EFFECT OF AN INVERTED SEATED POSITION WITH UPPER ARM BLOOD FLOW RESTRICTION ON NEUROMUSCULAR FATIGUE

By

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Abstract

Change in body position, in addition to disturbances to the homeostasis of our body, can exacerbate neuromuscular fatigue. Experiencing a voluntary or involuntary inverted position is a stressful condition and can alter sympathetic nervous system activity, which has been suggested as a primary mechanism that may inhibit neuromuscular and cardiovascular function. Moreover, there is a possibility of complete or partial blood flow due to limb compression during life-threatening conditions such as overturned vehicles. Blood flow restriction (BFR) due to a decrease in perfusion to a target muscle, moderate to high intensity muscle contractions, and BFR (partial occlusion during a contraction with low intensity) can lead to force reductions and dependency on type II fibres. This shift to an anaerobic phase yields metabolic by-products accumulation, stimulating muscle fibres afferents with small diameters (group III and IV). The increases in peripheral inputs to the central level may cause inhibition of final motor output, fatigue-induced greater perceived pain and effort, and increased cardiovascular stress.

In view of many interacting systems during inversion, the purpose of this thesis was to explore how BFR of the upper arm while participants were securely inverted can influence isometric force production, muscle activity, fatigue, perceived pain, and cardiovascular responses. Understanding the possible mechanisms can be used by safety and survival centers during limited time rescue missions.

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LIST OF ABBREVIATIONS

ADP - Adenosine Diphosphate
AP - Action Potential
ATP – Adenosine Triphosphate
BCAA - Branched Chain Amino Acids
BFR - Blood Flow Restriction
BP - Blood Pressure
C° - Centigrade (Celsius)
Ca^{++} - Calcium
Cl^{-} - Chloride
CMEP - Cervicomedullary Motor Evoked Potential
CNS - Central Nervous System
EMG - Electromyography
GABA - Gamma-Aminobutyric Acid
HR - Heart Rate
Hz - Hertz
IL - Interleukin
ITT - Interpolated Twitch Technique
K^{+} - Potassium
Km - Kilometer
MAP - Mean Arterial Pressure
MEP - Motor Evoked Potential
mM - Millimole
MmHg - Millimeters of Mercury
Ms - Milliseconds
MVC - Maximum Voluntary Contraction
M-Wave - Compound Muscle Action Potential
Na^{+} - Sodium
P^{+} - Phosphate
S - Second
SR - Sarcoplasmic Reticulum
TMS - Transcranial Magnetic Stimulation
TRP - Tryptophan
α-MN - Alpha Motoneurons
5-HT - 5-Hydroxytryptophan

Chapter1: Review of Literature

1.1 Introduction

An inverted seated body position can happen following either during voluntary (e.g., zip line, military pilot, inversion therapy) or involuntary (e.g., car accident, submersed helicopter) activity. Previous studies have shown that a seated inversion induced an impairment in neuromuscular responses such as, electrical activity of skeletal muscle, reaction time, decreased heart rate and blood pressure (Paddock & Behm, 2009; Hearn et al., 2009; Johar et al., 2013; Smith et al., 2013; Neary at al., 2015). Authors of these studies suggest that a down-regulation of the sympathetic nervous system influenced the above-mentioned responses.

The ability of the overturned person, following an overturned vehicle, to escape from this stressful and uncomfortable position demands a higher neuromuscular response, fast stabilizing strategy, and problem-solving function. Meanwhile, it seems rational to consider that following this life-threatening situation, the presence of fatigue may increase progressively. Immediately after inversion, or during prolonged inversion, multiple intermittent muscle contraction in addition to a problem-solving task may require higher physical output leading to greater fatigue.

In common parlance, “neuromuscular fatigue” is a term to express a decrease in the force or power generation of a muscle or group of muscles (Gandevia, 2001). This force reduction can be followed by an increase in perceived difficulty to do either a task or physical activity (exercise) (MacIntosh et al., 2005). Fatigue also can occur immediately after the start of muscle contraction, while the individual has an ability to follow the requested task (Sogaard

et al., 2006). Moreover, the muscle's output can be maintained at a constant level during a fatiguing task (prolonged duration), due to the balance between faciliatory and inhibitory factors. Processes such as "post-activation potentiation" and "muscle wisdom" (decreases in firing frequency) can counterbalance the fatigue effects (Behm, 2004).

Further, previous evidence has been presented that the presence of a fatigued muscle can increase via tilting the body under different angles (Egana & Green, 2007) and decreasing perfusion pressure (Wright et al., 1999). A position change of working muscle to the level of the heart (perfusion changes), or raising either an upper or lower limb can influence force output, and resistance to fatigue (Fitzpatrick, 1996; Egana & Green, 2005). There is also the possibility of complete blood flow restriction to a muscle during contractions with moderate to high intensity (Sadamoto et al., 1983). Following the overturning of a vehicle, there is a possibility of a compressed limb, which may occlude blood flow or neural drive to the target muscle. Thus, an impeded bloodstream due to both voluntary activation and compressed limb can induce by-product accumulation (i.e., lactate, hydrogen ions), neural drive suppression and increasingly higher inhibitory effects of group III and IV muscle afferents on spinal motoneuron reflexes (Leonard et al., 1994; Bigland-Ritchie et al., 1986; Garland, 1991).

To maintain homeostasis of the human body, following a change in posture, coordination between the efferent and afferent systems are critical (i.e., a synchronized autonomic and motoneuron output) (Kollmitzer et al., 2000). The sensory responses from exercised muscles plus stretch inputs of arterial and cardiopulmonary receptors are regulated by feedforward mechanism of central command (Kerman et al., 2000). Hence, in terms of feedback mechanisms, somatic and visceral inputs, can influence sympathetic outflow to the working muscle (Kerman et al., 2000). It has been shown that the pattern of vascular tone can

be influenced through vestibular stimulation (Kerman & Yates, 1998). As Kerman et al. (2000) point out, electrical vestibular stimulation resulted in altered limb vasculature. During the inverted body position, there is a change in both central and peripheral elements. The purpose of this literature review is to explore the potential effects of an inverted seated body position with upper arm blood flow restriction (BFR) on acute muscle isometric force production, electromyographic (EMG) activity, cardiovascular responses, pain perception, and fatigue.

1.1.2 Potential Mechanisms of Fatigue

Fatigue is considered a multidimensional phenomenon, so it would be naive to imagine that it can be explained via a single mechanism. The process of fatigue occurs gradually and can be related to neurophysiological changes that appear prior and during different kinds of muscle contraction (Enoka & Duchateau., 2008; Hoffman et al., 2009). Following maximal or submaximal contractions that induced fatigue, neuromuscular fatigue can be attributed to different sites (Enoka, 2008). In other words, the underlying mechanisms can be originated from central and peripheral levels (Gardiner, 2011).

1.1.2.1 Central Fatigue Contributions

Central fatigue refers to a gradual degradation of the central nervous system's capability to excite and recruit muscle motoneurons (i.e., more motor units) (Gandevia et al., 1994). Central components of fatigue cover all of the mechanisms that are occurring at sites proximal to the peripheral nerve (spinal cord and above) (Carrol et al., 2017).

A chain of processes may contribute to neurotransmitters release, for instance serotonin, dopamine, glutamate, acetylcholine, angiotensin II, nitric oxide, adenosine, and gamma-aminobutyric acid (Cordeiro et al., 2017; Boyas & Guevel, 2011). Serotonin (5-hydroxytryptamine, 5-HT) is an important monoamine that regulates the spinal motor pattern through both intra-synaptic and post-synaptic receptors (Perrier & Cotel, 2015). 5-HT cannot pass through the blood-brain barrier, and thus it needs to be synthesized by brain's neurons (Bowker et al., 1981; Jacobs et al., 1992). It means that an increase in serotonergic activity may affect the central neural drive and lead to a decrease in motor unit recruitment (Newsholme et al., 1987). Following prolonged exercise, with the energy needs of the muscles from free fatty acids and branched chain amino acids (BCAA), there is a competition between free tryptophan (TRP, the precursor of 5-HT) and BCAA to transport to the brain. Thus, there is an increase in the plasma ratio of TRP to BCAA (Boyas & Guevel, 2011). Previous studies (Newsholme et al., 1987; Davis & Bailey, 1996; Bolmstrand et al., 2005) regarding 5-HT mechanisms on the brain function (during fatigue), proposed that TRP ingestion and BCAA should induce an increased and decreased level of brain's tryptophan, respectively. However, their results did not support the 5-HT hypothesis. Further, animal studies illustrate that there was an intracellular increase in dopamine and 5-HT in the brainstem and hypothalamus (Blomstrand et al., 1989), subthalamic nucleus (Hu et al., 2015) for exhausted rats. Some studies (Snow et al., 2010; Bachmann, 2002) demonstrated that there was a higher level of ammonia during prolonged exercise that seems to originate from the deamination of BCAA. Since the majority of ammonium released in circulation can cross the blood-brain barrier, its accumulation could act as a detrimental factor for motor cortex activity, through effects on synaptic neurotransmission and cerebral metabolism (Banister & Cameron, 1990).

Central fatigue can be affected via changes in gamma-aminobutyric acid (GABA) and glutamate neurotransmitter (Meeusen & Meirleir, 1995). Guezennec et al. (1998) observed cerebral accumulation of ammonia alters the concentration of glutamate, glutamine, and GABA. Tergau et al. (2000) requested that their participants accomplish a task failure (i.e., pull-ups). Intracortical inhibition and facilitation were assessed via transcranial magnetic stimulation (i.e., a conditioned-test double pulse), for the right brachioradialis and abductor pollicis brevis muscles. They concluded that reduced intracortical facilitation, due to the effect of GABAergic neurotransmission, as a possible mediator for supraspinal fatigue (i.e., a decrease in motor cortex excitability). Furthermore, the findings of Sidhu et al. (2018) indicate that facilitated intracortical inhibition of $GABA_B$ partially originated from fatigue-related small-diameter muscle afferents feedback.

Fatigue can also be experienced with illness, which can cause reduced daily activity (Kramer et al., 2005). Interleukin (IL)-6 and IL-1B, as a pro-inflammatory cytokine, can lead to fever and sickness behaviours in rats (Harden et al., 2008). Both brain and muscle can produce and secrete cytokines (Carmichael et al., 2006). Harden and her colleagues showed that a decrease in voluntary activity [i.e., daily running~1 Kilometer (Km)] might contribute to the effect of “the species-homologous rat IL-6 and IL-8” on the brain. Moreover, Robson-Ansley et al. (2004) reported a significant reduction in trained male runner’s performance (a 10-Km running time trial) when they were given a low dose recombinant of human IL-6 (subcutaneous injection). Carmichael et al. (2006) showed that an increase in brain IL-1B, following a strenuous unaccustomed exercise-induced muscle damage, can play a key role in fatigue.

The central command may be restricted by certain muscle afferents (group III and IV) due to muscle's biochemical status (Gardiner, 2011). Since group III and IV muscle afferents are located on different sites (e.g., brainstem, within the skeletal muscle), the stress in terms of mechanical and chemical stimuli, results in the discharge of these muscle afferents (Amann et al., 2014). In other words, the Group III fibres (myelinated) are more mechanosensitive during muscle contraction, while group IV fibres (unmyelinated) are more metabosensitive in response to muscle force generation and stretching (Enoka, 2008). Moreover, following a sustained muscle contraction (moderate to high intensity level) and fatiguing task, which induced a decrease in muscle perfusion, the discharge rate of the muscle afferents with small diameter can increase (Gandevia, 2001). Bigland-Ritchie et al. (1986) used a protocol to explore whether local ischemia during a rest period, in the form of arterial occlusion to the right upper arm by a narrow rubber band following a fatiguing task, could hinder optimal neuromuscular transmission. Their results illustrate the regulatory effect of peripheral feedback on central excitability. The underlying mechanisms will be discussed in the inversion section, regarding the potential effects of BFR.

On the other hand, Taylor et al. (2000) revealed that BFR did not relate to reduced muscle voluntary activation. Taylor and colleagues proposed that following a sustained MVC, there is a decrease in motor unit firing rates and contractile speed (2000). Also, there is a decline in motor cortical and corticospinal stimulus response (i.e., post-contraction depression). Thus, with BFR (while elbow positioned at a raised level) after a 2-min sustained isometric elbow flexion, due to the reflex effects of group III and IV muscle afferents, the post-contraction depression can be mediated. Whereas, the post-contraction ischaemia did not mediate the reduction of corticospinal and motor cortical responses.

Further, Darques and Jammes, (1997) showed a close relationship between fatigued muscle and group IV afferents; when rabbits tibialis anterior muscle was electrically stimulated via different frequencies. There was an increase in group IV afferent activity, following both high and low-frequency fatigue, in parallel with reduced force and compound muscle action potential (M-wave) amplitudes (mainly high frequency fatigue). It was concluded that this fatigue-induced stimulation of group IV could not only originate from increased potassium efflux, but that other factors should be involved (Darques & Jammes, 1997). Another effective factor could be related to metabolic by-product accumulation, which was higher during low-frequency fatigue trials.

Following exhaustive activity, activation of these thin fibre muscle afferents also can counteract muscle impairment (Gandevia, 2001). As Kniffki et al. (1981) demonstrated the chemical activation of group III and IV gastrocnemius soleus muscle afferents could influence the alpha-motoneuron (α-MN), by acting as a facilitator and inhibitor on homonymous flexors and extensors, respectively. Schomburg et al., (1999) tested the projection of the fine muscle afferents on multisensorial segmental reflex pathways, based on Kniffki and colleagues' method. In this manner, spatial facilitation of various inputs (the fine and non-nociceptor afferent fibres) on post-synaptic potentials in α-MN were assessed. The pre-motoneuronal integration of input (versus individual separate afferent inputs) from different afferent fibre groups (e.g., during active movements) result in effective control of movement (Schomburg et al., 1999). Also, there is an interneuronal convergence between different groups of afferents (muscle afferents with low-medium threshold, nociceptive, non-nociceptive and joint afferents), which are projected to α-MN (reflex pathways) (Schomburg, 1990; Jankowska, 1992). Moreover, there is a possibility of contaminated effects between fibre

afferents with low - and high threshold, if only electrical nerve stimulation is manipulated to examine the interneuronal convergence. Thus, using an intra-arterial injection of bradykinin and potassium chloride helped them to test (selectively) the synaptic effects of group III and IV afferents upon α-MN in decerebrate cats, without intervention impacts of large muscle afferents (Kniffki et al., 1981; Schomburg et al., 1999).

Group Ia and II afferents (stretch receptors) are positioned in parallel to the muscle fibres and convey signals - via the fusimotor system - regarding the length of the muscle and velocity of this change (Enoka, 2008). Generally, following an isometric voluntary contraction, there is an initial increase in activity of muscle spindle activity, due to the effect of α-MN in response to the firing of Ia fibres (Gardiner, 2011). However, there is evidence (Macefield et al., 1991) that indicates a decrease in the firing of spindle afferents following a sustained isometric contraction (i.e., disfacilitation develops). Avela et al. (1999) showed a noticeable reduction in sensitivity of Ia afferent and stretch reflexes following sustained and repeated passive stretching, which induced a decrease in the discharge of α-MN. The altered reflex sensitivity indirectly can be related to the effect of group III and IV (metabolic stimulation – induced presynaptic inhibition of the Ia), and intrafusal fatigue due to "progressive withdrawal of spindle-mediated fusimotor support" (for review, Avela et al., 1999). Further, changes in sensitivity of the muscle spindle can be altered by the activity of gamma-motoneuron (Prochazka et al., 1988). Biro et al. (2007) following a fatiguing task showed that an increase in the gain of gamma loop could help to maintain optimal force output.

Furthermore, group Ib afferents innervate Golgi tendon organs which placed at the musculotendinous unit are sensitive to static and dynamic characteristics of force generation and thus provide intramuscular tension feedback (Enoka, 2008). The discharge rate of Ib

afferents may be influenced by strong contractions. Thompson et al. (1990) reported that following a conditioning contraction, desensitization of tendon organ could lead to an increase in errors in force estimation. Moreover, this afferent might act as a down-regulator of homonymous activity (Gandevia, 1998). While, during fatigue, "spindle afferent convergence on Ib effects can be excitatory" (Gandevia, 1998), previous evidence (Priori et al., 1998) also showed that, pre-synaptic inhibition of Ia afferents can originate from the activation of group III tendon afferents.

Additionally, the Renshaw cells via a post-synaptic recurrent pathway can influence α-MN output (Gandevia, 2001). In terms of 'classical autogenic inhibition', these cells can influence the activity of homonymous and synergist motoneurons. The fast-recruited motor units in comparison with late-recruited motor units are more efficiently affected by recurrent inhibition (Hultborn et al., 1988). Using a graded nerve stimulus of triceps surae-induced excited Renshaw cells (i.e., the monosynaptic reflex to triceps surae); Hultborn and colleagues reported a higher contribution from fast-fatigable MN to Renshaw cell excitation. Moreover, during submaximal and maximal fatiguing efforts, Renshaw cell inhibition is regulated via a different mechanism. To simplify, during sustained contraction, greater descending drive to MN results in reduced recurrent inhibition activities (Behm, 2004; Gandevia, 2001).

A sustained maximal fatiguing task can lead to a decrease in MN discharge and EMG activity (Gandevia, 1998), i.e., "initially fast reduction to reach a plateau." This decrement (i.e., matches with the contractile speed of muscle) can be explained in terms of "muscular wisdom". During fatigue, a lack of correspondence between the firing rate of the MN and muscle's contractile speed can cause a neural dilemma (Gandevia, 2001). Kernell and Monster, (1982) revealed that intrinsic properties of MN in terms of "late adaptation" can

cause a decreasing in firing frequency, thereby helping to save energy. In other words, the decreased firing rate attempts to keep optimal force output; “increased firing rate for some MN resulting decreased for others” (Garland et al., 1994). Meanwhile, previous studies (Bigland-Ritchie et al., 1986; Fuglevand et al., 1993) show an increase in EMG activity (for a submaximal fatiguing task) before the participant failed to maintain the desired force. It seems that central nervous system (CNS) via a compensatory mechanism, i.e., gradual recruitment of unfatigued motor units, increases the time to the task failure. Loscher et al. (1996) revealed there was an excitatory drive into the α-MN pool of triceps surae muscle during sustained fatigue task at 30% MVC. Consequently, the reduced force during fatigue can lead to a gradual decrease in extrafusal unloading, then increasing muscle spindle coactivation. Akima et al. (2002) showed that the pattern of muscle recruitment could be changed due to the flexibility of the CNS; an induced fatiguing stimulation (i.e., transcutaneous electromyostimulation) applied to the vastus lateralis, the aim was to limit vastus lateralis involvement (i.e., during a submaximal knee extension protocol). The results (Akima et al., 2002) show a lower contribution of fatigued muscle in comparison with greater involvement of rectus femoris and vastus medialis muscle. As a good example, during daily activity, the postural muscles activity in terms of “substitution phenomenon” can lead to an alteration in muscle recruitment (Westgard et al., 1999). As a consequence, at the spinal level, the neuromodulator factors such as intrinsic motoneuron specificity, inhibition of recurrence, alpha and gamma motoneuron’s input influence both the motoneuron’s function and spinal circuitry.

