Department of Physical Education and Sport
Phd in Sport Science, Physical Education and Physical Activity for Health

SET CONFIGURATION AS A MODULATOR OF NEUROMUSCULAR FATIGUE

Doctoral Thesis

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A todas aquellas personas de las que tanto aprendí

pero hoy ya no están…

Abuelas Lorenza, Ara y Teresa

Tia Cuca y Tio Pepe

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La ciencia será siempre una búsqueda, jamás un descubrimiento real.

Es un viaje, nunca una llegada.

RESUMO

A configuración da serie (SC) é clave no manexo da fatiga muscular. Esta tese presenta tres estudos que exploraron a interacción entre a SC e os sistemas neuromuscular, cardiovascular, perceptivo e sensoriomotor ao exercicio de forza. Nun primeiro estudio, o tempo ata o fallo (TTF) ao 50% da forza máxima seleccionouse como paradigma configurando as series de forma tradicional (80% TTF) e clúster (20% TTF) durante 4 e 16 series respectivamente cun tempo total de descanso de 9 minutos para distribuír entre series. Un segundo estudo para abrir os parámetros sensoriomotores aferentes da extremidade inferior. Finalmente, realizouse un terceiro para corroborar os resultados do primeiro e para explorar a integración sensoriomotora no campo da fatiga do exercicio proporcionado pola SC. Os resultados mostraron unha resposta xeral de menor fatiga para o clúster como indica a menor perdida de forza, fatiga cortico-espinal e menor estrés cardiovascular acompañado dunha menor percepción de esforzo. Atopáronse fortes correlacións entre as respostas cardiovasculares e centrais. A integración sensoriomotora está presente no cuádriceps e a inhibición aferente longa e corta é sensible á fatiga durante o exercicio de forza.

Palabras Clave: configuración da serie, fatiga, exercicio de forza, neuromuscular, resposta cardiovascular, integración sensoriomotora, esforzo percibido.

RESUMEN

La configuración de la serie (SC) es clave en el manejo de la fatiga muscular. Esta tesis presenta tres estudios que exploraron la interacción entre la SC y los sistemas neuromuscular, cardiovascular, perceptivo y sensoriomotor al ejercicio de fuerza. En un primer estudio, el tiempo hasta el fallo (TTF) al 50% de la fuerza máxima se seleccionó como paradigma configurando las series de forma tradicional (80% TTF) y clúster (20% TTF) durante 4 y 16 series respectivamente con un tiempo total de descanso de 9 minutos para distribuir entre series. Un segundo estudio para obruvo los parámetros sensoriomotores aferentes de la extremidad inferior. Finalmente, se realizó un tercero para corroborar los resultados del primero y para explorar la integración sensoriomotora en el campo de la fatiga del ejercicio proporcionada por la SC. Los resultados mostraron una respuesta general de menor fatiga para el clúster como indica la menor pérdida de fuerza, fatiga cortico-espinal y menor estés cardiovascular acompañado de una menor percepción de esfuerzo. Fueron encontradas fuertes correlaciones entre las respuestas cardiovascular y central. La integración sensoriomotora está presente en el cuádriceps y la inhibición aferente larga y corta es sensible a la fatiga durante el ejercicio de fuerza.

Palabras Clave: configuración de la serie, fatiga, ejercicio de fuerza, neuromuscular, respuesta cardiovascular, integración sensoriomotora, esfuerzo percibido.

ABSTRACT

Set configuration plays a key role in the fatigue management. This thesis present three studies that explored the interaction between set configuration, neuromuscular, cardiovascular, perceptual and afferent integration responses to resistance exercise. In a first study the time to failure (TTF) at the 50% of maximal voluntary force were selected as paradigm of study configuring the sets for traditional (80%TTF) and cluster (20%TTF) configuration during 4 and 16 sets respectively with a total rest time of 9 minutes to distribute between sets. A second study was carried out for obtaining afferent sensorimotor parameters of the lower limb. Finally, a last study was performed to corroborate the results of the former and to explore the sensorimotor integration on the field of exercise fatigue provided by set configuration. The results showed a general lower fatigue response for cluster as outlined the lower loss of force for cluster, central and peripheral fatigue, minor cortical effects in the MEP and SICI and cardiovascular stress accompanied with a reduced perception of effort. Strong correlations were found between cardiovascular and central fatigue responses. Sensorimotor integration is present on the quadriceps muscle and long and short afferent inhibition are sensitive to fatigue during resistance exercise.

Keywords: set configuration, fatigue, resistance exercise, neuromuscular, cardiovascular response, sensorimotor integration, perceived exertion.

CONTENTS

ABBREVIATIONS

½RRT	half relaxation time	**RF**	rectus femoris
ANOVA	analysis of variance	**RFD**	rate of force development
BP	blood pressure	**RMT**	resting motor threshold
BRS	baroreflex sensitvity	**RPP**	rate pressure product
CS	cluster set	**RRI**	R-R interval
DBP	diastolic blood pressure	**SBP**	systolic blood pressure
EMG	electromyography	**SC**	set configuration
HF	high frequency	**sec**	seconds
HR	heart rate	**SICI**	short intracortical inhibition
ICF	intracortical facilitation	**ST**	single twitch
LF	low frequency	**TMS**	transcranial magnetic stimulation
LFF	low frequency fatigue	**TS**	traditional set
MAP	mean arterial pressure	**TTF**	time to failure
MEP	motor evoked potential	**VA**	voluntary activation
MVC	maximal voluntary force	**wk**	week
reps	repetitions		

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STUDY I

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Hardvard was the citation style adopted for this document.

I. SET CONFIGURATION

Intensity and volume were the most well know variables of the sports training and programming. These variables were used to increase, decrease or adjust the training load. This vision corresponds to a traditional way to configuring training. When the goal is to manage the fatigue of the athlete, trainers should be more specific designing their training programs.

Between all modalities of training, resistance exercise was the most studied (see Fig 1) since firsts works of Brunton (1897). The evolution of the knowledge in the 80´s establishing the debate between “muscle training VS nerve training” (Stone et al., 1982) to later explore the effects on the muscular adaptations (Fleck and Kraemer, 1988) allowed to start the new millennium with the focus on the key variables of the strength training to promote long-term adaptations such the intensity (Fry, 2004) and recently the volume (Schoenfeld et al., 2018).

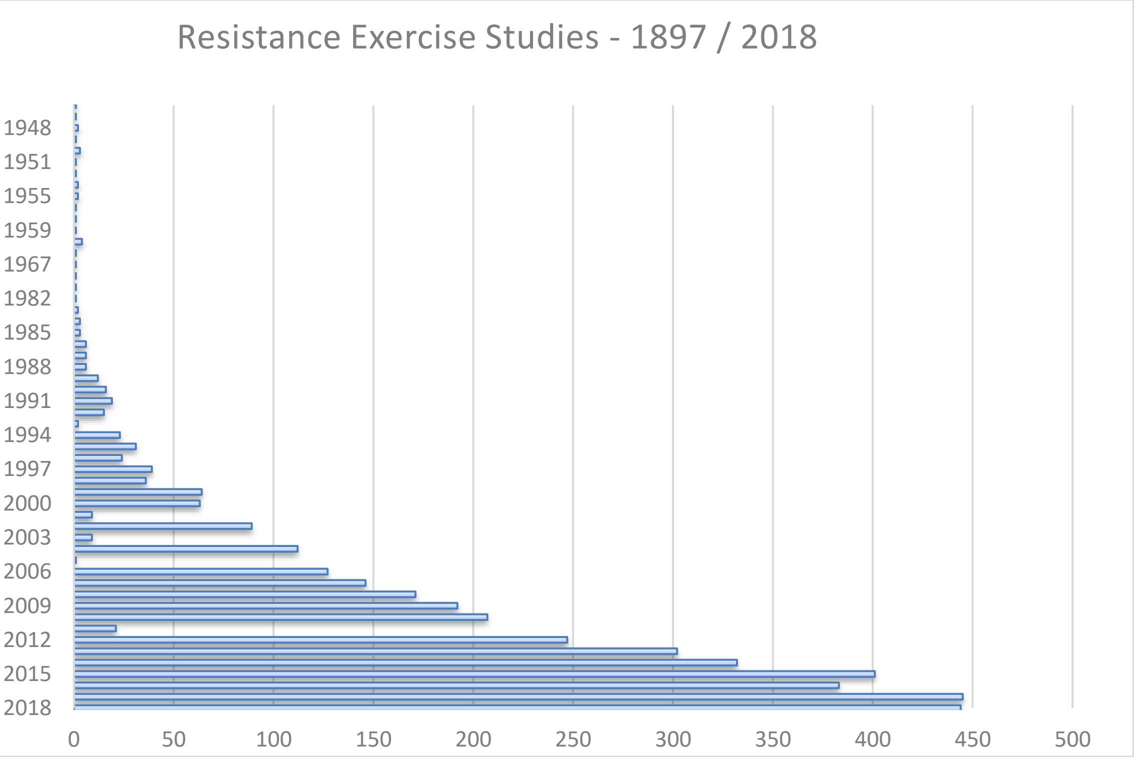

Figure 1. Evolution of Resistance Exercise studies from 1897 to 2018. Data extracted from MedLine (15 Oct)

In the last years one more variable comes to the light of the science: the set configuration. Set configuration could be defined as “the effort-time distribution” (Haff et al., 2008, 2003; Tufano et al., 2017a). It is different from density or pause because it manages the relationship between rest and work during resistance training (i.e. work-to-rest ratio) (Hansen et al. 2011; Mayo et al. 2014). Since now, in this document will be named set configuration (SC).

