University of Alberta

A Revolutionary Step Towards the Prevention of Pressure Ulcer: from Bench to Bedside

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

Centre for Neuroscience

Fall 2012
Edmonton, Alberta

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“Sve je moguće, sve je na dohvat ruke, samo se čovijek ne smije predati. Teško je dok se ne odlučiš, tada sve prepreke izgledaju neprelazne, sve teškoće nesavladive. Ali kad se otkineš od sebe neodlučnog, kad pobjediš svoju malodušnost, otvore se pred tobom neslućeni putevi, svijet više nije skučen i pun pretnji.”

~Meša Selimović~

ABSTRACT

Deep tissue injury (DTI) is a particularly serious subtype of pressure ulcer that first starts in the muscle layers over bony prominences as a result of unrelieved loading. Intermittent electrical stimulation (IES) induced muscle contractions have shown potential for prevention of DTI through contraction induced pressure shift and tissue perfusion. As part of this thesis, we conducted a clinical safety and feasibility study of the IES system and found that it was generally safe, feasible and acceptable in long term care and rehabilitation hospital settings. Furthermore, I demonstrated that prolonged IES did not cause muscle fatigue in neurologically intact and subjects with spinal cord injury. The therapeutic benefit of IES is critically dependent on its ability to induce muscle contraction, and thus this is an important parameter to monitor to ensure optimal performance of the IES system. I found a linear relationship between peak twitch tension and peak to peak M-wave amplitude in neurologically intact and subjects with spinal cord injury, suggesting that electromyography may be a useful non-invasive technique for providing feedback in an adaptable IES system. This thesis work helps to lay the foundation for future effectiveness study and in the development of an intelligent stimulator.

ACKNOWLEDGMENTS

Through continuous guidance, endless patience and sincere kindness, you helped me develop as a researcher and truly grow as a person:

- Dr. K. Ming Chan

Inspiring role model providing encouragement and support in helping me reach beyond the limits I set for myself:

- Dr. Vivian K. Mushahwar

Invaluable input and assistance with clinical, technical and experimental aspects of studies presented in this thesis:

- Lisa Kawasaki
- Glen Isaacson
- Ryan Sommer
- Dana Schnepf
- Robyn Warwaruk-Rogers
- Nursing staff at the clinical centers
- Dr. Sean Dukelow
- Dr. Richard Stein
- Dr. Martin Ferguson-Pell
- Michel Gautier
- Su Ling Chong
- Anita Clarke
- Cara Curtis
- Atif Khan
- Liping Qi
- Alfredo Arriola
- Mathew Wu
- Yang Hu

- Ben Kostiak
- Members of Pressure Ulcer Focus Group
- Ephrem Zewdi
- All study participants

Clinical Partners:

- Allen Gray Continuing Care Center
- Glenrose Rehabilitation Hospital
- Foothills Hospital

Financial Support:

- AIHS SMART Team Grant for Interdisciplinary Research
- TD Bank Financial Group Grant for Interdisciplinary Research
- Profiling Alberta's Graduate Students Award

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List of Abbreviations

ANR – acute neuro-rehabilitation

ATP – adenosine triphosphate

DTI – deep tissue injury

EMG – electromyography/ electromyogram

ES – electrical stimulation

ISMS – intra-spinal micro stimulation

IES – intermittent electrical stimulation

LTC – long term care

MF – median frequency

MPF – mean power frequency

NCS – nerve cuff stimulation

O_2 – molecular oxygen

PrUs – pressure ulcers

RH – rehabilitation hospital

ROMs – reactive oxygen metabolites

SCI – spinal cord injury

sDTI – suspected deep tissue injury

XO – xanthine oxidase

Chapter 1: Introduction

1.1 Importance of preventing pressure ulcers

Pressure ulcers (PrUs), also known as pressure sores, bedsores and decubitus ulcers, are serious secondary complications that afflict people with motor and sensory impairments (Berlowitz & Brienza, 2007). They are defined as a "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear" (European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel., 2009.) PrUs negatively impact the overall quality of life of those suffering from them, including physical, psychological and social well-being (Consortium for Spinal Cord Medicine, 2000) and can lead to sepsis and death (Gefen, 2009a). The monetary cost associated with treatment of hospital acquired PrUs is ~$12 billion USD per year, with the cost per PrU treatment ranging from $20,900 to $151,700 USD (Zulkowski, Langemo, Posthauer, & National Pressure Ulcer Advisory Panel, 2005).

1.2 Frequency of pressure ulcers

PrUs can occur in a wide range of clinical settings. The elderly patients are at the highest risk as 73% of all PrUs occur in persons 65 years old or older (Whittington, Patrick, & Roberts, 2000). Prevalence rates in Canadian long-term care facilities are up to 30% (Woodbury & Houghton, 2004). In acute and

intensive care units prevalence rates of PrUs range from 12 to 25% (Woodbury & Houghton, 2004; Jenkins & O'Neal, 2010).

Prevalence rates in people with spinal cord injury are up to 32% (Rabadi & Vincent, 2011; Saladin & Krause, 2009) with PrU recurrence rates at 35% (Niazi, Salzberg, Byrne, & Viehbeck, 1997). Incidence rates range from 15-70% (Bogie, Reger, Levine, & Sahgal, 2000b). PrU prevalence rates appear to be steady for the first 10 years afters spinal cord injury but tend to increase as time passes (Chen, Devivo, & Jackson, 2005).

1.3 Categories of pressure ulcers

1.3.1 Surface ulcers

Surface PrUs develop at the skin surface and progress inwards toward the bone, commonly due to friction of the skin against clothing and bed sheets causing shearing damage at the skin, and may further be exacerbated by moisture from sweat and incontinence (Gefen, 2009a). Surface ulcers are generally detectable in early stages by standard skin inspections.

1.3.2 Deep tissue injury

Deep tissue injury (DTI) is a type of PrU that develops as a result of prolonged pressure of bone on soft tissues underneath the bony prominence (Gefen, 2009a). Since muscle is more susceptible to injury from sustained pressure than skin, DTI tends to first occurs at the deep muscle and progress outward to the skin layers (Bouten, Oomens, Baaijens, & Bader, 2003). Early

stages of DTI may not be detectable with standard skin inspections, and it may not be suspected until after extensive damage spanning muscle and fat layers has already occurred (Gefen, 2009a). Consequently, they more often require longer hospital stays, higher costs, more aggressive treatments and repeated reconstructive surgery (Berlowitz & Brienza, 2007).

1.3.2.1 Prevalence of deep tissue injury

Information on suspected DTI (sDTI) is sparse, likely because DTI was only formally recognized as a separate type of PrU by the National Pressure Ulcer Advisory Panel in 2007 (Ankrom et al., 2005; Black & National Pressure Ulcer Advisory Panel, 2005). In an International Pressure Ulcer Prevalence survey over a 3 year period on 79 000 to 92 000 patients, the proportion of ulcers identified as sDTI was 9% of all observed ulcers in 2009, which is a 3 fold increase from prevalence rates reported in 2006. The increased rate of sDTI identification over the 3 year period of the study was likely a consequence of education on the new staging definition (VanGilder, MacFarlane, Harrison, Lachenbruch, & Meyer, 2010) and is likely to further increase as the concept of DTI gains wider understanding.

1.3.2.2 Common anatomical locations of deep tissue injury

47% of all PrUs occur over the ischia and sacrum and are believed to be initiated while the individuals are seated (Bogie, Nuseibeh, & Bader, 1995). Body locations commonly identified for sDTI are the heel (41%), the sacrum (19%), and the buttocks (13%) (VanGilder et al., 2010). DTI may be easier recognized at the heel and sacrum as compared to the buttocks because of relatively superficial

locations. In contrast, at the buttocks, it is more difficult to detect early stages of DTI as there is a much greater amount of subcutaneous tissue overlying the muscle and bone tissues.

1.4 Mechanisms of deep tissue injury

The etiology of DTI is not fully understood. The evidence suggests that sustained loading contributes to development of DTI through two mechanisms. First, surface pressure leads to occlusion of the circulatory system leading to ischemia, depletion of energy and accumulation of metabolites leading to irreversible cell damage. Restoration of blood flow after long periods of ischemia leads to exacerbated damage, a process called ischemia-reperfusion injury and no re-flow phenomena. Second, direct mechanical pressure leads to excessive tissue deformations and directly damages the cell through membrane and cytoskeleton disruption and cell bursting. External pressure leads to DTI through interactions of the above mentioned mechanisms. Their relative contribution depends on the amount and duration of the applied pressure.

1.4.1 Ischemia induced DTI mechanisms

1.4.1.1 Myocyte energy mechanisms

Muscle cells generate energy, adenosine triphosphate (ATP), through oxidative phosphorylation in the presence of molecular oxygen (O_2) from the bloodstream (aerobic respiration) and creatine phosphate and glycolysis in the absence of O_2 as shown in figure 1.1.

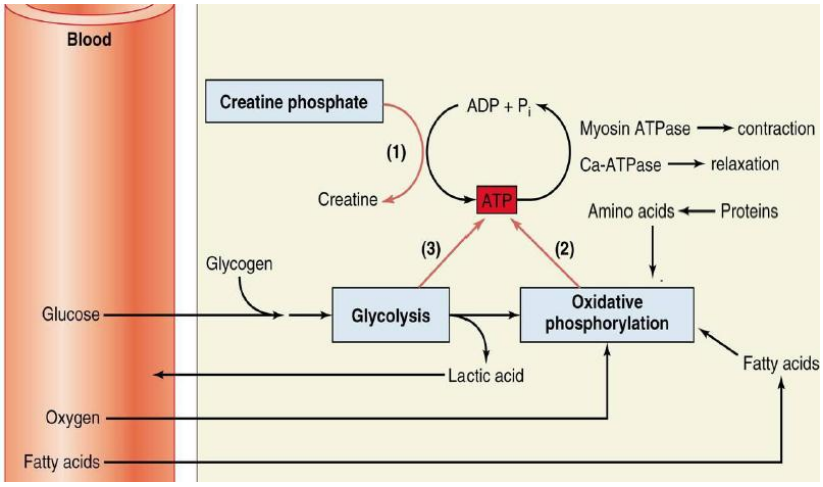

Figure 1.1 Sources of muscle cell energy.
(Source: http://howmed.net/physiology/skeletal-muscle)

The most efficient of the three, *aerobic respiration*, produces 36 molecules of ATP for each molecule of glucose (or glycogen) while glycolysis produces only 2. Each creatine phosphate molecule stored inside muscle produces only 1 molecule of ATP (Atalay & Hanninen, 2004) and its stores can be used up in as little as 10 seconds in cases of intense exercise (Benardot, 2006).

Glycolysis can sustain cell energy demands for a relatively long time; glycogen stores inside muscle are about 4-5% of the wet muscle weight. Under ischemic conditions, pyruvate – a product of glycolysis, is broken down into lactic acid. Due to compromised circulation from external pressure, accumulation of lactic acid leads to a decrease of cytosolic pH which inhibits glycolysis by inhibition of its rate limiting enzyme phosphofructokinase (PFK). Exhaustion of glucose and glycogen and accumulation of lactic acid eventually leads to failure of glycolysis to produce ATP during muscle ischemia (Atalay & Hanninen, 2004).

1.4.1.2 Reversible and irreversible ischemia-induced cell damage

Depletion of ATP initially leads to reversible cellular disturbances. Failure of energy-dependent ion pumps leads to organelle and cell swelling. Along with increased sodium, chlorine, calcium, and decreased potassium concentrations, they lead to formation of membrane blebs and overall reduction in protein synthesis (Kuma, Abbas, Fausto, & Mitchell, 2007). Unless oxygenation is restored at this point, further ischemia will lead to irreversible cell changes.

The main mechanism of irreversible damage is necrosis from a combination of factors including rapture of lysosomes and extensive damage to plasma membranes. Elevated calcium concentration inside the cell leads to deleterious effects by activating: 1) phospholipases and proteases that further damage the membrane and cytoskeleton, 2) endonucleases that cause DNA and chromatin fragmentation and nuclear damage, and 3) ATPases that hasten ATP depletion. High calcium concentration also results in apoptosis, by direct activation of capsases and increased mitochondrial permeability of apoptotic molecules (Kuma et al., 2007).

Myocytes and endothelial cells of the microvasculature undergo parallel changes during ischemia. Furthermore, ischemia-induced endothelial cell enzymatic changes lead to production of reactive oxygen metabolites (ROMs) upon restoration of blood flow that exacerbate tissue damage through ischemia-reperfusion injury and inflammation. Inflammatory responses following reperfusion vary greatly and depend on the extent of ischemic tissue injury (Blaisdell, 2002).

1.4.1.3 Ischemia-reperfusion injury

Ischemia leads to activation of enzyme xanthine oxidase (XO) localized in microvascular endothelial cells, and breakdown of ATP into hypoxanthine and xanthine – substrates for the O^2 dependent XO reaction which generates ROMs including superoxide (O^{2-}) and hydrogen peroxide (H_2O_2). Blood reperfusion creates the perfect conditions for the XO reaction. ROMs damage cell membranes via lipid peroxidation, induction of cross-linking, and degradation of proteins and nuclear content of the cell (Gute, Ishida, Yarimizu, & Korthuis, 1998).

Furthermore, ROMs activate adhesion molecules on the surface of endothelial cells which promote leukocyte accumulation and subsequent migration to the site of injury as guided by chemotactic signals released from damaged myocytes. The phagocytic leukocytes produce additional ROMs through a membrane-bound nicotinemide adenine dinucleotide phosphate (NADPH) oxidase enzyme. Endothelial cell and leukocyte generated ROMs damage the muscle by acting synergistically (Gute et al., 1998).

1.4.1.4 No-reflow phenomena

Swelling of endothelial cells leads to decreased diameter of the capillary lumen and aggregation of leukocytes in the post-capillary venules, causing increased resistance to flow in the capillaries. Furthermore, leukocyte migration past endothelial cells increases permeability of the microvasculature leading to accumulation of interstitial fluid volume. Because muscle facia does not allow muscle expansion, this leads increased extracellular pressure on the microvasculature and can in extreme cases lead to fully occluded blood flow

(Gute et al., 1998). Damage from ischemia-reperfusion can thus be further intensified by no-reflow phenomena in the capillary beds and exacerbate the magnitude of DTI.

1.4.1.5 Time-lines of ischemia induced DTI

Ischemia-induced muscle damage is gradual. Stekelenburg et al. (2007) showed that 2 hours of ischemia causes reversible cell changes only (Stekelenburg et al., 2007). Labbe et al. (1987) found that 3, 4, and 5 hours of ischemia caused 2, 30, and 90% respectively, of tissue necrosis in skeletal muscles of canines (Labbe, Lindsay, & Walker, 1987).

Ischemia-reperfusion induced through 4 compression-release cycles of 2hrs of ischemia followed by 1 hour of reperfusion induced significantly decreased functional capillary density compared to 8 hours of continuous compression, indicating that ischemia-reperfusion damages the microcirculation more than single prolonged ischemic insult of the same length of time (Tsuji, Ichioka, Sekiya, & Nakatsuka, 2005). Similar results were reported by Peirce et al. (2000), suggesting that tissue injury increases with an increasing duration of ischemia, as well as increased number and frequency of ischemia-reperfusion cycles (Peirce, Skalak, & Rodeheaver, 2000).

A recent study by Jiang et al. (2011) found that 2 hours of ischemia produced only minor tissue changes whereas 3 cycles of 2 hours of ischemia followed by 1, 2, 3 and 4 hours of offloading (reperfusion) produced significant increase in inflammatory mediators and considerable tissue damage including leukocyte infiltration, collagen fibrosis and edema in epidermal, dermal and

muscle tissue layers. Worst tissue damage occurred with the 3 hour reperfusion cycle and slightly decreased with the 4 hour cycle suggesting that ischemia-reperfusion mediated injury depends on the frequency of ischemia-reperfusion cycles (Jiang, Tu, Wang, & Zhang, 2011). This study suggests that prevention of DTI may require longer off-loading than the standard 2 hour turning schedule.

1.4.2 Direct pressure induced DTI mechanisms

As illustrated in figure 1.2, surface pressure under bony prominences causes tissue compression (compressive stress), elongation (tensile stress) and shearing (shearing stress) (Takahashi, Black, & Gefen, 2010) acting together to produce tissue injury through direct and ischemic mechanisms by causing tissue distortion, pinching and occlusion of capillaries crossing tissue planes and reduction in blood flow, and physical disruption of tissues and blood vessels (Reger et al., 2010).

It has been shown that 2 hours of compressive loading causes rat muscles to develop muscle necrosis (Stekelenburg et al., 2007;Solis et al., 2007). Solis et al. (2007) showed that 38% body weight loading, which represents the loading experienced around each ischial tuberosity of seated individuals, causes rat quadriceps to develop a DTI that affects up to 60% of muscle volume. Affected muscles were characterized with loss of striations, fragmentation of muscle fiber, swelling, large numbers of neutrophils and macrophages and even hemorrhaging in severely damaged tissues (Solis et al., 2007).

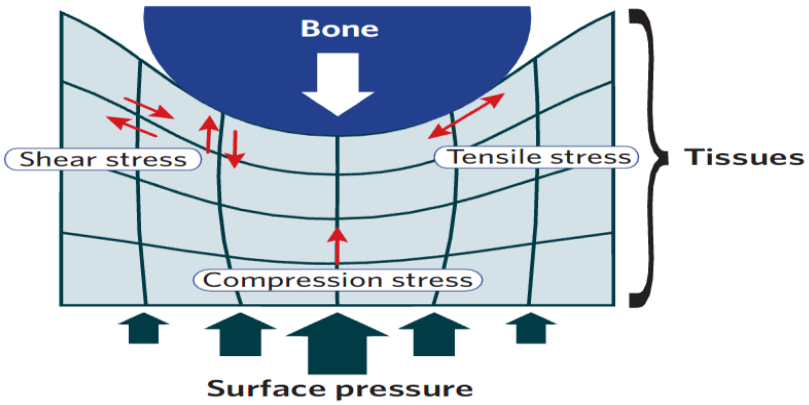

Figure 1.2 Surface pressure translates to shear, tensile and compressive stresses inside the tissue. *(Source: Takahashi et al., 2010).*

Direct compression of engineered muscle cell under aerobic conditions induced irreversible cell changes in as little as 1 hour of compressive loading (Stekelenburg, Gawlitta, Bader, & Oomens, 2008) indicating that direct tissue damage due to internal stresses is an important mechanism of DTI and can damage muscles faster than ischemia alone.

1.4.2.1 Assessment of deep tissue stresses

Finite element modeling studies incorporating human anatomy have shown that peak tissue stresses including compression and shear, appear in the deep muscle tissue adjacent to bony prominences (Gefen, 2008) which was confirmed in our lab by experiments on pig models with anatomy similar to that of humans.

Solis et al. (2012) found that in intact pigs under 25 and 50% of BW loading, the highest magnitudes of tension, compression and shear strains were located up to 2 cm ventrally from the ischial tuberosities and the lowest strains were located 1 cm dorsal of ischial tuberosities. Similar results were obtained in a

pig with SCI except that the dorsal region also had similar compression and shear levels as the center of ischial tuberosities, likely because of muscle atrophy. Average strain magnitude levels were about 10% higher in pig with SCI than those in intact pigs. One pig with SCI and DTI had similar trends for compression, tension and shear stresses as intact pigs but on average had 28% smaller strain magnitudes (Solis et al., 2012).

In a companion study on pigs, Solis et al. (2012) showed that highest internal pressure is located directly under the ischial tuberosities. They showed that the average peak internal pressure is ~2 times higher than maximal interfacial pressure measured at the level of the skin. In pig with SCI there was an increase in surface pressure due to muscle atrophy but internal pressures were similar to intact animals (Solis et al., 2012).

In summary, surface pressure leads to a complicated interaction of ischemic and direct tissue insults and ultimately DTI if tissue injury threshold is surpassed.

