	12C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.025	0.028	0.022	392.63	391.00	310.22
	Trial 2	0.024	0.017	0.019	430.19	404.21	355.32
	Trial 3	0.021	0.018	0.016	269.17	372.33	300.00
	PreAvg	**0.023**	**0.021**	**0.019**	**364.00**	**389.18**	**321.85**
	PreStDev	0.002	0.006	0.003	84.242	16.018	29.437
Post	Trial 4	0.021	0.012	0.03	328.05	394.24	358.29
	Trial 5	0.0135	0.019	0.021	441.40	401.49	355.32
	Trial 6	0.0255	0.026	0.023	429.11	366.33	299.89
	PostAvg	**0.020**	**0.019**	**0.024**	**399.52**	**387.35**	**337.83**
	PostStDev	0.006	0.007	0.004	62.200	18.564	32.894

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.142	2.665	0.015	1.32	2.018	0.015	0.67	1.828	0.069
	0.963	2.541	0.008	1.403	2.206	0.018	0.996	1.895	0.09
	0.918	2.587	0.007	1.145	1.965	0.039	0.904	2.133	0.098
	1.205	2.481	0.005	1.371	2.199	0.012	0.614	1.943	0.18
	0.932	2.666	0.012	1.183	2.437	0.091	0.717	2.189	0.138
	1.337	2.487	0.009	1.343	2.511	0.022	0.849	2.137	0.106
	1.236	2.51	0.006	1.361	2.305	0.012	0.995	2.299	0.116
	1.362	2.706	0.012	1.128	2.071	0.035	0.77	2.463	0.088
	1.143	2.685	0.013	1.489	2.149	0.056	0.728	2.17	0.09
	0.821	2.645	0.01	1.169	2.238	0.009	0.706	2.189	0.139
	1.276	2.489	0.014	1.183	2.426	0.012	0.767	2.077	0.151
	1.16	2.498	0.017	1.25	2.37	0.008	0.636	1.987	0.141
	1.297	2.675	0.014	1.36	2.565	0.02	0.727	2.108	0.02
	1.319	2.424	0.008	1.26	2.48	0.013	1.086	2.177	0.071
	0.941	2.613	0.012	1.454	2.219	0.009	1.046	2.093	0.15
Avg	1.1368	2.578133	0.0108	1.2946	2.277267	0.024733	0.814067	2.112533	0.1098
StDev	0.177727	0.092609	0.00355	0.115408	0.184274	0.022752	0.154832	0.158613	0.041013
% of Inhibition	**73.3**		**99.1**	**25**		**98.1**	**41.5**		**86.6**

Overall Trial Data

	13C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.025	0.038	0.022	392.63	391.00	310.22
	Trial 2	0.030	0.023	0.025	430.19	404.21	355.32
	Trial 3	0.021	0.020	0.022	269.17	372.33	300.00
	PreAvg	**0.025**	**0.027**	**0.023**	**364.00**	**389.18**	**321.85**
	PreStDev	0.005	0.010	0.002	84.242	16.018	29.437
Post	Trial 4	0.027	0.012	0.03	328.05	394.24	358.29
	Trial 5	0.025	0.022	0.021	441.40	401.49	355.32
	Trial 6	0.0255	0.036	0.021	429.11	366.33	299.89
	PostAvg	**0.026**	**0.023**	**0.023**	**399.52**	**387.35**	**337.83**
	PostStDev	0.001	0.012	0.004	62.200	18.564	32.894

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.409	0.33	0.541	1.32	2.018	0.015	1.406	0.255	0.509
	1.569	0.342	0.442	1.403	2.206	0.018	1.459	0.392	0.273
	1.976	0.147	0.252	1.145	1.965	0.039	1.404	0.241	0.558
	1.342	0.39	0.178	1.371	2.199	0.012	1.596	0.223	0.351
	1.675	0.172	0.169	1.183	2.437	0.091	1.641	0.241	0.648
	1.172	0.146	0.417	1.343	2.511	0.022	1.515	0.269	0.5
	1.564	0.17	0.136	1.361	2.305	0.012	1.629	0.381	0.538
	1.888	0.128	0.048	1.128	2.071	0.035	1.414	0.819	0.919
	1.299	0.123	0.198	1.489	2.149	0.056	1.511	0.439	0.5
	1.422	0.896	0.084	1.169	2.238	0.009	1.322	0.662	0.223
	1.319	0.035	0.442	1.183	2.426	0.012	1.865	0.643	0.881
	1.719	0.14	0.258	1.25	2.37	0.008	1.217	0.463	0.364
	1.825	0.126	0.246	1.36	2.565	0.02	1.426	0.497	0.477
	1.561	0.155	0.312	1.26	2.48	0.013	1.851	0.387	0.459
	1.799	0.085	0.103	1.454	2.219	0.009	1.382	0.587	0.136
Avg	1.569267	0.225667	0.255067	1.2946	2.277267	0.024733	1.5092	0.433267	0.489067
StDev	0.240745	0.210063	0.148144	0.115408	0.184274	0.022752	0.181175	0.180711	0.215371
% of Inhibition	**54.6**		**62.6**	**58.3**		**67**	**58.6**		**69.4**

Overall Trial Data

	14C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.015	0.016	0.018	284.76	398.43	364.48
	Trial 2	0.018	0.015	0.017	312.49	520.63	343.38
	Trial 3	0.012	0.014	0.015	374.65	476.31	421.13
	PreAvg	**0.015**	**0.015**	**0.017**	**323.97**	**465.12**	**376.33**
	PreStDev	0.003	0.001	0.001	46.029	61.862	40.206
Post	Trial 4	0.012	0.012	0.02	257.25	446.53	380.46
	Trial 5	0.015	0.015	0.024	228.88	406.94	397.62
	Trial 6	0.009	0.017	0.019	292.16	441.00	423.51
	PostAvg	**0.012**	**0.015**	**0.021**	**259.43**	**431.49**	**400.53**
	PostStDev	0.003	0.002	0.002	31.696	21.436	21.671

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	0.925	0.245	1.216	1.112	0.685	1.298	0.941	0.197	1.295
	1.025	0.299	1.417	1.428	0.443	1.858	0.892	0.245	1.057
	0.989	0.351	1.528	1.334	0.435	1.754	1.212	0.171	1.317
	1.036	0.285	1.805	1.274	0.439	1.879	0.993	0.318	1.185
	1	0.496	1.368	1.407	0.657	1.382	1.045	0.318	1.321
	1.243	0.368	1.426	1.178	0.568	1.492	1.131	0.24	1.403
	1.035	0.382	1.507	1.277	0.374	1.974	0.935	0.276	1.351
	1.171	0.331	1.464	1.23	0.454	1.423	1.146	0.288	1.339
	1.132	0.575	1.656	1.247	0.179	1.325	1.056	0.308	1.256
	1.051	0.403	1.377	1.335	0.348	1.69	0.844	0.21	1.243
	1.08	0.426	1.391	1.377	0.773	1.565	1.062	0.299	1.272
	1.237	0.439	1.239	1.246	0.328	1.575	1.134	0.255	1.196
	1.246	0.449	1.467	1.015	0.296	1.823	0.958	0.228	1.317
	1.135	0.427	1.579	0.984	0.505	1.581	1.108	0.203	1.199
	1.1	0.234	1.331	1.332	0.408	1.923	0.846	0.104	1.014
Avg	1.093667	0.380667	1.4514	1.251733	0.459467	1.636133	1.0202	0.244	1.251
StDev	0.098892	0.093765	0.152486	0.132385	0.157753	0.225219	0.115003	0.060593	0.107177
% of Inhibition	**65.2**		**-18.8**	**63.3**		**-34**	**76.1**		**-87.2**

Overall Trial Data

	15C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.014	0.020	0.015	429.90	409.41	343.51
	Trial 2	0.013	0.011	0.017	305.21	337.56	424.51
	Trial 3	0.018	0.016	0.019	362.02	393.31	459.49
	PreAvg	**0.015**	**0.015**	**0.017**	**365.71**	**380.10**	**409.17**
	PreStDev	0.002	0.005	0.002	62.430	37.705	59.492
Post	Trial 4	0.010	0.025	0.01	569.43	377.21	350.87
	Trial 5	0.017	0.020	0.014	298.44	406.32	395.01
	Trial 6	0.013	0.011	0.020	350.01	454.19	369.27
	PostAvg	**0.013**	**0.018**	**0.015**	**405.96**	**412.57**	**371.72**
	PostStDev	0.004	0.007	0.004	143.896	38.868	22.170

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	0.677	0.273	0.202	0.788	0.235	0.261	0.957	0.22	0.292
	0.829	0.152	0.192	0.891	0.282	0.12	1.036	0.304	0.275
	0.71	0.231	0.032	0.752	0.151	0.167	0.958	0.457	0.091
	0.874	0.226	0.227	0.892	0.176	0.175	0.91	0.146	0.276
	0.881	0.234	0.259	0.872	0.33	0.152	0.763	0.258	0.125
	0.839	0.182	0.237	0.745	0.223	0.272	0.722	0.247	0.176
	0.757	0.213	0.29	0.79	0.182	0.164	0.79	0.243	0.238
	0.869	0.172	0.279	0.88	0.13	0.265	0.725	0.311	0.349
	0.874	0.245	0.086	0.889	0.256	0.254	0.978	0.427	0.247
	0.945	0.235	0.16	0.791	0.165	0.215	0.83	0.283	0.104
	0.828	0.293	0.279	0.677	0.153	0.275	0.866	0.375	0.161
	0.96	0.205	0.3	0.904	0.191	0.115	1.022	0.192	0.172
	0.931	0.317	0.432	0.889	0.234	0.223	0.955	0.315	0.206
	0.902	0.355	0.43	0.898	0.251	0.237	1.067	0.256	0.155
	0.993	0.45	0.429	0.974	0.267	0.27	0.837	0.214	0.177
Avg	0.857933	0.2522	0.2556	0.842133	0.215067	0.211	0.8944	0.2832	0.202933
StDev	0.08928	0.076983	0.11706	0.079741	0.056739	0.057208	0.113334	0.085254	0.074538
% of Inhibition	**70.7**		**70.3**	**74.7**		**75**	**68.4**		**77.4**

Overall Trial Data

	16C	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.014	0.018	0.018	343.36	300.35	270.74
	Trial 2	0.021	0.034	0.018	343.36	309.10	326.98
	Trial 3	0.019	0.017	0.021	336.43	337.27	480.82
	PreAvg	**0.018**	**0.023**	**0.019**	**341.05**	**315.57**	**359.52**
	PreStDev	0.004	0.010	0.002	4.004	19.294	108.753
Post	Trial 4	0.020	0.030	0.02	254.61	443.11	315.72
	Trial 5	0.021	0.023	0.018	391.87	322.63	430.46
	Trial 6	0.02	0.020	0.026	254.61	369.66	332.19
	PostAvg	**0.020**	**0.024**	**0.021**	**300.36**	**378.47**	**359.46**
	PostStDev	0.001	0.005	0.005	79.251	60.723	62.041

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.52	0.063	0.4265	1.697	0.005	0.833	1.636	0.032	0.623
	2.015	0.121	0.622	1.501	0.036	0.736	1.638	0.068	1.373
	1.915	0.056	0.424	1.32	0.088	0.876	1.709	0.044	0.681
	1.468	0.028	0.578	1.599	0.09	1.211	1.759	0.069	1.001
	1.614	0.006	0.439	1.639	0.09	1.292	1.254	0.068	0.931
	1.996	0.086	0.37	1.317	0.034	0.285	1.529	0.055	0.812
	1.988	0.085	0.739	1.475	0.004	0.825	1.429	0.056	0.862
	1.712	0.02	0.551	1.471	0.067	1.194	1.266	0.05	0.507
	1.849	0.045	0.847	1.356	0.004	1.283	1.518	0.054	0.72
	1.915	0.058	0.185	1.688	0.091	1.011	1.37	0.056	0.93
	1.732	0.114	0.257	1.667	0.078	0.842	1.862	0.074	0.796
	1.729	0.074	0.557	1.709	0.129	0.451	1.612	0.096	1.169
	1.559	0.072	0.717	1.303	0.059	0.526	1.823	0.06	1.221
	2.04	0.13	0.863	1.614	0.048	0.827	1.302	0.041	1.291
	1.605	0.047	0.722	1.223	0.051	0.463	1.866	0.054	1.041
Avg	1.777133	0.067	0.553167	1.505267	0.058267	0.843667	1.571533	0.058467	0.930533
StDev	0.195545	0.036259	0.203569	0.16713	0.037234	0.316812	0.212301	0.015343	0.253759
% of Inhibition	**96.6**		**68.9**	**96.2**		**44**	**96.3**		**40.8**

Overall Trial Data

	17C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.004	0.004	0.003	621.86	576.06	509.14
	Trial 2	0.022	0.016	0.028	654.57	531.12	394.26
	Trial 3	0.008	0.009	0.016	741.94	498.18	547.43
	PreAvg	**0.012**	**0.009**	**0.016**	**672.79**	**535.12**	**483.61**
	PreStDev	0.009	0.006	0.012	62.080	39.093	79.714
Post	Trial 4	0.017	0.007	0.02	589.77	562.99	578.52
	Trial 5	0.018	0.017	0.015	742.07	362.75	534.01
	Trial 6	0.017	0.017	0.015	512.73	481.38	534.01
	PostAvg	**0.017**	**0.014**	**0.017**	**614.86**	**469.04**	**548.85**
	PostStDev	0.001	0.006	0.004	116.708	100.689	25.700

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.326	1.829	2.063	2.188	0.291	0.686	2.107	0.387	0.881
	2.532	1.68	2.155	2.087	0.252	0.873	1.718	0.73	0.893
	2.378	1.721	1.708	2.104	0.526	1.163	2.158	0.411	0.788
	2.354	1.468	1.772	1.963	0.466	1.253	2.104	0.794	0.773
	2.328	1.451	2.067	2.299	0.49	0.788	1.783	0.782	0.834
	2.201	1.786	1.741	2.515	0.42	1.148	2.367	0.749	0.787
	2.107	1.162	1.279	2.01	0.379	1.157	2.124	0.707	0.8
	2.309	1.076	2.108	2.043	0.391	1.442	2.191	0.579	1.105
	2.535	0.84	1.673	2.206	0.458	0.829	1.78	0.769	1.319
	2.018	0.769	1.842	2.167	0.318	1.773	1.742	0.843	1.22
	2.468	1.402	2.204	2.543	0.353	0.903	2.053	1.292	1.158
	2.485	1.088	1.512	2.345	0.512	1.135	2.143	1.03	0.918
	2.042	0.701	1.858	2.162	0.312	1.268	2.207	1.115	1.166
	2.028	0.66	1.447	2.174	0.512	1.391	2.373	0.829	0.976
	2.547	0.97	1.717	2.078	0.402	0.369	2.197	0.695	1.236
Avg	2.310533	1.2402	1.809733	2.192267	0.405467	1.078533	2.0698	0.7808	0.990267
StDev	0.190583	0.408	0.272948	0.169869	0.087719	0.346093	0.214861	0.237634	0.190917
% of Inhibition	**46.4**		**21.7**	**71.6**		**50.9**	**62.3**		**52.2**

Overall Trial Data

	18C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.004	0.015	0.017	212.38	137.80	221.39
	Trial 2	0.022	0.016	0.012	219.85	216.56	173.64
	Trial 3	0.008	0.018	0.021	213.19	136.36	148.50
	PreAvg	**0.012**	**0.016**	**0.017**	**215.14**	**163.57**	**181.18**
	PreStDev	0.009	0.001	0.005	4.101	45.894	37.022
Post	Trial 4	0.012	0.014	0.01	168.68	180.62	176.09
	Trial 5	0.013	0.016	0.011	205.02	130.76	177.19
	Trial 6	0.011	0.025	0.012	194.23	130.77	169.59
	PostAvg	**0.012**	**0.018**	**0.011**	**189.31**	**147.38**	**174.29**
	PostStDev	0.001	0.006	0.001	18.663	28.779	4.104

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.223	0.032	0.596	1.385	0.028	0.265	1.36	0.077	0.695
	1.479	0.062	0.034	1.41	0.074	0.523	1.143	0.03	0.458
	1.58	0.029	0.756	1.246	0.075	0.605	1.298	0.03	0.616
	1.549	0.016	0.414	1.445	0.046	0.568	1.317	0.034	0.381
	1.126	0.016	0.181	1.415	0.067	0.318	1.499	0.07	0.495
	1.133	0.02	0.363	1.437	0.059	0.619	1.541	0.137	0.593
	1.356	0.027	0.289	1.352	0.075	0.697	1.444	0.043	1.019
	1.201	0.049	0.209	1.392	0.042	0.978	1.41	0.058	0.577
	1.482	0.012	0.489	1.151	0.037	0.781	1.435	0.038	0.977
	1.458	0.042	0.429	1.514	0.025	0.514	1.44	0.069	0.51
	1.74	0.014	0.394	1.19	0.042	0.743	1.3	0.063	0.305
	1.253	0.013	0.306	1.292	0.068	0.786	1.339	0.089	0.584
	1.389	0.015	0.494	1.309	0.027	0.9	1.426	0.038	0.737
	1.639	0.044	0.277	1.496	0.095	0.801	1.31	0.053	0.57
	1.241	0.024	0.243	1.355	0.064	0.826	1.446	0.018	1.068
Avg	1.389933	0.027667	0.364933	1.359267	0.054933	0.6616	1.380533	0.056467	0.639
StDev	0.190558	0.015305	0.178333	0.105364	0.021258	0.20198	0.099432	0.030014	0.226457
% of Inhibition	**98.1**		**73.8**	**96**		**51.4**	**96**		**53.8**

Overall Trial Data

	19C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.024	0.028	0.024	184.29	236.68	188.55
	Trial 2	0.015	0.010	0.019	161.27	226.77	192.22
	Trial 3	0.020	0.016	0.014	152.50	188.32	209.99
	PreAvg	**0.020**	**0.018**	**0.019**	**166.02**	**217.26**	**196.92**
	PreStDev	0.004	0.009	0.005	16.417	25.541	11.468
Post	Trial 4	0.024	0.018	0.02	142.88	210.64	219.62
	Trial 5	0.021	0.032	0.005	159.09	186.37	210.60
	Trial 6	0.024	0.013	0.018	219.62	218.12	210.64
	PostAvg	**0.023**	**0.021**	**0.015**	**173.86**	**205.04**	**213.62**
	PostStDev	0.002	0.010	0.009	40.446	16.596	5.195

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.227	0.146	0.433	1.69	0.101	0.766	1.65	0.23	0.628
	1.174	0.154	0.406	1.379	0.019	0.862	1.788	0.14	0.638
	1.371	0.02	0.375	1.353	0.009	0.695	1.771	0.14	0.761
	1.371	0.114	0.602	1.857	0.072	0.405	1.648	0.145	0.355
	1.673	0.07	0.643	1.732	0.016	0.383	1.496	0.215	0.503
	1.443	0.127	0.654	1.617	0.013	0.855	1.436	0.154	0.592
	1.483	0.042	0.498	1.374	0.006	0.38	1.208	0.042	0.366
	1.534	0.085	0.735	1.724	0.02	0.568	1.552	0.119	0.434
	1.509	0.092	0.661	1.509	0.005	0.516	1.274	0.088	0.401
	1.343	0.039	1.043	1.341	0.011	0.633	1.379	0.097	0.627
	1.526	0.207	0.55	1.502	0.006	0.407	1.632	0.12	0.651
	1.497	0.062	0.453	1.423	0.005	0.554	1.524	0.08	0.796
	1.332	0.032	0.424	1.393	0.061	0.68	1.584	0.233	0.777
	1.256	0.013	0.755	1.613	0.005	0.599	1.665	0.1	0.682
	1.699	0.112	0.502	1.597	0.015	0.222	1.735	0.249	0.834
Avg	1.4292	0.087667	0.582267	1.540267	0.024267	0.568333	1.556133	0.143467	0.603
StDev	0.152666	0.055793	0.17597	0.163437	0.029317	0.186421	0.172963	0.062389	0.15901
% of Inhibition	**93.9**		**59.3**	**98.5**		**63.2**	**90.8**		**61.3**

Overall Trial Data

	20C						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.025	0.015	0.023	127.80	187.42	163.34
	Trial 2	0.034	0.018	0.027	162.23	178.79	182.28
	Trial 3	0.034	0.020	0.016	157.26	159.37	122.96
	PreAvg	**0.031**	**0.017**	**0.022**	**149.10**	**175.20**	**156.19**
	PreStDev	0.005	0.003	0.005	18.609	14.366	30.301
Post	Trial 4	0.027	0.022	0.02	155.47	173.12	172.99
	Trial 5	0.033	0.025	0.022	149.91	191.56	172.99
	Trial 6	0.0285	0.021	0.022	166.20	157.05	171.50
	PostAvg	**0.029**	**0.022**	**0.022**	**157.20**	**173.91**	**172.50**
	PostStDev	0.003	0.002	0.000	8.282	17.266	0.859

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.327	0.006	0.564	1.925	0.008	0.047	1.926	0.007	0.079
	2.984	0.012	0.212	2.066	0.005	0.088	1.779	0.005	0.018
	2.657	0.007	0.152	1.862	0.005	0.028	1.987	0.01	0.068
	3.173	0.006	0.192	2.28	0.006	0.057	1.855	0.007	0.028
	2.534	0.027	0.16	2.022	0.006	0.041	1.88	0.007	0.099
	2.627	0.006	0.399	2.518	0.017	0.105	1.886	0.009	0.064
	2.639	0.01	0.267	2.36	0.005	0.034	2.28	0.008	0.033
	2.084	0.007	0.678	2.337	0.007	0.1	1.92	0.006	0.089
	2.852	0.006	0.13	2.23	0.007	0.069	2.065	0.01	0.099
	2.42	0.005	0.141	2.026	0.035	0.038	2.17	0.006	0.018
	2.552	0.012	0.433	2.169	0.017	0.08	2.049	0.005	0.067
	2.847	0.012	0.261	2.245	0.008	0.082	2.212	0.03	0.092
	2.102	0.012	0.414	2.097	0.034	0.087	1.45	0.008	0.057
	2.77	0.005	0.324	2.346	0.007	0.012	1.93	0.009	0.088
	2.409	0.015	0.436	2.063	0.004	0.101	2.091	0.038	0.042
Avg	2.598467	0.009867	0.317533	2.169733	0.0114	0.0646	1.965333	0.011	0.062733
StDev	0.304607	0.005743	0.165881	0.181761	0.010169	0.029873	0.201039	0.009592	0.028888
% of Inhibition	**99.7**		**87.8**	**99.5**		**97.1**	**99.5**		**96.9**