Traditionally, set configuration in resistance training was understood as a continuous way of performing repetitions during the set. Then rest with a concrete time or pause and start again. This way of configuring sets will be called Traditional set configuration (TS). This set configuration provokes high and large states of fatigue (Bottaro et al., 2009; Iglesias-Soler et al., 2015, 2012).

Trainers and researchers developed a new way of understanding the set configuration, splitting the traditional sets in small clusters of repetitions. This was called intra-set rest or cluster set (CS) training.

There are many ways to configuring the CS structure such performing repetitions by one, two, three, etc. and then rest, or redistributing the total training time in order to equate the work-to-rest ratio to a TS configuration as we can see in the Fig 2.

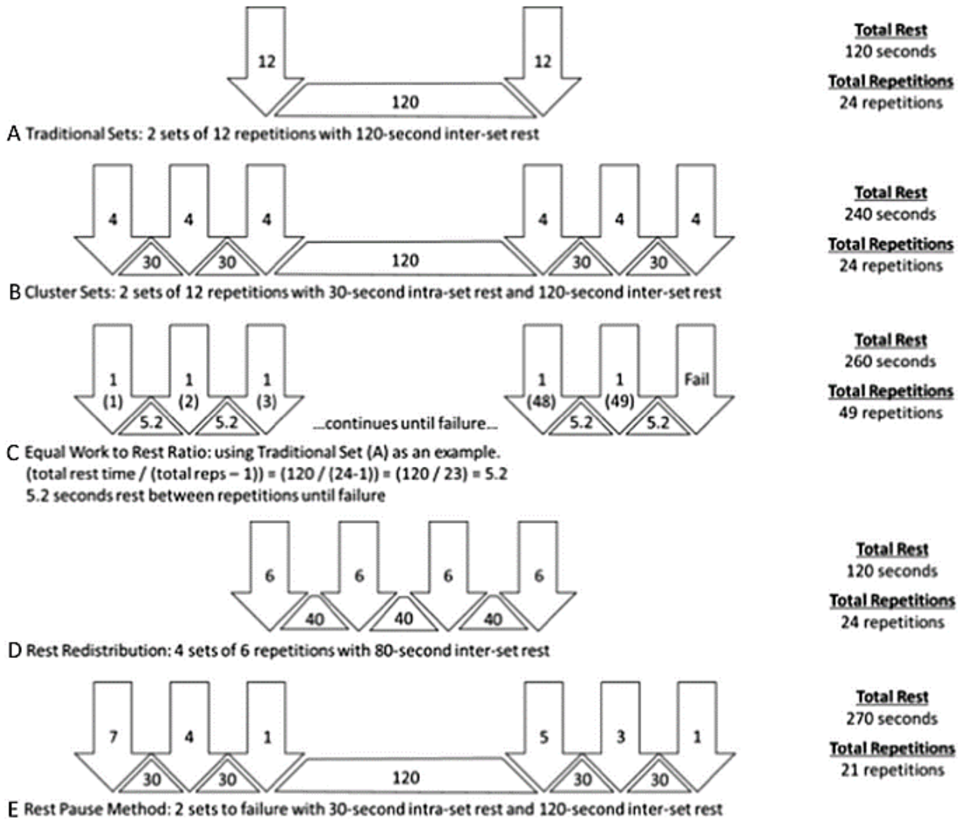

Figure 2. Representation of traditional (A) and cluster set schemes (B,C,D,E) Arrows indicate a number of repetitions performed in sequence, triangles indicate intraset or inter-repetition rest periods and quadrilateral shapes indicate interset rest periods. Reproduced from (Tufano et al., 2017a)..

A. Mechanical effects

The mechanical performance during the set is is of great importance to increase the quality of the training stimulus. In the next section, a general vision of the mechanical effects in response to the set configuration from speed and power to long term adaptations.

The differences between TS and CS structures were profoundly studied by authors like (Tufano et al., 2017a). The initial studies explored the ability of the CS configuration to provide high mechanic stimulus (Haff et al., 2003). Later, other works were designed to explore the differences when the work-to-rest ratio was equated. This studies completed the same work as the TS configuration with less fatigue (Iglesias-Soler et al., 2015; Mayo et al., 2014). The latter provided a real way to compare this set structures.

Speed and Power

The speed and power of each repetition are performed are critical variables to increase the quality of the training stimulus. Many studies compared the use of the cluster set structure over high performance in sport. One of the first studies (Haff et al., 2003) about SC in weightlifting performance explored the factors that affect barbell velocity and displacement. In this investigation, it appears that configuring the set schemes of a resistance training program with a cluster set model may produce specific alterations to both performance parameters. These alterations to both the barbell velocity and displacement may ultimately result in improved performance due to the relationship of these variables to lifting performance. Based on the concept of velocity and movement specificity it appears that the cluster set configuration allows the athlete to optimize the pull velocity and displacement (Haff et al., 2003). A study with elite rugby players using different cluster configurations on ballistic performance (i.e. jump squat) compared TS and CS structures. Cluster sets showed an advantage in the power maintenance across the set, but no differences were found between cluster variations (Hansen et al., 2011).

Power is fundamental to the successful performance of many athletic activities, and therefore training methods that optimize the development of power are of great interest to strength and conditioning coaches. Power output was studied in different CS configuration in elite-junior athletes with different inter-repetition loading schemes. Authors found that cluster structures are equally effective in providing an immediate intervention strategy by which weight training repetition power output and total power output can be enhanced. Authors like Lawton et al. (2006) have suggested that CS training may result in superior power adaptation as compared to TS training. This type of loading scheme may enhance neural adaptations resulting in maximal strength gains. It is less likely that a hypertrophic response will occur if the muscle is under tension for shorter durations. Further, CS loading schemes have the potential to maintain the integrity of the faster-type muscle fibers (Lawton et al., 2006).

Mechanical Work

In 2010 a study of Iglesias-Soler et al. explored the performance of the maximum number of repetitions in the bench press and biceps curls exercises with two loads (70% and 90%RM) and two SC. The authors conclude that CS configuration would be an interesting method to achieve a high upper-body work amount at high intensities in the same training session (e.g., 90% RM). *So assessment of the maximum number of repetitions and training at high intensities with CS configuration could be interesting for sports with the objective of high-load muscular endurance* (Iglesias-Soler et al., 2010).

High-intensity volume and large muscle mass exercises are fundamental for trainers and athletes. The study of Iglesias-Soler et al. (2014) compared the maximum number of repetitions with high loads (90%RM) in the parallel squat exercise. The current study showed that CT is useful to improve volume and to ensure sustainability of mechanical stimuli when resistance exercises are performed with high loads. Tufano et al. (2016) performed a similar experiment comparing high volume TS training versus two CS configurations in free weight back squats. Their principal outcome was that the velocity and power were maximized when intraset rest was most frequent and the total rest time was greater.

As Iglesias-Soler et al. (2014) suggested, coaches should consider this type of set configuration for developing high-intensity muscle endurance. This is of interest for specialties such as weightlifting, wrestling, or judo. In a recent experiment (Rio-Rodriguez et al., 2018) performed in two large muscle mass exercises (Deadlift and Bench

Press) with experienced lifters, heavy loads (4RM) but different intensity-effort (25% VS 50%, 1(4) VS 2(4) respectively), the authors explored the maximal volume of repetitions reached in cluster scheme and its reliability. They confirmed initial findings of Iglesias et al. (2014) about the very high volume of repetitions with high loads that CS configuration allowed to perform in every participant and its ability to replicate the effort in a reliable manner.

Strength Adaptations

The acute effects of CS configuration were compared with TS configuration in the previous paragraphs revealing the enhanced mechanical stimuli provided by the former. But, is it the improved mechanical stimuli the necessary condition to produce improvements with CS? The influential work of Folland et al. in 2002 provided a solid scientific argument to avoid the maximal fatigue in every training. In other words, it is not necessary to exhaust all the repetitions in reserve to produce adaptations.

However, an early study of Rooney et al. (1994) on CS structure comparing two elbow flexors training of 6RM 3 days a week during 6 weeks with 42 participants divided into three groups: With 30 seconds rest between each rep, without rest and control. After the training period, the no-rest group improved 56% respect to 41% of the rest-group (Rooney et al., 1994). The authors make a point on the fact that a minimum amount of fatigue is necessary on the neuromuscular system so that the adaptations are triggered.

Short-term studies in high performance (Hansen et al., 2011) in elite Rugby Union players did not find differences in the maximal force development after 8 weeks but they did find an improvement on speed and power with light to moderate loads in upper and lower limb exercises. This suggests that cluster training would be a proper scheme to speed and power development. A midterm work with 19 sports participants in a 12 wk training programme that included a final 3 wk power cycle revealed the efficiency of the CS respect to TS training to induce adaptations in high-speed jumping movements (Morales-Artacho et al., 2017). Another study (Asadi and Ramírez-Campillo, 2016) in college athletes applying CS and TS to plyometric training methods improved lower body maximal-intensity exercise performance but the TS method resulted in greater adaptations in horizontal sprint performance, while the CS method resulted in a greater horizontal jump, vertical jump and multidirectional movement (i.e. agility t-test) adaptations.