1.4.2.2 Tissue injury threshold

Kosiak showed in animal models that tissue damage depends not only on the intensity, but also on the duration of applied pressure (Kosiak, 1959; Kosiak, 1961). The inverse exponential relationship between pressure and exposure to loading was validated in humans by Reswick and Rogers, and recently improved based on collaborated research efforts, as shown in figure 1.3 (Gefen, 2009b). The sigmoid injury threshold curve that defines the failure strength for muscle tissue is consistent with experimental results (Linder-Ganz, Engelberg, Scheinowitz, &

Gefen, 2006). In addition to pressure threshold (left axis) the curve was fine-tuned to show tissue deformations that cause irreversible damage based on tissue-engineered muscle cell cultures (Gefen, van Nierop, Bader, & Oomens, 2008).

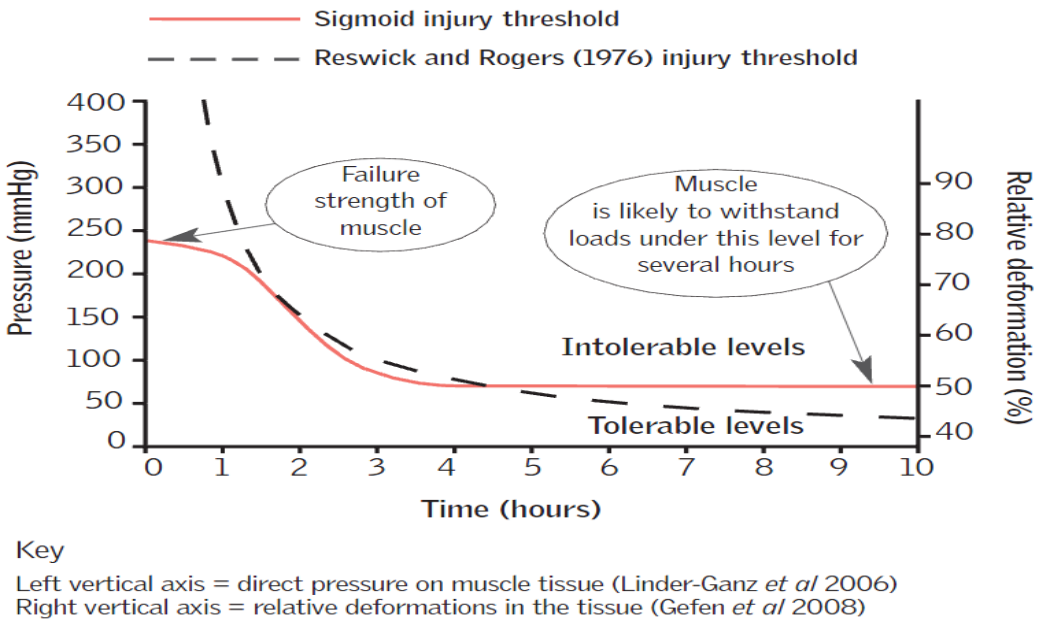

Figure 1.3 Muscle injury threshold curves. *(Source: (Gefen, 2009b))*

The sigmoid injury threshold curve shows that high pressures can cause direct muscle damage in a relatively short time or even instantly, whereas low pressures can be tolerated by muscles for long period of time. This curve points to the importance of minimizing surface pressure, the magnitude of which at least doubles the internal pressures (Solis et al., 2012). Periodic pressure relief especially in regions of focused pressure under and around the ischial tuberosities in seated individuals plays an important role in preventing DTI. This situation is even more critical in SCI patients whose muscle changes that further exacerbate the risk of DTI as will be described in detail below.

1.5 Muscle properties after SCI

1.5.1 Functional muscle changes

Functional muscles fiber changes after SCI include contractile properties, force production and fatigue resistance. As a consequence of SCI-induced paralysis, their motor units undergo a conversion from slow-twitch fatigue-resistant (S) to fast-twitch fast-fatigable (FF) (Scott, Stevens, & Binder-Macleod, 2001; Martin, Stein, Hoeppner, & Reid, 1992). FF motor units generate the largest amount of force, have the fastest contraction/relaxation speed, but fatigue easily and contain Type II muscle fibers with high glycolytic and low oxidative capacity. S units generate the smallest amount of force, have slow contraction and relaxation speed, high fatigue resistance and contain Type I muscle fibers with high anaerobic capacity (Bell & Syrotuik, 2004). A significantly lower concentration of sarcolemma Na^+/K^+ ATPase was found in subjects with SCI which may further contribute to the fatigability of paralyzed muscles after SCI (Ditor et al., 2004).

1.5.2 Structural muscle changes

In parallel with functional muscle changes, structural changes such as muscle atrophy, also occurs relatively quickly after SCI. It has been shown that lower limb lean body mass decreases 10.1 and 21.4% after 3 and 6 months after injury, and similarly gluteal lean body mass decreases 12.4 and 26.8% after 3 and 6 months after SCI, respectively (Baldi, Jackson, Moraille, & Mysiw, 1998). Castro et al. (1999) showed that the average cross-sectional area of atrophied

skeletal muscle in patients with complete SCI was 45-80% that of age and weight matched able-bodied controls 24 weeks after injury (Castro, Apple, Hillegass, & Dudley, 1999).

In rat models it was shown that 8 weeks after SCI muscle atrophy leads to 30% lower muscle stiffness compared to controls (Zamarioli et al., 2009). Computer model by Loerakker et al. (2012) showed that decreased muscle stiffness leads to increased shear strains in subcutaneous muscle and fat layers (Loerakker et al., 2012) suggesting that a person with SCI will have lower tissue breakdown thresholds that a non-injured individual with same weight.

1.5.3 Vascular changes

Additional to decreased circulation experienced by gluteal muscles due to external pressure, it has also been shown that SCI-induced vascular changes results in decreased blood flow below the level of injury. Hopman et al. (2002) showed that resting vascular resistance is significantly enhanced after SCI and may be caused by a combination of factors including decreased number of arterioles and capillaries and decrease in vessel diameter or changes in endothelium-derived factors and/or sympathetic vascular regulation (Hopman, Groothuis, Flendrie, Gerrits, & Houtman, 2002). Martin et al. (1992) also found that capillary-to-fiber ratio was significantly lower in paralyzed muscles of subjects with SCI (Martin et al., 1992).

1.5.3 Clinical significance

Atrophy, decreased stiffness and compromised circulation of gluteal muscles after SCI combined with circulatory and mechanical insults from unrelieved external pressure, such as body weight while sitting, exacerbates the risk of DTI.

Figure 1.4 demonstrates a clinical scenario of two people with SCI. An obese patient with atrophied muscles placing larger internal pressures and deformations on the soft tissues between sit bone and wheelchair cushion will develop DTI if pressure relief is not achieved within 1.5 hours of loading. The non-obese patient with non-atrophied muscles can, on the other hand, tolerate 3 hours of sitting without pressure relief. This example clearly indicates the importance of restoring muscle properties, maintaining healthy weight, and inducing periodic pressure relief in order to redistribute internal tissue pressures and increase blood flow to muscle at risk for breakdown.

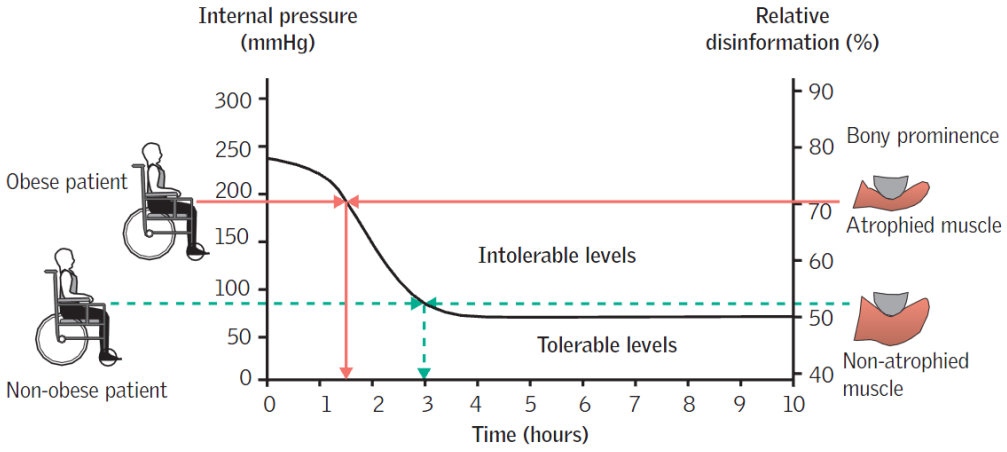

Figure 1.4 Example of clinical implications of tissue pressure tolerance. *Top left, obese patient ischial tuberosities apply 180mm Hg pressure on the gluteal muscles where a non-obese patient gluteals experience only 80 mmHg, while both are sitting in a chair. (Source: Gefen, 2009b)*

1.6 Pressure management after SCI

Mitigation of the ischemic and mechanical factors leading to DTI from prolonged loading includes surface pressure minimization by increasing contact area and periodic pressure relief to achieve complete pressure relief and tissue perfusion (Takahashi et al., 2010).

Clinically, increased contact area is achieved by using reactive support surfaces such as foam, gel, air filled and fluidised mattresses and wheel-chair cushions which conform to the shape of the body.

Pressure relief is traditionally achieved by repositioning bed-bound patient every 2 hours or encouraging vertical push-ups in seated individuals, and/ or using active support surfaces that automatically alternate pressure. This is summarised in figure 1.5.

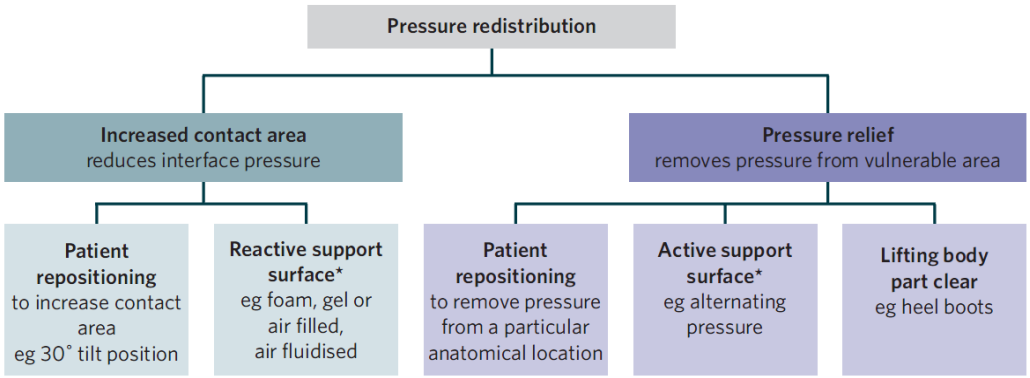

Figure 1.5 Pressure relief techniques. **Reactive support surfaces change its load distribution properties only in response to an applied load; active support surface change its load distribution properties with or without an applied load. (Source: Takahashi et al., 2010)*

However, traditional pressure relieving practices have not been successful in preventing PrUs. Currently prescribed pressure relief for seated individuals, 15 to 30 second long vertical push-up, was found to be ineffective in increasing

tissue oxygenation levels to preload conditions and instead a 2 minute liftoff was necessary (Coggrave & Rose, 2003). Some individuals with SCI are physically unable to perform pressure relieving activities and rely on assistance.

Redistribution surfaces help in minimizing pressure at the tissue/surface interface, however lower pressures can still lead to DTI if the pressure relief isn't achieved in a critical time period as shown by the tissue threshold curve above.

Consequently it is important to further investigate the mechanisms leading to DTI and to look beyond the traditional methods for achieving pressure relief and improving blood flow in tissues at risk.

1.7 Electrical stimulation after SCI

Electrical stimulation (ES) is regularly used for restoring function in upper and lower extremities, bladder, bowel and respiratory systems (Peckham & Knutson, 2005) and for restoring muscle properties (Rochester, Chandler, Johnson, Sutton, & Miller, 1995; Gould, Donnermeyer, Pope, & Ashikaga, 1982; Stein et al., 2002). Its biggest drawback is that it leads to muscle fatigue faster than voluntarily contracted muscles (Binder-Macleod & Snyder-Mackler, 1993) due to synchronised recruitment pattern and inability to modulate firing frequency (Gregory & Bickel, 2005).

1.7.1 Effect of electrical stimulation on functional properties

Long term use of ES could convert fast fatigable muscle fibers to ones that are more fatigue resistant (Martin et al., 1992; Stein et al., 1992). Bamford et al.

(2011) showed that both intra-spinal micro stimulation (ISMS) and nerve cuff stimulation (NCS) (4 hrs per day for 30 days) leads to a similar conversion of faster (type IId) to slower (type IIa) muscle fibers in rat quadriceps. This was a surprising result since ISMS recruits motor units in a near-normal physiological order whereas NCS recruits motor units in a reversed order (Bamford, Putman, & Mushahwar, 2011). Surface (motor point) electrical stimulation recruits muscle fibers in non-selective/random, spatially fixed and temporally synchronous pattern (Knaflitz, Merletti, & De Luca, 1990; Gregory & Bickel, 2005)

Kernell et al. similarly found that 5-5.5% of daily stimulation leads to an increased number of slow, type I fibers, in cat peroneal longus, normally a fast-twitch muscle, regardless of stimulation frequency (10 or 100Hz) within 2-3 weeks of a chronic stimulation paradigm, where as 0.5% of daily stimulation did not lead to significant fiber conversion (Kernell, Eerbeek, Verhey, & Donselaar, 1987). Thus, stimulation applied periodically for short bursts may not lead to changes in muscle fiber composition which is important for ES systems that rely on strong muscle contractions afforded by fast twitch motor units.

1.7.2 Effect of electrical stimulation on structural properties

Chronic ES has been found useful for preventing muscle atrophy and building muscle mass after SCI. Functional electrical stimulation (FES) assisted cycling with resistance was shown to prevent muscle atrophy and increase cross-sectional area of lower limb muscles (Scremin et al., 1999; Baldi et al., 1998). In the same study, Baldi et al. (1998) found that unloaded isometric FES

contractions attenuated but did not prevent disuse atrophy of lower limbs. Similar findings were reported by Martin et al. (1992) who found that chronic ES without external resistance increased the endurance properties of the paralyzed leg muscles but had no effect on fiber size and strength (Martin et al., 1992). Similarly, gluteal muscles stimulated long term with ES under body-weight loading (loaded isometric contractions) lead to significant (up to 50%) increases in gluteal muscle mass (Bogie, Reger, Levine, & Sahgal, 2000a; Bogie, Wang, & Triolo, 2006).

1.7.3 Effect of electrical stimulation on vascular properties

Six weeks of ES of paralyzed leg muscles increased cross-sectional area of the large conduit arteries and significantly improved blood flow to paralyzed legs of individuals with SCI (Gerrits, de Haan, Sargeant, van Langen, & Hopman, 2001). The same group showed that 6 weeks of ES increased leg blood flow by due to a marketed reduction in vascular resistance (Hopman et al., 2002). Martin et al. found that ES enhances the oxidative capacity of muscle via increased capillary-to-fiber density. ES-induced muscle contractions also have an acute effect on tissue perfusion and will be discussed below as it applies to DTI.

1.7.4 Electrical stimulation for prevention of deep tissue injury

Levine showed that ES-elicited muscle contractions lead to positive **acute changes** in the gluteal muscles including redistributing pressure underneath ischial tuberosities, increasing muscle oxygenation levels and changing the shape

of the muscle under load (Levine, Kett, Cederna, Bowers, & Brooks, 1989; Levine et al., 1990; Levine, Kett, Cederna, & Brooks, 1990). Similar changes were reported with sacral nerve root stimulation induced gluteal contractions. Liu et al. (2006) found that the gluteal contractions were sufficient to cause a mild pelvic tilt to sufficiently decrease pressure on the ischial tuberosities during sitting (Liu, Nicholson, Knight, Chelvarajah, Gall, Middleton, Ferguson-Pell, & Craggs, 2006a; Liu, Nicholson, Knight, Chelvarajah, Gall, Middleton, Ferguson-Pell, & Craggs, 2006b).

Bogie et al. (2000, 2006) demonstrated that **long-term use of ES** can in addition to acute benefits also lead to long term tissue changes. Regular use of electrical stimulation increased gluteal muscle thickness up to 50% leading to concurrent 20% decrease in regional interface pressures and significant increases in tissue oxygenation (Bogie, Reger, Levine, & Sahgal, 2000a; Bogie et al., 2006).

Levine et al. (1989) concluded that only a few paralyzed individuals may have enough residual muscle function to produce adequate pressure variation under therapeutic ES regime, and that majority of SCI subjects will need chronic stimulation to obtain useful muscle properties such as large muscle bulk and fatigue resistance (Levine et al., 1989).

In contrast, we showed that intermittent electrical stimulation can mitigate the circulatory and loading factors leading to DTI independent of muscle mass; this was demonstrated on subjects with SCI (Gyawali et al., 2011).

1.8 Intermittent electrical stimulation for prevention of DTI

Early researchers working on electrical stimulation for prevention of DTI failed to recognize that periodical muscle contractions mimicking the subconscious fidgeting of people with intact spinal cords could be a useful paradigm for prevention of DTI. During prolonged wheelchair-sitting, subjects with intact spinal cords adjust their posture every 6-9 minutes, which is significantly less than the frequency of postural adjustments of people who develop pressure sores (Linder-Ganz, Scheinowitz, Yizhar, Margulies, & Gefen, 2007). In people with intact sensation, continuous pressure signals small yet frequent body movements to relieve the load and restore tissue perfusion. This type of fidgeting is not possible in patients who are unconscious, anaesthetised or paralysed as they cannot sense and/or respond to these signals and do not move spontaneously.

Intermittent electrical stimulation (IES) (patent pending) (Mushahwar & Solis-Aguilar, 2009) induced fidgeting may be useful for preventing DTI of the buttocks. The IES protocol involves 5-30 seconds of surface gluteal stimulation causing a muscle contraction every 5-30 minutes during the hours of sitting or lying down, depending on individual needs. Its mechanisms of action are elaborated below.

1.8.1 Animal studies

Loading levels that exceed the tissue threshold can lead to DTI within minutes or even instantly. IES-induced contractions in up to 75% body weight

loaded muscles of pigs reshaped the muscles significantly increasing the thickness of tissue between ischial tuberosities and skin in intact and SCI pigs (Solis et al., 2012). The tissue thickness increased by 25% in 25% BW loading, and 32 and 31% for 50 and 75% BW loading, between ischial tuberosities and the indenter. In pig with SCI, muscle thickness increased to 38, 43 and 35 % for 25, 50 and 75% BW loading. IES significantly redistributed internal pressures shifting the maximal pressures away from ischial tuberosities (Solis et al., 2012).

Solis et al. (2007) showed that IES can minimize the extent of DTI of loaded rat quadriceps from 60 to 16% of muscle mass in 2 hours of continuous loading (Solis et al., 2007). Direct measurements of oxygenation showed that IES can increase rat muscle oxygenation levels up to 100% (Gyawali et al., 2011).

Curtis et al. (2011) compared the conventional pressure relief with 4 stimulation paradigms, 5 and 10 second long contractions at maximal and moderate strength, in preventing DTI at 18, 28 and 38% BW loading levels on rat triceps. They found that conventional pressure relief was inadequate for prevention DTI. However, all 4 IES stimulation paradigms were equally effective at significantly reducing (about 50% reduction of edema as assessed by MRI) the extent of DTI caused by 28 and 38% loading levels (Curtis et al., 2011).

1.8.2 Human studies

Solis et al. (2011) demonstrated in individuals without SCI that IES significantly reduced surface pressure around loaded ischial tuberosities (Solis et al., 2011) and sacrum (Solis et al., 2007). IES-elicited muscle contractions

changed the shape of gluteal muscles under pressure and were better at producing elevated and sustained increases in oxygenation than conventional pressure relief. Reduction in sitting discomfort was perceived as good-as or better than relief achieved by voluntary gluteal contractions and complete unloading through chair push-ups (Solis et al., 2011).

Similar results were found in subjects with SCI and atrophied gluteal muscles (Gyawali et al., 2011). IES redistributed pressure under the ischial tuberosities, and changed the shape of the atrophied muscles. IES increased the fMRI signal intensity by 2-4% indicating that muscle oxygenation levels were increased up to 28%. IES also lead to sustained and cumulative oxygenation effect (Gyawali et al., 2011).

The effectiveness of IES to induce pressure relief and increase oxygenation did not appear to be dependent on muscle mass or contractile characteristics of atrophied muscle fibers after SCI (Gyawali et al., 2011) as was previously suggested (Levine et al., 1989).