Impaired muscle performance also can be attributed to intracortical inhibition. McNeil et al. (2009) suggested that intracortical inhibition, following a 2-minute maximum voluntary

elbow flexion, increased progressively as muscle fatigued gradually. A suprastimulation by transcranial magnetic stimulation (TMS) over the motor cortex, leads to a short-latency inhibition for evoked muscle which is interpreted as the ''silent period'' (Gandevia et al., 1996). The greater the degree of fatigue, the higher motor evoked potential (MEP) and longer silent period, respectively (Gandevia et al., 1996). Since tracking a MEP cannot clarify whether this change originated from supraspinal or spinal levels, a paired stimulation [e.g., over the mastoids level, in terms of cervicomedullary motor evoked potential (CMEP)] in addition to the cortical stimulation, provides a better localisation of the involved site (Gandevia et al., 1999). Therefore, an increased MEP plus lengthened silent period can imply cortical inhibition (Gandevia et al., 1999).

Electrophysiological techniques, like the interpolated twitch technique (ITT) and TMS (e.g., paired and triple stimulation techniques), have provided a great ability to track MN drive during various types of muscle efforts and motor pathways (Ranieri & Di Lazzaro, 2012). An existence of additional force and twitch by an external voltage source, either with ITT on a peripheral nerve or TMS over the primary motor cortex, during a sustained contraction is considered as a sign of central fatigue (Gardiner, 2011). It means that some motor units are not fired at an optimal rate or fully recruited during the voluntary activation. The reduction of MN firing rate in addition to originating from above-mentioned supraspinal factors can be related to the muscle properties (i.e., peripheral level).

A single evoked stimulus elicits a peak twitch that is approximately 5-20% of the maximum muscle force generation of a high frequency completely fused contraction (MacIntosh et al., 2012). An elicited twitch after long tetanus elicits much higher peak force due to post-tetanic twitch potentiation (Behm et al., 1997). Hence, there is a staircase

phenomenon that represents a subsequent increase in force development (following frequency ~lower than 10 Hz). In contrast with the gradual twitch force development, the twitch time course is less influenced by potentiation (MacIntosh & Gardiner, 1987). The underlying mechanisms can be attributed to changes in the intracellular muscle mechanisms (MacIntosh et al., 2012; Behm, 2004), such as phosphorylation of myosin regulatory light chain, a sensitivity of calcium and kinetics of cross-bridge, which will be addressed in the following peripheral factors section.

1.1.2.2 Peripheral Fatigue Contributions

Peripheral fatigue refers to alterations in neuromuscular transmission, largely within the intracellular level, which could affect optimal muscle action potential (AP) propagation and excitation-contraction (E-C) coupling (Enoka & Duchateau, 2008). In other words, the processes "in the peripheral nerve, and neuromuscular junction" (Allen et al., 2008b, p.289), may affect kinetics, the number of actomyosin cross bridges, electrical activity, and force generating capacity (Gardiner, 2011).

The possible mechanisms underlying impaired neuromuscular transmission can be related to depletion of neurotransmitters in the synaptic cleft, post synaptic receptor activity and branch block failure (Krnjevic & Miledi., 1959; Gardiner, 2011). Decrease in the number of neurotransmitters (e.g., acetylcholine) can lead to a reduction in the motor end-plate's amplitude, which could originate from the number of exocytotic vesicles (Reid et al., 1999). Van Lunteren and Moyer, (1996) showed that a fatigue task can be influenced by neurotransmission failure. The authors of this study added 3,4-diaminopyridine to facilitate neurotransmitter release, which induced an increase in force maintenance during tetanic

contraction. In addition, in terms of neuromuscular junction fatigue, the post-synaptic membrane sensitivity is considered an effective player, which influences pre-synaptic activity following a continued activation (Enoka, 2008). Previous studies (Thesleff, 1959; Giniatullin et al., 1986) have shown that a desensitized neurotransmitter receptor can contribute to end plate desensitization.

The propagated AP into a muscle fibre is influenced by a chain of events including the potential membrane, the extracellular and intracellular concentration of sodium (Na^{+}) and potassium (K^{+}), resistance of the membrane, calcium (Ca^{++}) conduction and concentration along the sarcoplasmic, and within the myoplasmic (Enoka, 2008). A failure at each of these events can affect optimal neuromuscular transmission, force velocity and time to relaxation (Allen et al., 2008b). Moreover, an imbalance of adenosine diphosphate (ADP), inorganic phosphate (Pi), Ca^{++}, hydrogen (H^{+}), reactive species of oxygen and nitrogen can influence optimal contractile activity (Sahlin et al., 1998; Allen et al., 2008a).

During a progressive muscle contraction, there are transition states for the intracellular contractile apparatus, i.e., shifts from weakly bound to strongly bound along the actomyosin cross bridge, if it persists enough, thereby leading to changes in inorganic metabolites (Gardiner, 2011). Following physical activity, the rate of used adenosine triphosphate (ATP) hydrolysis for involved skeletal muscle, can exceed over 100 times the rested state (Hochachka & McClelland, 1997). The consumed ATP in addition to be used for myosin ATPase during force output, is regulated by intracellular and extracellular Ca^{++} concentration, and Na/K - ATPase which controls the efflux of Na and influx of K after the AP (Gardiner, 2011). In fact, the triad junction of muscle fibre is considered as the main site for depleted ATP (MacIntosh et al., 2012). Since the rate of regenerated ATP cannot be fully

supplied by aerobic metabolism, the non-aerobic (anaerobic) replenished ATP (limited capacity) leads to lactate formation (Maclntosh et al., 2012). The cytoplasmic ATP for muscle fibre is preserved at a nearly constant level (rarely may decrease by half of its initial concentration) (Karatzaferi et al., 2001). The lactate and H accumulation following a fatigue task may be considered a detrimental factor for contraction, while playing a protective role for the nervous system (Cairns, 2006). During intensive stress, the ATP is depleted at the triad junction slowing sarcoplasmic reticulum (SR) channel release of Ca^{2+}, decreasing actin-myosin interaction and the Ca^{2+} uptake by SR, thereby decreasing power generation (Maclntosh et al., 2012). The products of phosphocreatine's breakdown are Pi and creatine (Cr) (Sahlin et al., 1998). An increased Pi, through decreasing Ca^{2+} sensitivity and ryanodine receptor impairment, may induce force reduction (Allen et al., 2008a). Further, cross-bridge, and Ca^{2+} troponin binding, can be inhibited due to an increased Pi (e.g., following a fatiguing tetanic task in fast twitch fibres) [Maclntosh et al., 2012]. Also, the metabolic stress (i.e., a reduced ATP, pH and an increased ADP's intracellular level) activate K-ATP channels, which help to prevent muscle fibre damage (Allen et al., 2008b). In terms of metabolic catastrophe effects, it has been illustrated that the main underlying mechanisms for a damaged muscle fibre is attributed to large elevation of Ca^{2+} resting status, higher ATP hydrolysis or Ca^{2+} and myosin in intracellular level, and the impaired function of the K^+ channels (Jackson et al., 1984; Cifelli et al., 2008).

A task can result in fatigue due to the accumulation of K outside of the surface membrane resulting in impairment of Na^+ channels, thereby decreasing AP velocity along the membrane (Allen et al., 2008a). The ion's permeability of the membrane changes during an AP, e.g., extracellular K increases from 3.5-4 mM (at rest) to 10-14 mM during muscle

activation (Juel et al., 2000). Previous evidence (Cairns et al., 2011) suggested a possibility of force reduction if the K level was less than 10 mM, and submaximal tetanic forces demand to raise about 12 mM (Holmberg & Waldech, 1980). A failure to maintain initial Na^+ and K concentration also may reduce the excitability of the membrane (Juel at al., 2000). Microdialysis of human vastus lateralis muscle, during dynamic knee extension, showed a significant increase in interstitial K (Juel et al., 2000). An AP impairment also can happen either by an external reduction of Na^+ or an intracellular increase of Na^+ due to a greater potential polarization (e.g., following repeated intensive activations, Cairns et al., 2003). Meanwhile, inward Na^+ needs a greater membrane permeability than K and chloride (Cl^-) to activate an AP (Enoka, 2008). Hence, the membrane excitability can recover by decreasing Cl^- permeability, which contributes to the higher extracellular K levels (Pedersen et al., 2005). There is a decrease in inward Na^+ current (inactivated Na^+ channels) if K concentration reached around 11 mM (Pedersen et al., 2005). This inactivation results in Cl^- counteracting Na^+ depolarization (decreasing amplitude of AP). As a consequence, the lowered Cl^- permeability, because of the Cl^- counteracted Na, allows a higher AP amplitude (MacIntosh et al., 2012; Pederson et al., 2005).

A triggered muscle contraction originates due to an AP, from Na^+ influx, and K efflux via their voltage-sensitive channels resulting in depolarization and repolarization (Gardiner, 2011). The accumulated K in the transverse tubules (t-tubules) can attenuate the voltage sensors, which in turn can reduce the Ca^{++} transient (Allen et al., 2008b). The t-tubules volume is small and includes a high concentration of dihydropyridine Ca^{++} channels (or L-type Ca channels). AP is propagated over t-tubules and detected by dihydropyridine receptors channels, which regulate Ca^{++} current activity in the SR (MacIntosh et al., 2012). Therefore,

their conformation is affected by ion changes and the electrical charge, which induced the AP propagation (Enoka, 2008). Hence, there is a close relationship between the voltage sensor and ryanodine (RyR) receptors. AP detected by L-type channels results in a spatial change of RyR (Ca-release channels in the SR) receptor, thereby releasing calcium (Allen et al., 2008b).

The function of Ca^{++} (force at a given Ca) is expressed in terms of Ca^{++} sensitivity (for additional review, MacIntosh, 2003). The sensitivity of Ca^{++} affects Ca^{++}-bound troponin and cross-bridge kinetics (MacIntosh et al., 2012). The kinetics can be influenced by: "sarcomere length, pH, myosin regulatory light chain (RLC) phosphorylation, and temperature" (MacIntosh, 2003). Meanwhile, the binding site of actin-myosin can be blocked by tropomyosin, in the presence of a low concentration of Ca^{++} (MacIntosh et al., 2012). As Sweeney and Stull, (1990) pointed out, the number of engaged cross-bridges (rate of engagement), following a quick longitudinal stiffness, is considered a main factor, which influences potentiation. Moreover, an increase in Ca^{++} level, following muscle contraction, affects Ca^{++}-calmodulin compounds with myosin light chain kinase (MacIntosh et al., 1993); the repetitive contraction results in progressive phosphorylated RLCs. MacIntosh and colleagues also illustrated that, in a fatigued state, while there was a decrease in the rate of phosphate incorporation, the RLC phosphorylation persists (1993).

The AP propagation activated-dihydropyridine receptor is directly connected to the RyR channels. The Ca-release channels in the SR, in terms of regulatory ligands, are mediated mostly by ATP, Ca^{2+} and magnesium (Mg) [MacIntosh et al., 2012]. There are two main locations with higher and lower affinity, on the Ca-release channel, which result in activation and inhibition of the RyR (Lamb, 2000). Binding Ca^{++} and ATP - high-affinity sites, against binding Ca^{++} and Mg – low affinity sites- increase the probability of opening of the RyR

(Meissner, 1986). In fact, Mg plays an inhibitory role, which is critical at rest and following decreased ATP (Meissner, 1986); i.e., ATP decreases-Mg rises, resulting in attenuated RyR activities.

The net ATP (produced vs. consumed ATP) is the crucial concept which influences fatigue-resistance of a single muscle fibre. The fatigue-resistance can be decreased if the rate of ATP hydrolysis exceeds the supplied ATP (i.e., maximum rate via aerobic pathway) [Van der Laarse et al., 1991]. As Zhang et al. (2006) showed that regardless of the muscle fibre type (fast or slow twitch), fatigue sensitivity can be affected via a decrease in the provided O_2. Also, based on the "Henneman's size principle", during a simple isometric muscle contraction, there is an orderly recruitment of motor units, i.e., more excitable motoneurons with small size to less excitable with large size (Gardiner, 2011). Moreover, the O_2 delivered to a target muscle by blood flow (Guyton, 2015), may be considered a main factor influencing the resistance to fatigue (Egana & Green, 2007). The position of a limb related to the heart also can influence the rate and extent of fatigue due to perfusion pressure effects (Wright et al., 1999; 2000). O_2 perfusion can also be altered due to a change in body position.

Therefore, it would be of interest to examine how changes in posture, body position, and or active muscle relative to the heart level can influence fatigue-resistance of muscle. The aim of this literature review is to explore how BFR in an arm muscle, following inversion, can influence the acute muscle isometric force production, EMG activity, cardiovascular, pain and fatigue. In the upcoming section, in view of the many interacting systems, the underlying strategies will be presented in response to varying body positions.

1.2 Understanding Potential Mechanisms During an Inverted Body Position

Although our knowledge regarding human performance in extreme environments has been improved extensively, there is still a need for further investigations on the underlying physiological and psycho-physiological factors responsible for neuromuscular fatigue in varying body positions. As we will see in the following sections of the literature review, (inversion section), the underlying factors (the vestibular and postural adjustment mechanisms, neuromuscular performance, regulation of hemodynamics and cardiovascular contributions) will be discussed concomitant with a comparison between responses to upright (erect) and various body positions.

1.2.1 Vestibular System

A key sensory input which helps to modify posture, following a disturbance in balance, is from the vestibular system (Horak et al., 1994). This fast-automated response, context-based, can be influenced by various types of sensory input, e.g., visual, cutaneous and proprioceptive (for more review, Fitzpatrick & Day, 2004). The vestibular apparatus, i.e., three semicircular and two otolith organs, which are positioned in the internal ear of the labyrinths, due to internal inertia, enable us to detect the magnitude of the head's rotation and translation (Kandel, 2013). The superior and lateral canals of the semicircular and the utricle of the otolith organ are innervated by the superior part of the vestibular nerve. While, the posterior canal and the saccule are innervated via the inferior segment of the vestibular's cell body; the hair cells carry signals, i.e., mechano-sensing responses to endolymph movement, thus transmitting data via vestibular nuclei, and medulla to higher centers (Kandel, 2013). Furthermore, in terms of the motor characteristics, the vestibular system projects to the

cervical and thoracic segments, via the vestibulospinal pathway (Horak et al., 1994). Hence, previous studies (Kerman & Yates, 1998; Kerman et al., 2000) illustrate that sympathetic discharge, following postural changes, can be modulated by activation of the vestibular system. Recording sympathetic nerve activities of the kidney, adrenal gland, gastrointestinal pathway, bladder and external carotid during electrical stimulation of vestibular afferents showed an altered autonomic function (Kerman & Yates, 1998). However, Ray et al. (1997) found that a head down neck flexion, which activates the otolith organ, did not influence sympathetic activities of the skin nerve.

It is well known that the altered discharge rate of vestibular afferents through electrical activation of the nerve (Yates & Miller, 1994), head down neck flexion (Ray et al., 1997), off-vertical axis rotation (Kaufmann et al., 2002), can lead to changes in discharge of the sympathetic outflow (changed vasoconstrictor efferent discharges). Further, a bilateral vestibular neurectomy study during a whole-body tilting showed a regionally increased vascular resistance (altered femoral vascular resistance), which illustrates the roles of the vestibular system on orthostatic hypotension (Wilson et al., 2006). It may raise a question; is there any vestibulosympathetic pattern or adjustment mechanism to control the blood flow (following changing in posture) to the target muscle or organ.

The CNS via inputs (descending or ascending) (i.e., neural, mechanical and chemical receptors) into the medulla oblongata as the control centers, regulates the heart and peripheral circulation (Mitchell & Victor, 1996). Furthermore, an induced autonomic outflow of the sympathetic and parasympathetic nerves, in terms of the neural control system, results in immediate cardiovascular feedback following various types of physiological perturbation (e.g., postural change, exercise, microgravity) (Mitchell & Victor, 1996). Hence, in terms of

feedback mechanisms, afferent inputs from working muscle and viscera can change and decrease the blood flow and blood pressure (following muscle contraction) (Kerman et al., 2000). There is a third order of vestibular and fastigial - afferent inputs to the nucleus of the solitary tract (Balaban & Beryozki, 1994), which influence the motor nuclei of the vagus (dorsal part) as well. In addition, the carotid sinus baroreflex, first synapse, is located in the solitary tract nuclei and plays an important role to regulate cardiovascular function (for more review, Costa et al., 1995). Therefore, because the seated inverted body position can activate vestibular response. It becomes a question whether the decreased heart rate and blood pressure (i.e., reduced sympathetic activities), (Paddock & Behm, 2009; Hearn et al., 2009; Johar et al., 2013; Smith et al., 2013; Neary at al., 2015), could be attributed to the vestibulosympathetic inhibition effects or other graviceptors.