Overall Trial Data

	01T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.033	0.023	0.014	277.15	432.31	552.22
	Trial 2	0.036	0.025	0.015	262.19	557.99	646.67
	Trial 3	0.031	0.022	0.015	272.35	493.34	710.20
	PreAvg	**0.033**	**0.023**	**0.015**	**270.56**	**494.54**	**636.36**
	PreStDev	0.003	0.002	0.001	7.642	62.851	79.496
Post	Trial 4	0.027	0.018	0.01	415.46	540.60	666.62
	Trial 5	0.032	0.017	0.014	461.96	562.33	649.09
	Trial 6	0.03	0.016	0.012	461.91	595.98	661.73
	PostAvg	**0.030**	**0.017**	**0.013**	**446.45**	**566.30**	**659.15**
	PostStDev	0.003	0.001	0.001	26.830	27.903	9.047

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.339	0.667	0.577	2.697	0.447	0.995	2.744	1.035	1.867
	2.168	0.53	0.457	3.174	0.322	0.642	2.766	1.621	0.812
	1.881	0.509	0.414	3.159	0.406	0.714	2.55	1.066	0.816
	1.977	0.867	0.766	2.591	0.275	0.648	2.594	1.197	0.956
	2.081	0.557	0.544	2.214	0.275	0.847	2.563	1.447	1.742
	1.927	0.674	0.427	2.859	0.006	0.647	2.982	1.241	0.992
	2.553	0.948	0.328	2.589	0.046	0.459	2.666	1.082	1.245
	2.528	0.527	0.652	2.977	0.005	0.884	2.475	1.168	0.818
	2.447	0.743	0.412	2.969	0.377	0.65	2.358	1.253	0.899
	2.308	1.054	0.672	2.636	0.246	0.624	2.277	1.37	0.734
	2.568	0.836	0.833	2.373	0.21	0.593	3.073	1.339	1.216
	2.354	0.661	0.542	2.58	0.147	0.51	3.11	1.141	0.777
	2.719	0.789	0.847	2.585	0.06	0.496	2.617	1.266	1.255
	2.168	0.849	0.51	2.771	0.118	0.57	2.497	1.105	0.795
	2.265	0.88	0.414	2.266	0.316	0.546	2.701	1.601	0.844
Avg	2.285533	0.7394	0.559667	2.696	0.217067	0.655	2.664867	1.262133	1.0512
StDev	0.252049	0.167617	0.162649	0.293007	0.146561	0.150553	0.242429	0.183391	0.352137
% of Inhibition	**97.9**		**96.9**	**93.1**		**63.7**	**87.8**		**49.6**

Overall Trial Data

	02T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.037	0.030	0.013	140.02	211.03	247.66
	Trial 2	0.036	0.019	0.018	160.76	245.15	258.26
	Trial 3	0.027	0.022	0.022	148.58	223.74	264.30
	PreAvg	**0.033**	**0.024**	**0.017**	**149.79**	**226.64**	**256.74**
	PreStDev	0.005	0.006	0.004	10.425	17.246	8.422
Post	Trial 4	0.027	0.025	0.01	158.50	231.05	297.75
	Trial 5	0.034	0.025	0.012	155.45	258.53	278.44
	Trial 6	0.03	0.019	0.010	150.43	245.15	277.86
	PostAvg	**0.030**	**0.023**	**0.012**	**154.79**	**244.91**	**284.68**
	PostStDev	0.004	0.004	0.002	4.077	13.742	11.317

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	0.588	0.027	0.004	1.075	0.146	0.331	0.598	0.017	0.075
	0.648	0.003	0.068	1.068	0.123	0.322	0.737	0.041	0.37
	0.568	0.003	0.02	0.85	0.045	0.282	0.848	0.011	0.08
	0.822	0.026	0.006	1.017	0.064	0.221	0.667	0.017	0.72
	0.763	0.009	0.017	1.133	0.083	0.69	0.782	0.105	0.35
	0.716	0.009	0.045	0.807	0.045	0.394	0.677	0.04	0.592
	0.651	0.005	0.003	0.941	0.143	0.284	0.829	0.045	0.32
	0.608	0.004	0.004	0.923	0.031	0.214	0.735	0.084	0.438
	0.861	0.005	0.007	0.846	0.063	0.434	0.854	0.034	0.522
	0.777	0.005	0.003	1.144	0.084	0.35	0.642	0.079	0.332
	0.78	0.003	0.003	0.892	0.01	0.388	0.603	0.039	0.296
	0.858	0.009	0.017	0.771	0.012	0.144	0.763	0.009	0.188
	0.716	0.11	0.005	0.724	0.029	0.206	0.866	0.76	0.495
	0.652	0.005	0.077	1.137	0.013	0.542	0.806	0.051	0.32
	0.602	0.01	0.053	1.119	0.115	0.453	0.63	0.018	0.471
Avg	0.707333	0.015533	0.022133	0.963133	0.067067	0.350333	0.7358	0.09	0.371267
StDev	0.099001	0.027218	0.025615	0.145077	0.046999	0.141911	0.094419	0.187485	0.17766
% of Inhibition	**67.7**		**75.6**	**92**		**75.8**	**52.7**		**65.8**

Overall Trial Data

	03T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.029	0.022	0.008	145.82	383.36	551.76
	Trial 2	0.026	0.023	0.011	164.90	460.61	510.51
	Trial 3	0.024	0.023	0.004	230.64	491.89	474.91
	PreAvg	**0.026**	**0.023**	**0.008**	**180.45**	**445.28**	**512.39**
	PreStDev	0.003	0.001	0.004	44.497	55.865	38.462
Post	Trial 4	0.021	0.016	0.01	365.36	534.46	621.39
	Trial 5	0.025	0.015	0.005	310.99	588.69	502.48
	Trial 6	0.023	0.017	0.006	331.29	681.94	686.00
	PostAvg	**0.023**	**0.016**	**0.006**	**335.88**	**601.70**	**603.29**
	PostStDev	0.002	0.001	0.002	27.475	74.593	93.089

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.844	1.137	2.557	3.067	0.294	2.934	2.8	0.6	2.176
	2.859	0.978	2.377	3.387	0.694	2.58	2.49	0.7	2.108
	2.759	1.136	2.652	3.506	0.503	1.967	2.768	0.447	1.982
	2.994	1.152	2.315	3.308	0.357	1.412	2.514	0.471	1.651
	2.895	1.117	2.112	3.348	0.324	1.7	2.733	0.887	2.611
	2.463	0.873	2.041	3.439	0.353	2.691	2.933	0.767	2.055
	3.013	1.255	2.083	3.173	0.354	2.723	2.915	0.933	2.837
	2.417	1.007	2.016	3.454	0.329	1.752	3.484	1.261	2.141
	2.342	1.018	2.471	3.405	0.3	2.476	3.103	0.894	2.441
	2.646	0.979	2.061	3.233	0.269	2.128	3.117	0.658	2.71
	2.857	1.123	2.461	3.105	0.458	2.282	3.059	0.622	2.39
	2.814	1.091	1.953	3.109	0.377	2.264	3.103	0.468	2.754
	2.739	1.014	2.552	3.296	0.496	2.345	2.87	0.401	2.538
	2.426	1.063	2.119	3.369	0.491	2.278	3.156	0.973	1.926
	2.741	1.148	2.469	3.488	0.504	2.688	3.154	0.907	1.883
Avg	2.7206	1.072733	2.2826	3.312467	0.406867	2.281333	2.9466	0.7326	2.2802
StDev	0.215278	0.095108	0.235926	0.144824	0.114621	0.429444	0.262943	0.242761	0.359731
% of Inhibition	**87.8**		**22.7**	**75.2**		**31.2**	**60.6**		**16.1**

Overall Trial Data

	04T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.012	0.005	0.008	607.56	617.72	675.23
	Trial 2	0.013	0.004	0.011	591.94	595.09	
	Trial 3	0.013	0.004	0.004	645.98	576.76	
	PreAvg	**0.012**	**0.004**	**0.008**	**615.16**	**596.52**	**675.23**
	PreStDev	0.001	0.001	0.004	27.808	20.516	
Post	Trial 4	0.010	0.009	0.01	681.21	550.40	607.16
	Trial 5	0.008	0.009	0.005	683.15	560.88	
	Trial 6	0.0085	0.005	0.006	514.75	528.14	
	PostAvg	**0.009**	**0.007**	**0.006**	**626.37**	**546.47**	**607.16**
	PostStDev	0.001	0.002	0.002	96.668	16.723	

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.302	0.009	0.12	1.787	0.003	0.593	1.143	0.051	1.256
	1.55	0.005	0.149	1.524	0.009	0.244	1.55	0.014	0.636
	1.327	0.006	0.151	1.715	0.003	0.221	1.155	0.006	0.549
	1.601	0.004	0.465	1.507	0.013	0.239	1.342	0.017	0.635
	1.407	0.008	0.218	1.486	0.07	0.684	1.401	0.005	0.545
	1.447	0.008	0.1	1.652	0.005	0.309	1.105	0.004	1.017
	1.317	0.005	0.139	1.609	0.006	0.338	1.482	0.025	1.038
	1.44	0.005	0.208	1.862	0.005	0.458	1.528	0.029	0.586
	1.485	0.007	0.117	1.209	0.002	0.228	1.135	0.026	0.607
	1.774	0.018	0.225	1.866	0.009	0.771	1.018	0.006	0.741
	1.418	0.013	0.461	1.632	0.005	0.727	1.149	0.025	0.537
	1.772	0.012	0.15	1.224	0.019	0.224	1.246	0.005	0.56
	1.391	0.008	0.472	1.793	0.004	0.314	1.472	0.008	0.383
	1.243	0.005	0.674	1.37	0.122	0.723	1.521	0.003	0.818
	1.453	0.006	0.452	1.768	0.007	0.372	1.46	0.009	0.67
Avg	1.4618	0.007933	0.2734	1.600267	0.0188	0.429667	1.3138	0.015533	0.7052
StDev	0.156899	0.003807	0.180321	0.212377	0.033137	0.210464	0.184566	0.013432	0.233516
% of Inhibition	**99.5**		**81.3**	**98.9**		**73.2**	**98.9**		**56.4**

Overall Trial Data

	05T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.023	0.019	0.006	412.33	418.93	489.76
	Trial 2	0.017	0.017	0.011	464.51	426.36	530.00
	Trial 3	0.020	0.010	0.003	419.48	387.65	518.98
	PreAvg	**0.020**	**0.015**	**0.007**	**432.11**	**410.98**	**512.91**
	PreStDev	0.003	0.005	0.004	28.294	20.542	20.795
Post	Trial 4	0.022	0.006	0.01	483.61	544.05	586.93
	Trial 5	0.009	0.012	0.005	503.47	502.05	589.33
	Trial 6	0.005	0.006	0.006	459.04	478.97	630.34
	PostAvg	**0.012**	**0.008**	**0.006**	**482.04**	**508.36**	**602.20**
	PostStDev	0.009	0.003	0.002	22.258	32.994	24.399

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.798	0.079	0.104	2.568	0.322	0.236	3.215	0.125	0.341
	2.727	0.102	0.109	2.948	0.071	0.551	3.524	0.103	0.359
	2.784	0.043	0.103	2.884	0.036	0.332	3.705	0.073	0.391
	2.737	0.073	0.274	2.588	0.089	0.117	3.317	0.087	0.203
	2.684	0.151	0.141	2.7	0.086	0.305	3.419	0.045	0.569
	2.78	0.006	0.064	2.618	0.046	0.251	2.728	0.055	0.233
	2.787	0.045	0.122	3.044	0.061	0.133	2.553	0.007	0.306
	2.622	0.211	0.057	3.154	0.294	0.339	3.149	0.005	0.262
	2.699	0.12	0.143	2.635	0.075	0.103	3.245	0.065	0.24
	2.543	0.11	0.067	2.882	0.077	0.333	2.751	0.034	0.209
	2.378	0.075	0.055	3.222	0.176	0.345	3.425	0.096	0.182
	2.484	0.148	0.074	2.997	0.046	0.198	3.599	0.095	0.186
	2.504	0.12	0.185	3.31	0.369	0.292	2.899	0.189	0.391
	2.672	0.044	0.358	2.649	0.097	0.181	3.214	0.049	0.586
	2.699	0.069	0.218	3.369	0.094	0.701	3.198	0.019	0.101
Avg	2.659867	0.093067	0.138267	2.904533	0.129267	0.294467	3.196067	0.0698	0.303933
StDev	0.127922	0.05238	0.087456	0.27377	0.108895	0.160432	0.334866	0.048756	0.138726
% of Inhibition	**96.5**		**94.9**	**95.6**		**89.9**	**97.9**		**90.5**

Overall Trial Data

	06T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	32.00	33.000	0.029	177.61	130.37	304.52
	Trial 2	35.00	36.000	0.032	149.15	137.51	262.54
	Trial 3	36.00	32.000	0.015	131.76	183.48	229.61
	PreAvg	**34.33**	**33.667**	**0.025**	**152.84**	**150.45**	**265.55**
	PreStDev	2.08	2.082	0.009	23.144	28.826	37.543
Post	Trial 4	39.00	32.000	0.01	209.50	183.48	275.39
	Trial 5	28.00	23.000	0.002	194.23	171.79	238.86
	Trial 6	23.00	18.000	0.021	191.15	155.03	286.23
	PostAvg	**30.00**	**24.333**	**0.012**	**198.29**	**170.10**	**266.83**
	PostStDev	8.19	7.095	0.009	9.828	14.300	24.823

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.13	0.193	1.096	0.851	0.091	0.708	0.959	0.088	1.342
	1.415	0.166	0.646	0.848	0.091	0.71	1.033	0.16	1.094
	1.221	0.125	0.591	0.987	0.121	0.952	1.026	0.183	0.893
	1.263	0.171	0.583	1.057	0.077	0.313	1.051	0.158	1.234
	1.246	0.148	0.903	0.946	0.077	1.069	1.352	0.242	0.902
	1.016	0.259	0.803	1.183	0.294	0.26	1.184	0.175	0.846
	1.164	0.187	1.299	0.847	0.066	0.383	1.053	0.196	1.075
	1.381	0.132	0.779	0.754	0.134	0.989	1.385	0.172	1.115
	1.342	0.23	1.031	0.939	0.008	0.76	1.161	0.115	0.956
	1.565	0.126	0.575	0.821	0.027	0.631	1.211	0.113	0.796
	1.051	0.094	0.643	0.833	0.066	0.636	1.254	0.128	0.888
	1.135	0.147	0.908	0.82	0.099	0.641	1.241	0.144	1.058
	1.774	0.215	1.134	1.089	0.085	0.608	1.167	0.15	0.78
	1.277	0.185	0.313	0.806	0.07	0.977	1.15	0.121	0.528
	1.301	0.236	0.362	0.81	0.05	0.392	1.187	0.108	1.045
Avg	1.2854	0.174267	0.777733	0.906067	0.0904	0.6686	1.160933	0.1502	0.970133
StDev	0.196685	0.046967	0.284805	0.123753	0.064808	0.254729	0.120932	0.040093	0.200618
% of Inhibition	**86.5**		**39.5**	**90.1**		**26.3**	**87.1**		**16.5**

Overall Trial Data

	07T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.02	0.019	0.021	209.96	228.31	274.36
	Trial 2	0.01	0.019	0.017	283.43	211.60	260.03
	Trial 3	0.02	0.025	0.017	267.66	217.56	248.48
	PreAvg	**0.02**	**0.021**	**0.018**	**253.68**	**219.16**	**260.95**
	PreStDev	0.00	0.003	0.002	38.681	8.466	12.965
Post	Trial 4	0.01	0.020	0.02	374.88	312.82	272.51
	Trial 5	0.02	0.015	0.016	367.66	303.68	288.89
	Trial 6	0.02	0.017	0.015	344.47	295.51	268.06
	PostAvg	**0.02**	**0.017**	**0.016**	**362.34**	**304.00**	**276.49**
	PostStDev	0.00	0.003	0.002	15.886	8.659	10.973

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.262	0.228	0.609	1.35	0.164	0.615	0.98	0.283	1.172
	1.438	0.551	0.832	1.45	0.184	0.939	0.826	0.371	1.004
	1.583	0.309	0.508	1.198	0.22	0.963	0.965	0.262	0.881
	1.409	0.34	0.613	1.494	0.107	0.977	1.043	0.349	1.049
	1.491	0.418	0.355	1.351	0.168	1.06	0.897	0.391	0.597
	1.356	0.334	0.497	1.504	0.151	0.584	0.923	0.393	0.734
	1.348	0.483	0.893	1.491	0.13	0.901	0.897	0.305	0.866
	1.347	0.446	0.665	1.457	0.195	0.905	1.003	0.164	0.528
	1.518	0.348	0.811	1.486	0.112	0.883	0.941	0.247	0.766
	1.546	0.494	0.757	1.485	0.114	1.175	0.716	0.262	0.855
	1.565	0.341	0.81	1.539	0.231	0.745	0.783	0.098	0.553
	1.429	0.69	0.798	1.412	0.244	0.544	0.611	0.36	1.029
	1.216	0.237	0.409	1.212	0.254	0.918	0.859	0.238	1.098
	1.224	0.346	0.293	1.458	0.153	1.469	0.978	0.147	0.755
	1.488	0.255	0.403	1.449	0.202	0.915	0.727	0.46	0.866
Avg	1.414667	0.388	0.616867	1.4224	0.175267	0.9062	0.8766	0.288667	0.8502
StDev	0.120251	0.126892	0.196576	0.102489	0.048507	0.234297	0.122455	0.101492	0.197752
% of Inhibition	**72.6**		**56.4**	**77.7**		**36.3**	**67.1**		**3.1**

Overall Trial Data

	08T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.03	0.041	0.024	232.01	134.44	208.03
	Trial 2	0.02	0.034	0.021	104.09	204.38	254.84
	Trial 3	0.03	0.018	0.017	223.38	199.12	287.29
	PreAvg	**0.03**	**0.031**	**0.021**	**186.49**	**179.31**	**250.05**
	PreStDev	0.00	0.012	0.004	71.495	38.951	39.846
Post	Trial 4	0.01	0.016	0.02	139.64	221.25	288.09
	Trial 5	0.02	0.019	0.033	157.96	169.83	278.55
	Trial 6	0.01	0.013	0.014	178.71	198.53	281.04
	PostAvg	**0.01**	**0.016**	**0.024**	**158.77**	**196.54**	**282.56**
	PostStDev	0.00	0.003	0.010	19.547	25.765	4.950

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.46	0.012	0.007	1.059	0.03	0.063	1.012	0.216	0.552
	1.313	0.009	0.009	1.032	0.07	0.245	1.283	0.271	0.222
	1.746	0.047	0.028	1.158	0.021	0.03	1.1	0.201	0.223
	1.697	0.082	0.013	1.116	0.109	0.22	0.962	0.225	0.105
	1.716	0.034	0.039	1.15	0.134	0.221	1.047	0.284	0.105
	1.747	0.085	0.032	1.168	0.074	0.2	0.98	0.488	0.174
	1.171	0.007	0.034	1.032	0.018	0.107	1.387	0.313	0.433
	1.506	0.008	0.04	0.963	0.031	0.211	1.24	0.226	0.275
	1.369	0.016	0.01	1.267	0.083	0.175	1.373	0.134	0.154
	1.248	0.009	0.033	1.045	0.043	0.147	1.27	0.103	0.341
	1.623	0.024	0.007	0.829	0.034	0.132	1.166	0.239	0.677
	1.321	0.049	0.006	1.232	0.046	0.052	1.291	0.242	0.33
	1.759	0.031	0.034	1.001	0.066	0.147	1.273	0.22	0.325
	1.465	0.013	0.014	1.125	0.046	0.041	1.129	0.076	0.063
	1.879	0.036	0.026	0.936	0.036	0.063	1.072	0.079	0.117
Avg	1.534667	0.0308	0.022133	1.0742	0.056067	0.136933	1.172333	0.221133	0.273067
StDev	0.219348	0.025582	0.012922	0.116361	0.033236	0.073904	0.140609	0.103557	0.175496
% of Inhibition	**98**		**98.6**	**94.8**		**87.3**	**81.2**		**76.1**

Overall Trial Data

	09T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.020	0.024	0.016	205.06	221.69	354.82
	Trial 2	0.032	0.028	0.021	309.30	153.84	407.81
	Trial 3	0.018	0.015	0.025	190.97	187.90	377.95
	PreAvg	**0.023**	**0.022**	**0.020**	**235.11**	**187.81**	**380.19**
	PreStDev	0.007	0.007	0.005	64.636	33.925	26.568
Post	Trial 4	0.021	0.009	0.008	274.47	199.90	416.58
	Trial 5	0.009	0.026	0.011	202.43	213.68	398.44
	Trial 6	0.006	0.026	0.017	296.82	264.39	390.31
	PostAvg	**0.012**	**0.020**	**0.012**	**257.91**	**225.99**	**401.78**
	PostStDev	0.008	0.010	0.005	49.325	33.964	13.450

