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Physical Work May Be Risky—But Why?
The Underlying Pathomechanics of Musculoskeletal Injury

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Abstract. One of the curiosities associated with the groundswell of interest in the field of ergonomics—and the increasing awareness of the potential for injury as a consequence of physical work—is the schism that exists between the disciplines of ergonomics and those relating to physiology. With few exceptions, the conferences on ergonomics—and the ergonomics portions of those on industrial hygiene—rarely provide papers or presentations that relate to the physiological mechanisms that are associated with the occurrence of musculoskeletal injuries. However, it is believed that developing an appreciation of the basic factors that underlie musculoskeletal injury will provide both a more coherent understanding of why injuries occur as well as a broader, better integrated, and more generalizable basis for developing appropriate interventions. At the National Institute of Occupational Safety and Health, the epidemiological and intervention studies that have been a major focus of ongoing MSD-related research have been joined by a new research program dedicated to achieving a more basic understanding of factors that produce injury. The presentations comprising this session depict the nature of this new research initiative and provides examples of research being undertaken elsewhere that are also contributing to this research base. The present paper provides an overview of the NIOSH Health Effects Laboratory Division's pathomechanics research program.

1. Introduction

At the present time, most ergonomics guidelines and standards are predicated on the results of epidemiologic studies, psychophysical studies, studies of physiologic cost, or studies of biomechanical demands. Due to their nature, such studies rarely investigate the pathology underlying injury and attempt to link it with the physical activities involved. Appropriately, when concerned with human activities, most studies, laboratory or field studies, do not address the underlying pathomechanics associated with the manifestation of injury. The laboratory approach to repetitive stress injury uses the inferential model that presumes sustained exposure to unduly demanding physical activities, if continued unabated, will result in the following chain of events: fatigue, discomfort, pain, and injury. Such investigations must, appropriately, stop at the halfway point; i.e., they must stop prior to inducing pain to any human participant.

The National Research Council and Institute of Medicine (NRC&IM), in its recent review (2001) of musculoskeletal disorders (MSDs) and the workplace, has recognized the inherent limitations of such approaches as relates to the study of underlying causes of MSDs, and in their recommended *RESEARCH AGENDA* placed considerable emphasis on the use of alternative approaches—in particular, those involving human surrogate models (HSMs).

2. NRC&IM Research Agenda

The initial category of recommendations on the NRC&IM's research agenda pertains to methodological research concerns. The first recommendation in the *METHODOLOGICAL RESEARCH* area calls for the development of improved tools for exposure (i.e., dose) assessment. This recommendation cites the need for the development of practical, consistent, and accurate methods with which to obtain objective measurements of physical stress in the work place. A principal objective of the application of these improved exposure assessment tools would be the development of enhanced, quantitative relationships between occupational exposures (doses) and their consequent impacts (responses) upon workers. An inherent, recognized component of these developments is the need to be able to accurately and reliably quantify the nature and extent of the musculoskeletal disorders incurred.

Also included in the NRC&IM's category of MEHODOLOGICAL RESEARCH recommendations was a call for further development and refinement of sensory discrimination criteria with which to identify musculoskeletal outcomes.