1.2.1.1 Heart Rate and Blood Pressure Response. The interaction between peripheral and central factors can change the HR and BP responses. Previous studies (Paddock & Behm, 2009; Hearn et al., 2009; Johar et al., 2013) have shown that an inverted body position resulted in HR and BP decreases. Meanwhile, it would be expected that being upside down (inverted position), may be stressful and should activate the sympathetic “alarm reaction” or “fight-or-flight reaction” (Hall, 2015). However, the decreased HR and BP responses imply that other mechanisms are involved. As Bosone et al. (2004) pointed out, a negative head down tilt causes acute intracranial hypertension, which leads to decreasing sympathetic system activity. It can be attributed to the activation of baroreceptors. Baroreceptors are mechanoreceptors, which are sensitive to tension changes in the arterial wall, which are positioned in the carotid sinuses and aortic arc. Their signals are transmitted via glossopharyngeal and vagus nerves in the medullary area (Guyton, 2015). Baroreflex

performance can be influenced via changes in posture and can affect the activity of the sympathetic system (i.e., an altered noradrenaline circulation due to the chronotropic and inotropic impacts) (Hinghofer-Szalkay, 2011). A shift from a supine or sitting position to upright posture may induce orthostatic hypotension, which is defined as a 20-mmHg decrease in systolic blood pressure or 10-mmHg diastolic decrease (Lanier et al., 2011). The blood volume can be maintained steady in the presence of a change in body position, which is called the volume indifferent point (i.e., an unaffected blood volume and blood pressure) (Jarvis & Pawelczyk, 2010). In fact, the tolerance of a person following orthostatic stress contributes to the cardiac preload stability (Jarvis & Pawelczyk, 2010). Since the portion of the venous system of the lower body includes the vast majority of whole blood volume, it integrally influences the cardiac output (Rowell, 1993). Jarvis and Pawelczyk, (2010) showed that the splanchnic circulation significantly affected the location of the volume indifferent point, which counteracted with orthostatic stress. Moreover, following a head-up tilt test, accumulated blood in the legs, can cause decreased central blood volume (Matzen et al., 1991). This test helps to assess the cardiovascular reflexes like hemodynamics, HR and baroreceptors, which can be inhibited in patients with orthostatic hypotension and vasovagal problems, and predict vasovagal syncope recurrence (Matzen et al., 1991; Iacoviello et al., 2010). As Charkoudian et al. (2004) showed a minor increase in central venous pressure caused a lower sensitivity of the baroreflex response, which regulates sympathetic nerve activity of the muscle.

Another possible candidate is a sense of freezing (“remaining motionless” protocol), which may be identified during inversion, resulting in bradycardia and decreased body sway (Roelofs et al., 2010). Using a posturographic technique participants who stood on a

stabilometric force platform experienced freeze-like behavior. The data revealed that participants with an angry face versus those who had neutral and happy faces, based on a social threat cues feedback, had less body sway and bradycardia (Roelofs et al., 2010). It is noted that freezing is considered a defensive feedback in animals to predator threat, which causes both the above-mentioned outcomes (Blanchard et al., 1986).

Therefore, with body inversion, due to the gravity impacts and the plausible increase in the central venous pressure, we can expect a decreased in the baroreceptor function. Also, it appears reasonable to expect desensitized sympathetic activity following body inversion, causing a decrease in the HR and BP output. Hence, the presence of bradycardia during inversion may originate from the freezing (remaining motionless) effects.

1.2.2 How Postural Threatening Can Affect Neuromuscular Response?

A postural adjustment needs to be processed by both central and peripheral structures (Ivanenko et al. 2000). An input (e.g., vestibular or visual) via sensorimotor and anticipatory postural system affects balance (Kollmitzer et al., 2000; Slijper and Latash, 2000). Generally, a shift in body position is accommodated by an anticipatory postural adjustment strategy, which occurs before postural perturbations, helping to minimize postural disturbances (Massion, 1998). Additionally, a post-postural perturbations mechanism (i.e., compensatory postural adjustment), plays a vital role during predictable and unpredictable destabilization, helping to diminish the instability effects (Nashner & McCollum, 1985; Claudino et al., 2013). The magnitude of these pre-post responses can be influenced by the direction (Latesh et al., 1995; Horak et al., 2005), and the degree of the perturbations (Bouisset et al., 2000). Grover et al. (2013) proposed that platform simulated wave motions

provide similar effects like instability and falling risks (Wertheim, 1998; Matsangas et al., 2014), resulting in perturbed equilibrium, which may induce fatigue (tiredness due to adjusting balance), and can also influence neuromuscular responses. Since during body inversion, the participants have a sense of stumbling, while secured completely in their position via straps, it seems rational to direct, partially, the results of the decreased force output (Grover et al, 2013; Hearn et al., 2008; Paddock & Behm, 2009; Johar et al., 2013), to a muscle stiffening mechanism (Carpenter et al., 2001). The stiffness refers to "the difference between center of pressure – center of mass", (Carpenter et al., 2001). Further, calculating a ground reaction force illustrates the center of pressure, which reflects the required torque to control an acceleration of body-mass (Palmieri et al., 2002). Joint stiffness, in terms of muscle tone, helps to control the upright posture. In the horizontal plane a plantar/dorsal flexion about the ankle joint, and in the frontal plane an abduction/adduction about the hip joint, help to control center of pressure (Winter et al., 1998).

1.2.2.1 Psycho-Physiological Impacts. An upper back destabilizing force can lead to a decrease in the center of mass displacement in people suffering from fall issues (Adkin et al., 2002). Horak et al. (2005) showed an individual with Parkinson's had an impairment of the trunk and knee flexion following lateral and backward postural destabilization, respectively. With Parkinson's patients, the inflexible postural control may cause an increase in postural sway, for instance with raised toes above the ground level. The ineffective stiffening reflexes are attributed to the regulation of muscle tone and the basal ganglia's function (Horak et al., 2005). In patient with Parkinson's, the problem of akinesia (muscle rigidity and a limited willpower) originates from impairment of dopamine secretion along the basal ganglia (Guyton, 2015, p.734).

A postural threatening protocol that alters the center of mass is compensated by an anticipatory postural adjustment strategy, to support the balance (Adkin et al., 2002). The difference between center of pressure (neuromuscular feedback following a shift in the center of mass) and center of mass, contributed to swaying which induces changes in the center of mass velocity (in the sagittal plane) (Winter et al., 1998). Carpenter et al., (1999) proposed that an ankle stiffness strategy is adopted with a perceived risk of falling, i.e., lower supporting versus higher supporting surface. An absence of this anticipatory postural adjustment mechanism, i.e., activated anterior tibialis and deactivated gastrocnemius, leads to change in the magnitude and timing of the feedback, which is common in people with Parkinson's (Frank et al., 2000).

It is well known that balance as a fundamental ability, based on a task, is necessary to maintain during daily function and athletic activity; thus, a stabilized center of mass or posture (related to a base of support) contributes to a good balance (Knudson, 2007). Adkin et al., (2002) found that the stiffening strategy, as a conservative mechanism of the CNS, can negatively influence voluntary movement. The inversion study by Hearn et al., (2008) showed that there was an increase in contralateral EMG activity for core muscles (abdominal and trunk); performing an isometric elbow flexion while inverted versus minimal activity during seating in the upright position. As Grover et al. (2013) demonstrated that wave-motion can cause a feeling of instability and balance threats, thus increasing the vestibulospinal function, which can influence autonomic adjustments (Doba & Reis, 1974). An increased co-activation of the flexor-extensor, trunk muscles, resulted in a more stabilized trunk (Arokoski et al., 2001). Previous studies (Anderson & Behm, 2004; Drinkwater et al., 2007) demonstrate that inducing a higher stress on musculature, e.g., isometric chest press on a swiss ball versus

performing on a stable platform, resulted in greater efforts to maintain joint stability, and a significant suppression of force production. This reduction in the ability to exert force can be attributed to a shift from mobilizing to stabilizing strategies of the neuromuscular system (Anderson & Behm, 2004). Moreover, Behm and Anderson, (2006) recommended that increases in co-contractions contributed to the force reduction. As a consequence, it can provide a logical reason for the inversion-induced neuromuscular impairment, due to increased co-contraction ratio, triceps to biceps EMG activity (Hearn et al., 2009), hamstring to quadriceps EMG activity (Paddock & Behm, 2009).

Following a postural threatening protocol (altered surface height), raising toes as a voluntary movement helped to control balance (Adkin et al., 2002). A higher level of fear of falling and anxiety can lower the magnitude of this strategy and decreased control of posture (Adkin et al., 2002). Fear of falling may also influence balance. Carpenter et al. (2001) demonstrated a decreased postural sway amplitude, but an increased postural sway frequency in healthy people who stood above the ground. Further, a lean away from the edge of a raised platform, shifted in center of mass, leading to skin conductance increases; which reflect the higher anxiety and arousal levels (Cleworth et al., 2012). Anxiety is described as an individual-based fearful arousal, which can be perceived at any moment; and can be related to autonomic and cognitive factors (Staab et al., 2013). The fear of falling is described as a low perceived self-efficacy, which may cause falling, following extreme circumstances or non-hazardous activities (Tinetti et al., 1990). The prevalence of this problem is common in neurological patients with balance and vestibular impairment (Yardley & Hallam, 1996), and elderly individuals (Tinetti et al., 1988). It has been shown that a previous fear of falling in

elderly individuals, results in a higher risk of future falls in comparison to individuals who have never fallen (Nevitt et al., 1989; Speechley & Tinetti, 1990).

Johar et al. (2013), demonstrated slightly greater reduction in EMG values, following a rapid inversion rotation (1-s) versus a slower 3-s rotation, which may be attributed to a higher postural threat. Smith et al. (2013) illustrate that the seated inversion led to a 25% increase in anxiety scores and execution time in comparison to an upright position. These findings suggest an inversion-induced inhibition of optimal cognitive function, thus decreasing neuromuscular functioning. Moreover, previous evidence (Button & Behm, 2008) explained that a decrease in muscle force and activation could happen through expecting a supramaximal stimulation, such as using ITT, which may be considered as a noxious stimulus. They concluded that the CNS - consciously or subconsciously induced this impairment (Button & Behm, 2008). Although, Behm and St-Pierre, (1997) provided evidence regarding the possibility to fully activate quadricep muscle. Hortobagyi et al. (1992) suggested that discomfort might hinder the ability for full muscle activation. Since the prior seated inversion studies (Neary et al., 2015; Paddock & Behm, 2009) have mentioned that there was a distinct perception of swelling around the head region, plus using a supramaximal stimulation, it seems logical to expect the CNS impairments.

1.2.2.2 Function of Respiratory System. Changes in body posture can affect the activation of the inspiratory muscles (Konno & Mead., 1967). During inversion, it would be rational to expect an altered activation of thoracoabdominal and intra-thoracic pressure, which can originate from gravity effects. If so, it means that the respiratory system requires more work to adapt with the inverted body position; thereby probably resulting in fatiguing of these muscles.

The respiratory muscles have a similar mechanical function during muscle contracting (attached to a bony structure with a displacement capability), i.e., there is an expansion of the abdominal wall, and ribcage versus gravity for inspiratory muscles during standing position (Hudson et al., 2016). This mechanical action can alter following changes in the body position. With supine posture, previous studies (Butler et al., 2001; Segizbaeva et al., 2011) showed that the abdominal and pleural pressures and activity of the inspiratory muscles could change. Hagbarth & Vallbo, (1968) found that there was a low conduction velocity for some of the afferent fibres which led to a synchronous pulse between the nerve discharge and respiratory cycle. Hudson et al. (2016) showed a decrease in rib cage expansion, increased inspiratory pressures, unchanged diaphragm EMG, and also a reduced scalene activity following an upside-down posture. Hudson and colleagues proposed that the different activation of the muscles, in terms of the coordinated activity, in comparison with a standing and supine position, can reflect as an altered neural output (2016). Theoretically, this decrease in motoneuron output (Hudson et al., 2016), i.e., the scalene muscles to raise the ribcage, can be interpreted, indirectly, based on a result of the study by Hudson et al. (2009) (feedback of a non-respiratory muscle). A force produced at a joint can be determined via finding the link between projected nerve to a muscle and its biomechanical contributions. In a study by Hudson et al. (2009), the function of first dorsal interosseous to index finger flexion force and evoked twitch, around the metacarpophalangeal joint, were measured during thumb abduction and extension. Hudson et al. (2009) showed an increase in mechanical properties of the first dorsal interosseous muscle, to produce index flexion, were related to an increase in the neural drive of the muscle.

Furthermore, changes in body posture can also cause an impairment of gaseous exchange (Prisk et al., 2002), and alteration in pulmonary blood flow (Hillebrecht et al., 1992). Prisk et al. (2002) demonstrate that a 6 degrees head down tilt-induced different pulmonary and cardiovascular performance, which were attributed to altered mechanical contributions (lung, chest, abdominal wall) and fluid transitions along the body, respectively. Further, it has been shown that head down body tilt induced decreases in sympathetic activities (Bosone et al., 2004), and the sympathetic outflow affected bronchodilation (Van der Velden & Hulsmann, 1999). A 30 degrees head-down tilt causes a reduced rate of respiration, and increased the airway resistance (Segizbaeva et al., 2010). The results showed a reduction in inspiratory thoracic muscles factors and increased EMG activation of the diaphragm. With these contexts and dependency of skeletal muscle to oxygen, therefore the resistance airflow increases can lead to a suppressed in O2-conductance to the muscle fibre which may result in inhibition of optimal excitation-contraction coupling (Hepple et al., 2002) and force generation.

1.2.2.3 ***Hemodynamic Changes*****.** The control of blood flow can be influenced by two mechanisms, acute and long-term regulation (Hall, 2015). Acute control providing a rapid function to keep appropriate blood flow for local tissue (e.g., via arteriolar vasodilators or vasoconstrictors). The long-term regulator (slower mechanism in comparison with acute control) controls the flow via changing the numbers and size of the vessels (Hall, 2015).

An altered circulation (centrally and peripherally) can influence the perfusion pressure of the muscles. Fitzpatrick et al. (1996) demonstrated that an arm lifted above the heart level (45cm) causes a decreased hand perfusion pressure and force generation. Whereas, lowering the arm below the heart level (45 cm) resulted in force output increases (Fitzpatrick et al.,

1996). Sundberg and Kaisjer, (1992) showed a decrease in muscle performance when graded ischemia (up to 50mmHg) induced a progressive decrease in perfusion of the lower limb. Further, the presence of fatigue was significant in the supine position in comparison with an inclined posture, during both moderately and highly intensive exercise (Egana & Green, 2007). However, it was not significant following low-intensity fatiguing contraction (30%MVC) [Egana & Green, (2007]. One possible reason could be attributed to muscle blood flow (Egana & Green, 2005; Fitzpatrick et al., 1996), and delivery of O_2 to working muscle (Hogan et al., 1994). MacDonald et al. (1998) found a supine position induced slower rate of alveolar oxygen transport and muscle blood flow, which could be attributed to the decreased perfusion pressure. Also, Hobbs and McCloskey, (1987) show a decreased local arterial pressure in addition to a reduced bloodstream, can result in a force reduction. The arterial pressure decreases affected less fatigable muscle fibres type (in this study soleus and medial gastrocnemius), and it did not influence the caudofemoralis as a fast-fatigable fibre type (~ 90% IIb). Then, in the second part of this research (human participants), a decreased muscle perfusion via raising the leg above the heart induced an increased EMG activity following a repeated plantar flexion at the given target force (Hobbs & McCloskey, 1987). This increase in EMG implies that the higher level of motor unit recruitment was needed to keep the produced force at a given level. Further, Lanza et al. (2006) proposed that an ischaemic skeletal muscle can alter ATP synthesis. Because there was a balance between the supplied and demanded ATP, the decreased in ATP's demand during this ischaemic condition may have contributed to the reduced force and induced fatigue (Lanza et al., 2006).

BFR can also be impeded by the intensity of the muscle contraction. Sadamoto et al., (1983) illustrated that there was a complete BFR to the target muscle (biceps brachii, calf,

vastus lateralis and rectus femoris) during sustained muscle contraction at 50-64% MVC. Sjogaard et al. (1988) and Gaffney et al. (1990) have found a steady blood perfusion to exercised muscle following submaximal isometric fatiguing task at 5-15% MVC, while reduced perfusion at the end of the contraction with moderate intensity (25-50% MVC). The results of Griffin et al. (2001) verify the aforesaid outcomes. During 2-min isometric elbow extension (20% MVC) and recording of the profunda brachii artery (triceps brachii muscle is supplied by this artery), there was a constant perfusion, even though it was followed by an initial rise.

Previous inversion studies have revealed that the decreased upper and lower limb force generation can be associated with the altered hemodynamic contributions. Since one of the hypotheses of this literature is to discover how BFR of the arm muscle can affect force generation and fatigability during inversion. It appears logical to speculate a greater decrease in force production, and a higher rate of fatigue with less O_2 supply and perfusion pressure.

1.2.2.4 Gravitational Pressure Effects. Inversion can lead to an increase in hydrostatic pressure for upper body and head region, while suppressing hydrostatic pressure in the lower limbs. It may raise a question whether or not the upper limbs and cerebrum, during inversion, can efficiently regulate this exposure to higher hydrostatic pressure and blood pooling.

Gravitational or hydrostatic pressure is defined as an exerted pressure by the weight of a fluid, exposed to air, to a point within it (Hall, 2015). It means that there is an increase in hydrostatic pressure from the surface to the depth. During a standing position, a reduction in hydrostatic pressure for lower body is regulated via different mechanisms. Respiratory muscle pressure plays a key role to modulate the returned venous flow from the lower limbs (Miller et al., 2005). Also, functional hyperemia during muscle contractions, induces

metabolites accumulation, affecting arterioles resistance via a decrease in noradrenaline release (Delp & Laughlin, 1998). In addition, Vissing et al. (1997) showed that the cutaneous circulation through sending veno-arteriolar feedbacks caused vasoconstriction responses. The above-mentioned mechanisms also, can provide evidence how the human body through decreasing hydrostatic pressure impacts orthostasis.

To clarify the possible effects of increased hydrostatic pressure on the cellular level, both pathological signs and neurophysiological responses are important. With high gravitational pressure, previous animal studies show an altered function of acetylcholine receptor (Heinemann et al., 1987), relative decreased in isometric activity of psoas single muscle fibre (Geeves & Ranatunga, 1987), and change in twitch tension contributions of extensor digitorum longus muscle (Ranatunga & Geeves, 1991). Harper et al. (1981) illustrated a reduction in depolarization and repolarization rate of propagated AP in Helix (snail) neurons, following a high hydrostatic pressure on the membrane currents. Moreover, a kinetics decrease in Na^+ and K channels were observed following high hydrostatic pressure (more than 100 MPa), while it did not influence the conductance of these channels (Macdonald, 2002). In fact, this higher pressure can influence the function of the charge sensor and can cause altered conformational activity of the voltage-gated channels, which may provide a rational reason regarding the adaptability of aquatic animals with the ambient pressure (i.e., most likely pressure-dependent) [for review, Macdonald, 2002]. However, exposure to high-pressure may evoke a neurological problem, which is known as the high-pressure nervous syndrome (Gilman et al., 1989); it can also be found among deep-divers (Brubakk & Neuman, 2003).

