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EXERCISE BASED- PAIN RELIEF PROGRAM: IS THERE ANY EFFECT OF REPEATED BOUT OF ECCENTRIC EXERCISE FOR RELIEVING MUSCULOSKELETAL PAIN?

BY
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Exercise Based- Pain Relief Program: Is there any Effect of Repeated Bout of Eccentric Exercise for Relieving Musculoskeletal Pain?

PhD Dissertation

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Mahdi Hosseinzadeh was born in 1983 in Mahmoudabad, Iran. He studied physical education and sport science (BSc) at Shahid Rajaei University, Tehran, Iran. He gained his Master degree of exercise physiology in 2009 in Mazandaran University, Babolsar, Iran. In 2011 he initiated his PhD study at Aalborg University, Denmark. His main research interest is to investigate the effect of exercise training on pain sensitivity and the effect of musculoskeletal pain on exercise performance.

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Aalborg, April 2015

Mahdi Hosseinzadeh

Preface

The present studies were carried out at Center for Sensory-Motor Interaction (SMI), Aalborg University, Denmark, in the period from 2011 to 2014.

This dissertation is based on the following three peer-reviewed papers. In the text these are referred to as Study (I), Study (II), and Study (III) (full-length papers in Appendix).

Study (I): Hosseinzadeh M, Andersen OK, Arendt-Nielsen L, Madeleine P. **Pain sensitivity is normalized after a repeated bout of eccentric exercise.** *Eur J Appl Physiol., 2013; 113(10): 2595-602.*(Hosseinzadeh et al., 2013)

Study (II): Hosseinzadeh M, Andersen OK, Arendt-Nielsen L, Samani A, Kamavuako EN, Madeleine P. **Adaptation of local muscle blood flow and surface electromyography to repeated bouts of eccentric exercise**. *J Strength Cond Res. 2015;29(4):1017-26.* (Hosseinzadeh et al., 2014)

Study (III): Hosseinzadeh M, Samani A, Andersen OK, Arendt-Nielsen L, Nosaka K, Madeleine P. **Ipsilateral resistance exercise prevents exercise induced-central sensitization over the contralateral limb– a randomized control study**. *Submitted.*

Contents

Summary

Musculoskeletal pain is one of the most common causes of chronic pain. Exercise-based pain management programs have been suggested as an effective alternative for relieving from musculoskeletal pain; however the pain which is experienced after unaccustomed, especially eccentric exercise (ECC) can alter people´s ability or willingness to participate in therapeutic exercises or sports. Subsequent muscle pain and tenderness after ECC, most commonly known as delayed-onset muscle soreness (DOMS), has been shown to cause localized pressure pain, hyperalgesia and to decrease the muscle performance. A prior bout of ECC has been repeatedly reported to produce a protective adaptation known as repeated bout effect (RBE). There is no prior study, to our knowledge, investigating the effect of DOMS and RBE concomitantly on the sensitivity of the nociceptive system, blood supply, and functional capacity in healthy subjects. One of the main scopes of the current project was to investigate the adaptations by which the RBE can be resulted from. The approach in the current study was to use exercise induced- muscle damage followed by ECC exercise as an endogenous acute pain model and observe its effects on the sensitivity of the nociceptive system, blood supply, and functional capacity in healthy subjects. Then, the effect of a repeated bout of the same exercise as a healthy pain relief strategy on these parameters was assessed. This dissertation indicated that high intensity unaccustomed ECC can lead to central sensitization depicted by lower nociceptive withdrawal reflex threshold. Central sensitization induced by an initial ECC probably demonstrates a mechanism for the tenderness in the muscle and pain during movement. A lack of central sensitization is seen after the repeated bouts of ECC irrespective if the initial bout of ECC involved the ipsi- or the contralateral limb. The protective effects regarding RBE to the contralateral limb are specific to the contralateral homologous innervation level. Muscle oxygen re-perfusion can be improved after a single bout of high intensity damaging ECC; however it does not play a major role in cross-transfer adaptations due to repeated bouts of ECC.

Dansk resumé (summary in Danish)

Muskuloskeletale smerter er en af de mest almindelige årsager til kroniske smerter. Trænings-baserede programmer er blevet foreslået som et effektivt alternativ til at lindre smerter i bevægeapparatet. Smerten som typisk opleves efter uvant, især excentrisk arbejde (ECC), kan påvirke folks evne eller vilje til at deltage i terapeutiske programmer. Det er tidligere vist at muskelsmerter og ømhed efter ECC, mest almindeligt kendt som forsinket indsættende muskelømhed (DOMS), medfører lokal tryksmerte hyperalgesi og reducerer den muskulære ydeevne. En forudgående ECC træning kan virke beskyttende for udtrætningen af musklen hvilket kaldes " repeated bout effect" (RBE). Man har ikke tidligere undersøgt effekten af både DOMS og RBE på følsomheden af det nociceptive system, blodforsyning, og muskel funktionsevne hos raske forsøgspersoner. Et af hovedmålene i dette projekt var at undersøge hvilke adaptationer der kan forårsage RBE. I dette projekt er DOMS efterfulgt af ECC træning, brugt som en endogen akut smerte model og for efterfølgende at kunne observere virkningerne på følsomheden af det nociceptive system, blodforsyning, og funktionsevne hos raske forsøgspersoner. Endelig blev virkningen af gentagne gange af samme øvelse som en sund smertelindringsstrategi på disse parametre vurderet. Denne afhandling viste, at uvant ECC med høj intensitet kan føre til en central sensibilisering gengivet ved en lavere tærskel for den nociceptive tilbagetrækningsrefleks. Central sensibilisering induceret af en indledende ECC viser sandsynligvis en mekanisme på ømhed i muskler og smerter under bevægelse. En mangel på central sensibilisering ses efter gentagne gange af ECC uanset om den oprindelige ECC involverede den ipsi- eller kontralaterale side. De beskyttende virkninger vedrørende RBE til den kontralaterale side er specifikke for det kontralaterale homologe innervations niveau. Muskel oxygen re-perfusion kan forbedres efter en enkelt gang af høj intens beskadigende ECC; men det spiller ikke nogen stor rolle i cross-transfer adaptationerne på grund af gentagne gange af ECC.

List of Abbreviations

ANOVA	: Analysis of variance
DOMS	: Delayed onset muscle soreness
EIMD	: Exercise induced muscle damage
ECC	: High intensity eccentric exercise
EMG	: Electromyography
MDF	: Median power frequency
MVC	: Maximal voluntary contraction
NWRT	: Nociceptive withdrawal reflex threshold
PPT	: Pressure pain threshold
IPSI	: Ipsilateral group
CONTRA	: Contralateral group
RMS	: Root mean square
SD	: Standard deviation
VAS	: Visual analogue scale

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1 Introduction

This section presents a brief overview of the background and scope of the present project.

1.1 Musculoskeletal pain & pain management protocols

Musculoskeletal pain is the most common cause of pain among young people (Sjogren et al., 2009). It is difficult to treat this type of pain as our knowledge about the neuronal mechanisms mediating and modulating musculoskeletal pain is limited. Alternative approaches for pain treatment are appealing. Exercise-based pain management program is suggested as an effective alternative program for relieving musculoskeletal pain (Marinko et al., 2011) and many other chronic conditions such as metabolic syndrome-related disorders, and heart and pulmonary diseases (Pedersen and Saltin, 2006). For instance, structured exercise induces pain alleviation and improves functional capacity; e.g. it decreases the pain intensity and pressure pain sensitivity in patients suffering from musculoskeletal disorders (Marinko et al., 2011,Ludewig and Borstad, 2003). Pain management protocols typically include long-term periods of aerobic exercise training or a combination of both aerobic and strength training (Imamura et al., 2009). Single session of resistance exercise alone (O'Connor et al., 2011) has also been suggested to provide pain relief and is especially applicable for people unable to engage in high-intensity or long-term aerobic exercise programs (Marinko et al., 2011,Ludewig and Borstad, 2003,O'Connor et al., 2011,Di Monaco et al., 2009). Eccentric exercise (ECC) and stretching have been studied as training regimens for relieving of chronic tendinopathy (Norregaard et al., 2007). However, the pain associated with unaccustomed, especially eccentric exercise often decreases the ability or willingness to participate in physical activity or therapeutic exercise (Dannecker et al., 2005,van Santen et al., 2002,Dannecker and Koltyn, 2014).

1.2 Delayed-onset muscle soreness

Subsequent muscle pain and tenderness after exercise training, consisting of an ECC component, is called commonly delayed-onset muscle soreness (DOMS) (Dannecker and Koltyn, 2014). This kind of exercise induced muscle damage

(EIMD) peaks at about 24–48 h (MacIntyre et al., 2001), and starts to be vanished 5 to 7 days after exercise (MacIntyre et al., 2001,Gulick and Kimura, 1996). EIMD is reported to cause localized pressure pain hyperalgesia (Binderup et al., 2010,Hedayatpour et al., 2008) and to reduce the muscle performance. Hyperalgesia is defined as increased pain from a stimulus that normally provokes pain; it reflects increased pain on suprathreshold stimulation. Current evidence suggests that hyperalgesia is a consequence of perturbation of the nociceptive system with peripheral and/or central sensitization. Hyperalgesia is observed after somatosensory stimulations like electrical stimulation applied to biological tissues as well (Merskey and Bogduk, 2004,Cervero and Laird, 1996).

High intensity ECC can also lead to ultra-structural changes, t-tubules damages, mitochondrial swelling, and intramuscular pressure enhancement (Friden et al., 1983,Friden and Lieber, 2001,Crameri et al., 2007). An increase in intramuscular pressure, vasodilation and changes in water content of the muscle immediately following ECC may change the pattern of local muscle blood flow and thereby muscle oxygenation. The effect of ECC on muscle oxygenation however, is not fully understood and contradictory results have been reported in the few studies available in the literature. Ahmadi et al. (2008) reported a significant increase in muscle oxygenation rate for up to four days following an exhaustive session of downhill walking (Ahmadi et al., 2008). In contrast, no significant change in oxygen utilization was observed after a 30 min session of high intensity ECC (Walsh et al., 2001). Similarly, oxygen uptake did not changed after an exhaustive ECC, despite a significant increase in muscle blood flow (Laaksonen et al., 2006). Although, the deleterious effects of EIMD are well documented (Byrnes and Clarkson, 1986,Saxton and Donnelly, 1995,Francis, 1983), yet there is no standard treatment or prophylaxis for the condition. Active or passive modalities for preventing or reducing EIMD have been investigated (Eston and Peters, 1999,Howatson et al., 2005,Zainuddin et al., 2005,Howatson et al., 2007). A prior bout of ECC however, has been repeatedly reported to produce a protective adaptation known as repeated bout effect.

1.3 Repeated bout effect

Although an unaccustomed bout of ECC can lead to EIMD, a repeated bout of the same or similar ECC performed as early as one-two days and up to six months after the first bout leads to lower muscle damage and faster recovery of the muscle strength and soreness. This phenomenon was introduced as repeated bout effect (RBE) (McHugh, 2003,Barss et al., 2014). Both peripheral (connective tissue and cellular) and central (neural) adaptation has been attributed to the adaptation seen by RBE (McHugh et al., 1999), however there is little consensus as to the actual mechanism. Peripheral adaptation theory states that remodeling of the intermediate filaments and an increase in the number of sarcomeres connected in series decreases the amount of stress on sarcomeres during the exercise and confines the subsequent EIMD. Central (neural) adaptation theory however, states that an enhancement in the number of motor unit activation or a shift from fast to slow-twitch fiber activation distributes the contractile stress over a larger number of active fibers and therefore leads to the RBE (McHugh et al., 1999).