1.8.3 IES and muscle fatigue

Prevention of DTI depends on at least moderate **periodical muscle contractions** (Curtis et al., 2011). Muscle fatigue induced by ES might attenuate the strength of the muscle contraction leading to insufficient pressure relief and tissue perfusion, and subsequent development of DTI.

Muscle fatigue can be minimized during repetitive activation by selecting the lowest stimulation frequency and highest intensity settings that produce the

targeted muscle contraction (Binder-Macleod & Snyder-Mackler, 1993). Furthermore, the rate of ES-induced muscle fatigue depends on the duration of rest period between contractions, with shorter rests leading to greater fatigue. During muscle strengthening with electrical stimulation, it was shown that at least a 60s rest period between 10s long muscle contraction was necessary to avoid muscle fatigue (Binder-Macleod & Snyder-Mackler, 1993).

As pressure relief and tissue perfusion depend on tetanic muscle contractions, knowing the magnitude of force in the gluteal muscles is indeed important.

1.9 Electromyographic monitoring of muscle contractions

Mechanical force production is initiated by the electrophysiological activation of muscle fibers (Disselhorst-Klug, Schmitz-Rode, & Rau, 2009). Figure 1.6 demonstrates the delayed mechanical response of a single muscle fiber (force twitch) to an action potential (AP) across the fiber membrane. Electrophysiological depolarization of sarcolemma causes a chain reaction that result in calcium ions release within the muscle fiber which subsequently activates the contractile actin-myosin filaments causing force generation (Disselhorst-Klug et al., 2009).

As non-invasive, direct force measurements within a muscle are not possible, generally the reaction forces supplied to external loads, such as a force plates, are used for quantifying the force produced by a muscle (Disselhorst-Klug et al., 2009).

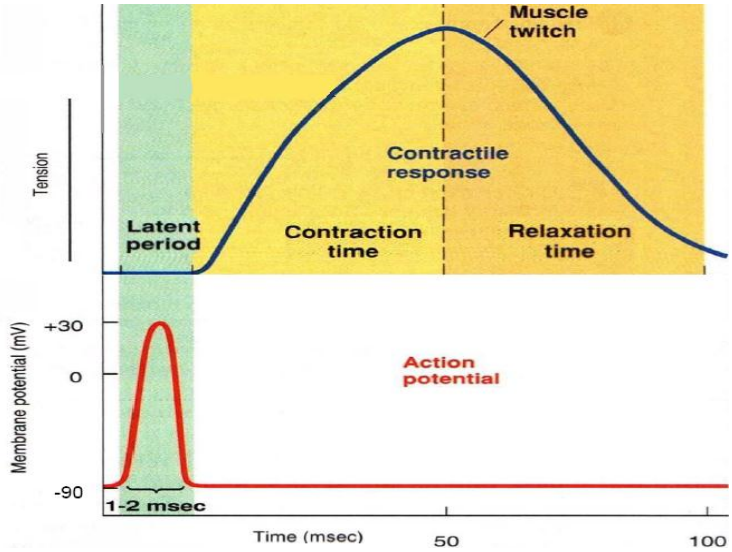

Figure 1.6 Relationship between the mechanical response of a single muscle fiber (muscle twitch) and its action potential.
(Source: http://howmed.net/physiology/skeletal-muscle)

1.9.1 Relationships between EMG and force

Surface electromyography (EMG) is a non-invasive technique used for recording the electrical activity of muscle fiber membranes of contracting muscles through electrodes placed on the surface of the skin. The EMG record of electrically stimulated muscles is called an M-wave and its amplitude reflects the degree of muscle activation with increasing amplitude indicating increasing force development (Disselhorst-Klug et al., 2009).

The reported relationships between EMG and force across different muscle groups have not been consistent. For example, in voluntary isometric muscle contractions a linear relationship between integrated EMG and force has been found in the tricep-surae muscles (Lippold, 1952). Similarly, Bigland-Ritchie (1981) found linear integrated EMG force relationships for soleus, adductor pollicis and first dorsal interossous muscles and quadriceps but not in the

biceps, triceps and brachioradialis muscles. They concluded that non-linear relationships in voluntary contractions were predominantly found in muscles with mixed fiber compositions indicating that non-linearities arise from physiological differences of various motor unit types (Bigland-Ritchie, 1981).

In nerve cuff stimulation of cat gastrocnemius muscle where the EMG signal was recorded with a needle near the muscle motor point, Solomonow et al. (1986) found that EMG (mean absolute value)- force relationship varies with the frequency of stimulation. Sigmoidal curve was found at 28Hz and a 2^{nd}-order polynomial at 51Hz but that an approximate linearized models best predicted muscle force in a closed loop control system (Solomonow, Baratta, Shoji, & D'Ambrosia, 1986; Solomonow, Baratta, Zhou, Shoji, & D'Ambrosia, 1987).

1.9.2 EMG as indicator of muscle fatigue

To further complicate matter, the EMG-force relationships may not hold under conditions of muscle fatigue (Bigland-Ritchie, Jones, & Woods, 1979). As shown in figure 6, electrical activation of muscle fibers precedes force generation and thus EMG changes may occur independent of force output if the mechanism for fatigue is located inside the muscle fiber. Therefore during fatigue, EMG may only reflect neural activation of muscle fibers (Vollestad, 1997).

In contrast, EMG may be a useful indicator of muscle fatigue in cases when fatigue is localized in the excitation mechanism. EMG can detect the power spectrum shifts to lower frequencies due to slowing of muscle fiber conduction velocity (De Luca, 1984).Various authors have explored the usefulness of surface

EMG for monitoring ES-induced contractions in humans and have shown promising results both in fatigued and non-fatigued muscle (Erfanian, Chizeck, & Hashemi, 1998; Hayashibe, Zhang, Guiraud, & Fattal, 2011; Zhang et al., 2010). EMG-force relationship for gluteal muscles has not been previously reported.

1.10 Overview master's project

Mushahwar's lab demonstrated that intermittent electrical stimulation paradigm has the potential for prevention of DTI in animal models. However, the clinical feasibility was yet to be demonstrated. Therefore, the first objective of my master's project was to investigate the feasibility of a non-adaptable IES system in long term care and rehabilitation hospital settings. The second objective was to investigate the feasibility of electromyography for monitoring the strength of IES-induced muscle contraction in an adaptive IES system and if IES causes muscle fatigue during prolonged stimulation.

1.10.1 Clinical implementation of IES system

1.10.1.1 Summary of study protocol

With the help of clinical coordinators and nursing staff in a long term care facility and a rehabilitation hospital in Edmonton, AB and an acute neuro-rehabilitation hospital unit in Calgary, AB, we implemented the IES system on participants with compromised mobility and sensation.

The IES system consists of a pre-programmed stimulator (10s ON, 10min OFF) with data recording capabilities. Stimulation was administered to gluteal

muscles via surface electrodes through 1) direct skin placement, i.e. **no-garment** system, and 2) mesh panels in a **Smart-e-Pants** garment (patent pending). Each participant tested the IES system 12 hours per day, 4 days per week for 4 weeks.

Custom designed data collection instruments were used to collect data after IES system was donned and 12 hours later after the system was removed. Data collection was performed by clinical co-ordinators, research staff, and trained nurses.

By establishing a close relationship with participants and caregivers, we obtained feedback on how to improve the Smart-e-Pants garment. Design ideas were continually incorporated into the Smart-e-Pants garment by Mr. Glen Isaacson.

1.10.1.2 Hypothesis

I hypothesize that IES system (no-garment and Smart-e-Pants garment systems) is safe, feasible and acceptable in long term care and rehabilitation hospital settings. Specifically, I postulate that IES system (no-garment and Smart-e-Pants garment) will:

1) not cause adverse skin reactions
2) place acceptable demands on caregivers during daily implementation
3) deliver visible muscle contractions throughout hours of use
4) be acceptable by participants as part of their daily routine

1.10.2 EMG monitoring IES-induced muscle contractions

1.10.2.1 Summary of experimental protocol

Prevention of DTI depends on fused muscle contractions which induce lasting tissue perfusion and pressure redistribution inside the deep tissues making monitoring of contractions of utmost importance. Furthermore, electrical stimulation induced muscle fatigue may cause the strength of muscle contraction to decrease below adequate levels needed for prevention of DTI. With this in mind, I investigated if surface electromyography (EMG) is a feasible technique for monitoring IES-induced gluteal muscle contraction strength and if IES causes muscle fatigue with 8 hours of daily use in subjects with spinal cord injury and subjects with intact spinal cords.

1.10.2.2 Hypothesis

I hypothesize that in subjects with spinal cord injury and those with intact spinal cords electromyography is a feasible technique for monitoring the strength of IES-induced muscle contractions and 8 hours of IES will not cause gluteal muscle fatigue. Specifically, I postulate that:

1) peak twitch tensions and corresponding peak-to-peak M-wave amplitudes will have a linear relationship
2) peak twitch tension and corresponding M-wave amplitude magnitudes will not significantly change throughout the 8 hours of IES stimulation
3) M-wave mean and median power density spectrum characteristics during the 1^{st} and 8^{th} hours of IES will not be significantly different

1.10.3 Description of thesis content

This is a paper-based thesis. Chapter 2 is a paper detailing clinical implementation of IES in different care settings. Chapter 3 is a paper detailing the investigations on electromyographic monitoring of IES-induced muscle contractions and IES-induced muscle fatigue. In Chapter 4, overall conclusions and future directions for the project are outlined.

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Chapter 2: Clinical trial of intermittent electrical stimulation for the prevention of deep tissue injury in different care settings

2.0 Introduction

Pressure ulcers are serious, common secondary complications that afflict people with limited mobility and sensation in a wide range of clinical settings. In Canada, prevalence of pressure ulcers for acute and non-acute (i.e., long term care, nursing homes, rehabilitation) settings is 25% and 30%, respectively (Woodbury & Houghton, 2004).

Pressure ulcers can have a major negative impact on quality of life. Affected individuals reported severe pain, loss of independence and social isolation (Fox, 2002). Besides the physiological and psychological effects, treatment of pressure ulcers also places a large monetary burden on society. The annual cost for treatment of pressure ulcers is ~ $12 billion in the United States, with costs up to $152,000 for treatments of a single ulcer (Zulkowski, Langemo, Posthauer, & National Pressure Ulcer Advisory Panel, 2005). It is estimated that prevention of pressure ulcers is approximately 2.5 times more economical than treatment (Lyder & Ayello, 2008). Given the large financial burden of treating pressure ulcers after they have developed, it would be more efficient and economical to prevent them in the first place.

Deep tissue injury (DTI), a subtype of pressure ulcers, is particularly serious. It starts in the deep muscle layers overlying bony prominences (Daniel,

Priest, & Wheatley, 1981). Clinically, it is very difficult to detect and is often unrealized until it breaches the skin. Major contributing factors leading to the formation of DTI include unrelieved mechanical deformation, tissue ischemia and ischemia-reperfusion injury (Blaisdell, 2002; Kosiak, 1959; Kosiak, 1961; Loerakker et al., 2011; Stekelenburg et al., 2007; Stekelenburg, Gawlitta, Bader, & Oomens, 2008). Risk of DTI is further exacerbated as muscles at risk become atrophic and their stiffness decreases (Loerakker et al., 2012). Current prevention strategies such as pressure distributing mattresses, foams and periodical weight shifts have been insufficient, and the prevalence of DTI is on the rise (VanGilder, MacFarlane, Harrison, Lachenbruch, & Meyer, 2010).

To address limitations in current treatment methods, we proposed that intermittent electrical stimulation (IES) may be an effective alternative. Indeed, we have shown that 10s of stimulation causing fused muscle contractions in the gluteus muscles every 10 min while sitting is capable of redistributing surface pressure away from the ischial tuberosities, and significantly increasing tissue oxygenation human subjects independent of gluteal muscle mass (Gyawali et al., 2011; Solis et al., 2011). IES-induced contractions significantly redistribute internal pressure away from the bony prominences (Solis et al., 2012) and increase the thickness of tissue between ischial tuberosity and skin in loading levels as high at 75% of body weight in spinally intact and injured pigs. Furthermore, IES reduced the size of DTI in loaded muscles in rat and pig models of DTI (Curtis et al., 2011; Solis, Twist, Seres, Thompson, & Mushahwar, under review; Solis et al., 2007).

To be clinically useful, IES needs to be applied to muscles at risk on a daily basis for an extended period of time. Indeed, we have shown that chronic application of IES minimized the extent of DTI in loaded muscles in a pig model of spinal cord injury (Solis et al., under review). To test the feasibility of this for human use, we developed an IES system for delivering IES to the gluteal region. IES (10s of stimulation every 10 minutes) was delivered through surface electrodes placed directly on the skin surface in incontinent patients or through mesh panels in a garment known as Smart-e-Pants (smart electronic pants).

The goal of the present study was to test the hypothesis that the IES system is safe and feasible in various hospital settings and on a number of different patient groups. Specifically, we postulated that long term use of the IES system would not cause skin irritation, IES-elicited contractions would remain visibly strong for long durations of daily use, donning and doffing of the system would place minimal demands on caregivers and that regular use of the system would be acceptable to the end-users.

2.1 Methods

To test the safety and feasibility of an IES system for prevention of DTI in a range of settings through the spectrum of care, participants were recruited from an acute neuro-rehabilitation (ANR) hospital in Calgary, a rehabilitation hospital (RH), and a long term care (LTC) facility in Edmonton, Alberta, Canada. Ethics approval was given by the institutional review boards at the University of Alberta and University of Calgary. A dedicated research coordinator familiar with the local setting was recruited at each site to handle the administrative logistics,

participant recruitment, organize nursing and caregiver training sessions, and facilitate implementation such as donning, doffing and system monitoring.

Subject Inclusion / Exclusion Criteria

Eligible participants were inpatients at risk for developing DTI due to conditions resulting in impaired lower body sensation and decreased mobility. Other inclusion criteria included a body mass index (BMI) less than 32, intact skin in the gluteal region for the past 3 months and ability to provide informed consent.

Recruitment

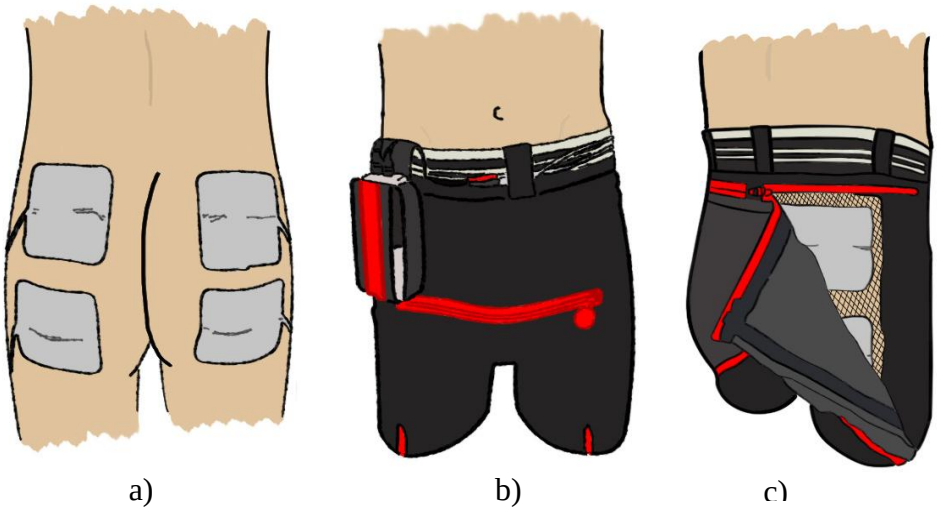
To avoid potential conflict of interest, participants meeting the inclusion criteria were first approached by their attending physician or charge nurse (individuals not associated with the research team) to obtain verbal consent to be approached by the research coordinator to discuss potential enrollment. Full details of the study were given verbally and in writing.

Treatment

Intermittent electrical stimulation (IES) system

The IES system is comprised of a stimulator (Impulse EMS D7, Biomedical Life Sciences Inc., Vista, California, US) and self-adhesive surface gel electrodes (Axelgaard Pals Platinum Neeurostimulation electrodes, 3” x 4”, Model 895340-4-40, Fallbrook, California, USA) applied directly to the skin (fig.

1a) or through mesh pannels in a form fitted undergarment (fig. 1b,c), the Smart-e-Pants. The stimulator, with a compliance voltage of 50V at 100mA, was modified to include recording capabilities and safety features in case if shorting or electrode peeling occurred.



a) b) c)

Figure 1 *Clinical administration of IES a) surface electrodes applied directly to the skin (no garment); b, c) surface electrodes applied through a mesh in a Smart-e-Pants garment.*

IES testing time and stimulation parameters

Trains of charge-balanced bi-phasic 300μs pulses at 17.5Hz with stimulation intensity sufficient to generate strong visibly fused muscle contractions were delivered to the gluteus maximus muscles on both sides of the buttocks for 10 s every 10 mins, 12 hours a day, 4 days per week, with an initial goal of 4 weeks. Many participants elected to continue using the IES system until their hospital discharge date.

Features of the Smart-e-Pants garment

This garment is intended to replace the participants' underwear and is made of cotton and lycra fabrics to provide maximal comfort, breathability, and optimal fit. The material withstands regular laundry without tears or change in form. Horizontal front zipper facilitates catheterization, midline thigh markers guide pants alignment and belt loops help route the electrode leads and prevent them from inadvertently getting caught (Fig. 1 b). The surface electrodes are placed onto low impedance mesh panels in the rear (Fig. 1c). The electrode panels are additionally protected by a smooth top cover that glides during transfers and weight shifts without risking dislodging, peeling or rolling the edges of the electrodes. The stimulator is held in place in a detachable pocket at the waist. These design features are the end product of several iterations based on feedback from wheelchair users, participants in the study, and caregivers deliberately sought after through information and training workshops, and daily evaluation of the use of various Smart-e-Pants prototypes.

Procedure

Clinical administration of IES

IES was administered to the gluteus maximus muscle through surface stimulation of the muscle's motor point located approximately 1" above the ischial tuberosities while the participant is turned to their side with hips and knees bent at 90º to mimic the sitting position. In incontinent participants, electrodes were placed directly on the skin as shown in fig. 1a, with an incontinent product

covering the electrodes. Continent participants tested the IES systems both without garment and with the Smart-e-Pants (fig 1). After the electrodes had been applied to one side, the patient was log rolled for the electrodes to be applied to the opposite side.

In LTC and RH setting, researchers donned the system after the morning care routine was finished and doffed the system approximately 12 hours later. In ANR the system was donned during the morning care routine by regular nursing staff and researchers and doffed approximately 12 hours later by nursing staff.

Performance measures and evaluation

Data collection was performed in the morning after the IES system was donned and approximately 12 hours later after it was removed. In LTC and RH settings, the same researchers collected most of the data with an occasional help of well-trained nursing staff, while at the ANR setting, researchers collected the data after the system was donned while trained regular evening nursing staff performed the evening data collection. Outcome measures include caregiver demands such as time needed to use the IES system, skin redness monitoring, sustainability of muscle contractions throughout the hours of stimulation, and participant acceptability of the IES system. Appendix 1 is a sample data collection instrument used at the rehabilitation hospital in Edmonton.

Demands on the caregiver. To assess the demands using the IES system places on caregivers, every day after the IES system was donned, the researcher or the nurse rated how easy it was to position or turn the participant on their side with legs and hips bent at 90º on a scale from 1-5: 1 = very easy (participant

independently achieves desired position) and 5 = very difficult (unable to achieve desired position due to heavy weight, contractures, poor range of motion, pain etc). Similarly, easy of finding adequate (visibly fused) muscle contractions on the left and right side was rated on a scale from 1-5; 1 = very easy (adequate muscle contraction localized on a first attempt/ electrode/ shorts placement) and 5 = very difficult (no visible or palpable muscle contraction found despite numerous adjustments to electrodes/ Smart-e-Pants garment).

Participant positioning and localization of muscle contractions contribute to the length of time caregiver spends using the IES system. The time, estimated by the person applying the system, includes turning the participant in side lying position (in LTC and ANR settings, but not in ANR as participant was already in position during morning care routine), applying the system, and setting the stimulator to achieve visible muscle contractions on left and right side of the buttocks. Additionally in 5/7 subjects in RH, and 1 week of the 4 week protocol in 3 participants in LTC, the total time also includes taping electrode edges. In ANR electrode edges were not taped.