Exposure to higher pressure can lead to a slowed conduction velocity of peripheral nerves, a decreased synaptic transmission, reduced amplitude of AP; while a severe hyperexcitability of CNS in patients with high-pressure syndrome (for more review, Talpalar & Grossman, 2006). Meanwhile, this hyperexcitability can be differently interpreted when the subject of study is the entire nervous system versus a simple invertebrate, respectively (Etzion & Grossman, 1999). As Rostain et al. (1986) pointed out, GABA was not the primary neurotransmitter which affected the behavioural aspects of their rats with high-pressure neurological syndrome (e.g., tremor, myoclonus and convulsions). A series of drugs like sodium valproate, nipecotic acid, diaminobutyric acid and beta-adenine were used to increase the mediatory transmission impacts of GABA (for review, Rostain et al., 1986). The results show that only sodium valproate had a protective effect on the behavioural symptoms following exposure to high pressure (Rostain et al., 1986).

Moreover, a potential mechanism for the impaired brain function in the presence of higher hydrostatic pressure may be attributed to the metabolic function. The brain in fact, needs a continuous supply of glucose and O_2 transported across the blood-brain barrier. However, metabolic substrates cannot be store within the brain (Diringer, 2008). Approximately twenty percent of consumed O_2, is consumed by the brain (Diringer, 2008). However, Arbeille t al. (2001) showed that there was a moderate alteration in cerebral blood flow during a four days head down tilt. Frey et al. (1993) recommend that an increase cerebral vascular resistance, following a 2-day head tilting experiment, is due to intracranial pressure increases.

Increased hydrostatic pressure was observed by Bosone et al. (2004) following a head-down tilt manoeuvre. An altered body posture can cause a rise in intracranial arterial pressure

(Bosone et al., 2004), higher pressure around head (Paddock & Behm, 2009), and intraocular pressure (Linder et al., 1998), respectively. As Linder et al. (1998) pointed out there was a 3-fold increase in intraocular pressure following a complete gravity inversion, which can be attributed to the shift in cephalic fluid. This inversion-induced higher intraocular pressure resulted in a significant decrease in neurophysiological performance (retinal and cortical levels) [Linda et al., 1998]. Baweja et al. (2009) show that a removal of visual feedback to match with target force, during isometric muscle contraction, induced an amplified error. Significant difference of lower limb EMG activity (50% and 75% MVC) during inversion against upright seated position (Paddock & Behm, 2009), maybe attributed to the decrease in visual function, thereby increasing force error.

1.2.2.5 Potential Effects of BFR on Neuromuscular Function. At the onset and during both isometric and dynamic contractions, there is an increase in human pressor response. The increased exercise-pressor reflexes are partially regulated by the peripheral reflex from the small diameter muscle afferents (Amann et al., 2014). Arrested local blood supply can lead to altered human pressor response during voluntary and involuntary evoked isometric muscle contraction (Bull et al., 1988; Gladwell & Coote, 2002). As Bull et al. (1988) pointed out there was a constant increase in HR and BP following a 2-min seated sustained plantar flexion and evoked contraction of the triceps surae, at 30% MVC. Moreover, Gladwell and Coote, (2002) showed that the rise in HR was a bit faster in comparison with BP, during voluntary isometric contraction of triceps surae at 40% MVC. A different mechanism is suggested in terms of beginning the pressor response, and muscle afferents effects. Because, for instance, in another experiment by Gladwell and Coote, (2002), a significant increase in HR response was observed following a 1-min passive stretching of triceps surae, though it was

not significant for BP. Further, a circulatory occlusion on cessation of contraction resulted in a higher BP (relative to the pre-exercise level) while HR decreased to baseline levels (Bull et al., 1988; Gladwell & Coote, 2002). It is well known that a conducted signal to both cardiovascular centers and exercised muscle are regulated by the descending motor command (Goodwin et al., 1972; Thornton et al., 2001). While, the inputs from muscle afferents (Group III and IV) play an important role to control HR; in the presence of abolished central command-muscle for example, HR still remains elevated above the baseline levels (Fisher & White, 1999).

Muscle afferents with small diameter help to modulate cardiovascular responses. Previous studies show polymodal functions for these slowly conducting afferents, which are sensitive to both mechanical and chemical stress (Mense & Meyer, 1985; Kaufman et al., 1983). As Kaufman et al. (1983) pointed out there was a sensitivity for group III, due to stretched and contracted muscle, while it did not influence the activity of group IV, which can verify the results of Gladwell and Coote, (2002) on human participants.

Furthermore, the increasingly higher metabolite by-products can cause the greater activation of group III and IV afferent fibres (Bull et al., 1988; Yasuda et al., 2010). Previous investigations (Sundberg et al., 1994; Yasuda et al., 2009) suggest that BFR during a low-intensity training because of increasing muscular adaptation, can induce a higher muscle activation (integrated EMG activity). The net balance between the energy demand-supply can be attributed to the greater muscle activation. Since there is a progressive increase in the intramuscular tissue pressure, squeezed vessels and blood flow occlusion, during a static muscle contraction, thus indirectly causes a dependency on anaerobic ATP production (Sadamoto et al., 1983). These effects were partially verified in animal studies under the

influence of lactic acid (as a metabolic product during muscular contraction). Rotto & Kaufman, (1988) through cutting L7 and S1 ventral roots and recording from dorsal, anesthetized cats, and increasing the metabolic products concentration like lactic acid, showed a significant increase in discharge of group III and IV afferents. As mentioned earlier, there is a possibility of compensatory function (probably a greater neural activation) due to the altered provided energy (Bigland-Ritchie et al., 1986), which it was reported as well during a combination of muscle contraction with low intensity and complete BFR (Yasuda et al., 2009).

The chemoreceptive afferents, in terms of induced inhibition reflex can decrease the firing rate of motor unit during a fatiguing task with BFR (Bigland-Richie et al., 1986), and intermittent fatiguing protocol under ischaemia of the muscle (Garland, 1991). To simplify, Garland, (1991) speculates that the excitability of the H-reflex can be reduced during a fatiguing task, and this reduction can match with EMG activity and inhibited α-MN reflex (input from sensory afferent). Therefore, by compressing the sciatic nerve, blocking large afferents, before the intermittent fatiguing trial of the soleus (electrically stimulated at 15Hz), there was a further reduction in maximal plantar flexion torque and mean EMG, in comparison to the pre-fatigue compressed nerve (Garland, 1991). Later, the moderately altered M-wave and superimposed twitch, in this study, clarified the presence of adequate peripheral excitability and descending motor drive, respectively. The mentioned findings suggested that fatigue-induced inhibition α-MN could be regulated by small diameter muscle afferents.

The failure to maintain the required task or produced force leads to fatigue. Both mechanical and metabolic factors have a key role in the appearance of muscle fatigue.

Although, altered neural drive, changes in descending command from supraspinal and/or spinal reflexes, can be attributed to the fatigue as well. Moreover, various synaptic inputs (cortex, spinal and muscle) – monosynaptically or polysynaptically - are projected to α-MN pool, which can affect final motor output (Gardiner, 2011). With these contexts and the well-known concepts regarding the effects of excitatory and inhibitory inputs on the α-Mn pool (Gandevia, 2001; Leonard et al., 1994), a key concept which would be valuable to discuss here is the sensitivity of the Hoffman (H)-reflex following a change in body posture. Meaning, it would be feasible to clarify other involved factors that may influence the neuromuscular responses following the inverted body position.

1.2.2.5.1 Hoffman (H-)Reflex

The indirect way to assess the afferent excitability of the spinal motoneuron pool is with the Hoffman (H-)reflex. The amplitude of this reflex reflects the excitatory-inhibitory net balance (Schieppati, 1987), though as Leonard et al. (1994) pointed out the sensitivity of H-reflexes, based on the different circumstances, are the "demands placed on muscle". The following explanation help to shed light this statement. The EMG is useful and standard task-dependent measurement to find final motor output (Enoka, 2008). Following a fatiguing task, electrically or volitionally, there is a reduction in EMG features like mean power frequency and root mean square (Bigland-Ritchie et al., 1986; Moritani et al., 1986). Moreover, modulation of α-MN pool can be differentially influenced via receiving inputs, in terms of voluntary or involuntary activation. Because, a voluntary activity induces an orderly motor unit recruitment, "Henneman's size principle", while electrical stimulation leading different pattern (Leonard et al., 1994), and can be influenced by fatigue too (Enoka et al., 1989).

The electrical analogue stretch reflex (H-reflex) as it is stated, is indirectly representative of the excitability of the spinal MN pool. Since in this literature review the aim was to find the potential factors which can affect the neuromuscular response, following the body inversion. The other candidate mechanisms here, will cover under the excitability of soleus MNs.

As Knikou and Rymer, (2003) displayed that, statically or dynamically altered body angle, related to the frontal plane, induced a facilitated soleus H-reflex. The data reflect a substantial facilitation effect following tilting from supine to both upright and head-down body position, against strong depression in a vertical position. Knikou and Rymer, (2003) concluded that the underlying factors could be attributed to the gravity-induced vestibulospinal effects and may be influenced by Ia-presynaptic inhibition, and cutaneous mechanoreceptors contributions. Moreover, it has been illustrated that a reduced excitability of soleus MNs occurred following the swing phase of walking and immediate stance stage, versus standing controls (Capaday & Stein, 1986; Crenna & Frigo, 1987). In Knikou and Rymer, (2003) research since there was a modest stumbling perception for their participant, during static body angle alterations, it would reasonable to expect an augmented H-reflex ("vestibular-induced soleus H-reflex facilitation").

In addition, changes in body posture can happen following a postural threat, which may occur during the inversion as well. Horslen et al., (2013) via operating an elevated surface (3.2 m above the ground), without and with tilting conditions, examined the effect of postural threat on spinal stretch responses. Tendon (T) reflexes demonstrated a rise in the amplitude of tendon responses while H-reflex amplitudes were unchanged. These results (Horslen et al. 2013) may reflect the engagement of the muscle due to change in body posture, since muscle

spindles can be activated directly by tendon reflexes. Meanwhile, comparing the results of T- and H-reflexes together would be problematic, due to activating afferent fibres with different pattern and dissimilar sensitivity of reflex changes (for more review, Burke et al. 1983).

Furthermore, standing above the ground (Horslen et al. 2013; Sibley et al., 2007), and inverted position (Smith et al. 2013) can lead to a higher level of anxiety. Sibley et al. (2007) examined the effect of standing over an elevated platform, high and low height, on the soleus H-reflex. An attenuated H-reflex in addition to higher anxiety level (high height impacts) in healthy people indicates that there is inhibition of spinal reflex excitability following the postural instability (Sibley et al., 2007). Therefore, since during inversion a sense of stumbling, freezing or falling can be detected, it would be logical to direct partially the decreased neuromuscular response to suppressed spinal motor excitability; i.e., the potential effect of pre-synaptic inhibition.

1.3 Concluding Remarks

The purpose of this literature review was to examine how upper arm BFR can influence neuromuscular fatigue. Descending and ascending inputs from different sensory receptors help to maintain homeostasis of the human body at any moment. With inversion, there is a higher gravitational effect for upper limb and head region. BFR hypothetically can decrease the hydrostatic pressure to the target muscle. Perfusion to exercised muscle can change due to altered working muscle's position relative to the heart level. O_2 delivery to the muscle can affect neuromuscular output. Meanwhile, during contraction with moderate to high intensity, blood flow can be occluded completely. Inhibited optimal final motor output can originate from both mechanical and metabolic factors. Altered provided energy can stimulate small

diameter muscle fibres, which can negatively influence motoneuron function. The metabolic by-products accumulation may induce a dependency on anaerobic ATP production. Therefore, with BFR and muscle contraction, there is a possibility for greater neural activation, originating from a shift to a motor unit with less fatigue resistance.

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Chapter 2: Co-Authorship Statement

The details of my (Hamid Ahmadi) role with the manuscript is outlined below:

Research Design

Methodology was developed based on previous investigations by Dr. David Behm in combination with other studies on blood flow restriction, and work from inversion protocols. Refined details of this study prepared via receiving constructive feedbacks and revisions from Dr. David Behm.

Data Collection

All experimental records were collected by me with assistance from Ms. Nehara Herat and Dr. Shahab Alizadeh.

Data Analysis

All procedures of data analysis were performed by Hamid Ahmadi.

Manuscript Preparation

I (Hamid Ahmadi) prepared the manuscript with constructive feedback and assistance from my supervisor, Dr. David Behm.

Chapter 3: Manuscript

Effect of An Inverted Seated Position with Upper Arm Blood Flow Restriction on Neuromuscular Fatigue

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3.1 Abstract

Altered sympathetic nervous outflow is a predominant factor contributing to impaired neuromuscular performance when shifting from an upright to inverted position. Concomitant with voluntary or involuntary inversion, a compressed limb in terms of blood flow restriction (BFR) to a muscle can influence tissue metabolism. Meanwhile, there is a higher hydrostatic pressure for the upper body versus lower pressure for the lower body, which increases vagal input. The intent was to investigate how BFR on upper arm during inversion can affect acute muscle isometric force production, electromyographic (EMG) activity, fatigue, cardiovascular function, and perceived pain. **Methods:** Thirteen healthy physically active volunteers were randomly allocated to perform four conditions: rest (control, 1-min upright position without BFR), control (1-min upright with BFR), 1-min inverted (without BFR), and 1-min inverted with BFR. Interpolated twitch technique (ITT), evoked and voluntary contractile properties and forces, during a 30-s maximum voluntary contraction (30-s MVC: fatigue task), pre- and post-fatigue were examined. Also, cardiovascular contributions and pain tolerance were measured for pre- and post-fatigue, and during 1-min upright/inversion. Partial BFR on right upper arm was set for upright/inverted position relative to 50% of pulse elimination pressure. **Results:** Inversion-induced significantly greater decreases in elbow flexor MVC (p=0.02) and resting evoked twitch (p=0.03) forces. Fatigue induced significantly greater decreases in potentiated twitch force (p<0.001) during inversion. For upright position, BFR-induced greater reductions in M-wave amplitude (p=0.04). Condition versus blood flow showed that between initial and pre-fatigue testing, there were significant mean arterial pressure increases for upright BFR, contrasting with decreases for the inverted without BFR. With the exception of significant heart rate (HR) decreases (p=0.05) between pre-fatigue and 0-20s intervals, an overall increase in HR was observed from initial to post-fatigue for both without BFR and BFR. For all

conditions, there was a significant increase in pain scale between the 40-60s intervals and post-fatigue (upright<inversion, and without BFR<BFR). **Conclusions:** It was concluded that increased perfusion pressure during inversion, contributed to decreases in resting twitch and post-fatigue potentiated twitch forces, respectively. It is postulated that BFR activates pressor reflexes, irrespective of the posture increasing cardiovascular output.

Key words: Inversion; Blood Flow Restriction; Electromyography; Cardiovascular

3.2 Introduction

Although inhibited neuromuscular and cardiovascular function have been reported when shifting from upright to an inverted position (Paddock & Behm, 2009; Hearn et al., 2009; Johar et al., 2013; Smith et al., 2013; Neary et al., 2015), the underlying mechanisms are not clearly elucidated. Altered sympathetic nervous system activity during inversion (i.e., a higher hydrostatic pressure causes increase in vagal inputs), has been suggested as a primary mechanism(s) that may influence changes in neuromuscular and cardiovascular functions with inversion.

Experiencing an involuntary inverted posture such as with an overturned vehicle is possible. Following this stressful and life-threatening condition, with/without compressed limb, the capability of an overturned person to have a proper coping strategy (physically and mentally) before receiving any emergency medical service is critical. Meanwhile, the presence of fatigue with multiple intermittent muscle contractions in addition to a problem-solving task, can produce a high physical output, immediately after inversion, or during prolonged inversion, which can contribute to fatigue. A decrease in force or power generation, with/without greater increase in perceived difficulty to do a task, can reflect as

"neuromuscular fatigue" (Gandevia, 2001; Soggard et al., 2006). Neuromuscular fatigue is composed of both central and peripheral components (Behm, 2004). During exercise, the development of fatigue is influenced by the availability of oxygen to a target muscle. Central fatigue and perceived exertion can be exacerbated by reduced oxygen-induced peripheral fatigue (Amann & Calbet, 2008).

The central excitability can be inhibited with a restriction of blood flow, which can stimulate muscle afferents with small diameter (Bigland-Ritchie et al., 1986). Changes in perfusion pressure to a target muscle can be found during contractions with moderate-high intensity (Sadamoto et al., 1983), low-intensity contractions combined with blood flow restriction (BFR) (Yasuda et al., 2009), and when position of a working muscle changes in respect to the level of heart (Wright et al., 1999). Also, compressed limb-induced ischemic skeletal muscle may occur with an overturned vehicle for example. Decreased force production and muscle performance observed following an arm lifted above the heart level (Fitzpatrick et al., 1996) and graded ischaemia of the lower limb (Sundberg & Kaisjer, 1992). Hobbs and McCloskey, (1987) showed that under ischemia there was greater electromyography (EMG) activity to keep the force output at the requisite level.

A squeezed or compressed limb (voluntarily or involuntarily) can lead to ischaemia, increasing metabolic by-product accumulation, thereby activating pain afferents (Group III and IV) [Leonard et al., 1994; Bigland-Ritchie et al., 1996; Garland, 1991]. Partial occlusion concomitant with fatigue could influence the perception of effort and sense of pain (Hollander et al. 2010). Moreover, at the onset and during both isometric and dynamic contractions, there is an increase in the human pressor response (sympathetic nervous system reflex with increases in catecholamines and blood pressure). The increased exercise-

pressor reflexes are partially regulated by the peripheral reflex from the small diameter muscle afferents (Amann et al., 2014). However, the combination of inversion with blood flow restriction (BFR), which can occur with vehicle accidents, high speed military airplane maneuvers and other situations has not been previously investigated. With these contexts, the intent of this search was to investigate the potential effects of one-minute inverted position with upper arm BFR on acute muscle isometric force production, electromyographic (EMG) activity, perceived pain, fatigue, and cardiovascular responses.

It was hypothesized**,** inversion would decrease force output and increase fatigue, BFR would amplify the impairments to neuromuscular function, and Inversion would not decrease HR and BP to the same extent as prior studies due to the pressor reflex associated with BFR.

3.3 Methodology

Participants

Based on previous studies (Hearn et al., 2009; Johar et al., 2013), a statistical power analysis (G*Power 3.1, Dusseldorf, Germany) indicated that a minimum of six would be needed to attain an alpha of 0.05 (α error) with a power of 0.8 (1-β error). We were able to recruit a convenience sample of 13 healthy physically active volunteers (university students) (i.e., structured activity 3-4 days per week) with no previous history of cerebral, hypertensive, or visual health problems or injuries. The participants were given an overview of all procedures (i.e., orientation and testing sessions) before data collection. If willing to participate, participants signed the consent form and completed a 'Physical Activity Readiness Questionnaire for Everyone' (PAR-Q+: Canadian Society for Exercise Physiology, approved September 12, 2011 version). The Interdisciplinary Committee on Ethics in Human Research, Memorial University of Newfoundland (ICEHR Approval #: 20192154-HK) approved this study.