Lastly, to increase the effectiveness of resistance training, acute sessions should include a minimum of systematic overload stimuli to promote adaptations due to increases in systemic stress (Selye, 1952). When the work-to-rest ratio, volume and time under tension is completely equated, the strength adaptations are similar as revealed the study of Iglesias-Soler et al. (2016) after 5 wk of dynamic training of the knee extensors. Once again, CS configuration showed as an alternative to do the same amount of work with less effort. So it is plausible that the potential benefits that offer the cluster set configurations in sports training were being underexploited. As Folland et al. (2002) stated is not only not necessary to reach the maximum to generate adaptatións but also a minimum threshold of effort to trigger the adaptation processes. And as the studies revealed CS configuration could perform until even higher workload thresholds with less or similar fatigue. In this line it has been pointed out (Tufano et al. 2017) that if decreases in velocity due to fatigue are not of paramount importance, CS configurations could be used to achieve superior loads for a given number of repetitions, resulting in higher total work without sacrificing peak power.

B. Effects over the body systems

A general overview of the mechanical characteristics of the CS configuration was provided in the last section. Rest intervals between training sets are one of the most critical variables affecting both mechanical and metabolic acute effects of training. The length of the intervals affects the total volume completed during a workout and also the sustainability of repetitions along a training session (Iglesias-Soler et al., 2012). To further understand the causes that elicited observed differences with the TS configuration it is necessary to explore the underlying mechanisms that support the performance enhancement and the ability of CS configuration to manage fatigue.

Metabolic and Endocrine Response

Lactate concentration $[La^+]$ is one of the byproduct outcomes of muscular contraction (Tran et al., 2006). Continuous high-intensity muscular work demands higher implication of glycolytic metabolism, and it has been demonstrated that an elevation in lactate is concomitant with a reduction in mechanical performance. However, breaking the set in small clusters of repetitions is supposed to inhibit the effects of metabolic accumulation and substrate depletion (Haff et al., 2008; Izquierdo et al., 2006). It is also known that elevated blood $[La^+]$ could affect muscular function by producing neural inhibition from the stimulation of III and IV muscle afferents due to muscular acidosis (Gandevia, 2001).

A study has explored the metabolic response of high-intensity resistance (4RM) exercise when the set is performed until muscular failure compared to not leading to failure with the use of cluster sets (Iglesias-Soler et al., 2012). They found a blunted $[La^+]$ response with the CS configuration confirming the initial hypothesis. Shorter periods of muscular ischemia avoided the increases in muscular acidosis. An earlier study of Denton & Cronin

(2006) showed that high intensity (6RM) CS configuration equated in volume offered an advantage in diminished [La^+] with no differences in mechanical performance. These conflicting results could be related to the total number of repetitions. Authors speculated that less vasoconstriction could result in less muscle hypoxia/anoxia, potentially diminishing the previously observed fast to slow twitch fiber-type transformations in resistance training.

The hormonal response is one of the steps to favor the anabolism and therefore the muscular improvement via hypertrophy. A recent study (Tufano et al. 2017) explored the effects of different CS schemes to induce a positive anabolic environment. They found similar increases in growth hormone after exercise in each protocol with no change in post-exercise cortisol levels showing that the mechanical stress provided during each of the protocols most likely favored anabolism over catabolism (Tufano et al. 2017).

Cardiovascular Response

The cardiovascular impact of a modality of exercise is a measure of internal load (Foster et al., 2017). The heart and lungs work together as a system to supply oxygenated blood to the active muscles. Traditional RE could be an obstacle to the system normal function because of the restricted periods of blood flow generated by the contraction of the active muscles. In order to surpass the physical barrier, the cardiovascular system raise the pressure to irrigate the distal musculature overcoming the ischaemic barrier. If prolonged periods of work are added, then an elevated heart rate will be obtained resulting in a high-stressful combination over the whole system. In other words, a high rate pressure product would be obtained which reflects the total load over the cardiovascular system (Buchheit, 2014; Sembulingam and Ilango, 2015).

One of the first scientific works which compared the effects of set configuration on cardiovascular responses during dynamic high-intensity resistance exercise with equated volume, intensity and total resting time was the study of Iglesias-Soler et al. (2014). The authors found that CS configuration elicited lower systolic blood pressure and rate pressure product than TS configuration with a lower loss of velocity in each repetition. Hence, faster contractions may promote lower periods of time under tension and, consequently, shorter periods of restriction of the arterial flow. As Denton & Cronin (2006) suggested, CS configuration resulted in lower vasoconstriction, accordingly, this loading scheme may be more appropriate, and safer, for populations susceptible to high blood pressure periods (i.e., hypertension).

Heart rate variability (HRV), the fluctuation of instantaneous heartbeat over time, is a correlate of cardiac autonomic regulation (Heathers, 2014). Cardiac vagal control after a resistance training session has been shown to be affected by load and volume. This is of relevance since 30 min after exercise there is a decreased vagal activity which increases the probability of suffering a sudden cardiac death (Mayo et al., 2016). For this reason, this parameter takes importance in the resistance exercise prescription.

To that end, the works of Iglesias-Soler and cols explored the autonomic modulations caused by SC. Their results showed a lower cardiac autonomic modulation after both training regimes with TS and CS configuration (Iglesias-Soler et al., 2015), but the type of exercise affected the cardiac vagal control after resistance exercise, with higher reductions in a smith machine parallel squat in comparison with smith machine flat bench press (Mayo et al., 2016). The authors stated *that interactions between the type of exercise and set configurations showed that the cardiac vagal control after resistance exercise is affected by both factors simultaneously*. However, set configuration affected post-exercise hypotension, with lower values of blood pressure after the TS configuration session but not after the CS configuration (i.e. lower pressor response).

Perceived Exertion

The perception of effort is the conscious sensation of how hard, heavy, and strenuous a physical task is (DeMorree et al., 2012). Changes in metabolic, hormonal or neuromuscular parameters due to different SC loading schemes could be tracked by a perceived effort scale. It estimates the extent of effort, strain, discomfort, and fatigue that an individual feels while exercising (Mayo et al., 2017).

The study of Hardee et al. (2012) explored the perception of effort with different SC during three sets of a power clean weightlifting exercise. They observed a direct inverse relationship between RPE and power output. Authors concluded that RPE *might be a good indication as to the level of fatigue induced by resistance exercise but not necessarily the intensity.* Mayo et al. (2014) compared the RPE as well as power in two exercises differing in muscle mass and SC. The findings were that a TS configuration session leads to higher RPE and lower power compared with the CS. Moreover, differences between exercises showed greater RPEs for the squat than in the bench press, suggesting that muscle mass may cause differences in the RPE response. Thus, RPE might be used as an intrinsic regulator of muscular fatigue with regards to power training.

Peripheral and Central adaptations

The physiological modifications induced by strength training have been widely explored, and it has been suggested that the resultant outcomes can be attributed to peripheral and or central factors (Gabriel et al., 2006; Gandevia, 1999; Pensini et al., 2002). A common approach used to distinct neural versus muscular tissue adaptations is the examination of the relationship between electromyographic (EMG) activity and voluntary force output (e.g. maximal voluntary contraction).

During the progress of this dissertation, parallel studies (Iglesias-Soler et al., 2016) about set configuration long-term effects were performed with some of the techniques (i.e. twitch interpolation, TMS, etc.) and methodologies that distinguish the present research work about the central and peripheral adaptations. Its main outcomes are discussed below.

The peripheral adaptations were evaluated by M-wave and its related evoked contractile properties. The M-wave represents the synchronous activation of the entire pool of motoneuron units, and its modulation has been related to changes in membrane ionic activity (Rodriguez-Falces et al., 2013; Yochum et al., 2012). The results of this study (Iglesias-Soler et al., 2016) showed greater M-wave amplitudes after the training period specially for TS configuration suggesting an enhancement in membrane excitability. However, this improvement did not affect the maximal voluntary force, which was comparable between SC after the training period.

The mechanical evoked twitch properties associated with the M-wave (e.g. evoked force, RFD, RRT…) improved both in TS and CS configurations. Those changes are attributed to muscular mechanisms such as modifications in passive stiffness of the series of elastic component and excitation-contraction coupling process (Folland and Williams, 2007). The calcium kinetics (release and uptake) and ATPase activity would also be responsible for this enhancement varying the twitch contractile properties (Rodriguez-Falces and Place, 2017).

Musculature receives a neural triggering signal from the pool of innervating motor neurons (Heckman and Enoka, 2004). This neuronal signal is the summation of the motor neurons spiking activities, and it is called the neural drive to the muscle. This neural drive is produced by the transformation of the synaptic input to the motor neurons into output spike trains to the muscle to achieve or maintain a given level of force (Farina et al., 2014; Proske and Gandevia, 2012). It could be assessed by electromyography (EMG), mechanical records and transcranial magnetic stimulation (TMS). Analysis of the raw EMG signal with the root mean square normalized to M-wave, to remove the muscle membrane properties, reflects a central neural drive to muscles. Also, the voluntary activation (VA) represents the level of motor neuron drive during a maximal voluntary contraction (MVC) values lower than 100% could represent suboptimal firing incomplete recruitment (Goodall et al., 2009) . In this SC training study, the authors did not find neural changes (RMS and VA) related to set configuration after training.

TMS is used to activate neurons in the human cerebral cortex through the scalp without any pain. It has has been used to study neural transmission from the motor cortex to the muscles. An index of the entire corticospinal pathway responsiveness, from the brain to muscle, can be obtained from the size of the compound muscle action potentials recorded at the muscle via electromyography (Carroll et al., 2011). In this study, no changes in TMS parámeters (MEP, SICI, ICF) were found. This is in agreement with previous studies that suggest more extended periods of training to produce cortical adaptations. Although, it is likely that the precision required to detect subtle cortical modulations produced by resistance training may be not assured with resting motor-evoked potentials (Carroll et al., 2011).

