University of Alberta

A functional electrical stimulation technique for the prevention of deep tissue injury

by

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ABSTRACT

Pressure ulcers are a common medical complication afflicting individuals with diminished mobility and sensation. Pressure ulcers develop due to morphological and biochemical changes triggered by the combined effects of mechanical deformation, ischemia, and reperfusion that occur during extended periods of immobility. Once developed, the quality of life of the person is severely affected and the necessary treatments are long and expensive. Common preventative interventions include frequent repositioning to relieve areas of the body at risk of developing an ulcer, as well as the use of pressure relieving specialized cushions and mattresses. The main goal of this thesis is to test the effectiveness of an electrical stimulation technique for preventing the formation of deep tissue injury, as well as to obtain an insight into its mechanisms of action. The results of this thesis indicate that this technique could become a viable intervention for the prevention of pressure ulcers.

DEDICATION

"Para mis padres, por permitirme soñar, por enseñarme a seguir adelante ante la adversidad, y por siempre estar a mi lado en cada paso de este camino, en el cual, lo mejor aún está por venir"

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AC	Alternate current
ANOVA	Analysis of variance
APAC	Alternating pressure air cushion
APAM	Alternating pressure air mattress
ATP	Adenosine triphosphate
BW	Body weight
DC	Direct current
DNA	Deoxyribonucleic acid
DTI	Deep tissue injury
EPUAP	European pressure ulcer advisory panel
FOV	Field of view
H&E	Hematoxylin and Eosin
H_2O_2	Hydrogen peroxide
IES	Intermittent electrical stimulation
K^+	Potasium
LG	Lateral gastrocnemius
LS	Lateral soleus
MG	Medial gastrocnemius
MRI	Magnetic resonance imaging
MS	Medial soleus
Na^+	Sodium
NPUAP	National pressure ulcer advisory panel
$O_{2\text{-}}$	Superoxide
OH	Hydroxyl radical
Pi	Inorganic phosphate
PCr	Creatine phosphate
PSST	Pressure sore status tool

LIST OF ABBREVIATIONS

Abbreviation	Definition
PUSH	Pressure ulcer scale for healing
ROI	Region of interest
SCI	Spinal cord injury
T_2	Transverse relaxation
TE	Echo time
TR	Relaxation time
USD	United States dollars
VAC	Vacuum-assisted closure
XDH	Xanthine dehydrogenase
XO	Xanthine oxidase

CHAPTER 1

PRESSURE ULCER ASSESSMENT, TREATMENT, AND PREVENTION*

1.1 Introduction

A routine day in the life of most people involves spending a significant amount of the time seated, whether it is in a classroom or at work, in a vehicle, or at home. The seat we use is often chosen by chance or availability (classroom, work). In other instances, a seat is chosen based on one's own personal preference (home). The process of picking the appropriate seat might seem trivial to most people, but when considering that one spends a significant part of the day seated, much thought should be given to the seat of choice in order to reduce the chances of medical complications associated with prolonged sitting. Several studies have shown that prolonged sitting can increase the risk of developing lower back pain, shoulder pain, and neck pain. These musculoskeletal disorders are frequent causes of sick-leave that lead to the loss of millions of work days every year (Cagnie et al. 2007; Johanning 2000; Krismer et al. 2007; Kvarnstrom 1983; Morken et al. 2003).

Ariëns et al (Ariëns et al. 2001) reported that sitting at work for more than 95% of the working hours is a risk factor for developing neck pain. A study performed with European truck drivers found that 81% of the participants reported a musculoskeletal problem in at least one area of the body during the year prior to the study. Lower back pain had the highest incidence at 60%,

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followed by shoulder pain (39%), knee pain (36%), and neck pain (34%) (Robb and Mansfield 2007). An increase in car driving time also leads to an increase in the number of absent days from work due to lower back pain (Porter and Gyi 2002). Even among teenagers, prolonged periods of sitting are associated with a higher incidence of neck and shoulder pain (Auvinen et al. 2007). Moreover, sedentary activities such as watching television and reading, were associated with neck pain in girls, while working or playing on a computer were associated with neck pain in boys.

While most able-bodied individuals can experience some type of posture related pain at any time during their life due to prolonged sitting, postural disorders are not the only medical complication associated with prolonged sitting. A different disorder arises when the seated individual has reduced mobility and sensation, such as a person with a spinal cord injury (SCI) who is wheelchair dependent. While an able-bodied individual subconsciously moves periodically in his/her chair to relieve the discomfort of sitting, the same may not be possible for a person with SCI.

Approximately 75% of a person's body weight is supported by the buttocks and the ischial tuberosities when sitting upright. In this position, the soft tissue (skin, fat, fascia, muscle) between the seat surface and the ischial tuberosities is compressed, thereby reducing blood flow and generating mechanical stresses and strains in the tissue, especially in the muscles around the bony

prominences. If this condition is maintained for an extended period of time, a pressure ulcer begins to develop in the affected tissue, in particular the muscle. The time required for an ulcer to begin developing can vary for each individual depending on the muscle mass and overall health of the person; however, a seat that distributes pressure around the buttocks poorly will lead to a reduction in the time required for an ulcer to begin forming.

1.2 Incidence of Pressure Ulcers

A pressure ulcer is defined by the National Pressure Ulcer Advisory Panel (NPUAP) in the United States, as a "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure in combination with shear and/or friction" (Black et al. 2007). Although the general layperson is usually unaware of the prevalence of pressure ulcers, ulcers are one of the main complications associated with immobilization and loss of sensation. Populations at risk of developing pressure ulcers include the elderly, residents of long-term care facilities and nursing homes, patients in acute and critical care units, patients who must undergo lengthy surgeries, as well as individuals who have suffered neurological insults such as SCI or stroke (Conine et al. 1989; Edlich et al. 2004; Labbe et al. 1987; Salzberg et al. 1996; Woolsey and McGarry 1991; Zanca et al. 2003). A review of all published Medline articles during the 1990 - 2000 decade conducted by the NPUAP, indicated that clinical incidence rate of pressure ulcers is 7 – 38% in acute care settings; 8 – 40% in critical care settings; 4 – 21% in the operating room; 7 – 23% in long-

term care; and 16 – 17% in homecare settings (Panel 2001). Variation in the incidence rates was reported to be due to variations in the definitions of an ulcer, formulae used to calculate incidence rates, mixed populations and sources of data, as well as random variation among the different studies.

Ulcers can develop within a few hours of immobilization. Aronovitch (Aronovitch 2007) reported that among patients who developed a pressure ulcer intraoperatively, the median time of the surgery was 4.48 hrs. The estimated annual cost of treating hospital-acquired pressure ulcers alone in North America is in the range of $2.2 to $3.6 billion USD (Zanca et al. 2003) and $2.6 to $4.0 billion USD in the United Kingdom (Bennett et al. 2004). Although the risk and incidence of pressure ulcers increase with age, pressure ulcers can also develop in immobilized infants and children, where the incidence rates in pediatric intensive care units have been reported to be as high as 27% (Curley et al. 2003).

Individuals with SCI are especially at risk of developing ulcers due to their impaired sensation and atrophied muscles (Guthrie and Goulian 1973; Thiyagarajan and Silver 1984). More than 80% of individuals with SCI develop pressure ulcers (Salzberg et al. 1996), with incidence rates varying depending on the level and completeness of injury. Richardson & Meyer (Richardson and Meyer 1981) reported a 60% incidence rate in individuals with complete quadriplegia, 42% in incomplete quadriplegia, 52% in complete paraplegia and

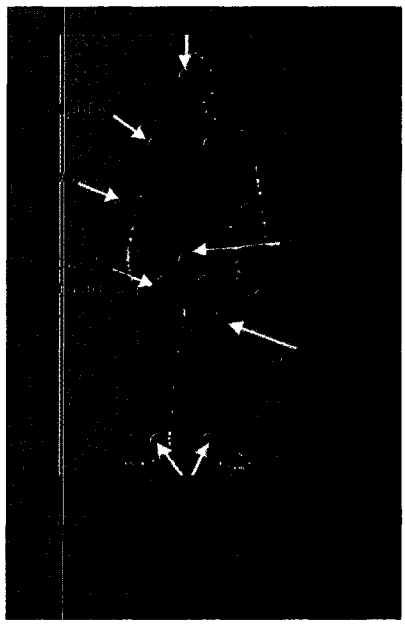
29% in incomplete paraplegia. Similarly, Young & Burns (Young J.S. 1981) reported a 40 to 45% incidence of pressure ulcers per year in all grades of sensory and motor quadriplegia. In a 3-year study focusing on veterans with SCI, Garber and Rintala (Garber and Rintala 2003) showed that 39% of the participants were diagnosed with at least one pressure ulcer at any given time of the study and each experienced an average of 4 ulcers. Pressure ulcers on the pelvic area accounted for 67% of all ulcers and 76% of those required hospitalization. Originally, pressure ulcers were referred to as "bedsores" or "decubitus ulcers" due to the high incidence of this type of lesions in individuals confined to a bed; however, ulcers also develop in wheelchair users. The most susceptible location for pressure ulcers in wheelchair users is the tissue over the ischial tuberosities where muscle-bone interface forces are greatest (Breuls et al. 2003b; Drummond et al. 1982; Ferguson-Pell 1980). Ischial ulcers represent 24% of the total incidence of pressure ulcers (Liu et al. 1999).

Severe ulcers require an average hospital stay of two months and cost $15,800 to $72,680 to heal (Rischbieth et al. 1998). Given that 320,000 North Americans are currently living with SCI, the annual costs of treating pelvic ulcers in 39% of this population alone are $1.0 to $4.6 billion USD. In addition to the financial consequences, pressure ulcers lead to further debilitation in individuals whose physical abilities are already compromised, further reduction in general independence and productivity, and lowering of self-esteem and self-worth (Krouskop et al. 1983). This results in a considerable decrease in the

individual's overall quality of life.

The gravest risk associated with a developed pressure ulcer is the possibility of death from complications associated with an open infected wound, such as bacteremia (Bryan et al. 1983; Galpin et al. 1976; Wall et al. 2003). Higher mortality rates have been observed in individuals with pressure ulcers compared to age-matched subjects without ulcers, in particular among the elderly (Brandeis et al. 1990). In the United States between 1990 and 2001, pressure ulcers were reported as a cause of death for 114,380 persons (Redelings et al. 2005). A widely known case of death due to complications associated with a pressure ulcer was the tragic loss of the actor Christopher Reeve, who in 2004 died of cardiac complications caused by an infected pressure ulcer.

1.3 Etiology of pressure ulcers



Pressure ulcers are a medical complication associated with immobilization, affecting bedridden individuals and wheelchair users. Pressue ulcers develop when soft tissue is compressed between a bony prominence and a surface for an extended period of time (Fennegan 1983; Guthrie and Goulian 1973; Salcido et al. 1995; Swarts et al. 1988; Woolsey and McGarry 1991). The regions of the body commonly

affected by pressure ulcers include the sacrum, ischium, heels, elbows, scapulae, trochanters, and the occiput (Figure 1-1). The main factors behind the formation of a pressure ulcer are the high mechanical stress and shear forces generated during the compression of the soft tissue. The prolonged exposure of the tissue to these excessive forces can directly lead to irreparable cell damage due to tissue deformation (Bouten et al. 2003; Breuls et al. 2003b; Daniel et al. 1981; Linder-Ganz et al. 2006a; Linder-Ganz and Gefen 2004; Linder-Ganz et al. 2006b; Stekelenburg et al. 2006b; Stekelenburg et al. 2007). In addition, extended loading of the tissue renders the tissue ischemic, limiting or eliminating the flow of oxygen and nutrients into the affected tissue and the removal of metabolic waste away from it. In the process of pressure ulcer development, ischemia is a major cause of injury to the tissue (Kosiak 1959, 1961; Kosiak et al. 1958). Subsequent reperfusion of ischemic and already injured tissue can further increase the damage to the tissue (Grace 1994; Gute et al. 1998; Peirce et al. 2000; Tsuji et al. 2005), initiating a negative cycle of metabolic changes in the tissue that lead to the formation of a pressure ulcer (Figure 1-2).

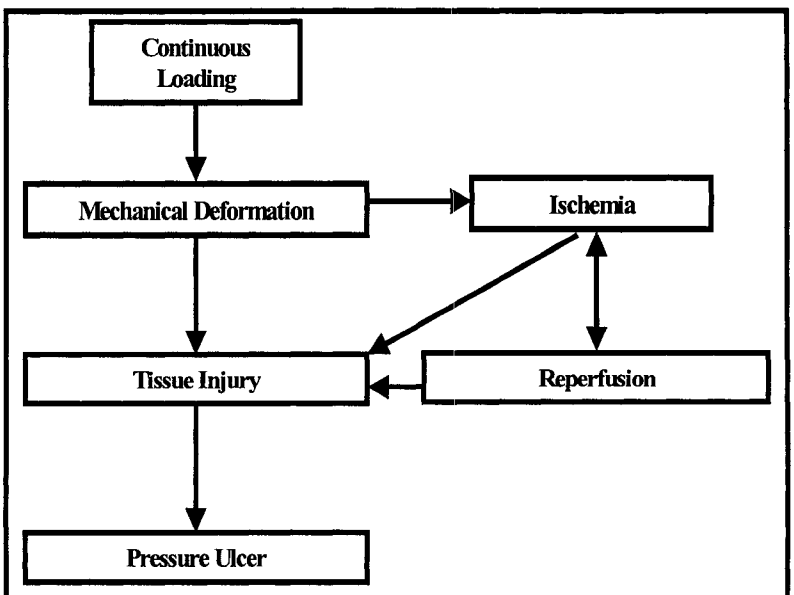


Figure 1- 2: Pressure ulcer formation process

1.3.1 Effects of ischemia and reperfusion

Pressure in excess of that for capillary perfusion causes capillary occlusion, and interrupts the supply of oxygen and nutrients to the tissue and the removal of carbon dioxide and metabolic waste (Lyder 2003). The lack of oxygen forces the cells to switch to anaerobic respiration which in turn alters the concentration of energy metabolites important for cell function and homeostasis. The rate of adenosine triphosphate (ATP) production decreases and the levels of creatine phosphate (PCr) and glycogen decrease as they are used to produce new ATP. The levels of lactic acid and inorganic phosphate (Pi) increase, causing a decrease in pH, which in turn leads to clumping of nuclear chromatin and DNA inactivation (Grace 1994; Tupling et al. 2001b). The duration of cell survival under anaerobic conditions depends on the type of the cell: skeletal muscles being highly sensitive to the lack of oxygen. Levels of ATP in the intracellular muscle space are reduced by 26% and 96% 30 minutes and 4 hrs after ischemia, while lactic acid is increased by 35% and 1000%, respectively (Kabaroudis et al. 2003; Tupling et al. 2001a, b). Levels of PCr and glycogen are reduced by 99.4% and 88% and Pi is increased by 400% 4 hrs after ischemia (Tupling et al. 2001a, b). Depletion of ATP also disrupts the Na^+K^+-ATPase pump which maintains the balance of osmotic pressure between the intra- and extra-cellular environments. Upon failure of the pump, K^+ diffuses out of the cell while Na^+ accumulates inside accompanied by an accumulation of water, leading to cell swelling and eventual bursting of the membrane.