Table 3.1. Participants Characteristics

Subjects (n)	Age (Years)	Height (cm)	Weight (Kg)	Dominant/Non-Dominant hand (n)
Male: 7	24.71 $\pm$ 4.95	178.30 $\pm$ 8.26	79.95 $\pm$ 8.58	Dominant = 5, Non-Dominant = 2
Female:6	24.50 $\pm$ 4.80	162.04 $\pm$ 3.56	73.52 $\pm$ 14.26	Dominant = 5, Non-Dominant = 1

*Dominant hand (the hand with which the participant would throw a baseball)

Experimental design

Based on the recommendation of Canadian Society for Exercise Physiology (2004), participants were advised to not smoke, drink alcohol or partake in intensive physical activity six hours prior to testing and to not eat food two hours before participating in the testing procedure. Participants attended an orientation session, at least a week before data collection, where they were familiarized with both upright and inversion postures; and also became familiar with BFR, the interpolated twitch technique (ITT), EMG, electrode placement, and isometric maximal voluntary contractions (MVC) techniques. Using random allocation (generated by Microsoft Excel) participants performed four conditions: 1) rest (control, 1-min upright position without BFR), 2) control (1-min upright position with BFR), 3) 1-min inversion (without BFR), and 4) 1-min inversion with BFR. There was approximately 48 h between each experimental condition (~ 60 minutes). To decrease diurnal rhythms effects, all of the procedures were completed at approximately the same time of day.

Maximal evoked muscle twitch (i.e., resting position) and voluntary (isometric maximal voluntary contraction [MVC] with interpolated twitch technique [ITT]) contractile properties were initially tested from an upright seated position. Following a 5-min rest period, cardiovascular variables (heart rate, mean arterial pressure), BFR testing procedures (relative to the posture) with the participant positioned in the inversion chair were tested. The participant then performed a warm-up, which consisted of a cycling (cycle ergometer: Monark Ltd. Sweden), at 70 rpm with 1kp for 5-min; followed by a specific warm-up of five 5-s isometric elbow flexion (~50% of perceived maximum) contractions. The subsequent condition/position (without/with an upper right arm BFR) also included an evoked twitch, MVC with ITT, cardiovascular factors, a 30-s MVC, followed by another evoked twitch and

MVC with ITT (**Table 3.2**). It is noted that there was a 5s transition from both upright to supine, and supine to inversion.

Table 3.2. Experimental Protocol Diagram

	Control (Upright Position) without BFR	**Control (Upright Position with BFR)**	**Inversion (1min) without BFR**	**Inversion (1min) with BFR**
Orientation Session	Preparation Procedure	Preparation Procedure	Preparation Procedure	Preparation Procedure
	Upright Maximal Evoked twitch (Resting Position)	Upright Maximal Evoked twitch (Resting Position)	Upright Maximal Evoked twitch (Resting Position)	Upright Maximal Evoked twitch (Resting Position)
	ITT, MAP, HR (Upright Position)	ITT, MAP, HR, BFR (Upright Position)	ITT, MAP, HR (Upright Position)	ITT, MAP, HR, (Upright Position);
	Upright Warm Up	Upright Warm Up	Upright Warm Up	Upright Warm Up
	5-min Rest	5-min Rest	5-min Rest	5-min Rest
	-	Upper Right Arm BFR	-	Upper Right Arm BFR
	Pain Scale	Pain Scale	Pain Scale	Pain Scale
	ITT (Upright Position)	ITT (Upright Position)	ITT (Inverted Position)	ITT (Inverted Position)
	MAP, HR, Pain Scale	MAP, HR, Pain Scale	MAP, HR, Pain Scale	MAP, HR, Pain Scale
	Upright position without BFR (1min), HR, Pain Scale	Upright position with BFR (1min), HR, Pain Scale	Inverted Position without BFR (1min), HR, Pain Scale	Inverted Position with BFR (1min), HR, Pain Scale
	30-s MVC Fatigue	30-s MVC Fatigue	30-s MVC Fatigue	30-s MVC Fatigue
	ITT	ITT	ITT	ITT
	MAP, HR, Pain Scale	MAP, HR, Pain Scale	MAP, HR, Pain Scale	MAP, HR, Pain Scale

*HR = Heart Rate, MAP = Mean Arterial Pressure, ITT = Interpolated Twitch Technique

The participants were seated in an inversion chair (initially in an upright position), which was designed and constructed by Technical Services of Memorial University of Newfoundland (Hearn et al., 2009; Paddock, & Behm, 2009; Neary et al., 2015). The chair can rotate through a 360-degree range. Straps secured the participant at the head, torso, shoulder, hip, and thighs. Hips and knees were positioned at 90 degrees during data collection. A Wheatstone bridge configuration strain gauge (Omega Engineering Inc., Don

Mills, Ont.) via a high-tension wire cable were attached to a reinforced strap around right wrist to assess force output, and forces were collected and amplified via analog to digital data collection hardware and software (i.e., Biopac System Inc. DA 100, A/D convertor MP100WSW; Holliston, MA). Due to the laboratory's structure the researcher had a limitation to measure data, from only the dominant elbow flexors.

For consistency, each session commenced with an initial evoked twitch. Since evoked single twitches are sensitive to prior contractions resulting in a potentiated response, the twitches need to be evoked prior to MVC testing (Behm, 2004a; Behm et al., 2004b). Following the evoked twitch, participants performed 2-3 MVCs for a 4-s duration with 2-min rest between each MVC. Two twitches were evoked during and following the MVC respectively (ITT). One twitch was superimposed upon the MVC at the 3-s point of the 4-s contraction to give the participant time to reach peak force. The subsequent potentiated twitch was evoked 3-s after the MVC. This procedure was repeated if the MVC force of the second MVC was 5% higher than the first MVC.

A fatiguing protocol consisting of a 30-s MVC of the elbow flexors, was performed using an isometric elbow flexion MVC (right arm). The researcher provided consistent verbal encouragement in terms of wording and timing (e.g., "keep it up" every 10 s, starting at 10 s point).

Evoked Contractile Properties

To assess excitation-contraction coupling and muscle membrane action potentials, evoked contractile properties were measured. To stimulate the biceps brachii nerve, stimulating electrodes (electrode width was 5 cm) were wrapped around the bicipital (anode) and proximal portion of elbow crease (cathode), respectively (Halperin et al., 2014). Furthermore, the electrodes placement was marked with ink from test to test to maintain the

correct position of electrodes during each session. Stimulating electrodes were connected to a stimulator (Digitimer Stimulator, Model DS7AH, Hertfordshire, UK) with a maximum of one ampere (A) and 400 volts (V). Then, both amperage and voltage were increased sequentially till a plateau in the twitch torque was attained. While the initial resting twitch involved a single stimulus, the superimposed and subsequent potentiated twitches had a 200 ms inter-pulse interval between two maximal twitches during biceps brachii nerve stimulation (Behm et al., 1996). The ITT has been reported to be a valid and reliable measure of muscle inactivation (Behm et al., 1996).

Previous studies (Behm et al., 1996; Behm & St-Pierre., 1997, Merton 1954) have shown that there is a possibility to activate all muscle fibres via a superimposed twitch on a voluntary contraction (ITT). Superimposed twitches were delivered during the 2-3 MVCs before the BFR and fatigue intervention, and once following the BFR and 30-s MVC fatiguing muscle contraction (i.e., MVC during elbow flexion). The first supramaximal electrical stimulation was delivered at the 3-s point of the MVC (to allow time to achieve maximal force), and the second twitch (as a potentiated twitch) was evoked at a 3-s interval after the MVC (subject was instructed to relax). To estimate maximal voluntary activation, the amplitudes of the superimposed and post-contraction stimulation were compared [voluntary activation = [1 – (superimposed twitch/potentiated twitch)] * 100] (Behm et al. 1996).

Voluntary Contractile Properties

The MVC isometric force was measured, with a reinforced strap around the right elbow flexor, with the participant seated and secured in the inversion chair. An instruction (“as hard as fast possible”), with verbal encouragement (“go go”) was provided by researcher during the entire 4-s isometric MVC. The forces detected by the strain gauge, were used to analyze peak isometric MVC and the instantaneous strength (F100).

Electromyography (EMG)

Surface EMG was monitored during evoked twitches (muscle action potential: M-wave), 4-s MVC and 30-s MVC. First, skin was prepared before electrode placement with shaving (removal hair), abrading (to remove possible dead epithelial cells), and cleaning the area with an alcohol swab to remove oils. Then, two pairs of electrodes (Kendall Medi-trace 100 series, Chikopee, Mass.) were positioned (established by SENIAM, Hermens et al. 1999) at the mid-belly of biceps brachii (i.e., at 50% on the line from medial acromion to the fossa cubit) as an agonist muscle (corresponding to the muscle fibres), and lateral head of triceps brachii (i.e., halfway from the posterior crista of the acromion to the olecranon as an antagonist muscle). The reference electrode was positioned on the ulnar styloid process.

The EMG signal was collected at 2000 Hz, band-pass filter 10-500 Hz and amplified 1000x [Biopac System MEC 100 amplifier, Santa Barbara, Calif; input impedance = 2M, common mode rejection ratio > 100 dB minimum (50/60 Hz)]. The collected data (via the A/D converter, Biopac MP150) was stored on a personal computer for post-processing analysis. The final data (i.e., raw EMG) was rectified and integrated (iEMG) over 500 ms following an MVC (Neary et al., 2015; Johar et al., 2013; Paddock & Behm, 2009).

Blood Flow Restriction (BFR)

Previous evidence (Takarada et al., 2000) using Doppler ultrasonograms showed that a moderate BFR and partial occlusion of brachial artery can lead to 100% venous restriction and partial arterial BFR, respectively. Yasuda et al. (2009) revealed that during contraction with moderate BFR, there was a detectable pulse signal versus the absence of a signal with complete BFR. It would be logical to manipulate a low/moderate dose of BFR to decrease the potential harmful biological effect, which can occur following an extremely high dose of BFR (Loenneke et al., 2014).

In order to reduce hydrostatic pressure effects, and perfusion to the right arm muscle, BFR was implemented. At the resting position, a pressure cuff (A+ Med 7-62 pressure cuff; Toronto, Canada) was placed around the upper right arm, while positioned at the level of the heart. Then, the hand bulb was squeezed to find a pulse elimination pressure (100% BFR). The individualized BFR in the present study was set relative to brachial systolic blood pressure. To create partial BFR for upright/inverted position, the hand bulb was squeezed to 50% of complete BFR. Furthermore, with a maximal isometric contraction, the blood flow would be further restricted, obviating the need for maximal BFR with a cuff.

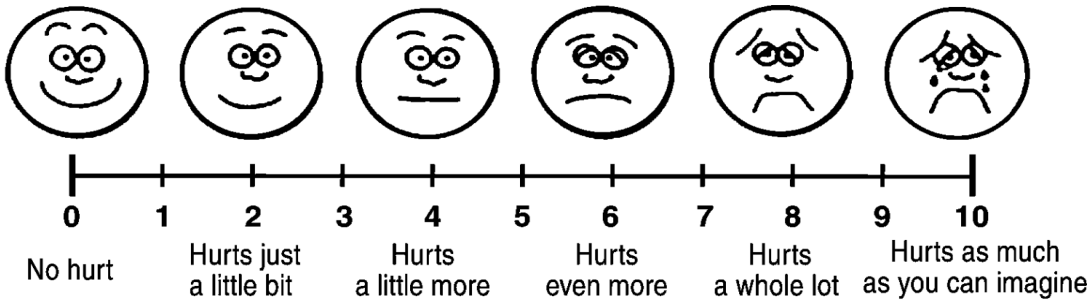
Heart Rate (HR) and Blood Pressure (BP)

HR and BP were used to monitor cardiovascular measures via a 3-lead electrocardiograph (ECG) [Biopac System MEC 110C amplifier, Santa Barbara, Calif] and an A+ Med 7-62 pressure cuff, respectively. Near the right shoulder and below the pectoral muscle, one pair of electrodes was placed under the right clavicle and edge of the left rib cage, respectively. The reference electrode was positioned under the right clavicle. Hence, to monitor BP at rest, both upright and inverted with BFR, the cuff was wrapped around the upper left arm.

Universal Pain Assessment Tool

Previous seated inversion studies (Neary et al., 2015; Johar et al., 2013; Paddock & Behm, 2009) have mentioned that there was a sense of discomfort (i.e., a distinct swelling around the head region) during inversion. The researcher utilized a Universal pain assessment tool (Belcheva & Shindova, 2014) to assess the degree of discomfort (pain perception) during inversion (**Figure 3.1**). Also, to find whether there was any interaction between the effects of inversion and BFR (during two control sessions), the sense of discomfort with and without BFR was examined.

Figure 3.1. Universal Pain Assessment Tool



Data Analysis

With the single electrical stimulation, peak twitch force, time to peak twitch force, half relaxation time were measured for resting and potentiated twitches. Peak MVC forces (peak to peak by the presence of superimposed twitch artifact) and instantaneous strength represented by the force produced within the first 100 ms (F100) of the maximal contraction (Perrine & Edgerton, 1978) were analyzed. The mass of the arm was recorded in the inverted position and this value subtracted from the peak force and F100 in order to counterbalance the force of gravity negatively affecting force output in the upright position.

The integrated EMGs, from biceps and triceps brachii, were analyzed from a one second period of the 3-s MVC (before the superimposed twitch) (Button & Behm, 2008). Furthermore, a Fast Fourier transform (FFT) was used to report the EMG median frequency following the fatigue protocol, as it is a reliable indicator for signal conduction velocity (following a fatigued-exercise) and considered a generally more sensitive indicator of fatigue that a raw EMG signal (Kwatny et al. 1970; Agarwal et al. 1975; Daanen et al. 1990; Dimitrova et al. 2003).

Statistical Analysis

The SPSS software (version 23.0, SPSS, Inc. Chicago, IL) was used for statistical analysis. For the normality of the data, a histogram chart was utilized to illustrate skewness and kurtosis, and a Shapiro-Wilks test was performed. The value of Greenhouse-Geisser were

reported if the assumption of sphericity was not met. To determine the effect of inversion with BFR on neuromuscular fatigue, fatigue Index, a two-way repeated measures ANOVA (2 seated positions $\times$ 2 blood flow conditions), while three-way repeated measures ANOVA (2 seated positions $\times$ 2 blood flow conditions $\times$ 2 times) was conducted for EMG median frequency. For the evoked twitches, MVCs, ITT, potentiation twitches, M-waves, EMG, mean arterial pressure, a three-way ANOVA [2 seated positions and 2 blood flow conditions and three times (initial upright resting position, pre-fatigue, and post-fatigue)] was applied. Further, a factorial ANOVA with repeated measures was conducted to analyze HR and pain scale. Differences were considered significant when a minimum value of p=0.05 was reached. A planned pairwise comparisons, Bonferroni adjustment, was selected to compare main effects. Additionally, the calculated partial eta squared (η_p^2) by SPSS was reported as a magnitude of outcomes (effect sizes); which is classified as small ($0.00 \leq f \leq 0.24$), medium ($0.25 \leq f \leq 0.39$), and large ($f \geq 0.40$) (Cohen, 1988). Day to day reliability of measures (for initial upright resting position test) was assessed with Cronbach's alpha intraclass correlation coefficient (ICC).

3.4 Results:

Reliability

With the exception of poor internal consistency ($0.5 \leq \alpha < 0.6$) for HR, moderate consistency ($0.6 \leq \alpha < 0.7$) for biceps- and triceps brachii's M-wave, and acceptable ($0.7 \leq \alpha < 0.8$) for resting twitch force and MAP, ICC reliability scores were consistently excellent ($0.82 \leq \alpha < 0.94$) for MVC, F100, potentiated twitch forces, biceps- and triceps brachii EMG (**Table 3.3**).

Table 3.3. Diurnal Intraclass correlation coefficient reliability (initial resting position test performed on separate days).

	MVC	F100	BB EMG	TB EMG	RTF	BB M-wave	TB M-wave	PTF	HR	MAP
ICC	0.93	0.82	0.94	0.83	0.77	0.66	0.6	0.87	0.53	0.71

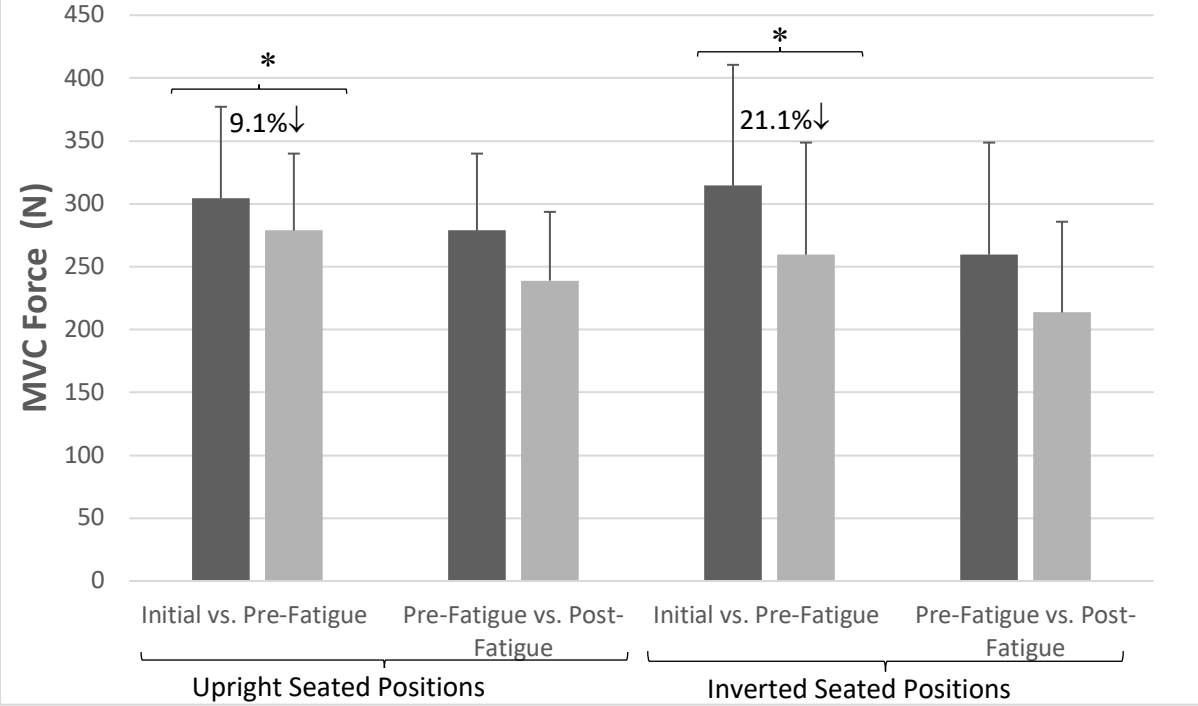
*BB = Biceps Brachii, TB = Triceps Brachii, PTF = Potentiated Twitch Force, RTF = Resting Twitch Force.