C. Synthesis and perspectives

The variables studied up to now are related to the fatigue response of each one of the systems of the organism to the configuration of the series. Many variables continue unexplored and its necessary to know more about the response of the rest of the systems to have a multifactorial view of the fatigue processes.

To summarize, the cluster set configuration:

- Reduces the loss of velocity throughout the set.
- Allows to complete the same amount of work with less perception of fatigue.
- Blunts the cardiovascular and metabolic response.
- Stands as a safer alternative to the traditional resistance training configuration risky populations (hypertensión, coronary disease, etc.)
- Has a superior effect in the fast movements in long-term training.
- Has similar effects on central and peripheral adaptations as the TS configuration in the short term (5wk).

To explore the relationships of these variables in the context of resistance exercise is of interest when the available evidence is divided into unilateral approaches. Hence, the study of the possible relationship between the mechanical, cardiovascular and perceptual variables in the fatigue response could offer a complete vision of the processes that might be occurring in the human physiology.

II. MUSCULAR FATIGUE CAUSED BY RESISTANCE EXERCISE

Fatigue is a multifactorial process that could arise from central or peripheral systems. There are multiple ways that fatigue has to manifest. Fatigue is commonly defined as any reduction in the maximal capacity to generate force (Vøllestad, 1997). Although most definitions of fatigue focus on force production, fatigue not only impedes a fiber's capacity for maximal force generation but importantly the maximum speed of shortening or lengthening and consequently, power output will also to be affected (Gandevia, 2001; Gandevia et al., 1996). In the next lines, a review on all the process that underlies the fatigue response will be exposed. Although it might be almost impossible to identify the single most important limiting factor of fatigue, this should not deter scientist and clinicians from attempting to resolve many of the issues which confound this concept.

A. Fatigue Models

Whether it will be ever possible to identify the limiting cause of fatigue during a task is debatable. What is clear is that fatigue comprises a spectrum of events for which there is no single causative factor, with many factors occupying potential roles in its etiology (see Fig 3). These factors make fatigue such a complex and controversial concept. (Williams and Ratel, 2009).The interaction between the status of the individual, the type of task and where the fatigue develops is the principal factor to understand the fatigue response. The rest of the variables related to the latter would be a direct consequence of this three-dimensional interaction. It exemplifies the relationships between

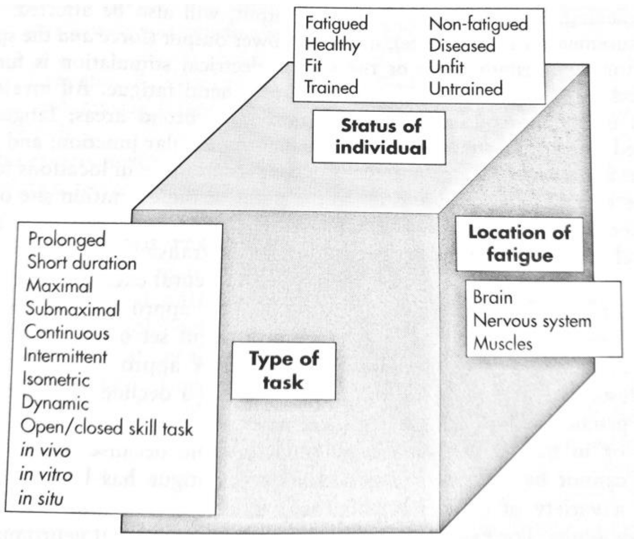

Figure 3. Multifactorial perspective of fatigue (Williams and Ratel, 2009).

the energy exchange, the central or peripheral fatigue and the reduction in the force-generating capabilities of the actin and myosin cross-bridges.

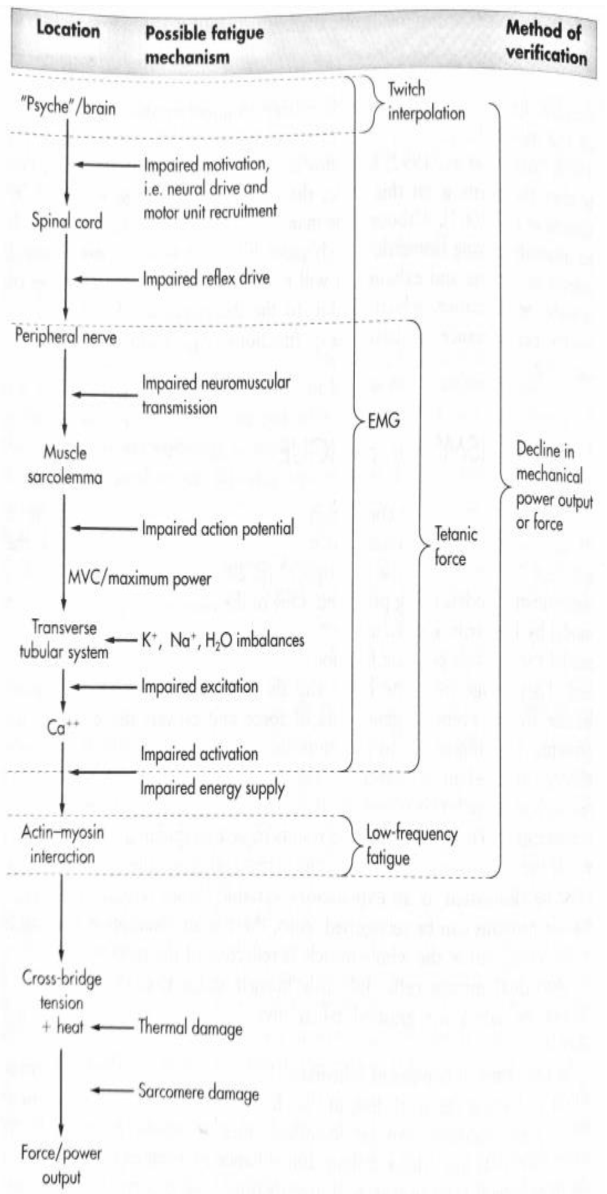

Figure 4. Linear chain model of fatigue. (Williams and Ratel, 2009).

It is possible to simplify the dozens of possible combinations if the vision of the fatigue is limited to a classic catastrophe theory model as Edwards proposed in 1983 named *Command chain for muscular contraction in man* (Gibson and Edwards, 1985). This model posits that exercise terminates when the physiological and biochemical limits of the body are exceeded, causing a catastrophic failure of intracellular homeostasis. This proposal accounts for the changing scenario of losses of energy and excitation/activation losses on force production. It provides a theoretical mapping of what is likely occurring when there is a decline in force or power output.

However, other models were proposed in order to advance in the knowledge of an integratory relationship of the body systems. Noakes in 2005 proposed the Central Governor Model where the definition of fatigue changed to *a sensation that results from* *the conscious perception and interpretation of subconscious regulatory processes in the brain, and is therefore not the expression of a physical event.* (Noakes et al., 2005).

This central governor model is an example of a complex dynamic system in which multiple physiological processes in many different systems interact with each other continuously. As a result, changes in any physiological variable results from alterations in neural command or peripheral regulatory systems in response to prior system perturbation. The continuous interaction between feed forward and feedback control mechanisms in the brain and peripheral physiological systems produces a robust, self sustaining mechanism that maintains homoeostasis by ensuring that no system is ever overwhelmed or used to absolute maximal capacity (Noakes et al., 2005)

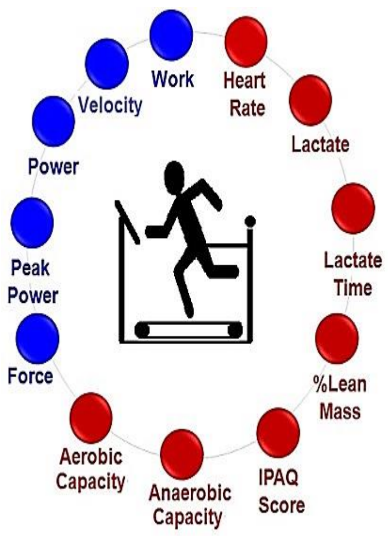

Figure 5. Variables confronted in computational model (Pereira et al., 2015).

Modern computational advances were applied to create a computational model of exercise fatigue based on know true correlations developed four possible models (Pereira et al., 2015). Authors explained the main limiting factors depending on the task nature, intensity. They proposed a complex network model (Fig 5) where nodes are measurements of changes in body systems at the mechanical (blue) and physiological (red) related levels and IPAQ score (red) during four different intensities of exercise tests. (Pereira et al., 2015)

Regardless of the model, the primary mission when studying the fatigue response to a type of exercise, intensity or load parameter is the relationship between neuromuscular factors (e.g. neural drive), cardiovascular, metabolic and all sensorial and regulatory mechanisms (muscular afferents, baroreflexes…).

B. Central Fatigue

Some terms should be clarified to correctly understand the factors that underlie the fatigue response at the nervous system. Central fatigue is *a progressive reduction in voluntary activation of muscle during exercise* (Gandevia, 2001). The Supraspinal fatigue, a subset of the latter, could be present when a *failure to generate output from the motor cortex is observed*. This is of relevance if we use the Voluntary Activation to measure the central fatigue which is the *level of voluntary drive during an effort*. Unless specified, the concept does not differentiate between the neural discharge to the motoneurons and that to the muscle. Voluntary activation can be measured using electrophysiological techniques as the twitch interpolation during a maximal voluntary contraction.