Under ischemic conditions, substrates for producing oxygen free radicals are formed. The enzyme xanthine dehydrogenase (XDH), which is found in the sarcolemma and mitochondria of aerobic muscle fibers and in the capillary endothelial cells of skeletal muscle, is converted to xanthine oxidase (XO). Moreover, ATP is broken down into hypoxanthine and xanthine, releasing iron in the process (Gute et al. 1998). As the duration of ischemia increases, the concentrations of XO, hypoxanthine and xanthine increase.

Paradoxically, reperfusion of tissue following prolonged periods of ischemia can result in further injury even though restoration of blood flow is essential to maintain the living conditions of the cells (Grace 1994). In the presence of oxygen, XO reacts with hypoxanthine to produce superoxide (O_2-), and with xanthine to produce hydrogen peroxide (H_2O_2). Hydrogen peroxide in turn reacts with iron and produces hydroxyl radical (OH). Therefore, the sudden increase in available oxygen triggers a large production of H_2O_2 and free radicals that have three main harmful effects: 1) peroxidation of cell membranes; 2) oxidative modifications of proteins; 3) lesions in DNA. These changes further damage the cell leading it to necrosis (Appell et al. 1999; Grace 1994; Gute et al. 1998; Kabaroudis et al. 2003; Labbe et al. 1987). Reperfusion also brings to the affected tissue large amounts of neutrophils whose increased infiltration has been associated with increased amounts of damage to the tissue (Grace 1994; Gute et al. 1998). It is believed that leukocyte accumulation leads to an increase in tissue edema. Moreover, some leukocytes are believed to

aggregate in the capillaries, occluding them, and partly contributing to the "no-reflow" effect, where tissue oxygenation is not restored even when there is normal blood flow in the arteries. This cascade of morphological, biochemical, and functional changes in the cell leads to its death (Finestone et al. 1991; Gilsdorf et al. 1991; Grace 1994; Sagach et al. 1992; Tupling et al. 2001a, b).

1.3.2 Effects of Excessive Mechanical Deformation

Excessive deformation of tissue, caused by the mechanical forces generated during loading is recognized not only as the cause of ischemia in the tissue that leads to pressure ulcer formation, but also as a direct cause of tissue injury. These mechanical forces are 1) normal stress, 2) shear stress, and 3) friction. Normal stress is the distribution of force applied to a determined area of the tissue in a direction perpendicular to the support surface, as a result of the loading of the tissue. This type of stress is commonly referred to as "pressure", and causes the compression of the tissue between a bony prominence and the support surface. A study of the effects of pressure and its role in the etiology of pressure ulcers conducted by Kosiak identified an inverse relationship between the magnitude of pressure applied to the tissue, and the duration of the application (Kosiak 1959). Higher levels of pressure applied for shorter periods of time were found to be as damaging to the tissue as lower levels of pressure applied for prolonged periods (Kosiak 1959). Although traditionally high pressure levels were only considered the main cause for ischemia, which was in turn considered as the main cause for pressure ulcer formation, recent studies

have shown that high pressure levels are cabable of directly injurying the tissue. At the cellular level, in-vitro studies have shown that the compression of single cells as well as that of engineered tissue, causes deformation in the cell's membrane which can be irreversible and lead to cell death (Bouten et al. 2001; Breuls et al. 2003a; Peeters et al. 2003). Animal experiments have also indicated that the combined effects of compressive loading and ischemia cause greater tissue injury than ischemia alone (Stekelenburg et al. 2007). Normal stress is the main cause for the formation of deep tissue injury (see section III below).

Shear stresses are forces distributed parallel to the support surface. In the etiology of pressure ulcers they are usually accompanied by friction, which is the force that opposes the movement between two surfaces. These types of forces are generated by the degree of inclination of the upper body in an individual lying in bed or sitting in a wheelchair, or by the manner in which a person is repositioned. When inclined, the body tends to slide downwards due to gravity, generating friction between the skin and the bed which opposes the direction of movement. This generates shear stresses in the tissue, with the deep tissue pulling downward as the superficial tissue pulls upward. Similar forces are generated when a person is repositioned without being completely lifted. A study conducted by Goldstein and Sanders (Goldstein and Sanders 1998) showed that shear forces injure superficial tissue layers, and the onset of injury becomes more rapid as the shear forces increase. Repeated exposure to

friction causes tearing of the skin, and is considered a factor in the etiology of superficial pressure ulcers (Dinsdale 1973; Dinsdale 1974). Tissue could also be subjected to torsional stress, however, this specific type of stress is not considered a cause for tissue injury in the pressure ulcer formation process.

1.3.3 Other Factors

Several other factors have been associated with the formation of pressure ulcers, such as incontinence, poor nutritional status, cardiovascular dieases, atrophied muscles, and the presence of scar tissue from previous pressure ulcers. Although these factors on their own do not generate a pressure ulcer, a person afflicted by any of them is at a higher risk of developing a pressure ulcer.

Incontinence typically arises as a complication from a SCI or as a result of aging. When present, incontinence increases the amount of moisture in the skin. Prolonged exposure to moisture can lead to maceration and breakdown of the skin. Several studies have associated the presence of incontinece with a higher risk of pressure ulcer development (Benoit and Watts 2007; Brandeis et al. 1994; Schnelle et al. 1997). Besides providing excesive moisture, incontinence can also lead to skin breakdown because of its contents. Urine contains several metabolism waste prodcuts, in particular urea, which can lead to skin irritation due to its acidic nature. In addition, once an ulcer has developed incontince increases the risk of infection of the wound.

A poor nutritional status can affect a person's health in many forms, in addition to the risk of development of pressure ulcers. In the latter case in particular, individuals with nutritional defecits are more likely to develop a pressure ulcer and have lower healing rates once an ulcer has developed (Mathus-Vliegen 2004; Thomas 1997). In particular, lower levels of serum albumin have been associated with higher risks of developing pressure ulcers (Gengenbacher et al. 2002; Reed et al. 2003).

One effect of immobilization, especially after a SCI is the lack of muscle tone and atrophy of the muscles below the lesion level. Loss of muscle mass in the gluteal region leads to higher interface pressure levels around the ischial tuberosites, the location most at risk of developing pressure ulcers in wheelchair users.

People who have had a pressure ulcer are also at higher risk of developing a recurring ulcer, primarily due to scar formation and compromised tissue integrity after the ulcer has healed (Woolsey and McGarry 1991). Deep scars act as promoters for pressure ulcer development because of their mismatched mechanical properties with the surrounding muscle; this subjects the surrounding tissue to heightened interfacial stresses, increasing the likelihood of ischemia and excessive mechanical deformation.

1.4 Classification of Pressure Ulcers

Traditionally, pressure ulcer development had been considered to initiate at the level of the skin and progress to encompass the underlying fat, muscle, and bone tissue. Based on the progression of the lesion, pressure ulcers are classified according to a scale set forth by the NPUAP (Black et al. 2007). This scale was originally defined in 1989 and has been updated over the years as knowledge related to pressure ulcers advanced. These are the 4 stages in the scale (Figure 1 – 3):

Stage I: Redness or discoloration of intact skin compared to surrounding areas, usually over bony-prominences. Changes in skin temperature and consistency may also be present.

Stage II: Shallow wound that may appear as an open blister or abrasion. Damage to the tissue is limited to the dermis and/or epidermis.

Stage III: Full thickness tissue loss appearing as a deep crater wound. Damage to the tissue involves the skin and subcutaneous fat, but not the muscle or bone.

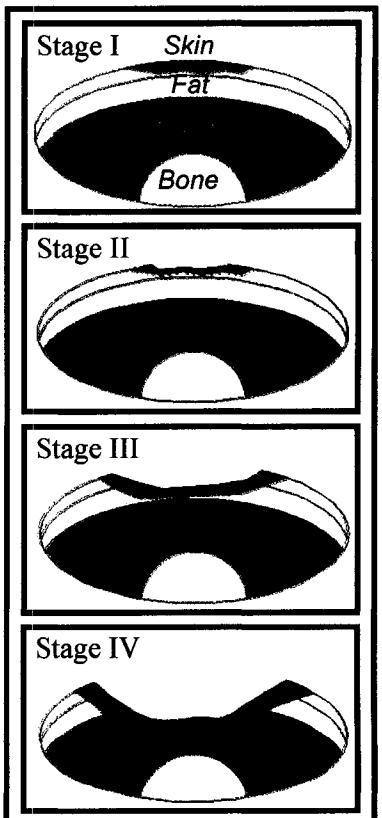


Figure 1 – 3: Pressure ulcer classification

Stage IV: Full thickness tissue loss appearing as a deep crater wound. Extensive damage to the skin and all underlying tissues, including the fat, muscle and bone may be present.

Candidate factors for ulcers originating at the level of the skin are friction between skin and an external surface, tissue hygiene, moisture, increased temperature, circulatory integrity, and nutrition (Salcido et al. 1995).

The development of pressure ulcers can also initiate at deep bone-muscle interfaces, and progress towards the skin destroying the surrounding tissue (Daniel et al. 1981) (Figure 1 - 4). This type of ulcer would first appear as a bruise or purple lesion on the skin that would quickly deteriorate into a Stage III or IV ulcer. Pressure ulcers with this etiology had not been formally considered as a type of pressure ulcer. It was not until 2001 when the NPUAP defined this type of pressure ulcer "deep tissue injury" (DTI), and created a task force to review the literature regarding this type of pressure ulcer etiology. Recently, the NPUAP has updated its pressure ulcer staging system to include DTI:

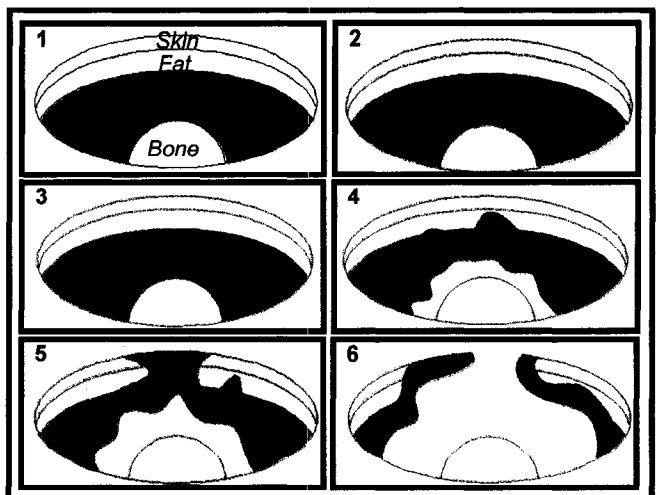


Figure 1 – 4: Progression of DTI from unaffected tissue (1) to stage IV ulcer (6)

Deep tissue injury: Injury to the deep layers of tissue due to pressure and/or shear forces under intact skin. Indications of deep damage may appear as a purple discoloration of the skin, resembling a bruise. Tissue may also exhibit a different consistency compared to adjacent areas.

The leading factor for the formation of DTI is the entrapment and compression of tissue between a bony prominence and an external hard surface for extended periods of time (Fennegan 1983; Guthrie and Goulian 1973; Salcido et al. 1995; Swarts et al. 1988; Woolsey and McGarry 1991). Deep tissue injury is more perilous than surface ulcers as it is difficult to detect and can cause severe damage in bone, ligament, muscle, and fat prior to exhibiting obvious skin signs.

1.5 Detection of Deep Pressure Ulcers

1.5.1 Visual Inspection of the Skin

Pressure ulcer detection relies almost exclusively on the judgment of the nursing staff and attending physicians for individuals being cared for at a clinical institution. The most commonly used technique for detection of a pressure ulcer is frequent inspections of the skin to assess the presence of visible redness or ulcerations. The assessment is typically based on the visual appearance of the skin; however, it is recommended that the visual inspection be accompanied by palpation. Palpation is of particular importance in individuals with darkly pigmented skin, in whom the early changes in skin discoloration and non-

blanchable erythema associated with the onset of a superficial pressure ulcer are harder to detect visually (Black et al. 2007; Lyder 1996; Lyder et al. 1999; Lyder et al. 1998; Rosen et al. 2006). A universal system for classifying detected pressure ulcers quantitatively does not exist. However, the most frequently used technique is composed of the 4-stage scale set forth by the NPUAP in the United States. A similar 4-grade scale developed by the European Pressure Ulcer Advisory Panel (EPUAP) is utilized in Europe (Black et al. 2007).

There are three main limitations associated with skin inspections and the NPUAP scale for pressure ulcer detection and classification: 1) The results are highly subjective and examiner dependent (Bergstrom 1992; Garber et al. 1996). 2) Although the scale now recognizes the etiology of DTI as a type of pressure ulcer, by the time these deep ulcers exhibit skin signs, large volumes of bone, muscle, and fat would have already been destroyed. 3) Visual inspections are time consuming and labor intensive. In addition, measurement of the depth of ulcers for proper assessment of their stage, and description of wound characteristics such as amount of fluid discharge are not commonly performed (Lyder 2003). These limitations can increase the chance of misclassification and inappropriate treatment of ulcers if no other system is utilized.