It is expected that alterations in muscle fiber recruitment in presence of EIMD can change the pattern of muscle oxygenation. An impairment of fast twitch glycolytic fibers after the initial bout of ECC (Lieber and Friden, 1988) can result to recruitment of fewer fast twitch type II fibers compensated by additional slow twitch type I fibers. Type I fibers have a developed potential for oxidative capacity which may lead to an improvement of muscle oxygenation (Chen, 2003). A lower electromyographic (EMG) median power frequency (MDF) with a minimal EMG root-mean-square (RMS) alteration have been reported during a second bout of ECC, indicating greater reliance on type I motor unites (Warren et al., 2000). Muthalib et al. (2011) however, reported that EMG amplitude and muscle oxygenation during eccentric exercise are not different between two consecutive bouts of ECC (Muthalib et al., 2011). On the contrary, Wakefieldl et al. (2011) reported that enhanced nociceptive input from the trapezius muscle elevates habitual trapezius activity in the homonymous EIMD-suffering region of the muscle (Wakefieldl et al., 2011). Mc Hugh (2003) also reported that a neural adaptation is most likely demonstrated after a first bout of ECC. This adaptation is reflected in the

surface EMG by an increase in amplitude or a decrease in frequency contents after the first bout of ECC (Madeleine et al., 2011,McHugh, 2003,Chen, 2003,Warren et al., 2000,Nosaka et al., 2001). The controversy related to muscle oxygenation and EMG activity, predominantly regarding the RBE shows the need for performing more studies. Moreover, the relationship between RBE and muscle pain/soreness has not been fully understood yet as well. General increased pain sensitivity has been reported after the first bout of ECC in the presence of EIMD. A consecutive bout of ECC however, did not lead to EIMD and had no impact on the pain sensitivity (Kawczynski et al., 2012). There is some evidence suggesting central sensitization after the EIMD followed by unaccustomed ECC (Slater et al., 2005,Nie et al., 2006).

1.4 Central sensitization

Central sensitization, defined as an enhanced alertness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input, is regarded as a short-term, reversible defense mechanism. Central sensitization contributes to sustaining the integrity of the organism by generating pain hypersensitivity, and, in this way, protecting the organism from additional damage (Latremoliere and Woolf, 2010). It is well-known that localized musculoskeletal conditions such as tendinopathy (Fernandez-Carnero et al., 2009) or knee osteoarthrosis (Arendt-Nielsen et al., 2010) may cause localized and generalized hyperalgesia (central sensitization). An involvement of central sensitization has been suggested by assessing pressure pain threshold after a first bout of ECC and therefore manifestation of a remarkable plasticity of the somatosensory nervous system demonstrating by RBE (Kawczynski et al., 2012). However, to the best of knowledge there is no prior study investigating features of central sensitization related to perform repeated bouts of ECC.

1.5 Nociceptive withdrawal reflex threshold

The nociceptive withdrawal reflex threshold (NWRT) is reported as a reliable electrophysiological outcome for central sensitization (Banic et al., 2004). NWR is a usual defense response in order to withdraw the extremities from possible harmful stimuli. The spinal reflex to nociceptive stimuli is used to evaluate the effect of different interventions and investigate basic pain mechanisms related to central

sensitization in humans (Andersen, 2007). In this dissertation NWRT is used as an objective outcome assessing the possible central adaptation caused by performing the repeated bouts of ECC.

1.6 Muscle oxygenation and RBE

Muthalib et al. (2011) have described that the RBE can be demonstrated as a faster recovery of biceps brachii oxygenation and activation toward baseline levels. Near-infrared spectroscopy (NIRS) has been used in their study in order to investigate local changes in muscle oxygenation and hemodynamics. Using multiple wavelengths and non-invasively, NIRS provides the information concerning to muscle oxygenation. Compared to a number of studies demonstrating the RBE on isolated eccentric contraction of elbow flexors (Muthalib et al., 2011) and knee extensors (Behrens et al., 2012), no study has been performed on tibialis anterior (TA) muscle. Furthermore, the effect of severe EIMD on nociceptive pain characteristics in TA muscles during voluntary contraction has not been investigated yet. Further studies are necessary to explain the effect of severe DOMS on neuromuscular performance. Furthermore, it would be reasonably worthy to investigate the effect of an exercise based pain relieving intervention followed by EIMD on EMG activity, nociceptive pain measurements, and muscle oxygenation concomitantly as with our knowledge, there is no study performed in this background.

1.7 Cross-transfer

Cross-transfer of adaptation to training is referring to the performance enhancement of an inactive contralateral homologous muscles group following physical exercise from the same group of muscles on the ipsilateral side (Hortobagyi et al., 1997,Shima et al., 2002). Cross-transfer, i.e., contralateral adaptations to skeletal muscle exercises is suggested also to occur following eccentric exercise (Hortobagyi et al., 1997). The real mechanism of cross transfer is not known yet. However, the enhancement of strength on the contralateral limb in the absence of direct training stimulus and without parallel adaptive changes in muscle anthropometric features confirms a neurally rather than peripherally mediated mechanism contributing to the cross-transfer (Munn et al., 2004). However, other localized but non-muscular

adaptations such as blood flow augmentation have also been observed in the contralateral untrained limb after several weeks of strength training (Yasuda and Miyamura, 1983). Therefore unknown neural mechanisms and blood flow augmentation on the contralateral limb have been suggested as the potential mechanisms behind the contralateral limb training effect (Yasuda and Miyamura, 1983). Less attention though has been given to the protective effect of a single high intensity bout of eccentric exercise carried out on the contralateral limb and contradictory results have been reported (Connolly et al., 2002,Ferreira et al., 2012,Howatson and Van Someren, 2007,Starbuck and Eston, 2012). Connolly et al. (2002) have investigated a contralateral repeated bout effect following a single bout of maximal eccentric exercise of the quadriceps group muscles (Connolly et al., 2002). The authors have observed neither protective nor cross-transfer effects. They concluded therefore that the RBE could be essentially related to a localized response rather than a neural mechanism. For example, the authors have suggested that the connective tissue theory and the cellular theory may be involved in occurrence of RBE. Connolly et al. (2002) have further argued that the significant pain reduction after the second bout of ECC was the result of habituation to pain from the initial bout (Connolly et al., 2002). Contrary to that, a reduction of creatine kinase, DOMS, and decrement in strength have been found after a repeated bout of ECC on the contralateral elbow flexors (Ferreira et al., 2012,Howatson and Van Someren, 2007). More recently, Starbuck and Eston (2012) investigated surface electromyography (EMG) during two bouts of ECC in both ipsilateral and contralateral limbs (Starbuck and Eston, 2012). They have reported a decreased median frequency between bouts with no difference between limbs, and therefore suggested that a bout of ipsilateral ECC provides protection against development of DOMS to the contralateral limb (elbow flexors).

All the aforementioned studies except for Connolly et al. (2002) support that the protective effect of initial bout of ECC is cross-transferred to the contralateral limb (Ferreira et al., 2012,Howatson and Van Someren, 2007,Starbuck and Eston, 2012). Therefore the authors have proposed neural adaptation manifested in the observed changes in the contralateral limb following the initial bout in the ipsilateral limb as

the most likely mechanism for this cross transfer (Howatson and Van Someren, 2007). Since the exact nature of the neural adaptation related to RBE even in the ipsilateral limb is still unknown (McHugh et al., 1999), consideration of the mechanisms underpinning the contralateral RBE can be restricted to identifying sites of cross-limb neural interaction that can contribute to the contralateral training effect. Increase in the efficacy of spinal and cortical motor pathways to the contractile limb has been suggested as one of the plausible explanations for this cross-transfer effect (Carroll et al., 2006,Lee and Carroll, 2007). Both active and passive contralateral movements could depress the gain of the H-reflex in the upper and lower limbs (Carson et al., 2004,McIllroy et al., 1992), which can be indicative of the role of afferent inputs in this modulation. In cats, interneurons that receive ascending and descending inputs cross the midline to excite or inhibit contralateral motoneurons (Jankowska et al., 2005a,Jankowska et al., 2005b). A similar synaptic organization pattern has been reported after stimulation of the contralateral afferent leading to reflex conditioning in humans (Delwaide and Pepin, 1991). It seems therefore likely that this type of interneurons can contribute to crossed effects in humans as well. Although there are extensive cross-limb spinal interactions during ipsilateral contraction, specific experiments that directly compare the changes in threshold and gain of specific neural circuits were suggested to delineate possible mechanisms underlying cross transfer (Carroll et al., 2006). Moreover, considering the multiple plausible sites of adaptation for cross transfer such as spinal or supra-spinal pathways, and that the gain in contralateral strength is typically small, sensitive physiological measures are needed to establish the underpinning mechanisms of this phenomenon. To the best of our knowledge there is no study investigating cross-transfer effects related to RBE which include assessment of sensitivity of the nociceptive system, blood supply, and functional capacity in healthy subjects. The main objective of this project was to investigate cross-transfer effects related to RBE by assessing these outcome measures.

1.8 Aims of the Ph.D. project

The overall aim of this Ph.D. project was to investigate the effect of an initial unaccustomed-, and then a repeated- bout of the same ECC on sensitivity of the

nociceptive system, blood supply, and functional capacity in healthy subjects. The approach in this study was to use pain followed by the initial ECC as an acute pain model and then administration of a repeated bout of the same ECC as a healthy pain relief strategy on sensitivity of the nociceptive system, blood supply, and functional capacity. We therefore aimed to provide new insights into the mechanisms of RBE.

The specific aims of this Ph.D. project were:

1. to investigate the effects of two bouts of high intensity ECC exercise on the sensitivity in the spinal nociceptive system and deep structure sensitivity to pressure pain.
2. to investigate whether local muscle blood flow, EMG MDF, and EMG RMS change after a bout of high intensity eccentric exercise within the tibialis anterior (TA) muscle.
3. to investigate cross-transfer effects related to RBE by assessing changes in sensitivity in the spinal nociceptive system, deep structure sensitivity to pressure pain and local muscle oxygenation.

The flow of this dissertation is illustrated in *Figure 1*.

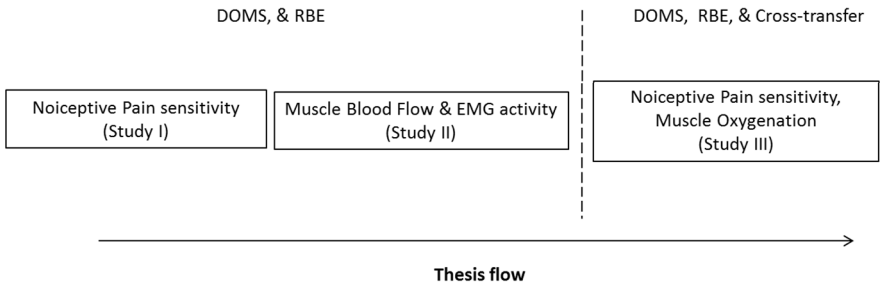

Figure 1: Overview of the performed studies.