Voluntary Contractile Properties

Elbow Flexors MVC and F100

A significant seated position*time interaction ($F_{(2,16)}$ = 5.07, p=0.02) and time effect ($F_{(2,16)}$ = 52.58, p<0.001) was observed for elbow flexor MVC. The interaction revealed 9.1% and 21.1% MVC force decreases (η_p^2=0.48) (initial > pre-fatigue) for upright and inverted positions, respectively (**Figure 3.2**). Contrasts for time revealed significant decreases from initial to pre-fatigue (η_p^2=0.82, 14.9%↓), and from pre to post-fatigue measures (η_p^2=0.84, 18.9%↓). Further, significant main effects for BFR showed a 4.8% decrease with the BFR versus without BFR condition ($F_{(1,8)}$ = 4.84, p=0.05, η_p^2=0.37), and seated position*BFR interaction ($F_{(1,8)}$ = 3.79, p=0.08, η_p^2=0.32); with 0.8% and 9.1% decreases from without BFR to BFR conditions, for both upright and inverted seated positions were observed.

Figure 3.2: Interaction effects for seated position and time. Star (∗) symbol represents that significant MVC force decreases between initial and pre-fatigue tests, for upright seated positions (without BFR and BFR) and inverted seated positions (without BFR and BFR).



A significant time effect ($F_{(2,18)}$ = 31.81, p<0.001) revealed significant decreases in elbow flexors F100 between the initial and pre-fatigue values (η_p^2=0.63, 40.5%↓), pre- and post-fatigue (η_p^2=0.8, 51.9%↓), respectively. In terms of seated position effects, there was no significant decrement with the inverted versus the upright positions ($F_{(1,9)}$ = 3.42, p=0.09, η_p^2=0.27, 8.3%↓).

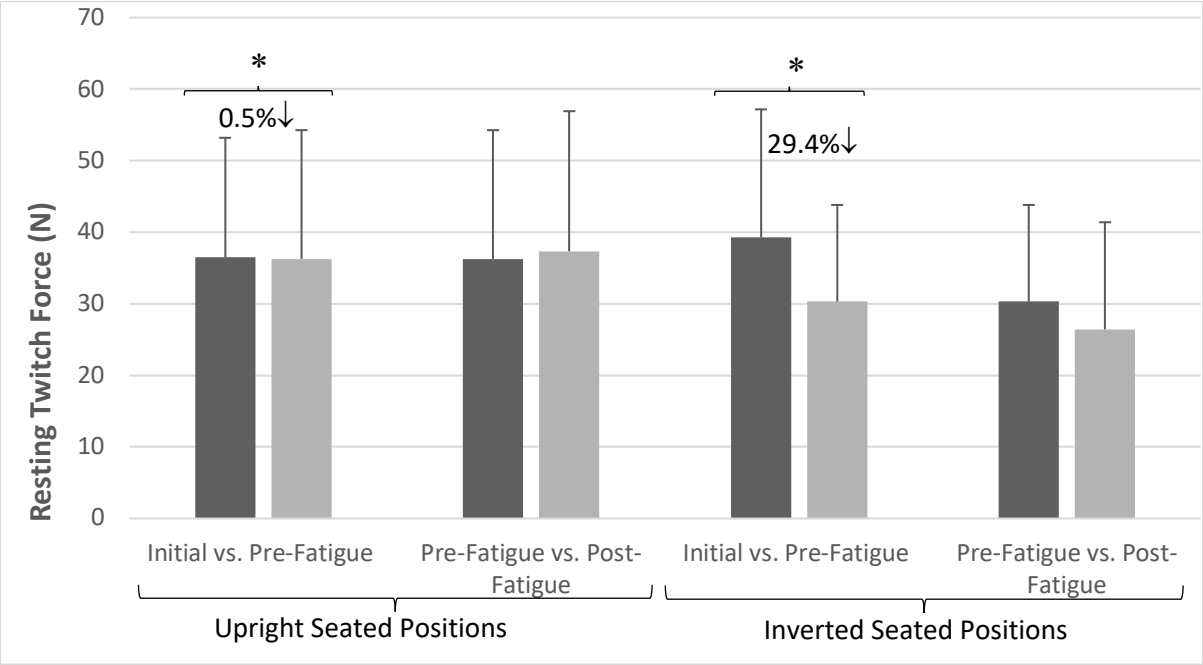
Biceps and Triceps Brachii EMG

A significant time effect ($F_{(1,12)}$ = 22.41, p<0.001) showed 22% (η_p^2=0.65) biceps brachii EMG decreases at post-fatigue, when compared with pre-fatigue. A significant time effect, for triceps brachii EMG, displayed decreases between the values of initial and pre-fatigue ($F_{(1,8)}$ = 7.34, p=0.02, η_p^2=0.47, 16.6%↓), and pre- and post-fatigue ($F_{(1,8)}$ = 16.93, p=0.003, η_p^2=0.67, 20%↓).

Evoked Twitch Contractile Properties

A significant seated position*time interaction ($F_{(1,11)}$ = 5.80, p=0.03), for resting twitch force revealed that initial values exceeded pre-fatigue, by 0.5% for upright and 29.4% for inverted seated positions [η_p^2= 0.34] (**Figure 3.3**).

Figure 3.3: Interaction effects for seated position and time. Star (∗) symbol represents that significant Resting Twitch Force decreases between initial and pre-fatigue tests, for upright (include both without BFR and BFR) and inverted seated positions.



No significant effects or interaction were found for baseline time to peak twitch force. Meanwhile, a near significant effect was observed ($F_{(1,6)}$ = 4.81, p=0.07, η_p^2=0.44), in terms of seated position and BFR, when comparing upright values (without BFR<BFR, 3.9%↑) with inverted seated positions (without BFR>BFR, 5.6%↓). No significant effects were observed for half relaxation time-twitch force.

M-Wave

Biceps Brachii M-wave

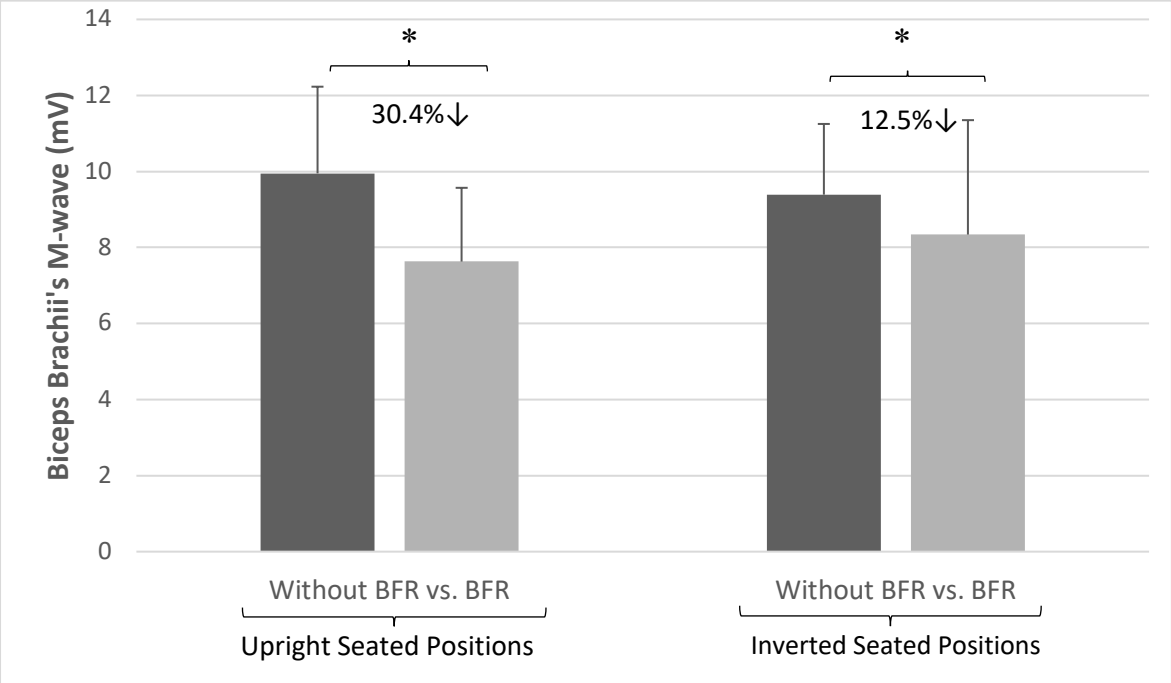
A significant seated position*BFR interaction ($F_{(1,7)}$ = 5.69, p=0.04, η_p^2=0.44), revealed that the without BFR condition exceeded BFR condition biceps brachii's M-wave by 30.4% and 12.5% for upright, and inverted seated positions respectively (**Figure 3.4**). A significant effect

for BFR revealed 21% M-wave decreases for biceps brachii with the BFR values versus without BFR conditions ($F_{(1,7)}$ = 7.28, p=0.03, η_p^2=0.51). Moreover, a near significant effect for time, showed 7.6% decreases in M-wave, between pre- and post-fatigue measures ($F_{(1,7)}$ = 3.89, p=0.08, η_p^2=0.35).

Triceps Brachii's M-wave

No significant effects and trends were observed for triceps brachii's M-wave.

Figure 3.4: Interaction effects for seated position and BFR. Star (∗) symbol represents that significant decreases in amplitude of M-wave for Biceps Brachii, between without BFR and BFR, with 30.4% and 12.5% for upright and inverted seated positions, respectively.



Evoked Potentiated Twitch Contractile Properties

Significant effects for time ($F_{(2,10)}$ = 36.30, p<0.001), and seated position*time interaction ($F_{(2,10)}$ = 7.91, p=0.009) were observed for potentiated twitch force (PTF). For seated position*time interaction, between pre- and post-fatigue, results showed 85.3% and 175% PTF decreases (η_p^2=0.67) for upright and inverted positions from pre-to post fatigue, respectively (**Figure 3.5**). For time, contrasts revealed significant decreases between pre- and post-fatigue measures (η_p^2= 0.93, 121.1%↓).

Though no significant interactions were observed for time to potentiated peak twitch force, a significant impact was observed for time ($F_{(2,16)}$ = 3.64, p=0.05). Contrasts revealed significant increases between the values of initial and pre-fatigue ($F_{(1,8)}$ = 6.09, p=0.03, η_p^2=0.43, 0.9%↑), and decreases between pre- and post-fatigue ($F_{(1,8)}$ = 5.78, p=0.04, η_p^2=0.42, 13%↓), respectively.

A significant time effect showed 31.9% increases in ½ relaxation time-PTF, between pre- and post-fatigue values ($F_{(1,10)}$ = 12.24, p=0.006, η_p^2= 0.55). Also, a near significant interaction of BFR*time ($F_{(1,10)}$ = 3.76, p=0.08, η_p^2=0.27) revealed 35% (without BFR conditions) and 28.2% (BFR conditions) increases in ½ relaxation time for PTF, when comparing pre- and post-fatigue measures (**Figure 3.6**).

Figure 3.5: Interaction effects for seated position and time. Star (∗) symbol represents that significant Potentiation Twitch Force decreases between pre- and post-fatigue tests, for upright seated positions (without BFR and BFR) and inverted seated positions (without BFR and BFR).

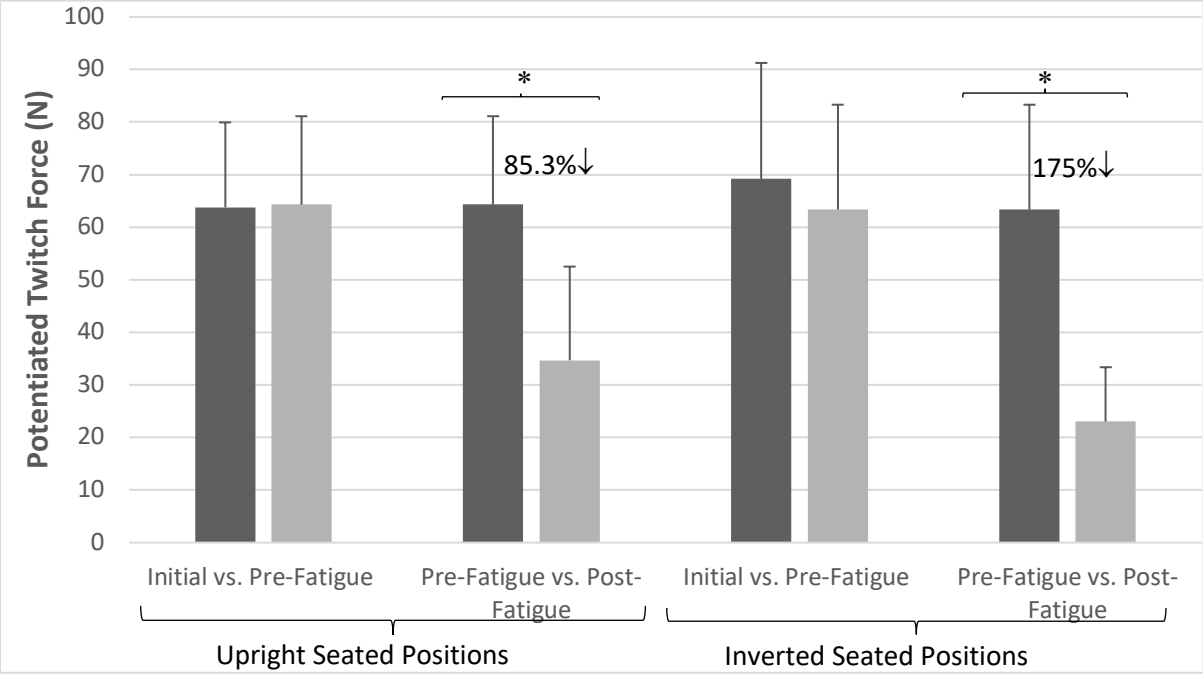
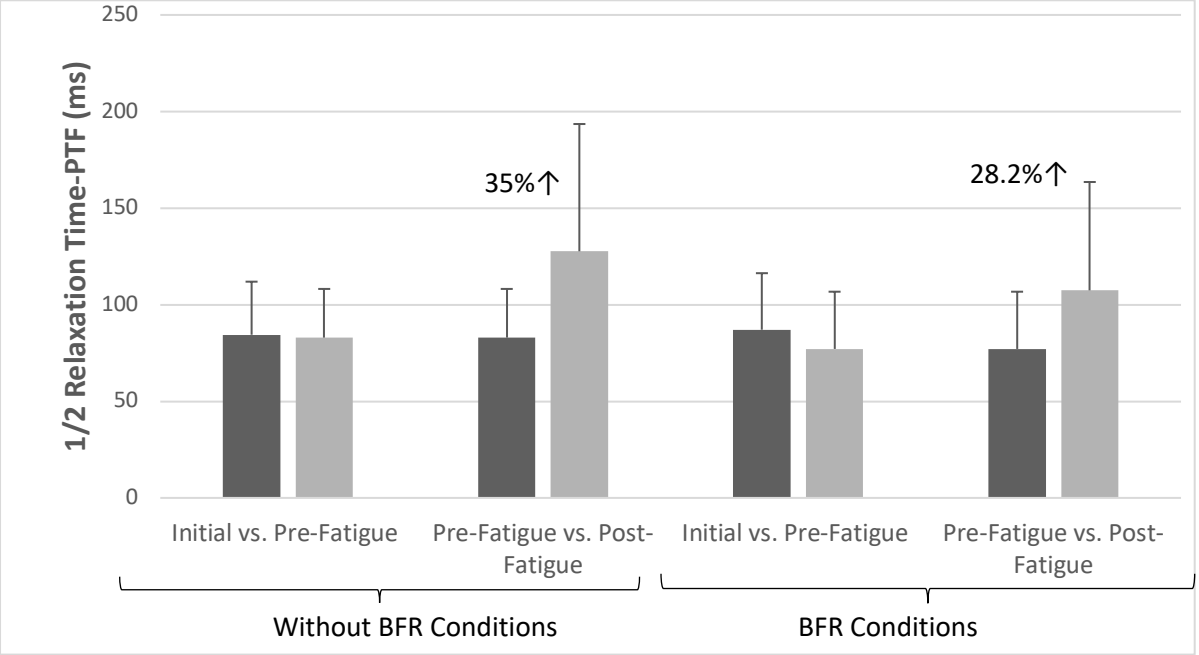


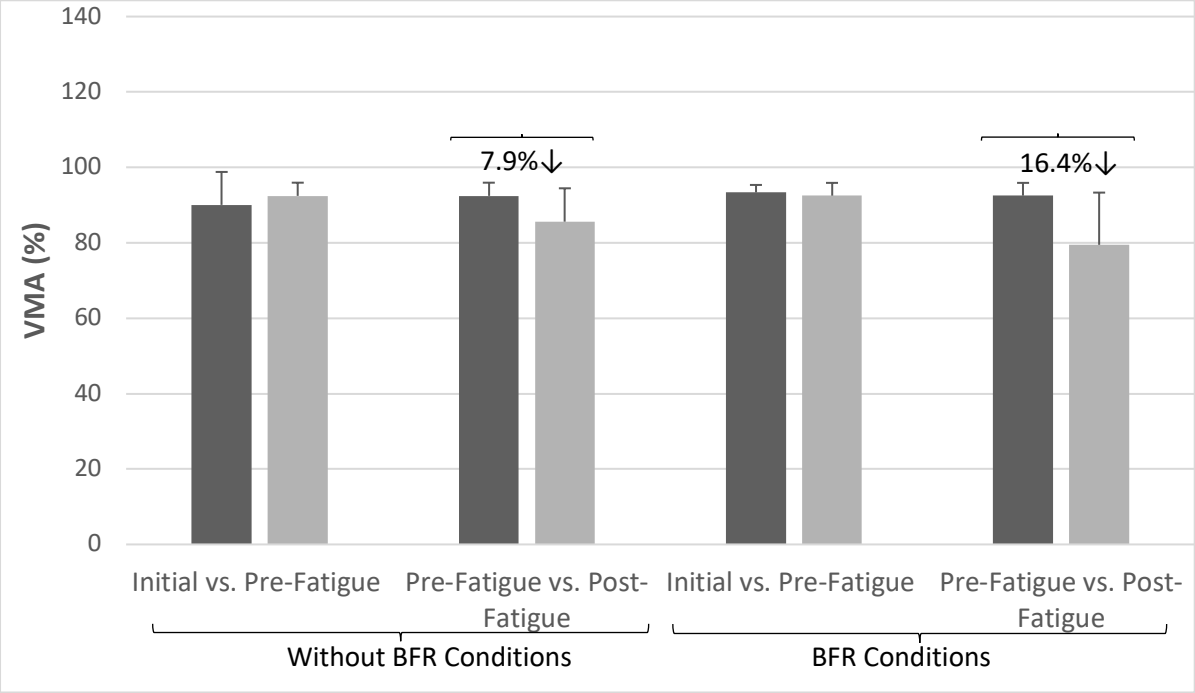
Figure 3.6: Interaction effects for BFR and time. As can be seen there was a near significant effects for ½ relaxation time for PTF (*p*=0.08), the difference values between without BFR conditions and BFR.