The initial set of recommendations included within the NRC&IM's second category of research recommendations, "TOPIC AREA RESEARCH" related to the conduct of "tissue mechanobiology studies." This set of recommendations contained a total of three broad areas that incorporated many specific recommendations. These recommendations included the need for better characterization of ultrastructural and cellular responses to cyclical physical loading; the need to clarify whether injury responses to repeated loadings were due primarily to factors such as rate-of-loading, peak loadings, and duration of loadings or due to some other factors; and the need to identify the sources and mechanisms of pain as related to ultrastructural injury and biomechanical changes associated with exposures to physical loading. The eight specific recommendations related to the first recommendation (identifying the need for better characterization of responses to physical loading) cited the need to better determine the time frame, capacity, and mechanisms of the physiological repair; the specific need to address patterns of rest and reuse after injury as relates to underlying injury mechanisms and the time course of recovery; the need to develop quantitative dose-response models applicable to muscles and nerves and tendons; the need to recognize the impact of the nature and pattern of the loading (e.g., the rate of loading and the duty cycle) in the dose-response models developed; the need to develop similar models for neuromuscular disorders; and the need to include an appreciation the role of health and physical condition as they affect injury susceptibility. Additionally, the recommendations pertaining to tissue mechanobiology included the need to identify injury thresholds and the earliest molecular changes that precede structural damage and inflammatory responses as a consequence of various types of repetitive loading. These recommendations also cited the need to be able to validate noninvasive measures of functional skeletal muscle changes and repetitive stress injury symptoms associated with repetitive stress injuries by determining their biological bases via the use of controlled scientific studies. A specific goal of such studies was identified as the need to identify noninvasive means of detecting threshold-level skeletal muscle damage.

Other recommendations included in the area of tissue mechanobiology reflected the need to better understand how different types of tissue respond to repetitive loading, and to assess the roles of conditioning and age as they may affect such responses.

3. NIOSH/HELD HSM-Based Musculoskeletal Disorder Research Program

Whereas the more traditional approaches to the study of ergonomics issues (epidemiologic studies, psychophysical studies, and studies of physical cost and biomechanical demand) have used human subjects, none are capable of contributing directly to an appreciation of the physiological and biological mechanisms that underlie the occurrence of injury as a consequence of undue, sustained physical demands. To gain more direct insight as to the underlying pathomechanic injury mechanisms requires the direct examination of the injury process. Given the very appropriate ethical concerns that exist regarding the utilization of humans in such studies, the alternative is to develop other injury models.

In addition to conducting traditional studies of the types cited above, NIOSH is pursuing knowledge of the ergonomics injury-related processes via the use of two other avenues of research. For repetitive stress, human surrogate models (rodents) are being developed; for the investigation of the additional factor, hand-arm vibration (being investigated within the context of traditional ergonomics risk factors), a cellular model is also being studied.

The advantage of using human surrogate models (HSMs; i.e., rodents) to study ergonomics-related injury processes are many. Two predominate: (a) they are compatible with the imposition of highly controlled exposures, and (b) they permit the direct study of the affected tissues and associated physiological and biological processes. Accordingly, they permit an elegant opportunity to qualitatively and quantitatively study the relationship between dose and response—in (nearly) all their potential variations.

Many of the NRC&IM's recommendations relate directly to, and are consistent with, the MSD research program that is being pursued in NIOSH's Health Effects Laboratory Division (HELD). The NIOSH/HELD MSD research program, initially conceptualized in 1998, addresses the underlying biomechanical and sensorineural components of MSDs via the extensive use of a Human Surrogate Model (HSM).

The HSM-based MSD research program that has been developed and implemented within NIOSH/HELD has two overall goals. The first is the detailed examination of the relationship between the nature and extent of physical demands and the nature and extent of the physiological responses (and potential injuries) that occur. The major product of the efforts undertaken in pursuit of this goal will be the identification of the boundary conditions of the multivariate response surface that defines the transition from physical demands that are healthful (e.g., avoid injury, yield increases in strength and endurance) to those that are injurious. The second major goal is the pursuit of the development of objective indices (e.g., non-invasively or minimally invasively assessed biomarkers) of the status of the underlying physiological responses to the cumulative effects of the demands of the workplace. Each goal is described further, below. Subsequent to these descriptions, the current activities of the ongoing NIOSH/HELD program are briefly summarized.