2 Methods

2.1 Subjects

A total number of 42 healthy male volunteers participated in the three studies. Table 1 shows mean (SD) of the baseline characteristics of the subjects of these studies. The subjects for study I & II were the same. All the subjects were untrained and maintained their normal daily activity during the course of the study. They were

restrained from performing any kind of high intensity exercise during the period of recordings. None of the subjects had participated in strength training for the last six months prior to the studies. Subjects were demanded not to take any anti-inflammatory medication during the study period. The subjects were vocally informed about the procedures of the studies. All the subjects read and signed an informed consent form before participation. The studies were approved by the local ethical committee (approval no. N-20070019 and N-20130029) and conducted in accordance with the Declaration of Helsinki. In order to fulfil the overall and specific aims of this dissertation both the subjective and objective methods had been used. An overview of the methods used in the studies is summarized in table 2 and described in more detail below.

Table 1: Characteristics of the subjects in study (I & II) and (III).

	study	
	(I & II)	(III)
Number of subjects	16	26 (13+13)
Age (years)	25.7(0.6)	A:27.23(5.40) B:26.92(4.27)
Body mass (kg)	79.9(3.3)	A:75.07(7.56) B:77.46(11.78)
Height (cm)	179.2(1.7)	A:177.38(5.78) B:175.54(5.75)
Body mass index (kg/m^2)	24.8(1.0)	A:23.86(2.28) B:25.11(3.38)

26 subjects participating in study (III) were assigned in two groups of contralateral (A) and ipsilateral (B).

Table 2: *Overview of the methods used in study (I & II) and (III).*

	Study		
	(I)	(II)	(III)
Electrical stimulation	X	-	X
Reflex detection	X	-	X
Pressure algometry	X	-	X
EMG recordings	X	X	X
EMG MDF & RMS	-	X	-
Eccentric shoulder exercises	X	X	X
Force recording	X	X	X
Muscle soreness	X	X	X
TA muscle blood flow	-	X	X
TA muscle oxygenation	-	-	X

2.2 Exhausting isokinetic eccentric exercise

The high intensity ECC exercise in this PhD project was performed by a Kin-Com isokinetic dynamometer (KINETIC COMMUNICATOR 125 AP, Software Version 4.03, Chattecx Corp., Chattanooga, TN, 37405, USA) with a plantar/dorsi attachment (PN. 54708). The participants performed 6 repetitions per set, with 20 seconds of rest in between the sets. The intensity of the ECC was set as 80% of the MVC force of the subjects. The subjects performed the ECC as many sets as required to achieve a condition where they were not able to keep a sufficient ECC ankle DF. The sufficient ECC ankle DF was defined as 80% of subjects' isometric MVC force measured before ECC1 in study I & II, and before ECCs in study III. The participants were provided with visual feedback of the force during the ECCs and were verbally encouraged by the experimenter to keep their maximal force.

2.3 Isometric maximum voluntary contractions

Subjects completed six repetitions of maximum isometric dorsi-flexion (DF) (100% MVC). The six repetitions of the MVC lasting five seconds each were accomplished with 60 seconds of rest in between the repetitions. The average of the six repetitions was reported as the isometric MVC force of the subjects.

2.4 Soreness intensity and soreness area

In all studies the level of soreness was assessed using a 10-cm visual analogue scale, where 0 indicated “no soreness” and 10 indicated “maximal soreness”.

2.5 Local muscle oxygenation evaluation by near-infrared spectroscopy

Local tissue oxygenation was monitored concurrently with the isometric MVC using a continuous wave NIRS system (Oxymon MK III Artinis Medical Systems BV, Netherlands).

2.5.1 TA muscle blood flow

In study II, three transmitter- and three receiver- optodes were arranged in pairs to form seven channels (see *Figure 2*). Channels were subdivided to medial, lateral, proximal and distal part for further statistical analysis (see *Figure 2* for the right placement of the channels). NIRS optodes were secure over the mid-belly of the TA muscle with a stretch tape (*Figure 2*).

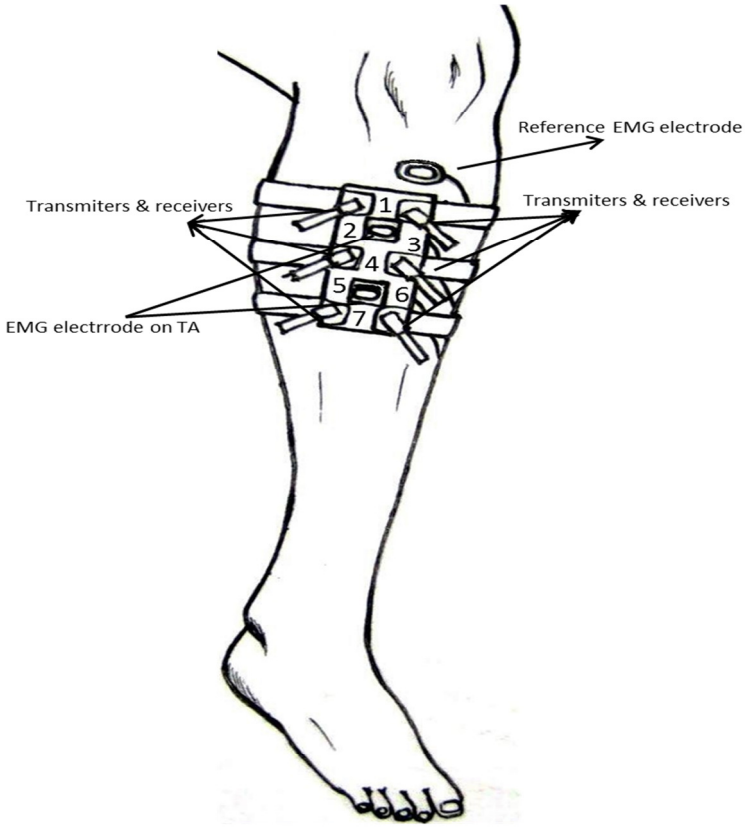

Figure 2: Alignment of NIRS channels; the EMG electrode were placed in between the NIRS channels on the belly of the tibialis anterior (TA) muscle. The numbers shows the exact placement of the NIRS channels 1-7. This FIGURE was adopted and modified from study II.

2.5.2 TA muscle oxygenation

For local TA muscle oxygenation at study III the NIRS probe setup consisted of one receiver and three transmitters. The absolute concentration of O2Hb and HHb in the underlying tissue ([O2Hb] and [HHb]) was obtained by the application of a spatially resolved spectroscopy method (Patterson et al., 1989). The concentrations were calculated from the attenuation slope of NIRS beam along the distance from the three transmitter optodes to the receiving one (Patterson et al., 1989). Subsequently,

the tissue saturation index TSI (%) was calculated as the ratio of [O2Hb] and the summation of [O2Hb] and [HHb]. The quality of the measured concentrations was continuously monitored in terms of a Quality Control Factor (QCF) ranging from zero (extreme bad quality) to one (good quality). The QCF quantifies how well the attenuation slope of NIRS beam fits a linear function of the inter-optode distance. The linear relationship between the attenuation slope of NIRS beam and the inter-optode distance constitutes the theoretical foundation of the applied method. Typically, following each bout of isometric muscle contraction with an intensity of above 50%, the [O2Hb] and [HHb] gradually drops and increases, respectively. Conversely, as the muscle relaxes, [O2Hb] and [HHb] gradually start to increase and decrease again, respectively (Ferrari et al., 2004). As the bouts of MVC contractions were performed on regular basis the onset and offset of the contraction could be specified on the time line of [O2Hb] and [HHb] signals. For each bout of MVC contractions, a time window of the concentrations signals were selected to compute indices (explained below) associated with the local oxidative capacity. The time window started five second before the onset of the MVC contraction and finished 60 second after the contraction offset. The peak/trough point of the concentration signals was determined and the concentration signals were divided into a descending and an ascending part. The descending leg of the window was fitted to a trapezoidal shape function starting with a steady level followed by a linear decay. A non-linear least square routine was applied to derive an optimal level and slope of decay for the trapezoidal function (Seber and Wild, 2003). A similar procedure was performed to derive the level and slope of increase in the ascending leg of the concentration signals. The quality of the fitting was checked by computing the cross-correlation coefficient (CC) between fitted trapezoidal function and the experimental values and if the CC was below 0.9 that window of concentration signals was removed from the rest of the analysis. The difference between the steady level and the trough/peak of the concentration signals (drop/jump) of the descending and ascending leg of trapezoidal function were calculated for each window on [O2Hb], [HHb] and TSI. So that TSIdrop was defined as the value of the drop in the TSI (the amount of oxygen usage), TSIjump was defined as the value of the recovery in the TSI (the

amount of recovery) respectively. The difference between TSI drop and jump (TSIdrop-TSIjump) was also calculated to have an index of oxygen deficiency after the isometric MVC (Hilgert Elcadi, 2012). This procedure was repeated for each of the 6 repetitions of MVC in each of the instants of the study (an average of 6 MVC repetitions was calculated as the grand TSI value for each instant).

2.6 Surface electromyography

Surface EMG was recorded using a bipolar surface electrode configuration (Ambu A/S, Neuroline, 72001k, Ballerup, Denmark). The electrodes were located on the TA muscle belly along the direction of the muscle fibers (inter-electrodes distance: 2 cm). Since, the level of activity in proximal and distal muscle portion of TA was similar only a single EMG channel was collected (Crenshaw et al., 2010). The reference electrode was positioned on the head of the tibia bone. See studies I, II, and III for more detailed information.

2.7 Electrical stimulation

In study I and III a surface electrode located on the arch of the foot was used for electrical stimulation to elicit the NWR. One large common anode was located on the dorsum of the foot. Each stimulus contained a constant current pulse train of five individual 1-ms pulses delivered at 200 Hz by a computer controlled electrical stimulator (Noxitest IES 230, Aalborg, Denmark). The stimulation was applied with an inter-stimulus interval of approximately 10-15 s. See studies I, and III for more detailed information.

2.8 Reflex detection

2.8.1 Manually

The criterion used to calculate the NWRT in study II was if at least one significant different peak occurred in the 60–200 ms post-stimulation interval of the signals recorded from the TA muscle. The current intensity was increased by steps of 1-mA increments until an NWR was identified and then the intensity was decreased at the same increments until the reflex was not detected any more. The procedure was repeated three times and the average of the six points (3 peaks and 3 troughs) was used for NWRT estimation. The ascending/descending staircase method was applied by experimenter (MH). See study I for more detailed information.

2.8.2 Automatically

In study III finding at least one significant different peak with an interval peak z-score larger than 12 in the 60–200 ms post-stimulation interval was used for identifying the NWR (Rhudy and France, 2007). The entire NWRT estimation procedure was done automatically by custom made software (Mr Kick III preview version 2.9, Aalborg University, Denmark). See study III for more detailed information.