Voluntary Muscle Activation (%)

For voluntary muscle activation (%), a significant pre- to post-fatigue time decrement was observed ($F_{(1,4)}$ = 6.62, *p*=0.06, η_p^2=0.62, 12%↓). A near significant BFR*time interaction revealed 7.9% and 16.4% decreases post-fatigue ($F_{(1,4)}$ = 5.48, *p*=0.07, η_p^2=0.57) for without BFR and BFR conditions, respectively (**Figure 3.7**).

Figure 3.7: Interaction effects for BFR and time. There was a near significant effect for percentage of VMA (p=0.07), with 7.9% and 16.4% decreases post-fatigue for without BFR and BFR conditions.



Fatigue – Force Relationship

No significant main effects or interactions were observed for the fatigue index. However, when comparing force output values, at 0-5s and 25-30s intervals of the fatigue task in the without BFR conditions versus 0-5s and 25-30s of BFR conditions, there was 4.1% force decreases for BFR effects ($F_{(1,11)}$ = 5.54, p=0.03, η_p^2=0.33). The results for time effects also, showed an overall 14.6% decreases in force output, when comparing 0-5s intervals values with 25-30s intervals (without BFR and BFR conditions for upright and inverted positions) [$F_{(1,11)}$ = 29.96, p<0.001, η_p^2=0.73].

Fatigue - EMG Relationship

Biceps Brachii

Significant main effects for time ($F_{(1,10)}$ = 84.65, p<0.001) revealed 39.5% (η_p^2=0.89) decreases in the biceps brachii EMG median frequency, between 0-5s and 25-30s intervals (both without BFR and BFR conditions) of the fatigue protocol. Furthermore, contrasts

revealed a near significant seated position*time interaction ($F_{(1,10)}$ = 3.84, p=0.07, η_p^2=0.27); with 45.6% and 38.6% decreases in biceps brachii EMG median frequency during upright without BFR and BFR conditions respectively, versus similar 32.8% and 41.4% median frequency decreases during the inverted seated position for without BFR and BFR conditions, respectively.

Triceps Brachii

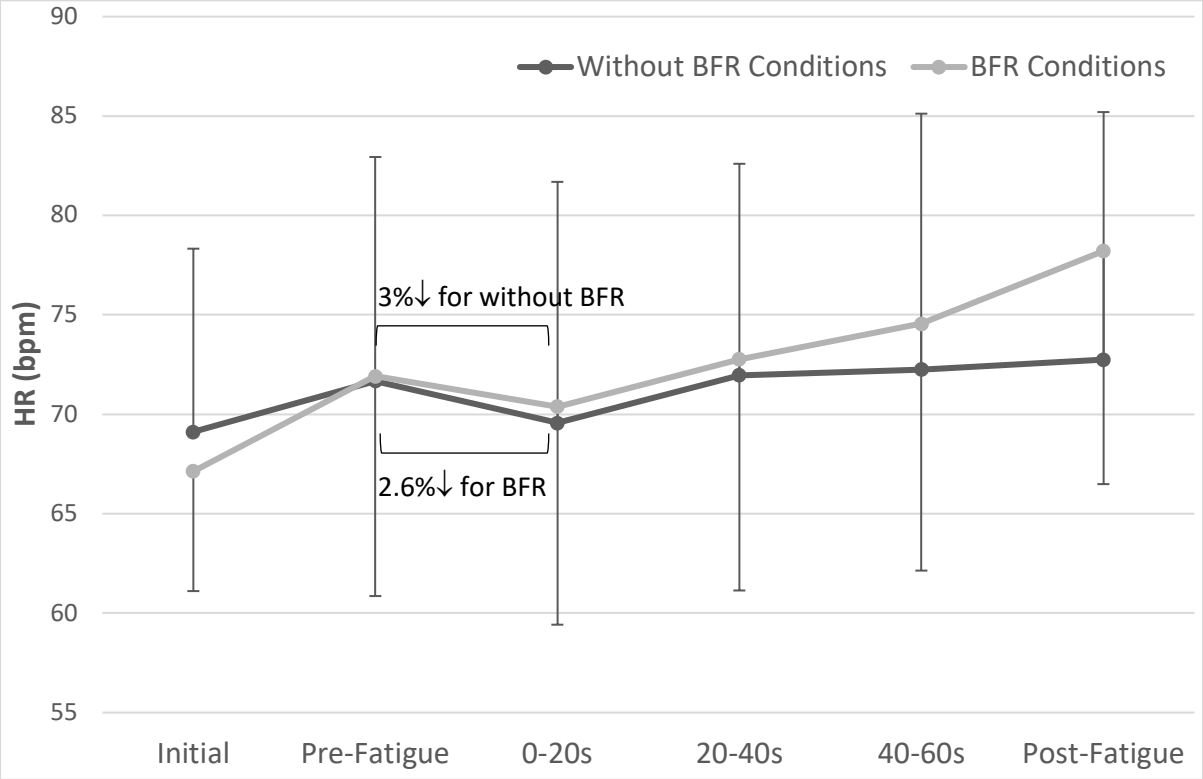
Significant main effects for time ($F_{(1,12)}$ = 86.69, p<0.001, η_p^2=0.87) showed 33.8% reduction in the triceps brachii EMG median frequency between 0-5s (without BFR and BFR conditions) and 25-30s intervals (without BFR and BFR conditions combined) of the fatigue protocol.

Cardiovascular Measures

Heart Rate (HR)

Significant time effects were observed for HR [$F_{(2.27,24.97)}$ = 6.41, p=0.004]. Contrasts revealed 2.6% (η_p^2=0.2) HR decreases between pre-fatigue and 0-20s interval; while an increase in HR between initial and pre-fatigue (η_p^2=0.22, 5.1%↑), 0-20s and 20-40s intervals (η_p^2=0.54, 3.3%↑), 20-40s and 40-60s intervals (η_p^2=0.17, 1.4%↑), and 40-60s and post-fatigue test (η_p^2=0.11, 2.7%↑). For the interaction of BFR*time [$F_{(5,55)}$ = 2.33, p=0.05, η_p^2=0.17], a 3% and 2.6% HR decrease between pre-fatigue and 0-20s interval for without BFR and BFR conditions, contrasted with an overall (both without BFR and BFR) increase from initial to post-fatigue measures (**Figure 3.8**).

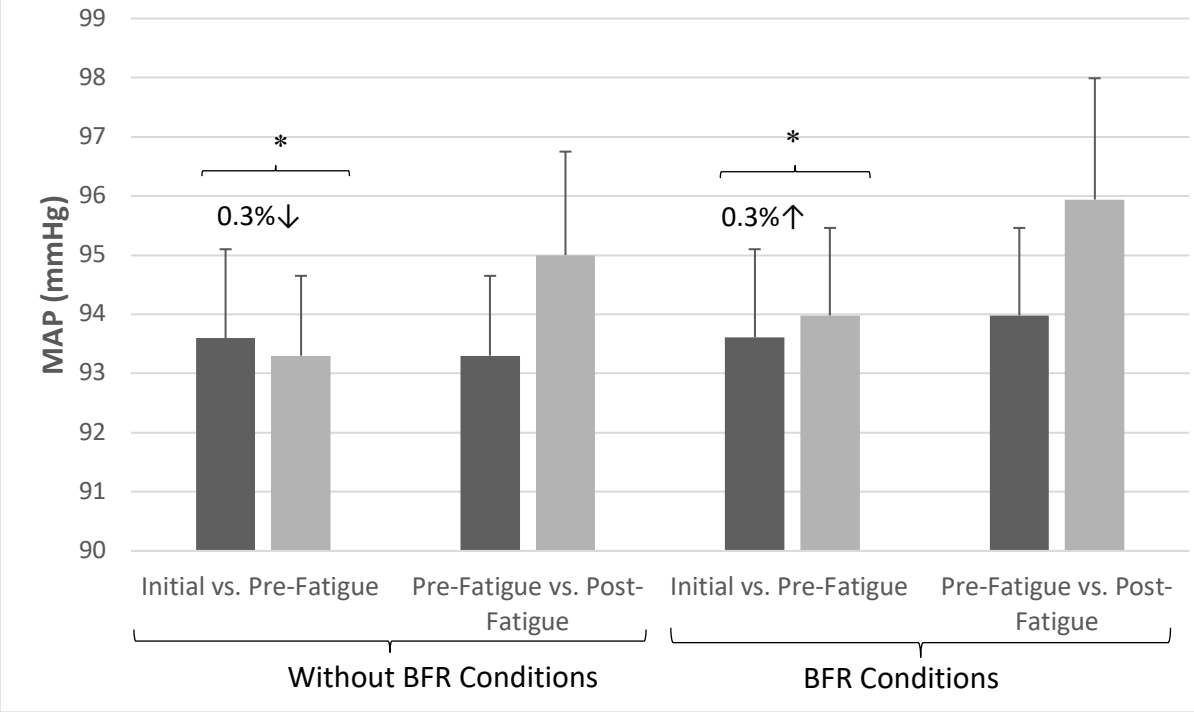
Figure 3.8: Interaction effects for BFR and time on HR. There was a significant effect (p=0.05) for HR, with 3% and 2.6% decreases 0-20s for without BFR and BFR conditions; and overall increase between initial and pre-fatigue, and 20-40s and post-fatigue for both without BFR and BFR.



Blood Pressure – Mean Arterial Pressure (MAP)

A significant interaction of seated position*time, and BFR*time, as well as main effects of seated position, and time were observed for MAP. For seated position*time interaction, there was a significant increase for upright (0.5%↑) versus inverted positions values (0.4%↓), when comparing initial with pre-fatigue measures ($F_{(1,12)}$ = 10.92, p=0.006, η_p^2=0.47). For BFR*time interaction, there was an initial to pre-fatigue 0.3% decrease in the without BFR conditions versus 0.3% increase with the BFR conditions ($F_{(1,12)}$ = 12.0, p=0.005, η_p^2=0.5) [**Figure 3.9**]. For seated position, contrasts revealed 1% MAP decreases with upright versus inverted positions ($F_{(1,12)}$ = 7.52, p=0.01, η_p^2=0.38), and for time showed 1.9% increases, pre- versus post-fatigue, ($F_{(1,12)}$ = 80.36, p<0.001, η_p^2=0.87).

Figure 3.9: Interaction effects for BFR and time. Star (∗) symbol represents that there was a significant BFR and time interaction for MAP, without BFR versus BFR conditions.



Perceived Pain - Pain Scale

Seated position*BFR interaction revealed significant decreases ($F_{(1,12)}$ = 6.55, p=0.02, η_p^2=0.35) between upright (without BFR < BFR, 58.1%↑) and inversion (without BFR > BFR, 11.1%↓) positions. For the interaction of BFR*time (without BFR vs. BFR conditions) [$F_{(2.05,24.62)}$ = 4.68, p=0.01, η_p^2=0.28], a 4.6% pain scale decrease between 20-40s and 40-60s intervals for the without BFR condition, contrasted with an overall (both without BFR and BFR) increase from initial (upright/inverted) to post-fatigue measures. Furthermore, a seated position*BFR*time interaction ($F_{(2.87,34.47)}$ = 3.18, p=0.03) indicated that when comparing without BFR and BFR upright versus inverted conditions between 0-20s and 20-40s intervals (η_p^2=0.29, 32.6%↓ for without BFR and 13.6%↑ for BFR upright positions, versus 7.8%↑ and 3.2%↑ for inverted without BFR and BFR conditions), and between 40-60s and post-fatigue (η_p^2=0.29, 77.5%↑ and 35.2%↑ for upright without BFR and for BFR versus 13.9%↑ and 26%↑ for inverted without BFR and BFR conditions). A main effect for seated position and BFR

showed 26.5% (upright < inversion) [$F_{(1,12)}$ = 14.56, p=0.002, η_p^2=0.54] and 15.6% increases (without BFR < BFR) [$F_{(1,12)}$ = 7.85, p=0.01, η_p^2=0.39] for pain scale. A main effect for time ($F_{(1.37, 16.49)}$ = 11.39, p=0.002) showed 34.6% (η_p^2=0.45, initial < pre-fatigue), 14% (η_p^2=0.26, pre-fatigue < 0-20s interval), and 32.3% (η_p^2=0.49, 40-60s interval < post-fatigue) pain scale increases.

3.5 Discussion

The findings in this research were in line with previous studies (Hearn et al., 2009; Paddock & Behm, 2009; Johar et al., 2013; Grover et al., 2013; Neary et al., 2015). By applying another stressor such as BFR, we have endeavoured to address unresolved factors in previous studies. The major objectives of this study were to investigate voluntary and evoked contractile properties, cardiovascular responses and perceived pain changes with a) seated upright vs. inverted positions, b) BFR vs. without BFR and c) the interactive effects of inversion and BFR conditions. Major findings, before the fatigue task, included that inversion induced significantly greater decreases in resting twitch and elbow flexor MVC forces. Following the fatigue task, inversion induced greater decreases in potentiated twitch forces. BFR lead to a greater decrease in M-Wave amplitude for the upright versus inverted position. Also, there were significant MAP increases for the upright BFR condition, contrasting with decreases for the inverted without BFR. Perceived pain increased for all conditions between 0-20s and 20-40s intervals with the exception of decreases with the upright without BFR condition.

Prior to the fatigue task *(between initial and pre-fatigue values)*

Evoked Contractile Properties

Significant reductions in evoked twitch force with inversion are partially in accord with a previous inversion study that showed non-significant, moderate magnitude decreases

(18.6%, ES = 0.74) for elbow flexors resting twitch force from upright to the inverted position (Neary et al., 2015), contrasting with non-significant moderate magnitude increases (17.5%, ES = 0.76) for knee extensors. The inversion induced reductions in evoked twitch, and elbow flexors MVC forces with these studies, may be attributed to both peripheral and central mechanisms.

With inversion, the position of arm and leg induces higher and lower hydrostatic pressure respectively. With high gravitational pressure, previous animal studies have shown an altered function of acetylcholine receptors (Heinemann et al., 1987), relative decrease in psoas single muscle fibre isometric force (Geeves & Ranatunga, 1987), decreased tetanic force for extensor digitorum longus muscle (Ranatunga & Geeves, 1991), and decreased Ca^{++} influx into the nerve terminal (Grossman & Kendig, 1990). The evoked contractile force increases during inversion with lower hydrostatic pressure for leg extensor in the Neary et al. (2015) study could attributed to a less efficient muscle pump (Delp & Laughlin, 1998) with leg extensors, when compared to upright. These indirect results suggest how higher hydrostatic pressure on the arm during inversion could be related to significant reductions in resting twitch force.

Voluntary Contractile Properties

The greater decreases in elbow flexors MVC force with inversion can be related to several factors. The decreased force output can be related to a muscle stiffening mechanism, associated with a threat of instability (Carpenter et al., 2001), that the participants could have perceived when inverted with only straps holding them in the chair. Adkin et al. (2002) found that the stiffening strategy can negatively influence voluntary movement. Increased co-contractile activity with inversion has been previously reported as a factor counteracting target force output (Hearn et al. 2009; Paddock & Behm, 2009), however there were no

significant increases in triceps brachii EMG in the present study. It is possible that an increased focus on stabilizing functions of the shoulders, and trunk muscles (Arokoski et al., 2001), could negatively impact the force output of the elbow flexors (Anderson & Behm, 2004; Drinkwater et al., 2007). A shift from mobilizing to stabilizing strategies of the neuromuscular system has been reported to contribute to force reduction (Anderson & Behm, 2004; Behm & Anderson, 2006).

Fatigue Protocol

Perceived Pain

Perceived pain decreases between 0-20s and 20-40s intervals for upright without BFR condition contrasted with increases for upright BFR, and inverted without BFR and BFR conditions. These responses can be related to the increased pressure around the head region with inversion (Paddock & Behm, 2009), and/or BFR effects (Hollander et al., 2010). Meanwhile, the perceived pain increased for all conditions between the 40-60s intervals and post-fatigue [26.5% (upright<inversion) and 15.6% (without BFR<BFR) increases] could be related to the combination of BFR and fatigue (Hollander et al., 2010).

Following the fatigue task *(comparing pre- and post-fatigue values)*

The observed greater fatigue-induced PTF decreases with inversion versus upright, in this research, is in accord with a similar protocol by Neary et al. (2015), who showed near significant, small magnitude, decreases for elbow flexor (p=0.06, ES = 0.44, 11.8% from upright to inverted); while large magnitude increases (p=0.03, ES=1.27, 27.3%) for leg extensor forces during inverted posture. The differences in responsiveness may have originated from the increased hydrostatic pressure for the upper body in comparison with lower muscle groups.

During the upright position, the hydrostatic pressure is adjusted by various mechanisms like respiratory muscle pressure (Miller et al., 2005), functional hyperemia to the target muscle [Delp & Laughlin, 1998], and locally activated veno-arteriolar feedbacks (Vissing et al., 1997). In the present study, it was postulated that hydrostatic pressure changes, in terms of perfusion pressure to the target muscle, plus BFR (that result in changing arterial flow to the biceps brachii and returning venous) would affect motoneuron output. Also, partial BFR in addition to maximum isometric muscle contraction could lead to further restricted blood flow, which may have been related to the progressive increase in perceived pain.