3.1 Boundary Conditions and Dose-Response Relationships

The use of the terminology "dose-response" is an accepted one, but it often refers to relationships between broad categories of work exposures and broad categories of health-related consequences to the worker. Too often, however, these relationships are stated without providing an adequate appreciation of the qualitative differences involved; i.e., appreciations of the differences in the nature of the "dose" and of the "response." The NIOSH/HELD HSM-based MSD research program will provide a more complete characterization of both the nature and the extent of the dose parameters and the response patterns. The use of the HSM allows the "dose" parameters (e.g., type of exertion or movements, range-of-motion, force levels, number of exertions, work-recovery cycles, etc.) be highly controlled, and the associated investigation of the "response" to be undertaken in a very comprehensive manner (e.g., via the use of real-time monitoring of electrical muscle activity during exposure as well as biochemical and histological analyses of the consequent impacts on the blood chemistries and the muscle fibers). Within this research paradigm, the "dose-response" relationship has the potential of being expanded from a rather broadly defined bivariate concept to that of the multivariate relationship between vectors of dose parameters and vectors of response measures. The NIOSH/HELD research program will result in the development of a multivariate model of the relationships between physical demands and their resultant impacts; a model that can reliably discriminate between conditions and exposures that are adaptive and those that are maladaptive (i.e., between those that are non-injurious or produce a stronger, better-conditioned workforce and those that produce injury, impairment, or disability).

Within the NIOSH/HELD HSM-based program, two general approaches are used to pursue the goal of better understanding and better quantification of the relationships between exposures to various patterns of physical demands and their consequent impacts on the performer: the electrostimulation of the muscle of anesthetized rats (ESM approach) and the operant conditioning of intact rats (Operant approach). Each has its advantages and disadvantages.

3.1.1 ESM Approach

The ESM approach entails the use of electrical stimulation techniques coupled with the use of a very elaborate, computer controlled "exercise" apparatus (dynamometer) to produce very precisely controlled exposures (see Cutlip and Wirth, this volume). The computer-controlled, feed-back coupled apparatus can effectively control nearly all aspects of the exposure conditions: level of muscle force/tension applied throughout the exertion, the range of motion, the rate of movement, the work-recovery intervals, the total number of exertions per exposure period, etc. And the subsequent biochemical and physiological analyses (e.g., blood chemistries, histologies, electron-microscope examinations of muscle tissue) coupled with functional assessments of the rat's performance (e.g., evaluations of maximal force-production capabilities or decrements) provide superb, detailed documentation of the consequences of the exposures.

The potential concern with the ESM approach is that the participant rodent is anesthetized, and the potential impact of the anesthesia on the results is unknown. It may be that the exposure regimen imposed could be beyond the volitional capabilities of an intact rodent. Or it might be that the nature of the responses is somehow affected by the fact that the animal's responses are not under full volitional control. And, relative to those of an intact animal, it may be the case that the changes in the blood chemistries or tissue responses are somehow altered because the normal, adaptive feed-back loops of the animals response mechanisms have been interrupted to some degree by the use of anesthetics. To examine these possibilities—and explore additional areas—the NIOSH/HELD HSM MSD research program also includes a fully intact model that uses rodents that have been operantly conditioned (in the Skinnerian sense) to perform simulated work regimens (see Wirth and Cutlip, this volume).

3.1.2 Operant approach

Much like the ESM-model, in the operant model, a high degree of control is exerted over the activities performed such that the exposure conditions can be well specified. The operant-conditioning apparatus is computer controlled, and the rats are trained to perform particular responses using particular response topographies at specified intervals and rates, with specified force levels for specified force durations, etc. Compared to the ESM model, the volitional model does lack the millisecond-level of temporal control and the milligram-level of force-exertion specification. However, the level of exposure control and response reliability is believed to be quite adequate for the types of research questions being asked. The operant approach also offers the opportunities to address issues and questions that cannot be investigated with the ESM model. Among them are the following: Will an intact rat willingly work itself into an injurious state when responding for (food) rewards (i.e., instead of responding to avoid aversive consequences)? What is the maximum level of physical demand to which a fully intact rat will be willing to respond? How do variations in such work factors such as rate-of-response, duration of individual response, force level, total number of responses, work-recovery intervals, response topographies, etc., affect this "maximum"? When and how do variations in these parameters, considered separately and in combinations, begin to produce functional performance decrements and/or physiological injury? How do motivational and magnitude-of-reward parameters interact with these

factors and their combinations to impact behavior and injury potential? And, once answers have been obtained to these questions, questions about the potential impacts of workplace stressors and adverse environmental working conditions—and their potential interactions—can also begin to be addressed.