Similarly, time needed to doff the system included positioning participant to their side and checking the presence of muscle contraction on one side followed by the other, and removing the electrodes/ Smart-e-Pants garment. Data collection (including taking pictures of the skin and videos of muscle contraction which was estimated to take about 5 minutes), was also included in time to apply and remove system in LTC setting.

IES system performance. To assess how the IES system performs after prolonged stimulation, at the end of each day individual removing the IES system rated (yes/no) if any of the 4 electrodes had peeling or edge rolling and if a visible muscle contraction was still present.

Skin monitoring. Skin was inspected each day after the IES system was removed and each day there were 8 possible skin observations, 4 electrode pads and 4 electrode leads. Skin condition was rated on a scale from 1-5; 1 = no redness, 2 = blanchable redness, 3 = stage 1 non blanchable, 4 = stage 2 open skin, 5 = stage 3 full thickness skin loss.

Participant feedback. At the end of each day participants were asked to give feedback on their acceptability of the system by answering 5 questions. "Was the stimulation distracting/ irritating/ uncomfortable?" and "Was the system cumbersome to use?" were rated on a scale from 1-5; 1 = not at all, 2 = very little, 3 = moderate, 4 = quite a bit, 5 = severely. Participants we also asked (yes/no) if they thought they could (or did) fall asleep while being stimulated and if the stimulation was acceptable as part of their daily routine.

Data analysis

Patient characteristics, skin assessment, IES system performance including assessment of electrode peeling and sustainability of muscle contractions when system was doffed, and participant feedback are reported using descriptive statistics. Similarly, for caregivers' demand, descriptive statistics are used to report easy of positioning the subject and ease of obtaining a visible contraction and the time requirements for donning and doffing the system.

2.2 Results

Participant description

A summary of the 37 participants enrolled in the study from the LTC, RH and ANR settings is shown in Table 1. The vast majority used the IES system for at least 4 weeks and in 1 case for 3 weeks due to earlier hospital discharge. Data from four participants were excluded from the final results. In the LTC facility, 1 participant stopped using the IES system after 1 week due to unrelated medical complications, and 1 other due to skin irritation from electrode edge as will be discussed in detail below in the "skin monitoring" section. In the RH setting, 1 subject requested to stop the study after 1 week as he was not ready to commit to research demands due to the recent nature of his accident and an un-established bowl routine. In the ANR setting, 1 participant was discharged only after 1 week of enrolment in the study.

In the RH setting, eleven subjects used the IES system until their discharge date, six of which went beyond the 4-week protocol for an additional 2-5 weeks. In the ANR setting, one participant used the IES system until hospital discharge 8 months after enrolment in the study. Participants tested the IES system each day for 11.5 ± 2, 11.2 ± 1.4, and 12.3 ± 2.9 hours in LTC, RH and ANR settings, respectively. While involved in the study, none of the subjects developed a pressure ulcer.

Table 1 *Summary of study participants testing the IES system through direct application of electrodes on the skin (no-garment) or through the Smart-e-Pants garment. *Two participants in LTC, 1 in RH and 1 in ANR were excluded from the final analysis (reasons stated in the text).* $^{+}$*1 participant tested direct electrode application for 4 weeks and subsequently Smart-e-Pants garment for additional 2 weeks. Notations used: MSA: multiple system atrophy; TBI: traumatic brain injury; SCI: spinal cord injury; GBS: Guillian Barre syndrome.*

	Recruited Subjects (#)	Age ± stand. dev.	Sex (%) males	Sensation (%)	Incontinent (%)	Smart-e-Pants/ no-garment	Primary cause of immobility (# subjects)
LTC	9*	68±13	33	100	100	no-garment – 7	Stroke (3), MSA, TBI, Multiple sclerosis (2), diabetes, hip fracture
RH	18^{+}	44±21	83	65	6	garment – 11 no-garment – 7	SCI-paraplegia (9) SCI-quadriplegia (4) Stroke (4)
ANR	10	51±12	67	55	10	garment – 3 no-garment – 6	SCI-paraplegia (3) SCI-quadriplegia (4) Stroke, GBS

IES Implementation

The IES system implementation was initiated at the LTC facility. At first, system components were tested for safety and feasibility. For example, two subjects at the LTC facility tested electrodes on skin without stimulation for 4 weeks in order to assess whether electrodes caused skin concerns in this patient population. We also tested early prototypes of the Smart-e-Pants garment, realizing that they were not applicable for incontinent participants at that time because the fabrics did not have moisture wicking properties. Furthermore, we learned that when electrodes were applied directly to the skin, sometimes edges peeled and rolled. In the last 3 LTC participants we tested taping electrodes down for approximately 1 week of the 4-week enrollement. Subsequently in 5/7 RH

participants who tested electrodes on their skin directly, electrode edges were taped down with soft, breathable silicon tape (Mepitac ®). In ANR setting, as a result of combined morning routine and system donning, electrode edges were not taped down.

Demands on the Caregiver

In order to assess the demands using the IES system places on the caregivers in different clinical settings, individuals applying the IES system rated the effort required to position the participants, localize visible muscle contractions and overall time requirements to apply and remove the IES system on daily basis. The ease of: 1) participant positioning, and 2) localizing visible muscle contractions, data are presented in stacked histograms in figure 2 as percentages of total responses across all patients using either the garment or no-garment IES systems in each center in 4 categories: easy (responses "very-easy" and "easy" combined), moderate, difficult and impossible.

The electrodes were applied directly to the skin and to the mesh panels inside the Smart-e-Pants garment with the participants lying on their side and the hips and knees bent at 90 degrees to mimic a sitting position. Participant positioning in LTC and RH settings was rated as easy in 74 and 87% of the cases. That is perhaps not surprising given the substantially older age range and frailty of the participants in the LTC facility.

Since the participants in ANR setting were already set up in position during the morning caregiver routine, their abilities to maintain optimal position for caregiver to apply and work with the IES system were captured. In

participants receiving direct electrode application and the Smart-e-Pants garment, it was rated 73 and 97% of the time, respectively that participants were able to use their upper body strength to maintain desired position independently or only with a one person assist.

Localization and confirmation of visible muscle contraction in RH and ANR settings was easy and was readily obtained with electrodes applied directly on the skin 88 and 87% of the time, respectively as shown in fig 2b and in remaining cases contractions were also localized after a few adjustments to the electrodes. In comparison, at the LTC facility contractions were localized with ease 75% of the time, however 10% of the time the contractions were not found regardless of where the electrodes were placed. That is perhaps not surprising considering that participants in LTC were generally elderly with atrophic muscles due to years of immobility. The task of visibly observing muscle contractions was more challenging when using the Smart-e-Pants garment because the garment fibric partially obscured direct visualization of the skin and the underlying muscle contraction. In RH setting, it was impossible to visualize muscle contractions 19% of the time. In ANR setting, in 3 subjects who tested the garment it was possible to observe visible muscle contractions 100% of the time.

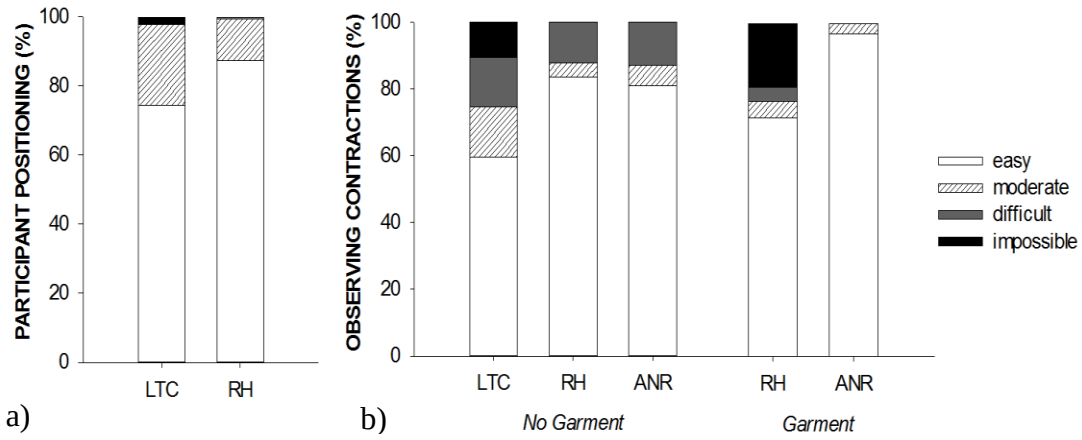


Figure 2 *Participant positioning needs for applying the IES system and ease of observing visible muscle contractions. Stacked bars show percentages of total responses. a) Ease of participant positioning on their side for IES system application (b) Ease of observing visible muscle contractions duing system application.*

Time was the primary measure used to determine the work load associated with using the IES system in various clinical settings. The total time requirement of using the IES system (donning and doffing) in the three centers are shown in fig 3. In LTC, time needed to apply electrodes directly to the skin including positioning the participant on their side, applying electrodes, confirming presence of physical muscle contractions and taking photos and videos of the contractions on both sides took 15 ± 6 minutes. Removing the system which involves turning the participant to side, checking presence of contractions, taking videos and photos and removing the electrodes took 10 ± 4 minutes. The data points when electrode edges were taped were excluded.

In RH, time needed to apply electrodes directly to skin including participant positioning, electrode application, taping 16 electrode edges and

confirming contractions on both sides of the buttocks took about 14 ± 4 minutes while removing the electrodes took 6 ± 2 minutes.

In ANR, time to apply electrodes directly to the skin on both sides including electrode application and confirming presence of contractions on both sides (patient positioning not included as the patient was already in position during the morning care routine) took 8 ± 2 minutes, while removing the electrodes took 5 ± 2 minutes.

In RH and ANR, applying IES through the Smart-e-Pants garment including applying electrodes to the mesh and checking presence of contractions on both sides of the buttocks takes 10 ± 2 and 7 ± 2 minutes, respectively. Removing the Smart-e-Pants garment, including checking contractions on both sides of buttocks in RH and ANR takes 4 ± 2 and 4 ± 3 minutes, respectively.

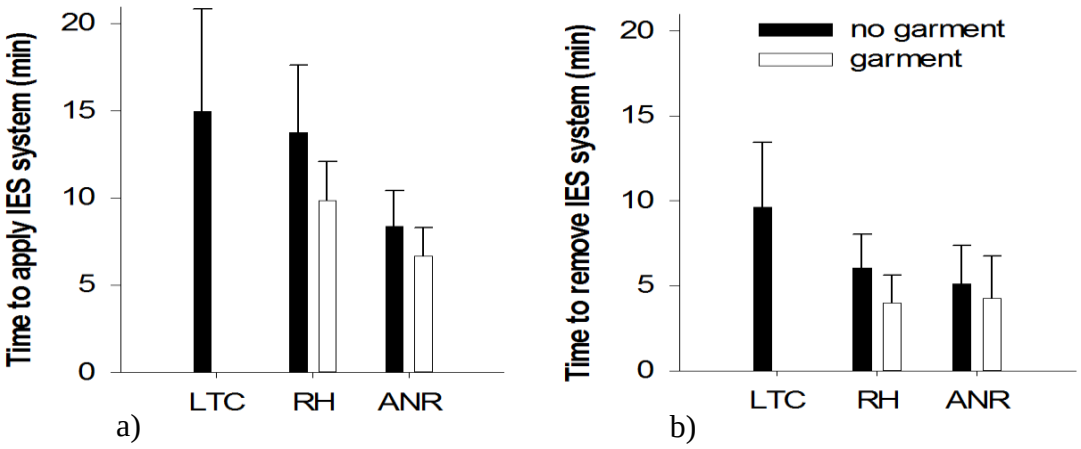


Figure 3 *Time requirements for using the IES system (mean ± standard deviation). a) Time required donning the system; b) Time required doffing the system. Black bars represent application of electrodes on skin directly without a garment, while white bars represent using the Smart-e-Pants garment..*

IES system performance

After each day of testing was done (i.e. ~12 hours) we assessed the IES system performance by determining: 1) if any of the 4 electrodes had edges peeled or rolled, and 2) if the gluteal muscle contractions were still visible. The data are presented as bar graphs showing: 1) the overall percent of electrode edges that did not peel or roll in cases of taping and not taping electrode edges, as well as using the Smart-e-Pants garment, and 2) the overall percent of visible muscle contractions in participants when the muscle contraction was visualized in the morning.

Direct electrode application to the skin without electrode edge taping resulted in no electrode peeling 66, 71 and 78% of the time in LTC, RH and ANR setting as shown in fig 4a. In contrast, taping the electrode edges let to substantially less peeling at 83 and 94% in LTC and RH settings, respectively. The Smart-e-Pants garment was able to keep the electrodes from peeling or rolling 95% of the time in RH and ANR settings.

With electrodes applied directly to skin in participants whose muscle contractions were visible in the morning, visible muscle contractions were also observed in the evening when the system was removed in 86, 98 and 83% of cases in LTC, RH, ANR settings, respectively (fig 4b). In LTC setting in the 10% of cases when it was impossible to localize visible muscle contraction in the morning (see figure 2b, 10% “impossible”), 50% of the time a visible muscle contraction was observed in the evening. With electrodes applied through the Smart-e-Pants garment, those in whom muscle contractions were visually observable in the

morning, in the evening 93 and 71% of cases in RH and ANR, respectively were also observable in the evening (fig 4b). Of the 19% of cases in RH setting where muscle contractions were impossible to observe in the morning (see figure 2b), when the system was removed in the evening, 65% of the time visible contractions were present. Visualization of muscle contractions through the garment is difficult as the observer must look for movement of muscle through the garment.

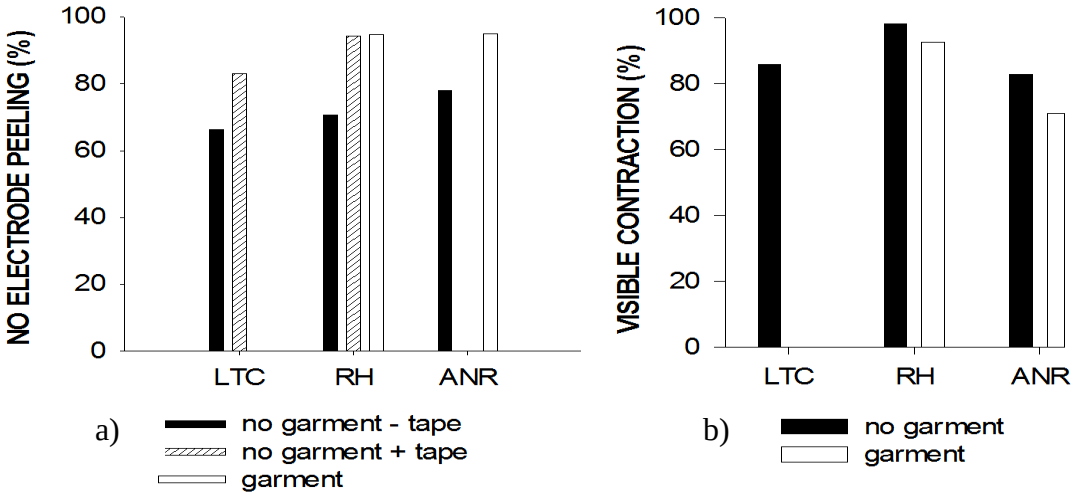


Figure 4 *Performance of IES system. Bars show overall percentages. a) Percent of no electrode edge peeling or rolling after 12 hours of being worn by the participant. b) Presence of visible gluteal muscle contractions after 12 hours of IES.*

Skin Monitoring

In general, no adverse skin reactions were observed after wearing the IES system for ~12 hours, whether the electrodes were placed directly on the skin or through the Smart-e-Pants garment (Table 2). The total number of observations in each clinical center categorized as direct electrode application (no garment) and

Smart-e-Pants garment are shown, as well as the percent of total observations that were blanchable redness. There were 2 adverse skin observations at the LTC facility and they are discussed in detail as well.

Table 2 *Skin responses to wearing the IES system for 12 hours. Table summarizes the total number of skin observations in each clinical setting on participants either testing the electrodes directly on their skin or Smart-e-Pants garment only.*

		Long-term care	**Rehabilitation hospital**	**Acute neuro-rehabilitation**
Direct electrode application	Observations	396	968	496
	Blanchable redness (% of observations)	3	3	2
Smart-e-Pants garment	Observations	not tested	1132	184
	Blanchable redness (% of observations)		0	0

Application of electrodes directly on the skin caused blanchable redness in 3% (out of total 396 and 968 observations, respectively) of skin observations in LTC and RH settings. Application of electrodes through the Smart-e-Pants garment resulted in no skin redness in over 1,200 observations. The blanchable redness was rare and was evenly distributed across all subjects.

Two incidents of minor skin tears occurred in incontinent subjects with compromised skin quality (fig 5) in the LTC facility. The first incident occurred in a 90 year old female (the oldest participant in the study) with a history of corticosteroid use for over 20 years that may have contributed to compromised skin integrity. Skin irritation causing a 0.3cm long tear arose due to loose skin rubbing against the electrode edge that healed over 21 days (Fig 5a). Subsequent to this incident, electrode stickiness used for the LTC study participants was attenuated by applying soft cotton fuzz, and no further skin concerns were observed due to the electrodes themselves. The second incident occurred

in a 47 year old female on whom we applied standard clinical paper tape (1530-1 1" Tape, 3M™ Micropore™ , St. Paul, Minneapolis, United States) to secure the electrode edges and prevent them from peeling or rolling. Removal of the tape resulted in a 1cm long skin loss around one edge, which healed over 14 days (Fig 5b). To mitigate this problem soft silicon tape (Mepitac®) was used instead of the paper tape, and no further skin concerns were observed in any of the subjects. After the skin loss in fig 5b healed, the participant used the IES system for another 3 weeks in conjunction with the soft silicon tape (Mepitac®), and no adverse skin reactions were observed.

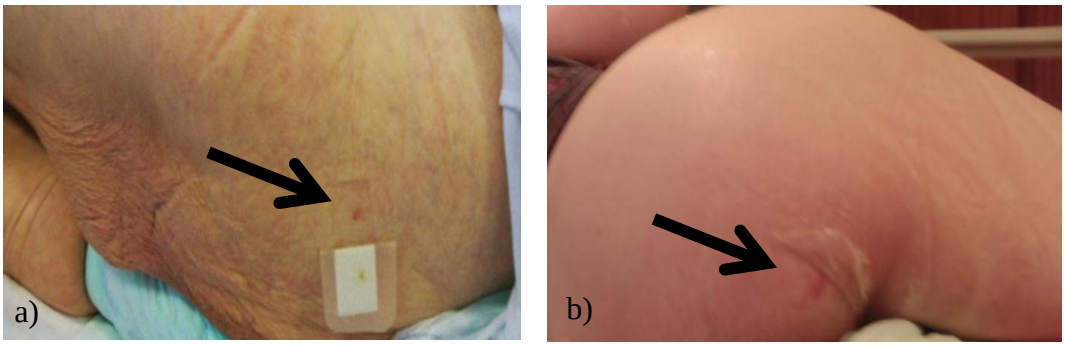


Figure 5 *Two incidents of adverse skin reactions associated with the application of electrodes directly on the skin in the LTC facility. a) Skin irritation (0.3 cm long) at one electrode edge. b) Skin tear (1.0 cm long) upon removal of the paper tape used to retain the electrode edges in place.*

Participant Feedback

Generally, the IES system was well accepted by the end-users. In figures 6a and 6c data are represented as stacked bars showing percentages of total responses of not-at-all (white), very little (striped), and moderate or above (black). In figure 6b data are represented in stacked graphs showing percentage of total yes (white) and no (black) responses.

Participants reported that the stimulation was not-at-all or very little irritating, distracting or uncomfortable more than 96% of the time regardless of the clinical setting (fig 6a). For example, in the RH setting, participants reported that stimulation was not-at-all irritating, distracting or uncomfortable 94% (247/263), 98% (257/263), and 99% (260/263) of the time, respectively. Furthermore, the participants reported that they thought they could (or in fact did) fall asleep 84% (62/74), 86% (213/248) and 90% (84/93) of the time in LTC, RH, and ANR settings, respectively (fig 6b). When asked if IES is acceptable (yes/no) as part of their daily routine, participants reported 97% (57/59), 97% (250/259), and 100% (91/91) of the time in LTC, RH and ANR settings, respectively.

