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A MOUSE MODEL FOR HAND-ARM VIBRATION SYNDROME

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Abstract- **Hand-arm vibration syndrome (HAVS) occurs in workers who use vibrating hand tools. Symptoms of HAVS include finger paresthesia and numbness, a loss of manual dexterity and grip strength, and vasospasms in the fingers in response to cold. Although the relationship between vibration exposure and HAVS is well-established, it is not clear how vibration causes tissue damage. The purpose of our research is to identify the fundamental physiological mechanisms involved in the development of HAVS. Toward that end, we have developed a vibration exposure system in which mice are placed in a small cage with a rigid floor that vibrates vertically. The system is capable of exposing mice to sinusoidal vibration at 125 to 1250 Hz with accelerations of up to 49 m/s^2 rms. Exposures last for 4 hours/day, 5 days/week, for up to 24 weeks. Initial results indicate that 11 weeks of 125 Hz vibration did not significantly affect the body weights of the mice, and that 12 and 24 weeks of vibration did not significantly affect the liver, kidneys, or stomach. These results suggest that this model can be used to examine the effect of vibration on the mouse foot and lower leg without confounding effects from systemic damage.**

Keywords - **hand-arm vibration syndrome, musculoskeletal disorders, occupational health, vibration, mice**

INTRODUCTION

Workers who use vibrating hand-operated tools are at risk for developing a range of pathologies known collectively as hand-arm vibration syndrome (HAVS). Symptoms of HAVS include numbness and paresthesia in the fingers and hands; impaired grip strength and manual dexterity; and vasospasms in the fingers when exposed to cold temperatures (called vibration white finger, or Raynaud's phenomenon of occupational origin) [1]. Studies of tissue from workers with HAVS have found demyelination and nerve fiber loss in the peripheral nerves, hypertrophy of arterial smooth muscle, and fibrosis in the nerves, blood vessels, and skin [1]. Numerous epidemiological studies have been conducted on the association between vibrating tool use and HAVS, and the relationship is considered to be well-established [2]. However, studies of the physiological processes by which HAVS develops and progresses have been limited, and there still is no generally accepted theory as to how vibration leads to tissue damage.

The purpose of our research is to identify the fundamental physiological mechanisms involved in vibration-induced injury and the development of hand-arm vibration syndrome (HAVS). As a first step, we have developed and tested a mouse vibration exposure system. The system is designed to expose the hind limbs of mice to well-defined sinusoidal vibration regimen at frequencies of 125 to 1250 Hz and amplitudes of up to 49 m/s^2. This system will allow us to reproduce in the laboratory the types of tissue damage seen in workers suffering from HAVS, providing greater insight into the pathological processes leading to the development of HAVS.

METHODOLOGY

Vibration exposure system. To expose mice to hind-limb vibration, polycarbonate cages with rigid 10 x 10 x 1.2 cm aluminum floors are mounted on top of air-cooled electromagnetic shakers capable of generating 98 N force. Each cage holds two mice in separate 5 x 10 x 7.5 cm high compartments which are ventilated at the top. The shaker oscillates the cage in the vertical direction, with the cage acceleration measured by a piezoelectronic accelerometer. A computerized linear control system ramps up to and down from the chosen vibration magnitude and maintains the vibration at the chosen frequency and magnitude. An interlock prevents mechanical transients as equipment is powered on and off. Cages for the control animals are identical, but are placed on foam isolation blocks to prevent transmission of vibration to them. The blocks are kept next to the shaker-mounted cages so that noise levels in both sets of cages are similar. For spectral analysis, the accelerometer signal is passed through a programmable low-pass filter set to 50X the primary mode frequency, and digital sampling is performed at 128X the primary mode frequency.

V408 electromagnetic shakers and PA100E amplifiers are from Ling Dynamic Systems (Royston, Herts, England). The 353B15 accelerometers and 482A20 signal conditioner are from PCB Piezotronics (Depew, NY). Data acquisition and control are performed through a PCI-MIO-16XE-10 data acquisition board and a PCI-6713 analog output board (National Instruments, Austin, TX) mounted in an Optiplex GX1 computer (Dell Computer, Round Rock, TX). Control software was written using LabView (National Instruments, Austin, TX). The 3382 programmable filter is made by Krohn-Hite (Avon, MA).

Mice. Six-week old female C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME) were used for these experiments. The mice were fed NIH-31 6% fat rodent chow (T. R. Last, Gibsonia, PA) and tap water *ad libitum*. The mice were maintained on a 12 hour light cycle. Vibration exposures began between 9:30 AM and 11:30 AM daily and lasted for 4 hours. All animal experiments in this study were approved by the NIOSH ACUC.

Plasma enzymes. Blood was collected at sacrifice from the posterior vena cava using sodium citrate (0.4% w/v) as an anticoagulant. After centrifugation, plasma was aliquoted and stored at -80°C until analysis. Analysis of AST, ALT, and LDH levels was conducted by AniLytics (Gaithersburg, MD).