3.2 Objective Measures: Biomarkers

In addition to the two advantages cited above, the use of HSMs provides another very significant advantage that is beyond the immediate reach of most traditional ergonomic research approaches; i.e., the opportunity to investigate and identify biomarkers as potentially viable, objective indicators of existing or imminent injury. As previously indicated, a major goal of the NIOSH/HELD HSM-based ergonomics research program is the pursuit of the identification of non-invasive (or minimally invasive) objective biomarkers that are indicative of the physiological responses of the workers to the task demands being imposed upon them. The term "non-invasive" is used to mean biomarkers that can be obtained from samples of urine, salivation, perspiration, and/or exhalation byproducts.

The identification of such biomarkers and their relationship to ongoing and cumulative physical demands will be initially pursued via HSM research activities. Those found to be most promising will then be re-examined in carefully reviewed, approved, and executed studies with human participants. When the merits of such biomarkers have been established, and an inexpensive and reliable means of capturing and processing them has been developed, they will provide an additional, relatively rapid, affordable, and, perhaps most importantly, objective means of assessing the consequences of the ergonomic demands associated with the workplace.

4. ESM Studies: Near Term

Currently, the NIOSH/HELD ESM research program has studied the performance of rat plantar flexor and dorsi flexor muscles subsequent to high levels of exposure. An investigation of the response of rat tibialis anterior muscle to an acute exposure of oscillatory contractions has also been completed. The levels of force exertion capability, tissue histologies, and biochemical responses were examined immediately after exposure, and (in separate animals) up to 10 days after exposure. The histological cross-section studies have yielded indications of severe fiber disruption and swelling, and the presence of inflammatory cells within the tissue. Necrotic fibers were also encountered in the histological sections. The examination of the force-exertion capabilities data from acute-exposure dynamometry studies of eccentric muscle actions indicate a reduction in the force-generating capacity of nearly ½ the pre-exposure level—a significant level of functional impairment. This area of research continues to be oriented toward the refinement of the animal models, the identification of representative biomarkers, and will further investigate maladaptive mechanisms of contraction-induced muscle injury. The *in vivo* investigation of dynamic parameters such as level-of-force, range-of-motion, velocity-of-movement, and the number of repetitions continues using single, acute exposures of eccentric muscle actions as are needed to produce a transient non-recoverable force decrement and myofiber disruption of the dorsi flexor muscle of anesthetized rats. Future studies will pursue acute, single high-level eccentric muscle action exposures to investigate the relationships between the levels of inflammatory agents present in muscle tissues and the degree of decrement in the static and dynamic force-exertion capabilities.

5. Operant Studies: Near Term

The focus of HSM operant research program in the near term will be on the development of the specific operant conditioning procedures—and the refinement of schedule parameters—that yield maximum control over response topographies when the force levels and force durations are systematically varied. The willingness of intact rats to continue working for food reward under repetitive, high-demand response conditions will also be investigated. (NOTE: The rat's weights are maintained at desired levels by access to food outside of the experimental chamber; i.e., an "unwillingness" to work at high levels of physical demands during experimental sessions will not affect their total daily food intake and body weight.) A continuing focus of these research activities, as well as those of the ESM program, is upon efforts to (a) identify viable biomarkers, and (b) better understand the time-course of injury development and the recovery process as they relate to repetitive exposure conditions.