2.9 Deep structure sensitivity to pressure pain

Pressure pain threshold (PPT) recordings were performed in study I & III to investigate deep structure pain sensitivity. PPTs were assessed at five sites on the TA muscle with the participants in supine position. Five sites (PPT1-5) were equally interspaced between the distal and proximal musculotendinous junction of the TA muscle. In study III one more site, far from TA muscle, on the belly of the biceps brachii muscle was also measured as a reference/control site. The PPTs were measured using an electronic hand-held pressure algometer (Somedic Algometer type 2, Sweden). The mean value of the three recordings was used as the PPT value in the later statistical analysis. A grand average determined as a mean value of the PPT values on five sites was measured. Pain sensitivity maps of the TA muscle were made using the averaged PPT values over the 5 sites. The interpolation was accomplished using an inverse distance weighted interpolation to obtain an easy reading of the PPT distribution (Binderup et al., 2010). See studies I, and III for more detailed information.

3 Statistical analysis

The normality of the entire dataset was checked and confirmed by Shapiro-Wilk tests. A linear mixed model analysis of variance with factors of instant (pre-ECC, post-ECC, and 24 hr after ECCs and rests) and sessions (ECC1, ECC2, Rest1, Rest2) was performed for the dependent variables included NWRT, PPTs, MVC, and ROM in study I, and mean RMS, mean MDF, [ΔtHb], pain/soreness scores, and pain area in study II. A linear regression (Pearson correlation coefficient) was used to test the correlation between grand [ΔtHb] and MVC force or mean RMS or mean

MDF. In study III changes in average dependent variables, NWRT, PPTs, muscle soreness scores, MVC force, and muscle oxygenation outcomes were compared using a general linear model (GLM). Instants (pre vs. post vs. 24 hr after), and bouts (ECC1 vs. ECC2) were introduced as within-subject factors of the GLM. A between-subject factor of groups (REF vs. CONTRA) was also added. Bonferroni correction for multiple comparisons was used for post hoc test in all the studies. An independent samples t-test was used for comparison of the baseline characteristics of the subjects in the two groups. In all tests $p< 0.05$ was considered as statistically significant. The mean (SD) are reported.

4 Results and Discussions

All the subjects participating at studies I-III completed their own specific training procedures. In average, 57(5) sets of ECC in study I and II, and 43(21) sets of ECC in study III, mean (SD), were completed across all the subjects.

4.1 The effect of two bouts of high intensity ECC on muscle strength and soreness in ipsi- and contra-lateral TA

The overall aim of this PhD project was to use pain followed by the initial ECC as an acute pain model and then to investigate the effect of administration of a repeated bout of the same ECC as a healthy pain relief strategy on the specific subjective and objective outcome measures of this project. Principally, the specific procedure of the high intensity ECC used in this project was able to induce soreness to TA (*Figure 3* and *Figure 4*). A 40% decline in muscle strength is regarded as one of the most valid and reliable indicators of muscle damage in humans (Warren et al., 1999). The specific design of high intensity ECC of the current project resulted to 75 % decline in isometric MVC force in study I & II (*Figure 5*), and 70 % decline in isometric MVC force in study III (*Figure 6*). This specific ECC protocol was designed based on the 80% of the MVC force of the each single subject of the studies. Therefore the number of the sets of the ECC was different between the subjects; however it was reported that such an ECC protocol will result to the similar amounts of muscle soreness and reduction in range of motion for several days following the exercise (Prasartwuth et al., 2005). Another kind of design of ECC is to set a similar number

of ECC contractions for all the subjects. However, it has been reported that performing a similar number of ECC contractions will result to a huge differences in muscle strength deficits in between the subjects after ECC exercise (Hubal et al., 2007). Therefore, it is likely that different amount of EIMD in between the subjects could be an important limitation across studies in the area of DOMS and RBE. This limitation can be diminished using a protocol similar to the present study.

Unlike ECC1, performing the repeated bout of ECC2 resulted to an attenuated decline in isometric MVC force (*Figure 5* & *Figure 6*) and subsequently attenuated amounts of muscle soreness both post and 24 hr after ECC2. This attenuated responses of the MVC force and muscle soreness was irrespective if the first bout of ECC was performed on the ipsi- or the contra- lateral TA (*Figure 4* & *Figure 6*). The pain distribution report before and after both bouts of ECCs can be also addressed as evidence for attainment of TA muscle damage and soreness after ECC1 and then attenuation of the sourness due to RBE after ECC2 (*Figure 3*). A theoretical model of the relationship between muscle soreness and central motor drive was proposed by Mastaglia (2012). Under certain circumstances the soreness and tenderness during contractions due to EIMD reduces the motor drive to the active muscles and thereby reduces the level of force production and the ability to sustain it (Mastaglia, 2012). The significant decrease of the MVC force 24 hr after ECC1 in the existence of significant muscle soreness and moreover no soreness at 24 hr after ECC2 confirms this theory (see *Figure 3*, *Figure 4*, *Figure 5*, *Figure 6*).

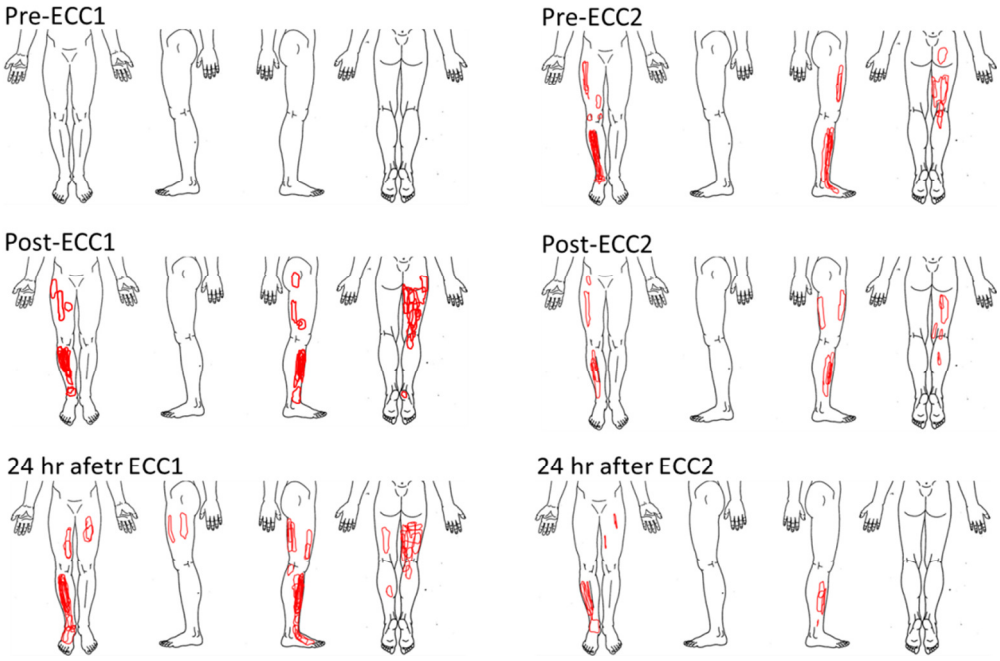

Figure 3: Distribution of soreness area reported before (Pre-), after (Post-), and 24 hr after the first (ECC1) and the second (ECC2) bouts of ECC exercise of the TA muscle. The figure is adopted and modified from Study II.

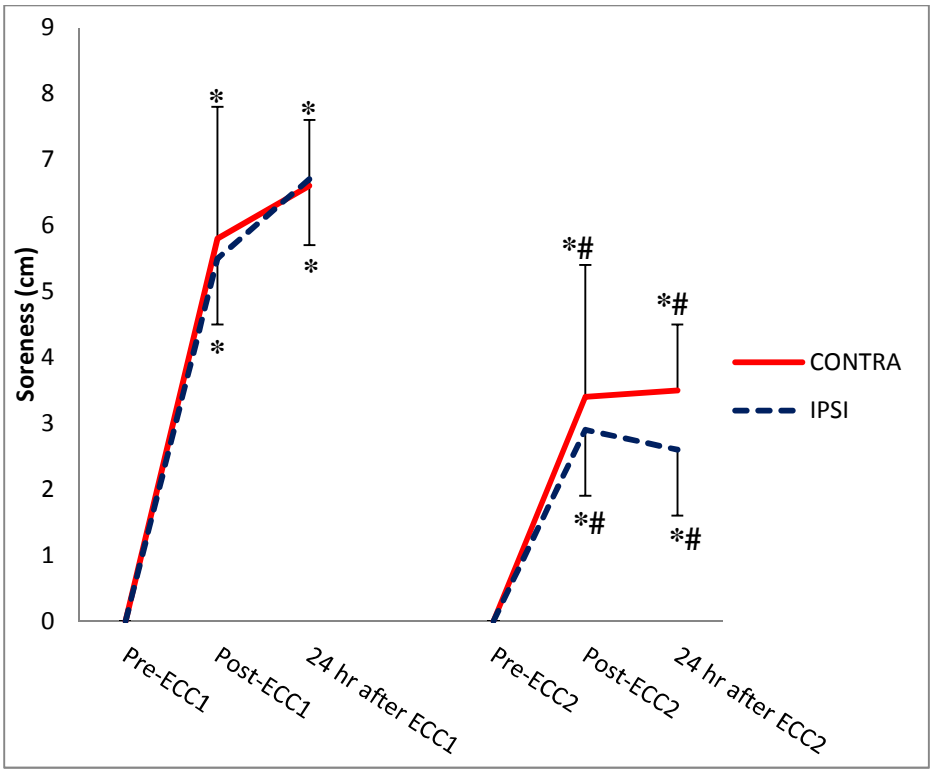

Figure 4: Mean (SD) of muscle soreness at pre-, post- and 24 hr after first (ECC1), and second bout of ECC exercise (ECC2).: Significantly different from before ECCs; #: Significantly different from the same instant in bout 1; $p \leq 0.05$; (Study III).*

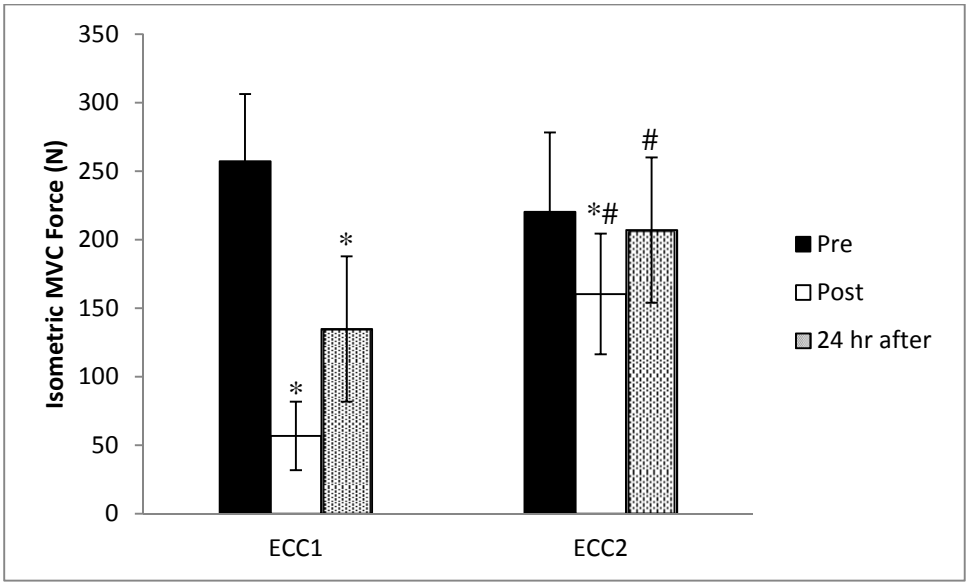

Figure 5: Mean (SD) of isometric MVC force at pre-, post- and 24 hr after first (ECC1), and second bout of ECC exercise (ECC2); #: Significantly different from the same instant in bout 1; p≤0.05; (Study I &II).