Central fatigue can originate at spinal and supraspinal sites. Spinal regulation primarily involves the control of alpha and gamma motor neuron activity by some different mechanisms as we see in Fig. 6. Briefly, spinal motor neurons have an intrinsic property to reduce their natural discharge frequency over time that is regulated by muscle afferents (muscle spindles, Golgi tendon organs, small diameter fibers), spinal interneurons and presynaptic inhibition of afferent inputs from propriospinal and other supraspinal sites (Fig 7) (Ranieri and Di Lazzaro, 2012).

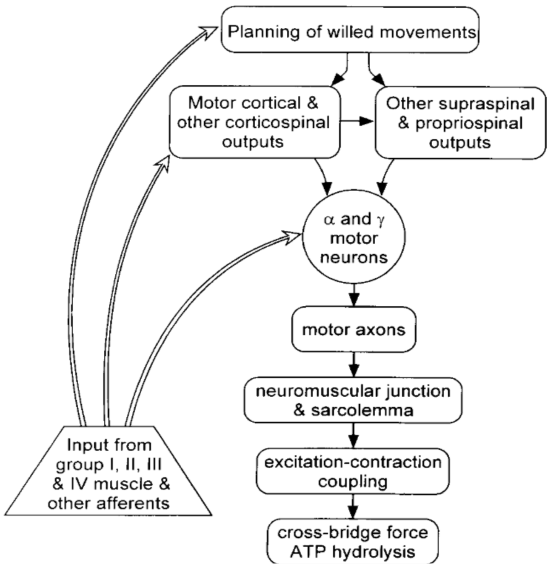

Figure 6. Steps involved in voluntary force production and factors acting at motoneuronal level (Gandevia, 2001).

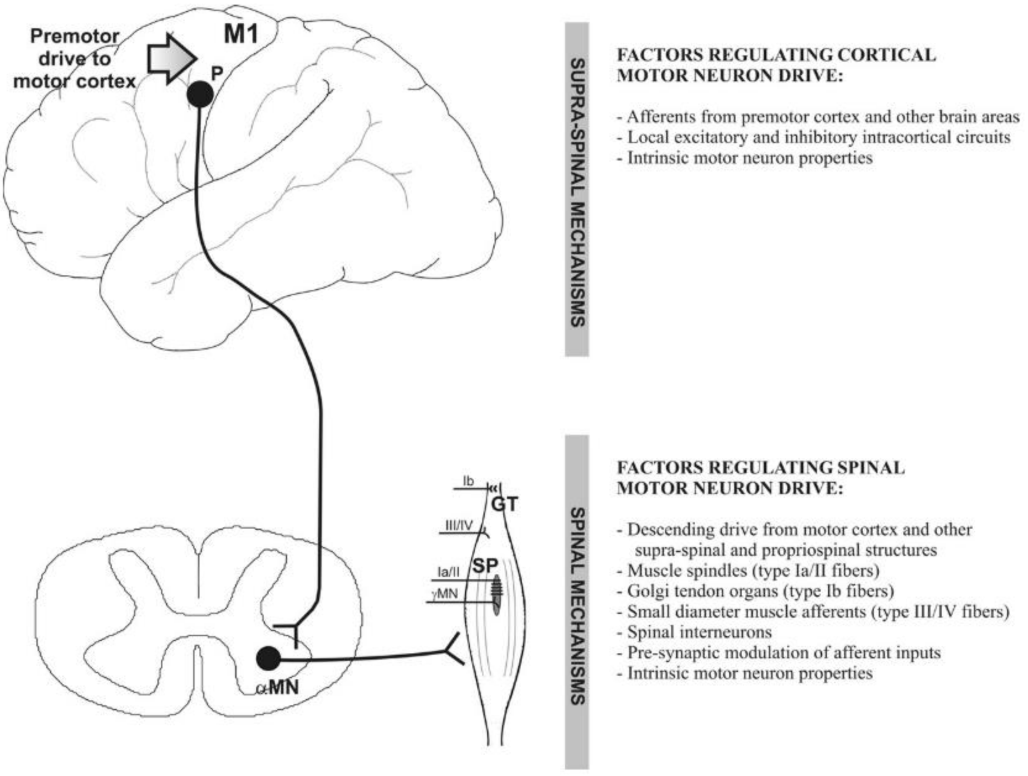

Figure 7. Schematic representation of the main spinal and supra-spinal mechanisms of regulation of motor neuron drive. M1: primary motor cortex; P: pyramidal corticospinal cell; αMN: alpha motor neuron; γMN: gamma motor neuron; GT: Golgi tendon organs; SP: muscle spindles. (Ranieri and Di Lazzaro, 2012).

Supraspinal regulation relies not only on the activity of primary motor cortex but also on the function of the brain structures involved in planning and control of movement and on the feedback information.

DeMorree et al. (2012) find promising relating the cortical motor activity and the subjective perception of the participants. They stated that perception of effort is the *conscious awareness of the central motor command sent to the active muscles.* The gradual increase in effort as fatigue supervenes derives from the increased central command needed to recruit more motoneurons, to increase their rate of discharge in initially submaximal tasks, and to attempt to maintain their output in maximal ones. Motoneuronal properties request that if a motoneuron is transiently unrecruited during a fatiguing effort, a relatively more considerable input will be required to recruit it again than would have been necessary to maintain its output.

C. Peripheral fatigue

The physiological changes produced at or distal to the neuromuscular junction are considered peripheral fatigue. In the next section, a general vision of the metabolic processes within the muscle fiber and the motor plate will be reviewed.

Muscular metabolic changes

Acute skeletal muscle fatigue develops in situations with high energy demand and large dependency on anaerobic metabolism. The mechanisms of fatigue when muscles are contracting at high workloads promotes the consumption of muscular stores of energy and the products of these reactions start to accumulate. Muscular tissues become acid because glycogen is broken down anaerobically to lactic acid; inorganic phosphate ions (P_i) accumulates because phosphocreatine (PCr) is broken down to creatine (Cr) and Pi (Allen and Westerblad, 2001). When fatigued, muscles become weaker and slower, and two end products of anaerobic metabolism, H^+ and inorganic P_i, have received the utmost attention as causes of the impaired contractility in fatigue. Acidosis may decrease isometric force by reducing the myofibrillar Ca^{2+} sensitivity, which will have a large effect on the submaximal forces used during most types of exercise (Westerblad, 2016).

Furthermore, there are several other metabolic changes during fatigue. There is cellular mechanisms of force control that includes: (i) the Ca^{2+} concentration surrounding the myofilaments, (ii) the sensitivity of the myofilaments to Ca^{2+}, and (iii) the force produced by the crossbridges characterized by the maximum Ca^{2+}-activated force (Allen and Westerblad, 2001). Hence, at the cellular level, fatigue is generally thought to be produced by the cumulative consequences of multiple metabolite changes acting throughout these three mechanisms. Failure of sarcoplasmic reticulum (SR) Ca^{2+} release has been shown to be a significant contributor to the muscular fatigue. Growing evidence supports the hypothesis that precipitation of calcium phosphate in the SR contributes to the failure of SR Ca^{2+} release (Allen and Westerblad, 2001). This mechanism may be central in high-intensity actions which lead to fatigue in the short-term (1-2 min), but other mechanisms are possibly more important in lesser intensity activities which cause fatigue in >1 h.

In summary, H^+ and P_i contribute to fatigue, primarily both by their inhibitory effects on the cross-bridge and by reducing the sensitivity of the myofilaments to Ca^{2+}. Indeed, it is now clear that elevations in H^+ and P_i are the major contributors to the loss in force and velocity when are studied in skinned muscle fibers works demonstrating that the metabolic by-products directly inhibit the force and the motion-generating capacity of muscle during fatigue (Debold et al., 2016). However, experimental evidence from human muscle studied in situ and isolated intact muscle fibers clearly speak against acidosis as a central factor underlying the impaired contractile function in fatigued mammalian muscle (Westerblad, 2016). To sum up, acidosis as such has only minor direct effects on the contractile function of mammalian muscle studied at physiological temperatures.

D. Sensory and afferent integration:

From brain to muscles and back again

Contraction-induced mechanical and chemical stimuli activate molecular receptors on the terminal end of both thinly myelinated (group III) and unmyelinated (group IV) nerve fibers located within skeletal muscle (Sidhu et al., 2017). Muscular Group III and IV afferents innervate free nerve endings distributed widely throughout the muscle. These receptors are either silent or maintain low background discharge rates responding to local mechanical, biochemical, and thermal events. Several factors cause their discharge to increase during strong contractions and fatigue, mainly if the contraction intensity is sufficient to impair muscle perfusion which also depends on the specific exercise being performed (see Fig 8).