6. HSM-Based Hand-Arm Vibration Studies

The purpose of this project is to investigate the physiological and biomechanical factors associated with the development of hand-arm vibration syndrome (HAVS). HAVS occurs in workers who use vibrating tools such as grinders, jackhammers, and chainsaws. It is characterized by nerve damage, circulatory problems, and loss of strength in the hand and arm. Although the epidemiological evidence for HAVS is well established, the physiological mechanism by which vibration causes tissue damage is not clear. In previously published human studies, endothelin-1, a vasoactive factor, has been suggested as a key component in the development of vibration white finger syndrome. However, the results of the studies conducted in this area, and those undertaken in other, related areas, have been unclear. The consequent lack of understanding of HAVS injury mechanisms has hampered efforts to reduce the incidence of HAVS. Our project will provide a better understanding of the physiological and psychophysical changes that occur with vibration exposure, and will identify possible biological indicators (biomarkers) that may be used to reliably predict the development of HAVS. We are approaching the study of HAVS via the development of two models: a cellular model and a rodent model.

6.1 HAVS Cellular model

In our efforts to develop a cellular model of the HAVS we are exposing dermal microvascular endothelial and vascular smooth muscle cells to vibrations of various frequencies and acceleration levels normally produced by vibrating tools. Changes in the production of vasoactive factors (endothelin-1, prostaglandin E_2, and nitric oxide) and coagulation/fibrinolysis factors (von Willebrand factor, thrombomodulin, tissue type plasminogen activator, and plasminogen activator inhibitor-1) as well as the expression of genes related to inflammation (intercellular adhesion molecule-1) and intimal hyperplasia (platelet derived growth factor-B) will be monitored to investigate the etiology of vibration-induced injury and provide a better understanding of the injury mechanisms associated with occupational exposure to vibration.

To date, our experiments have shown for the first time that vibration exposure in an *in vitro* system can directly result in an increase in endothelin-1 (ET-1) secretion by endothelial cells. We are now conducting further experiments over a wider range of frequencies and amplitudes to better characterize this effect. We are also examining the effects of vibration on the secretion of von Willebrand factor (vWF), a coagulation/fibrinolysis factor, and interleukin-8 (IL-8).

6.2 HAVS HSM model

We are also assessing the viability and utility of three animal models for HAVS: a rat-tail vibration model, an operant-conditioning-based rat front paw model, and a mouse whole-body model. The initial set of vibration exposure experiments has been completed and the tissue is now being evaluated. Pilot studies using the operant-conditioning-based model have been completed, and experiments involving total daily vibration exposure times of up to 2 hours/day have been initiated. Pilot studies to support HSM research using whole-body exposure model are also underway. For each model, tissue from exposed animals will be evaluated histologically and biochemically for evidence of inflammation and damage.

Additionally, because workers having HAVS also suffer impaired sensory function in their hands (numbness, tingling, and a degraded sense of vibrotactile discrimination) we are developing several quantitative sensory testing methods to determine if they can provide an indication of the progress of vibration-induced sensorineural pathology. For the rat-tail vibration model, we will examine the utility of laser-Doppler cold challenge blood flow measurements, tail flick tests, and nerve conduction studies. Rat tail temperature will be studied via an infrared camera. For the operant-based rat front paw model, we are evaluating the staircase test. For the mouse whole-body vibration model, we will study an electronic aesthesiometer and a thermal plantar analgesia test.

7. Summary

To complement the knowledge base that has been created using more traditional approaches, the NIOSH/HELD musculoskeletal research program is developing human surrogate models of chronic strain and overload injury to achieve a greater understanding of the pathomechanics that underlie the occurrence of MSDs. The program uses both electrical stimulation and behavioral methods. State-of-the-art, computer-controlled apparatus (to provide precise exposures) will be combined with equally sophisticated histological, biochemical, and muscle-performance measurement technologies (to record responses) to undertake detailed investigations of the dose-response relationships associated with physical loadings and to study the time course of the inflammatory processes and the physiological repair processes.

The research program will provide the empirical basis for the development of multivariate models of injury that can discriminate between acceptable and adaptive levels of physical demands and those that are maladaptive and potentially injurious. It will also vigorously pursue the identification and development of biomarkers and accompanying analytic techniques and technologies that are capable of being used by both researchers and practitioners in laboratory and field environments to provide objective indicators of the underlying physiological state of workers.

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