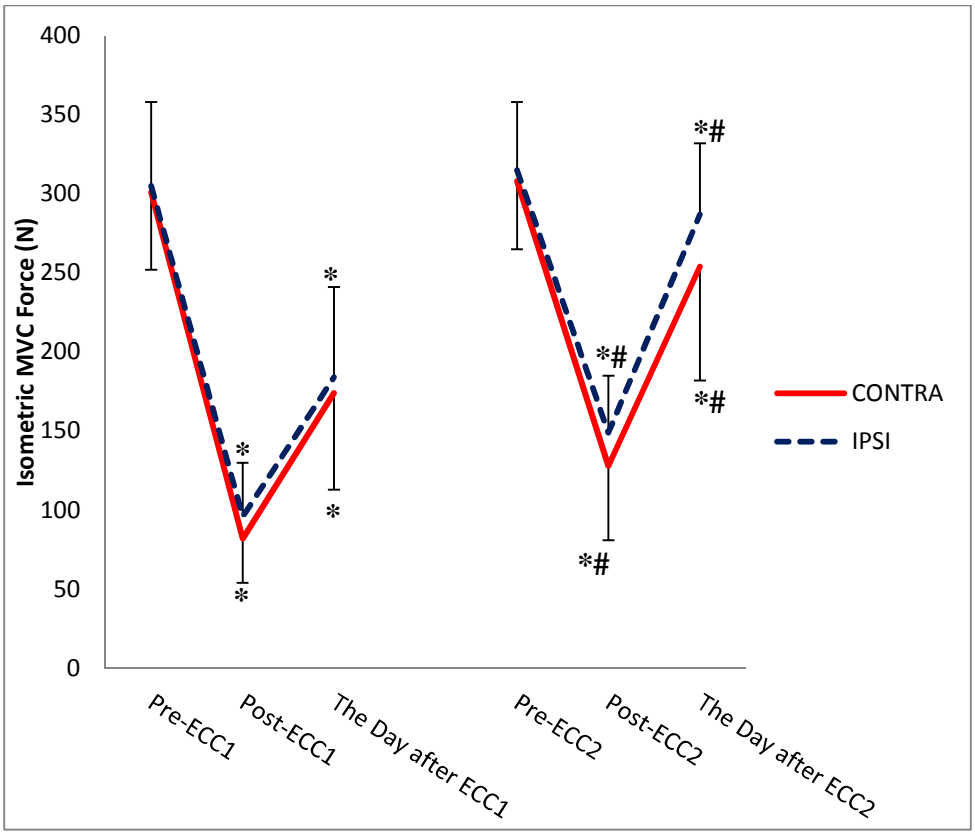

Figure 6: Mean (SD) of isometric MVC force at pre-, post- and 24 hr after first (ECC1), and second bout of ECC exercise (ECC2); #: Significantly different from the same instant in bout 1; p≤0.05; (Study III).

4.2 Exercise induced muscle damage, Central Sensitization, and RBE

In this section the results regarding NWRT and PPT after two bouts of ECC at either the same or contra-lateral TA will be discussed.

4.2.1 The effect of two bouts of high intensity ECC on NWRT and PPT in ipsilateral TA

As shown in the *Figure 7* and *Figure 8*, both NWRT and PPTs decreased 24 hr after ECC1 in study I, indicating that the high intensity ECC induced EIMD-related muscle hyperalgesia and generalized pain hyperexcitability (central sensitization). 24 hr after ECC2 however, no change in the NWRT and a normalization of PPTs compared with 24 hr after ECC1 were observed. These observations demonstrate RBE in the current project. The results regarding to NWRT and PPTs in the ipsilateral group of the study III also confirmed the above mentioned changes (*Figure 9* and *Figure 10*). Assessed by PPT as a subjective outcome measure, decreased pain sensitivity after ECC2 comparing to ECC1 has been already reported as evidence for RBE (Kawczynski et al., 2012). Further, a clear hyperalgesia in the TA muscle belly sites to pressure pain stimulus was observed post- and 24 hr after ECC1 which was at the same line with Fernandez-Carnero et al. (Fernandez-Carnero et al., 2010). In addition, in the current PhD project EIMD and RBE have been demonstrated by NWRT modulation. NWRT is an objective outcome measure of spinal cord hyperexcitability. The modulation of NWRT before and after ECC1 and ECC2 demonstrated that the repetition of ECC exercise may further facilitate inherent protective spinal mechanisms against the development of EIMD.

RBE has mostly been explained by three main theories including neural, connective tissue, and cellular- adaptations. Given the observation of an adaptive effect of ECC exercise prior to full recovery (Nosaka and Clarkson, 1995,Mair et al., 1995), neural adaptation and its underlying central modulation has been reported as the most likely theory for explaining the RBE (McHugh et al., 1999). In the study I, lower muscle soreness and subsequently an attenuation of the changes in NWRT, PPT, and muscle strength were observed after ECC2 compared to ECC1. This adaptive response indicates the presence of an RBE. Further, existence of muscle soreness (*Figure 3*) pre-ECC2 compared to pre-ECC1 in study I indicates that the second bout of ECC was performed prior to full recovery. These observations therefore, confirm that the RBE of ECC exercise is not dependent on full recovery. This fact was in line with

previous studies (Kawczynski et al., 2012,Nosaka and Clarkson, 1995,Mair et al., 1995,Lavender and Nosaka, 2008).

In the study I and III, NWRT significantly decreased 24 hr after ECC1 (*Figure 7* & *Figure 9*). The decrease in NWRT is considered as hyperexcitability of the spinal nociceptive system (Banic et al., 2004). This central sensitization seems therefore likely to occur after a strong stimulus caused by EIMD after ECC1. The results related to NWRT after ECC2 however, did not show any evidence of sensitization. Muscle inflammation and chemical stimulation of the muscle nociceptors (group III/IV afferents) are reported to activate other afferents in the reflex pathways, i.e. low threshold mechanoreceptors, cutaneous nociceptive afferents, group II muscle afferents as well as joint afferents (Mense, 1993). Mense (1993) suggested this mechanism can demonstrate an explanation for the tenderness in the muscle and pain during movement. These afferents together develop a widespread multisensorial convergence onto common interneurons in the spinal cord (Schomburg, 1990). Interaction of afferents input at an interneuronal level, presumably in the dorsal horn of the reflex pathway (Andersen et al., 2000) furnishes a plausible explanation of the NWRT modulation by ECC as well as muscle hyperalgesia and soreness. In study III, the results regarding NWRT, PPT, muscle soreness intensity, and muscle strength in the reference group all showed attenuation of the changes following bout 2 compared with bout 1 in the ipsilateral limb as well. These results resemble RBE in the study I. The current results revealed that the NWR can be used to assess spinal modulation due to EIMD and RBE.

There was no decrease in the NWRT post ECC2 and 24 hr after ECC2 in study I and in the ipsilateral group in the study III. In fact, NWRT increased 24 hr after ECC2 compared with 24 hr after ECC1 (see *Figure 7* & *Figure 9*). This NWRT modulation indicating a protective effect of ECC can be interpreted as RBE. Exercise training has been suggested to modulate various neurotrophins at central and peripheral levels (Ying et al., 2003) leading to a synaptic efficacy (Hutchinson et al., 2004) of sensory motoneurons and signal transduction receptors (Ying et al., 2003). Given the results regarding the NWRT after ECC1 and ECC2 in study I and in the ipsilateral group of the study III, it seems possible that ECC1 could provide a

sufficient physiological stimulus to cause central sensitization and therefore manifestation of a plasticity of the somatosensory nervous system (Latremoliere and Woolf, 2009). This central facilitation in response to ECC1 possibly could provide an opportunity for rapid functional plasticity that could lead to accommodate with ECC2 more efficiently.

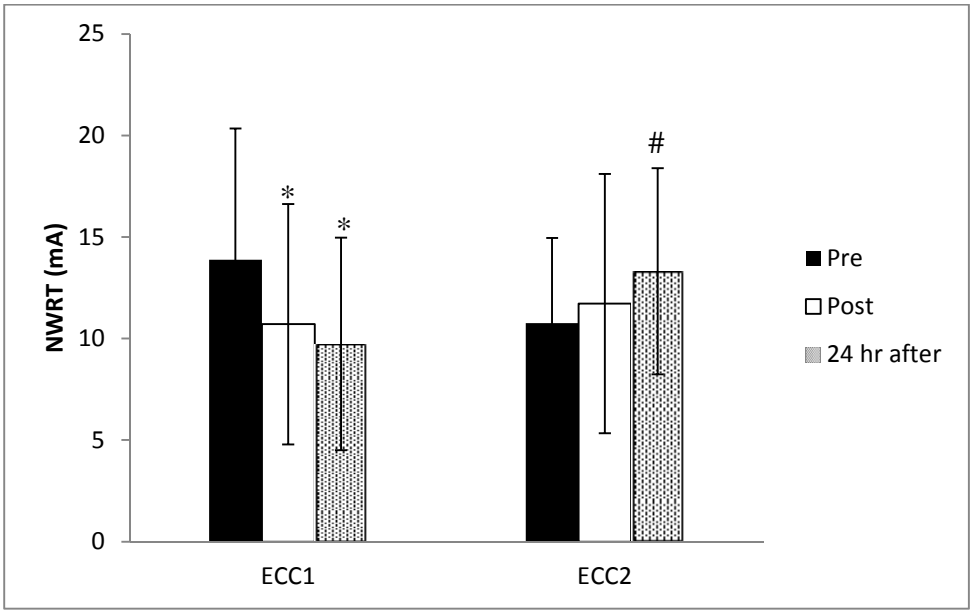

*Figure 7: Mean (SD) of nociceptive withdrawal reflex threshold (NWRT) at pre-ECC, post-ECC and 24 hr after first bout of ECC exercise (ECC1), and second bout of ECC exercise (ECC2); (N=16); * Significantly different from Pre-ECC1; # Significantly different from the same instant in bout 1; p≤0.05; (Modified from study I).*

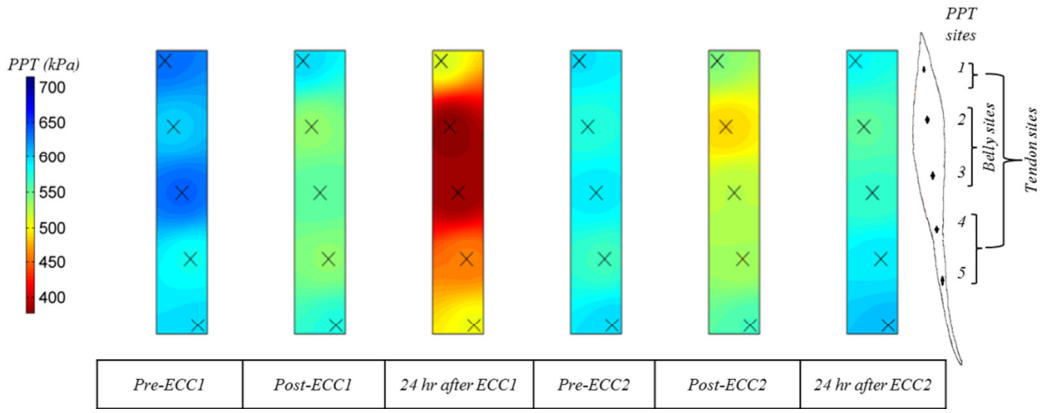

Figure 8: Pressure pain threshold (PPT) maps from the tibialis anterior muscle pre-, post-, and 24 hr after first ECC exercise (ECC1), and second ECC exercise (ECC2) (N=16). Points 1 to 5 correspond to PPT sites; Modified from Study I.