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.054	0.055	0.216	1.298	0.016	0.144	1.472	0.013	0.699
	0.936	0.058	0.055	1.256	0.016	0.123	1.71	0.016	0.65
	1.164	0.012	0.009	1.476	0.019	0.306	1.54	0.027	1.707
	1.038	0.054	0.099	1.342	0.019	0.623	1.657	0.062	0.513
	0.94	0.056	0.216	1.381	0.027	1.279	1.671	0.012	0.615
	1.031	0.053	0.011	1.673	0.024	0.328	1.306	0.015	0.946
	1.178	0.012	0.424	1.838	0.024	0.26	1.644	0.059	0.436
	0.986	0.021	0.107	1.599	0.026	0.646	1.768	0.065	1.17
	1.252	0.027	0.228	1.676	0.025	0.649	1.56	0.077	0.871
	1.159	0.053	0.164	1.382	0.027	0.284	1.476	0.044	0.684
	0.992	0.016	0.053	1.786	0.057	0.483	1.461	0.045	1.422
	1.154	0.058	0.059	1.715	0.029	0.485	1.741	0.038	0.825
	1.286	0.056	0.114	1.75	0.034	0.762	1.403	0.048	0.74
	0.87	0.06	0.206	1.718	0.032	0.568	1.585	0.04	1.496
	1.178	0.06	0.061	1.593	0.025	0.136	1.66	0.036	0.918
Avg	1.0812	0.0434	0.1348	1.565533	0.026667	0.471733	1.576933	0.0398	0.9128
StDev	0.124165	0.019309	0.109975	0.192945	0.009904	0.304739	0.133042	0.020435	0.376046
% of Inhibition	**96**		**87.6**	**98.3**		**69.9**	**97.5**		**42.2**

Overall Trial Data

	10T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.023	0.014	0.016	267.88	304.70	549.56
	Trial 2	0.017	0.013	0.019	206.57	439.76	432.44
	Trial 3	0.021	0.013	0.014	234.52	425.47	505.29
	PreAvg	**0.020**	**0.013**	**0.016**	**236.32**	**389.98**	**495.77**
	PreStDev	0.003	0.001	0.003	30.694	74.193	59.138
Post	Trial 4	0.029	0.005	0.017	210.14	352.71	487.42
	Trial 5	0.027	0.026	0.013	173.00	356.92	425.47
	Trial 6	0.020	0.007	0.014	264.58	487.42	505.29
	PostAvg	**0.025**	**0.013**	**0.015**	**215.91**	**399.02**	**472.73**
	PostStDev	0.005	0.012	0.002	46.064	76.588	41.891

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.497	0.444	0.887	2.625	0.382	2.207	3.098	0.503	3.666
	2.579	0.184	1.126	2.894	0.605	1.521	2.99	0.824	3.204
	2.293	0.068	1.614	2.958	0.522	1.668	3.196	0.422	2.625
	2.217	0.1	1.294	2.661	0.399	1.485	2.751	0.537	3.344
	2.766	0.56	1.037	2.535	0.249	1.403	2.936	0.36	3.419
	2.65	0.467	1.585	2.309	0.325	2.379	3.265	0.659	2.556
	2.728	0.593	1.708	2.684	0.449	1.209	2.965	0.359	3.577
	2.301	0.711	0.814	2.832	0.287	1.561	2.842	0.397	2.771
	2.601	0.613	1.119	2.509	0.212	1.594	3.078	0.616	3.059
	2.877	0.695	1.958	2.321	0.213	2.071	3.129	0.378	3.202
	2.824	0.45	1.906	3.109	0.228	1.262	2.956	0.324	2.364
	2.913	0.562	2.058	2.353	0.135	2.646	2.691	0.494	2.829
	2.928	0.515	1.714	2.945	0.373	1.594	2.818	0.162	1.453
	2.747	0.31	1.813	2.78	0.342	1.494	2.746	0.244	1.852
	2.894	0.488	2.124	2.906	0.215	1.974	2.779	0.341	3.009
Avg	2.654333	0.450667	1.517133	2.694733	0.329067	1.737867	2.949333	0.441333	2.862
StDev	0.236651	0.200815	0.436413	0.25148	0.129228	0.421635	0.177029	0.169157	0.62139
% of Inhibition	**83.1**		**42.9**	**87.8**		**35.6**	**85.1**		**3**

Overall Trial Data

	11T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.028	0.041	0.023	170.79	161.90	204.66
	Trial 2	0.028	0.020	0.026	169.32	154.97	177.58
	Trial 3	0.025	0.018	0.030	119.44	197.31	194.70
	PreAvg	**0.027**	**0.026**	**0.026**	**153.18**	**171.40**	**192.32**
	PreStDev	0.002	0.013	0.004	29.233	22.710	13.695
Post	Trial 4	0.023	0.022	0.015	137.64	198.88	208.44
	Trial 5	0.025	0.012	0.021	145.96	196.08	201.70
	Trial 6	0.030	0.019	0.016	167.88	159.12	209.62
	PostAvg	**0.026**	**0.018**	**0.017**	**150.49**	**184.69**	**206.59**
	PostStDev	0.004	0.005	0.003	15.621	22.192	4.272

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.137	0.038	1.344	2.249	0.148	1.285	1.965	0.069	1.393
	2.238	0.034	1.121	2.196	0.01	1.19	2.199	0.027	0.989
	2.427	0.068	1.608	2.222	0.012	1.234	2.345	0.093	1.128
	2.259	0.029	1.108	1.81	0.097	1.259	2.006	0.1	0.923
	1.847	0.027	0.942	1.961	0.007	1.197	2.191	0.109	1.136
	2.039	0.03	0.222	2.299	0.029	1.119	1.765	0.081	0.939
	2.099	0.035	0.613	2.367	0.113	1.384	1.649	0.117	1.269
	2.484	0.018	0.823	2.133	0.159	1.374	2.204	0.128	1.301
	2.222	0.025	0.504	2.282	0.096	1.339	2.162	0.102	1.542
	2.356	0.069	0.985	2.256	0.134	0.95	2.259	0.107	1.467
	2.256	0.036	1.038	2.379	0.014	0.672	1.728	0.107	2.208
	2.066	0.02	1.229	2.37	0.094	1.003	2.096	0.103	1.843
	2.369	0.022	0.889	2.314	0.025	1.064	2.318	0.035	1.373
	2.288	0.027	1.1	2.004	0.031	1.318	2.264	0.114	0.851
	1.702	0.022	0.863	2.421	0.031	1.182	1.917	0.108	0.986
Avg	2.185933	0.033333	0.959267	2.217533	0.066667	1.171333	2.0712	0.093333	1.289867
StDev	0.211974	0.015481	0.340208	0.173358	0.05515	0.189453	0.222743	0.029011	0.372733
% of Inhibition	**88.5**		**56.2**	**97**		**47.2**	**95.5**		**37.8**

Overall Trial Data

	12T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.016	0.017	0.007	567.88	432.44	718.09
	Trial 2	0.029	0.021	0.015	658.94	562.17	870.54
	Trial 3	0.007	0.014	0.013	585.27	505.29	805.95
	PreAvg	**0.017**	**0.017**	**0.012**	**604.03**	**499.97**	**798.19**
	PreStDev	0.011	0.004	0.004	48.346	65.025	76.524
Post	Trial 4	0.021	0.016	0.018	695.25	549.56	862.92
	Trial 5	0.026	0.014	0.005	572.49	655.08	818.58
	Trial 6	0.010	0.017	0.001	667.88	591.45	917.32
	PostAvg	**0.019**	**0.015**	**0.008**	**645.21**	**598.70**	**866.27**
	PostStDev	0.008	0.002	0.009	64.444	53.129	49.454

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.279	0.134	0.634	1.284	0.969	0.043	2.481	0.096	1.393
	1.375	0.067	0.901	1.668	1.408	0.058	2.335	0.061	0.989
	1.592	0.214	0.723	1.584	1.219	0.008	2.806	0.054	1.128
	1.419	0.408	0.724	1.761	1.239	0.28	2.694	0.1	0.923
	1.279	0.086	0.831	1.568	1.589	0.049	2.133	0.063	1.136
	1.19	0.131	0.565	1.559	0.93	0.033	2.866	0.067	0.939
	1.485	0.4	0.734	1.485	2.167	0.029	2.636	0.09	1.269
	1.551	0.215	0.968	1.528	1.373	0.021	3.141	0.138	1.301
	1.405	0.146	0.748	1.706	1.842	0.012	2.205	0.098	1.542
	1.472	0.117	0.663	1.199	1.359	0.012	3.069	0.088	1.467
	1.468	0.12	0.866	1.621	0.419	0.065	2.119	0.065	2.208
	1.488	0.051	0.891	1.363	1.285	0.034	2.595	0.091	1.843
	1.648	0.304	0.491	1.714	2.01	0.027	2.033	0.061	1.373
	1.692	0.115	0.551	1.466	0.442	0.018	3.269	0.147	0.851
	1.399	0.111	0.704	1.453	2.013	0.015	2.689	0.147	0.986
Avg	1.449467	0.1746	0.732933	1.5306	1.350933	0.046933	2.604733	0.091067	1.289867
StDev	0.13859	0.112814	0.139275	0.16052	0.527277	0.066738	0.387528	0.031454	0.372733
% of Inhibition	**88**		**49.5**	**96.6**		**68.1**	**94.8**		**60.9**

Overall Trial Data

	13T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.027	0.020	0.011	195.15	314.32	503.28
	Trial 2	0.023	0.022	0.011	392.47	594.37	636.02
	Trial 3	0.017	0.011	0.001	360.64	472.95	561.13
	PreAvg	**0.022**	**0.017**	**0.008**	**316.08**	**460.55**	**566.81**
	PreStDev	0.005	0.006	0.006	105.935	140.434	66.551
Post	Trial 4	0.020	0.017	0.001	341.80	566.55	561.13
	Trial 5	0.016	0.001	0.010	526.53	677.93	686.61
	Trial 6	0.015	0.000	0.003	515.47	683.18	748.80
	PostAvg	**0.017**	**0.006**	**0.005**	**461.27**	**642.56**	**665.52**
	PostStDev	0.002	0.010	0.004	103.609	65.872	95.599

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.407	0.353	0.021	1.539	0.06	0.034	2.267	0.589	0.05
	1.337	0.062	0.028	1.367	0.06	0.037	1.817	0.565	0.092
	2.153	0.164	0.02	1.191	0.1	0.039	1.908	0.672	0.11
	1.955	0.153	0.339	1.584	0.114	0.044	1.735	0.737	0.069
	1.797	0.363	0.016	1.458	0.187	0.038	2.142	0.41	0.093
	1.238	0.439	0.021	1.485	0.177	0.034	2.098	0.658	0.072
	1.897	0.774	0.048	1.215	0.116	0.044	1.917	0.512	0.139
	1.49	0.357	0.033	1.759	0.098	0.06	2.16	0.822	0.13
	1.927	0.309	0.068	1.413	0.049	0.036	2.119	0.165	0.161
	1.085	0.162	0.033	1.594	0.183	0.044	2.052	0.235	0.136
	1.362	0.13	0.045	1.463	0.326	0.055	1.889	0.345	0.087
	1.291	0.214	0.042	1.577	0.117	0.045	2.234	0.752	0.062
	1.333	0.109	0.033	1.124	0.063	0.044	1.84	0.229	0.088
	2.296	0.653	0.137	1.178	0.066	0.051	1.728	0.221	0.085
	1.952	0.647	0.131	1.184	0.061	0.051	1.714	0.158	0.07
Avg	1.634667	0.325933	0.067667	1.408733	0.118467	0.043733	1.974667	0.471333	0.096267
StDev	0.377423	0.220001	0.083869	0.191929	0.074133	0.007787	0.18925	0.233099	0.032259
% of Inhibition	**80.1**		**95.9**	**91.6**		**96.9**	**76.2**		**95.2**

Overall Trial Data

	14T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.014	0.013	0.009	182.93	174.85	255.82
	Trial 2	0.012	0.009	0.005	186.21	223.14	234.62
	Trial 3	0.014	0.015	0.005	133.80	309.76	280.98
	PreAvg	**0.013**	**0.012**	**0.006**	**167.65**	**235.92**	**257.14**
	PreStDev	0.001	0.003	0.002	29.360	68.355	23.212
Post	Trial 4	0.011	0.013	0.007	211.25	256.54	286.75
	Trial 5	0.012	0.009	0.002	178.48	221.05	255.58
	Trial 6	0.019	0.011	0.004	151.77	227.04	321.90
	PostAvg	**0.014**	**0.011**	**0.004**	**180.50**	**234.88**	**288.08**
	PostStDev	0.004	0.002	0.003	29.788	18.997	33.178

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.25	0.019	0.023	1.291	0.008	0.045	1.016	0.004	0.109
	2.762	0.016	0.021	1.3132	0.011	0.075	1.093	0.009	0.151
	2.7	0.015	0.017	1.011	0.023	0.032	1.274	0.014	0.364
	2.67	0.016	0.022	1.446	0.006	0.008	1.088	0.005	0.17
	2.689	0.023	0.021	0.919	0.006	0.014	1.185	0.009	0.3
	2.821	0.016	0.057	1.046	0.009	0.018	1.298	0.01	0.319
	2.471	0.019	0.031	1.603	0.023	0.014	1.186	0.011	0.148
	2.137	0.017	0.018	1.422	0.02	0.033	1.066	0.031	0.335
	1.97	0.016	0.019	0.096	0.008	0.013	1.098	0.023	0.338
	2.656	0.013	0.024	1.113	0.025	0.015	1.139	0.009	0.276
	2.724	0.016	0.021	1.418	0.007	0.041	1.222	0.007	0.414
	1.99	0.017	0.016	1.213	0.007	0.06	1.592	0.01	0.447
	2.711	0.017	0.03	1.562	0.023	0.03	1.258	0.019	0.157
	1.948	0.018	0.017	1.256	0.008	0.023	1.242	0.015	0.199
	2.431	0.029	0.021	1.338	0.008	0.06	1.621	0.006	0.324
Avg	2.462	0.0178	0.023867	1.203147	0.0128	0.032067	1.2252	0.012133	0.270067
StDev	0.318395	0.003821	0.010134	0.364384	0.007476	0.020394	0.175748	0.007337	0.106496
% of Inhibition	**99.3**		**99.1**	**98.1**		**97.4**	**76.2**		**78**

Overall Trial Data

	15T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.025	0.023	0.014	264.53	365.41	436.94
	Trial 2	0.021	0.017	0.005	436.36	468.19	321.52
	Trial 3	0.012	0.001	0.005	311.40	587.86	373.50
	PreAvg	**0.019**	**0.014**	**0.008**	**337.43**	**473.82**	**377.32**
	PreStDev	0.007	0.011	0.005	88.823	111.331	57.804
Post	Trial 4	0.012	0.010	0.011	488.93	442.90	318.68
	Trial 5	0.019	0.001	0.007	531.51	568.07	531.64
	Trial 6	0.012	0.003	0.011	385.61	713.07	336.04
	PostAvg	**0.014**	**0.005**	**0.010**	**468.68**	**574.68**	**395.45**
	PostStDev	0.004	0.004	0.003	75.027	135.208	118.258

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.22	2.683	0.154	2.19	2.678	0.53	2.426	5.177	2.528
	2.061	2.558	0.144	2.191	2.169	0.717	3.055	5.3	2.585
	2.682	2.599	0.155	2.393	1.718	0.409	2.605	6.507	2.808
	2.31	2.455	0.151	1.871	2.108	0.629	2.644	4.118	2.386
	2.459	2.389	0.14	1.985	1.69	1.139	2.635	4.936	1.828
	2.162	2.604	0.145	1.989	2.245	0.391	2.448	5.485	2.908
	2.513	2.368	0.198	2.269	2.629	0.586	2.907	5.54	2.213
	2.53	1.873	0.151	2.307	1.591	0.472	2.761	5.466	2.758
	2.661	2.514	0.145	2.326	3.26	0.559	2.599	5.793	2.08
	2.259	2.585	0.146	2.315	2.343	0.422	2.778	4.886	1.83
	2.077	2.74	0.165	2.404	2.612	0.273	2.811	5.606	1.971
	2.587	2.681	0.157	2.231	2.236	0.58	2.366	5.306	2.207
	2.592	2.555	0.143	2.41	2.011	0.752	3.159	5.092	2.723
	2.347	2.782	0.145	2.433	1.738	0.528	2.738	5.36	1.943
	2.153	2.323	0.153	2.321	2.408	0.907	2.73	4.639	2.364
Avg	2.3742	2.513933	0.1528	2.242333	2.229067	0.592933	2.7108	5.280733	2.342133
StDev	0.214266	0.222183	0.014113	0.171225	0.453725	0.218628	0.220227	0.541645	0.366303
% of Inhibition	**-5**		**93.6**	**0.1**		**73.6**	**-0.6**		**13.6**

Overall Trial Data

	16T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.013	0.028	0.016	147.99	286.74	512.82
	Trial 2	0.021	0.018	0.009	200.32	239.31	603.76
	Trial 3	0.050	0.028	0.009	345.29	330.33	603.76
	PreAvg	**0.028**	**0.025**	**0.011**	**231.20**	**285.46**	**573.45**
	PreStDev	0.019	0.006	0.004	102.211	45.526	52.509
Post	Trial 4	0.022	0.011	0.009	202.86	315.72	583.00
	Trial 5	0.016	0.021	0.007	260.22	538.21	708.76
	Trial 6	0.023	0.015	0.007	202.50	451.38	847.69
	PostAvg	**0.020**	**0.016**	**0.008**	**221.86**	**435.10**	**713.15**
	PostStDev	0.004	0.005	0.001	33.223	112.136	132.397

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.577	0.178	0.836	2.2	0.211	1.102	2.341	0.356	1.69
	1.58	0.234	0.827	2.162	0.079	1.264	2.27	0.028	1.946
	1.734	0.331	0.903	2.338	0.067	0.482	1.755	0.009	1.937
	1.403	0.106	0.208	2.277	0.113	1.751	2.255	0.069	1.164
	1.592	0.432	0.974	2.13	0.029	1.951	2.115	0.009	0.891
	1.417	0.336	0.23	2.558	0.484	1.705	1.825	0.025	1.143
	1.653	0.37	0.779	2.699	0.316	1.93	2.095	0.042	0.949
	1.744	0.274	0.88	2.452	0.187	0.89	1.891	0.023	1.048
	1.462	0.491	0.572	2.583	0.159	1.033	1.96	0.01	0.983
	1.389	0.477	0.543	2.076	0.014	0.895	2.211	0.029	1.223
	1.584	0.258	0.623	2.666	0.313	1.273	2.178	0.029	1.256
	1.993	0.279	0.514	2.108	0.132	0.94	2.271	0.097	1.159
	1.714	0.228	0.635	2.557	0.086	0.785	1.839	0.119	1.237
	1.212	0.11	0.407	2.315	0.111	0.653	1.869	0.117	1.236
	1.588	0.449	0.398	2.366	0.037	0.907	2.086	0.054	1.245
Avg	1.576133	0.303533	0.621933	2.3658	0.155867	1.170733	2.064067	0.067733	1.2738
StDev	0.186739	0.124052	0.242595	0.209686	0.129692	0.464384	0.192566	0.088034	0.327473
% of Inhibition	**80.8**		**60.6**	**93.5**		**49.8**	**96.8**		**38.3**

Overall Trial Data

	17T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.027	0.018	0.018	295.48	470.38	470.38
	Trial 2	0.032	0.022	0.026	309.30	419.71	453.86
	Trial 3	0.019	0.025	0.027	387.42	283.94	358.88
	PreAvg	**0.026**	**0.022**	**0.023**	**330.74**	**391.34**	**427.71**
	PreStDev	0.007	0.004	0.005	49.576	96.402	60.179
Post	Trial 4	0.013	0.030	0.013	480.11	395.72	504.07
	Trial 5	0.037	0.034	0.013	464.41	368.78	504.07
	Trial 6	0.024	0.030	0.009	425.90	495.72	420.62
	PostAvg	**0.024**	**0.031**	**0.012**	**456.81**	**420.07**	**476.26**
	PostStDev	0.012	0.003	0.002	27.895	66.880	48.182

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.75	0.468	0.046	2.633	0.013	0.64	1.006	0.049	0.28
	1.79	0.75	0.031	1.887	0.018	0.702	1.078	0.032	0.693
	1.8	0.723	0.172	2.33	0.005	0.66	0.833	0.099	0.67
	1.529	0.557	0.083	1.885	0.008	1.135	0.993	0.006	0.186
	1.614	0.822	0.099	2.05	0.008	0.927	1.016	0.054	0.297
	1.563	0.767	0.193	2.2	0.009	0.544	0.895	0.007	0.637
	2.059	0.728	0.052	2.267	0.007	0.642	1.023	0.005	0.315
	2.179	0.84	0.074	2.692	0.012	1.569	0.88	0.035	0.247
	1.989	0.672	0.178	1.925	0.021	1.685	0.796	0.099	0.288
	1.985	0.721	0.068	2.193	0.013	1.652	0.55	0.005	0.326
	1.648	0.916	0.089	2.309	0.007	1.273	0.747	0.005	0.374
	2.132	0.211	0.183	2.762	0.018	0.796	1.052	0.036	0.311
	1.402	0.874	0.07	2.378	0.082	1.012	0.75	0.009	0.854
	1.219	0.796	0.111	2.676	0.013	0.906	0.856	0.008	1.113
	1.696	0.681	0.067	2.604	0.059	0.798	1.105	0.032	0.558
Avg	1.757	0.701733	0.101067	2.3194	0.019533	0.996067	0.905333	0.032067	0.4766
StDev	0.275143	0.178059	0.05411	0.302568	0.021636	0.385213	0.153746	0.032037	0.266513
% of Inhibition	**60.1**		**94.3**	**99.2**		**57.1**	**96.5**		**47.3**

Overall Trial Data

	18T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.027	0.018	0.018	295.48	470.38	470.38
	Trial 2	0.032	0.022	0.026	309.30	419.71	453.86
	Trial 3	0.019	0.025	0.027	387.42	283.94	358.88
	PreAvg	**0.026**	**0.022**	**0.023**	**330.74**	**391.34**	**427.71**
	PreStDev	0.007	0.004	0.005	49.576	96.402	60.179
Post	Trial 4	0.013	0.030	0.013	480.11	395.72	504.07
	Trial 5	0.037	0.034	0.013	464.41	368.78	504.07
	Trial 6	0.024	0.030	0.009	425.90	495.72	420.62
	PostAvg	**0.024**	**0.031**	**0.012**	**456.81**	**420.07**	**476.26**
	PostStDev	0.012	0.003	0.002	27.895	66.880	48.182