Histology. Animals were sacrificed by CO_2 asphyxiation within 60 minutes after the last vibration exposure. Liver and kidney samples were fixed in buffered formalin. Stomachs were fixed with Karnovsky's fixative. All organ specimens were then embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

RESULTS

Initial tests on the vibration exposure system examined the mechanical performance. Acceleration data showed that the exposure system generated a sinusoidal acceleration profile with a total harmonic distortion < 2% at 125 Hz. Thermal tests conducted with a simulated load showed that the interior floor of the vibrated exposure cage remained within 1°C of ambient throughout the exposure.

Because the entire body of the mouse is exposed to vibration in our system, this study next focused on determining if vibration exposure was causing systemic effects which might confound studies of tissue damage in the hind limb. Nine mice were exposed to 125 Hz vibration at 49 m/s^2 acceleration 4 hours/day, 5 days/week, for 12 weeks, with nine control animals kept in identical cages but not vibrated. An additional four mice were exposed to the same level of vibration for 24 weeks, with four controls. The 4 hour/day exposure time was chosen because it approximates an average daily vibration exposure. According to American National Standards Institute (ANSI) guidelines, a worker using a tool vibrating at this frequency and magnitude should be restricted to 1 to 2 hours of use per day [3].

Histological examination of livers and kidneys showed no significant differences between vibrated and control animals after 12 or 24 weeks of vibration. Examination of stomachs of 3 vibrated and 3 control animals after 12 weeks of exposure also found no difference. Plasma enzyme levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) did not vary significantly between vibrated and control animals (fig. 1).

A separate group of eight mice (4 vibrated, 4 control) was weighed weekly over 11 weeks. For the first week of vibration, the average body weight of the animals exposed to vibration decreased slightly while the average weight of the controls increased, although the difference was not statistically significant (fig. 2). After one week of vibration exposure, the weights of the vibrated and control animals increased at approximately the same rate. Overall, vibration did not have a significant effect on animal body weight gain over an 11 week exposure.

DISCUSSION

The purpose of these experiments was to conduct initial tests on a mouse hind-limb vibration exposure system to be used for investigating the pathophysiology of hand-arm vibration syndrome. Our results indicate that the system generates a sinusoidal vibration exposure regimen at the chosen frequency with minimal distortion. The vibration is well-tolerated by the animals and does not have a significant impact on body weight, plasma enzymes, or abdominal organ tissues examined microscopically. This suggests that our system can be used to study the effects of vibration on mouse hind limbs without confounding effects from damage to other tissue. Future work will focus on determining if this model produces pathologies similar to those seen in workers with HAVS and on identifying physiological pathways that are affected by vibration exposure.

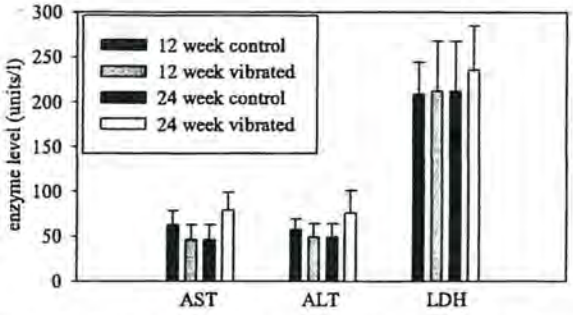

Fig. 1. Plasma enzyme levels for AST, ALT, and LDH. Each treatment combination included 4 animals (16 total). Error bars indicate standard error of the mean. No significant difference was found between mice exposed to vibration and controls (AST, p=0.55; ALT, p=0.28; LDH, p=0.81).

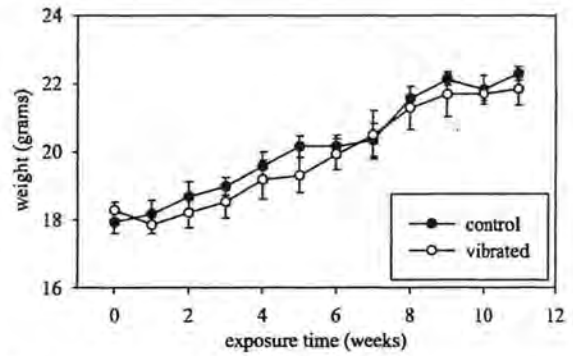

Fig. 2. Body weight vs. exposure time. Each treatment group included 4 animals (8 total). Error bars indicate standard error of the mean. Data was analyzed by comparing absolute weights and also by comparing change in weights over time. For both analyses, no significant difference was found between mice exposed to vibration and controls.

ACKNOWLEDGMENT

We would like to thank Chunlin Dong for her assistance in performing these experiments and Michael Kashon for his help in analyzing the data.

REFERENCES

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[2] B. P. Bernard, "Hand-Arm Vibration Syndrome," in *Musculoskeletal Disorders and Workplace Factors*, NIOSH Publication No. 97-141, 1997, pp. 5c-1 to 31.

[3] ANSI, "American national standard guide for the measurement and evaluation of human exposure to vibration transmitted to the hand," ANSI Standard No. S3.34-1986, 1986.

3) ***Use of Carbomethylcellulose to Improve the Mechanical and Handling Characteristics of Calcium Sulfate Bone Graft Material,*** Lewis, Kevin N.