1.5.2 Risk Assessment Scales

In addition to frequent skin inspections, a widely used tool that helps not only in the detection of pressure ulcers but also in their prevention, is the use of risk assessment scales such as the Braden, Norton, and Waterlow scales. These scales try to classify individuals based on their risk of developing a pressure ulcer. Based on the assessed risk, resources can be better allocated to attend more carefully and frequently to those individuals at higher risk; this is of particular importance in centers with limited staff and resources dedicated to pressure ulcer detection and prevention. Of these three scales, the Braden scale offers the best validity and reliability and has been used in a larger number of studies compared to the Norton and Waterlow scales (Pancorbo-Hidalgo et al. 2006). The Braden scale evaluates a person's risk of developing a pressure ulcer using six different subscales. These subscales are: 1) sensory perception, 2) activity level, 3) mobility, 4) nutrition status, 5) skin's exposure to moisture, and 6) skin's exposure to shear and friction forces. For subscales 1 to 5 a score ranging from 1 – 4 is given, and for the 6^{th} subscale the score ranges from 1 – 3. Once a score has been given in each subscale, the scores are summed to give a final score that ranges from 6 – 23, with lower scores being associated with a higher risk of developing a pressure ulcer (Braden and Maklebust 2005). Despite the fact that the score given to the individual in each subscale is still based on the judgment of the caregiver, the use of this scale has improved the prediction of those at risk of developing pressure ulcers (Pancorbo-Hidalgo et al. 2006). The frequency of each assessment varies

depending on the individual's overall health and skin condition, as well as the institution's settings; however, it is recommended that it be performed on admission and then at least every 48 hours for patients in acute care units; on admission and then every 48 hours during the first week, weekly for the first month and then monthly or quarterly for patients in long term care; and on admission and then during every visit for patients in home care (Braden and Maklebust 2005).

1.5.3 Superficial Pressure Measurements

Prolonged exposure to high loads has long been considered the main cause behind the formation of pressure ulcers. Although there is debate regarding the main source of tissue injury in pressure ulcer formation (excessive mechanical deformation or ischemia), it is agreed that high pressure is the main cause for both processes. For this reason, superficial pressure measurements, which are measurements made at the surface-skin interface, have been a valuable tool in the study of pressure ulcers. By measuring superficial pressures, it is possible to predict which regions of the body are most at risk for developing a pressure ulcer. In 1961, Lindan performed a study which provided pressure measurements in a healthy adult male lying supine, prone, on his side, and seated (Lindan 1961). Pressure measurements were made by having the person lie down or sit on a "bed" of inverted nails. Each nail was attached to a spring with a specific stiffness, so as the man's weight pressed down on the nails' heads, pressure was calculated by measuring the amount of compression

in the springs. In this manner, whole body pressure maps were obtained. Later studies utilized air-filled bladders connected to a pressure transducer to obtain superficial pressure measurements with the objective of comparing the effectiveness of different support surfaces and sitting postures (Berjian et al. 1983; Palmieri et al. 1980; Rosenthal et al. 1996). With the technological advancements in electronic sensors, resistive and capacitive pressure sensors became common place, making pressure sensing systems more easily available. Some commercially available pressure sensing pads include XSENSOR (Calgary, AB, Canada), TEKSCAN (Boston, MA, USA), FSA (Panningen, The Netherlands), and Novel (Munich, Germany).

Clinically, the use of superficial pressure measurements has two applications that are vital for the detection and prevention of pressure ulcers: 1) It allows the prescription of the best pressure relieving cushion or mattress and/or the best repositioning regime for each individual; 2) It provides an assessment of the risk of developing a pressure ulcer for each person, allowing physicians and nursing staff to focus their attention on the individuals most at risk of developing a pressure ulcer.

Although very useful, superficial pressure measurements have some limitations: 1) They are dependent on the arrangement of the sensors, therefore, variation in the measurements will arise if the positioning of the subject over the sensors differs between testing sessions; 2) Differences in body shape and

mass between subjects make it difficult to generalize results and obtain statistically valid measurements between subjects. This can even become an issue within subjects if their body characteristics change between measurements; 3) Most importantly, numerical models studying the distribution of mechanical forces between the surface-skin interface and deeper layers of tissue, indicate that superficial pressure measurements may not accurately predict the stresses and strains experienced by the deeper layers of tissue, due to the different mechanical properties of skin, fat and muscle (Linder-Ganz and Gefen 2004; Oomens et al. 2003). This could lead to an improper assessment of people at risk of developing a pressure ulcer based on these measurements.

1.5.4 Objective Methods of Pressure Ulcer Detection

While frequent skin inspections and the use of risk assessment scales are the norm for pressure ulcer detection, over the years a series of techniques have been proposed to indicate the viability and status of soft tissues subjected to periods of loading, and have assisted in the early detection of pressure ulcers. Laser Doppler flowmetry has been utilized in several studies to measure changes in skin blood perfusion under loading conditions and its relationship to pressure ulcer formation (Colin and Saumet 1996; Ek et al. 1987; Frantz and Xakellis 1989; Sachse et al. 1998; Schubert and Fagrell 1991; Schubert and Heraud 1994); however, results have been mixed and with great degree of variability. Measurements of transcutaneous gas tensions (T_cPO_2 and T_cPCO_2) (Bader 1990a; Bader 1990b; Colin et al. 1996; Colin and Saumet 1996; Knight

et al. 2001; Newson and Rolfe 1982) have provided solid practical education for both patients and care givers (Bogie et al. 1995, 1992; Coggrave and Rose 2003); however, use of transcutaneous gas tensions has yielded no clear relationship between gas levels of compromised tissue and the onset of progressive tissue breakdown that will ultimately result in a pressure ulcer (Bogie and Bader 2005). Sweat analyses have also been proposed as indicators of increased risk of developing pressure ulcers (Ferguson-Pell and Hagisawa 1988; Knight et al. 2001; Polliack et al. 1993, 1997; Taylor et al. 1994). When pressure is applied over a region of the body, sweat secretion in that region is reduced and the concentration of metabolites like lactate and urea is increased. After the removal of pressure, these levels return to normal. Although these results indicate that sweat analyses could present a viable technique for predicting the formation of pressure ulcers, to date they have not received widespread use.

During the last decade, magnetic resonance imaging (MRI) has been utilized to assess the damage in deep tissue generated by the external loading of the muscles. Magnetic resonance imaging provides excellent soft tissue contrast as well as high spatial and temporal resolution of deep tissue (Bosboom et al. 2003; Bosboom et al. 2001; Hencey et al. 1996; Solis et al. 2007; Stekelenburg et al. 2006a; Stekelenburg et al. 2006b; Stekelenburg et al. 2007). It allows for the assessment and quantification of changes in different muscle properties as a result of extended compression of the muscle (Linder-Ganz et al. 2006b;

Stekelenburg et al. 2007). While the results indicate that MRI is capable of detecting early morphological and physiological changes that result from extended loading of the muscles, its current moderate availability and high cost have limited its use to experimental testing only.

Given the startling prevalence of pressure ulcers and the great difficulty and expense associated with their treatment, early detection methods of deep tissue damage and objective predictors of individuals at risk are notably lacking. In particular, quantitative methods for the early detection and assessment of DTI prior to their development into open wounds are needed.

1.6 Treatment of pressure ulcers

Treating pressure ulcers is difficult, often requiring prolonged hospitalization (Grip and Merbitz 1986). Once a pressure ulcer is detected, it is assessed by documenting its location, size, depth, and amount of exudates, and classified according to the NPUAP staging scale or an equivalent tool (Baranoski 2006; Thomas 2006). Once the assessment is complete, the first step for treating a pressure ulcer is the removal of the mechanical forces, namely pressure, shear and friction, which contributed to its development. Complete relief of pressure from the affected tissue is necessary to allow proper healing of the ulcer and stop its progression. Although necessary, the removal of pressure can be an extremely taxing procedure on the affected individual, since the person is unable to lie down on the affected area. This can become even more difficult

when ulcers are present in more than one part of the body. For individuals in wheelchairs in particular, whose mobility is already limited, this can compromise their ability to use the wheelchair as they risk applying pressure to the affected region.

The next step in the treatment process varies depending on the severity of the ulcer. After the removal of pressure, ulcers that do not require debridement can be managed by the application of a variety of local wound dressings. Maintaining an appropriate level of moisture in the wound has been associated with improved healing; towards this end, different types of moist dressings can be used. Moist wound healing dressings can be classified into: a) dressings that absorb exudate, such as alginates, hydro fibers, and foams; b) dressings that maintain moisture, such as hydrocolloids and transparent films; and c) dressings that donate moisture, such as hydrogels (Ovington 2007). Dressings that provide an antimicrobial effect in addition to moisture control, such as silver containing dressings are also available (Ovington 2007). While there are hundreds of different available dressings, there is no single treatment or dressing that can be universally applied to guarantee healing (Whitney et al. 2001), because the best dressing for each case is dictated by the wound conditions.

If the pressure ulcer already shows signs of necrosis, debridement of the necrotic tissue is recommended to allow proper healing. The debridement of

the ulcer can be performed in several ways, such as (Baranoski 2006):

Surgical debridement: This type of debridement consists of cutting away unviable tissue to clean the wound. Depending on the severity of the ulcer, this can be performed at the bedside if only small amounts of tissue are involved, or in a surgical suite which is usually required in the case of stage IV pressure ulcers.

Mechanical debridement: Examples of this type of debridement include the use of wet-to-dry gauze dressings, whirlpool treatments, or wound irrigation treatments (pulsed lavage) to remove necrotic tissue by force. Of the three, pulsed lavage is the most commonly used method, consisting in the use of a handheld device (syringe) to apply saline solutions at safe pressure levels.

Autolytical debridement: While autolytical debridement takes longer than surgical debridement methods, it is relatively painless and easy to apply. The principle behind this method is to use the enzymes naturally present in the body to soften and breakdown the eschar and degrade the necrotic tissue. These enzymes are selective to necrotic tissue and spare viable tissue. To promote such autolysis, moisture-retaining dressings such as semi-occlusive and occlusive (transparent films, hydrocolloids, and hydrogels) dressings are used, as they provide an enclosed space over the

wound in which a proper moisture environment facilitates cell movement. This method however, is not appropriate for infected wounds.

Enzymatical debridement: This method utilizes proteolytical enzymes and is best suited for situations when surgical debridement is not possible. Even though this debridement process is slow, it can be utilized on infected wounds. Care must be taken because certain wound cleaners can deactivate the enzymes. While several enzymatical agents are commercially available, they require a prescription and are expensive, which limits their use.

Biological debridement: Maggot larvae are placed in the wound, where they break the necrotic tissue and ingest microorganisms. They help remove bacteria from the wound and promote healing.

Ultrasound-assisted debridement: Necrotic tissue is removed by applying ultrasonic energy through a saline fluid pressure wave.

After debridement is performed, the appropriate dressing is applied and periodical assessments of the wound are made to track its progression. The Pressure Sore Status Tool (PSST) and Pressure Ulcer Scale for Healing (PUSH) are the two most widely used instruments to assess and track the healing of a pressure ulcer. These tools provide a numeric indicator of different

characteristics of the pressure ulcer, such as wound size and depth, tissue appearance and coloration, and amount of exudate present (Baranoski 2006; Thomas 2006).

Severe ulcers, in which bone, muscle, and skin become necrotic, are often dealt with surgically. Necrotic tissue is excised and a musculocutaneous flap is sometimes used to fill the void created by the excision (Lyder 2003). The flaps provide wound closure and in some cases supply a sensory patch in an otherwise insensate region that is susceptible to sustained external pressures incurred while seated in a wheelchair. These surgical procedures are technically demanding, and complications involving irregularities in blood supply to the muscle or skin and potential damage to nerves providing sensory input to the flap are relatively high. High recurrence of ulcers following musculocutaneous flap surgeries has also been reported (Lyder 2003).

Even though debridement and dressings are utilized to treat and heal a localized pressure ulcer, care is taken to ensure the overall health of the patient. Given that a pressure ulcer is a potential entry point for bacteria into the body, the risk of infection is always latent. Infection of the wound can hinder the healing of skin grafts and muscle flaps (Thomas 2006). More dangerously, an infected wound can lead to bacteremia, which can be lethal, especially in individuals with already compromised health (Bryan et al. 1983; Galpin et al.

1976; Wall et al. 2003). Culture swabs are often obtained from the wound site to quantify the colonization of bacteria and determine its type. To prevent the spread of infection, prophylactic antibiotic treatment is administered as necessary, in particular when there are signs of systemic infection.

An alternative technique to facilitate wound closure, recommended in particular for stage III and IV ulcers with high amounts of exudate, is the use of vacuum-assisted closure (VAC) (Kaufman and Pahl 2003; Smith 2004). This technique consists of applying topical negative pressure to the wound surface to promote healing. To apply this technique, a porous foam dressing is placed directly over the wound surface and an adhesive dressing is placed over the foam, creating a contained environment. Negative pressure is achieved by inserting a tube attached to a vacuum pump into the foam dressing. The negative pressure cleans the wound, removing excessive exudate; it also promotes vasodilation, increasing blood flow and promoting granulation. Negative pressure also reduces bacterial colonization in the wound (Argenta and Morykwas 1997; Morykwas et al. 1997). The use of VAC in the treatment of pressure ulcers induces faster healing rates and better wound closure when compared to hydrocolloid or alginate dressings (Smith 2004).

Although not widely utilized in the treatment of pressure ulcers, the use of electrical stimulation has shown improved healing in chronic wounds and pressure ulcers (Allen and Houghton 2004; Bogie et al. 2000; Gardner et al.

1999; Griffin et al. 1991; Houghton et al. 2003; Reger et al. 1999). There is no consensus about the exact mechanism by which electrical stimulation improves healing. Suggested mechanisms include a reduction in bacterial growth due to electrical stimulation (Rowley et al. 1974); facilitation of white cell movement into the wound (Petrofsky et al. 2005); promotion of angiogenesis (Zhao et al. 2004); and an increase in blood flow in the wound area (Petrofsky et al. 2005). The electrical stimulation modalities typically utilized to treat wounds are low intensity direct current (LIDC), high voltage pulsed current (HVPC), alternate current (AC), and micro amperage electrical stimulation (MES).

A final step in the treatment of pressure ulcers is the monitoring and maintenance of a proper nutritional status of the person. In particular, higher intakes of vitamin C, zinc, and protein have been associated with improved healing (Breslow et al. 1993; Desneves et al. 2005; Lee et al. 2006). Vitamin C helps in the formation of connective tissue and scar formation. Zinc is a component of several enzymes and is required for several metabolic processes. Proteins (amino acids, peptides, polypeptides) are required for the formation of the wound healing matrix, as well as helping to stabilize the intracellular oncotic pressure (Zagoren 2001).

Even after a pressure ulcer has fully healed, the possibility of recurring pressure ulcers is extremely high, in particular in wheelchair users, in whom Niazi et al (Niazi et al. 1997) reported a pressure ulcer recurrence rate of 91%.

This exemplifies the need to focus on preventing the initial onset of pressure ulcer formation in those persons at risk.