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.75	0.468	0.046	2.633	0.013	0.64	1.006	0.049	0.28
	1.79	0.75	0.031	1.887	0.018	0.702	1.078	0.032	0.693
	1.8	0.723	0.172	2.33	0.005	0.66	0.833	0.099	0.67
	1.529	0.557	0.083	1.885	0.008	1.135	0.993	0.006	0.186
	1.614	0.822	0.099	2.05	0.008	0.927	1.016	0.054	0.297
	1.563	0.767	0.193	2.2	0.009	0.544	0.895	0.007	0.637
	2.059	0.728	0.052	2.267	0.007	0.642	1.023	0.005	0.315
	2.179	0.84	0.074	2.692	0.012	1.569	0.88	0.035	0.247
	1.989	0.672	0.178	1.925	0.021	1.685	0.796	0.099	0.288
	1.985	0.721	0.068	2.193	0.013	1.652	0.55	0.005	0.326
	1.648	0.916	0.089	2.309	0.007	1.273	0.747	0.005	0.374
	2.132	0.211	0.183	2.762	0.018	0.796	1.052	0.036	0.311
	1.402	0.874	0.07	2.378	0.082	1.012	0.75	0.009	0.854
	1.219	0.796	0.111	2.676	0.013	0.906	0.856	0.008	1.113
	1.696	0.681	0.067	2.604	0.059	0.798	1.105	0.032	0.558
Avg	1.757	0.701733	0.101067	2.3194	0.019533	0.996067	0.905333	0.032067	0.4766
StDev	0.275143	0.178059	0.05411	0.302568	0.021636	0.385213	0.153746	0.032037	0.266513
% of Inhibition	**60.1**		**94.3**	**99.2**		**57.1**	**96.5**		**47.3**

Overall Trial Data

	19T	EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.011	0.010	0.019	292.39	256.51	335.557
	Trial 2	0.006	0.023	0.016	213.24	305.47	269.233
	Trial 3	0.021	0.012	0.014	262.89	308.11	291.088
	PreAvg	**0.012**	**0.015**	**0.016**	**256.17**	**290.03**	**298.63**
	PreStDev	0.008	0.007	0.003	40.000	29.060	33.798
Post	Trial 4	0.005	0.014	0.012	224.149	290.46	361.16
	Trial 5	0.009	0.010	0.011	329.283	333.15	433.09
	Trial 6	0.004	0.010	0.011	353.474	391.91	365.98
	PostAvg	**0.006**	**0.011**	**0.011**	**302.30**	**338.51**	**386.74**
	PostStDev	0.003	0.002	0.001	68.755	50.940	40.213

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	1.802	0.038	1.012	1.094	0.004	0.913	0.755	0.008	0.821
	1.714	0.043	0.902	1.423	0.004	0.744	0.921	0.006	0.368
	1.524	0.038	1.144	1.124	0.006	0.673	1.198	0.006	1.086
	1.842	0.038	0.857	1.459	0.006	0.977	0.949	0.004	0.486
	1.439	0.042	0.967	1.544	0.005	1.401	0.919	0.005	0.454
	1.919	0.04	1.237	1.104	0.005	1.442	1.031	0.006	0.84
	1.87	0.045	1.049	1.538	0.006	1.222	1.006	0.007	0.857
	1.569	0.044	1.117	1.547	0.007	0.801	0.866	0.008	0.897
	2.022	0.047	1.169	1.103	0.005	0.563	1.017	0.005	1.305
	1.643	0.044	1.037	1.5	0.005	0.817	0.892	0.006	0.955
	2.191	0.048	1.13	1.285	0.003	0.826	0.978	0.006	0.724
	1.938	0.044	0.907	1.27	0.006	0.947	1.086	0.007	0.892
	2.242	0.04	0.959	1.559	0.008	1.152	1.111	0.005	1.253
	1.52	0.04	1.035	1.381	0.004	1.14	0.952	0.006	0.581
	2.095	0.042	1.021	1.147	0.006	0.686	1.203	0.006	0.581
Avg	1.822	0.0422	1.0362	1.338533	0.005333	0.9536	0.992267	0.006067	0.806667
StDev	0.251775	0.003189	0.108051	0.185961	0.001291	0.266212	0.121994	0.0011	0.279692
% of Inhibition	**97.7**		**41.2**	**99.7**		**28.8**	**99.4**		**18.8**

Overall Trial Data

	20T						
		EMD1	EMD2	EMD3	RFD1	RFD2	RFD3
Pre	Trial 1	0.031	0.041	0.026	150.13	141.57	145.971
	Trial 2	0.037	0.034	0.028	99.22	133.94	178.968
	Trial 3	0.048	0.047	0.028	119.04	135.45	153.341
	PreAvg	**0.039**	**0.041**	**0.027**	**122.79**	**136.99**	**159.43**
	PreStDev	0.009	0.006	0.001	25.663	4.037	17.320
Post	Trial 4	0.039	0.054	0.033	61.240	171.52	209.71
	Trial 5	0.033	0.030	0.006	136.140	145.02	194.18
	Trial 6	0.039	0.026	0.021	133.772	186.23	136.04
	PostAvg	**0.037**	**0.036**	**0.020**	**110.38**	**167.59**	**179.98**
	PostStDev	0.003	0.015	0.014	42.576	20.880	38.832

	EPI1		PRD1	EPI2		PRD2	EPI3		PRD3
	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H	TEST H	Cond H	Cond H
	2.48	0.038	0.488	1.732	0.016	0.643	1.988	0.055	0.977
	2.366	0.046	0.658	1.978	0.081	0.858	2.208	0.104	1.263
	2.52	0.081	0.71	2.321	0.01	0.634	2.055	0.04	0.844
	2.278	0.058	0.751	2.016	0.038	0.596	2.041	0.106	1.127
	2.014	0	0.837	2.228	0.05	0.811	1.888	0.044	1.101
	2.402	0.059	1.15	2.291	0.006	0.714	2.469	0.04	1.023
	1.996	0.044	0.886	2.314	0.026	0.798	2.036	0.042	1.079
	2.281	0	0.977	1.968	0.056	0.634	2.693	0.043	1.524
	1.76	0	0.76	1.877	0.036	1.079	2.037	0.061	0.869
	1.857	0	0.612	1.905	0.042	0.894	2.1	0.05	1.628
	2.585	0.018	1.239	1.885	0.004	0.847	2.36	0.065	1.435
	2.562	0.028	0.68	2.216	0.038	0.502	2.039	0.027	1.415
	2.346	0.047	0.981	2.122	0.028	0.831	2.407	0.107	1.257
	2.68	0.306	1.119	2.144	0.13	0.533	2.315	0.037	1.357
	2.095	0.042	1.021	2.358	0.022	0.696	2.464	0.119	1.289
Avg	2.281467	0.051133	0.857933	2.090333	0.038867	0.738	2.206667	0.062667	1.212533
StDev	0.279249	0.074833	0.218385	0.195906	0.032445	0.154771	0.230552	0.030558	0.235155
% of Inhibition	**97.5**		**63.2**	**98.2**		**64.7**	**97.2**		**45.1**

APPENDIX THREE: REVIEW OF LITERATURE

Introduction to Whole Body Vibration

Vibration in various forms has been a topic of interest to exercise science researchers for many of years. In the 1960's – 70's, high frequency vibration was used as a research method to study the actions of muscle spindles (De Gail et al. 1966; Desmedt and Godaux 1978). Vibration was studied at first through the use of electromagnetic vibration (Desmedt and Godaux 1978) and was explored again in 2003 (Jackson and Turner 2003). Vibration research then moved to studying direct vibration or manual vibration applied to a tendon or muscle belly using a probe in both animals and humans (Bongiovanni and Hagbarth 1990; Bongiovanni et al. 1990; De Gail et al. 1966; McCloskey et al. 1972). However, vibration in the past has also been considered an occupational hazard, and therefore was studied as a phenomenon which was harmful to one's health (Cardinale and Pope 2003), such as the excessive torque placed on the spine due to vibration (Seroussi et al. 1989). Other studies have considered vibration as a means of rehabilitation for such ailments as lower back pain and osteoporosis (Rittweger et al. 2002b; Verschueren et al. 2004). Although much research on vibration at high frequencies has been completed in the past, only recently vibration at lower frequencies has been considered to improve muscular performance, such as explosive arm movements utilized by boxers (Bosco et al. 1999; Issurin and Tenenbaum 1999).

The research has moved to studying more specific muscle adaptation. Researchers more recently explored weight training where a weight, cable, and pulley machine was modified by transmitting vibration into the cable, to look at muscle adaptations (Bosco et al. 1999; Issurin et al. 1994; Issurin and Tenenbaum 1999). Vibration has also been

observed where subjects were seated and the vibration treatment was given through the seat (Ando and Noguchi 2003; Seroussi et al. 1989). The positive findings in vibration research have led to more recent studies focused on using vibration as an exercise method. More specifically, whole-body vibration (WBV) using a vibration platform is being researched as a possible training tool for athletes and others to train and exercise.

Whole body vibration (WBV) uses a method that exposes the entire body to mechanical vibrations as the individual stands on a vibrating platform (Mahieu et al. 2006). Mechanical stimulations, characterized by direction, amplitude, velocity, and frequency, are transmitted through the entire body. Recently, the whole-body vibration(WBV) training has gained much attention and has been used among athletes as a part of their exercise program (Cardinale and Wakeling 2005; Cochrane et al. 2004) The potentially beneficial effects of WBV are induced by the transmission of mechanical, sinusoidal vibrations throughout the body via the feet when standing on an oscillating platform (Abercromby et al. 2007a; Abercromby et al. 2007b). The exercise devices currently available on the market deliver vibration to the whole body by means of oscillating plates using two different systems: (a) reciprocating vertical displacements on the left and right side of a fulcrum; (b) the whole plate oscillating uniformly up and down. The mechanical variables that determine its intensity are the frequency and amplitude (peak to peak displacement, in mm) of the vibration. The repetition rate of the cycles of oscillation determines the frequency of the vibration (measured in Hz).WBV exercise devices deliver vibrations across a range of frequencies (15-60 Hz) and displacement from <1 mm to 10 mm. The acceleration delivered can reach 15 g (where 1 g is the acceleration due to the Earth's gravitational field or 9.81 m/s²). The methodology of

vibration training includes the vibration characteristics and exercise protocol. Vibration characteristics include the method of vibration application, vibration amplitude and vibration frequency. The intensity of the vibration load on the neuromuscular system is determined by the vibration amplitude and frequency (Mester J 2002). The exercise protocol includes the type of exercise, training intensity, training volume, number of duration of rest period and frequency of training (Luo et al. 2005).

There are two methods of applying vibration to the human body during exercises. In the first method, vibration is applied directly to the muscle belly (Curry and Clelland 1981; Jackson and Turner 2003; Warman et al. 2002) or the tendon (Bongiovanni et al. 1990) of the muscle being trained, by a vibration unit that may either be held by hand or be fixed to an exterior support (Jackson and Turner 2003; Warman et al. 2002). In the second method, vibration is applied indirectly to the muscle being trained, i.e. the vibration is transmitted from a vibrating source away from the target muscle, through part of the body to the target muscle (Delecluse et al. 2003; Issurin et al. 1994). For example, during the training of the quadriceps, the subject may stand on a vibrating platform that oscillates up and down in the vertical direction and perform various exercises (such as squatting). The vibration is transmitted from the vibrating platform through the lower extremities to the quadriceps (Delecluse et al. 2003; Torvinen et al. 2002a; Torvinen et al. 2002b). This method has been termed “whole body vibration training” (Delecluse et al. 2003). As another example, during the training of the biceps brachii, the subject may grasp a vibrating handle while performing a bicep curl exercises (Issurin 2005).The key differences in these methods is the magnitude of amplitude and frequency of the original vibration that reaches the target muscle (Luo et al. 2005) It has been suggested that with

direct vibration, the amplitude and frequency does not differ notably from the reported values measured at the vibration source (Curry and Clelland 1981; Issurin 2005; Jackson and Turner 2003). In contrast, it has been known that with indirectly applied vibration, the amplitude and frequency may be attenuated in a non-linear manner by soft tissues during transmission of the vibration to the target muscle (Mester J 2002).

The possibility of using vibrations as an exercise intervention is a relatively recent idea. The first application of vibration as an exercise intervention was conducted by Russian scientists, who found that vibration was effective in enhancing strength in well-trained subjects (Issurin et al. 1994; Issurin and Tenenbaum 1999). Subsequently, the effects of vibration exercise have been examined after acute and chronic exposure using different protocols.

Acute Effects of WBV

The acute effect of WBV on the muscular properties has been documented by previous studies. Bosco et al. (Bosco et al. 1999) revealed that a single whole body vibration bout resulted in a significant increase in muscle strength of the arm flexors and lower extremities. Cardinale and Pope (Cardinale and Pope 2003) investigated the effects of two different frequencies (20 Hz and 40 Hz) of acute WBV on flexibility and squat jump in 15 untrained subjects. The result of the study showed that 5 min of low frequency (20 Hz) WBV stimulation significantly increased hamstrings' flexibility by 10% and squat jump by 4%. The authors speculated that the untrained subjects in the presented study, showed acute enhancement in neuromuscular performance with low-frequency WBV stimulation (Cardinale and Pope 2003). Cochrane et al. (Cochrane and Hawks 2007) measured arm countermovement vertical jump (ACMVJ), grip strength, and flexibility performance in 18 female elite field hockey players before and after a 5-

min of WBV (26Hz) stimulation. The authors concluded that acute WBV causes neural potentiation of the stretch reflex as shown by the improved ACMVJ and flexibility performance. Additionally, muscle groups less proportionally exposed to vibration do not exhibit physiological changes that potentiate muscular performance (Cochrane and Hawks 2007).

The acute effect of WBV on the muscular performance related variables has been documented. Recently, two studies by Rittweger et al. and Ruiter et al. have demonstrated acute effects of WBV on the muscular performance as measured with vertical jump, maximal isometric force and maximal force rise time. Rittweger et al. assessed jump height, ground contact time, and tendon reflex before and after WBV stimulation in 19 healthy young volunteers (Rittweger et al. 2003). After squatting exercise, the subjects who performed the squatting exercise on the vibration platform had greater tendon reflex amplitude and the vastus lateralis mean frequency during isometric torque. The authors speculated that superimposed 26 Hz vibration appears to elicit an alteration in neuromuscular recruitment patterns, which apparently enhance neuromuscular excitability (Rittweger et al. 2003). Ruiter et al. investigated the effects of 5x1 min vibrations (frequency 30 Hz, amplitude 8 mm) with 2 min rest between and showed that after the acute WBV, maximal isometric force production (MVC) and maximal rate of force rise (MRFR) of the knee extensors increased.

The acute effects of WBV on joint position sense have been reported. Fontana et al. showed that the experimental group that had performed 5 minutes of WBV between pre and post joint position sense test demonstrated 39% improvements in lumbosacral repositioning accuracy (Fontana et al. 2005). The acute effect of WBV not only on the

muscular performance but also on the body balance has been investigated. Torvinen et al. showed a transient 2.5% net benefit in the jump height, 3.2% benefit in the isometric extension strength of lower extremities and 15.7% improvement in the body balance (Torvinen et al. 2002b). The authors concluded that a single bout of whole body vibration transiently improves muscle performance of lower extremities and body balance in young healthy adults (Torvinen et al. 2002b).

Individuals with neuromuscular impairment seem to benefit from acute bouts of WBV training. Unilateral chronic stroke patients, for example, have been shown to improve postural stability after a few minutes of WBV at 30 Hz and 3 mm amplitude (van Nes et al. 2004). Tihanyi et al. in their recent study with stroke patients have reported that six bouts of 1 minute whole body vibration treatment improved stroke patients' isometric and eccentric knee extension torque by about 36.6% and 22.2% (Tihanyi et al. 2007). The beneficial effect of acute WBV in patients with multiple sclerosis has been reported. Schuhfried et al. (Schuhfried et al. 2005) showed that five bouts of 1 min WBV improved the Sensory Organization Test and the Timed Get Up and Go Test scores in multiple sclerosis patients indicating that WBV may positively influence the postural control and mobility in multiple sclerosis patients (Schuhfried et al. 2005).

Despite these acute improvements in muscular performances after WBV training, it is important to recognize that not all studies have been shown acute increases in muscular performances. For example, recent work from de Ruiter et al, in which subjects exercised on a vibrating plate for five bouts of 1 min(frequency 30 Hz, amplitude 8 mm) with two minutes rest in between, showed an acute reduction in maximal voluntary knee

extension force (de Ruiter et al. 2003a). Also in their well controlled study, the authors showed that vibration depressed voluntary activation of the leg extensor muscles up to 180 minutes after the exercise bout (de Ruiter et al. 2003a). Finally, Torvinen et al. (Torvinen et al. 2002b) have shown acute increases in knee extension maximal strength and vertical jumping height after four minutes of WBV when a relatively large amplitude was applied (4 mm) as compared with no significant acute effects when low amplitude whole plate oscillation (2 mm) was applied.

Chronic Effects of WBV

Studies investigating the chronic effects of WBV seem to provide more supportive evidence for the possibility of using WBV training effectively in different populations. The various durations for chronic WBV has been shown ranging from 5 days to 24 weeks training period (Bogaerts et al. 2007; Bongiovanni et al. 1990; Bosco 1998; Cardinale 2003; Rittweger et al. 2003). Another study by Cardinale et al. (Cardinale and Pope 2003) performing 10 days of WBV (26Hz, 10 mm, total exposure time 100 minutes) showed an increase in average jumping height (+11.9%) and power output during repeated hopping in active subjects. Paradisis et al. (Paradisis 2007) investigated the effect of 6 week of WBV training on sprint running kinematics and explosive strength performance. The results of the study showed that performance in 10 m, 20 m, 40 m, 50 m and 60 m improved significantly after 6 week of WBV training with an overall improvement of 2.7%. The study also showed that the counter-movement jump height increased by.3.3%, and the explosive strength endurance improved overall by 7.8% (Paradisis 2007).

Torvinen et al. (Torvinen et al. 2002a) showed a net improvement of 8.5% in vertical jumping ability after four months of WBV training performed with static and dynamic squatting exercises with small vibration amplitudes (2 mm) and frequencies ranging from 25 to 40 Hz in sedentary subjects. However, the result of the study showed no improvement in the lower limb extension strength as well as grip strength, shuttle run and balance (Torvinen et al. 2002a). Delecluse et al. (Delecluse et al. 2003) showed that a 12 week WBV training program (frequency 35-40 Hz and amplitude 2.5-5 mm) induced a significant enhancement in isometric, dynamic, and explosive strength of knee extensor muscles in healthy, untrained, young adult women (Delecluse et al. 2003).

During recent years, relatively long-term effects of WBV have been reported. Roelants et al. (Roelants et al. 2004) showed that 24 weeks of WBVs were effective in producing a rightward shift in the force-velocity relation of knee extensor muscles and an increase in fat-free mass in untrained female subjects (Roelants et al. 2004). Both Delecluse et al. and Roelants et al. highlight the possibility that long term programs of WBV may produce significant improvements in muscle function of the leg extensors in untrained subjects (Delecluse et al. 2003; Roelants et al. 2004). As more supportive evidence, a recent study from Verschueren et al. (Verschueren et al. 2004) showed that WBV program was superior to a low intensity resistance training program in improving isometric and dynamic muscle strength in middle aged and older women (58-74 years). The WBV training program was also effective in increasing bone mineral density of the hip even though the improvement was very small (0.93%) and within the error of measurement used for establishing bone mineral density. Finally, Torvinen et al. (Torvinen et al. 2003)have shown that eight months of WBV with small amplitude (2

mm) improved vertical jumping ability in young healthy sedentary subjects compared with a control group, but did not change dual energy x-ray absorptiometry derived bone mineral content measures, markers of bone turn over, and postural sway (Verschueren et al. 2004). Contrast to the study by Torvinen et al., in a study by Gusi et al., after 8 months of WBV training (12.6 Hz, 3 cm amplitude and 3 sessions per week), bone mineral density at the femoral neck in the increased by 4.3% compared to the control group (Gusi et al. 2006).

Similarly to the conflicting results of WBV on the muscular performances, the chronic effects of WBV observed in the previous studies seem to produce conflicting results. Bosco et al. (Bosco 1998) showed that 10 days of WBV (26 Hz, 10 mm, total exposure time 100 minutes) resulted in an increase in average jumping height (11.9%) and power output during repeated hopping in active subjects, however, in the study no change was observed in counter movement jump performance (Bosco 1998). de Ruiter et al. also showed that five training sessions of five minutes each (30 Hz, 8 mm amplitude, total exposure 25 minutes) did not affect maximal voluntary contraction and voluntary activation of leg extensors in untrained students (de Ruiter et al. 2003a). de Ruiter et al. also analyzed the effects of 11 weeks of WBV training on maximal voluntary contraction measured with an isometric leg extension task (maximal voluntary contraction), maximal force generating capacity, and stimulated maximal rate of force rise (de Ruiter et al. 2003b). The results showed no change in all variables except for an increase in stimulated maximal force rise in the group undergoing WBV training detected at week 14 (de Ruiter et al. 2003b). Nine days of WBV training have also been recently shown to have no effect

on jumping ability, sprinting, and agility tests in sports science students (Cochrane et al. 2004).

As reviewed above, many studies have shown performance increases after WBV training. However, some of the studies didn't show any changes in muscular performances. Based on these findings, it is likely that the short-term and long-term effects of vibration on the muscular performances seem to be affected by the vibration training methodology, which includes vibration characteristics (vibration amplitude, vibration frequency, duration, and the method of vibration application) and exercise protocols (type of exercise, intensity and volume of exercise). However, while it seems that WBV might be an effective modality to enhance muscular performances, the inconsistency in experimental protocols within the current published studies makes comparison of study outcomes difficult and consequently, the proper prescription of WBV and its mechanisms remain unknown. Nevertheless, improper control, differences in population, differences in vibration frequency, amplitudes, and duration, lack of or use of a warm up, and different exercise positions may explain the discrepancies in the results.

Vibration Characteristics

Vibration frequency

Most WBV platform devices are made to vibrate using oscillating motion in an up and down direction. Frequency is the rate of reoccurrence of oscillations (Rittweger et al. 2000). Originally vibration was studied at high frequencies (60-300 Hz). For instance, one study observed effects of vibration at a frequency of 150 Hz. Two minutes of vibration did stimulate a tonic vibration reflex, but also decreased muscle electromyography (EMG) activity and maximal voluntary contraction (Bongiovanni et al.