The subjects were also asked to rate if the use of IES system was cumbersome, (i.e. not easily managed/handled, bulky, annoying, complex or awkward to use) during their daily routine (fig 6c). When testing the no-garment IES system, subjects in RH and ANR settings reported that using the system was moderately cumbersome 10% (24/121) and 11% (7/65)) of the time respectively, while only 2% (1/55) in LTC facility found the system cumbersome. In contrast, 6% (9/142) and 4% (1/28) of the time participants in the RH and ANR settings using the Smart-e-Pants garment found it moderately cumbersome to use.

More importantly, 4 individuals with partial gluteal sensation and spinal cord injury causing quadriplegia and 1 with paraplegia reported that wearing the IES system allowed them to sit more comfortably in their chair for extended periods of time and decreased the discomfort associated with sitting for up to 12

hours compared to 3 or 4 hours on days without IES. They reported that their lower back as well as trunk felt better on days they tested IES.

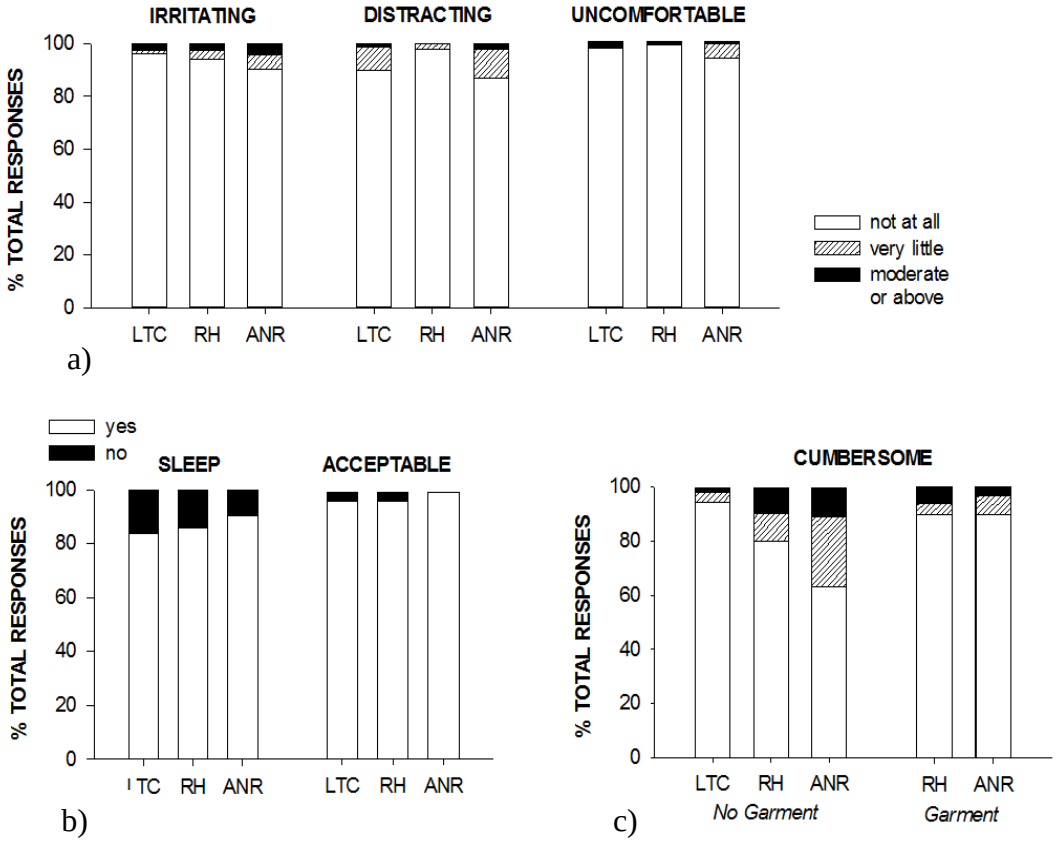


Figure 6 *Acceptability of IES system in LTC, RH and ANR settings. Bars represent percentages of overall participant feedback to questions asked at the end of each day of IES application. Participants were asked a) "Was the stimulation irritating/ distracting/ uncomfortable?" b) "Could you fall asleep while being stimulated?" and "Is stimulation acceptable as part of your daily routine?" c) "Is the IES system cumbersome to use?" Participants responded on a scale from 1-5 based on that days perception: 1 (nota-at-all), 2 (very-little), 3 (moderate), 4(quite a bit), and 5 (severely).*

2.3 Discussion

In this clinical testing study, we found that use of the IES system, whether with direct electrode application on the skin or through the Smart-e-Pants garment, is feasible in long term care and two rehabilitation hospital settings. The study protocol (12 hours/day, 4 days/week for 4 weeks) was chosen based on the availability of resources and the ability of the study participants and associated staff to meet the research demands. Those limits do not necessarily reflect the capability of the IES system or patient tolerance. Indeed, when study participants were free to continue using the IES system beyond the study period and when they were not constrained by the protocol demands or hospital discharge date, 6 elected to carry on using the system for an additional 2-5 weeks and 1 for up to 8 months longer until hospital discharge on a daily basis with no adverse effect.

Overall, the system was generally safe and time demands were reasonable. Most of the time muscle contractions were still clearly visible after 12 hours of stimulation. IES was deemed acceptable to the participants and did not interfere with their daily routines. More importantly, some subjects found the system beneficial and continued using it until they were discharged from hospital.

What lessons were learned in different healthcare settings?

We deliberately selected the LTC facility to start testing the IES system as we foresaw that environment as one of the most challenging clinical settings. Learning from that was helpful in guiding later implementation in the rehabilitation hospitals. From that experience, we realized that incontinence, skin fragility, high body mass index and compromised cognition in residents who

needed continuous round the clock care were major factors that must be taken into consideration. All participants at the LTC facility were incontinent making them ill-suited for the Smart-e-Pants garment at the time, which necessitated the application of electrodes directly to the skin. The skin condition was more fragile due to a combination of factors including older age and co-morbidities, which were exacerbated by constant moisture. Large amount of adipose tissue around the buttock in some potential study participants (i.e., high BMI ratio) attenuated the stimulator output leading to insufficient muscle contractions even at the maximal stimulation setting. Higher patient to staff ratio also made implementation more challenging. Finally, low patient turn-over rate made it difficult to recruit a large number of suitable candidates who fit the study inclusion criteria. Given the relatively modest success in patient recruitment in the long term care setting, future studies will have to be deliberately designed to address the above concerns to enhance the feasibility of IES for pressure ulcer prevention in this setting.

In contrast, within the rehabilitation hospital settings both in Edmonton and in Calgary, patient turn-over rate was higher with lengths of stay ranging from 2 weeks to 3 months. Many patients at those sites considered at high risk of developing pressure ulcers were young males with recent spinal cord injury, had healthy skin and were cognitively intact, making participant recruitment easier. Incontinence in RH and ANR sites was only at 6 and 11%, respectively making it possible to test the Smart-e-Pants garment.

Smart-e-Pants garment vs. no-garment direct electrode application

Study participants in the rehabilitation settings (RH and ANR) found the no-garment IES system with electrodes applied directly to the skin more cumbersome than the Smart-e-Pants garment. Without the garment, especially during rehabilitation sessions or independent transfers, the cables and the stimulator sometimes got in the way. Participants at the LTC facility found the IES system least cumbersome, likely because of their generally lower level of activity with time mostly spent in a wheelchair or bed, fewer hours of rehabilitation and fewer activities requiring transfers.

Because the Smart-e-Pants garment channelled the cables through the waist band and provided housing for the stimulator in a detachable pouch, the cables were more easily managed than in the IES system with no garment. Most participants with SCI had well established bowl routines which were completed in the morning before the IES system was donned. The horizontal zipper in the front facilitated easy catheterization.

The Smart-e-Pants garment made donning the IES system easier for the caregivers as it clearly marked out the locations where the electrodes should be placed. The garment also made the implementation of the IES system easier for less trained nursing staff and less frequent users compared with the no-garment approach with the electrode placed directly on the skin. Nonetheless, regardless of the system deployed, time to administer (don and doff) IES was approximately 15 minutes in total. Indeed applying the IES system can easily be incorporated into participant's daily care routines as was demonstrated in the ANR setting where

the system donning and morning care routine were completed at the same time, decreasing the perceived time needed to don the system to less than 10 minutes.

Was IES acceptable to end-user?

All study participants in the LTC facility were sensate while in rehabilitation hospitals approximately 60% of the participants had gluteal sensation, albeit impaired in many cases. Even with fully intact sensation, participants found the stimulation non-irritating and acceptable as part of their daily routine. More than 80% of the cases regardless of setting, participants thought they could fall asleep while receiving IES, which was indeed confirmed by actual observations. This is an important finding suggesting that undue discomfort should not be a barrier for using the IES system. Moreover 5 participants with partial sensation, 4 of which were those with quadriplegia, reported that the IES system helped relieve the discomfort associated with prolonged sitting. This allowed them to sit more comfortably in their chair for up to 12 hours. This is an important finding suggesting that IES system may not only be important for preventing DTI, but may also be important in mitigating pain associated with prolonged sitting and improve the quality of life of individuals confined to a wheelchair, especially those who have less voluntary upper body ability and are unable to complete pressure relieving manoeuvres independently.

Sustainability of visible muscle contractions after 12 hours of IES use

Pressure relief is critical for prevention of pressure ulcers. Standard clinical technique for reducing pressure involves turning and repositioned bed-

ridden patients frequently, i.e. every 2 hours (Thomas, 2001). Seated individuals are encouraged to periodically complete 15 to 30 second long lift-offs to achieve pressure relief and tissue perfusion in the buttock region. However suggested liftoff time may not be sufficiently long and a 2 minute liftoff may be necessary to achieve the pre-loading level tissue oxygenation levels (Coggrave & Rose, 2003). Some individuals with spinal cord injury are physically even unable to adjust their posture and depend on caregivers for pressure relief.

In our lab we demonstrated that IES induced periodical muscle contractions indeed led to significant pressure redistribution and tissue oxygenation with each muscle contraction in loaded buttocks independent of muscle mass (Gyawali et al., 2011; L. R. Solis et al., 2011). The therapeutic benefits of IES for prevention of DTI therefore depend on fused muscle contractions at maximal or moderate strength (Curtis et al., 2011) administered throughout the hours of sitting on regular basis. In this study, strength of muscle contractions was visually assessed when the system was donned and again doffed; indeed most of the time muscle contractions were still present when the system was removed 12 hours later suggesting that IES system was providing the intended pressure relief and oxygenation benefits.

When IES was administered through electrodes applied to skin directly, shifting in the electrode position or peeling away from the motor points can occur, leading to loss of muscle contraction. We found that electrodes placed on skin without taping electrode edges did in fact lead to peeling and rolling in up to 34% of the cases. When electrode edges were taped down or IES was administered

though the Smart-e-Pants garment, electrode peeling and rolling was substantially less with only 5% peeling and rolling in cases when the garment was used.

Direct electrode application allowed easier contraction visualization compared to the Smart-e-Pants garment which made it difficult as the caregiver was required to observe muscle movement through the garment covering the contraction. This likely contributed to the 7 and 29% of undetectable muscle contractions in RH and ANR settings, respectively. The number is higher in ANR likely due ever-changing nursing staff inspecting the muscle contractions when the IES system was removed and their unfamiliarity with detecting electrically induced muscle contractions compared to consistent researchers who inspected the evening contractions in the RH setting. This highlights to the importance of investigating objective methods of detecting presence of muscle contractions. This may be achieved for example using electromyography (EMG) (Erfanian, Chizeck, & Hashemi, 1998). In our lab we are currently investigating if EMG is a feasible technique for monitoring the strength of IES-evoked muscle contractions in the buttocks.

Finally, some of the loss of muscle contractions might be due to muscle fatigue. In our participants we optimized the stimulation parameters to minimize fatigue by inducing fused muscle contractions at lowest frequency (i.e. 17.5Hz) and highest intensity needed to obtain a fused muscle contraction (Binder-Macleod & Snyder-Mackler, 1993). We are currently systematically investigating if IES induces muscle fatigue after prolonged 8 hour use.

Advantages of long-term muscle stimulation

IES mimics the frequent, subconscious postural adjustments performed by able-bodied individuals in response to discomfort while sitting or lying down. Each muscle contraction redistributes pressure and increases oxygenation in the loaded tissue. Additional to short term changes with each contraction, long term use of electrical stimulation was found to increase the gluteal muscle thickness by 50%, decrease regional interface pressures by 20% and increase overall oxygenation levels (Bogie, Reger, Levine, & Sahgal, 2000) further mitigating factors leading to DTI.

2.4 Conclusion

This study demonstrated, for the first time, that the IES system is safe and feasible in a range of healthcare settings. We showed that IES was generally safe and acceptable as part of daily routines of long-term facility residents and inpatients of two rehabilitation hospitals. Wearing IES system did not interfere with daily rehabilitation routines and demands placed on the caregivers were deemed reasonable. Future studies will have to demonstrate the effectiveness of IES to prevent DTI. Considering that prevention of DTI is estimated to be 2.5 times more cost effective than treatment (Lyder & Ayello, 2008), and that prevalence of DTI is on the rise (VanGilder et al., 2010), the findings in this study suggest that IES system has the potential to become an important clinical complement for preventing DTI in populations at risk.

2.5 Acknowledgements

This study was conducted with funding from the Alberta Innovates - Health Solutions (AIHS) Interdisciplinary Team Grant. Alisa Ahmetović was partly supported by a TD Bank Financial Group Scholarship for Interdisciplinary Research; Vivian Mushahwar is an Alberta Heritage Foundation for Medical Research Senior Scholar.

Contributors and coauthors include: Ryan Sommer, Dana Schnepf, Lisa Kawasaki, Robyn Warwaruk-Rogers, Glen Isaacson, Martin Ferguson-Pell, Vivian K. Mushahwar, Sean Dukelow, K. Ming Chan. Ryan Sommer, Dana Schnepf and Robyn Warwaruk-Rogers performed recruitment and data collection. Lisa Kawasaki also helped with data collection. Special thanks to Anita Clarke and Su Ling Chong for help with recruitment and conducting training workshops for caregivers. Thanks to Naomi Hui for the artistic work and to all members of the Pressure Ulcer Focus Group (AIHS Interdisciplinary Team) for their input and support throughout the study.

Appendix 1: Sample of data collection instrument

Pressure Ulcer Prevention Study

Alberta Health Services

Participant: _____
Date: _____

Contact: Ryan Sommer
Pager: 780-445-5496
Contact: Alisa Ahmetovic
Cell: 780-298-4169

Caregiver Demands (AM)

Time electrodes were put on_____AM/PM
Staff name(s) & designation putting on system: 1. _____ 2._____

Stimulator: _____ **Mode**: _____µs (Constant II) **Frequency**: _____Hz

Ease of positioning participant to desired position (knees & hips at 90°):

1 2 3 4 5

1(very easy): participant independently achieves desired position
2(easy): desired position achieved by caregiver(s) with minimal effort (# of caregivers does not affect score)
3(moderate): desired position achieved by caregiver(s) with moderate assistance (due to ex. heavy weight, tone in legs, pain, etc)
4(difficult): desired position achieved by caregiver with significant effort (due to ex. contractures, poor range of motion, pain, etc)
5(very difficult): unable to achieve desired position (due to ex. heavy weight, contractures, poor range of motion, pain, etc)

Ease of finding adequate muscle contraction: **Left:** 1 2 3 4 5
Right: 1 2 3 4 5

1(very easy): adequate muscle contraction on first attempt/ electrode/ shorts placement
2(easy): adequate muscle contraction with minor adjustments needed to electrodes/ shorts
3(moderate): adequate muscle contraction after several electrode/ shorts adjustments
4(difficult): only able to achieve inadequate muscle contraction (visible weak/ flicker or palpable) after several adjustments
5(very difficult): no visible or palpable muscle contraction found despite numerous adjustments to electrodes/ shorts

Stimulation levels used (how many power bars 1-20) Left buttock:_____ Right buttock:_____

Contraction strength (rate according to legend below) Left buttock:_____ Right buttock:_____

1(CANT see it or feel it) 2(CAN'T see it, CAN feel it) 3(CAN see weak/flicker) 4(CAN see strong contraction)

Total Time needed to put on system: _____minutes
Distribute total time used (min): Pt. position_____, electrodes/shorts_____, other_____

Circle all that apply:
electrodes directly on skin / all edges taped / only corners taped / incontinent product worn / Smart-e-Pants / underwear / none

Caregiver Demands Throughout the Day

1. When (time) was assistance was needed:
2. How much time was needed to provide assistance:
3. What assistance was needed (check off):
   - Change battery
   - Re-connect wires
   - Take system off for shower, swimming, bowl/bladder accident/ reapply system after
   - Participant/ caregiver notes inadequate contractions requiring minor adjustments
   - Other:

Extra notes:

Data Collection Flow Chart, Version 4.8

Caregiver Demands (PM)

Time electrodes were taken off_____ AM/ PM
Staff name(s) & designation taking off system: 1. _____ 2._____

Time it took you to remove the system: _____ minutes

Is adequate muscle contraction still visible? **Left** Buttock: Yes / No **Right** Buttock: Yes / No

Contraction strength (rate according to legend below) **Left** buttock:_____ **Right** buttock:_____
1(CANT see it or feel it) 2(CAN'T see it, CAN feel it) 3(CAN see weak/flicker) 4(CAN see strong contraction)

Were any of the electrodes peeled or not in the proper place (fill in/ legend below)?

- Upper Left electrode peeled: _____
- Upper Right electrode peeled:_____
- Lower Left electrode peeled:_____
- Lower Right electrode peeled:_____

LEGEND: How Much has Peeled OFF: ¼, ½, ¾ , completely off, corner rolled Other notes:_____

Skin Monitoring

Skin redness from **Electrode Pads** (circle):
Upper Left: 1 2 3 4 5 **U.** Right: 1 2 3 4 5 **Lower** Left: 1 2 3 4 5 **L.** Right: 1 2 3 4 5

Skin redness from **Leads** (circle):
Upper Left: 1 2 3 4 5 **U.** Right: 1 2 3 4 5 **Lower** Left: 1 2 3 4 5 **L.** Right: 1 2 3 4 5

1 (no redness), **2** (pink/red blanchable), **3**(stage 1 non blanchable), **4**(stage 2 open skin), **5** (stage 3 full thickness skin loss)

Skin redness from **Smart-e-Pants garment/ garment seams** (write note below):

General skin redness **NOT ASSOCIATED WITH THE SYSTEM** (write note below):

Participant Feedback

Was the stimulation distracting?	1 2 3 4 5
Was the stimulation irritating / bothersome? (to provoke impatience, anger, or displeasure)	1 2 3 4 5
Was the stimulation uncomfortable/ painful?	1 2 3 4 5
Was the system cumbersome to use? (not easily managed/handled: bulky, annoying, complex, or awkward)	1 2 3 4 5
Do you think you could fall asleep with the system on?	Yes / No
Did you sleep with the system on?	Yes / No
Is the stimulation acceptable as part of your daily routine?	Yes / No

1 (not at all) **2** (very little) **3** (moderate) **4** (quite a bit) **5** (severely)

Suggestions

Any ideas on how to make this system more user friendly:

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Chapter 3: Use of Electromyography to Assess Gluteal Muscle Contractions and Fatigue during Prolonged use of Intermittent Electrical Stimulation

3.0 Introduction

Pressure ulcers are a common, serious complication associated with compromised mobility and sensation. The prevalence rate of pressure ulcers in Canada is 30% (Woodbury & Houghton, 2004) with an 11.6% mortality rate in those patients admitted to hospital with pressure ulcers as a secondary diagnosis (Russo, Steiner, & Spector, 2008). Of the different types of pressure ulcers, deep tissue injury (DTI) is particularly serious. It starts in the deep muscle layers under and around bony prominences due to unrelieved external pressure. Prolonged loading leads to DTI through a combination of factors including direct mechanical deformation of tissue and compromised circulation leading to ischemia and ischemia-reperfusion injury (Blaisdell, 2002; Gefen, 2009a; Gefen, 2009b; Kosiak, 1959; Kosiak, 1961; Loerakker et al., 2011; Stekelenburg et al., 2007; Stekelenburg, Gawlitta, Bader, & Oomens, 2008). We recently demonstrated that using intermittent electrical stimulation (IES) to induce contractions in muscles at risk may be an effective alternative for mitigating mechanical and circulatory mechanisms that lead to DTI. Muscle contractions induced by IES may be able to combat 2 of the major mechanisms that lead to DTI by redistributing pressure away from ischial tuberosities and producing a sustained increase in tissue oxygenation (Gyawali et al., 2011; Solis et al., 2007; Solis et al., 2011; Solis et al.,

2012). To apply this clinically to patients at risk of DTI, we developed an IES system that includes a programmable stimulator with recording capabilities that can deliver the same stimulation paradigm using regular trains of stimuli (10 seconds ON, 10 minutes OFF) in an open loop manner through surface electrodes placed over the gluteus maximus muscles throughout the hours of sitting or lying. Although the safety, feasibility and acceptability of this system has been demonstrated in a wide range of clinical settings (Ahmetović et al., 2012) the current first generation open loop IES system does not have the capability to monitor and adjust the strength of the gluteal muscle contraction throughout the day. Since oxygenation and pressure redistribution are dependent on muscle activation, this is of critical importance. Furthermore, it is not known whether the IES paradigm would lead to muscle fatigue after prolonged use. This is a particular concern in patients with insults to the central nervous system (CNS) such as those with spinal cord injury (SCI) whose muscles are more prone to fatigue. Therefore, means of monitoring muscle contractions could serve as useful feedback control inputs to optimize the stimulator outputs.