1.7 Prevention of Pressure Ulcers

1.7.1 Repositioning

Given that excessive pressure, shear forces, and friction applied to the tissue around bony prominences are the main cause for pressure ulcer development, prevention methods are aimed at eliminating or reducing these forces. The golden standard for pressure ulcer prevention is the frequent repositioning of the individual to allow periodical relief of pressure in areas at risk (i.e. sacrum, ischial tuberosities, trochanters). At locales were individuals at risk of developing pressure ulcers are under the care of health professionals, for example at hospitals and nursing homes, the staff of the institution plays a vital role in preventing the formation of pressure ulcers. Patients or residents in these institutions who are unable to leave their bed or move by themselves rely entirely on the institution staff to be repositioned. While there is no conclusive evidence of an ideal repositioning frequency (Defloor et al. 2005; Thomas 2006, 2001; Vanderwee et al. 2007), traditionally the recommended repositioning time is every two hours (Baranoski 2006). This time, however, can vary for each individual, with some people requiring more frequent repositioning (Baranoski 2006; Thomas 2006, 2001). In practice, each institution establishes its own pressure ulcer prevention program (Catania et al. 2007; de Laat et al. 2007), with repositioning frequency being determined by the patient's condition, staff's

availability, and costs associated with the repositioning (Baranoski 2006; Thomas 2006; Xakellis et al. 2001). When repositioning a person, utmost care is taken to avoid dragging of the person against the support surface, thus reducing friction at the skin and shear at the bone-muscle interfaces. For inpatient populations, frequent skin inspections and pressure ulcer risk assessments are also performed by the staff in conjunction with the repositioning program to further reduce the incidence of pressure ulcers. For people confined to bed but living at home, the repositioning and inspections are dependent on the individuals themselves, a relative or a private caregiver.

Repositioning is not only required for individuals in bed, but also for wheelchair users, in particular for individuals with SCI. Frequent postural adjustments to relieve internal pressure when seated, emulating the constant subconscious adjustments performed by able-bodied individuals in reaction to discomfort, are a critical factor in the prevention of pressure ulcers. To this end, wheelchair users are encouraged to adjust their posture regularly. People with paraplegia are trained to perform wheelchair push-ups and those with quadriplegia are trained to perform side leans and front-to-back rocking to relieve ischial tuberosity pressure (Grip and Merbitz 1986; Merbitz et al. 1985; White et al. 1989). However, for wheelchair users effective prevention through a regime of regular pressure relief is largely dependent on: 1) individual compliance, 2) the ease with which the exercises can be performed, and 3) the effectiveness of these adjustments in producing adequate relief of internal

pressure at the bone-muscle interface.

1.7.2 Specialized cushions and mattresses

A common and widely used method to aid in the prevention of pressure ulcers is the use of specialized wheelchair cushions, bed mattresses, and overlays to reduce the pressure at the interface between the skin and the chair/bed (Ferguson-Pell et al. 1986; Garber 1979, 1985a, b; Marshall and Overstall 1983). Although the use of these special surfaces does not eliminate the need for periodical repositioning, by reducing interface pressures these devices may allow a person to remain in the same position for a longer period of time without compromising the integrity of the tissue. This is of particular importance for wheelchair users, who perform most of their daily activities sitting in the wheelchair, as well as for institutions where the staff available to aid in the repositioning is limited, and the time between repositions is longer than that usually recommended. Based on their operating mode, support surfaces can be divided into non-powered and powered systems. Non-powered systems provide a static redistribution of pressure while powered systems provide a dynamic redistribution of pressure.

a. Non-powered pressure redistribution surfaces

These surfaces do not require any source of power to function. They are designed to maximize the surface area in contact with the skin, thus reducing the pressure at the skin-surface interface. Also, their compliant surface allows

regions of high pressure under bony prominences to sink into the surface, thus diffusing the pressure to surrounding areas (Woolsey and McGarry 1991). Non-powered support surfaces can be made of different components including, viscoelastic foams, elastic foams, closed cell foams, open cell foams, and elastomers. They can also be composed of cells or bladders filled with water, air, gel, and viscous fluids. The support surface can be made of any single type of component (Figure 1 – 5d) or a combination of different components (Figure 1 – 5c). Specialized wheelchair cushions are currently the only devices available for providing pressure relief while sitting, and are routinely prescribed by physical and occupational therapists.

Air-filled cushions are composed of multiple cells that are inflated to a desired air pressure (Figure 1 – 5a). The amount of pressure reduction provided by air filled cushions can be affected by variables such as the size, shape, material, air capacity, and air pressure of the inflated cushion. In particular the inflating pressure of the cushion has been studied and associated with the cushion's performance. Varying the inflating pressure can change the amount of pressure relief provided by the cushion. Pitfalls of this type of cushion include difficulties to adjust the inflating air pressure by the user and/or caregiver (Hamanami et al. 2004). In addition, if not enough air pressure is utilized to inflate the cushion the user can "bottom out" in the cushion, eliminating any pressure relief to the user.

Viscoelastic foam mattresses (Figure 1 – 5e) are made of heat-sensitive foam that allows them to mold to the contour of the body, providing a reduction in the interface pressures and a reduction of friction and shear forces (Beldon 2002). In a study performed with patients in an acute care setting, the reported benefits of using this type of mattress were a reduction in the ward's pressure ulcer incidence from 3.5 – 4% to less than 1%; however, no direct comparison was made against other pressure relieving systems (Beldon 2002). Different studies have compared the use of standard hospital mattresses and cushions against mattresses and cushions made from viscoelastic foam in the same population. The results indicate that the use of the specialized support surfaces offers better pressure reduction (Hampton and Collins 2005), and significantly reduces the incidence of blanchable erythema compared to standard devices; however, in the cases were blanchable erythema developed, the progression of the lesion seemed to be unaffected by the type of support surface utilized (Russell et al. 2003). When comfort was assessed, patients who utilized this type of mattresses found them more comfortable than their standard mattresses (Hampton and Collins 2005; Russell et al. 2003), or other systems such as the alternating pressure air mattresses (Beldon 2002; Russell et al. 2003).

b. Powered pressure redistribution surfaces

This type of support surface requires an external source of power to function, whether in the form of batteries, or an AC plug. They are capable of providing a dynamic redistribution of pressure, wherein air or water is actively pumped so

that the pressure within the supporting surface is continuously changing.

Alternating pressure air systems include cushions, mattresses (Figure 1 – 5b) and overlays. This type of system is made of air-filled cells through which air is pumped to maintain an alternating interface pressure (Gray 1999).

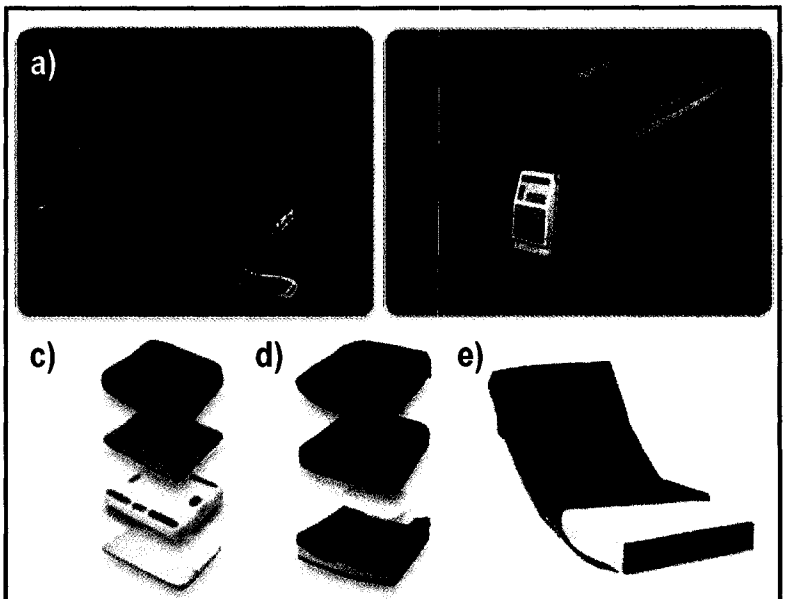


Figure 1 – 5: Different types of specialized support surfaces. a) Air filled cushion. b) Alternating air pressure mattress. c) Gel/foam cushion. d) Foam cushion. e) Viscoelastic foam mattress.

Some systems are equipped with a liquid crystal display through which adjustments to the alternating cycle can be made. In addition, they can also be equipped with audio alarms in case of electrical or pressure failure (Gray 1999). Other alternating pressure air systems use variable density foam within the air cells; this makes the flow of air through the cells more subtle, and reduces the unpleasant sensations that some alternating pressure air systems can generate (Gray 1999).

Some drawbacks of alternating air pressure mattresses include 1) generating a sensation of "seasickness" in some people; 2) they are noisy,

which makes sleeping more difficult; and 3) they can be easily damaged (Beldon 2002).

Because the operation of powered wheelchair pressure reduction devices is dependent on compressors and power supplies, wheelchair systems can limit the person's mobility and in turn, the users' level of activity (Conine et al. 1989). Reclining and "tilt-in-space" wheelchairs are also available for periodical relief of pressure (Burns and Betz 1999; Cooper et al. 2000). These types of wheelchairs are designed for individuals who do not have enough upper body strength to perform the recommended periodical wheelchair push-ups and side leans for pressure relief (Burns and Betz 1999). These wheelchairs are equipped with a motor that tilts the backrest of the wheelchair to different angles. The change in inclination shifts the weight bearing of the body from the ischial tuberosities to the sacrum and the back, thus redistributing the pressure with each setting (Burns and Betz 1999). Drawbacks of this type of chair include the risk of generating shear forces (Cooper et al. 2000), malpositioning for some individuals (Burns and Betz 1999; Cooper et al. 2000), high cost, and larger size than regular wheelchairs, which limits the accessibility and transportation of the wheelchair (Burns and Betz 1999).

1.7.3 Alternative Pressure Relief Systems

Given the importance of preventing the onset of pressure ulcers, continuous investigations into the improvement of standard prevention techniques are

conducted, and focus on the development of new support surfaces as well as optimizing existing procedures for pressure ulcer prevention. An alternative prevention technique that has been studied irregularly for the past 15 years is the use of electrical stimulation. While the results of treating developed ulcers with electrical stimulation have been positive, its effectiveness in preventing the development of new ulcers remains unclear. Levine et al. (Levine et al. 1989; Levine et al. 1990a; Levine et al. 1990b) first proposed the use of electrical stimulation for preventing the formation of pressure ulcers in people with SCI. Their studies indicated that electrical stimulation generates changes in muscle shape (Levine et al. 1990a), redistribution of pressure at the seating interface (Levine et al. 1989), and increases in blood flow (Levine et al. 1990b). Studies by Bogie et al. (Bogie et al. 2000), and Rischbieth et al. (Rischbieth et al. 1998) indicated that frequent use of electrical stimulation increases muscle mass, which could allow wheelchair users to remain seated for longer periods of time. Increases in transcutaneous oxygen levels, in addition to the previously mentioned benefits have also been reported in a long-term study with a single subject (Bogie et al. 2006). While these studies have focused on the application of electrical stimulation through the use of surface electrodes, placed directly over the skin of the target muscle, electrical stimulation through implanted electrodes has shown similar results (Bogie and Triolo 2003; Liu et al. 2006a, b). These studies indicated that the benefits obtained through the daily use of an electrical stimulation system (increased blood flow and larger muscle mass), could lead to the prevention of pressure ulcers.

Although these studies indicate that electrical stimulation could become a valuable technique in the prevention of pressure ulcers, measurements to date have been limited to a small number of subjects, and more importantly, the effectiveness of an electrical stimulation system has not been tested against a DTI control group. The main goal of this thesis is to test the effectiveness of an intermittent electrical stimulation system (IES) for the prevention of DTI. The underlying principle of IES is to evoke periodical readjustments of posture that can redestribute pressure and increase tissue oxygenation levels, mimicking the effects of voluntary repositioning. To accomplish this goal, a DTI animal model was developed and the effectiveness of two IES paradigms for preventing DTI were tested. In addition to the animal experimentation, studies in humans were also performed to measure changes in pressure levels at the seating interface, as well as tissue oxygenation changes under different loading conditions.

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CHAPTER 2

PREVENTION OF PRESSURE-INDUCED DEEP TISSUE INJURY USING INTERMITTENT ELECTRICAL STIMULATION*

2.1 INTRODUCTION

Pressure ulcers are typically associated with individuals of compromised mobility, namely the infirm, the elderly, and people with spinal cord injury (Conine et al. 1989; Edlich et al. 2004; Labbe et al. 1987; Salzberg et al. 1996; Woolsey and McGarry 1991; Zanca et al. 2003). A pressure ulcer is any lesion caused by unrelieved pressure resulting in damage of underlying tissue (Agency for Health Care Policy & Research 1994), involving both the skin, fat, fascia, muscle, and bone. Pressure ulcers develop following a prolonged period of compression of the tissue between a bony prominence and a surface (Fennegan 1983; Guthrie and Goulian 1973; Salcido et al. 1995; Swarts et al. 1988; Woolsey and McGarry 1991) which causes the occlusion of capillaries and leads to ischemia. Ischemia, therefore, has historically been considered a major factor leading to pressure ulcer formation (Kosiak 1959, 1961; Kosiak et al. 1958). Paradoxically, the restoration of blood flow, vital to preserving tissue viability, has also been identified to cause extended damage of the tissue (Grace 1994; Gute et al. 1998; Peirce et al. 2000; Tsuji et al. 2005). In instances where the ischemic state has been maintained for prolonged

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durations, the influx of oxygen-rich blood causes the activation of free radicals, further damaging the cells in the tissue (Grace 1994; Gute et al. 1998; Peirce et al. 2000; Tsuji et al. 2005). In addition to the injury caused by biochemical changes occurring during tissue ischemia and ensuing reperfusion, high stress levels at the bone-muscle interface and the duration of their application, have also been reported as direct causes of tissue injury (Bouten et al. 2003; Breuls et al. 2003; Daniel et al. 1981; Linder-Ganz et al. 2006a; Linder-Ganz and Gefen 2004; Linder-Ganz et al. 2006b). Furthermore, injury to the muscle results in the formation of scar tissue; thus, creating more foci for increased stress, and leading to injury of adjacent previously healthy tissue (Gefen et al. 2005; Linder-Ganz and Gefen 2004). It is the combined effects of these processes that cause the edema, inflammation and necrosis that ultimately lead to the formation of a pressure ulcer (Finestone et al. 1991; Gilsdorf et al. 1991; Grace 1994; Sagach et al. 1992; Tupling et al. 2001a, b).