1990). In a study of adult cats, where direct vibration at frequencies of 100-200 Hz was applied to the triceps surae of hind limbs, no reflex contractions or muscle spindle afferents were significantly activated (McCloskey et al. 1972). Another study observed vibration effects at low frequencies (< 50 Hz) and found tonic contraction to reach maximum within 30 – 60 seconds with progressive increase of frequency (De Gail et al. 1966). However, the tonic contraction began to decrease at frequencies above 50 Hz (De Gail et al. 1966).

Cardinale and Lim compared the effects of 20 Hz and 40 Hz WBV frequency (4 mm amplitude, five minutes) on squat jump (SJ) and counter movement jump (CMJ) performances. A 4% increase in SJ at 20 Hz was observed, while decrements in SJ and CMJ were associated with the 40 Hz stimulus. Cochrane and Stannard (Cochrane and Stannard 2005) used five minutes of 26 Hz, 6 mm WBV to enhance CMJ height by 8.1%. Most recently, Comie et al. (Comie 2006) found a small but significant increase in CMJ height after only a single WBV bout (30Hz, 2.5 mm) of 30 sec. Bosco et al. (Bosco 1998) reported the effect of a 10 day training program of a daily series (5 bouts, 90 sec) of vertical sinusoidal vibrations at a frequency of 26 Hz. They found a significant improvement of the height and mechanical power during the 5-s continuous-jumping test. Runge et al. (Runge et al. 2000) showed gains of 18% in chair rising time in elderly person after 12 weeks WBV training (27Hz). Recently, Torvinen et al. (Torvinen et al. 2002b) reported a significant increase in jump performance (8.5%) and a nonsignificant increase in isometric limb extension strength (2.5%) after a 4-month WBV intervention (25Hz-30Hz) in young nonathletic adults. A recent study by Roelants et al. used a vertical vibration stimulus to examine the effect of a 20 s exposure of a 35 Hz, 2.5 mm vibration.

The result of the study demonstrated that WBV led to significant increases in EMG in all muscles during all squat positions (high, low, and one legged squat). According to the results of the study, during the high squat, WBV resulted in increases between 92.5 % and 301% when compared with the control condition.

The effect of low frequency on the neuromuscular system (joint position sense, Hoffmann reflex) has been assessed by recent studies. Fontana et al. in their current study showed that a single session of five minutes WBV (18 Hz) significantly improved in repositioning accuracy of pelvic tilting in standing (Fontana et al. 2005). Recently, Nishihara et al. (2002) investigated the effect of WBV on motoneuron excitability. The study used 3 sets of 25 Hz WBV with a set interval 10 minutes. The result of the study demonstrated that WBV with a low frequency increased motoneuron excitability as measured with H/M ratio. The results of the above studies suggest that low-frequency (20 – 35Hz) vibration may have a greater effect in vibration training. Based on the findings of the previous studies, it can be concluded that the range of frequency (18Hz to 35Hz) for WBV training appear to have an effect on the muscular performance. However, relatively high frequency (40Hz to 50Hz) appears to have negative effects on the muscular performances.

Vibration Amplitude

Amplitude on WBV platform refers to the magnitude of oscillation, usually given in millimeters (Rittweger et al. 2002b). The vibration component of amplitude has not been exclusively studied. One study compared a vibration treatment at constant frequency but at different amplitudes. The results showed greater VO2 increases between amplitudes of 2.5-7.5 mm (Rittweger et al. 2002b). The most common amplitude used in

WBV is the amplitude less than10 mm (Bosco 1998; Rittweger et al. 2000; Torvinen et al. 2003). Another common WBV amplitude is 6 mm (Bosco 1998; Rittweger et al. 2000; Rittweger et al. 2002a; Rittweger et al. 2002b; Rittweger et al. 2003; Torvinen et al. 2003), while other studies range in amplitudes from 1-8 mm (Bosco et al. 2000; de Ruiter et al. 2003a; de Ruiter et al. 2003b; Roelants et al. 2004; Torvinen et al. 2002a; Torvinen et al. 2002b).

Two studies by Torvinen et al. (Torvinen et al. 2002a; Torvinen et al. 2002b) were identical except for the vibration amplitude (4 mm and 1 mm) employed. Therefore, comparison of their findings provides insights into the influence of vibration amplitude on vibration training effect. In both studies, subjects received a 4 minutes whole body vibration training session in which light exercises (e.g. light squatting, standing in erect position, standing with knee flexed, light jumping, standing on heels) were performed on the vibration platform. EMG activity was measured on calf muscles and thigh muscles during the vibration training process, but was not measured in the sham-vibration condition. Therefore, while it is not possible to determine the absolute effect of vibration training on EMG activity, it is possible to examine the relative effect of vibration amplitude on muscle EMG response by comparing these studies. Both of the above studies measured the change of EMG activity on the soleus and vastus lateralis muscles during the 4 minute vibration training process (Torvinen et al. 2002a; Torvinen et al. 2002b). The larger vibration amplitude (4 mm) induced a significant decrease of mean power frequency of EMG on both muscles (soleus: 18.8%; vastus lateralis: 8.6%) and a significant increase of EMG in the soleus muscle (21.6%), from the first minute to the fourth minute of the training process. The latter finding was suggested to be indicative of

more pronounced muscle fatigue on soleus muscle (Torvinen et al. 2002b). In contrast to this study, there was no significant change of these EMG parameters on either muscle in the study with the smaller vibration amplitude (1 mm) during the 4-minute training process (Torvinen et al. 2002a). These results suggest that the larger vibration amplitude was more able to activate both muscles during training and thus induced more pronounced muscle fatigue. In addition, the results of the study showed that only the vibration with the larger amplitude (4 mm) induced a significantly larger increase in MVC strength and jump height than the sham-vibration group (Torvinen et al. 2002a; Torvinen et al. 2002b).

These results support the postulates that the whole body vibration with larger amplitude may activate the leg muscles more effectively, inducing a residual effect on MVC strength and jump height. The authors also suggest that the vibration amplitude may have to be of a sufficient threshold level in order to effectively activate the muscle being trained. A study by Rittweger et al. (Rittweger et al. 2003) also indicated that the enhancement of central motor excitability was elicited by whole body vibration with sufficient amplitude (6 mm). Although these findings discussed above were from the studies that investigated the acute effects of WBV training on muscular performances, it seems reasonable to speculate that these finding are likely to be equally applicable to chronic-based adaptations, as chronic adaptations are reflective of acute responses. However, to date, there are no studies have directly examined this.

Vibration Duration

Duration of vibration is also a factor that should be considered in examining the effect of vibration training. It has been suggested that its influence should be analyzed in

conjunction with the point of time when the neuromuscular performances was evaluated (Luo et al. 2005). The duration of exercises with applied vibration varies among studies, ranging from only 5 seconds (Curry and Clelland 1981; Humphries 2004; Issurin et al. 1994) to 30 minutes (Jackson and Turner 2003) in each set, and with different numbers of sets employed, ranging from one set (Bongiovanni et al. 1990; Rittweger et al. 2003; Torvinen et al. 2002a; Torvinen et al. 2002b) to several session (de Ruiter et al. 2003b; Delecluse et al. 2003; Issurin and Tenenbaum 1999). Many studies have looked at acute or short-term vibration responses where the total vibration treatment consists of 10 sec - 10 minutes of vibration exposure (Bosco 1998; Bosco et al. 2000; Cardinale and Pope 2003; Torvinen et al. 2002a; Torvinen et al. 2002b). Bosco et al. (Bosco et al. 2000) used a WBV session consisting of 10, 60 sec exposures, with 60 sec rest between, and an additional six minutes of rest after the fifth exposure, resulting in an enhancement of counter movement jump (CMJ) height. In a study by Torvinen et al. (Torvinen et al. 2002b) a 2.5% improvement in vertical jump height at two minutes following vibration was found using a four minute WBV session (four, one minute intervals with one minute rest). In a recent study by Luo et al, it has been hypothesized that if vibration stimulation is short in duration, resulting in the measurement of neuromuscular capacity without fatigue, any enhancement is indicative of an increase in neuromuscular performances by vibration stimulation (Luo et al. 2005).

Other researchers have looked at the effects of WBV when the subjects stand or do exercises on a vibration platform until exhaustion (Rittweger et al. 2000; Rittweger et al. 2003) with relatively similar range of duration (3 to 10 minutes). In a study by Bosco et al. (Bosco et al. 1999), the results showed that when vibration duration is relatively

long (seven minutes), an acute decrease in vertical jumping ability is observed even in well trained subjects(Bosco et al. 1999). Recent work from de Ruiter et al. (de Ruiter et al. 2003a) in which subjects exercised on a vibrating plate for 5 sets of one minute with two minutes rest in between showed an acute reduction in maximal voluntary knee extension force. (de Ruiter et al. 2003a). According to Luo et al, with increases in the duration of vibration, fatigue will become more predominant (Luo et al. 2005). In the study of Samuelson et al. (Samuelson et al. 1989) subjects performed sustained maximal knee extension until exhausted. The time to exhaustion decreased significantly by 30% in the vibration condition compared with a control group. Also in a study by Bongiovanni et al. (Bongiovanni et al. 1990), subjects were asked to maintain their maximal contraction for 1 minute. The results showed that the decline of the maximal isometric force measured at the end of the 1 minute contraction was significantly greater (13%; $p<0.05$) when vibration was applied. These findings indicate that vibration could accentuate the muscle fatigue of sustained maximal contractions. Bongiovanni et al. in their study suggested that vibration had a suppression effect that increased gradually with the sustained vibration on motor output of maximal voluntary contractions. This suppression effect mainly decreased the subject's ability to generate high firing rates in high threshold motor units (Bongiovanni et al. 1990). Therefore, it is hypothesized that prolonged vibration decreases the neuromuscular performance of maximal voluntary contraction by inhibiting motor units from recruitment, rather than by fatiguing the motor units by recruitment (Bongiovanni et al. 1990).

Recently, regarding the effects of duration of WBV training, some of possible negative effects of prolonged WBV duration has been reported (Abercromby et al.

2007b). It has been well accepted that chronic whole body vibration, which is unintentional vibration exposure resulting from an individual's chosen occupation has been reported to have a number of negative side effects that are known to disturb normal physiology and structure in the back, digestive, reproductive, visual, and vestibular systems (Bovenzi 2005; Lings and Leboeuf-Yde 2000; Seidel 1993) These studies which reported the negative effects of prolonged WBV also suggested that high magnitude vibration for prolonged duration might cause intervertebral disc displacement, spinal vertebrae degeneration, and osteoarthritis (Bovenzi 2005; Lings and Leboeuf-Yde 2000; Seidel 1993) and vibration that is transmitted through the spinal column to the head may induce hearing loss, visual impairment, vestibular damage, and can even induce brain hemorrhaging at very high vibration magnitude with prolonged duration (Griffin 1996; Ishitake et al. 1998). Abercromby et al. in their recent study evaluating the comparing the risk of negative side effects for a given dose of WBV training (30 Hz, 4 mm, 10 min/d) suggested that 10 minute of WBV (30 Hz, 4 mm) exceeds the recommended daily vibration exposure as defined by ISO 2631-1 (Abercromby et al. 2007b). The result of the study indicated that the least hazardous WBV training protocols are theoretically those involving low mechanical impedance, low head acceleration, and low estimated vibration dose value which is calculated using direction, frequency, magnitude, and duration of the vibration applied to a human body (Abercromby et al. 2007b)., although such conditions are not necessarily the most effective in terms of inducing the desired training outcome (Abercromby et al. 2007b). The authors also suggest that short-duration exposures to rotational (horizontal) at small knee flexion angles (26 - 30º) have the lower risk of

negative side effects on the basis of head acceleration and mechanical impedance (Abercromby et al. 2007b).

In conclusion, previous studies vary widely in frequency (17-60Hz), amplitude (1-10 mm), and duration (10 sec – 30 minutes), possibly the inconsistent results in performance and making it difficult to identify the most effective vibration prescription. Without correct recommendations (frequency, amplitude and duration), WBV over exposure could lead to injury (Abercromby et al. 2007b; Jordan 2005) and insignificant exposure may not elicit sufficient training effects. Throughout the review of previous studies, it has been hypothesized that low frequency (20 to 25 Hz), relatively low amplitude (4 to 6 mm), and short duration is a safe and effective WBV training protocols (Abercromby et al. 2007b; Cardinale and Pope 2003; Fontana et al. 2005). However, future research should focus on identifying optimal vibration amplitudes and frequencies for training based on the method of vibration application (direct or indirect), and the type, intensity and duration of exercise.

Proposed Neural Mechanisms of WBV

It has been suggested that the effects of WBV on muscle performance are elicited via reflex muscle activation leading to "neurogenic adaptation" (Rittweger et al. 2000). Indeed, early studies, most of which used tendon vibration showed a vibration-induced increase in muscle activation, a so-called tonic vibration reflex (TVR) which involves the activation of muscle spindle afferents resulting in increased discharge and enhanced neural drive (Burke et al. 1976; Gillies et al. 1971; Issurin et al. 1994). To understand the mechanisms responsible for vibration-induced enhancement of performance, it is necessary to distinguish between the effects of vibration when the vibration is delivered to the body directly (tendon vibration) and indirectly (WBV).

Although there is a lack of strictly controlled studies, the available studies on WBV training to date still allow us to make some conclusions about the mechanism of this new training method (Delecluse et al. 2003; Roelants et al. 2004; Sale 1992). Specifically one of the theoretical mechanisms for enhancement of neuromuscular system after WBV training is neural adaptation related to increased muscle activation caused by augmented excitability input from muscle spindles exposed to a vibration (Abercromby et al. 2007a). To better understand this theoretical mechanism of WBV, it is important to review the early tendon vibration studies that describe the characteristics of TVR.

Tonic Vibration Reflex (TVR)

Bishop et al. in their early study identified two very important motor effects resulted from vibrating a muscle (Bishop 1974). First, the vibrated muscle actively contracts. This sustained contraction is known as the tonic vibration reflex or TVR(Bishop 1974). Secondly, they found that the excitability of motoneurone innervating the antagonistic muscles is depressed via reciprocal inhibition (De Gail et al. 1966; Hagbarth et al. 1976; Hagbarth 1976)Regarding TVR, the authors indicated three experimental evidences that support the fact that the sustained muscle contraction evoked by vibration is a reflexly mediated response (Eklund 1965; Hagbarth et al. 1976; Hagbarth 1976; Lance 1966). First evidence is that a denervated muscle has no TVR. The authors suggest that after cutting a muscle nerve, the TVR of that muscle is abolished; hence, the TVR cannot be the result of any direct effect of the vibration on the muscle (Eklund 1965; Hagbarth et al. 1976; Lance 1966). The second evidence why TVR is a reflexly mediated response is that a deafferentated muscle has not TVR. The authors suggest that after appropriate dorsal roots are sectioned, the TVR is abolished. This

observation shows that sensory input is essential for the response. Lastly, the third experimental evidence is that a TVR is suppressed by vibration of an antagonistic muscles (Eklund 1965; Hagbarth et al. 1976; Lance 1966). Regarding this reciprocal inhibition, it has been known that if a repetitive electric shock is applied to the muscle nerve innervating the antagonistic muscle, the TVR of the muscle being vibrated is depressed or inhibited. It has been shown that this reciprocal inhibition exerted by sensory signals from the antagonistic muscle, therefore, acts on the same motoneuron pool as the sensory signals initiated by the vibratory stimulus (Bishop 1974). Based on the findings from these basic experiments, the effects of this reflex muscle activation on the muscular performances have been investigated. Boosco et al. have reported that an increase in EMG activity is usually observed during vibration treatment with values higher than the ones observed during voluntary muscular activity (Bosco et al. 1999). Accordingly, same investigators found the root mean square EMG of biceps brachii muscle to be 200% higher in boxers exercising with a vibrating dumbbell compared with performing a voluntary arm flexion with a load equal to 5% of the subjects' body mass (Bosco et al. 1999). The result of the study suggested that this enhancement might be related to an increased synchronization of motor units due to the application of vibration (Bosco et al. 1999).

Potential mechanisms for vibration-induced neuromuscular enhancement

It has been suggested that muscle activation by means of vibration may induce improvements in strength and power performance similar to those observed with strength training (Bosco 1998; Bosco et al. 1999). Researchers have suggested that the similarity of the effect is likely to be related to the characteristics of the load imposed by vibration,

which, as with strengthening and plyometric exercises, increase the gravitational load imposed on the neuromuscular system (Bosco 1998; Bosco et al. 1999; Bosco et al. 2000; Torvinen et al. 2002a). Skeletal muscle is a specialized tissue that modifies its overall functional capacity in response to different stimuli (Fitts 2001; Sale 1992). The influence of gravitational load on muscular performance is of paramount of importance. According to Fitts et al., in normal conditions, muscles experiencing the daily action of gravity are capable of maintaining their performance capabilities. When the gravitational load is reduced (microgravity), a marked decrease in muscle mass and force-generating capability is observed (Fitts 2001). In contrast, it has been suggested that an increase in the gravitational load (hyper-gravity) will increase in the cross sectional area and force-generating capacity of muscle (Fitts 2001). Exercise programs designed to increase strength and power are characterized by performing exercises with an increase in gravitational load. These forms of exercise have been shown to produce specific adaptive responses in skeletal muscles involving both morphological and neural factors attributable to the absence of an increase in cross-sectional area of muscle fibers in the first several week of training program.

Whole body vibration exercise imposes hyper-gravity activity due to the high accelerations (Bosco 1998; Bosco et al. 1999; Bosco et al. 2000). The mechanical action of vibration is to produce fast and short changes in the length of the muscle tendon complex (Torvinen et al. 2003). This perturbation is detected by the sensory receptors that modulate muscle stiffness through reflex muscular activity and attempt to dampen the vibratory waves (Issurin 2005; Issurin et al. 1994; Torvinen et al. 2003). As reviewed in the earlier section, mechanical vibrations applied to the muscle itself or the tendon can

elicit a reflex muscle contraction named “Tonic Vibration Reflex” (Bosco 1998; Cardinale and Pope 2003). The deformation of the soft tissue caused by vibration is capable of activating muscle spindles and leading to an enhancement of the stretch-reflex loop (Rittweger et al. 2000). Therefore, the excitatory inflow during vibration stimulation is mainly related to the reflex activation of the alpha motoneuron (Hagbarth et al. 1976). An increase in EMG activity is usually observed during vibration treatment with values higher than the ones observed during voluntary muscular activity (Bosco 1998).According to Bosco et al., this effect could be related to an increased synchronization of motor units due to the application of vibration. Reflex muscle activity represents the response of neuromuscular system to a strong perturbation caused by mechanical vibration(Bosco 1998). Ribot-Ciscar et al. stated that this reaction can be mediated not only by monosynaptic but also by polysynaptic pathways (Ribot-Ciscar 1989). The authors suggested that the primary endings of the muscle spindles are more sensitive to vibration than are the secondary endings and Golgi tendon organs and vibration is perceived not only by neuromuscular spindles, but also by the skin, the joints, and secondary endings (Ribot-Ciscar 1989). Consequently, whether using whole-body or locally applied vibration, these sensory structures likely facilitate the gamma system during the application of vibration and enhance the sensitivity of the primary endings (Ribot-Ciscar 1989).

The acute enhancement of neuromuscular performance after vibration is likely due to an increase in the sensitivity of the stretch reflex (Cardinale and Pope 2003). Furthermore, vibration appears to inhibit activation of antagonist muscles through Ia-inhibitory neurons, thus altering the intramuscular coordination patterns leading to a

decreased braking force around the joints stimulated by vibration (Bosco 1998; Cardinale and Pope 2003). For example, pilot data from a recent study by Cardinale et al. have shown that after the application of vibration there was both an increased vertical jump height and in increase in the range of motion about the hip joint due to improved flexibility of the hamstrings (Bosco 1998; Cardinale and Pope 2003). Based on the findings of this study, it is suggested that vibration might stimulate the proprioceptive discharge occurring during muscle stretch and fast joint rotation although the actual change in the above parameter is minimal (Naito 2000). It is also considered that the influence of vibratory stimulation on central motor command. It has been shown that the primary and secondary somatosensory cortex, together with the supplementary motor area, constitutes the central processing unit of afferent signals (Naito 2000). Vibration applied at different frequencies that is capable of producing kinesthetic illusion has been shown to activate the supplementary motor area, the caudal cingulated motor area, and area of the brain(Naito 2000). Moreover, the supplementary motor area of the brain that is activated by vibration is activated early during self-initiated movements (Cunnington 2002). The vibration stimulus then influences the excitatory state of the peripheral and central structures, which could facilitate subsequent voluntary movements (Torvinen et al. 2002b). The post-vibration enhancement of performance includes an increase an vertical jump height by 2.5 % in the first minute after 4 minute of the treatment, and increase in vertical jump by 3.8% after a total of 10 minutes whole-body vibration, and an increase of 13% in the average power recorded during arm flexion in well trained subjects after 5 minutes of locally applied vibration (Torvinen et al. 2002b). Based on the findings of their study, Torvinen et al. suggested that it is likely that the greater levels of force after

vibration are due to both an enhancement of the stretch reflex and the excitatory state of the somatosensory area (Torvinen et al. 2002b). Current evidence, however, does not allow an explanation of the specific neural adaptations that accompany a vibration treatment.

Recent evidence suggests that relatively short exposure, for example, is capable of enhancing subsequent voluntary strength exertion. Long duration vibration however, reduces the force-generating capacity of muscle (Rittweger et al. 2000). The long duration effect could be due to either activation of inhibitory feedback or reduced sensitivity of muscle spindles (Cardinale and Pope 2003). The vibratory stimulus, being perceived by different sensory structures, stimulates the neuromuscular system to produce reflex muscle activation(Issurin et al. 1994). If the vibratory stimulus is relatively short, it creates the potential for a more powerful and effective voluntary activation of skeletal muscle (Cardinale and Pope 2003). The relative significance of these different mechanisms could be assessed by examining the effect of vibration on various evoked responses, such as with trans-cranial magnetic stimulation and the H-reflex (Cardinale and Pope 2003). It has been suggested that the contributing intrinsic neural mechanism for the improvement in muscle function after WBV training might be due to vibration induced presynaptic inhibition(Bongiovanni et al. 1990; Rittweger et al. 2000). The neural modulation of presynaptic inhibition pathways is known to affect the recruitment of motor units for voluntary movements (Capaday and Stein 1987). It has been proposed that modulation of the reflex depression associated with the frequency of reflex activation would allow the facilitation provided by the spindle afferents to temporarily summate and contribute to the neural drive when loads are resisted during

voluntary movements (Trimble et al. 2000). Specifically, with respect to the training-induced improvement in muscle function, it has been documented that an increased central descending motor drive results in an increased motorneuron recruitment and firing rate, which increases the outflow of efferent motor impulses in the axons. Therefore, any increase in descending motor drive will produce an increased cencellation of the antidromic impulses, thus allowing more of the evoked H-reflex volley to reach the muscle fibers as manifested by an increase in V-wave amplitude (Aagaard et al. 2002).