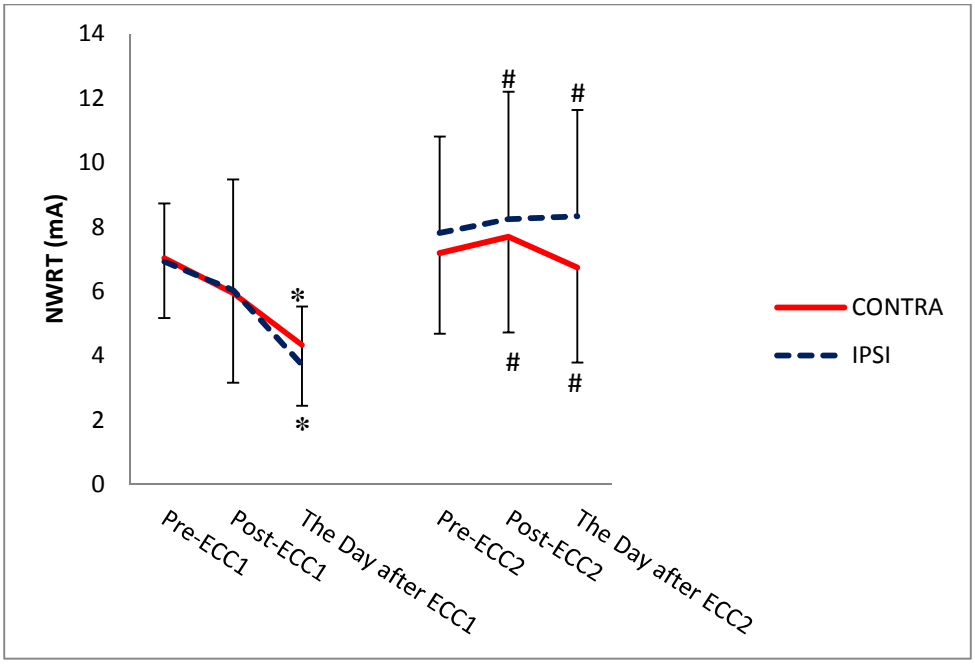

Figure 9: Mean (SD) of nociceptive withdrawal reflex threshold (NWRT) pre-, post- and 24 hr after ECCs.: Significantly different from before ECC; #: Significantly different from the same instant in bout 1; $p \leq 0.05$.*

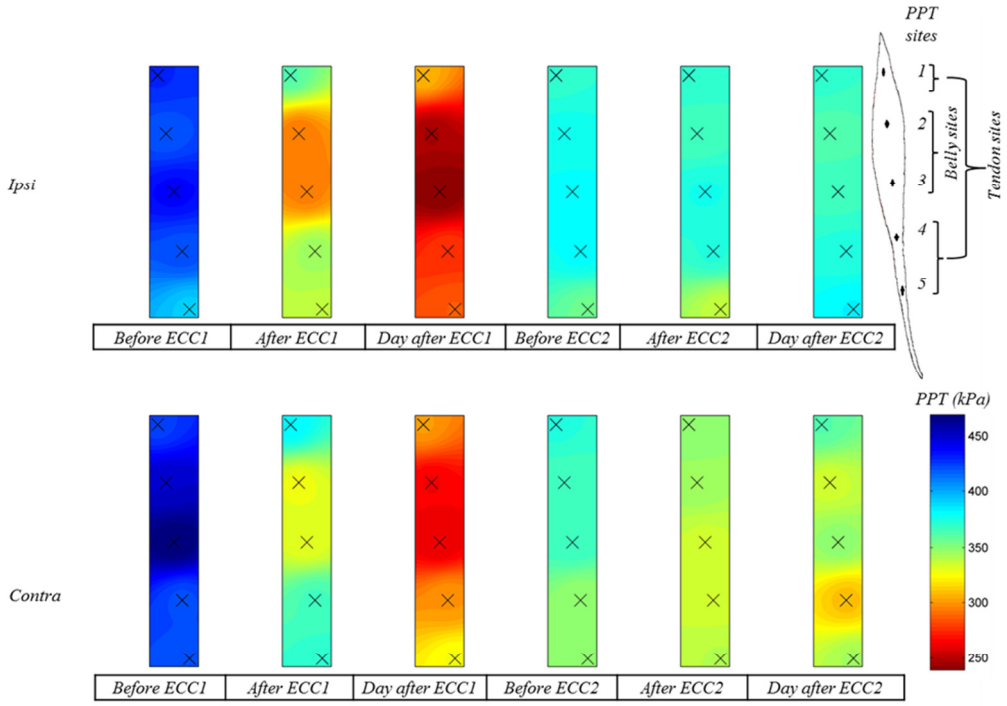

Figure 10: Pressure pain threshold (PPT) maps from the tibialis anterior muscle pre-, post-, and 24 hr after first ECC exercise (ECC1), second ECC exercise (ECC2); Points 1 to 5 correspond to PPT test sites; Ipsi: refrence group; contra: contralateral group.(Study III).

4.2.2 The effect of two bouts of high intensity ECC on NWRT and PPT in contralateral TA

One of the specific aims in the study III of this dissertation was to investigate cross-transfer effects related to RBE in the spinal nociceptive pathways by assessing the NWRT. NWRT decreased 24 hr after ECC1 while no change in the NWRT was observed after ECC2 in the contralateral TA. Additionally, the lower reductions of PPT (*Figure 10*), and MVC force (*Figure 6*), and significant reduction in muscle soreness score (*Figure 4*) following ECC2 in the CONTRA group shows an RBE in the contralateral limb as well. RBE related to contralateral limb has been already reported by assessing EMG activity, muscle strength and soreness in elbow flexors (Howatson and Van Someren, 2007,Starbuck and Eston, 2012). In the study III furthermore, contralateral RBE was observed by NWRT in TA muscle for the first time.

Contralateral adaptation by exercising the ipsilateral limb has been demonstrated following several weeks of strength training (Hortobagyi et al., 1997,Shima et al., 2002). There is no anthropometric (Moritani, 1979), imaging (Narici et al., 1989), or histological (Hortobagyi et al., 1996) evidence demonstrating that ipsilateral resistance training leads to contralateral muscular adaptation. Peripheral muscle adaptations were therefore suggested as unlikely mechanisms to explain the contralateral strength training effect (Carroll et al., 2006). Two candidate neural mechanisms were instead suggested to explain this type of adaptation. These include an enhancement of the efficacy in the spinal and cortical motor pathways of the contralateral limb and accessibility of the contralateral limb to the brain area responsible for motor control in which the adaptation to ipsilateral training occurred (Carroll et al., 2006,Lee and Carroll, 2007). The precise nature of these neural adaptations is not known yet. There is however, evidence that even a single bout of high intensity damaging ECC can provide rapid neural adaptation manifested as a reduction in surface EMG median frequency in the activated muscle (Warren et al., 2000). Changes in the pattern of neural activity associated with motor drive and adaptive modifications in neural circuits involved in motor planning and execution were therefore suggested as candidate mechanisms for this type of adaptation

(Carroll et al., 2006). In cats, interneurons that receive ascending and descending inputs cross the midline to excite or inhibit contralateral motoneurons (Jankowska et al., 2005a,Jankowska et al., 2005b). A similar synaptic organization was described after stimulation of the contralateral afferents leading to reflex conditioning in humans (Delwaide and Pepin, 1991). It seems therefore likely that this type of interneurons can contribute to crossed effects in humans as well. Additionally, there are other potential mechanisms underlying the crossed effects. Stevenson et al. (2013) demonstrated a trans-cortical pathway underlying the contralateral response (Stevenson et al., 2013). Animal studies reported spinal neuronal connections contributing to the occurrence of contralateral responses (Szentágothai, 1964,Light and Perl, 1979). Woolf (1983) demonstrated that neurons in the spinal dorsal horn may have bilateral receptive fields (Woolf, 1983). Lei et al. suggested the dorsal root reflexes as potential mechanisms for contralateral effect of ipsilateral experimental pain (Lei et al., 2008). Results related to NWRT in study I also suggested an interaction of afferents input at an interneuronal level, presumably in the dorsal horn of the reflex pathway after ECC. In the study III the result regarding the NWRT was replicated in the IPSI group in which both the ECCs were performed at the ipsilateral TA; additionally, it was shown that NWRT modulation elicited by repeated bouts of high intensity damaging ECC can be cross transferred to the contralateral homologous muscle and thereby it may play a role in cross transfer regarding RBE. In other words, a protective effect of central sensitization related to an initial high intensity damaging ECC crossed the midline to the contralateral homologous limb. Hence, since the RBE was observed by modulated NWRT over the contralateral limb it can be concluded that neural adaptation that leads to cross transfer may reside in the dorsal horn of the reflex pathway.

Given the results regarding PPT in the study III (*Figure 10*), it is also interesting to notice that we confirmed an initial bout of high intensity damaging ECC decreases PPT while repeating the ECC does not which is in accordance with results of study I (*Figure 8*). In study III additionally, the results showed that RBE for pressure pain sensitivity could cross the midline to the contralateral TA muscle. However, this fact that PPT was unchanged in the biceps brachii muscle at all the instants in both

groups may show that the RBE (protective effect of ECC) from a single high intensity damaging bout of ECC is specific to the exercised muscle and can only cross the midline to the contralateral homologous muscle and not to other muscles (in this case contralateral deep peroneal (fibular) nerve, branch of common peroneal (fibular) nerve (L4, L5, and S1)).

4.3 Exercise induced muscle damage, muscle oxygenation, and RBE

In this section the results regarding local muscle blood flow and hemodynamic after two bouts of ECC at either the same or contra-lateral TA will be discussed.