Pressure ulcers can be initiated at the dermis, usually in the presence of excessive friction and/or compromised dermal integrity and progress towards the deeper layers of tissue. Muscle is considered to be more susceptible to tissue degradation from mechanical loading and oxygen deprivation (Bouten et al. 2003; Labbe et al. 1987) than dermis, consequently injury can also be induced in the deep tissue and progress outwards (Daniel et al. 1981), evolving into a severe full-thickness pressure ulcer. This type of pressure-related injury to the deep tissue under intact skin has been defined by the National Pressure Ulcer Advisory Panel as deep tissue injury (DTI) (Ankrom et al. 2005; Black and

Panel. 2005). Deep tissue injury can be extremely perilous, as it can evolve undetected until a significant destruction of the tissue has occurred. Presently, pressure ulcers are detected by visual inspection of the skin (Russell 2002), which often belies existing extensive damage to deeper tissue (Daniel et al. 1981).

At the present time, techniques employed to prevent ulcer formation include frequent repositioning (Edlich et al. 2004) as well as the use of specialized cushions and mattresses that provide either static or dynamic pressure relief of the tissues at risk (Gunningberg et al. 2000; Russell et al. 2003). Recognizing the absence of a significant reduction in the incidence of pressure ulcers (Conine et al. 1989; Garber and Dyerly 1991; Garber and Krouskop 1982; Krause and Broderick 2004; Raghavan et al. 2003; Salzberg et al. 1996; Seymour and Lacefield 1985; Thomas 2003), new preventative interventions are needed, especially for DTI.

This study investigated the effectiveness of applying intermittent electrical stimulation (IES) to reduce muscle injury due to the presence of persistent external pressure. We hypothesized that the IES-induced muscle contractions would prevent the formation of DTI. These periodically-induced contractions may parallel the effects of voluntary or assisted repositioning, which is the standard method for preventing the formation of DTI. We suggested that the mechanism of action of IES is twofold: 1) IES-induced contractions would reshape the underlying muscle, thereby reducing the high stress levels experienced at the muscle-bone interface, minimizing the amount of damage

caused by the mechanical deformation and compression of the tissue. 2) Each contraction would also periodically restore blood flow and increase the oxygenation of the compressed tissue, reducing the amount of damage caused by long periods of ischemia and subsequent reperfusion.

Intermittent electrical stimulation may be a useful medical intervention that allows immobilized individuals to remain seated or supine for prolonged periods of time, reducing the frequency of assisted repositioning, and, most importantly, reducing the development of DTI.

2.2 METHODS

2.2.1 Overview of experimental procedures

A DTI rat model was developed prior to testing the effectiveness of IES in the prevention of DTI. The setup utilized to induce DTI allowed continuous recording and necessary adjustments of the pressure applied to the rats' quadriceps muscle group. In-vivo detection of DTI was conducted using T_2-weighted magnetic resonance imaging. A post-mortem assessment of the health of the skin around the area of pressure application and the affected muscles was also performed.

To investigate the effectiveness of IES in the prevention of DTI, a series of experiments were conducted in four groups of rats. The Control Group received 2 hours of external load applied to the quadriceps muscle of one hind limb. Experimental Groups 1 and 2 received the load application as well as IES at either 10-minute or 5-minute intervals. Experimental Group 3 received the

application of IES at 5-minute intervals but no load application. Deep tissue injury was quantified 24 hours later by *in-vivo* T_2-weighted magnetic resonance imaging (MRI) and post mortem histological assessment of the extracted quadriceps muscles. The quadriceps muscles from the untreated contralateral legs of all animals served as healthy controls (Contralateral Control Group).

To obtain an insight into the mechanisms of action of IES, the effect of IES on tissue oxygenation was measured in two experiments with able-bodied human volunteers. Tissue oxygenation measurements were obtained from an able-bodied volunteer by means of T_2* MRI quantification in muscles in both unloaded and loaded conditions, respectively. A single experiment in an able-bodied volunteer was also performed to measure changes in the surface (bed-buttocks interface) pressure profiles generated by the IES-elicited contractions. All volunteers provided written consent. All experimental protocols were approved by the Animal Care and Welfare Committee and the Health Research Ethics Board at the University of Alberta.

2.2.2 Induction and detection of DTI in the rats' quadriceps muscles

a. Pressure application

Three adult female, Sprague-Dawley rats (350g) were utilized to develop the procedure to induce a DTI and its subsequent detection. The rats were anesthetized with isoflurane (2 – 3 % isoflurane in 400 ml/min oxygen) and placed on a flat surface. Both hind limbs were fully extended and padded straps were used to hold both limbs in place. The right hind limb of each rat was

chosen as the experimental limb. To induce a DTI, pressure was applied for 2 hours to the quadriceps muscle of the experimental limb. This muscle group was targeted because the femur provides an accessible, relatively large, and flat surface to press against, facilitating the loading of the muscle. Pressure was applied through a 3-mm diameter indenter attached to a force transducer (Interface, Scottsdale, Arizona, U.S.A.) (Figure 2 – 1). The load applied to the quadriceps muscle of each rat was equivalent to 100%, 85% or 63% of the body weight. Adjustments were made as needed using a micromanipulator (Narishige, Japan) to maintain the desired level of applied pressure throughout the duration of the experiment. At the end of the 2 hours the load was removed, the rats were returned to their cages and buprenorphine (0.05 mg/kg) was administered subcutaneously to alleviate discomfort.

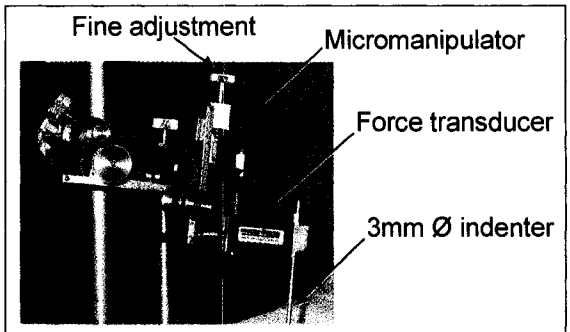

Figure 2 - 1: Setup utilized to apply pressure to rats' quadriceps

b. Detection of DTI

Detection of DTI was made through the use of magnetic resonance imaging. A T_2-weighted spin-echo sequence (echo time (TE) = 80 ms, relaxation time (TR) = 2000 ms)), which is an MRI modality sensitive to freedom of water mobility in soft tissues, was utilized to detect edema associated with the formation of a DTI. Twenty-four hours after the removal of pressure, the rats

were anesthetized with an intraperitoneal injection of sodium pentobarbital (40 mg/kg) and transported to the *in-vivo* Nuclear Magnetic Resonance Centre at the University of Alberta. The rats' hind limbs were extended and secured inside a 7-cm diameter birdcage coil and placed inside a 3.0 Tesla magnet (Magnex Scientific PCL). Ten MRI slices (2 mm slice thickness with 1 mm slice separation, field of view of 160 mm x 160 mm) were obtained in the transverse plane in relation to the rats' body, during a 1-hour scanning session. Both hind limbs were imaged in the same slice.

After the scanning session was completed, the animals were perfused transcardially (1% formaldehyde / 2.25% gluteraldehyde fixative) under deep anesthesia (sodium pentobarbital, 40 mg/kg). The skin covering the quadriceps muscles was carefully removed and inspected visually to identify signs of injury around the area of pressure application; photographs were taken of all skin samples. The quadriceps muscles from both hind limbs were then extracted, photographed, weighted, and their volume was estimated by submerging them in fixative inside a graduated cylinder. Once all measurements were obtained, the muscles were cut longitudinally and the deep portions of the muscles were photographed.

2.2.3 Effectiveness of IES in preventing DTI

a. Pressure application and electrical stimulation setup

Eighteen adult female, Sprague-Dawley rats (weight = 320 ± 36 g) were anesthetized with isoflurane (2-3% isoflurane in 400 ml/min oxygen) and a

nerve-cuff was implanted around the femoral nerve of each hind limb. Following implantation the rat was placed on a flat surface with a restraining device (Figure 2 – 2a). Both hind limbs were fully extended and a padded strap was placed around each ankle to tether the legs in place. The knee and upper calf in the experimental leg were also restrained using a padded clamp to prevent any off-sagittal movement of the leg.

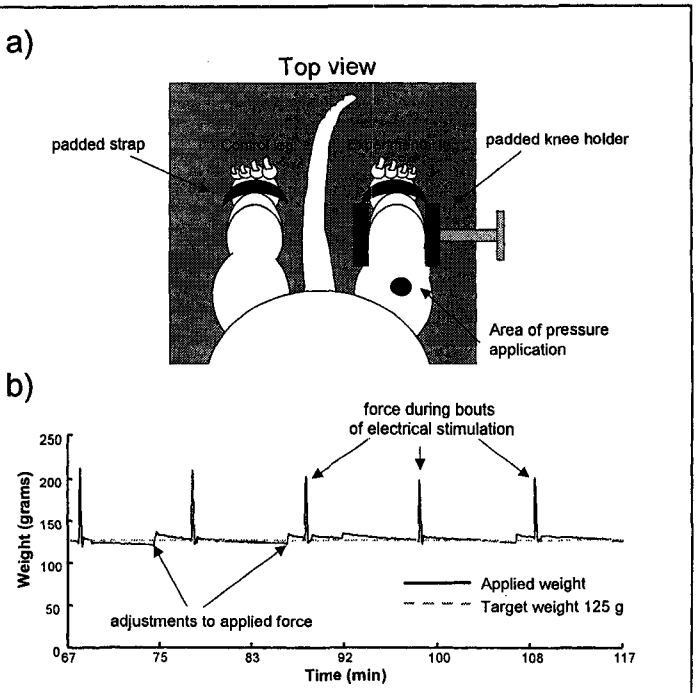

Figure 2 - 2: *Experimental setup.* (a) Constant pressure was applied to the quadriceps muscle of the right hind limb of each rat. (b) A 50-minute record of the force applied to the quadriceps muscle. The sharp increases in force correspond to the contraction of muscle due to IES.

Pressure was applied to the quadriceps muscle of the experimental leg using a 3-mm diameter indenter. The contralateral leg served as an internal control. Rats were randomly assigned to 3 groups of 6 animals each (Control Group, Experimental Group 1, Experimental Group 2). Rats in Experimental Group 1 received the application of pressure and simultaneous application of a 10-s stimulus bout (biphasic, charge-balanced, constant current, 10 – 40 mA, 250 μs, 50 pulses/s) to the femoral nerve of the experimental leg every 10 minutes

throughout the duration of pressure application. Rats in Experimental Group 2 received pressure and simultaneous electrical stimulation to the treated leg (10-s bouts) every 5 minutes. Rats in the Control Group received the pressure application but no electrical stimulation. In all animals, pressure was applied for a period of 2 hours. The load applied was normalized to 38% of the body weight of each rat, which is the expected unilateral amount of loading in the buttocks and thighs in seated individuals (Collins 2001). Loads were measured with a miniature beam force transducer (Interface, Scottsdale, Arizona, U.S.A.). The force was recorded at a sampling rate of 100 samples/s using a CED Power 1401 A/D board (Cambridge Equipment Design, Cambridge, UK) and SIGNAL 2 software (Cambridge Equipment Design, Cambridge, UK) throughout the duration of the experiment (Figure 2 – 2b). The indenter was adjusted as required using a micromanipulator (Narishige, Japan) to maintain the desired level of applied force (Figure 2 – 2b). Throughout the experiments, the pressure applied to each group was 164 ± 6.7 kPa for the Control Group, 167 ± 26.6 kPa for Experimental Group 1, and 165.2 ± 25.1 kPa for Experimental Group 2. Following the period of pressure application, the leg was unloaded, the nerve-cuffs from both limbs were removed and the skin was sutured. Post-operatively, buprenorphine (0.05 mg/kg) was administered subcutaneously, to alleviate any discomfort.

To test the effect IES alone may have on the stimulated muscles, experiments were conducted in a fourth group of six rats (285 ± 6 g), designated Experimental Group 3. The experimental procedures previously described were

maintained with the exception of no pressure application. The stimulation paradigm utilized was that of Experimental Group 2, with IES being applied to one hind limb of the animal every 5 minutes for a period of 2 hours.

b. Assessment of Deep Tissue Health using MRI

Magnetic resonance imaging was used to obtain an *in-vivo* assessment of DTI following pressure application and to quantify the effectiveness of IES in preventing such injury (Bosboom et al. 2003; Stekelenburg et al. 2006). Twenty-four hours after the removal of pressure each rat was anesthetized with an

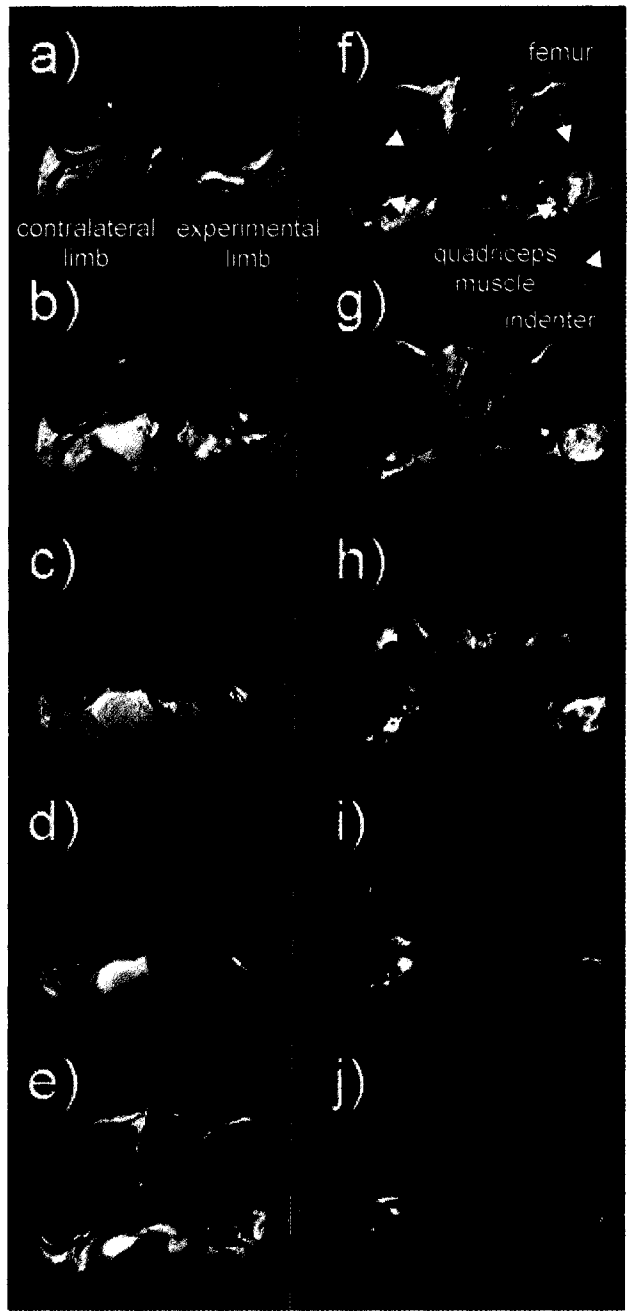

Figure 2 - 3: *Magnetic resonance imaging scans in one animal.* (a-j) Sequential T2-weighted spin echo magnetic resonance images of a rat's thigh ranging from the rostral extent of the quadriceps muscle (a) to its caudal end (j), obtained 24 hours after the application of external pressure. Approximate placement of indenter indicated in slice (f).

intraperitoneal injection of sodium pentobarbital (40 mg/kg). The rat's hind limbs were secured inside a 7-cm diameter birdcage coil and placed inside a 3.0 Tesla magnet (Magnex Scientific PCL). A T_2-weighted spin-echo sequence (echo time (TE) = 80 ms, relaxation time (TR) = 2000 ms) was employed. Data were collected during a 30-minute scanning session and twenty MRI slices (images) were acquired from each rat, with slice thickness of 2 mm and slice separation of 1 mm (every other slice shown in Figure 2 - 3). The acquisition matrix size was 256 pixel x 256 pixel within a field of view (FOV) of 120 mm x 120 mm, resulting in an in-plane resolution of 0.47 mm x 0.47 mm. Both hind legs were imaged in the same slice. MRI slices were obtained in the sagittal, coronal and transverse planes in relation to the rat's femur.