In this paper, we explore if surface electromyography (EMG), a non-invasive technique for recording muscle membrane electrical propagation, is a feasible technique for monitoring the strength of evoked gluteal muscle contractions. A second goal is to investigate whether the IES paradigm would cause muscle fatigue after 8 hours of stimulation in neurologically intact subjects as well as those with SCI.

3.1 Methods

Participants

Ten subjects with SCI and 8 neurologically intact subjects were recruited. The latter group was so selected to represent patients who are at risk of pressure ulcer formation not due to disrupted motor or sensory innervation but rather due to impaired consciousness such as those in the intensive care unit. Two of the SCI subjects did not respond to electrical stimulation due to associated caudal equina injury leading to complete denervation of the gluteus maximus muscle, and were excluded from the study. Table 1 details the remaining 8 participants with SCI qualifying for the study. These participants had an average age (± standard deviation) of 37.6 ± 10.2 and had their injury 9.4 ± 9.7 years earlier. The neurologically intact subjects were 25.1 ± 3.9 years old (4 male, 4 female, average weight = 65.1 ± 13.9 kg, average height = 169.4 ± 7.3 cm). The experimental protocol was approved by the University of Alberta Ethics Board. All participants gave their informed consent.

Table 1 *Subjects with spinal cord injury.*

Initial	Sex	Age	Height (cm)	Weight (kg)	Years injured	Injury level	Complete/ Incomplete
AH	M	34	165	68	1	T10	C
DR	M	34	173	86	2	T3-4	I
RE	F	43	170	98	3	T5-6	C
JB	M	24	191	82	4	C5-6	I
AV	M	31	191	99	8	C4-5	I
DS	M	55	191	102	13	C5-6-7	I
ALO	F	32	168	54	14	T7	C
KH	F	48	163	82	30	T1-2	C

EMG and force measurements

Electrode placement

The subjects' lay on their side on an examination bed with their hips and knees bent at 90°, mimicking the sitting position. The skin overlying the right gluteus maximus was cleaned with rubbing alcohol.

Self-adhesive surface stimulating electrodes (Axelgaard Pals Platinum Neurostimulation electrodes, 7.6cm x 10.2cm, Model 895340-4-40, Fallbrook, California, USA) were placed on the gluteal muscle. The cathode was placed over the motor point of the gluteus maximus muscle, proximal to the ischial tuberosity, and the anode was placed approximately 2" more proximally as shown in fig. 1.

The recording electrode was placed at a location that maximized the M-wave amplitude (black electrode) while minimizing the stimulus artifact. A ground (green) was placed between the stimulating and recording electrodes. The reference electrode (red) was placed over the greater trochanter of the femur.

Experimental procedure

Subjects with SCI were seated on their wheelchair while neurologically intact subjects were seated in a firm chair with arm and back support. The stimulated leg was placed onto a single axis force plate, as shown in figure 2, for recording of the isometric force of hip extension. The force plate was placed underneath the thigh just proximal to the knee with the leg raised off the floor. The subjects were asked to be still, remain relaxed and refrain from talking during data collection.

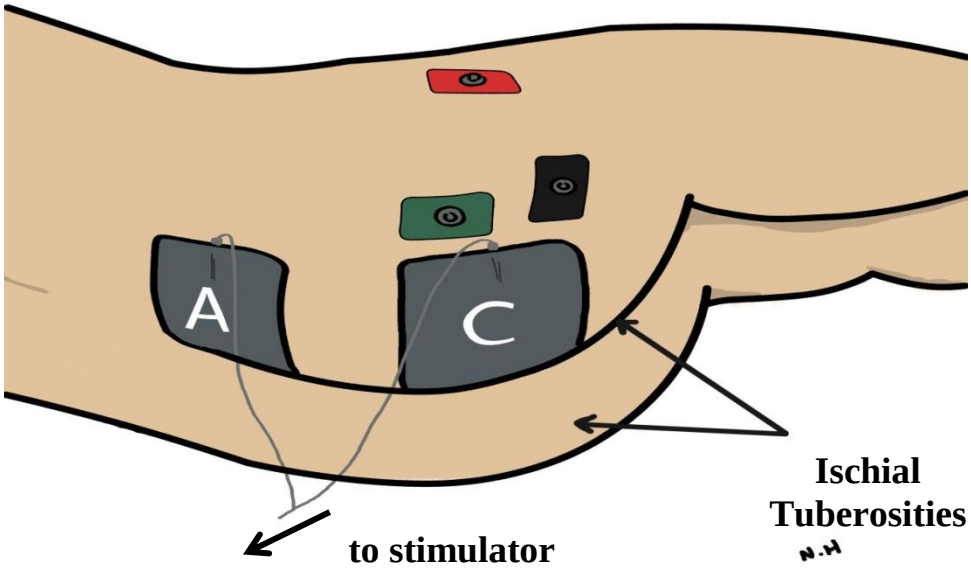

Figure 1 *Placement of stimulating and recording electrodes on the gluteus maximus muscle. Subjects lay on their side with knees and hips bent at approximately 90º. Large gray electrodes are the stimulating electrodes (C: cathode; A: anode). EMG recording electrodes (black: recording; red: reference; green: ground).*

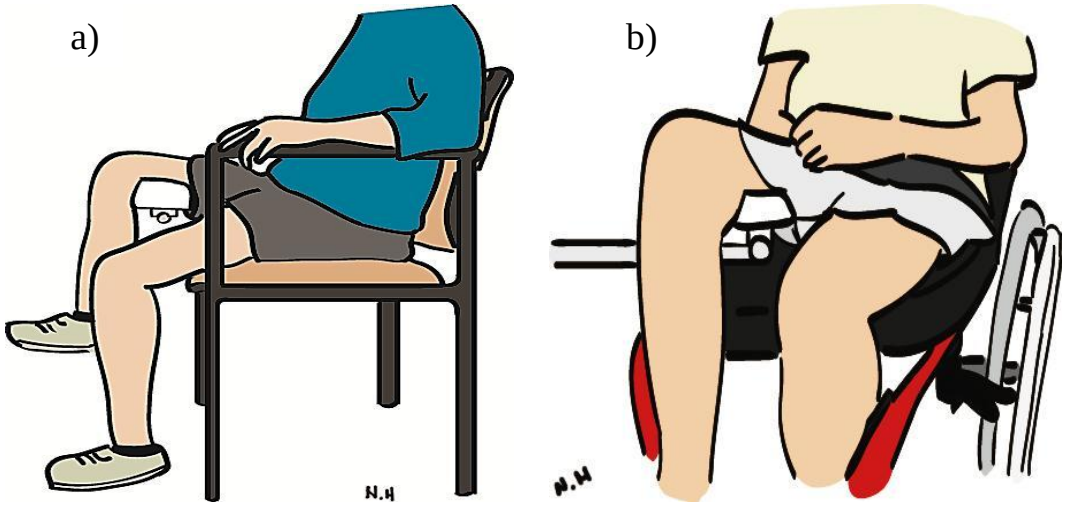

Figure 2 *Position of right leg on top of the force plate in neurologically intact subjects (a) and subjects with spinal cord injury (b). The unidirectional force transducer registered force in the downward direction.*

A constant current stimulator/ EMG recorder (Advantage Medical, London, ONT, Canada) at a pulse width 200µs or 500µs was used to deliver 4 single pulses approximately 5 s apart to the motor point of the gluteus maximus muscle starting from a maximal current output of 100mA. The intensity was decreased in 5-10mA steps until the twitch tension and M-wave were no longer detectable. Isometric twitch tension, measured through a custom designed force rig, as well as the EMG signals were captured and converted digitally via an A/D board (National Instruments, model: NI USB-6251, Austin, TX, US) using custom designed software in Labview$^{T.M.}$ 8.5 (National Instruments, Austin, TX, US) at a sampling rate of 2 kHz.

Assessment of muscle fatigue in association with prolonged IES use

The IES (10 seconds of stimulation every 10 minutes) intensity was set to produce strong visible muscle contractions with a 300µs pulse width at 20Hz for 8 consecutive hours. Although in some neurologically intact subjects the stimulation intensity often had to be submaximal to not induce undue discomfort, in animal models we have established that moderate and maximal stimulation intensities had equal effect for prevention of DTI (Curtis et al., 2011).

The experimental protocol for fatigue assessment is depicted in figure 5. Subjects received 8 hours of IES, but data were collected only in the 1st and 8th hours of stimulation. Before each 10s stimulus train in the 1st and 8th hours of IES, 4 single pulses at maximal intensity (100mA) were delivered to obtain maximal muscle activation. Twitch tensions and corresponding M-waves were

simultaneously recorded. During the intervening 6 hours, subjects received IES but data was not recorded. Subjects were asked to remain seated throughout the 8 hours of the experiment so that any fatigue detected could be attributed to IES.

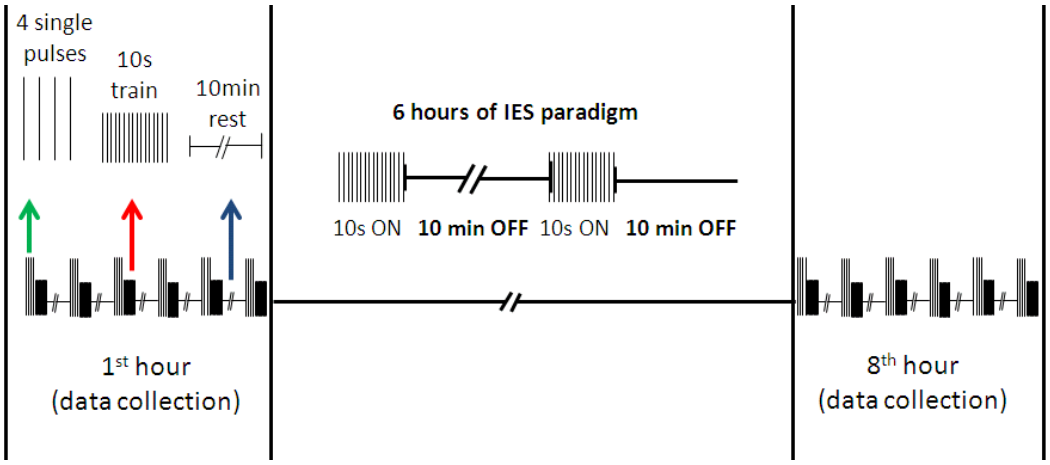

Figure 3 *Experimental protocol for assessing if IES induces muscle fatigue within 8 hours of stimulation. 4 single pulses at 100mA are given before each 10s stimulus train to activate the gluteus maximus maximally during data collection in the 1st and 8th hour of IES. Fatigue is assessed by comparing twitch tension amplitudes, peak to peak M-wave amplitudes, and mean and median frequency content of EMG signals recorded during the 1st and 8th hour of IES.*

Twitch tension – M-wave relationship

The responses (twitch tensions and the corresponding M-waves) to the first stimulus pulse in each series of 4 single pulses were discarded to ensure that soft tissue slack due to changing muscle length from static to dynamic condition, is taken up. The remaining 3 measurements of peak twitch tensions and the corresponding peak to peak M-wave amplitudes were analyzed and averaged at

each intensity setting. Data were analyzed offline using custom written Matlab (version R2007b) programs.

Twitch tension amplitude was measured by subtracting baseline from the maximum (peak) tension. Peak to peak M-wave amplitude was measured by subtraction the second positive peak from the preceding negative peak. The peak twitch tension and corresponding peak to peak M-wave amplitudes at maximal intensity (100mA) were used to normalize the submaximal M-wave and twitch tension amplitudes obtained at progressively lower stimulus intensities.

Assessment of fatigue from changes in twitch tension and M-wave amplitudes

Induced fatigue associated with prolonged IES was assessed by 2 different methods. First, differences in peak twitch tension and peak to peak M-wave amplitudes produced by the single pulses at maximal stimulation intensity during the 1^{st} (1^{st} session) and 8^{th} (2^{nd} session) hour of IES were compared.

For each subject, each session of data collection resulted in 6 averaged twitch tension and M-wave amplitudes taken at 10 minute intervals. The twitch tension and M-wave peak to peak amplitudes were normalized with respect to the average of first session twitch tensions and M-wave amplitudes.

Second, since the power spectrum of the M-wave is known to shift to lower frequency with muscle fatigue (Mizrahi, Levin, Aviram, Isakov, & Susak, 1997), we also compared the difference in power frequency between the beginning and the end of 8 hours of IES use by investigating the power density

spectrum shift of preceding single pulses. The process of analysing M-waves is demonstrated in figure 4. First, the stimulation artifact was removed using a stimulus artifact subtraction template method and raw signal as shown in fig. 4a is obtained. Then the M-waves were subdivided in epochs, each with 512 samples: 100 points preceding the peak of the M-wave and 412 points after the peak (fig. 4b). After segmenting the signal in epochs the power spectral density (PSD) function using Welch's averaged periodogram method (Matlab R2011a, MathWorks, Natick, MA, US) is computed (fig. 4d) by taking the square of the modulus of the discrete Fourier transform of the signal (fig 4c), which is computed by means of the 512-points fast Fourier transform (FFT) algorithms (Merletti et al. 1992). Mean frequency power frequency (MPF) is calculated as the frequency at which the average power within the epoch is reached. The median frequency (MF) is calculated as the frequency at which 50% of the total power within the epoch is reached.

Statistical analysis

To determine whether EMG is a good surrogate measure of the muscle contraction generated force, the relationship between twitch tension and corresponding M-wave amplitude was evaluated with linear regression method.

To detect muscle fatigue, the twitch tensions and M-wave amplitudes obtained in the 1st hour were compared to those in the final hour. Since those parameters were not normally distributed (Shapiro-Wilk test, $p<0.05$), non-parametric

statistical analysis was performed using the Kruskal-Wallis test for individual data and Mann-Whitney U test for group comparisons. Differences were considered significant at $p<0.05$.

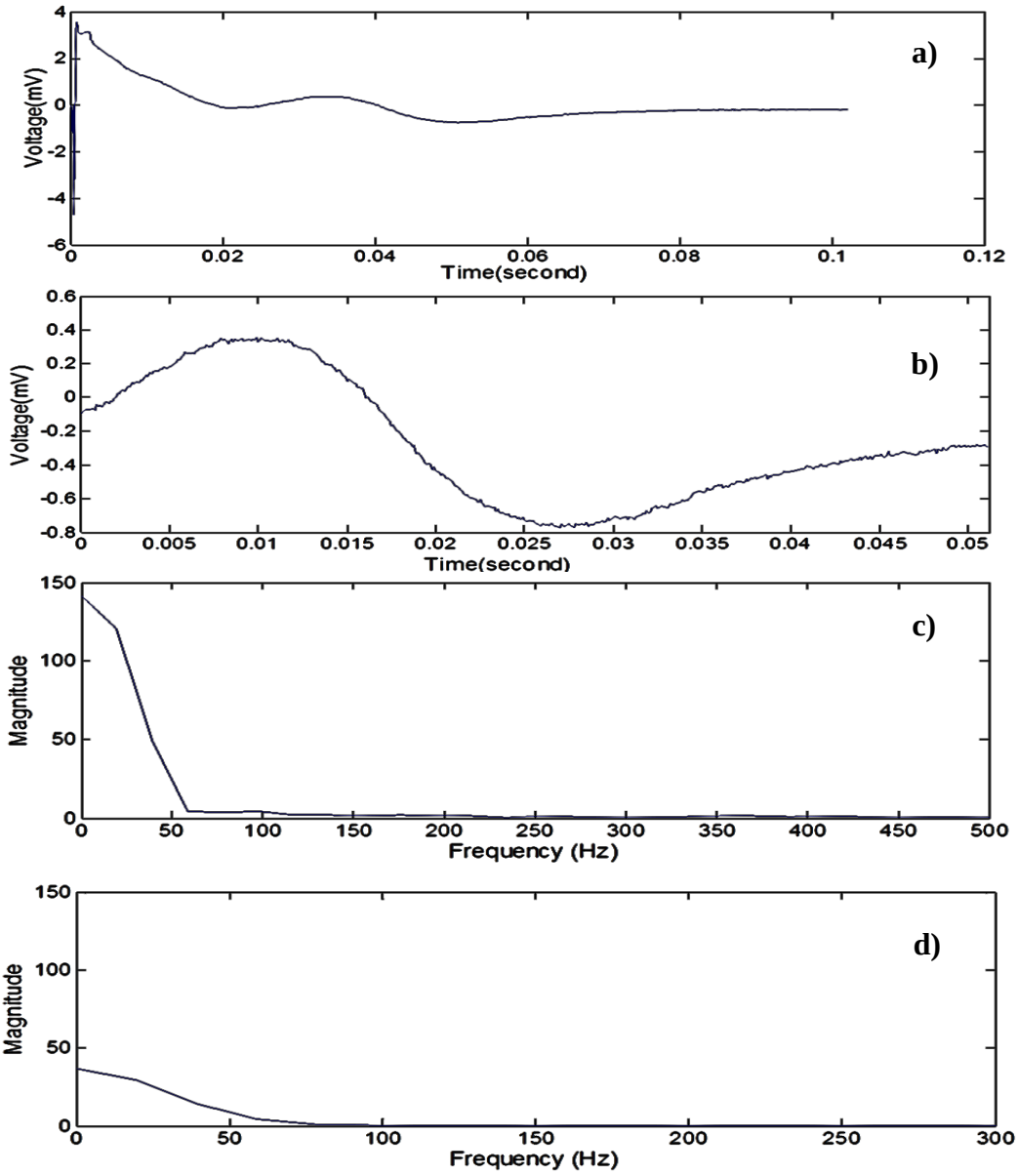

Figure 4 *The process of power spectrum density analysis of EMG data signal from one subject with spinal cord injury: a) Raw signal after template subtraction for 1 single pulse at 100mA; b) selected 512 point epoch; c) Fast Fourier Transform of selected epoch; d) Power spectrum density of selected epoch.*

3.2 Results

M-wave and twitch tension relationship in evoked contractions

To address the question of whether M-wave amplitude is a good surrogate measure of tension evoked through gluteal muscle stimulation, we examined the correlation between M-wave peak to peak amplitude and peak twitch tension amplitude. Typical raw twitch tension and the corresponding M-wave evoked by a 100mA, 200µs stimulus pulse in a person with intact spinal cord are shown in fig. 5a and b and a person with spinal cord injury in fig. 6a and b, respectively.