4.3.1 The effect of two bouts of high intensity ECC on local muscle blood flow and hemodynamic in the ipsilateral TA

The unaccustomed high intensity ECC1 in study II led to a significant decrease in [ΔtHb] 24 hr after ECC1 while there was no change 24 hr after ECC2 (*Figure 11*). The pattern of the changes in [ΔtHb] resembles the pattern of the changes in pain sensitivity (PPT and NWRT) in study I. Additionally, the [ΔtHb] pre- ECC2 was significantly lower than it was pre- ECC1 which could signal that ECC2 was performed while full recovery after ECC1 was not present. This is in line with the signs of central sensitization depicted by decreased values of NWRT after ECC1 in study I. Furthermore, the lack of a significant decrease of [ΔtHb] 24 hr after ECC2 may indicate that RBE was identified by NIRS measurements independent of full recovery after ECC1. Detection of RBE before full recovery substantiates further the role of neural adaptation mechanism in RBE (McHugh, 2003,McHugh et al., 1999).
It is suggested that due to increased intramuscular pressure during sustained isometric contractions at 50% MVC blood flow to the muscle would be completely impeded, (Sadamoto et al., 1983). The [ΔtHb] in study II was measured during 100% MVC. Although [ΔtHb] does not evaluate strictly the increase and decrease of blood volume, it gives an indication of the relative change in oxygen delivery and consumption by muscle blood volume (Kuwamori et al., 1995). Therefore it is likely that the variations in muscular force can affect [ΔtHb] during a constant muscle

work at 100 % MVC. Hence, in this condition changes in [ΔtHb] appears to be correlated with the changes in muscle force (*Figure 12*) and a marker of muscle performance. Demura & Nakada (2009) also has described this relationship (Demura and Nakada, 2009). Given the data related to the muscle soreness, MVC force, and [ΔtHb], in study II one could infer that the increased soreness after ECC1 resulted to a lower central motor drive which induced to a lower force production. Then, this lowered force production led to the lower [ΔtHb]. Finally, the rapid potential adaptation due to RBE moderated the EIMD and the soreness in the subsequent ECC which was inferred as increased local muscle blood flow pattern during MVC after ECC2.

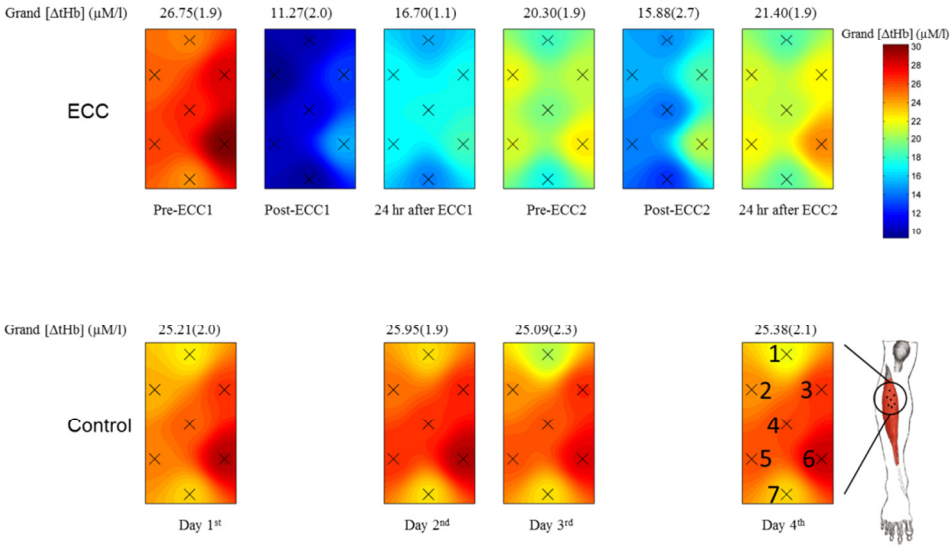

Figure 11: Maps of the changes in [ΔtHb] at instants following the two bouts of ECC comparing to the value before ECCs during maximum isometric MVC for the seven NIRS channels. Grand [ΔtHb] was calculated as an average (SEM) of the mean values of [ΔtHb] at all the channels. Numbers 1-7 corresponds to channels 1-7.

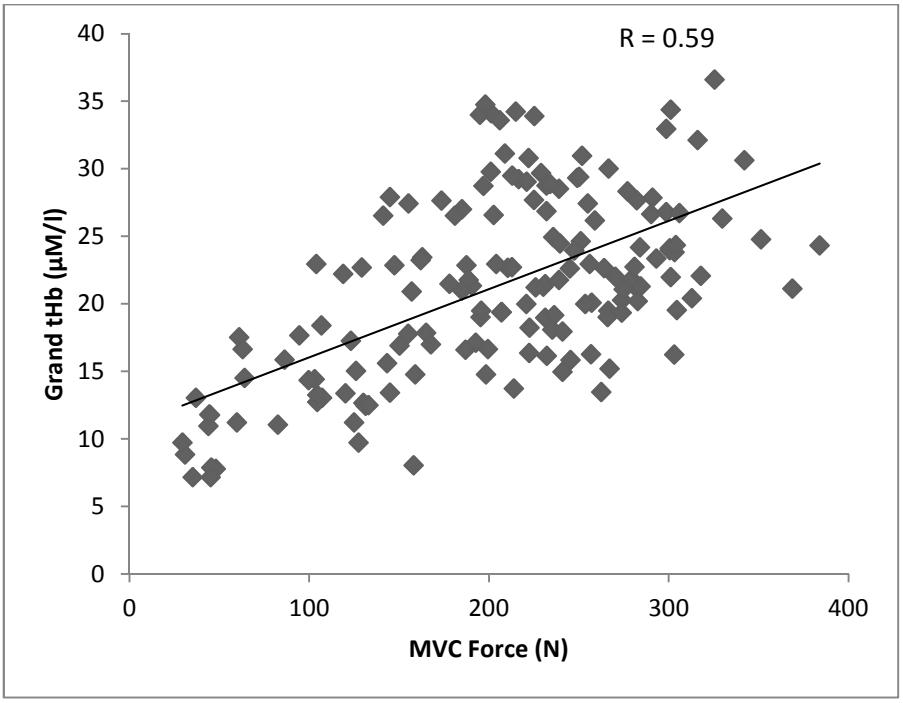

Figure 12: Correlation between changes in grand [ΔtHb] and isometric muscle strength; (Grand [ΔtHb] defined as an average of the [ΔtHb] over all the seven channels); p<0.01.

4.3.2 The effect of two bouts of high intensity ECC on hemodynamic in the contralateral TA

Both the oxygen utilization and oxygen delivery values were significantly lower 24 hr after ECC1 comparing with before ECC1 while there were no changes in these outcome measures 24 hr after ECC2 comparing with before ECC2 (*Figure 13* & *Figure 14*). With regards to the changes in the muscle oxygenation in the ipsilateral group, it was remarkable that the oxygen delivery pre-ECC2 increased significantly compared to pre-ECC1. This difference can demonstrate either passive or active hyperemia (improvement in oxygen reperfusion) during isometric MVC in the ipsilateral group. This potential hyperemia during isometric MVC was not observed

in the contralateral group. Furthermore, TSIdownslope and TSIupslope were unchanged during all instants of the study in both groups indicating that the rate of the oxygen use and recovery of the oxygen usage were unaffected at all instants in both groups. This may reveal that the muscle reperfusion can be improved after a single bout of high intensity damaging ECC only in the ipsilateral limb; it therefore seems unlikely that improvement in muscle oxygenation plays a substantial role in the RBE related to the contralateral limb.

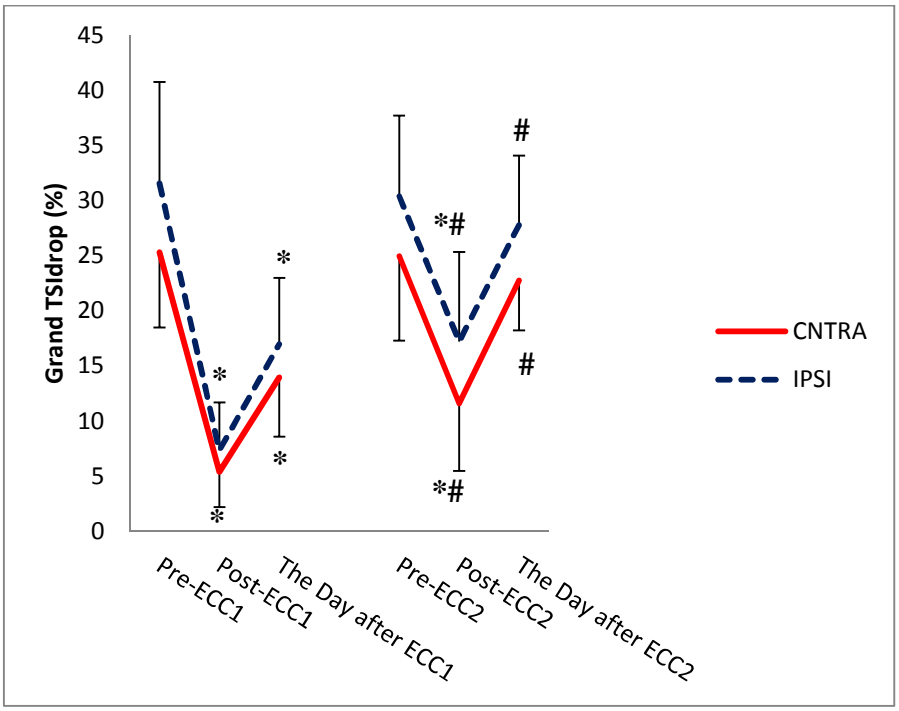

Figure 13: Mean values (SD) of the oxygen usage pre-, post-, and 24 hr after ECCs.: Significantly different from before ECC; #: Significantly different from the same instant in bout 1; p≤0.05, (Modified from study III).*

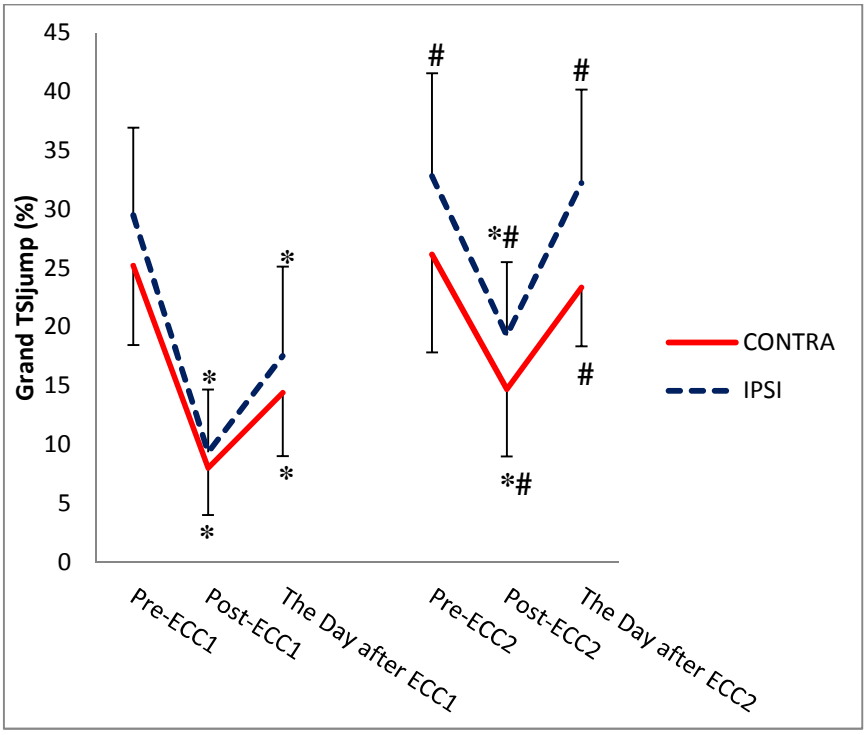

Figure 14: Mean (SD) of the Oxygen reperfusion Pre, Post and the 24 hr after ECCs.: Significantly different from Pre ECCs; #: Significantly different from the same instant in bout 1; p≤0.05 (Modified from study III).*

4.4 The effect of two consecutive bouts of high intensity ECC on EMG activity

Another specific aim of the study II was to investigate the effect of two bouts of high intensity ECC exercise on the amplitude and the frequency contents of the EMG signals. The MDF values significantly decreased at ECC2 session compared with ECC1 (*Figure 15*). On the contrary, EMG RMS did not change at any instants of the study. The data support the hypothesis that EMG spectral contents change with ECC experience. In other words, an unaccustomed ECC inducing muscle soreness can decrease the EMG spectral contents. This alteration provides a possible

mechanism for a rapid adaptation that can decrease vulnerability of the muscle to develop further EIMD after the subsequent ECC bout.