It's also been further reported that an increased excitability of spinal motor neuron or reduced presynaptic inhibition of Ia afferents would contribute to the increase in V-wave amplitude which can be interpreted as an increased ability activate motor units during maximal voluntary contraction (Aagaard et al. 2002). In the spinal cord, the preferentially activation of Ia afferents by muscle vibration initiates impulses in a polysynaptic excitatory pathway and a presynaptic inhibitory pathway (Romaiguere et al. 1993). The spinal polysynaptic excitatory pathway evokes the tonic vibration reflex (TVR), whereas the spinal presynaptic inhibitory pathway is responsible for the vibration-induced reflex inhibition. Earles et al. in their recent study reported that the power-trained group demonstrated less PRD than the endurance-trained group. They suggest that the decrease in the inhibition associated with presynaptic control (PRD) in power-trained athletes should intuitively increase the gain of the monosynaptic stretch reflex. This may in turn provide functional importance during the onset of a movement (particularly a ballistic movement) (Earles et al. 2002). It has been also suggested that this high gain may allow the monosynaptic stretch reflex to assist in the high-force movement. Moreover, Meunier and Pierrot-Deseilligny state that functionally, increased

reflex gains are important to meet appropriate loading during muscular action and this facilitation of reflex gains has been mainly attributed to reduced presynaptic inhibition of Ia afferents (Meunier and Pierrot-Deseilligny 1989).

Another possible explanation for the enhancement of muscular strength after vibration can be sought from the studies that investigated the effects of WBV on the recruitment of the motor units (Ando and Noguchi 2003). It has been suggested that the tonic vibration reflex (TVR) affects primarily the subjects' ability to generate high firing rates in high-threshold motor units (Bongiovanni et al. 1990). Romaiguere et al. suggested that the recruitment thresholds of the motor units during WBV are expected to be lower compared with voluntary contractions, probably resulting in a more rapid activation and training of high-threshold motor units (Bongiovanni et al. 1990; Romaiguere et al. 1993). Furthermore, according to Holtermann et al., the modulation of motor unit recruitment and discharge rate with training involve an enhanced net synaptic excitatory input to the motoneuron pool or increased motoneuron excitability (Holtermann et al. 2007). The role of the net synaptic input in increasing rate of force development (RFD) has been documented (Kukulka and Clamann 1981). Kukulka and Clamann suggested that the enhanced excitatory synaptic input or motoneuron excitability with training causes high-threshold motor units to be recruited earlier in a maximal voluntary contraction (MVC) increasing RFD, whereas recruitment of additional motor units ends before maximal tension (Kukulka and Clamann 1981). Based on these findings and plausible mechanisms documented in the previous studies, it is suggested that qualitative changes may occur with WBV training, i.e., potentially

involving alterations in motoneuron recruitment and firing frequency, and decreased recruitment threshold (Aagaard et al. 2002).

Hormonal factors could also be involved in the neuromuscular adaptations. The responses of mammals to external environmental changes inevitably involve neural and hormonal responses, including changes in gravitational acceleration (Fitts 2001). Prolonged exposure to microgravity has been shown to result in a decrease in muscle mass and force-generating capacity. Moreover, studies conducted on astronauts have shown that microgravity produces a decline in androgen levels and growth hormone in salivary, urinary, and plasma samples (McCall 2000). According to McCall et al., this phenomena is due to the fact that microgravity represents a strong perturbation to the homeostasis of the body because of the lack of physical tension on the neuromuscular system, loss of hydrostatic pressure, and alteration of the sensory motor system. In contrast, an increase in gravitational load by means of strengthening exercises has been shown to increase the previously mentioned hormones (McCall 2000). This particular form of exercise provides high stress on the musculoskeletal structures and required high levels of neural activity (Bosco et al. 2000). It represents an increased demand as compared with the homeostatic conditions and then stimulates rapid physiological responses (Fitts 2001). During strength training exercise, rapid endocrine activation is triggered by collaterals of the central motor command and transmitted to the hypothalamic neurosecretory and autonomic centers (Behm 1995). The responses are further supported by feedback influences from proprioceptors and metaboreceptors in the muscle (Mahieu et al. 2006). The mechanical characteristics of vibration could provide an adequate stimulus for specific hormonal secretion (Bosco et al. 2000). According to

Bosco et al., in addition to the effects on sensory feedback, vibration also increases testosterone and growth hormone level in humans (Bosco et al. 2000). Furthermore, recent investigations by McCall et al. reported that the modulation of a muscle afferent-pituitary axis on growth hormone secretion was identified after vibration-induced activation of specific muscles (McCall 2000). According to the findings of this study, it is suggested that the increased levels of testosterone observed after vibration treatment are related to the increased force output. Cardinale and Bosco suggested that in particular the possible influence of this androgen hormone on calcium-handling mechanisms in skeletal muscle could facilitate a more powerful muscular activation (Bosco et al. 2000).

Electromechanical Delay (EMD)

The time lag between the onset of electrical activity(electromyogram, EMG) and force development in human muscle, called electromechanical delay (EMD) has been considered important to the studies of the relationships between EMG activity and body segment motion (Komi 2000; Komi and Vitasalo 1976; Norman and Komi 1979). According to Moritani et al., muscle force generation during a maximum voluntary contraction is dependent on both "central" and "peripheral" factors (Moritani and deVries 1979). The central factors include the proportion of the available total motor unit pool which is recruited during contraction (Milner-Brown et al. 1973), motoneuron excitability (Sale 1992), and the type of motor unit recruited during contraction (Burke 1973). The peripheral factors include the cross sectional area of the contracting muscle (Ikai and Fukunaga 1970), and the biochemical and electrical events associated with the joining-sliding-relaxation of the contractile proteins (Bell and Jacobs 1986). These various factors result in several time delays during the course of muscle contraction and force

generation (Bell and Jacobs 1986). Such delays are known to include the interval between a stimulus and a change in electrical activity in skeletal muscle, and the delay between the change in electrical activity and actual force generation by the muscle (Weiss 1965). These time intervals are collectively referred to as "electromechanical delay." According to Komi et al., production of muscle tension under voluntary or reflex conditions is preceded by a series of delay in the various parts of the neuromuscular system (Komi and Vitasalo 1976). Nilsson et al. also reported that the magnitude of these delays in a given motor task may have some dependence on the structural differentiation of the neuromuscular system (Nilsson et al. 1977). The EMD, as a component of the stretch reflex, is considered vital for both the utilization of the stored energy in the series elastic component (SEC) and optimal sports performance (Komi 2000). To our knowledge no research has investigated the effects of whole body vibration on the electromechanical delay (EMD) and since the present study is set to investigate the effects of whole body vibration on the neuromuscular system, it seems reasonable to better understand this neuromuscular related variable.

The EMD has been suggested to include the time courses of the propagation of action potential on muscle membrane, the excitation-contraction coupling processes and the stretching of the series elastic components (SEC) by the contractile component (Cavanagh and Komi 1979; Komi and Vitasalo 1976). Any factor that influences the above mentioned processes are believed to influence EMD. It has been reported that EMD is significantly correlated to the maximal voluntary contraction (MVC) force, rate of force development (RFD) (Bell and Jacobs 1986) and muscle fiber types (Nilsson et al. 1977). The EMD has been found to be influenced by the type of muscle contraction

(Cavanagh and Komi 1979), joint angle (Grabiner 1986), the level of effort (Grabiner 1986), fatigue (Nilsson et al. 1977), and the age and sex of the subjects (Bell and Jacobs 1986; Zhou et al. 1996). Viitasalo suggested that a shorter EMD would be found in a muscle which has a higher percentage of fast twitch (FT) fibers, greater contraction force and rate of force development, and stiffer series elastic component. They also suggested that a shorter EMD would be expected in the motor responses that recruit mainly fast twitch fibers than in those that recruit slow twitch motor units (Viitasalo 1981).

EMD has been reported to be related to the maximal force generation and the rate of force development during a maximal voluntary contraction (Viitasalo 1981). Viitasalo and Komi reported that electromechanical delay under voluntary condition was significantly related to the rate of force development ($r=-.64$; $p<0.001$) so that the shorter electromechanical delay was associated with maximal force ($p<0.001$). The authors sought the explanation for this finding from the models of motor unit recruitment under various conditions. The results of Freund et al. and Gydikov and Kosarov have shown that the recruitment order of the phasic and tonic motor units differs depending on the velocity of dynamic contraction or the rate of rise of isometric tension (Freund et al. 1975; Gydikov and Kosarov 1974). Gydikov et al. also suggested that fast and slow motor units have been shown to differ greatly in their force-time curves (Gydikov and Kosarov 1974). Viitasalo and Komi reported that the maximal force and the rate of force development were greater in subjects who had more fast twitch fibers in their vastus lateralis muscle (Viitasalo 1981). Norman et al suggested that EMD includes both the events leading to the activation of the cross-bridges and the time spent by contractile component for stretching series elastic component (Norman and Komi 1979). They argue

that although the time spent for stretching SEC gives a greater contribution to the total electromechanical delay, the influence of the activation process (cross-bridges) should be considered (Norman and Komi 1979). Harigaya et al. suggest that a fast type muscle has been shown to release Ca^{2+} at a faster rate than the slow muscle (Harigaya 1969). Upon relaxation the uptake of Ca^{2+} by the sarcoplasmic reticulum appears to take place faster in fast twitch muscle and its rate is related to the rise time of the isometric contraction (Brody 1976). Lannergren et al. reported that the rate of cross bridge cycling is much lower in slow muscle fiber resulting in a lowered maximum rate of rise of isometric tension (Lannergren 1978). It has been speculated that on motor unit level it has also been demonstrated that fast and slow units have different mechanical characteristics so that the force-time curve of the fast twitch unit has both short rise time and shorter half relaxation time than that of the slow twitch unit (Gydikov and Kosarov 1974). Viitasalo and Komi were able to show in their study that a muscle containing predominantly fast type fibers (or motor units) is able to reach a certain submaximal force level sooner than the same muscle with higher percentage of slow twitch fibers (Viitasalo 1981).

EMD has been reported to be associated with the joint angle and stiffer muscle (Bell and Jacobs 1986; Vos et al. 1991). The theory behind the relationship between EMD and joint angle is that when the length of the series elastic component (SEC) in a muscle tendon complex is below the slack length beyond which the SEC can transmit the muscle contraction forces to bones, the SEC must be stretched beyond the slack length to transmit force. Therefore, a shorter EMD would be expected in a stretched muscle tendon complex (Muraoka et al. 2004). However, regarding the relationship between EMD and joint angle observed in experimental research, there have been conflicting results. Bell et

al. speculated that the use of a larger range of initial muscle lengths (e.g., 45º - 170º of knee joint angle, rather than the used 90º and 130º) in their study might have yielded different results (longer EMD with larger muscle length) (Bell and Jacobs 1986). In contrast, the study by Muraoka et al. demonstrated no significant differences in EMD among the joint angles (-10, 0, and 5º). More research is needed to investigate the effects of different joint angles on electromechanical delay of different muscles.

Another influencing factor of EMD, muscle stiffness has been investigated. The property of the passive component of SEC, which refers in the main to the tendons, is largely independent of contractile component activity, while the active component of SEC, which lies within the contractile component has been stated to relate to muscle contraction force (Shorten 1987). According to Zhou et al, it has been suggested that the stiffness of the active portion of SEC increases with contraction force because more cross-bridge are formed (Zhou et al. 1995). It has been also suggested that slow twitch fibers are stiffer than fast twitch fibers because the life time of the cross-bridge is longer (Aura 1987). It has been hypothesized that if slow twitch fibers are recruited at the beginning of a reflex, the effect of the higher stiffness of slow twitch fibers may offset some of the effects from their lower force and rate of force development (Zhou et al. 1995). Zhou et al. speculated that perhaps the synchronized motor unit activity during the involuntary twitches increases the stiffness and rate of force development of the muscle during the early stages of the contraction, and a shorter EMD results (Zhou et al. 1995).

The difference in maximal strength between males and females, in addition to being associated with differences in muscle mass, has been thought to be associated with differences in electromechanical response times (electromechanical delay) (Bell and

Jacobs 1986). Cavanagh and Komi suggested that the major portion of the measured EMD is used to stretch the SEC within the musculature (Cavanagh and Komi 1979). This was supported by their demonstration that when a maximal voluntary contraction (MVC) is performed during a concentric movement, EMD is longer than during an eccentric contraction, when the muscle is pre-stretched prior to the MVC. Based on this theory, Bell et al in their study investigating the gender differences in EMD speculated that the series elastic component in the males' muscle in their study was more resistant to stretching than was the case for the females, thereby shortening the EMD in the male group (Bell and Jacobs 1986). Such a structural differences in tissue elasticity was proposed by Komi and Vitasalo (Komi and Vitasalo 1976) to explain the almost twofold longer time required by females to attain 70% MVC than males (Komi and Vitasalo 1976). Wilmore suggested that the stiffer muscle in the males could be attributed to their prior activity history which, in our society, would probably include more daily activities likely to elicit a strength training effect than would be the case for females (Wilmore 1996).

Fatigue could affect not only the force generating capacities but also the temporal characteristics of the neuromuscular mechanism (Zhou et al. 1998). The temporal changes (electromechanical delay) associated with fatigue were widely investigated (Hayes 1975; Kroll 1973, 1974; Morris 1978; Zhou et al. 1998). Despite the numerous investigations, the results reported are equivocal. For instance, Kroll and Hayes have shown no significant changes of EMD and pre-motor time (PMT) following a fatigue protocol of bench stepping exercise and a plantar flexor fatigue protocol that resulted in a 15%-35% decrease in strength (Hayes 1975; Kroll 1973, 1974). Morris has investigated

the effects of isometric and isotonic fatigue on total reaction time (TRT) and shown an increase of TRT contributed by the lengthening of EMD (Morris 1978). Hanson and Lofthus have shown the increase in TRT to be contributed by an increase in PRT (Hanson 1978).

Apart from the simultaneous recordings of PMT and EMD, using different muscle groups, Stull and Kearney and Nilsson et al. have shown a significant lengthening of EMD following a fatigue protocol (Nilsson et al. 1977; Stull 1978). Similarly, in a recent study by Zhou et al. on the effects of fatigue on EMD of the knee extensor muscles, there has been shown to be a significant increase in EMD after a fatigue protocol of four periods of 30-s all-out sprint cycling exercise (Zhou et al. 1998). In contrast, Vos et al. found no significant change in EMD of the rectus femoris muscle following 150 repetitions of 50% isometric maximal voluntary contraction (Vos et al. 1991). It has been speculated that the discrepancies in these studies are probably related to the different classification of EMD and PMT, different types of muscle contraction and levels of fatigue in the exercise protocol (Zhou et al. 1998).

Mechanisms for shortened or lengthened EMD

There are several possible mechanisms and sites related to the lengthening of EMD. The process of converting motor unit action potentials (MUAP) into force generation has been suggested by Fitts (Fitts 1994) and the process involves several stages which include propagation of the MUAP along the sarcolemma and down to the transverse tubule, changes in the Ca^{2+} conductance of the sarcoplasm reticulum (SR) and Ca^{2+} movement down its concentration gradient into SR, reuptake of Ca^{2+} by the SR, binding of troponin, and interaction of the myosin and actin (Fitts 1994).

Zhou et al. in their recent study showed a significant increase in EMD following 30 bursts of isometric maximal voluntary contraction. The authors speculated that the decreased EMD was probably related to the impairment of the signal transmission distal to the neuromuscular junction (Zhou et al. 1998). It has been suggested that the changes in EMD before and after fatigue reflected the integrity of the central drive (Zhou et al. 1998).The components of central nervous system (CNS) which are involved in the execution of motor movement include the pre motor area of the motor cortex, the supplementary motor area, the primary motor cortex, the basal ganglia, the brainstem, the spinal cord and the interconnecting neurons and their synapses (Enoka 1994). Despite the postulates for the lengthening EMD, the exact mechanisms for that change in EMD are not known. Future studies should focus on elucidating possible mechanisms for the shortened or lengthened EMD following fatigue or any intervention.

Measurements of EMD

EMD measurements have been performed by voluntary or electrically evoked (involuntary) muscle activation (Moritani and deVries 1979; Muraoka et al. 2004; Muro 1985; Nilsson et al. 1977). Muro and Nagata have investigated the isometric contractions of the triceps surae muscle that were evoked by electrical stimulation applied to the posterior tibial nerve (Moritani and deVries 1979; Muro 1985). Those authors have reported an EMD of 10.9 ms(Muro 1985). In another study on electrically stimulated EMD of the same muscle group, Moritani et al. have reported an average value of 18.77 ms (Moritani and deVries 1979). However, Winter and Brooks have reported an EMD of 40.8 ms from the same muscle group in concentric voluntary contraction (Winter 1990). Hayes et al. have reported an EMD of 25.4 ms from the plantar flexor in concentric

contraction (Hayes 1975). EMD of other muscle group has been also assessed. According to Ralston et al., the EMD of quadriceps femoris group observed in their study was in the range of 30 ms – 40 ms (Ralston et al. 1976). EMD during isometric contraction has been also reported. Viitasalo et al. investigated electromechanical response times from the same muscle group (rectus femoris) and reported 38.3 ms (Viitasalo 1981). Dissimilarity of the above EMD values is thought to be due to the different muscle contraction and muscle group or different methods used.

Measurements of EMD during voluntary contraction have been performed with either concentric, eccentric or isometric contraction (Viitasalo 1981; Winter 1990; Zhou et al. 1998). Since our study is set to use isometric contraction to measure electromechanical delay of the soleus muscle, it seems reasonable to review the procedures of EMD measurements performed by previous studies.

To measure EMD, subjects were asked to perform three maximum voluntary isomtric contractions of the soleus muscle while the ankle is secured on the force plate. According to Winter and Brookes' protocol, with appropriate areas shaved and rubbed with alcohol to minimize inter-electrode resistance, surface electrodes 10-mm diameter were placed 3-4 cm apart over the lateral surface of the soleus muscle which had been identified by inspection and palpation (Winter 1990). The authors chose the soleus muscle because it is a single joint muscle and differences attributable to joint laxity are minimized (Winter 1990). The authors also explained that the knee was flexed to minimize the contribution from the gastrocnemius muscle (Winter 1990). For the stimulus to start the contraction, various methods (light, sound, or voluntary) have been used. Zhou et al, used the light stimulus in their study (Zhou et al. 1998; Zhou et al. 1996).

In the MVC trials, the subject was asked to exert MVC as quickly as possible when seeing a signal from a light bulb (Zhou et al. 1998; Zhou et al. 1996). In a study of Winter and Brookes, an auditory signal was used. After a verbal warning, a randomly ascribed auditory signal was delivered to the subject through headphones within 1 – 4 seconds. Upon receipt of the signal the subjects plantar flexed the foot as quickly as possible (Winter 1990). During each trail, the output from the force plate was amplified by a charge amplifier and the output from the charge amplifier were sampled at 2.5 kHz and recorded on a digital storage oscilloscope (Winter 1990). Throughout the measurements, five characteristics were determined. Total reaction time (TRT), pre-motor time defined as the time interval from the application of the stimulus to the change in electrical activity of the soleus muscle, electromechanical delay (EMD), defined as the time interval from the change in electrical activity in the soleus muscle to movement of the heel away from the pressure pad, force time (FT), defined as the time interval from the change in electrical activity to the registration of force, and lastly, elastic charge time (CT), defined as the time interval between the registration of force and movement of the heel away from the pressure pad (Winter 1990). A study by Zhou et al, assessed not only these above mentioned five characteristic, but also measured peak rate of force development, calculated every 5 ms by the force increment divided by the time, the maximal value from each contraction trial (Zhou et al. 1998; Zhou et al. 1996). During MVC trials, 1 min rest period was given to the subjects(Winter 1990).

Rate of Force Development (RFD)

The rate of force development (RFD), generally determined as the slope in the force time curve (Δforce/Δtime), is considered important to assess the explosive strength

qualities of the neuromuscular system (Hakkinen et al. 1985). It has been shown that an increase in the rate of force development is closely related to improvement in neural drive of the trained muscles, especially in a dynamic explosive type of strength training (Aagaard et al. 2002; Gruber and Gollhofer 2004). Possible connection between WBV and RFD can be postulated from several WBV studies (Bosco 1998; Cardinale and Wakeling 2005; Cheung et al. 2007; Cochrane et al. 2004; Kawanabe et al. 2007). As reviewed earlier in the WBV section, it has been speculated that WBV training might result in neuromuscular adaptation s similar to the effect produced by explosive strength training (Delecluse et al. 2003). For example, Bosco et al. reported the effect of a 10 day training program of a daily series (5× 9 s) of WBV at a frequency of 26 Hz. They found a significant improvement of the height and mechanical power during jumping test. In this respect, it is important to better understand first, the mechanisms of rate of force development and secondly, how this RFD can be affected by resistance training or other type of intervention such as WBV exercise.