All MRI data were imported to MATLAB 7.0.1 (Mathworks, Natick, Massachusetts, U.S.A.) for analysis using custom-written routines. The left and right quadriceps muscles were manually selected from every slice and all analyses were restricted to the pixels inside these two regions (Figure 2 – 4a). To quantify the amount of increased water mobility present within the experimental leg from each slice, the signal intensity of each pixel in that leg was compared to a threshold intensity level obtained from the contralateral leg (Figure 2 – 4b). The mean + 2*standard deviation in the signal intensity from the quadriceps muscle of the contralateral leg was chosen as the threshold intensity level. If the signal intensity of a pixel in the experimental leg was higher than the threshold, the pixel was considered to have an increase in water mobility, or edema (Figure 2 - 4c). A percentage of the affected area relative to

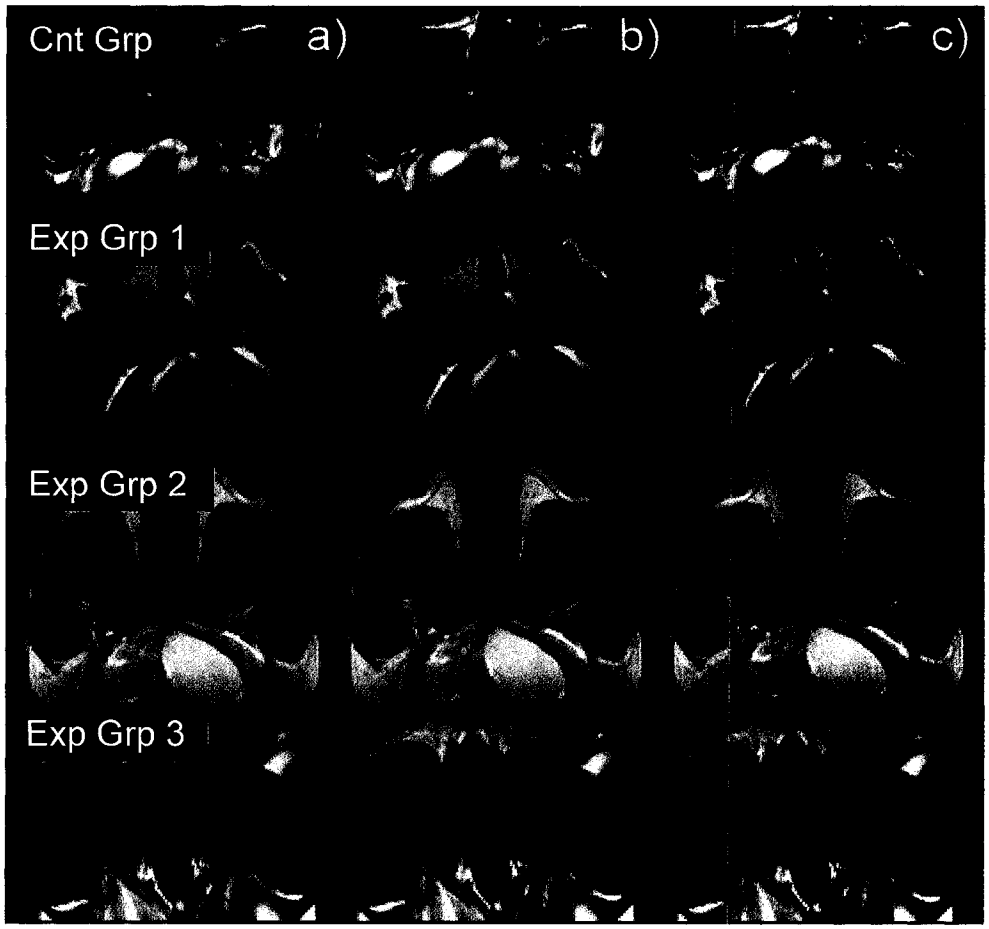

Figure 2 - 4: *Analysis of magnetic resonance imaging scans.* (a) T2-weighted spin-echo image of rat hind limbs 24 hours after the application of pressure. (b) The quadriceps muscle in both hind limbs was selected in each image. (c) The signal intensity of pixels within the region of the left and right quadriceps muscles was obtained, and the signal intensity from pixels in the experimental limb was compared to the average + 2*standard deviation intensity of those in the contralateral limb. Pixels with higher intensity in the experimental limb were marked with red and considered to contain increased water mobility. Pixels with higher intensity than threshold in the contralateral limb were marked with blue as a control.

the total area of the muscle was obtained from each slice and the total affected volume was calculated for each rat by summing the results from all slices. The threshold was also applied to each control (contralateral) limb from each rat to quantify the amount of increased water mobility that could be attributed to factors other than the application of pressure or IES, such as the electrode cuff

implantation or normal variation in the signal intensity. Results from the untreated contralateral limbs of all 24 rats were designated as the Contralateral Control Group. For measured comparisons between groups both one-way ANOVA and Tukey post-hoc tests were used. All P values less than 0.05 were considered statistically significant.

c. Histological assessment

To corroborate the extent of injury in the muscle from the MRI assessment, histological evaluation of the tissue was also performed. Under deep anesthesia (sodium pentobarbital, 40 mg/kg), the animal was transcardially perfused with a formaldehyde (1%) /gluteraldehyde (2.25%) fixative and the quadriceps muscles from both hind limbs were removed. The muscles were photographed, weighed and their volume calculated. The muscle tissue was stored in the same fixative, and subsequently dehydrated through washing in a graded series of ethanol dilutions and embedded in paraffin.

Muscle sections obtained from the region identified by the MR images as containing edema were longitudinally bisected. A 2 - 3 mm thick longitudinal section was obtained, as well as five 2 - 3 mm thick transverse sections. A 5 μm slice was obtained from each section and stained with hematoxylin and eosin (H&E).

A veterinary pathologist blinded to the experimental groups performed all histological analyses. A 4.9 mm^2 area from each slice was assessed to identify muscle fiber necrosis, inflammatory cell infiltration, hemorrhage and tissue

mineralization. A necrosis score (0 – 4) was assigned to each longitudinal slice based on the approximate area exhibiting necrosis out of the slice total area. Subsequently, the transverse slices from each animal were used to confirm the extension of necrosis throughout the muscle. The estimated volume of the muscle affected by necrosis from the histological assessment was compared against the estimated volume of the corresponding muscle affected by edema as calculated from MRI slices. Scoring of histological muscle sections between groups was assessed by a Kruskal-Wallis non-parametric test. All P values less than 0.05 were considered statistically significant. All results are expressed as mean ± standard deviation.

2.2.4 Mechanisms of action of IES

a. Muscle oxygenation measurements

In addition to testing the effectiveness of IES in preventing DTI, we sought to understand the mechanisms of action of IES. An initial experiment was conducted in an able-bodied volunteer (male, 22 yr) to assess changes in tissue oxygenation associated with contractions elicited by IES in an unloaded muscle. Surface, non-magnetic electrodes were placed over the motor point of the medial gastrocnemius (MG) muscle of one leg. Tissue oxygenation levels were estimated by quantifying changes in the T_2* signal in MR scans of the muscle in which an increase in the T_2* signal is attributed to an influx of oxygenated hemoglobin to the tissue (Jordan et al. 2004; Noseworthy et al. 2003). Magnetic resonance scans were acquired with a 1.5 Tesla whole body Siemens Sonata

scanner (Siemens Medical Solution, Malvern, Pennsylvania) and a 27-cm diameter transmit/receive knee coil circumscribing the lower leg. A custom-prepared multi-gradient-echo sequence (TR = 51.8 ms, 8 TEs ranging from 3.6 ms to 47 ms, single slice, 6 mm slice thickness, flip angle = 20°, FOV = 208 mm x 205 mm, readout matrix = 160 pixel x 158 pixel, in-plane resolution = 1.3 mm x 1.3 mm) was utilized for all data acquisitions. Baseline levels of oxygenation in MG were obtained as well as simultaneous measurements from the lateral gastrocnemius (LG), medial soleus (MS), and lateral soleus (LS) muscles for comparison. Following the acquisition of baseline scans, successive scans were acquired immediately after 30-s bouts of electrical stimulation delivered through the surface electrodes (biphasic, charge-balanced, constant current, 70 mA, 250 μs, 50 pulses/s).

To mimic a simulated sitting position in which muscles are compressed, albeit around the ischial tuberosities, a second experiment was performed on the gluteus maximus muscles to assess changes in oxygenation levels induced by IES. Surface, non-magnetic electrodes were placed over the motor points of the left and right gluteus maximus muscles of an able-bodied volunteer (male, 26 yr). Due to space limitations within the MRI scanner, which prohibits volunteers from sitting upright, muscle compression during sitting was simulated by adding weight over the pelvis of the person lying supine inside a 1.5 Tesla whole-body scanner. Oxygenation measurements were obtained at: 1) rest, 2) with a 20 kg (30% of body weight) load applied over the pelvis, and 3) with a 20 kg load and IES applied simultaneously.

Surface coils placed below the subject and a multi-gradient-echo sequence (TR = 90.3 ms, 20 TEs ranging from 3.8 to 89.6 ms, single slice, 8 mm slice thickness, flip angle = 30, FOV = 223 mm x 397 mm, readout matrix = 72 pixel x 128 pixel, in-plane resolution = 3.1 mm x 3.1 mm) were utilized for imaging the gluteus in the transverse plane. Three successive 31-s scans were acquired at rest to obtain baseline levels of oxygenation in the left and right gluteus maximus muscles. A 20 kg load was placed over the pelvic region to compress the gluteus muscles and 10 31-s scans were acquired over a 10-minute period of loading. Subsequently, 6 31-s scans were obtained each immediately following a 10-s stimulus bout (biphasic, charge-balanced, constant current, 70 mA, 250 μs, 50 pulses/s, 3-s ramp-up, 3-s ramp-down) applied every minute to the gluteus muscles with the load in place. The stimulation parameters utilized did not cause pain or discomfort to the volunteer (data not shown).

Magnetic resonance data were imported into MATLAB 7.0.1 (Mathworks, Natick, Massachusetts, U.S.A.) to measure changes in the T_2* signal in each muscle using a mono-exponential non-negative least squares fit routine (Whittall and Mackay 1989). A region of interest (ROI) was selected around each target muscle (MG, LG, SM, and SL, or right gluteus maximus, and left gluteus maximus) in each MR slice, and the T_2* levels in each ROI were determined. The T_2* values were normalized to their corresponding baseline levels obtained at rest.

b. Surface pressure measurements

In addition to injury due to ischemic changes, high stress levels and cell

deformation have also been associated with tissue damage (Bouten et al. 2003; Breuls et al. 2003; Daniel et al. 1981; Linder-Ganz et al. 2006a; Linder-Ganz and Gefen 2004). Ideally, stress levels should be measured at the bone-muscle interface, the place of origin for DTI. However, due to the lack of non-invasive measuring techniques at this deep level, an alternative and commonly used technique is to measure superficial pressure levels at the support surface-skin interface (Bogie et al. 2006). In order to obtain insight into the effects of IES in reshaping the gluteus maximus muscles, and modifying the surface pressure profiles with each contraction, a single experiment was performed. The experiment was conducted in the same able-bodied volunteer (male, 26 yr), using the same testing conditions as those utilized to assess oxygenation levels in the gluteus maximus muscles: 1) rest, 2) weight, and 3) weight + IES. To elicit contractions in the left and right gluteus maximus muscles, surface electrodes were placed over the motor point of each muscle. The volunteer was placed in a supine position with the buttocks over an X-3 System pressure sensitive mattress (XSensor, Calgary, AB, Canada). Measurements of surface pressure in the sacral region of the buttocks were obtained over a 1-minute period of rest. A 20-kg load, equivalent to 30% of the body weight of the volunteer, was applied over the pelvis to compress the tissue of the buttocks. Surface pressure measurements were acquired for 1 minute under this condition. Electrical stimulation was then applied simultaneously to both gluteus maximus muscles. A series of 3 15-s stimulus bouts (biphasic, charge-balanced, constant current, 70 mA, 250 μs, 50 pulses/s) were applied with the

load in place. Changes in surface pressure associated with IES were measured during each bout of stimulation.

2.3 RESULTS

2.3.1 Induction and detection of DTI in the rats' quadriceps muscles

Prior to testing the effectiveness of IES in preventing the formation of DTI, an animal model of DTI was developed. Our results show that edema and tissue injury can develop after a 2-hour application of constant pressure. In all three rats utilized to accomplish this objective, as well as in all subsequent experiments, the skin under the pressure indenter did not exhibit any external sign of inflammation or injury, underscoring the difficulty of identifying DTI by visual inspection of the skin. The only signs of injury visible on the skin were exhibited on the internal side, and were limited to an area the size of the indenter (Figure 2 - 5).

Figure 2 - 5: *Skin health.* Picture of the internal side of the skin covering the quadriceps muscles from rat #1 (100% BW). Arrow indicates area of visible injury.