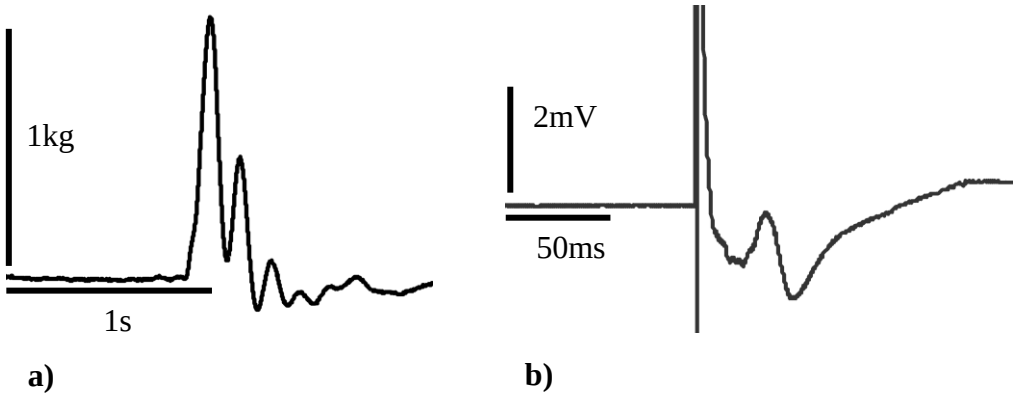

Figure 5 *Representative twitch tension (a) and corresponding M-wave (b) signals evoked by a single pulse at 100mA and 200µs in a person with intact spinal cord.*

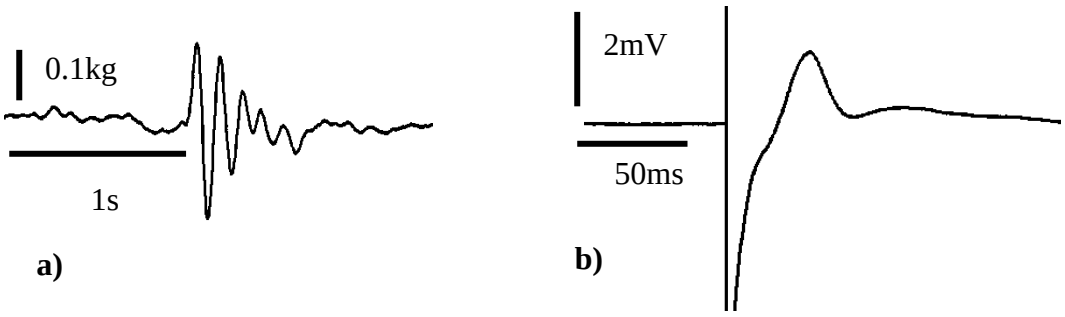

Figure 6 *Representative twitch tension (a) and corresponding M-wave (b) signals evoked by a single pulse at 100mA and 200µs in a person with spinal cord injury.*

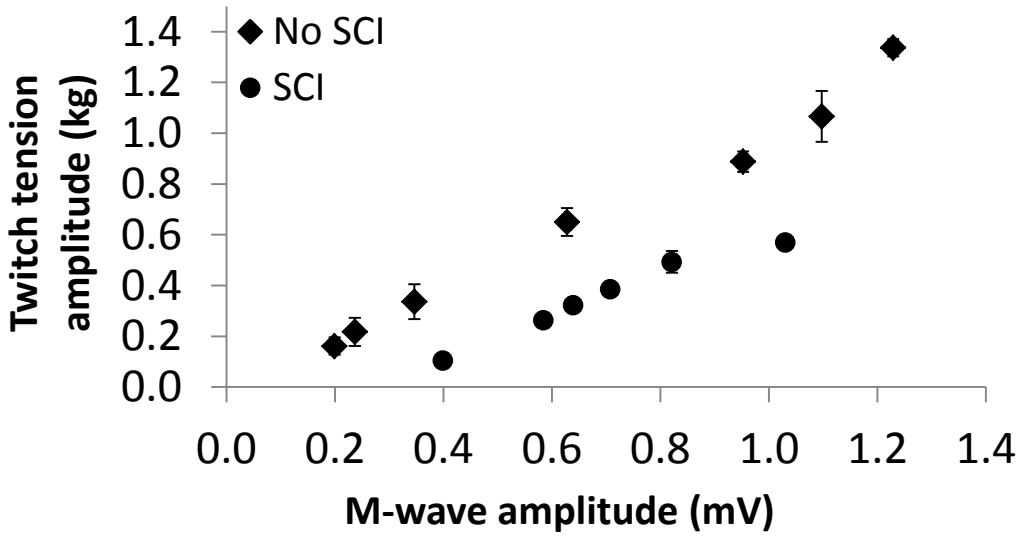

Figure 7 *Representative correlation between peak twitch tension amplitude and peak to peak M-wave amplitude for a subject with intact spinal cord (diamonds) and a subject with SCI (circles). Standard deviation bars are shown.*

Representative examples in the correlation between twitch tension and M-wave peak to peak amplitude in neurologically intact and subjects with SCI are shown in fig. 7. The maximal twitch tension in the neurologically intact subject was 1.3 kg compared to 0.57 kg in a subject with SCI. Overall, maximal mean twitch tension amplitudes (± standard deviation) in subjects with SCI were 75% smaller at 0.42 ± 0.19 kg compared to 1.74 ± 0.99 kg in neurologically intact subjects. Maximal mean peak to peak M-wave amplitudes in the SCI group was 25% smaller at 1.00 ± 0.40 mV compared to 1.33 ± 0.38 mV in the neurologically intact group.

The normalized twitch tension and M-wave recruitment curves for a single subject with SCI (red) and a single subject with intact spinal cord (black) are shown in fig. 8. Each data point respesents an average of 3 values with standard

deviation bars shown at the selected intensity normalized with respect to value obtained at 100mA. Normalized M-wave amplitudes and twitch tensions are closely correlated in both subjects, but the curves for the subject with SCI are shifted upwards for the same stimulation intesity.

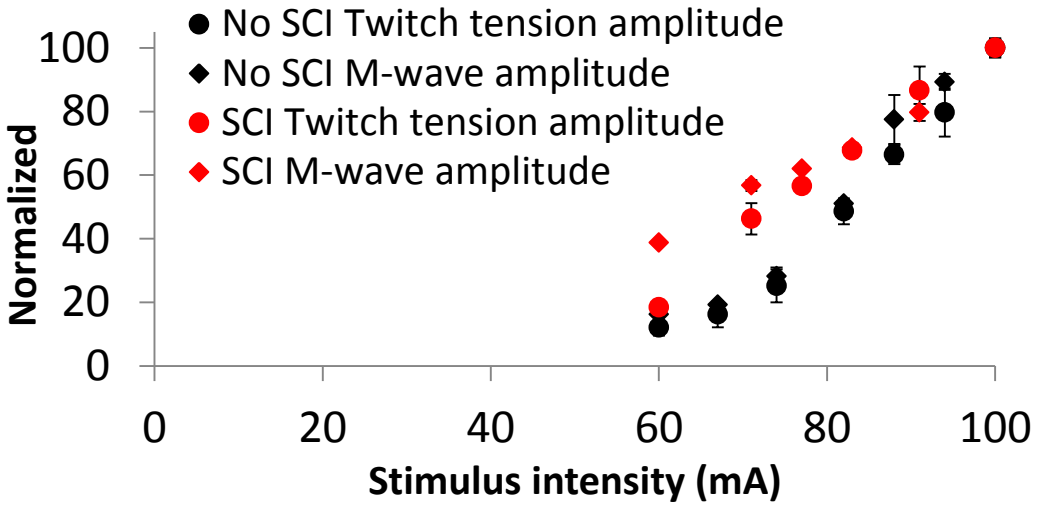

Figure 8 *Representative twitch tension and M-wave recruitment curves in a subject with intact spinal cord (black) and a subject with spinal cord injury (red). Normalized average of three peak twitch tension and peak to peak M-wave amplitudes at each intensity normalized with respect to average twitch tension and M-wave amplitude values at 100mA, respectively. Standard deviation bars are shown.*

For all neurologically intact subjects, the relationship between normalized peak twitch tensions and peak to peak M-wave amplitudes throughout the range of stimulus intensities is shown in fig 9a. A highly significant positive correlation with an R^2 value of 0.90 ($p<0.05$) was obtained. Similarly, the relationship between normalized twitch tensions and peak to peak M-wave amplitudes in the SCI subjects is shown in fig 9b. A positive correlation with an R^2 of 0.62 ($p<0.05$) was obtained.

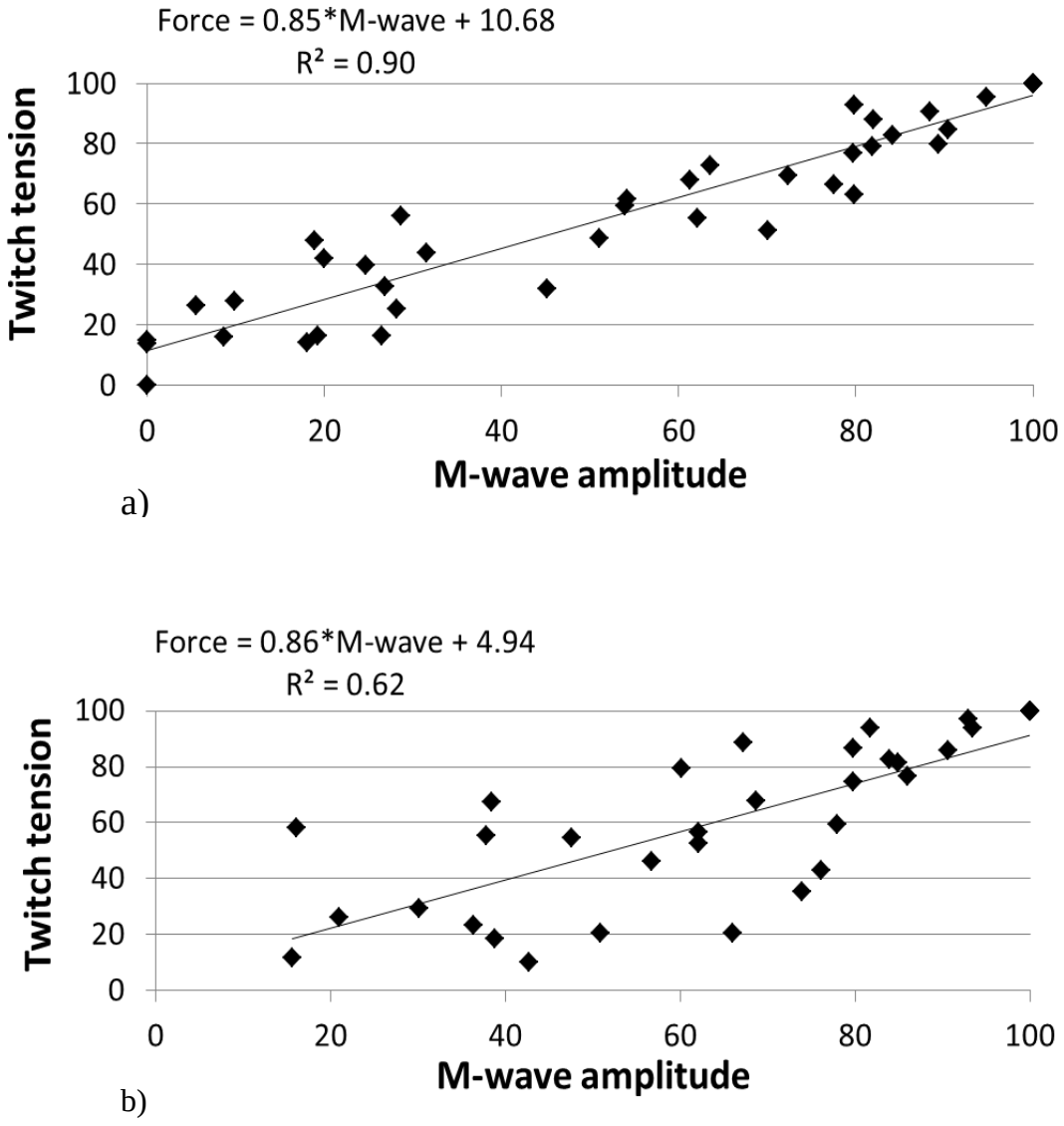

Figure 9 *Normalized M-wave peak to peak amplitude and normalized twitch tension amplitude relationship in 8 neurologically intact study participants (a) and 8 participants with spinal cord injury (b).*

Does IES induce gluteal muscle fatigue?

To test if IES causes muscle fatigue, the muscle is maximally activated with single pulses before each 10s train during the 1st and the 8th hour of the IES

protocol. The twitch tension, the corresponding M-wave amplitudes, the mean and median power spectrum frequencies were compared. Data from each individual subject (different coloured lines) are shown in fig. 10. Data from the 1st session were averaged and compared to the average of the 2nd session data.

The twitch tensions for subjects with SCI are plotted in (a) and neurologically intact subjects in (b). The neurologically intact subjects produced (mean ± standard devation) 1.45 ± 0.48 kg and 1.60 ± 0.85 kg of tension in the 1st and the 8th hour of testing, respectively. The subjects with SCI on the other hand generated less tension in the 1st and 8th hour of testing at 0.40 ± 0.17 and 0.38 ± 0.14 kg tension, respectively.

The coresponding peak to peak M-wave amplitudes for individual subjects with spinal cord injury (c) and neurologically intact subjects (d) in the 1st and 8th hours of IES stimulation showed a similar trend. Each color, connecting the averaged values from 1st and 2nd sessions, represent a different subject. The neurologically intact subjects' peak to peak M-wave amplitudes were (mean ± standard devation) 0.87 ± 0.39 mV and 0.93 ± 0.44 mV in the 1st and the 8th hour of testing, respectively. Similarly, subjects with SCI had similar peak to peak M-wave amplitudes in the 1st and 8th hour of testing at 0.93 ± 0.40 and 1.05 ± 0.64 mV, respectively.

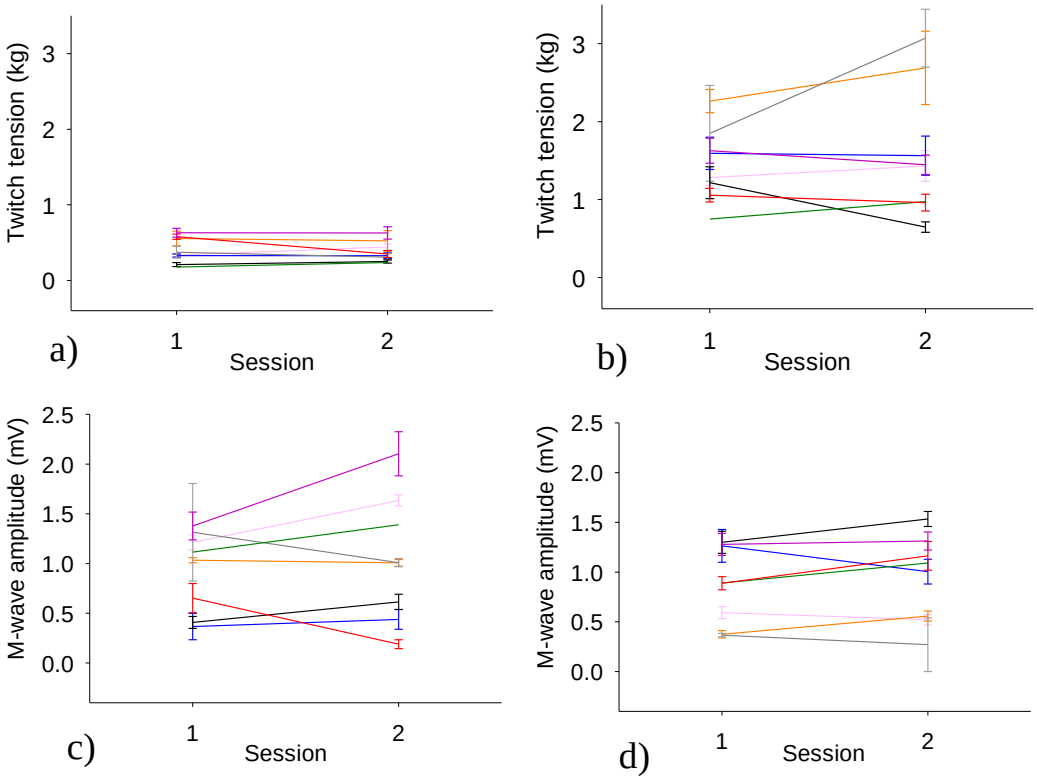

Figure 10 *Individual subject averaged* ***twitch tensions amplitudes*** *from the 1st session, and similarly twitch tension amplitudes from the second session. The average values are connected with a solid line. Each color represents a different subject: a) subjects with SCI; b) neurologically intact subjects. Similarly, individual subject* ***peak to peak M-wave amplitudes*** *from the first session were averaged and similarly from the second session and connected by a solid line: c) subjects with SCI; d) neurologically intact subjects. Standard deviation bars shown.*

Within-session comparisons

To determine if there are differences in twitch tension (or M-wave amplitudes) within a single session (see figure 11a for demonstration) twitch tension amplitudes obtained during the 1st hour of stimulation in 10 minute intervals were averaged across subjects in the same time period of stimulation. For example, twitch tension amplitudes obtained before the 1st 10 second train for

all the neurologically intact subjects was averaged. Similarly, data points for all 8 subjects obtained just before the 2nd train was averaged. The same procedure was applied to twitch tensions and M-wave amplitudes (figure 11c and 11d) from 2nd session. Results of the Kruskal-Wallis test ($p<0.05$) showed that there were no significant differences within data of session 1 or session 2 in neurologically intact and SCI subjects.

Similarly, there were no significant differences on EMG mean power frequency (MPF) and median frequency (MF) in neurologically intact or SCI group among the 6 data points within any of the sessions based on the Kruskal-Wallis test ($p<0.05$) (fig. 12).

Comparisons between 1st and 8th hours of stimulation

As no significant "within session" differences were found in any of the sessions, data points within each session were grouped so that session 1 can be compared to session 2 to determine if differences exist after prolonged stimulation to gluteal muscles. Using the Mann-Whitney U-test ($p<0.05$) no significant change was found in the twitch tensions and M-wave amplitudes by the end of 8 hours of IES in the neurologically intact and SCI subjects. Similarly, there is no statistically significant differences (Mann-Whitney U-test, $p<0.05$) between the first and second session of EMG MPF and MF for neurologically intact subjects. Also, no significant differences in EMG MPF and MF were found between the first and second session for the SCI subjects as well (fig. 12).