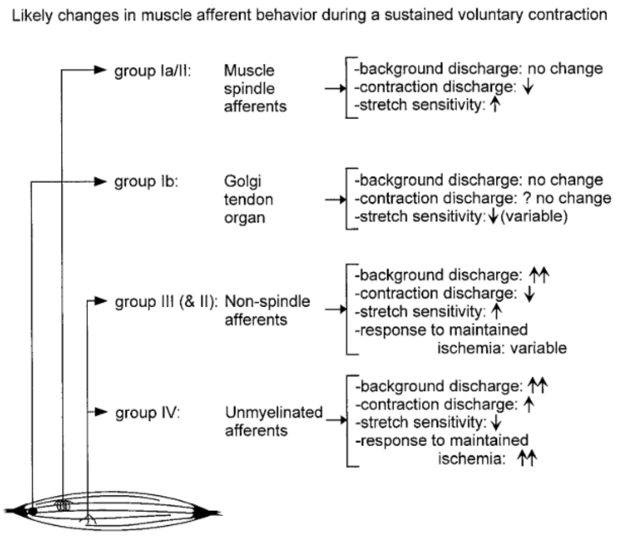

Figure 8. Likely effect of muscle fatigue on the input from different classes of muscle receptor. Data are shown for background discharge rate, responses to a muscle contraction, responses to muscle stretch, and responses to muscle ischemia maintained after a contraction (Gandevia, 2001).

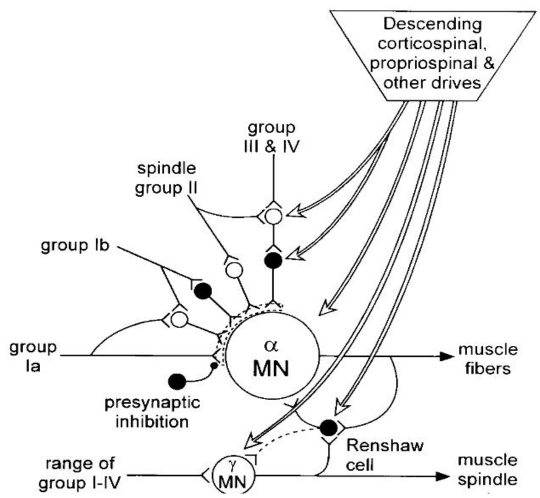

Figure 9. summary of inputs to α- and γ-motoneurons for an agonist muscle. Cells with solid circles are inhibitory. Dotted curved region at premotoneuronal terminals denotes presynaptic inhibition acting selectively on the afferent paths to motoneurons (Gandevia, 2001).

Through the dorsal horn of the spinal cord these neural sensory receptors project directly, and/or indirectly, to various sites within the central nervous system including areas which have been linked with central fatigue (e.g. a-motoneurons, motor cortex, insular or cingulate cortex) (Amann et al., 2015; Sidhu et al., 2017). During muscle fatigue, these muscle afferents provide strong feedback restricting motoneuronal output and muscle activation by limiting voluntary descending drive from ‘upstream’ of the motor cortex and depressing the excitability of the corticospinal pathway including the motor cortex and spinal motoneurons (see Fig 9). This sensory signal of fatigue from the firing of group III/IV muscle afferents interacts with the autonomic nervous system, as well as with various levels of the motor system and also contributes to awareness of muscular discomfort and fatigue (Taylor et al., 2016). Hence, the modifications in the sensory, neuromuscular, and homeostatic systems contribute all to exercise fatigue. The combination of influences on exercise performance will depend on the task and the conditions and under which it is performed. To sum up, group III/IV muscle afferents feedback during fatiguing exercise directly or indirectly impair the spinal motoneurons output (Fig 10), which can compromise voluntary muscle activation and, subsequently, exercise performance.

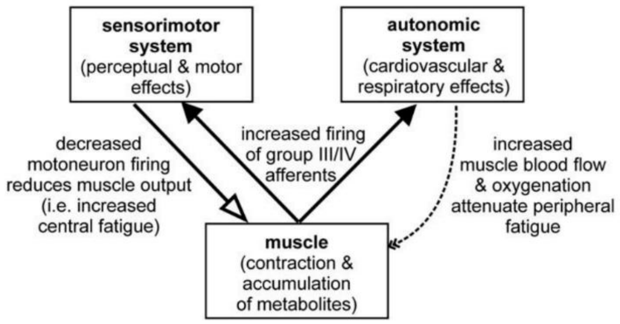

Figure 10. Group III/IV function and sensory modulation (Taylor et al., 2016).

The primary somatosensory cortex (S1) and primary motor cortex (M1) are commonly considered to be functionally segregated regions with S1 processing sensory input and M1 encoding motor output (Dubbioso et al., 2017a). Influential concepts of sensorimotor integration underline an active influence of cortical sensory input on motor output and vice versa. Somatosensory inputs notify both, reflexive and volitional actions (Dubbioso et al., 2017a; Ward et al., 2015). This comprises bodily feedback generated by the movement itself and somatosensory input signaling the consequence of a movement, for instance, the haptic experience when manipulating an object. Conversely, motor output impacts on perception. The relationships between sensorial and motor integration are of interest in order to adjust the motor output due to afferent information.

III. WHAT´S NEXT?

A comprehensive overview of the set configuration and fatigue responses was provided in the past chapters. Different studies have shown the effects of SC in the neuromuscular, cardiovascular, endocrine and perceptual responses. A complete vision of each system has been provided separately. In brief, the cluster set configuration provided a lower fatigue response with an enhanced mechanical performance.

Taken together the mechanical, cardiovascular, metabolic and perceptual responses offers a vision of the processes that the set configuration could be affecting. Thus, it is of great interest to explore whether these variables are related to the same proportion in the fatigue response. Regardless of the fatigue model, the primary mission when studying the fatigue response to a type of exercise, intensity or load parameter is the relationship between neuromuscular factors (e.g. neural drive), cardiovascular, metabolic and all sensorial and regulatory mechanisms (muscular afferents, baroreflexes).

Therefore, the primary purpose of this thesis was to explore the differences between the traditional and the cluster set configuration in the neuromuscular, cardiovascular, perception and sensorimotor systems and in a second order to find relationships between the fatigue manifestations in each system.

Thus, three experiments were performed in order to search for the answers to these aims. In the first study the differences due to set configuration were explored. In the second a methodological study was developed to establish the properties of the sesorimotor integration in the lower limb. Finally in the third experiment aimed to contrast the results of the former adding the sensorimotor variables in order to check if the set configuration could affect the sensorimotor properties of the lower limb.

IV. PURPOSES AND HYPOTHESES

Study I. Set configuration in resistance exercise: muscle fatigue and cardiovascular effects.

Purpose

To investigate differences in the neurophysiological, mechanical and cardiovascular acute responses of TS and CS configurations matched for volume, intensity, and work-to-rest ratio.

Hypothesis

The levels of muscle fatigue induced by different resistance set configurations account for the differences in the cardiovascular response.

Study II. Modulation of quadriceps motor cortex excitability by femoral nerve stimulation.

Purpose

To explore the conditioning effect of a percutaneous electrical pulse of the femoral nerve on cortical motor evoked responses in the rectus femoris muscle.

Hypothesis

An electrical pulse on the femoral nerve is able to modulate the cortical response of the rectus femoris muscle demonstrating that the sensorimotor integration processes are present in this musculature.

Study III. Sensorimotor integration is affected by set configuration.

Purpose

To describe the effects of the lower limb modulation during two equated training configurations in the rectus femoris muscle.

Hypothesis

The sensorimotor integration is affected by the amount of fatigue caused by different resistance set configurations.

V. STUDY I

Set configuration in resistance exercise: muscle fatigue and cardiovascular effects

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A. Introduction

Abbreviations

½RRT	half relaxation time	**MEP**	motor evoked potential
ANOVA	analysis of variance	**RF**	rectus femoris
BP	blood pressure	**RFD**	rate of force development
BRS	baroreflex sensitvity	**RMT**	resting motor threshold
CS	cluster set	**RPP**	rate pressure product
DBP	diastolic blood pressure	**RRI**	R-R interval
EMG	electromyography	**SBP**	systolic blood pressure
HF	high frequency	**SICI**	short intracortical inhibition
HR	heart rate	**ST**	single twitch
ICF	intracortical facilitation	**TMS**	transcranial magnetic stimulation
LF	low frequency	**TS**	traditional set
LFF	low frequency fatigue	**TTF**	time to failure
MAP	mean arterial pressure	**VA**	voluntary activation
MVC	maximal voluntary force		

Cardiovascular modulation and its association with resistance exercise have been the focus of extensive research(Mitchell, 2013). The blood pressure (BP) and heart rate (HR) responses to resistance training are thought to be modulated by peripheral and central mechanisms (McCartney, 1999; Mitchell, 2013). The role of these mechanisms may be mediated by the configuration features (i.e. volume, intensity, number of repetitions/set, rests between sets) of the resistance training, although this relationship has not been studied extensively. Traditional set configuration (TS) is the most common procedure of resistance training and consists of performing each repetition of a set without rest until failure (Izquierdo et al., 2006). This configuration induces fatigue and discomfort (Hardee et al., 2012). In addition, BP and HR rises proportionally with successive repetitions within a set (McCartney, 1999), and the rate at which BP increases is related with both the intensity and the length of a set (Taylor et al., 2003).