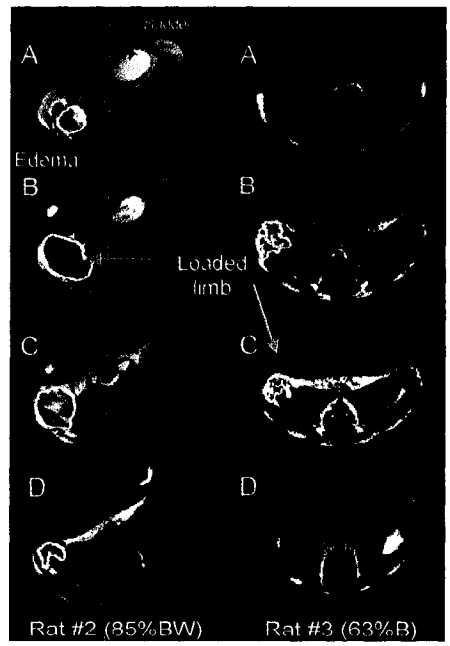

Figure 2 - 6: *Detection of DTI using MRI.* Progression of slices goes from rostral (A) to caudal (D) for rat #2 and rat #3. The area with edema is highlighted in yellow.

The MRI scans of rats 2 (85% BW) and 3 (63% BW) showed an increase in signal intensity in the loaded hind limb, compared to

the unloaded hind limb (Figure 2 – 6). This increase in signal is associated with the increased water mobility that takes place during edema formation. The size of the affected region in each rat was graded based on the amount of pressure utilized to induce the DTI. Twelve hours after the removal of pressure, rat 1 (100% BW) exhibited signs of pain and discomfort even with the administration of analgesics; for this reason the rat was euthanized ahead of schedule and an MRI scan was not performed.

The volume of the loaded quadriceps muscle group was larger in all three rats than that in the unloaded limbs. Similar to the MRI results, the increase in volume was graded based on the amount of pressure utilized to generate the DTI (Figure 2 – 7a). Other than the increase in the volume of the extracted muscle from the loaded limb, there were no visible areas of discoloration or signs of injury in any of the rats. However, after the muscles were cut longitudinally, a large area of necrotic tissue was observed in the regions closest to the bone and directly under the indenter in all of the loaded muscles (Figure 2 – 7b).

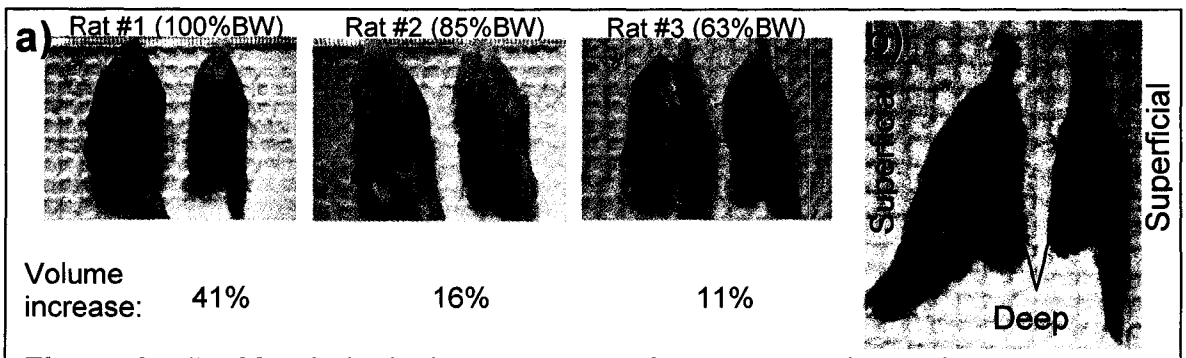

Figure 2 - 7: *Morphological assessment of the extracted muscles.* a) Increase in the volume of the affected muscles as a result of DTI. b) Longitudinal cut of the muscle. Loaded limb indicated by *

2.3.2 Effectiveness of IES in preventing the formation of DTI

The main objective of this investigation was to determine whether IES is an effective technique for preventing DTI. In the Control Group (pressure, No IES), the application of external pressure for 2 hours generated edema in 60 ± 15% of the muscle. In contrast (Figure 2 - 8, left axis, filled circles), Experimental Groups 1 (pressure + IES every 10min) and 2 (pressure + IES every 5min) exhibited a significantly reduced region of edema in the muscle, (16 ± 16% and 25 ± 13%, respectively). Experimental Group 3 (No pressure, IES every 5min) and Contralateral Control Group (untreated contralateral limbs) exhibited a 5 ± 4% and a 5 ± 4%, respectively. The extent of increased water content in all three experimental groups was significantly different from that in the Control Group (one-way ANOVA test, $p = 0.0001$), but was not significantly different from each other (Tukey post-hoc test, Exp 1 vs Exp 2, $p = 0.59$; Exp 1 vs Exp 3, $p = 0.45$; Exp 2 vs Exp 3, $p = 0.06$).

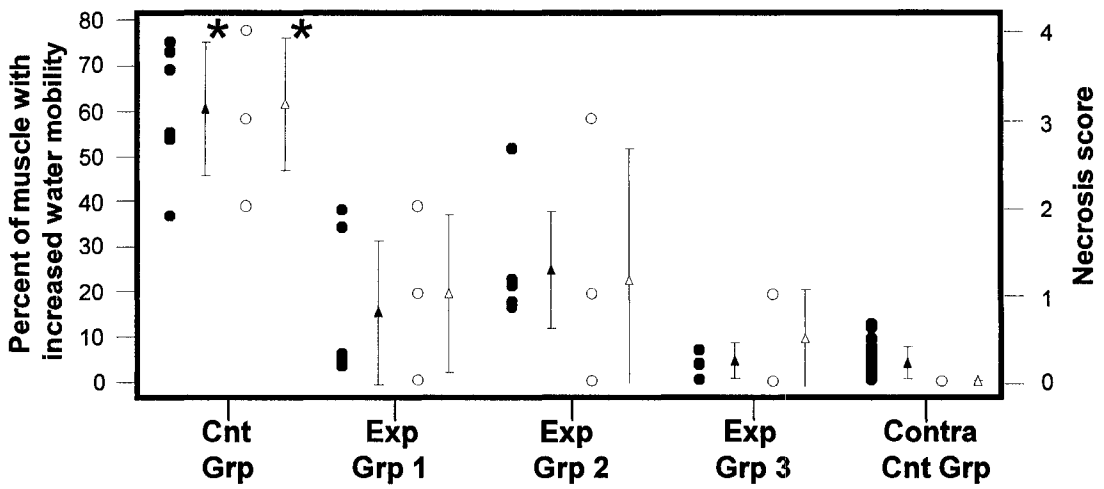

Figure 2 - 8: *Summary of magnetic resonance imaging and histology results.* Left Axis: Individual data points (filled circles) and mean ± SD (filled triangles) representing the percent of muscle volume with increased water mobility (edema) in the quadriceps muscle in all rat groups. Right Axis: Individual data points (empty circles) and mean ± SD (empty triangles) representing the necrosis score from the quadriceps muscle in all rat groups. Scoring for quantifying muscle necrosis (per 4.9 mm2 of muscle area) is: 0 = no necrosis in region analyzed; 1 = 0-10% of region analyzed exhibited necrosis; 2 = 10-25%; 3 = 25-50%; 4 > 50%. *Represents statistically significant difference.

Histological assessment of the quadriceps muscle tissue (Figure 2 - 9) showed that the severity of muscle injury varied between the control and experimental groups. In general, the lesions within the muscle were characterized by swelling, loss of striations, and fragmentation of muscle fibers. The connective tissue surrounding affected muscle fibers was often infiltrated by numerous neutrophils admixed with smaller numbers of macrophages. Hemorrhage into muscle bundles was most apparent in severely affected tissue. Figure 2 - 8 (right axis, open circles) summarizes the extent of tissue necrosis in the control and experimental groups. The Control Group had the largest

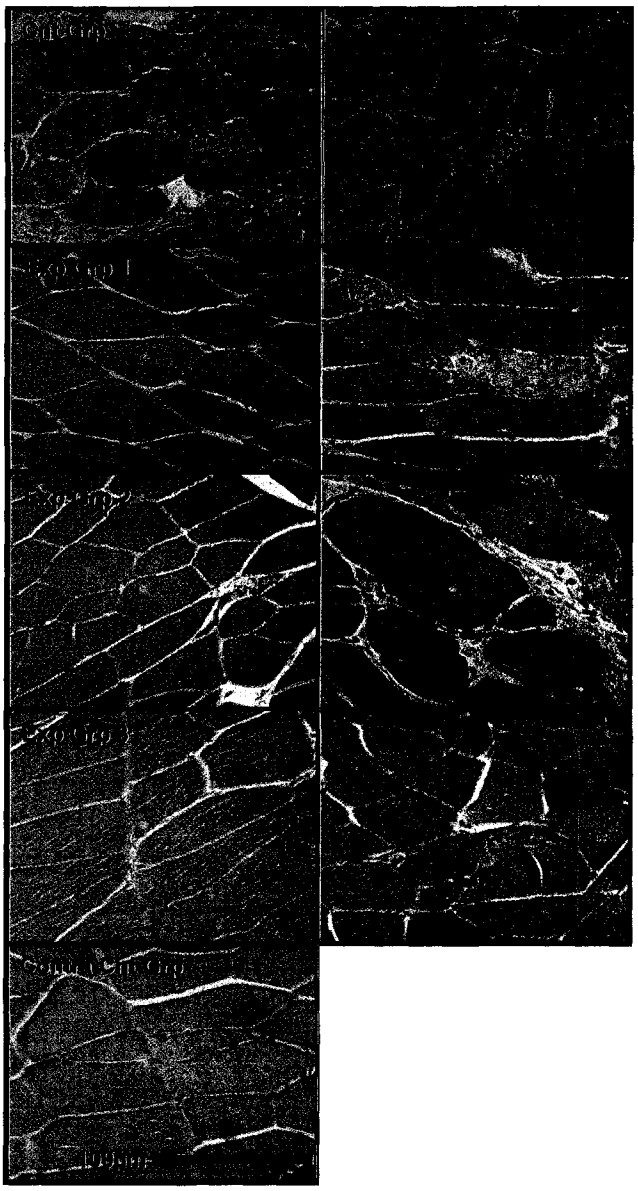

Figure 2 - 9: *Histological assessment of DTI.* Sample H&E-stained cross sections from different animals in each group. The amount of edema observed with MRI correlated well with the amount of necrotic fibers assessed from the histological slides. All histological sections were viewed at 100x magnification.

extension of necrotic fibers in the tissue with a score of 3.2 ± 0.8. This score represented a necrotic area occupying 25 to 50% of the region analyzed. The extent of tissue necrosis was significantly larger in the Control Group than that in Experimental Group 1, which had a score of 1.0 ± 0.9 (Kruskal-Wallis non-parametric test, p = 0.01), representing a necrotic area of less than 10%. Experimental Group 2 also exhibited a significantly smaller area of muscle necrosis than the Control Group (Kruskal-Wallis non-parametric test, p = 0.03), with a score of 1.2 ± 1.5, equivalent to a necrotic area between 10% and 20%. The necrosis score was also significantly smaller in Experimental Group 3 (Kruskal-Wallis non-parametric test, p=0.004), with a score of 0.5 ± 0.6. There was no significant difference between all three experimental groups in the amount of necrosis assessed. The infiltration of neutrophils and macrophages, as well as the presence of red blood cells and mineralization of the tissue, were not significantly different between the control and experimental groups.

2.3.3 Increases in tissue oxygenation due to IES-elicited contractions

Two experiments were performed with the goal of measuring the changes in tissue oxygenation levels associated with the use of IES. The effects of IES-elicited contractions on muscle oxygenation were first tested in a condition where the muscle was at rest and unloaded. Figure 2 – 10a summarizes the effect of IES on the level of oxygenation in the muscles of the lower leg. Normalized T_2* levels in MG, LG, LS, and MS are shown. Interestingly, IES selectively increased the T_2* level of MG, the stimulated muscle. This increase

in oxygenation was maintained throughout the experiment. Oxygenation levels in LG, LS, and MS did not show any change when compared to baseline measurements.

The second experiment measured the increase in tissue oxygenation following IES-elicited contractions of loaded muscles. These loaded muscles had a corresponding reduction in oxygen supply, a situation that represents the state of tissue around the ischial tuberosities in a seated individual. Figure 2 - 10b summarizes the effect of IES on the level of tissue oxygenation in the gluteus maximus muscles in the presence of an external pressure. Normalized T_2^* levels in the right and left gluteus maximus muscles are shown for each condition tested (rest, weight, weight + IES). The oxygenation levels in both muscles decreased immediately by ~4% after the load application; oxygenation remained at this lower level throughout the 10 minutes in which this condition was maintained. Following IES, the oxygenation levels in the muscles increased above the initial baseline levels by ~6%.

2.3.4 Changes in surface pressure profiles due to IES-elicited contractions

In a third experiment (Figure 2 - 10c) surface pressure measurements of the buttocks were obtained under the same three conditions previously tested (rest, weight, weight + IES). The average pressure throughout the buttocks at rest was 10.9 kPa, distributed over a 487 mm^2 area. As expected, the region of highest pressure was that surrounding the bony prominence (the sacrum in this case), and exhibited an average pressure of 21.7 kPa.