Fitzpatrick et al. (1996) by changing the position of the arm relative to the heart (at 45cm above and below the heart level) observed decreases and increases in force generation respectively. Sundberg and Kaisjer, (1992) showed that a graded occluded lower limb (up to 50mmHg) caused a progressively decrease in muscle function. Further, Egana & Green. (2007) revealed there was a change in fatigue-resistance of the human calf muscle during contraction with moderate to high intensity, following altered body tilt angle. This intensity-dependence of the limb's position could be attributed to muscle blood flow (Egana & Green, 2005; Fitzpatrick et al., 1996), and delivery of oxygen to working muscle (Hogan et al., 1994). MacDonald et al. (1998) following a change in position from upright to supine, observed slower increases in the rate of blood flow and alveolar oxygen for leg exercise.

Furthermore, BFR can also be impeded by the intensity of the muscle contraction. Sadamoto et al. (1983) illustrated that a muscle contraction with moderate intensity (50-64% MVC) induced a complete BFR to the target muscle. Previous evidence (Sjogaard et al., 1988; Gaffney et al., 1990) showed a steady blood flow to the exercised muscle during a submaximal

isometric fatiguing task at 5-15% MVC, while perfusion decreases at the end of contraction with 25-50% MVC.

The greater decreases in M-wave for the upright BFR condition in our study may have related to greater metabolite accumulation, and/or higher hydrostatic pressure during inversion with inhibited sympathetic nervous activity, which could affect the venoconstriction function. Impairment of muscle contractility may originate from acidity of intramuscular environment (decreased PH) and decrease in sarcoplasmic reticulum Ca^{2+} uptake, and could influence the action potential (Place et al., 2009).

In the present study, the greater MVC decreases with BFR can reflect the suppressed perfusion to exercised muscle. The fatigue-induced 5.6% decrease (without BFR > BFR) for time to peak twitch, could be in part attributed to an alteration in muscle fibre conduction velocity (Farina et al. 2004). Moreover, Ogata et al. (1991) showed that a short period of nerve compression could affect the nerve conduction response. Lundborg et al. (1982) observed a change in endoneural microcirculation, following a low-level compression (~30 mmHg) on the peripheral nerve trunk (median nerve compression in the carpal tunnel).

Also, the greater decreases in biceps brachii median frequency for inverted BFR condition, versus upright BFR and inverted without BFR conditions in our study may reflect a greater hypoxia of the elbow muscles. Meaning, there would be a more significant shift to an anaerobic phase, resulting in earlier motor unit recruitment of higher threshold units, and accelerating the onset of fatigue (Gerdle & Fugl-Meyer, 1992; Moore et al., 2004). Moreover, decreased median frequency can be related to muscle fibre conduction velocity reduction (Eberstein & Beattie, 1985).

Copithorne et al. (2020) showed that BFR induced faster and greater increases in motoneuronal excitability, following a submaximal isometric elbow flexion. Also, they showed

that BFR induced more significant decreases (~80%) in time to task failure during a sustained isometric fatiguing task, in comparison with normal blood flow condition. Thus, BFR-induced faster increases in EMG, may be related to increases in motor unit firing rate (Copithorne et al., 2020). Following moderate to high-intensity sustained-contractions (decrease in muscle perfusion) the discharge rate of muscle fibres with small diameters can increase (Gandevia, 2001). Occluding arterial flow in the arm, during the post-fatigue period, Bigland-Ritchie et al. (1986) observed an impairment of neuromuscular transmission, which can represent a regulatory effect for peripheral feedbacks on central excitability.

Prior to the fatigue task *(between initial and pre-fatigue values)*

Cardiovascular Responses

Related to the aforementioned stiffening strategy with unstable threats, another possible candidate for the greater inversion induced MVC decreases can be related to a sense of freezing with inversion. Roelofs et al. (2010) created a "remaining motionless" protocol, observing bradycardia, and a decrease in body sway in their participants. The MAP decreases in the inverted condition versus increases with upright, before the fatigue task can be indirectly attributed to a higher sense of freezing. Furthermore, a diminished sympathetic function (decreased MAP) may be related to an attempt by the central nervous system to decrease the inversion-induced higher hydrostatic pressure by increased vagal (parasympathetic input) input from baroreceptor activation (Paddock & Behm, 2009; Hearn et al., 2009; Johar et al., 2013).

It has been shown that sympathetic activity can influence the contractility of human muscle fibres. Roatta et al. (2008) by activating the sympathetic nervous system (left hand immersed in water at 4°C), and performing isometric dorsiflexion, found a modulatory effect for adrenergic stimulation on low-threshold motor units. Bosone et al. (2004) showed a -30°

head-down tilt due to acute intracranial hypertension, inhibited the sympathetic nervous system. Charkoudian et al. (2004) revealed that a small increase in central venous pressure could lead to inhibition of arterial baroreflex (as an integrator of sympathetic vascular activity).

Prior to the fatigue task, the increased HR for both without BFR and BFR conditions, and increased MAP for BFR conditions (versus decreased for without BFR) may indicate a difference in functions between MAP and HR. It reflects as the BFR activates pressor reflexes, and increased load on the central system with hyperemia (Willis et al., 2019). Inhibited sympathetic nervous function can be detected irrespective of rotation speed with inversion (Johar et al., 2013). Since in our study there was relatively slow rotation from upright (i.e., 5s from upright to supine and 5s from supine to inverted), an "autonomic conflict" (imbalanced between sympathetic and parasympathetic functions) [Tipton et al., 2010] would be highly unlikely.

Following the fatigue task *(comparing pre- and post-fatigue values)*

The higher accumulation of metabolic by-products causes greater activation of group III and IV afferent fibres (Bull et al., 1988; Yasuda et al., 2010). In the present research, the decreases in MAP for without BFR versus increases for BFR condition (BFR*time interaction), and greater increases in HR for BFR, can indicate a BFR-induced pressor reflex effect. Neary et al. (2015) showed the role of pressor reflex on HR similar to the inverted position in the present study. However, Neary et al. (2015) reported significant HR decreases after fatigue task. The participants of the present study were all recreationally active in contrast with highly trained cross country and track and field athletes in the Neary et al. (2015) study. Therefore, the differences in aerobic capacity would be the main factor in providing a better-coping strategy following both inversion and fatigue task (Midgley et al., 2007).

The increased exercise-pressor reflexes are partially regulated by the peripheral reflex from the small-diameter muscle afferents (Amann et al., 2014). Arrested local blood supply can lead to altered human pressor response during voluntary and involuntary evoked isometric muscle contraction (Bull et al., 1988; Gladwell & Coote, 2002). As Bull et al. (1988) pointed out, there was a constant increase in HR and BP following a 2-min seated sustained plantar flexion and evoked contraction of the triceps surae, at 30% MVC.

Moreover, Gladwell and Coote, (2002) showed that the rise in HR was a bit faster in comparison with BP, during voluntary isometric contraction of triceps surae at 40% MVC. A different mechanism is suggested in terms of beginning the pressor response, and muscle afferents effects. For instance, in another experiment by Gladwell and Coote, (2002), a significant increase in HR response was observed following a 1-min passive stretching of triceps surae, though it was not significant for BP. Further, a circulatory occlusion on cessation of contraction resulted in a higher BP (relative to the pre-exercise level) while HR decreased to baseline levels (Bull et al., 1988; Gladwell & Coote, 2002).

It is well known that neural signals to both the cardiovascular centers and exercised muscle are regulated by the descending motor command (Goodwin et al., 1972; Thornton et al., 2001). While, the inputs from muscle afferents (Group III and IV) play an important role to control HR; in the presence of abolished central command-muscle for example, HR still remains elevated above the baseline levels (Fisher & White, 999). Although inversion may induce inhibited sympathetic function (Paddock & Behm, 2009; Hearn et al., 2009; Johar et al., 2013), metabolic by-products activates group III and IV in addition to altered motor unit recruitment pattern, can play a primary modulatory role on cardiovascular function.

3.6 Limitations

Due to the laboratory's structure, data could not be obtained from only the dominant limb. Although selected participants were recreationally active student, their different aerobic capability and training background, and stressful lifestyle would affect the reliability of HR in our study (Winsley et al., 2003). Also, the lack of minute to minute HR measurement during upright resting position could decrease HR reliability. While the partial BFR was set relative to the position (upright/inverted), it could not exclusively indicate 50% upright is similar to inverted. Using a doppler ultrasound in future study would decrease the presence of any error during controlling the target BFR.

Whereas ITT is considered a gold standard to explore muscle inactivation, it cannot clarify whether this change occurred, at the supraspinal or spinal level. Therefore, stimulation such as transcranial magnetic stimulation should be pursued in future investigation to more specifically identify the loci of change.

3.7 Conclusion

The increase in hydrostatic pressure with inversion contributed to decreased resting evoked twitch. Muscle stiffening mechanism, and increased co-contractile activity, following the inverted position, may have contributed to decreases in elbow flexor MVC force before the fatigue task. Greater post-fatigue PTF decreases with inversion was likely associated with perfusion pressure decreases. As impeded blood flow during contraction with moderate-high intensity and/or BFR can cause greater hypoxia and shift to earlier motor unit recruitment with type II fibres. BFR likely activated pressor reflexes, irrespective of the posture, to induce greater increases in HR. A practical application of these findings can apply for emergency

medical service following an overturned vehicle. For example, for the individual with peripheral artery disease with a higher incidence of heart failure, a compressed limb in concomitant with multiple intermittent contractions induced impeded blood flow (to escape from the stressful and uncomfortable overturned vehicle) by increasing greater loads on the cardiovascular system, can be a life-threatening reaction.

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3.9 Appendices

Table 3.4. Main Effects for Time.

Parameter	Initial Test ($M \pm SD$)	Pre-Fatigue ($M \pm SD$)	Post-Fatigue ($M \pm SD$)	Initial to Pre-Fatigue	Pre to Post-Fatigue
MVC Force (N)	309.32 ± 84.55	269.18 ± 75.16	226.30 ± 63.38	p<0.001, η_p^2=0.82	p<0.001, η_p^2=0.84
F100 (N)	73.28 ± 36.47	52.14 ± 25.64	34.32 ± 18.17	p=0.003, η_p^2=0.63	p<0.001, η_p^2=0.80
BB EMG (mV/s)	0.30 ± 0.16	0.29 ± 0.15	0.24 ± 0.12	p>0.05	p<0.001, η_p^2=0.65
TB EMG (mV/s)	0.07 ± 0.02	0.06 ± 0.02	0.05 ± 0.01	p=0.02, η_p^2=0.47	p=0.003, η_p^2=0.67
PTF (N)	66.48 ± 19.11	63.82 ± 18.38	28.86 ± 14.07	p>0.05	p<0.001, η_p^2= 0.93
½ relaxation time - PTF (ms)	85.76 ± 28.37	80.04 ± 27.41	117.54 ± 60.99	p>0.05	p=0.006, η_p^2=0.55
VMA (%)	91.71 ± 5.36	92.47 ± 3.44	82.53 ± 11.35	p>0.05	p=0.06, η_p^2=0.62
MAP (MmHg)	93.60 ± 1.49	93.64 ± 1.42	95.47 ± 1.90	p>0.05	p<0.001, η_p^2=0.87

*BB = Biceps Brachii, TB = Triceps Brachii, PTF = Potentiated Twitch Force, VMA = Voluntary Muscle Activation, MAP = Mean Arterial Pressure.

Table 3.5. Main Effects for BFR.

Parameter	no BFR Conditions ($M \pm SD$)	BFR Conditions ($M \pm SD$)	no-BFR to BFR
MVC Force (N)	274.61 ± 76.60	261.93 ± 72.12	p=0.05, η_p^2=0.37
BB M-Wave (mV)	9.67 ± 2.11	7.99 ± 2.44	P=0.03, η_p^2=0.51

Table 3.6. Main Effects for Seated Position.

Parameter	Upright Seated Positions ($M \pm SD$)	Inverted Seated Positions ($M \pm SD$)	Upright *vs*. Inverted
F100 (N)	58.27 ± 28.01	48.22 ± 25.51	p=0.09, η_p^2=0.27
MAP (MmHg)	94.75 ± 1.74	93.73 ± 1.47	p=0.01, η_p^2=0.38

Table 3.7. Interaction Effects for Seated Position and Time.

Parameter	Initial ($M \pm SD$)	Pre-Fatigue ($M \pm SD$)	Post-Fatigue ($M \pm SD$)	Initial to Pre-Fatigue	Pre to Post-Fatigue
MVC Force (N)	USP:304.22 ± 72.98, ISP: 314.43 ± 96.13	USP:278.75 ± 61.2, ISP: 259.60 ± 89.12	USP:238.96 ±54.65, ISP: 213.65 ± 72.12	p=0.02, η_p^2=0.48	p>0.05
RTF (N)	USP: 36.49 ± 16.71, ISP: 39.25 ± 17.93	USP: 36.28 ± 17.99, ISP: 30.32 ± 13.5	USP: 37.36 ± 19.56, ISP: 26.43 ± 14.97	p=0.03, η_p^2=0.34	p>0.05

PTF (N)	USP: 63.77 ± 16.16, ISP: 69.18 ± 22.06	USP: 64.29 ± 16.81, ISP: 63.35 ± 19.94	USP: 34.69 ± 17.81, ISP: 23.03 ± 10.33	p>0.05	p=0.02, η_p^2=0.67
MAP (MmHg)	USP: 93.76 ± 1.62, ISP: 93.44 ± 1.37	USP: 94.28 ± 1.62, ISP: 93.01 ± 1.22	USP: 96.20 ± 1.98, ISP: 94.74 ± 1.83	p=0.006, η_p^2=0.47	p>0.05

*USP = Upright Seated Position, ISP = Inverted Seated Position, RTF = Resting Twitch Force

Table 3.8. Interaction Effects for Seated Position and BFR.

Parameter	Upright Seated Positions ($M \pm SD$)	Inverted Seated Positions ($M \pm SD$)	Upright *vs*. Inverted
MVC Force (N)	no-BFR: 275.18 ± 62.09 BFR: 272.77 ± 63.79	no-BFR: 274.04 ± 91.12 BFR: 251.08 ± 80.46	p=0.08, η_p^2=0.32
Resting Time - PTF	no-BFR: 110.19 ± 26.15 BFR: 114.59 ± 28.42	no-BFR: 111.31 ± 32.63 BFR: 105.38 ± 25.41	p=0.07, η_p^2=0.44
BB M-Wave (mV)	no-BFR: 9.95 ± 2.28 BFR: 7.63 ± 1.86	no-BFR: 9.39 ± 1.94 BFR: 8.34 ± 3.01	p=0.04, η_p^2=0.44

Table 3.9. Interaction Effects for BFR and Time.

Parameter	Initial ($M \pm SD$)	Pre-Fatigue ($M \pm SD$)	Post-Fatigue ($M \pm SD$)	Initial to Pre-Fatigue (no-BFR *vs*. BFR)	Pre to Post-Fatigue (no-BFR *vs*. BFR)
½relaxation time-PTF (ms)	noBFR: 84.45±27.48 BFR:87.06±29.26	noBFR: 82.97±25.2 BFR:77.11±30.79	noBFR:127.65±65.88 BFR: 107.43±56.09	p>0.05	p=0.08, η_p^2=0.27
VMA (%)	noBFR: 90.05±8.74 BFR: 93.36±1.98	noBFR: 92.44±3.50 BFR: 92.50±3.39	noBFR: 85.60±8.85 BFR: 79.46±13.85	p>0.05	p=0.07, η_p^2=0.57
MAP (MmHg)	noBFR: 93.60±1.5 BFR: 93.61±1.49	noBFR: 93.30±1.35 BFR: 93.98±1.48	noBFR: 95.00±1.75 BFR: 95.94±2.05	p=0.005, η_p^2=0.5	p>0.05

Table 3.10. Main Time Effects for Fatigue – Force, and Fatigue-EMG Relationships.

Parameter	0-5s interval (no-BFR and BFR) [$M \pm SD$]	25-30s interval (no-BFR and BFR) [$M \pm SD$]	0-5s to 25-30s intervals
Force (N)	278.42 ± 85.72	242.86 ± 74.45	p<0.001, η_p^2=0.73
BB EMG Median Frequency (Hz)	57.67 ± 10.61	41.32 ± 5.59	p<0.001, η_p^2=0.89
TB EMG Median Frequency (Hz)	59.25 ± 12.53	44.26 ± 9.25	p<0.001, η_p^2=0.87

Table 3.11. Heart Rate Variability from Initial to Post-Fatigue.

Parameter	Initial ($M \pm SD$)	Pre-Fatigue ($M \pm SD$)	0-20s ($M \pm SD$)	20-40s ($M \pm SD$)	40-60s ($M \pm SD$)	Post-Fatigue ($M \pm SD$)
USP no-BFR	68.24 ± 9.20	73.36 ± 10.08	70.76 ± 10.01	74.06 ± 10.14	74.50 ± 12.93	73.64 ± 11.15
USP + BFR	65.66 ± 6.67	69.91 ± 8.03	68.97 ± 8.98	72.58 ± 8.62	73.75 ± 6.73	74.89 ± 11.02
ISP no-BFR	70.01 ± 9.23	70.00 ± 12.45	68.36 ± 14.26	69.88 ± 11.13	70.00 ± 12.81	71.85 ± 13.76
ISP + BFR	68.60 ± 5.37	73.93 ± 14.09	71.81 ± 12.97	72.96 ± 14.64	75.37 ± 18.12	81.54 ± 12.43

Table 3.12. Pain Perception Changes from Initial Upright/Inverted to Post-Fatigue.

Parameter	Initial UPS/ISP ($M \pm SD$)	Pre-Fatigue ($M \pm SD$)	0-20s ($M \pm SD$)	20-40s ($M \pm SD$)	40-60s ($M \pm SD$)	Post-Fatigue ($M \pm SD$)
USP no-BFR	0.07 ± 0.27	0.61 ± 0.76	0.61 ± 0.50	0.46 ± 0.51	0.38 ± 0.50	1.69 ± 1.65
USP BFR	0.30 ± 0.48	1.07 ± 1.18	1.46 ± 1.19	1.69 ± 1.49	1.84 ± 1.62	2.84 ± 2.47
ISP no-BFR	2.00 ± 2.38	2.46 ± 2.53	2.69 ± 2.49	2.92 ± 2.49	2.84 ± 2.37	3.30 ± 3.09
ISP BFR	1.61 ± 1.66	2.00 ± 1.58	2.38 ± 1.75	2.46 ± 1.80	2.61 ± 2.21	3.53 ± 2.78

Figure 3.10: A prepared-seated participant within the inversion chair (upright posture)