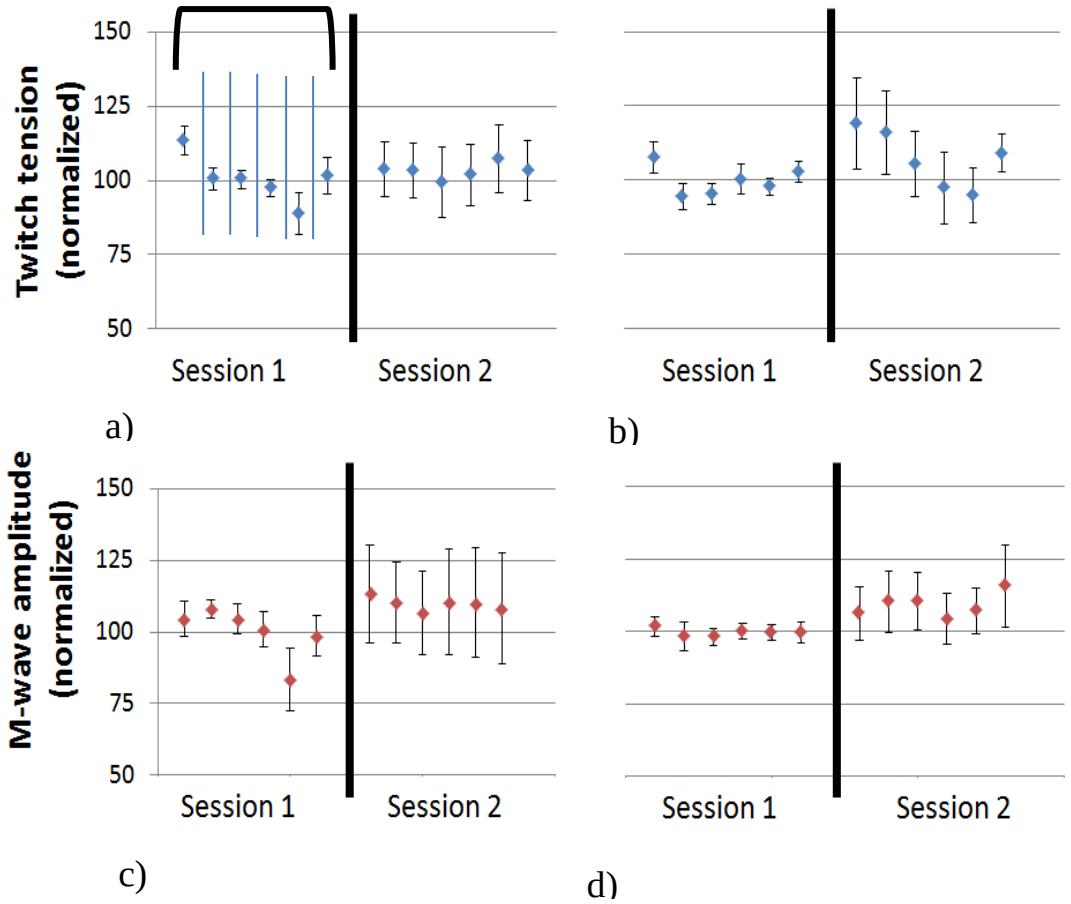

Figure 11 *Normalized twitch tension amplitudes (a, b) and corresponding peak to peak M-wave amplitudes (c, d) in the 1st (session 1) and 8th hour (session 2) of IES. Left panels (a, c) show subjects with SCI and right panels (b, d) show neurologically intact subjects. Each point is an average of 8 subject's data (standard error bars shown) collected every 10 minutes (blue lines represent 10 minute intervals). No significant differences were found "within" any of the individual sessions 6 twitch tension amplitudes or M-wave amplitudes at the 10 minute intervals (Kruskal-Wallis,* $p<0.05$*). Because there were no significant differences "within session" and time did not have an effect, data from each session were grouped. Similarly, no significant differences were found between grouped session 1 and grouped session 2 twitch tension or M-wave amplitudes (Mann-Whitney U test,* $p<0.05$*) in neurologically intact or subjects with SCI.*

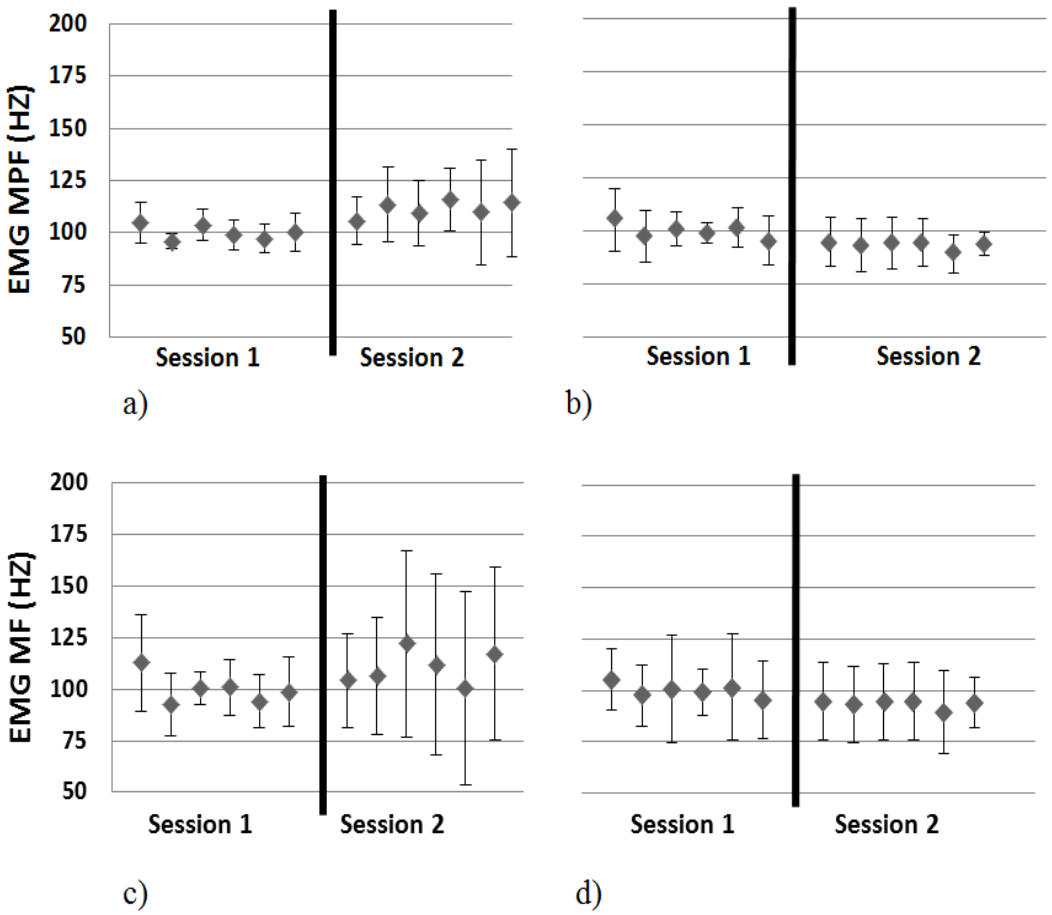

Figure 12 *Normalized EMG mean power frequency (MPF) (a, b) and EMG median frequency (MF) (c, d) in the 1st (session 1) and 8th hour (session 2) of IES. Left panels (a, c) show subjects with SCI and right panels (b, d) show neurologically intact subjects. Each point is an average of 8 subject's data (standard error bars shown) collected every 10 minutes (blue lines represent 10 minute intervals). No significant differences were found "within" any of the individual sessions 6 data points (Kruskal-Wallis,* $p<0.05$*). Because there were no significant differences "within session" and time did not have an effect, data from each session were grouped. Similarly, no significant differences were found between grouped session 1 and grouped session 2 MPF or MF (Mann-Whitney U test,* $p<0.05$*) in neurologically intact subjects or subjects with SCI.*

3.3 Discussion

We set out to investigate if surface electromyography (EMG) is a feasible technique for monitoring the strength of muscle contractions evoked by electrical stimulation of the gluteus maximus muscle. The rationale was that prevention of deep tissue injury (DTI) by way of IES, which induces pressure relief and tissue perfusion, is critically dependent on brief periods of fused muscle contractions. As an extension, we also investigated if the IES protocol (10 seconds of stimulation every 10 minutes) would induce muscle fatigue over 8 hours of stimulation.

Depolarization of the sarcolemma, whether voluntarily or electrically evoked, causes calcium ion release downstream within the muscle fiber and subsequently activation of actin-myosin cross bridge formation to produce force. EMG size should therefore reflect the degree of muscle activation (Disselhorst-Klug, Schmitz-Rode, & Rau, 2009). Indeed, EMG M-wave peak to peak amplitude correlated with force output better than area based parameters even under fatigue conditions (Mizrahi et al., 1997). In this study, we found that peak twitch tension and peak to peak M-wave amplitudes are linearly correlated, suggesting that EMG should be a good surrogate measure against which the extent of muscle activation can be gauged. EMG measurement has a distinct advantage over force in that miniaturized EMG amplifiers and recorders are readily available commercially and can be easily incorporated in IES system like Smart-e-Pants (Ahmetović et al., 2012). Our findings are in keeping with what has been reported in various muscles in both voluntarily (Lippold, 1952; Milner-Brown & Stein, 1975) and electrically evoked muscle contractions (Solomonow,

Baratta, Zhou, Shoji, & D'Ambrosia, 1987). Such correlation has not only been shown in human limb muscles (Woods & Bigland-Ritchie, 1983) but also in jaw muscles as well (Gonzalez et al., 2011). In the case of voluntary contraction, that linear relationship is thought to be the result of a square-root correlation between the EMG amplitude of the contributing motor units and the force (Milner-Brown & Stein, 1975).

Muscle fatigue is defined as a decrease in force-generating ability of a muscle resulting from recent activity (Binder-Macleod & Snyder-Mackler, 1993). It can occur anywhere along the central or peripheral nervous systems or inside the muscle fibers itself (Chan, 2002). Propagation of action potential in the peripheral nerves is relatively secure; it is the propagation of action potential along the muscle fiber that is more vulnerable and largely affected by trapping of potassium ions inside the confined space of transverse tubules. This leads to progressive depolarization and eventual depolarization block. Additionally, fatigue may occur independent of electrical propagation inside the excitation-contraction mechanism likely due to altered calcium dynamics during fatigue (Chan, 2002).

Muscle fatigue manifests itself in the myoelectric signal in its spectral and amplitude characteristics. Fatigue induced slowing of muscle fiber conduction velocity leads to a compression in the power spectrum manifested by changes in the mean and median frequency as well as the amplitude characteristics of the EMG signal (Merletti, Knaflitz, & De Luca, 1990). Both mean and median power frequency were found to be equally suitable for tracking spectral compression due

to localized muscle fatigue. Mean power frequency estimation has lower relative error while median power frequency is less sensitive to added white noise (Merletti, Knaflitz, & DeLuca, 1992). With respect of amplitude characteristics, peak-to-peak amplitude of the stimulus-evoked EMG (M-wave) was found to be a reliable indicator of muscle fatigue in isometric contractions (Mizrahi et al., 1994; Chen & Yu, 1997). M-wave peak to peak amplitude also had the highest correlation with isometric force under fatigued conditions compared to root-mean square and average rectified values (Mizrahi et al., 1997).

In this study, we did not find evidence of muscle fatigue; neither twitch tension amplitude, M-wave peak to peak amplitude nor mean or median power frequency showed significant changes following 8 hours of IES in neurologically intact subjects and subjects with SCI.

Theoretically, electrical stimulation evoked muscle contractions can lead to muscle fatigue more quickly than voluntarily evoked contractions (Binder-Macleod & Snyder-Mackler, 1993) due to the synchronous activation and inability to alternate motor unit recruitment and firing rates (Gregory & Bickel, 2005). However, in our paradigm, the 10s trains of stimulation at the lowest frequency (20Hz) necessary to obtain visibly fused muscle contractions were interspersed by a rest interval of 10 minutes. The rest period is likely sufficient to allow muscle recovery even in subjects with SCI who sustained the injury as long as 30 years earlier. Muscle fatigue can be minimized during electrical stimulation muscle strengthening by allowing 60s rest periods between 10s long contractions and by choosing the lowest frequency needed to obtain sufficient muscle

contractions (Binder-Macleod & Snyder-Mackler, 1993). Indeed, stimulation patterns commonly used to induce muscle fatigue are usually delivered repetitively on a much more frequent basis (Chou & Binder-Macleod, 2007; Badier, Guillot, Danger, Tagliarini, & Jammes, 1999).

A major technical obstacle in this study was recording EMG signals from a muscle that is simultaneously electrically stimulated through the motor point, a process that produces large stimulus artifacts in the EMG signal. Although this method of simultaneous stimulating and recording has been successfully demonstrated in large muscles like quadriceps (Chesler & Durfee, 1997; Hultman & Sjoholm, 1983) to our knowledge, this has not been done in the gluteus maximus muscle. Due to the shorter muscle length, it is difficult to physically separate the stimulating and recording electrodes. We managed to circumvent that problem by meticulous skin preparation to minimize skin impedance, placing the recording electrodes further away from the motor point while using a monopolar recording configuration with the reference electrode placed well away from the gluteal muscle.

The use of EMG feedback for functional electrical stimulation devices for predicting muscle force with surface stimulation has been investigated and demonstrated both in non-fatigued and fatigued muscle states (Chesler & Durfee, 1997; Erfanian, Chizeck, & Hashemi, 1998; Hayashibe, Zhang, Guiraud, & Fattal, 2011; Zhang et al., 2010). Results from our study confirm that EMG may be a useful technique for monitoring the strength of evoked gluteal muscle contractions in an adaptable IES system providing patient-specific personalized

treatment for prevention of DTI in gluteal muscles. These results will help in the design of a closed-loop stimulator for the prevention of DTI.

3.4 Conclusion

We have shown that peak twitch tension amplitude and corresponding M-wave peak to peak amplitude evoked at various stimulation intensities in the gluteus maximus muscle are linearly correlated, regardless of the atrophied or non-atrophied state of the muscle. This suggests that EMG may be a useful technique for monitoring evoked contractions in an adaptable IES system. We also demonstrated that IES does not cause muscle fatigue throughout 8 hours of muscle stimulation. This is an important finding suggesting that the strength of IES-induced muscle contractions does not diminish after many hours of stimulation. This should help to maintain tissue oxygenation and achieve the necessary pressure redistribution to prevent DTI, both in people with atrophied muscles, like those with spinal cord injury and in neurologically intact individuals such as some patients in the intensive care setting.

3.5 Acknowledgments

This work was funded by an Alberta-Innovates Health- Solutions Interdisciplinary Team Grant. Alisa Ahmetović held a TD Canada Group Grant for Interdisciplinary Research graduate scholarship and Vivian K. Mushahwar is an Alberta Heritage Foundation for Medical Research senior scholar.

Contributors and coauthors of this publication are Lisa Kawasaki, Liping Qi, Atif Khan, Vivian K. Mushahwar, K. Ming Chan. Liping Qi performed the spectral analysis of the EMG M-waves. Lisa Kawasaki and Atif Khan helped to run experiments. Thanks to Naomi Hui for the artwork in figures 1 and 2. Special thanks to Ephrem Takele Zewdie for the first ideas about an experiment to record M-waves on glutues maximus during IES stimulation and help in designing and running the proof-of-principle experiments.

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Chapter 4: General Discussion and Conclusions

4.1 Justifications

Deep tissue injury (DTI) is a serious type of pressure ulcer that starts in the deep muscle layers around bony prominences as a result of unrelieved pressure through a combination of direct mechanical and ischemia related insults. The overall goal of the project is to prevent DTI in at risk patient populations.

Traditional pressure relieving techniques have been inadequate as the prevalence of DTI is on the rise. In the Mushahwar lab, we have shown that periodic electrical stimulation causing brief contractions in muscles at risk may be able to combat the mechanisms leading to DTI. Indeed, animal and human studies confirmed that intermittent electrical stimulation (IES) has therapeutic benefits for prevention of DTI by inducing significant pressure relief and long lasting tissue perfusion. Moderate and maximal contractions were shown to have the same therapeutic effect that is independent of muscle bulk.

However, to be clinically useful, IES has to be administered to muscles at risk on a daily basis for extended period of time. To translate this to human use in different healthcare settings and patient populations, an IES system suitable for the buttocks where the majority of DTI occurs, has to be designed. Part of the goal of my thesis work was to assemble that by working alongside with biomedical engineers and to consult widely with patient groups, caregivers and healthcare workers. Since the therapeutic benefits of IES are critically dependent on muscle activation, means of monitoring that and to determine if muscle fatigue arises

following prolonged IES are of utmost importance. That was dealt with in the second part of my thesis.

4.2 Accomplishments

Based on those justifications, the goals of my master's thesis were to conduct a clinical implementation and testing of a non-adaptable IES system in different care settings and to investigate the feasibility of using electromyography feedback towards building an adaptable patient-specific, personalized IES system.

With respect to clinical testing, we found that the IES system was generally safe, feasible and acceptable in long-term care and rehabilitation hospital settings. Using the system placed minimal demands on the caregivers. It took approximately 15 minutes to use system regardless of the clinical setting, which should not add a significant burden to the nursing staff on top of their care routine. From a research standpoint, it was more challenging to implement the system in a large number of participants in long term care facility due to low resident turn-over, compromised skin integrity, cognitive capacity and high BMI. In contrast, this system was easily implemented on a large number of inpatients in rehabilitation hospitals due to generally younger, healthy population with a high turnover rate. The system was generally well accepted by the users and a large number of them continued using the system beyond the 4-week testing protocol because they found the system beneficial for pressure relief. A large number of sensate participants reported that the length of time they could sit was significantly increased on days when they were using IES system. Some users in

rehabilitation settings found the IES system somewhat cumbersome to use. Without the Smart-e-Pants garment, stimulator and cables got in the way, especially during rehabilitation sessions. Throughout the study, the Smart-e-Pants garment was streamlined based on user and caregiver feedback which improved the user ratings. One of the constraints of this clinical study was limited resources and manpower that would not allow us to implement the system on a continuous basis for the entire 4 weeks. Continuous implementation of the IES system for longer time period would have been preferable.

The therapeutic benefit of IES is a muscle contraction which leads to pressure redistribution and tissue perfusion. The first generation IES system which we used is not adaptable and does not have contraction monitoring capabilities. Even though most of the time visible muscle contractions were still present after 12 hours of use, we could not easily quantify if the IES caused muscle fatigue after prolonged use, particularly in subjects with spinal cord injury. Since fused muscle contraction is paramount for prevention of DTI, we set out to investigate the feasibility of a non-invasive technique, using electromyography as a surrogate measure for monitoring the strength of induced contractions in neurologically intact individuals and subjects with spinal cord injury. Neurologically intact patients may need EIS just as much as individuals with SCI, for example, during long surgeries and prolonged loss of consciousness (coma) among others. Patients in intensive care units are a good example of that.

We did not find evidence of muscle fatigue through 8 hours of IES in either group of subjects. Twitch tension and corresponding M-wave amplitude

didn't show significant changes between the 1st and 8th hours of stimulation. This is important suggesting that the stimulation parameters (low frequency and 10minute rest period) selected are sufficient to allow muscle recovery in being able to keep up the fused muscle contractions throughout the hours of stimulation. Furthermore, we found a linear relationship between twitch tensions and M-wave amplitudes in both groups of subjects suggesting that EMG should be a good surrogate for IES evoked force. Miniaturized EMG sensors are widely available and could theoretically be implemented in the Smart-e-Pants garment with relative ease. These results are an important step towards an adaptable and personalized Smart neuroprosthesis for prevention of DTI.

4.3 Future directions

Through my projects, I have demonstrated the potential usefulness of IES for prevention of DTI. We demonstrated the feasibility of the IES system in long term care and rehabilitation settings and have taken the first step towards developing an adaptable IES system. However, much more work is needed before this system is ready for commercial and widespread clinical use. The following is an outline of the current limitations and gaps in knowledge that should be addressed in future studies:

1) In isolated cases, placing electrodes on the skin of incontinent participants caused skin irritation from electrode edge rubbing over loose, fragile skin. This issue may be mitigated by decreasing electrode edge stickiness and protecting the loose skin from electrode edges. At present, the Smart-e-

Pants garment is not compatible with incontinent products. One potential solution is to design a disposable Smart-incontinent-product through which stimulation can be administered, even to those with fragile skin. Mr. Glen Isaacson has already created a few prototypes of the system and clinical testing has been initiated in a few subjects.

2) In addition to demonstrating the feasibility of using the IES system in long-term care and rehabilitation hospital settings, expansion to other care settings where the pressure ulcer risk is high and challenges are different, is equally important. These studies are critical for determining the versatility of the IES system in meeting the wide range of care setting and user demands. IES system testing has been initiated in Homecare and intensive care unit settings.

3) To progress from safety and feasibility study, it is essential to conduct a phase 2 clinical trial to evaluate IES system effectiveness for prevention of DTI. This study should be conducted in population of patients at high risk for developing a DTI in whom incidence rates are well established. Dr. Chester Ho is currently planning a small scale phase 2 clinical trial on out-patients with history of recurring pressure ulcers in Calgary, AB.

4) The non-adaptable stimulators used in this study are limited in that they are not capable of monitoring the strength of evoked contractions. The

next generation stimulators can be improved by incorporating non-invasive monitoring of evoked contraction.

To go even further, in the future we may be even able to non-invasively monitor the tissue oxygenation status and tissue viability. Surface pressure measurements can indicate regions of focused pressures and may be used to trigger pressure redistribution (i.e. muscle contraction) based on the amount and duration of sustained pressure. The next generation stimulator incorporating those parameters should be a worthwhile goal towards building a personalized, patient-specific IES system for prevention of DTI.

5) Beside prevention of DTI, IES may also be useful for treatment of DTI before the wound reaches skin surface. However, a major obstacle working towards that is at present a device for detecting DTI is not available. DTI is difficult to detect visually until the wound approaches the skin. Although magnetic resonance imaging is potentially able to detect DTI, it is not a practical solution for the bedside. Currently the feasibility of ultrasound techniques is being investigated in Ferguson-Pell and Moussa labs at the University of Alberta, Canada.