Several intervention studies have observed increased maximal force without being able to specify the physiological processes or mechanisms providing the improvement (Herbert et al. 1998; Holtermann et al. 2007; Jones and Rutherford 1987; Miller et al. 1981; Rutherford and Jones 1986; Thorstensson et al. 1976). Many of these studies have focused on muscle activation at the short time period of peak force during a maximal voluntary contraction (MVC) (Herbert et al. 1998; Jones and Rutherford 1987; Miller et al. 1981; Rutherford and Jones 1986; Thorstensson et al. 1976). However, it has been theorized that the maximal tension is not instantly reached, and muscle activation prior to maximal force, like doublet discharges and initial firing rate, could affect the MVC

performance (Burke et al. 1976; Miller et al. 1981). Based on this hypothesis, the rate of force development (RFD) prior to peak force has been well examined because of its impact on several human movement, e.g., explosive sports and postural balance in elderly (Moritani 2002; Thelen and Schultz 1996). Aagaard et al. suggested that the RFD increased after explosive strength training (Aagaard et al. 2002), and is often attributed to neural factors like increased doublet discharges and firing rate (Aagaard et al. 2002). The result of their study showed that contractile RFD after 15 weeks of resistance training increased 15% and furthermore, muscle EMG increased 22-143% in the early contraction phase (Aagaard et al. 2002). Behm and Sale reported that a few weeks of resistance training can cause increases in isometric single-joint tasks of up to 30% in maximal force and RFD (Behm and Sale 1993). In a recent study by Holtermann et al revealed that the resistance training provided increases in maximal force of 18%, RFD of 28% and H-reflex amplitude during voluntary contractions of 17% to 15% while no changes occurred in the control group (Holtermann 2007). The authors also reported that there was a positive correlation between percentage changes in H-reflex amplitude and RFD with training ($r=0.59$), while significant association between percentage changes in H-reflex amplitude and maximal force was not found (Holtermann 2007). In a current study by Gruber et al., the effects of sensorimotor training on the rate of force development has been investigated (Gruber and Gollhofer 2004). The results of the study showed that after 4 weeks of sensorimotor training, maximum rate of force development increased significantly (Gruber and Gollhofer 2004)and the gain in RFD was accompanied by increased EMG of the medial vastus lateralis muscle (Gruber and Gollhofer 2004)

The impact of heavy resistance training in the elderly on maximum voluntary contraction (MVC) and rate of force development (RFD) has been investigated (Fiatarone et al. 1990; Granacher et al. 2006).It has been frequently observed, that even in this age group heavy resistance training results in an increase in maximal as well as explosive force production capacity (Fiatarone et al. 1990; Granacher et al. 2006). Granacher et al. in their current study investigating the effects of resistance training on postural reflexes and RFD in elderly men reported that a 13 week of heavy resistance training and sensorimotor training had an impact on spinal motor control mechanisms and rate of force development in the elderly men (Granacher et al. 2006). Also reduced contractile RFD has been demonstrated in elderly compared with young individuals of both genders (Clarkson et al. 1981; Vandervoort and McComas 1986). Suetta et al. in their current study examining the age-related decline in muscle strength and neural function demonstrated that disuse leads to a marked loss of muscle strength and muscle mass in elderly individuals. Furthermore, the findings of the study indicate that neuromuscular activation and contractile RFD are more affected by long-term disuse than maximal muscle strength, which may increase the future risk for falls (Suetta et al. 2007).

The effects of whole body vibration on maximal voluntary isometric knee extensor force and rate of force development has been investigated (de Ruiter et al. 2003a). de Ruiter et al. reported that neither the electrically induced maximal rate of force rise nor voluntary maximal rate of force rise was significantly affected by WBV. The authors in addition reported that six WBV training session in 2 weeks did not enhance either voluntary muscle activation during MVC (de Ruiter et al. 2003a). Since there is only limited data on the effect of WBV on muscle contractile properties and activation

future studies should focus on investigating to what extent WBV will enhance the muscle contractile properties and activation.

Mechanisms for Increased RFD

It is well documented that improvements in force production capacity can be achieved either by enhancement of the muscular protein mass, or by adaptations in the neural control of the muscle (Aagaard et al. 2002; Moritani 2002; Moritani and deVries 1979). It has been hypothesized that while maximum voluntary strength largely depends on the cross sectional area of the muscle, RFD is basically related to the discharge rate of the motor units recruited (Nelson 1996; Van Cutsem et al. 1998), to alterations in the recruitment characteristics or to a combination of both (Kukulka and Clamann 1981). More recently, Van Cutsem et al. have proved that neural adaptations caused by an explosive type of training are primarily responsible for an increased RFD (Van Cutsem et al. 1998). By analyzing single motor unit recordings, the authors were able to demonstrated that after training, motor units were activated earlier and showed increased firing frequencies (Van Cutsem et al. 1998). Also, based on the EMG recordings from the study, Van Cutsem et al. supported the idea that explosive type of training is associated with high frequency discharges ("doublets") occurring at the onset of muscular action (Van Cutsem et al. 1998).

It is well known that cross bridge cycling rate of muscle fibers that are dominated by type IIa and IIx myosin heavy chain (MHC) are roughly four and nine fold faster than that of type I fibers (Bottinelli et al. 1996; Larsson and Moss 1993). Andersen and Aagaard suggested that it is likely that RFD is strongly influenced by the cross bridge cycling rate (Andersen et al. 2005). In addition, it has been suggested that sarcoplasmic

Ca^{2+} kinetics could influence the mechanical muscle twitch parameters (Brody 1976). According to Aagaard et al. and Van Cutsem et al., physiological factors besides maximal muscle strength and intrinsic muscle contractile properties could also influence the very early phase RFD (Aagaard et al. 2002; Van Cutsem et al. 1998). The authors in both of the studies suggested that based on the measurements of EMD in their experiments, neural drive to the muscle may have a very important influence on voluntary RFD during this phase of contraction (Aagaard et al. 2002; Van Cutsem et al. 1998). Aagaard et al. argued that voluntary RFD in the very early phase of muscle contraction is a multifactorial phenomenon that is influenced by several physiological variables, amongst those intrinsic muscle contractile properties, maximal muscle strength and neural drive (Aagaard et al. 2002; Van Cutsem et al. 1998) .

Duchataeu and Hainaut suggested that increased strength and neural activation require adaptations on the motoneuron level, i.e., motoneuron recruitment and/or firing frequency, alterations in synchronization of motor unit firing and/or even advanced incidences of discharge doublets (Duchateau and Enoka 2002). Burke et al. postulated that increases in RFD can be achieved by higher firing frequencies or by extra impulses (Burke et al. 1976; Burke 1973) even though the firing frequency for maximum titanic tension has already been reached (Desmedt 1983; Miller et al. 1981; Nelson 1996). Recently, Van Cutsem et al. reported that a ballistic type of resistance training led to an increase in RFD along with an elevated incidence of discharge doublets (interspike intervals 2 -5 ms) in the firing pattern of motor units (Van Cutsem et al. 1998) . The authors interpreted that the functional significance of these extra doublets is basically to enhance maximal force development (Van Cutsem et al. 1998).

It has to be mentioned that gains in neural drive may also be related to an alteration of the recruitment threshold of motoneuron (Henneman et al. 1965). Several authors suggested that based on single motor unit recordings, motor unit synchronization has been considered a potential mechanism to modulate force development (Milner-Brown et al. 1975; Semmler and Nordstrom 1998). Semmler argued that most likely the functional role of synchronization is to increase RFD, especially in situations where different muscles have to be coordinated (Semmler 2002).

According to Aagaard et al., the above mentioned factors for enhanced RFD; increased frequency, earlier recruitment and improved synchronization can be understood as an excitatory modulation of the spinal motoneuron pool (Aagaard et al. 2002). Several authors assumed that following strength training main adaptations occur in supraspinal structures caused by an enhanced neural drive in descending corticospinal pathways as indicated by higher V-wave amplitudes (Aagaard et al. 2002; Sale 1992). Aagaard et al. indicated that a reduction in presynaptic inhibition of Ia afferents may be closely related to the enhanced neural adaptation (Aagaard et al. 2002). Concerning the adaptations in spinal pathways after training, Meunier and Pierrot-Deseilligny produced some evidence that both homonymous and heteronymous Ia contributions are facilitated at the beginning of muscular action (Meunier and Pierrot-Deseilligny 1989). It has been hypothesized that the excitability of the spinal reflex system is linked to the requirements given by the functional tasks, i.e., sitting, standing, walking (Capaday and Stein 1987). It has also been supposed that a specific training regimen could influence spinal excitability (Nilsson et al. 1977), which has been shown for alternatively trained athletes (Casabona et al. 1990; Nielsen et al. 1993) as well as after a training intervention (Voigt et al. 1998). Recently,

Gollhofer and Gruber have reported functional improvements following a sensorimotor training (Gruber and Gollhofer 2004). The authors have suggested that adaptations seen in their study (sensorimotor training) are peripheral and basically mediated at the spinal level (Gruber and Gollhofer 2004). Hultborn et al. and others have also indicated that these reflex contributions could even activate the muscle during the onset of an isometric action (Garland and Miles 1997; Hultborn et al. 1987; Macefield et al. 1993).

Gruber and Gollhofer have postulated that enhanced afferent gain in neuromuscular control, especially at the onset of force development, is considered vital functional importance for the stiffening of muscles encompassing joint complexes (Gruber and Gollhofer 2004). Meunier and Pierrot-Deseilligny showed that motoneuron excitability is directly related to the target strength and this facilitation depends on the steepness of the ramp and thus at least indirectly on the rate of force development as well as on the intensity of the target action (Meunier and Pierrot-Deseilligny 1989). The authors have indicated that this facilitation has been mainly attributed to reduced presynpatic inhibition of Ia afferents (Meunier and Pierrot-Deseilligny 1989).

Although it has been suggested that the gains in RFD may comprise both supraspinal and spinal adaptations, to date there is only limited data on the relationship between the change in RFD and the change of other physiological or neuromuscular factors. In this respect, it seems important to investigate how these spinal adaptations occur with different types training (WBV) and to what extent this is related to other neuromuscular variables (EMD and RFD). Concerning the measurements of RFD, detail procedures have been addressed in the EMD section.

Presynaptic Inhibition

The synaptic efficacy of the afferent volleys entering the spinal cord can be modulated by presynaptic inhibition (Pierrot-Deseilligny 2005). As a result, the information flowing through sensory terminals can be modified before it reaches the target neurons through a process that can be controlled selectively by supraspinal centers to optimize motor performance and sensory discrimination (Pierrot-Deseilligny 2005). All afferents are subject to presynaptic inhibition controlled by descending tracts (Rudomin and Schmidt 1999) however, so far, methods have been developed for human subjects to estimate only presynaptic inhibition of Ia terminals due to the fact that it is easy to stimulate I a afferents selectively, and they are the only afferents to have significant monosynaptic projections onto motoneurones (Rudomin and Schmidt 1999).

Presynaptic inhibition in the monosymnaptic reflex pathway from group Ia muscle spindle afferents to motoneurones was first reported by Frank and Fuortes in 1957 (Frank 1957). They named this type of inhibition "presynaptic" because they were able to demonstrate that conditioning volleys in another nerve could produce a depression of the monosynaptic excitatory postsynaptic potential (EPSP) in motoneurons without a change in its time course, the postsynaptic membrance potential, and the excitability of the motoneurones (Willis 2006). In contrast, postsynaptic inhibition was known at that time to be associated with a change in the time course of the EPSP because of an increase in the conductance of the postsynaptic membrane, leading to a hyperpolarization of the postsynaptic membrane and concomitantly, a reduction in the excitability of the motoneurones (Willis 2006).

To date, most common studying presynaptic inhibition in humans is by measuring changes in the H-reflex (Stein 1995). It has been shown by Hultborn et al. that to measure

the presynaptic inhibition, the tibial nerve is stimulated at the popliteal fossa behind the knee and H-reflex is recorded over the tricep surae muscle (Hultborn et al. 1987). H-reflexes produced stimulating not only the tibial nerve, but also the femoral nerve to the quadriceps muscles, the common peroneal nerve to the tibialis anterior muscle, and the median nerve to the forearm flexor muscles have also been studied (Burke et al. 1992; Hultborn et al. 1987; Nielsen 1993). Stimulation is adjusted to a level that excites group I fibers and the effect observed is largely due to the monosynaptic connection from primary muscle spindles to alpha motoneurones, although some polysynaptic component cannot be ruled out (Burke et al. 1984). The H-reflex is the electrical analog of the tendon jerk (T-reflex) and in some studies comparisons have been made between the two (H-reflex and T-reflex) (Stein 1995). Among many of previous studies, Milanov studied 120 patients which spastic hemiparesis following a stroke and found that vibrating the tendon of tibialis anterior muscle inhibited both the H-reflex and the T-reflex (Milanov 1992). In that study, it has been shown that the magnitudes of the inhibitions were highly correlated in the patient group ($r=0.84$) (Milanov 1992). However, the inhibitions could be affected differently because the electrical and mechanical stimuli evoke different amounts of polysynaptic responses or because T-reflex might be more sensitive to the effect of motoneurones on the response of muscle spindle afferents to stretch of its tendon, in studying presynaptic inhibition, the H-reflex is preferable to the T-reflex on both counts (Stein 1995).

H-reflex and M-wave

The technique used to evoke the H-reflex involves electrical stimulation of a mixed (i.e., containing both motor and sensory axons) peripheral nerve (Zehr 2002).

Stimulation to evoke the H-reflex involves both afferent sensory (from the point of stimulation to the spinal cord) and efferent motor (from the alpha motoneurones in the spinal cord to the neuromuscular junction) arcs as well as a direct (from the point of stimulation to the neuromuscular junction) efferent motor response (M-wave) (Zehr 2002). It has been suggested by Kukulka that when percutaneous stimulation of increasing intensity is applied, the Ia afferents that innervate muscle spindle sensory receptors, because of their large diameter, will be recruited before the smaller diameter motor axons (Kukulka 1992). Therefore, the H-reflex can be observed with or without an M wave. It has been known that an H reflex is recorded if electrical stimulation of the nerve is above threshold for activation of Ia afferents and the afferent terminals are sufficiently depolarized to cause neurotransmitter release at the Ia afferent/alpha-motoneuron synapse (Zehr 2002). Zehr in his review article explained the spinal processing of the monosynaptic component of the H reflex (Zehr 2002). According to Zehr's explanation, significant release of a neurotransmitter from the primary afferent terminals will result in postsynaptic depolarization of alpha motoneurons and if this postsynaptic depolarization is above threshold, the alpha motoneurons will fire action potentials that will cause neurotransmitter release at the neuromuscular junction (Zehr 2002). This will result in depolarization and contraction of the muscle fibers which will then be recorded as an H-reflex in the muscle under study (Zehr 2002). These reflexes are typically recorded, using surface electromyography (EMG) electrodes placed over the muscle of interest (Stein 1995). Magladery has reported that increasing the level of electrical stimulation recruits additional I a afferent and motor axons (Magladery 1955). It has been shown that the amplitudes of the H reflex and M wave both increase fairly

linearly with the stimulation intensity until the maximum H-reflex (H_{max}), representing the fullest extent of reflex activation, and, at higher stimulation levels, the maximum M wave (M_{max}), representing the maximal muscle activation, are reached (Zehr 2002)

According to Henneman's size principle, it has been well known that recruitment of motor units by corticospinal or Ia afferent inputs (as in the H-reflex) proceeds in an orderly fashion from smallest to largest (Henneman et al. 1965). Taborikova has reported that the percentage of motoneurons recruited into the soleus H reflex averages around 50% (range 24 – 100%) (Taborikova 1968). Moreover, it has been suggested that the lower threshold and smaller, "slow' motor units predominate in the human H-reflex response of the soleus muscle (Buchthal 1970), and that recruitment according to stimulus intensity proceeds in an orderly manner from small to large motor units (Awiszus 1993).

H-reflexes have been evoked in many different muscles of both the upper and lower limbs (Stein 1995). The most commonly studies muscle in the lower limb is the soleus, and in the upper limb the FCR. Concerning the method to measure H-reflexes, the H-reflex has typically been evoked by placing surface electrodes in wither a bipolar configuration over the predicted path of the tibial nerve in the popoliteal fossa, or with one electrode in the popliteal fossa and one over the patella (Hugon 1973). It has been suggested that regardless of muscle under study, the general procedure is to initially place one electrode over the predicted path of the nerve and them to carefully move the electrodes until the best response (in terms of clarity of H reflex and M wave) is observed (Hugon 1973). It is also important to note that investigators must control for possible factors known to affect the amplitude of the H reflex. Since presynaptic inhibition is

measured by comparing H reflexes, accuracy of the measurements is critical. In order for the H reflex to accurately reflect changes in motoneuron pool excitability, it has been suggested to control the factors such as electrode placement, head position, hand placement, muscle contraction, stimulation technique, body posture, foot position, and eye movement (Funase and Miles 1999; Hugon 1973).

In order to limit the effects of extraneous factors on the H-reflex, Zehr has provided recommendations and considerations for application in an intervention study (Zehr 2002). First the author suggests that H reflexes should be evoked with a sufficient level of stimulation to provide constancy. Furthermore, similar M-wave amplitude should be maintained and used for comparisons across different condition. Secondly, it has been suggested that maximal M waves used for normalization of the H reflex should be evoked in each conditions where H reflexes are evoked to avoid time-dependent or movement dependent changes. Thirdly, the behavioral state as well as the posture of the subject must be the same when all measurements are taken to control for the task-dependency of reflex modulation and lastly, when examining the conditioning effect of another input on the H reflex, randomly alternate the conditioned and test stimulation (Zehr 2002).

In conclusion, It is likely that smaller motoneurons are recruited first when increasing nerve stimulation to evoke the H-reflex is applied in many muscles (Taborikova 1968). As reviewed above, investigators should focus on controlling the extraneous factors that might negatively affect the amplitude of H reflex. It has been supposed that if all above conditions are met, the H reflex might certainly be used as an effective tool in evaluating the changes in human reflex pathways and the plasticity of the neuromuscular system.

Presynaptic Inhibition and H-reflex

Presynaptic inhibition of spinal monosynaptic reflexes was initially described in the cat in 1957 (Eccles et al. 1962a; Frank 1957), and has received considerable experimental attention (Rudomin and Schmidt 1999). It has been speculated that presynaptic inhibition is mediated by the action of an inhibitory interneuron (using gamma aminobutyric acid as the neurotransmitter) (Rudomin and Schmidt 1999) acting on the Ia afferent terminals, leading to a reduction in neurotransmitter release and a concomitant reduction in motoneuron depolarization induced by Ia activity (Rudomin and Schmidt 1999). Frank and Fourtes demonstrated that in the presence of presynaptic inhibition where was no change in the postsynaptic membrane potential, despite activity in the Ia afferents (Frank 1957). Moreover, it has been found that the motoneurons remained receptive to other inputs that were unaffected by presynaptic inhibition (Frank 1957). Based on these findings, it has been speculated that presynaptic inhibition could selectively alter transmission in a monosynaptic reflex pathway (Frank 1957), and recently it has been demonstrated by Rudomin et al. that this mechanism is selective enough to affect different collaterals from the same muscle spindle afferent (Rudomin and Schmidt 1999). Despite the fact that H-reflex has been considered as a reflection of alpha motoneuron excitability for long time, Zehr in his review article argued that due to the mechanism discussed above (due to the effect of presynaptic inhibition on the amplitude of H-reflex), the level of alpha motoneuron excitability can't be evaluated by measuring H reflexes (Zehr 2002). Additionally, Zehr has suggested that because the H-reflex can be modified be presynaptic inhibition, it is dangerous to interpret the changes in H reflex size as changes in motoneuron excitability. (Zehr 2002)

Mechanisms of Presynaptic Inhibition

Eccles et al. described that presynaptic inhibition is associated with primary afferent depolarization (PAD), both phenomena most probably mediated by the same interneurones acting on Ia terminals through axo-axonic synapses (Eccles et al. 1962b). These interneurones are referred to as PAD interneurones. Although PAD interneurones have not yet been specifically labeled, there are strong indications that last-order PAD interneurones mediating presynaptic inhibition of I a terminals are located within the intermediate zone (Pierrot-Deseilligny 2005). The mechanism underlying presynaptic inhibition involves local modulation of transmitter release at the Ia motoneurone synapse by means of $GABA_A$ receptors. Activation of $GABA_A$ receptors in Ia terminals increases the efflux of CI^- ions and produces depolarization of the afferent terminals (Pierrot-Deseilligny 2005). As a result, the amplitude of the propagated action potential in the intraspinal afferent terminals is reduced, and that blocks or reduces Ca^{2+} influx and thereby transmitter release (Rudomin and Schmidt 1999).

$GABA_A$ receptors

The more detail mechanisms have been proposed to account for PAD. Pharmacological experiments showed that the administration of picrotoxin could block presynaptic inhibition of the monosynaptic reflex and the associated PAD in the cat spinal cord (Eccles 1963). Later experiments in the study by Curtis et al. revealed that GABA or $GABA_A$ receptor agonists released iontophoretically near group Ia afferent terminals produced an enhanced excitability of the terminals (Curtis 1977). Deschenes et al. have reported that $GABA_A$ receptors are associated with chloride channels, and so their activation results in a chloride current across the surface membrane of the afferent

neurons (Deschenes 1976). The potential change that results depends on the direction of the chloride current. It has been shown that chloride is concentrated in the cytoplasm of primary afferent neurons, as shown by the equilibrium potential for chloride in dorsal root ganglion cells; the chloride equilibrium potential is about -20 to – 35 mV (Deschenes 1976).

Axo-axonal synapses

As mentioned above, axo-axonal synapses have been found in contact with the terminals of primary afferent fibers in the spinal cord, including the terminals of group Ia muscle spindle afferents, group Ib afferents from Golgi tendon organs, group II muscle spindle afferents, and cutaneous afferents (Alvarez 1998; Gallhager 1978). Gollhager and Alvarez have suggested that the presynaptic elements of such synapses are thought to release GABA, which activates $GABA_A$ receptors on the afferent terminals. This is thought to open chloride channels, allowing the efflux of Cl^- ions from the terminals and consequently their depolarization (Alvarez 1998). Carlton and Hayes have postulated that GABA- containing dendro-axonic synapses made by vesicle-containing dendritic terminals on primary afferent endings are associated with GABAergic presynaptic inhibition (Alvarez 1998; Carlton and Hayes 1990). Eccles et al. have found that many axo-axonal synapses in the dorsal horn and intermediate zone contain both GABA and glycine and many such synapses from triadic synapses with primary afferent terminals and speculated that release of glycine and GABA are both likely to contribute to presynaptic inhibition (Eccles 1963).