In agreement with prior studies, the MDF during isometric MVC in study II was significantly lower after consecutive bout of ECC while RMS was unchanged (Chen, 2003,Warren et al., 2000). It has been reported that constant RMS amplitude after the initial and the consecutive bouts of ECCs reflects similar total neural activation between ECCs (Warren et al., 2000). The decreased MDF during MVC at instants of ECC2 is suggested to be a reflection of changes in muscle fiber activation pattern associated with RBE (Chen, 2003). Both the previous studies investigated the EMG activity of the biceps brachii muscle during ECC. The results from the study II confirmed their observations but in TA muscle and during isometric MVC. Warren et. al. (2000) has suggested that the decrease in MDF can be due to a shift between the recruitment of faster motor unit to the activation of slower motor units. It should, however be noted that a single bipolar surface EMG channel does not enable the extraction of neural strategies identifying the physiological mechanisms responsible for the neural control of movement (Farina et al., 2002,Farina et al., 2004).

Quaresima et al. (2001) demonstrated that changes in intramuscular pressure, local blood supply, and motor unit recruitment pattern will all affect the [ΔtHb] during exercise (Quaresima et al., 2001). Given the variations of the [ΔtHb], MVC force, and MDF at study II, one can infer that ECC1 induced muscle damages of type II fibers. This damage could lead to recruitment of fewer fast twitch fibers compensated by additional type I fibers for the consecutive ECC2 (Lieber and Friden, 1988,Warren et al., 2000). Finally, the higher oxidative capacity of type I fibers therefore, resulted to the higher tissue oxygenation during consecutive ECC2 compared with ECC1.

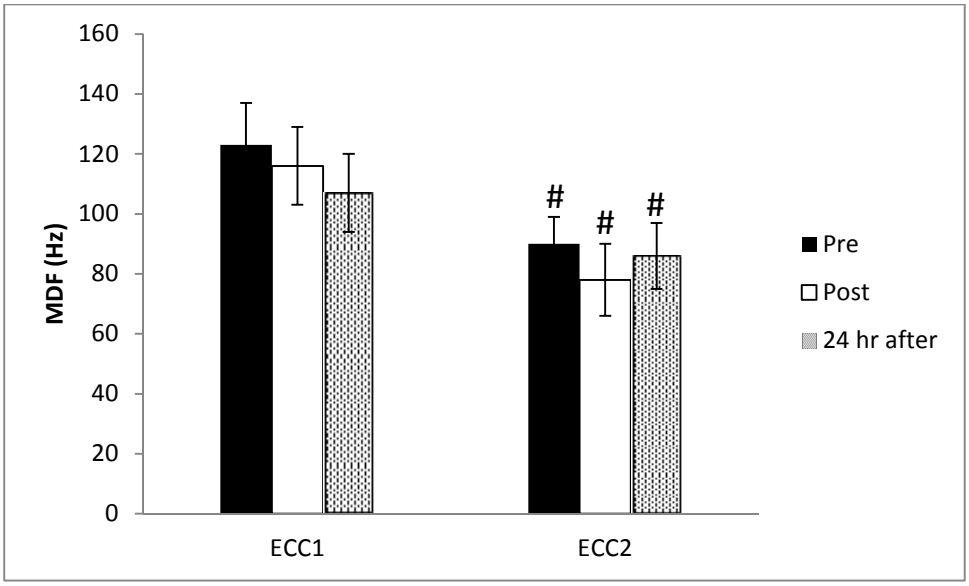

Figure 15: Mean (SD) of median power frequency (MDF) of the surface electromyographic signal recorded over the tibialis anterior muscle at pre-, post- and 24 hr after first (ECC1) and second (ECC2) bout of eccentric exercise; #: significantly different from the same instant in bout 1. $p < 0.05$.

4.5 Limitations and Future Perspectives

- The consecutive bout of ECC2 in study I & II was performed before full recovery. Since the relative set levels of exerted muscle force in the study I & II was the same across ECC bouts, one might infer that the absolute intensity of two ECCs might have differed. As muscle cannot produce as high a force as the initial bout while it is not fully recovered, then it might be expected that the lower extent of DOMS after the consecutive ECC2 could be due to lower level of exerted muscle force. This kind of limitation is common among most of the studies investigating RBE (Warren et al., 2000,Nosaka and Newton, 2002). This limitation is definitely more remarkable, when RBE is investigated before accomplishment of full recovery from the EIMD following the initial bout of ECC (typically, when the ECC2 is performed less than one week after ECC1).

- Some caution when interpreting the data in studies of RBE specially related to the contralateral limb is important. Carroll et al. (2006) reported that apparent contralateral strength training effect could be attributed to familiarity with testing procedures rather than a cross-transfer effect. So that performing the initial ECC, participants may learn the optimal positioning on the test apparatus, or the optimal exerting direction for the force against the dynamometer. Consequently, it may be familiarization with the testing protocol and not a repeated bout effect in the contralateral TA muscle. This issue is one of the common limitations in the studies investigating the RBE.
- Cross-transfer of the RBE has been reported between the elbow flexor muscles (Howatson and Van Someren, 2007,Starbuck and Eston, 2012). However, Connolly et al. (2002) investigating a contralateral repeated bout effect following a single bout of maximal eccentric exercise in the quadriceps group muscles have observed neither protective nor cross-transfer effect in their study. In the current PhD project the cross-transfer of the RBE was observed in TA muscle. Therefore, further studies on RBE in both ipsi- and contra- lateral limb targeting other body regions with different muscle groups are necessary to investigate the underpinning mechanisms of this protective effect.
- Finally, this dissertation revealed that only one session of high intensity ECC can modulate central sensitization. This would therefore be interesting to investigate the effect of a period of high intensity ECC training on sensitization in different healthy or patient populations.

5 Conclusion

- This dissertation highlighted that high intensity damaging ECC exercise can lead to central sensitization which is depicted by lower NWRT. A lack of central sensitization is however, expected after the consecutive bout of ECC. This adaptive response is called RBE.

- Central sensitization induced by an initial high intensity ECC probably demonstrates an explanation for the tenderness in the muscle and pain during movement.
- RBE was for the first time observed in the assessment of the NWRT in the contralateral lower limb which could indicate a spinal neural adaptation mechanism.
- The protective effects regarding RBE to the contralateral limb seems to be specific to the contralateral homologous innervation level.
- The local muscle blood flow and the spectral contents of surface EMG change following an initial bout of ECC. These changes are accompanied with signs of reduced muscle damage during the subsequent bout of ECC.
- Muscle oxygen re-perfusion can be improved after a single bout of high intensity damaging ECC, however, it does not play a major role in cross-transfer adaptations due to eccentric exercise.
- Conditioning professionals can consider consecutive bouts of ECC in training and rehabilitation programs as a way to limit the effects of central sensitization behind EIMD.
- Clinicians, and coaches, are advised to emphasize pre-season conditioning involving sports specific movement drills of ECC to induce the protective and potentially analgesic effect of ECC.
- Further studies on RBE targeting other body regions are necessary to investigate the underpinning mechanisms of this protective effect of ECC exercise.

6 Dissertation at a glance

Title of study	Primary aim	Method	Main findings
Study I:			
Pain sensitivity is normalized after a repeated bout of eccentric exercise	To investigate the effects of two bouts of high intensity ECC exercise on the sensitivity in the spinal nociceptive system and deep structure sensitivity to pressure pain in a randomized, controlled, crossover design.	Measuring NWRT and PPT before after and the day after an initial and then a repeated bout of high intensity ECC.	Unaccustomed ECC causing DOMS leads to central sensitization depicted by lower NWRT. A lack of central sensitization was observed after ECC2.
Study II:			
Adaptation of local muscle blood flow and surface electromyography to repeated bouts of eccentric exercise	To investigate whether local muscle blood flow, EMG MDF, and EMG RMS change after a bout of high intensity eccentric exercise within the tibialis anterior (TA) muscle.	Measuring [ΔtHb], EMG MDF, and EMG RMS changes before after and the day after an initial and then a repeated bout of high intensity ECC.	The local muscle blood flow and the spectral contents of surface EMG change following an initial bout of ECC. These changes were accompanied with signs of reduced muscle damage during the subsequent bout of ECC.
Study III:			
Ipsilateral resistance exercise prevents exercise induced-central sensitization over the contralateral limb– a randomized control study	To investigate cross-transfer effects related to RBE by assessing changes in sensitivity in the spinal nociceptive system, deep structure sensitivity to pressure pain and local muscle oxygenation.	Measuring NWRT, PPT, TSIdrop and TSIjump before after and the day after an initial bout of ECC on ipsilateral TA and then a repeated bout of high intensity ECC on either ipsi- or contra-lateral TA.	RBE was for the first time observed in the contralateral lower limb as depicted by NWRT modulation. Oxygen re-perfusion does not play a major role in cross-transfer adaptations due to repeated eccentric exercise.

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SUMMARY

Exercise-based pain management programs are suggested for relieving from musculoskeletal pain; however the pain experienced after unaccustomed, especially eccentric exercise (ECC) alters people´s ability to participate in therapeutic exercises. Subsequent muscle pain after ECC has been shown to cause localized pressure pain and hyperalgesia. A prior bout of ECC has been repeatedly reported to produce a protective adaptation known as repeated bout effect (RBE). One of the main scopes of the current project was to investigate the adaptations by which the RBE can be resulted from. The approach in the current study was to use exercise induced- muscle damage followed by ECC as an acute pain model and observe its effects on the sensitivity of the nociceptive system and blood supply in healthy subjects. Then, the effect of a repeated bout of the same exercise as a healthy pain relief strategy on these parameters was assessed. This study indicated that unaccustomed ECC can lead to central sensitization. Central sensitization induced by an initial ECC probably demonstrates a mechanism for the tenderness in the muscle and pain during movement. A lack of central sensitization is seen after the repeated bout of ECC irrespective if the initial bout of ECC involved the ipsi- or the contr-alateral limb. Muscle oxygen re-perfusion does not play a major role in cross-transfer adaptations due to repeated bout of ECC.

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