A novel approach to the set configuration is the cluster set (CS), which introduces pauses between single or small groups of repetitions (i.e cluster training). Thus, the perceived effort is reduced while the performance is maintained (Hardee et al., 2012). This type of intermittent resistance training reduces the BP response during dynamic (Baum et al., 2003) and isometric exercise (Heffernan et al., 2008) in comparison with TS configuration. The differential modulation of the BP in response to TS and CS may be due to the differences in the work-to-rest ratios (i.e. effort vs. resting time) between the configurations. However, a previous study has shown that the lower BP response during CS in comparison with TS remained even when the work-to-rest ratios are equated for both configurations (Iglesias-Soler et al., 2015), suggesting that other factors underlie these differences. We proposed that CS induces lower levels of muscle fatigue, compared with TS, since this configuration is associated with improved mechanical performance (Iglesias-Soler et al., 2012) and less perceived effort (Hardee et al., 2012; Iglesias-Soler et al., 2015; Mayo et al., 2014). Moreover, peripheral and central fatigue may play differential roles in each configuration. Peripheral fatigue reflects an impairment at, or distal to the neuromuscular junction, and can be evaluated by recording the twitch force that is induced by peripheral nerve stimulation while the muscle is at rest (Enoka and Stuart, 1992). Central fatigue indicates a failure to drive the motor neurons adequately (Gandevia, 2001), and can be tested by recording the force evoked by nerve stimulation during a maximal voluntary effort (Merton, 1954). In addition, muscle fatigue can be associated with changes that are elicited by transcranial magnetic stimulation (TMS), in the motor evoked potential (MEP) (Maruyama et al., 2006), short intracortical inhibition (SICI) (Maruyama et al., 2006) and intracortical facilitation (ICF) (Bäumer et al., 2002; Tergau et al., 2000), although these changes may be difficult to interpret (Gruet et al., 2013).

There are no studies to date that have investigated central and peripheral fatigue induced by TS and CS configurations, with an equal work-to-rest ratio, and their relationship with cardiovascular changes. Thus, the aim of this study was to investigate differences in the neurophysiological, mechanical and cardiovascular acute responses of TS and CS configurations matched for volume, intensity and work-to-rest ratio. This will allow us to test the hypothesis that the levels of muscle fatigue induced by different resistance exercise configurations account for the differences in their cardiovascular response. This will provide further insight into the mechanisms underlying the cardiovascular modulation in response to changes in the resistance set configuration.

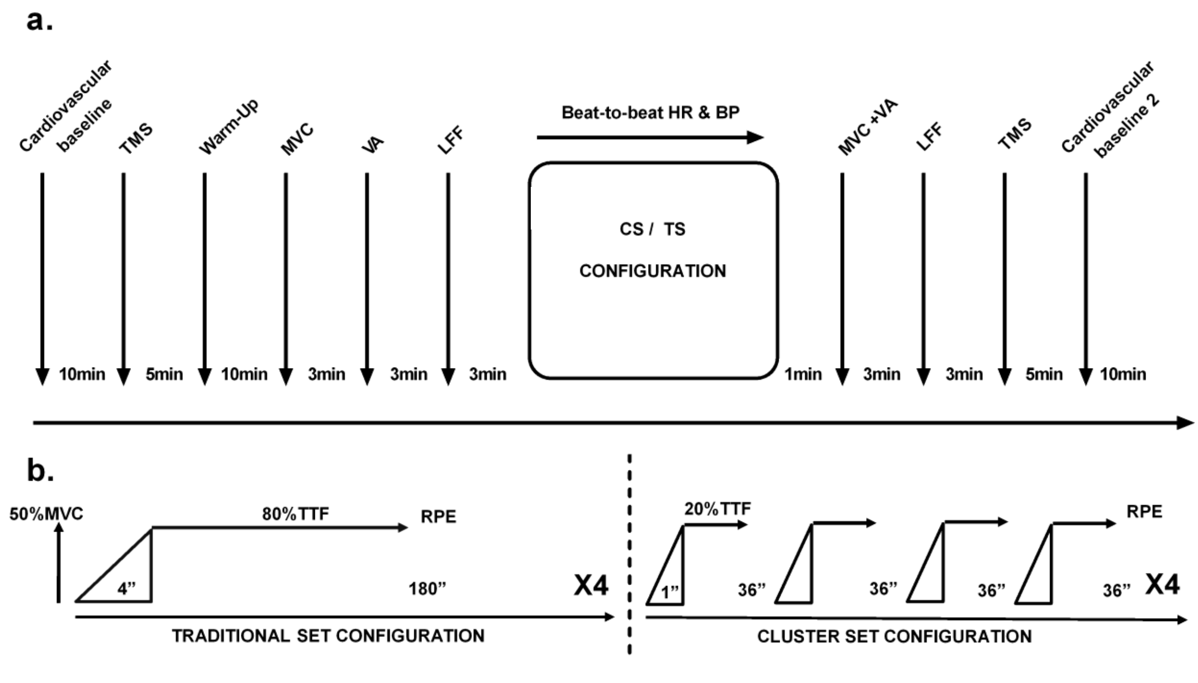
B. Methods

Subjects

Eleven young males participated in this study (age 21.0 ± 2, height 177.2 ± 0.08 cm, weight 72.4 ± 6.6 kg). The subjects were recruited from the Institute of Physical Education and Sport of A Coruña, Spain. All the subjects were physically active and none of them reported neurological impairment, lower limb injuries and/or contraindications to TMS. Written informed consent was obtained from all the subjects after a full explanation of the procedures and risks involved All the experimental procedures were approved by University of A Coruña ethics committee and conformed to the Declaration of Helsinki.

Experimental Procedure

Each subject participated in five familiarization and three experimental sessions. The protocol is described in Fig 11. The familiarization sessions were used to train the subjects with the maximal voluntary contractions, electrical and magnetic stimulations and with the rate of perceived effort scale. The first experimental session was conducted to calculate the maximal voluntary isometric contraction (MVC) during a knee extension exercise and the time to task failure (TTF) at a 50% of MVC. The other two experimental sessions correspond to two resistance-training sessions: with a traditional set configuration (TS) or with cluster set configuration (CS). The order of TS and CS sessions were counterbalanced, separated by 1 week and conducted at the same time of day for each subject. Each training session started with hemodynamic recordings and cortical measurements (using transcranial magnetic stimulation of the motor cortex) with the subject at rest. Then, after a standardized warm-up the subjects performed dynamic and neuromuscular assessments (maximal voluntary contractions and electrical stimulation, respectively). The subjects then started the exercising procedure (with TS or CS configuration) during which cardiovascular parameters were continuously recorded. Immediately after the exercise, dynamic and neuromuscular assessments were recorded, and the rate of perceived effort was reported by the subjects. Ten minutes later, cortical and cardiovascular recordings were obtained.



TMS trannscranial magnetic stimulation, *MVC* maximal voluntary contraction, *VA* voluntary activation, *LFF* low frequency fatigue index, *HR* heart rate, *BP* blood pressure, *ISR* intra ser rest configuration, *TS* traditional set configuration, *TTF* time to task failure, *RPE* rate of perceived effort.

Figure 11 Schematic representation of the experimental protocol. (a) time line of measurements. (b) the training protocols performed in each session. Each protocol (TS/CS) utilized the same intensity, total muscle contraction and rest time.

Maximal voluntary contraction

Subjects were seated in a modified knee extension machine (BF100, Biotech Bioiso, Brazil) attached to a force cell (sensitivity: 2 mV/V and 0.0028 V/N; NL63-200, Digitimer Ltd, Welwyn Garden City, UK) with the hips flexed at 90º and the right knee flexed at 90º and firmly strapped to the lever arm of the machine. To ensure that participants only used the knee extensors special care was taken positioning the lever arm above the ankle, and a belt was used to avoid hip and trunk movement. Participants were asked to perform an MVC "as fast and as forcefully as possible" and to maintain it for 4 seconds (Aagaard et al., 2002). We followed the recommendations of Gandevia (Gandevia, 2001) for a reliable MVC measurement: (i) feedback of performance was given during all the voluntary contractions (visual display), (ii) appropriate standardized verbal encouragement was given by the investigators, (iii) subjects were allowed to reject efforts that they did not regard as ‘‘maximal’ and attempted another trial 3 minutes later.

EMG recordings

Electromyographic (EMG) signals were recorded using bipolar self-adhesive Ag/AgCl electrodes of 10-mm diameter (F9079P, FIAB, Vicchio, Italy) in bipolar configuration of the rectus femoris (RF) and biceps femoris following the SENIAM recommendations (Hermens et al., 2000), with an inter-electrode distance of 25 mm and with the reference electrode on the patella. The position of the electrodes was marked on the skin so that these were used in the subsequent session. The recording sites were shaved, abraded and cleaned with isopropyl alcohol to obtain low impedance (Z, 5kΩ). EMG signals were amplified and filtered with a bandwidth frequency ranging from 10 Hz to 1 kHz (gain = 1,000). The EMG signals were simultaneously digitized with the torque signals, using an acquisition card at a sampling rate of 5 kHz per channel (Digitimer D360, Welwyn

Garden City, UK) and stored for later analysis on a computer with a custom built Signal script.

Force and EMG signals were synchronized using a Power 1401 A-D converter and Signal software [Cambridge Electronics Design (CED), Cambridge, UK].

Electrical stimulation

M wave. Electrical stimulation was used to activate the femoral nerve. A ball probe cathode was manually pressed over the femoral triangle 3-5cm below the inguinal ligament. The anode, a 130×80mm self-adhesive electrode (Cefar-Compex Scandinavia AB, Sweden), was applied to the gluteal fold. Square-wave pulses with a width of 1 ms at a maximal voltage of 400 V from a constant current stimulator (Digitimer DS7A, Welwyn Garden City, UK) were delivered to the resting muscle. The optimal stimulation intensity for a single stimulus was determined by increasing the intensity until the amplitude of the evoked twitch showed no further increase (M_{max}). The intensity used for subsequent stimulation techniques was 120% of that which evoked a maximal twitch torque with subsequent M_{max} of the RF (140–240 mA).

Low Frequency Fatigue. Two electrical stimuli at 100-Hz (Db100) and 10-Hz (Db10) were delivered 4 s apart over the femoral nerve two seconds after an MVC of the knee extensors (Millet et al., 2011).