Increased extracellular K^+ concentration

An increase in the concentration of potassium ions in the extracellular space following the activation of spinal cord interneurons has been discussed as an alternative mechanism for the production of PAD (Willis 2006). Rudomin et al. stated that changes in exracellular potassium can't account, however, for all of the changes in the excitability of primary afferent fibers observed following peripheral nerve stimulation, nor for the pharmacology of PAD and presynaptic inhibition (Rudomin and Schmidt 1999; Willis 2006)

Furthermore, it has been suggested that there is no presynaptic inhibition of descending tracts that terminate in areas of increased K+ concentration (Rudomin and Schmidt 1999; Willis 2006). Future studies are needed to elucidate the exact mechanism for the production of PAD and explain how these factors are associated with presynaptic inhibition.

Presynaptic Inhibition and WBV

Presynaptic inhibition has been suggested as a modulatory mechanism responsible for neurological changes seen with WBV. The possible connection between vibration and presynaptic inhibition has been explored through tendon and muscle vibration studies (Ashby 1987, 1975, 1980). In the study, the depression of the soleus H-reflex during vibration of the achilles tendon was less pronounced in spastic patients than in healthy subjects (Ashby 1980). The depression of tendon reflex by muscle vibration has also been reported. Another study by Ashby et al. showed that the 60% depression of the patellar tendon reflex caused by muscle vibration in young adults (Ashby 1987). Based on these findings observed in the previous studies, Rittweger et al. assumed a substantial evidence

for vibration exercise interaction with spinal reflex loops and possibly influencing these pathways(Rittweger et al. 2003). Further, the same authors in their recent WBV study suggested that the tonic vibration response, which is thought to be elicited via the spindle loop, causes a mitigation of reflex levels, probably due to presynaptic inhibition (Rittweger et al. 2003).

Possible mechanism for this vibration induced presynaptic inhibition has been introduced by several researchers (Desmedt 1983; Desmedt and Godaux 1978; Romaiguere et al. 1993). According to the proposed mechanism, in the spinal cord, the preferentially activation of Ia afferents by muscle vibration initiates impulses in a polysynaptic excitatory pathway and a presynaptic inhibitory pathway (Desmedt and Godaux 1978; Romaiguere et al. 1993). Then, the spinal polysynaptic excitatory pathway evokes the tonic vibration reflex (TVR), whereas the spinal presynaptic inhibitory pathway is responsible for the vibration-induced reflex inhibition (Ashby 1987, 1980). It is suggested that the gains on these spinal interneuronal pathways are set by supraspinal influences, eg, corticoreticulospinal and vestibulospinal tracts (Andrews 1973).

It is documented that motoneuron pool excitability is regulated by presynaptic inhibition of Ia afferents (Burke et al. 1992). Burke et al. regarding this relationship between the inhibition and facilitation of reflex, suggested that the vibration induced presynaptic inhibition reflects the amount of reflex facilitation (Burke et al. 1992). With regard to the effect of vibration on the spinal reflex excitability, It has been shown that facilitation of the excitability of the spinal reflex was elicited through vibration to the quadriceps muscle (Burke et al. 1984).

Despite the above mentioned findings and hypothesis, to date, there is no data available regarding the effects of WBV on presynaptic inhibition. Furthermore, how the changes in presynpatic inhibition induced by WBV affect the functional muscular performances which are described to be improved by WBV is not understood.

Methods to Study Presynaptic Inhibition

To study changes in presynaptic inhibition a variety of inputs have been used (Stein 1995). The most common methods for measureing the presynaptic inhibition has been vibration or electrical stimulation applied to the antagonist, with common peroneal nerve stimulation being the antagonist for the soleus (Stein 1995; Zehr 2002). In normal subjects this produces a marked inhibition of the H reflex and this inhibition is believed to be usually attributed to presynaptic inhibition (De Gail et al. 1966). It has been known that vibration can produce several effects in addition to presynaptic inhibition. Hultborn et al. suggested that prolonged vibration might lead to refractoriness of Ia fibers, transmitter depletion at Ia terminals, postsynaptic reciprocal and non-reciprocal Ia inhibition, and effects from cutaneous and other receptors that will be excited by vibration (Hultborn et al. 1996; Hultborn et al. 1987). Morin et al. developed a method whereby they vibrated the muscle for a very brief period (3 pulses in 10 msec) (Morin et al. 1984). The authors showed that there was a period of time between 25 and 60 ms after the stimuli where the inhibition was most probably due to presynaptic inhibition (Morin et al. 1984). The vibratory inhibition is reduced in paraplegics (Calancie et al. 1993), and in patients with spastic hemiparesis (Milanov 1992). Based on these findings, it has been suggested that presynaptic inhibition is reduced in conditions in which descending control is removed and may be associated with the spasticity often found under these

conditions (Stein 1995). Interestingly, vibratory inhibition was increased in the paraplegics during the acute phase and decreased in the chronic phase of recovery after spinal cord injury (Calancie et al. 1993). So it was speculated that the loss of presynaptic inhibitory mechanisms is slow to develop (Calancie et al. 1993).

Electrical activation of remote muscle afferents leads to presynaptic inhibition of the Ia afferent, and presynaptic suppression of the H-reflex (Stein 1995; Zehr and Stein 1999a; Zehr 2002). It has been identified that conditioning the soleus H-reflex with prior common peroneal nerve stimulation at set intervals of up to 120 ms is considered to increase presynaptic inhibition or decrease soleus H-reflex amplitude (Capaday and Stein 1987; Morin et al. 1984; Pierrot-Deseilligny 2005; Zehr and Stein 1999b). Current literature describes techniques that suggest using an inter-stimulus delay of between 80 and 120 ms to measure presynaptic inhibition (Zehr and Stein 1999b). Conditioning the H-reflex with prior common peroneal nerve stimulation at inter-stimulus intervals of 80 – 120 ms was found to increase presynaptic inhibition because the control H-reflex (one without an antagonist stimulation) compared to that with increased presynaptic inhibition (antagonist stimulus 80 -120 ms prior) was apparent even when the level of motoneuron pool excitability was held constant (Zehr and Stein 1999b). Presynaptic inhibition can be assessed with various techniques. The major difference in the technique is specifically where they induce this inhibition. Presynaptic inhibition can be either intrinsic or extrinsic based on the location of the inhibition to the synapse. Classical presynaptic inhibition is considered extrinsic inhibition (EPI) because of the involvement of the inhibitory interneurones effect on the synapse of the sensory and motor fibers.

Conversely intrinsic presynaptic inhibition (IPI) is a regulatory mechanism of the synapse that is internal to the sensory and motor synaptic connection.

EPI involves depolarization of primary afferents by inhibitory interneurons under descending control, which make axo-axonal synapses near the afferent terminals (Crenna and Frigo 1987). To assess IPI, a paired reflex depression (PRD) has been used. According to a previous report from Trimble et al. and Mendell, changes in the paired reflex depression (PRD), a measure of the relative influence of the reflex activation history on reflex excitability, represent another means by which reflex excitability is controlled (Mendell 1984; Trimble et al. 2000).

The EPI is measured by comparing conditioned and unconditioned H-reflexes of the soleus muscle (Iles 1996; Zehr and Stein 1999a). Following H-reflex and M-wave measurements, the intensity of the conditioning stimulation is set at 1to 1.5 times of motor threshold of the tibialis anterior and the intensity is maintained throughout testing. To condition the soleus motoneuron pool (MP), the stimulation of the tibial nerve precedes the soleus stimulation by 80 - 120 ms (Iles 1996; Zehr and Stein 1999a). Therefore, conditioned measurements are elicited by first stimulating the common peroneal nerve (1 to 1.5 times of motor threshold of Mmax) followed by 80 - 120 ms delay, and is concluded by stimulation to the tibial nerve at 15 - 25% of the total MNs available (Mmax). Unconditioned measures are assessed by stimulating the tibial nerve (15 - 25% of Mmax) with the same intensity and measuring the resulting reflex activity without the influence of a conditioning stimulus. In summary, vibration or electrical stimulation of the common peroneal nerve induces presynaptic inhibition of the soleus H reflex pathways(Stein 1995; Zehr and Stein 1999b). It has been suggested that a

maintained soleus contraction or background EMG is used to identify changes to the level of presynaptic inhibition by a conditioning stimulus (Stein 1995; Zehr and Stein 1999b). Therefore, any changes in H-reflex amplitude reflect changes in the level of presynaptic inhibition generated by stimulation of group I afferents from the tibialis anterior and stimulation of the common peroneal nerve (Stein 1995; Zehr and Stein 1999b).

However, limitations should be considered. Previous investigations have been limited to the examination of the change in H-reflex amplitude with environmental changes, or comparison between different populations. In general, these methods are limited due to the fact that they do not isolate the site, that is, pre or postsynaptic, responsible for the modulatory effects often observed. The protocols reviewed here may provide a means of isolating the spinal pathways responsible for motoneuron excitability differences among different population and perhaps may uncover important information about the role of training on the human nervous system.

Functional Implications

Changes in presynaptic inhibition of Ia afferent fibres to both soleus and quadriceps motoneurones have been assessed at the onset of a selective voluntary contraction involving either muscle (Hultborn et al. 1996; Hultborn et al. 1987; Rudomin and Schmidt 1999; Willis 2006). Hultborn et al have shown that presynaptic inhibition of Ia fibres to motoneurones of the contracting muscle was decreased at the onset of voluntary contraction, permitting Ia activity to contribute to excitation of voluntarily activated motoneurones; on the other hand, presynaptic inhibition of Ia fibres to motoneurones supplying the muscle not involved in the contraction was increased

(Hultborn et al. 1987). Earles et al. in their recent study examining the efficacy of two spinal mechanisms in gating motoneuron excitability in power trained athletes, endurance trained athletes, and untrained subjects reported that the endurance-trained athletes demonstrated greater presynaptic inhibition and the power-trained athletes showed a decrease in presynaptic inhibition (Earles et al. 2002).

The observations of an increase or decrease in presynaptic inhibition should be well explained for its functional application. Pierrot-Deseilligny and Burke have indicated that the decreased presynaptic inhibition of homonymous quadriceps Ia terminals insures that the full excitatory I a feedback is available to provide a safety factor for the quadriceps contraction, which supports the body weight (when the knees are not locked in extension). They also stated that increased presynaptic inhibition of soleus Ia terminals could play a role in depressing the stretch reflex during balancing tasks so that the balance of the subject is not endangered by a sudden perturbation (Pierrot-Deseilligny 2005). It has also been suggested that the increased presynaptic inhibition of soleus Ia terminals could contribute to the depression of reciprocal I a inhibition, through presynaptic inhibition of the Ia input to interneurones mediating reciprocal Ia inhibition, much as is likely during co-contraction of antagonistic muscles (Pierrot-Deseilligny 2005). When standing without support, posture is potentially unstable, and contractions may be required in either of the antagonistic muscles operating at the ankle. The authors suggested that this creates a situation where a decreased in reciprocal Ia inhibition may be helpful in controlling body sway (Pierrot-Deseilligny 2005).

Conclusion

The primary purpose of this review of literature is to better understand the characteristics of each of the variables chosen in this study. Throughout the review paper, not only the characteristics of whole body vibration, electromechanical delay, rate of force development, and presynaptic inhibition but also training protocols and effective assessment methods and functional implication have been discussed. It has been speculated that WBV training might result in neuromuscular adaptations similar to the effect produced by strength training. However, despite the theorized mechanisms and explanations provided by early and recent vibration and whole body vibration studies, the neural adaptation responsible for such a dramatic enhancement of muscular performance caused by whole body vibration training has been less understood. In this respect, this study is set to investigate the effects of whole body vibration training on the neuromuscular system. The contents discussed here in this review of literature may help the investigators to find plausible explanations for the outcomes of the study. Furthermore, this paper may be used as a cornerstone for the study that might uncover important information about the role of whole body vibration on the human nervous system.

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APPEDIX FOUR: INSTITUTIONAL REVIEW BOARD REQUEST/ APPROVAL

Institutional Review Board ▪ Office of Sponsored Programs and Research Compliance
Oregon State University, 312 Kerr Administration Building, Corvallis, Oregon 97331-2140
Tel 541-737-4933 | **Fax** 541-737-3093
| http://oregonstate.edu/research/osprc/rc/humansubjects.htm
IRB@oregonstate.edu

TO: Mark Hoffman

NES

IRB #: 3733 – The Effects of Vibration Training on the Neuromuscular System (Student Researcher: Junggi Hong)

Level of Review: Full Board

Expiration Date: 10-1-08

Approved Number of Participants: 40

The referenced project was reviewed under the guidelines of Oregon State University's Institutional Review Board (IRB). The IRB has **approved** the:

(X) Initial Application ( ) Continuing Review ( ) Project Revision

with a (if applicable): ( ) Waiver of documentation of Informed Consent ( ) Waiver of Consent

A copy of this information will be provided to the full IRB committee.

- **CONSENT FORM:** All participants must receive the IRB-stamped informed consent document. If the consent is in a format that could not have stamp placement (i.e. web site language, email language, etc), then the language must be **exactly** as the IRB approved it.
- **PROJECT REVISION REQUEST:** Any changes to the approved protocol (e.g. protocol, informed consent form(s), testing instrument(s), research staff, recruitment material, or increase in the number of participants) must be submitted for approval before implementation.
- **ADVERSE EVENTS:** Must be reported within three days of occurrence. This includes any outcome that is not expected, routine and that result in bodily injury and/or psychological, emotional, or physical harm or stress.
- **CONTINUING REVIEW:** A courtesy notice will be sent to remind researchers to complete the continuing review form to renew this project, however – it is the researcher's responsibility to ensure that continuing review occurs prior to the expiration date. Material must be submitted with adequate time for the office to process paperwork. If there is a lapse in approval, suspension of all activity including data analysis, will occur.

- **DEVIATION/EXCEPTIONS:** Any departure from the approved protocol must be reported within 10 business days of occurrence or when discovered.

Forms are available at: http://oregonstate.edu/research/osprc/rc/humansubjects.htm.

If you have any questions, please contact the IRB Human Protections Administrator at IRB@oregonstate.edu or by phone at (541) 737-8008.

Date: 12-19-07

Elisa Espinoza Fallows

IRB Human Protections Administrator

APPENDIX FIVE: INFORMED CONSENT DOCUMENT

Department of Nutrition and Exercise Sciences
Oregon State University, 101 Milam Hall, Corvallis, Oregon 97331
Tel 541-737-2643 | **Fax** 541-737-2788

INFORMED CONSENT DOCUMENT

Project Title:	The Effects of Vibration Training on the Neuromuscular System.
Principal Investigator:	Mark Hoffman, Associate Professor
	Department of Nutrition and Exercise Sciences
Co-Investigator:	**Error! Reference source not found.**, Doctoral Candidate
	Department of Nutrition and Exercise Sciences

WHAT IS THE PURPOSE OF THIS STUDY?

You are being invited to take part in a research study designed to test the effects of whole body vibration. Whole body vibration has been demonstrated to help increase muscular strength. However, it is not known why this occurs. One theory suggests whole body vibration helps train reflexes and muscle responses. To test this idea your reflexes, muscle strength, and muscle response will be tested before and after a short (9 minute) bout of whole body vibration and over 4-weeks of whole body vibration training. This information may be used for publication and presentation.

WHAT IS THE PURPOSE OF THIS FORM?

This consent form gives you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask any questions about the research, the possible risks and benefits, your rights as a volunteer, and anything else that is not clear. When all of your questions have been answered, you can decide if you want to be in this study or not.

WHY AM I BEING INVITED TO TAKE PART IN THIS STUDY?

You are being invited to take part in this study because you are over 18 years and under 35 years of age and you have had no serious injuries to either of your legs.

WHAT WILL HAPPEN DURING THIS STUDY AND HOW LONG WILL IT TAKE?

All testing will be done in the Sports Medicine Laboratory (Women's Building Room 8). Prior to inclusion in the study Informed Consent Form will be completed.

If you are included in this study, you will be randomly assigned (coin toss) to one of two training groups: Vibration or Non-vibration.

Training Details

If you are assigned to the vibration training group you will participate in 4-weeksof vibration training. This training will occur three times per week. Each training session will include vibrating on the vibration platform for 9 minutes (3 bouts of 3 minutes each) with an amplitude of 5 mm and a frequency of 20Hz. These are common parameters used during clinical interventions and other laboratory studies of whole body vibration.

If you are assigned to the non-vibration group you will not receive vibration training during the study period. On the testing day, you will receive a passive rest period while standing on the floor.

If you agree to take part in this study your involvement in the study as the vibration group is total 12 visits for the exercises and three visits for the test. If you are assigned to the non-vibration group, your involvement in the study is only three visits for the test. The approximate length of time for each training is 15-20 minutes, and the length of time for each test session is 40 -60 minutes.

Regardless of group assignment, during the study your reflexes, muscle strength, and muscle response will be tested 3 times, pretest (entry into the study), mid-point (the beginning of the 3rd week of the study) and posttest (at the end of the study).

The following is a brief description of the testing session:

- Electrode placement (~5 minutes):
  - While lying prone, three lubricated surface electrodes will be placed over the calf muscle to monitor activity in your muscle. A stimulating electrode that delivers a small shock, that has been described as feeling similar to a "carpet shock", will be placed behind your knee while a another electrode will be placed above the front of your

kneecap. All areas of skin where electrodes will be placed will be shaved and cleaned with alcohol prior to application of the electrodes.

- Pre-test / baseline spinal reflex testing (~5 minutes):
  - While lying prone, approximately 30 to 50 shocks will be applied to the back of your knee. This will be done to determine your baseline reflex values. Again, the shocks have been described as feeling similar to a "carpet shock."
- Pre-test / muscle response (~5 minutes):
  - While sitting on the testing chair of the dynamometer, you will be secured with body straps, while the hip and the knee joints are flexed. Three measurements will be obtained during maximal isometric voluntary plantar flexion. You will be instructed to "plantar flex the ankle as hard and as fast as possible" after seeing the light signal generated by the light stimulator
- Treatment / short bout of whole body vibration (~9 minutes):
  - You will then step onto the vibration platform and will be vibrated for 3 bouts of 3 minutes with amplitudes between 5 mm and frequencies between 20 Hz. These are common parameters used during clinical interventions and other laboratory studies of whole body vibration.
- Post-test / muscle response (~5 minutes):
  - While sitting on the testing chair of the dynamometer, you will be secured with body straps, while the hip and the knee joints are flexed at 90 deg. Three measurements will be obtained during maximal isometric voluntary plantar flexion. You will be instructed to "plantar flex the ankle as hard and as fast as possible" after seeing the light
- Cleanup (~5 minutes):
  - Electrodes and lubricant will be removed and testing is completed.

WHAT ARE THE RISKS OF THIS STUDY

Due to the use of electrical stimulation, there may be a slight level of discomfort associated with the testing. This level of discomfort has been described as a sensation of a "carpet shock." It is important to note a very small percentage of subjects experience dizziness, nausea, and fainting associated with this mode of testing. You will be encouraged and reminded to alert the investigator if any of these symptoms appear. If any of these symptoms do occur, the testing will be discontinued immediately and you will be monitored until symptoms diminish. If testing is discontinued, you will receive a telephone follow-up to ensure any residual concerns are alleviated and addressed.

Due to the use of electrical stimulation and the risk of electrical shock, there are two devices (stimulation isolation unit, and constant current unit) placed in the circuit between you and the stimulator, which greatly decrease the chances of receiving a harmful shock. This type of nerve stimulation is common and considered to be safe for human subjects. In the unlikely event you receive a harmful shock, immediate steps will be taken to assist him/her. First, the testing will be discontinued immediately and vital signs will be evaluated. The condition of the subject will be monitored and the emergency system will be contacted immediately. The investigator is CPR certified and Emergency System will be activated via phone in the lab.

Following testing, you may experience slight skin irritation from the electrodes. This irritation should subside within 24 hours and can be decreased by the application of a skin moisturizer.

Foreseeable risks to you are minimal. During standing on the surface of vibration machine may result in mild muscle soreness for 24 to 48 hours following the exercise period. Strength and neuromuscular control testing may also result in mild muscle soreness for 24 to 48 hours following the three data collection sessions, e.g., at 0, 2 and 4 weeks.

WHAT ARE THE BENEFITS OF THIS STUDY?

We do not know if you will benefit from being in this study. However, we hope, that in the future, other people might benefit from this study because we will have a better understanding whole body vibration effects muscle responses

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. If you are assigned to the Vibration Group you will receive a payment of $60 and If you are assigned to the No-vibration Group you will receive a payment of $40 at the conclusion of the 4-week study period. If you withdraw from the study prior to completion, you will be compensated at a rate of $15 per week (Vibration group) or $10 per week (No-vibration group) that you participated.

WHO WILL SEE THE INFORMATION I GIVE?

The information you provide during this research study will be kept confidential to the extent permitted by law. To help protect your confidentiality, we will code all data forms and files without any identifiable participant information. All forms will be locked in a filing cabinet in a secured office.

DO I HAVE A CHOICE TO BE IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study and still keep the benefits and rights you had before volunteering.

You will not be treated differently if you decide to stop taking part in the study. If you choose to withdraw from this project before it ends, the researchers may keep information collected about you and this information may be included in study reports.

WHAT IF I HAVE QUESTIONS?

If you have any questions about this research project, please contact: Dr. Mark Hoffman at 541-737-6787 (mark.hoffman@oregonstate.edu) or Junggi Hong at 541-737-6899 (hongj@onid.orst.edu).

If you have questions about your rights as a participant, please contact the Oregon State University Institutional Review Board (IRB) Human Protections Administrator, at (541) 737-3437 or by email at IRB@oregonstate.edu.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Participant's Name (printed):

_____

_____ _____

(Signature of Participant) (Date)

APPENDIX SIX: RECRUITMENT FLYERS

Participate in a study on

Whole Body Vibration

and earn up to **$60!**

The researchers in the Sports Medicine Laboratory are conducting a study to determine the effects of a short bout of whole body vibration on your reflexes and muscle responses.

If you are between the ages of 18 and 35,

have ***not*** injured your legs or spine in the past year,

and are interested in participating in this research study please contact:

Sports Medicine Lab at 737-6899

Whole Body Vibration Study 541.737.6899
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