Calcium sulfate has a long history of safe and effective use for repair of bone defects. However, the poor mechanical and physical properties have limited its clinical use. This project sought to augment the mechanical and handling characteristics of calcium sulfate cement by addition of either 5 and 10 wt% carboxymethylcellulose. Compared to control calcium sulfate, the augmented samples had lower density, higher workability, increased modulus of elasticity, and greater ultimate strength.

5) ***Micro-Mechanical Testing of Bone Tissues in Secondary Osteon and Interstitial Bone Regions,*** Osborn, Ronald W.; Wolf, John C.; Puram, Sreekar; Wang, Xiaodu

The purpose of this research was to develop methods for collecting and testing bone specimens acquired from interstitial and secondary osteon bone regions. These methods have been utilized to test the hypothesis that age related changes in collagen might be induced through the bone remodeling process. In order to isolate the two specific regions of interstitial and secondary osteon bone tissue, it was necessary to develop new techniques for precision positioning, machining, micro testing and finite element modeling. First, the desired sample is selected and marked by use of a microscope and an oil based ink. It is then placed in a micro mill vise and a laser positioning system determines the exact location of the machine head. New tools were developed, because of the small size of the sample (0.25mm in diameter, 3mm long), to precisely cut out the sample. A micro-three point bending testing machine was constructed and its controller software realized in Labview software. It is our hope that these methods will help prove the stated hypothesis and eventually provide a better quality of life for the elderly.

Session 2.2.5: Computational Tissue Mechanics (Posters) *Friday Oct-25-2002, 10:30 - 12:30 (Woodway III, Poster)*

1) ***A Mouse Model for Hand-Arm Vibration Syndrome,*** Lindsley, William G.; Jensen, Nancy; Kommineni, Choudari

Hand-arm vibration syndrome (HAVS) occurs in workers who use vibrating hand tools. Symptoms of HAVS include finger paresthesia and numbness, a loss of manual dexterity and grip strength, and vasospasms in the fingers in response to cold. Although the relationship between vibration exposure and HAVS is well-established, it is not clear how vibration causes tissue damage. The purpose of our research is to identify the fundamental physiological mechanisms involved in the development of HAVS. Toward that end, we have developed a vibration exposure system in which mice are placed in a small cage with a rigid floor that vibrates vertically. The system is capable of exposing mice to sinusoidal vibration at 125 to 1250 Hz with accelerations of up to 49 m/s^2 rms. Exposures last for 4 hours/day, 5 days/week, for up to 24 weeks. Initial results indicate that 11 weeks of 125 Hz vibration did not significantly affect the body weights of the mice, and that 12 and 24 weeks of vibration did not significantly affect the liver, kidneys, or stomach. These results suggest that this model can be used to examine the effect of vibration on the mouse foot and lower leg without confounding effects from systemic damage.

2) ***A Model for Pressure Enhancement in the Diabetic Nerve: Simulations of Diabetic Rat Peripheral Nerve and Nerve Collagens,*** Layton, Bradley E.; Sastry, Ann Marie; Wang, Hui; Sullivan, Kelli A.

We hypothesize that the extracellular matrix of both the endoneurium and epineurium remodel in response to the modified chemical and mechanical environment induced by diabetic peripheral neuropathy. Here, we describe quantitative comparisons of mechanical properties based on uniaxial testing, endoneurial fluid pressure (EFP) measurement, image analysis, and content (collagens I, III and IV) analysis of healthy and diabetic sciatic nerve collagens from Sprague-Dawley and BioBreeding rats. Nonlinear response of fibrous structures generally results from three phenomena: alignment of fibers, sequential failure of fibers in the array, or nonlinear response of the fibers themselves. Our preliminary approach employs a thin-walled pressure vessel assumption to model mechanical response of ex vivo tissue relaxation and uniaxial stretching at the millimeter scale. We also present results of a preliminary study of collagen fibers' mechanics, using a sinusoidal bundle-theory assumption, wherein equal load sharing among fibers is assumed. Measured moduli of epineuria are in general agreement with model results for the pressure vessel model, for literature values of modulus and measured EFP. The bundle theory demonstrably captures both the toe and yield regions in the tissue. Results suggest that a multiscale approach is needed to model tissue-property changes during remodeling.

4) ***Computational Modeling of a Triaxial Test for Soft Tissues,*** Doehring, Todd C.; Vesely, Ivan

Mechanical testing of soft biological tissues has generally been limited to 1D and 2D because of difficulties establishing uniform and controllable 3D deformation. To begin to address this problem, this study presents 3D computational models being developed for a novel triaxial experiment.

Session 2.2.6: Bone Adaptation (Posters)
Friday Oct-25-2002, 10:30 - 12:30 (Woodway III, Poster)

1) ***Do Cement Lines Restrict Osteoclastic Bone Resorption?,*** Sit, Sirena S.; Nagatomi, J.; Bizios, R.; Vashishth, D.

Bone is constantly remodeled throughout life, but whether the microstructure of the bone affects resorption is unknown. In this present study, longitudinal and transverse

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