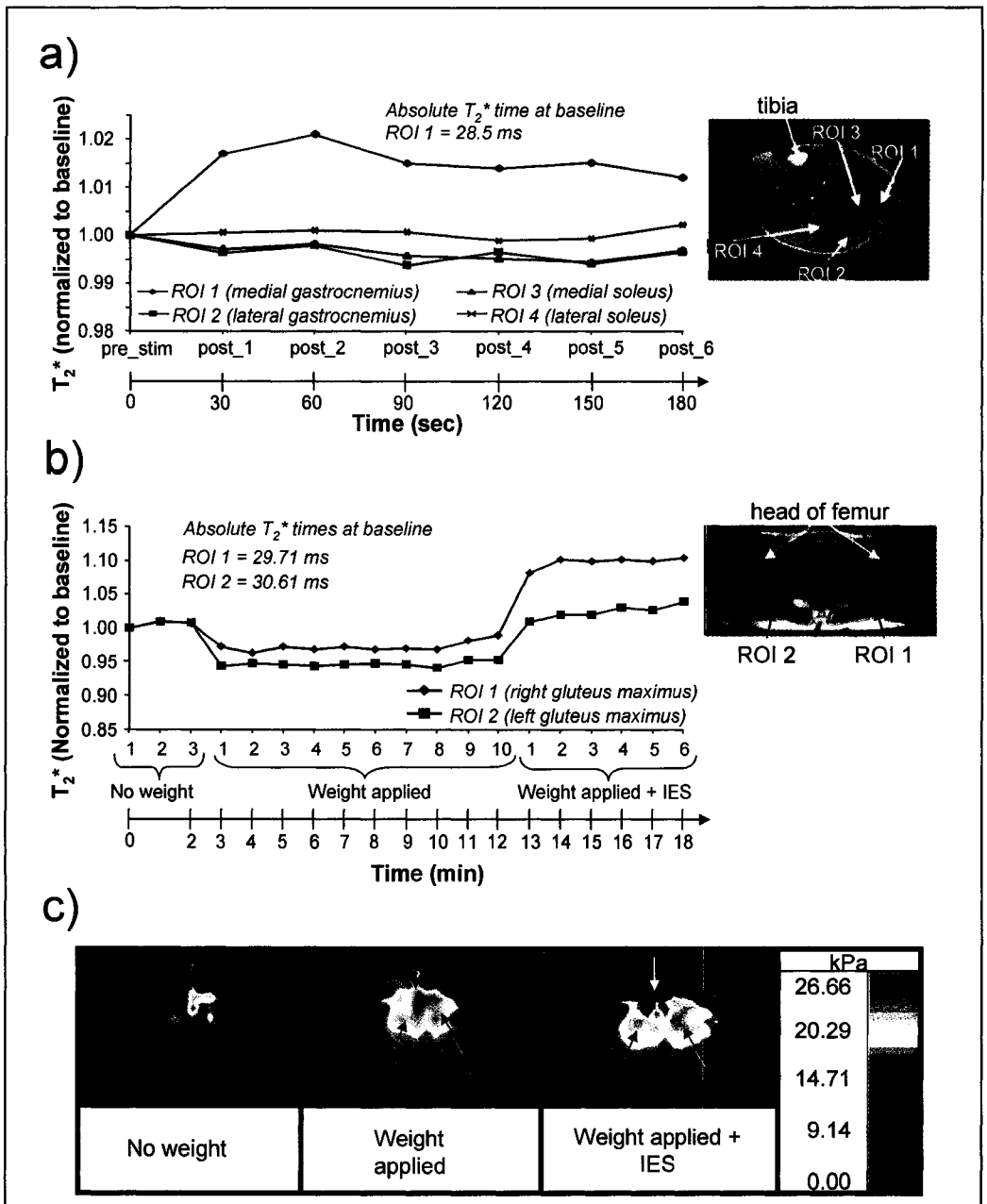

Figure 2- 10: *Changes in levels of oxygenation and surface pressure due to loading and IES* (a) Quantitative T2* imaging following 6, 30-sec bouts of electrical stimulation applied to medial gastrocnemius. Persistent regional increases in blood oxygenation were seen with IES. (b) Quantitative T2* imaging of the gluteus maximus muscles under different conditions. A persistent decrease in blood oxygenation was seen when the muscles were loaded, and a persistent increase was obtained with IES. (c) Surface-skin interface pressure map of the gluteus muscles under different conditions. Highest point of pressure with loading was observed around the sacrum (arrows). With IES, pressure became more evenly distributed, eliminating the previous concentrations of high pressure.

Following the loading of the pelvis, the average pressure throughout the buttocks increased to 13.9 kPa and was distributed over a 511 mm^2 area. The average pressure in the region around the sacrum increased to 25.8 kPa. Simultaneous bilateral application of IES to the loaded (compressed) gluteus maximus muscles induced contractions which reconfigured the shape of the muscles. The average pressure throughout the buttocks became 14.3 kPa distributed over an area of 424 mm^2. However, the average pressure around the sacrum was reduced to 19.5 kPa, a level lower than that seen even during the rest condition.

2.4 DISCUSSION

2.4.1 Induction and detection of DTI

None of the rats in this study showing indications of DTI displayed injury to the overlying skin. This emphasizes that skin appearance is a poor indicator of deep tissue health, and supports the need for other alternative methods to detect DTI. The results of this study, as well as those reported previously by Bosboom et al (Bosboom et al. 2003) and Stekelenburg et al (Stekelenburg et al. 2006), show that MRI is an effective tool for the detection of muscle edema associated with the presence of DTI, even when injury occurs in muscles as small as those in the rat hind limbs. Although MRI currently may not be ideal for screening patients with DTI due to cost and availability, in situations where an individual is considered to be at high risk of developing an ulcer or has a long history of ulcer development, it might be necessary to perform periodic

screenings. Identifying DTI before it fully evolves into a pressure ulcer would not only have a significant beneficial impact on the health and quality of life of the individual, but could greatly reduce costs associated with further medical and surgical treatments.

2.4.2 Effectiveness of IES in preventing the formation of DTI

Several studies have reported the beneficial effects of both alternating and direct current electrical stimulation for healing chronic wounds, including pressure ulcers (Bogie et al. 2000; Gardner et al. 1999; Griffin et al. 1991; Houghton et al. 2003; Reger et al. 1999; Stefanovska et al. 1993; Vodovnik and Karba 1992). The consensus is that when combined with traditional treatments, electrical stimulation improves wound healing. Very few studies however, have investigated electrical stimulation alone as a method for preventing the formation of pressure ulcers.

Levine et al. first proposed using electrical stimulation to prevent pressure ulcers and measured the effect of electrical muscle stimulation on 1) pressure at the seating interface (Levine et al. 1989), 2) muscle shape (Levine et al. 1990a), and 3) blood flow (Levine et al. 1990b). Their results indicated that during each contraction of the gluteus muscles 1) the superficial pressure surrounding the ischial tuberosities was reduced; 2) the shape of the compressed muscle was modified; and 3) blood flow increased in the stimulated muscle. Based on these observations, it was suggested that electrical stimulation might be an effective technique to prevent pressure ulcers.

Following the seminal study of Levine et al., Rischbieth et al (Rischbieth et al. 1998) and Bogie et al (Bogie et al. 2000) reported that an increase in muscle mass was achieved through long-term electrical stimulation. The increase in muscle mass was suggested to provide individuals with improved cushioning, which in turn, could prolong the time they can remain seated. Recently, Bogie et al (Bogie et al. 2006) analyzed the long-term effects of electrical stimulation of the gluteus muscles in one individual with spinal cord injury. Measurements of surface interface pressure, transcutaneus oxygen levels, and muscle thickness were similar to observations previously reported by Levine (Levine et al. 1989; Levine et al. 1990a; Levine et al. 1990b), Rischbieth (Rischbieth et al. 1998), and Bogie (Bogie et al. 2000). It was also determined that any benefits gained during the period of electrical stimulation were abolished once the electrical stimulation was discontinued. While the evidence from these studies suggested the potential effectiveness of IES in preventing the formation of pressure ulcers, heretofore no study had investigated the effects of IES on the integrity of deep muscle exposed to constant pressure.

The present study examined the efficacy of IES in preventing DTI in a rat model and its mechanism of action in human volunteers. Our results show, that within defined parameters of electrical stimulation, a considerable reduction in DTI was observed. Traditionally, tissue injury generated by ischemia following long periods of tissue compression, has been considered the principal etiological factor behind pressure ulcers (Kosiak 1959, 1961; Kosiak et al.

1958). Within this precept, more frequent stimulation should restore tissue oxygenation in the tissue to normal or near-normal levels, potentially eliminating tissue injury caused by ischemia. The finding that there was no significant difference between our experimental groups (IES every 10 minutes vs. 5 minutes) could indicate that the beneficial effects of an increase in oxygenation to the tissue may have reached their threshold when stimulation occurred every 10 minutes. It is possible that the amount of damage observed in both experimental groups could be attributed to damage generated directly by the high stress levels at the bone-muscle interface and excessive cell deformation, a factor that was further exaggerated in our experimental set up due to the fixation of the hind limb which led to an increase, rather than a decrease, in focal pressure during the IES-induced contractions (evident in the increases in recorded force in Figure 2 – 2 b). Although the application of pressure to the rats' limbs was done outside the MRI scanner, utmost care was taken in the placement of the indenter, such that it was as centered as possible over the QM and the femur.

Comparison of Experimental Group 3 and the Contralateral Control Group demonstrated that the use of IES as frequently as every 5 minutes does not cause an increase in the water mobility of the muscle. The minimal amount of increased water mobility identified in the Contralateral Control Group, as calculated in this study, indicates that ~5% of the increase in water mobility in the tissue quantified in the Control Group and Experimental Groups 1 and 2 was not caused by the load application.

It has been suggested that high stress levels at the bone-muscle interface is a primary factor in the development of pressure ulcers (Bouten et al. 2003; Breuls et al. 2003; Daniel et al. 1981; Linder-Ganz et al. 2006a; Linder-Ganz and Gefen 2004), but the extent of tissue injury that is associated with these mechanical forces (shear and stress) has yet to be determined. Although complete elimination of DTI has not been achieved, our results suggest that IES delivered every 10 minutes is sufficient to reduce greatly the extent of damage in deep tissue exposed to constant external pressure.

2.4.3 Mechanisms of Action of IES

Our results demonstrated that the levels of available oxygen in the tissue of gluteus maximus were reduced immediately after compressing the muscles (Figure 6). However, instantly following the first IES-induced contraction of the muscles, the levels of tissue oxygen increased. This increase was greater than baseline levels, and was most likely caused by reactive hyperemia, a process in which there is an increase in blood flow into the capillaries after brief periods of occlusion (Mollison et al. 2006). This increase in oxygenation was maintained after each of the 6 IES-induced contractions. While oxygenation levels in the unloaded medial gastrocnemius muscle also increased with IES, the increase was less than that in the gluteal measurements. This may be due to the fact that blood flow to the medial gastrocnemius muscle was not altered, and consequently oxygenation levels were already at normal levels.

While periodical increases in tissue oxygenation should have the beneficial

effect of negating tissue injury associated with ischemia-reperfusion, pressure relief is still needed to prevent further damage from persistent high stress levels of muscle cells. Our results demonstrated that IES of the compressed gluteus muscles reconfigured the shape of the muscles and distributed the pressure laterally in the buttocks. The net result was a periodical relief of the superficial pressure around the bony prominence and reduction in the overall pressure throughout the buttocks. The use of superficial pressure measurements combined with recently developed finite element models (Linder-Ganz et al. 2006b; Oomens et al. 2003) of the gluteal muscles which can estimate the stress levels at the bone-muscle interface, could provide a more accurate tool for predicting the risk of developing DTI.

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CHAPTER 3

CONCLUSION AND FUTURE DIRECTIONS

The main goal of my thesis was to test the effectiveness of IES in preventing the formation of DTI. To achieve this goal I established three specific objectives: 1) Develop a rat model of DTI; 2) Test the effectiveness of IES in preventing DTI; and 3) Identify the mechanisms of action of IES.

3.1 Develop a rat model of DTI

I successfully developed a rat model of DTI in which I induced a controlled deep injury in the quadriceps muscle group. The amount of induced DTI was dependent on the level of pressure utilized to load the muscle. While only one level of pressure was used to test the effectiveness of IES in preventing the formation of DTI, the rat model could be utilized in the future to test different IES parameters.

3.2 Effectiveness of IES in preventing DTI

My results show that the use of IES every 10 minutes is adequate to reduce significantly the amount of DTI in the muscles subjected to 2 hours of continuous loading. This is the first study that directly investigated the effectiveness of electrical stimulation in preventing the formation of pressure ulcers and suggests that a new intervention based on IES warrants development.

Given the promising results obtained so far, an IES system that can be used prophylactically without interfering with the users' daily activities has the potential to be an effective pressure ulcer prevention tool for those who spend their day in a wheelchair. Its use can also be extended to intensive care units, hospital wards, and nursing homes where the incidence of pressure ulcers is remarkably high.

3.3 Mechanisms of action of IES

My results demonstrated that IES is capable of redistributing the pressure around the buttocks during each induced contraction. In addition to this redistribution of pressure, each contraction generates an increase in the oxygenation levels of the stimulated muscles. When used chronically, IES would also increase muscle mass, which would provide further protection against the development of pressure ulcers.

3.4 Future directions

The results from this thesis indicate that IES could become a viable technique for the prevention of DTI; however, a number of questions need to be addressed before an IES system could be implemented clinically.

1) Although this study has shown that IES is capable of reducing the amount of DTI in a loaded muscle significantly, a test of a wide set of stimulation parameters was not investigated. Identification of IES

parameters that could provide a maximal increase in tissue oxygenation and maximal reduction in interface pressure is needed. These parameters could provide a complete prevention of DTI formation in wheelchair users with SCI.

2) The measurement of superficial pressure profiles is commonly performed to assess the appropriateness of a support surface in reducing pressure around bony prominences; however, stress levels at the deep bone-muscle interface are higher than those measured at the skin-surface interface. This difference in stress levels can lead to misjudgments regarding the effectiveness of pressure relieving systems, and repositioning frequency. While some finite element models have been developed with the objective of predicting internal stress levels based on superficial pressure measurements, none of these models has been validated in-vivo. An animal model of DTI that could compare measurements both at the deep and superficial level, and correlate those against predictions from existing or newly developed models, could provide clinicians a more accurate assessment of safe levels of seating pressure.

3) For this study pressure was applied in a single 2 hour-long session. This duration is enough to generate a DTI; however, in a real life situation, pressure to the gluteus muscles in a wheelchair user is applied consistently throughout the day. Therefore, the effectiveness of IES needs to be tested under such conditions, where repeated periods of

loading are incurred on a daily basis.

4) Regardless of how effective an IES system can be in preventing the onset of DTI, to have an impact on peoples' health the system needs to be readily utilized. Therefore, a vital step is developing a system that is affordable and easy to use and operate on a daily basis to encourage user compliance.

5) Given the current difficulty in detecting the early onset of DTI, the development of a clinically feasible early detection method is needed. Magnetic resonance imaging is capable of detecting the early stages of DTI 24 hours after the loading insult has occurred; however, its limited availability and high cost make its routine use for assessing deep tissue health prohibitive. A viable method for early DTI detection could be the identification of a set of biochemical markers present in the blood and which are sensitive to the local changes in tissue metabolism and inflammatory response that take place during DTI. By correlating specific changes in the levels of these markers to the progression of DTI, a simple blood test could become all that is needed to provide indications of the early stages of DTI, allowing timely intervention to stop the progression of DTI before it develops an open pressure ulcer.