Twitch interpolation. Twitch interpolation technique (Merton, 1954) was applied to the knee extensors. During an MVC, a superimposing supramaximal electrical stimulus was delivered to the femoral nerve, followed by a second electrical stimulus 1.5 s after the end of the MVC.

Transcranial magnetic stimulation (TMS) of the motor cortex.

Single TMS pulses of 1-ms duration Magstim BiStim 200^{2}, The Magstim Company, Dyfed, UK) were delivered via a concave double-cone coil (diameter: 110 mm; maximum output: 1.4 T). The handle of the TMS coil was positioned over the vertex of the head and held tangential to the skull in an anterior–posterior orientation. The coil was positioned over the left motor cortex and the orientation of the coil was determined by localizing the largest motor evoked potential (MEP) in the right RF, with the lowest motor response in the biceps femoris. The optimal stimulation site was marked with an indelible red marker to ensure reproducibility of the stimulus conditions for each subject throughout the sessions. The resting motor threshold (RMT) was determined as the minimum stimulus intensity required to elicit an MEP in the RF of at least 50 µV in 3 of 5 consecutive trials.

Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were recorded using techniques which have been previously described (Kujirai et al., 1993; Ridding and Rothwell, 1999). Paired magnetic stimuli at different interstimulus intervals were applied at the optimal scalp site for evoking responses in the right RF while the subject was at rest. The test (second) stimulus was set to intensity sufficient to evoke a response in the RF of approximately 0.5–1 mV. The conditioning (first) stimulus was at intensity 80% of stimulator output below the resting motor threshold for the target muscle. The interval between conditioning and test stimuli was 3 ms for the investigation of SICI and 15 ms for the investigation of ICF. Inhibitory, excitatory timings and TMS alone were incorporated into a single block of 45 stimuli. Therefore, in total there were 15 trials for each condition, and the orders of presentation of the conditions were randomized.

Cardiovascular recordings

Cardiovascular and autonomic parameters were recorded using a non-invasive measurement system Task Force Monitor (CNSystems Medizintechnik GmbH – Austria), with 4 electrodes for electrocardiograph recording and two pneumatic plethysmography devices placed on the first phalange of the second and third fingers of the left hand. The distal pressure measurement was regularly corrected by an oscillometric measurement taken from the right brachial artery. Recordings were conducted at a sample rate of 1000 Hz.

Rate of perceived effort (RPE)

Rate of perceived effort was recorded using a visual scale with verbal anchors (OMNI-Scale) (Lagally and Robertson, 2006). Before each exercise protocol the standard definition of the perceived exertion and instructions for the mode specific OMNI Scale were read to subjects. The scale was placed in front of the subjects below the feedback screen during the exercise trial.

Experimental sessions

First experimental session. The MVC during an isometric knee extension exercise and TTF at a 50% of MVC were recorded for each subject. The MVC was performed according with the instructions described previously. Five minutes later, the TTF test was performed. The subjects were required to exert continuously a force of 50% MVC as long as they could. They were encouraged during the duration of the test. The test was considered to be completed when the subjects were no longer able to achieve the required force.

Training sessions. Each training session began with a standardized warm-up that included 5 min of cycling on a cycle ergometer (Monark 828E; Monark Exercise AB, Vansbro, Sweden) at a power output equivalent to 60 W followed by 5 submaximal isometric knee contractions (2x50-2x70-1x90% MVC). After this warm-up the subjects perform one of the training sessions.

The TS configuration session consisted of 4 sets of 50% MVC isometric knee extensors. The duration of each set was adjusted to 80% of the TTF for each subject (obtained in the first experimental session). The rest interval between sets was 180 seconds.

The CS configuration session consisted of 16 sets of 50% MVC isometric knee extensors. The duration of each set was adjusted to 20% of the TTF for each subject. The rest interval between sets was 36 seconds.

The total time of muscle contraction and at rest for each subject was equivalent between training sessions (i.e. a subject with a TTF of 60 seconds performed both training sessions with a total muscle contraction time of 192 seconds and a total rest time of 540 seconds). In order to equate the muscle contraction time, each contraction started with a progressive slope of 4 seconds in TS and 1 second in CS. Fig 1b represents graphically both training set configurations.

Data analysis

Electrical stimulation. The amplitude of the M_{max} evoked during a single supramaximal electrical stimulus was recorded. Maximal rates of force development (ST-RFD) and half relaxation time (ST-½RRT) of the single twitch were measured using femoral nerve stimulation. Rate of force development was calculated as the maximum value of the first derivative over time of the force-time curve during a single twitch. Rate of relaxation was calculated from peak torque to half peak torque

Maximal voluntary activation was quantified using the twitch interpolation technique (Merton, 1954). Briefly, the force produced by a superimposed twitch delivered during the MVC was compared with the force produced by a single twitch delivered during relaxation ~2 s after the MVC:

Voluntary activation (%)=[1 – (superimposed twich/resting twicth)]×100.

Low frequency fatigue index (LFF) was quantified as the ratio between the torque produced with 10 Hz stimulation and that produced with 100 Hz (10 Hz / 100 Hz).

TMS. The peak-to-peak amplitude of the MEP was measured offline. The MEP measured on the RF was normalized to Mmax (Gruet et al., 2013). SICI and ICF values were expressed as a percentage of the unconditioned test MEP amplitude.

Cardiovascular variables. Mean systolic blood pressure (SBP_{mean}), diastolic blood pressure (DBP_{mean}), mean arterial pressure (MAP_{mean}) and heart rate (HR_{mean}) were recorded beat to beat and averaged at the end of each training session including the pauses. Rate-pressure Product (RPP) were calculated as the heart rate multiplied by the MAP (HR x MAP) as described in (Keller-Ross et al., 2014). Rate-pressure product is an indicator of the cardiac workload and the oxygen requirement of the heart.

Heart rate variability indices were analyzed according to the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (Task Force of the European Society of Cardiology ;The North American Society of Pacing and Electrophysiology;, 1996) and were calculated for the last 5 minutes of a 10 minute window before and after the exercise. Mean R-R intervals (RRI) power densities in the low (LF, 0.04 – 0.15 Hz) and high frequency band (HF, > 0.15 – 0.40 Hz) were analyzed with autoregressive frequency domain methods (Bianchi et al., 1997). Occasional ectopic beats and artefacts were visually identified and replaced with interpolated RRI (Buchheit and Gindre, 2006).

The baroreflex sensitivity (BRS) was determined using the sequence method as previously described (Kardos et al., 2001). The time series for RRI and SBP were scanned for sequences in which both RRI and SBP concurrently increased (BRS-Up) or decreased (BRS-Down) for a minimum of three consecutive beats. Task Force Software sets the threshold values to 1 mmHG in SPB and 6 ms in RRI (La Rovere et al., 2008). BRS was computed as the ratio RRI/SBP ($ms \cdot mmHg^{-1}$) during baseline rest and the end of the exercise.

Rate of perceived effort (RPE). A general perception of effort (RPE-Overall) and local perceived effort (RPE-Leg) were reported by the subjects at the end of each set using the OMNI Scale (Bolgar et al., 2010; Lagally and Robertson, 2006). The values reported by the subjects were averaged for each set configuration in order to obtain a mean RPE for each resistance exercise configuration.

Statistical Analysis

Analyses of variances (ANOVA) of repeated measurements with time (before, during and after the exercise) and set configuration (TS, CS) as main factors were applied to the mean and the maximum values of the cardiovascular variables (HR, SBP, DBP, MAP, RPP).

ANOVAs of repeated measurements with time(before vs. after the exercise) and set configuration (TS vs. CS) as main factor were performed for the following variables: MEP, SICI, ICF amplitude, Total Power, LF, HF, BRS-Up, BRS-Down,, MVC, M_{max}, VA, ST, ST-RFD, ST-½RRT, LFF. Post-hoc analyses were conducted using Bonferroni correction.

Normal distribution was checked by using a Shapiro-Wilk test of normality. When normality could not be assumed, logarithmic transforms were completed as required.

Student's paired t test was used to compare RPE between set configurations. Correlations between variables were determined using Pearson product moment or Spearman rho coefficients as appropriate in order to explore associations between cardiovascular, mechanical and neurophysiological variables. Statistical analysis was conducted with SPSS software version 15.0 (SPSS, Chicago, IL). Statistical significance was set at $P \leq 0.05$.

C. Results

All the subjects completed all the familiarization and experimental sessions. They were able to perform the training sessions and the tests as required. One subject was excluded from the analysis of cortical parameters since no MEP could be induced by TMS stimulation. The analyses for the remaining parameters were performed with and without this subject and no differences in the results were found. Therefore, this subject was only excluded from the MEP analysis. No significant differences were found in the baselines values between set configurations for all the variables recorded (P-values ranged from 0.188 to 0.854).

Maximal voluntary contractions

The results of the MVC are displayed in Fig 12a. There was a significant decrease in the MVC in both set configurations ($P \leq 0.001$). The MVC post-exercise was significantly lower for the TS in comparison with the CS configuration ($P = 0.019$) indicating a greater decrease in MVC for TS compared with CS (see table 1).

Table 1. mean, SD and P values of the mechanical effects, central and peripheral fatigue of each set configuration.

		CS	TS		ANOVA	
VARIABLE (unit)	**MOMENT**	MEAN	MEAN	SET	MOMENT	INTERACTION
MVC (N·m)	PRE	611 (±102)	633 (±105)	0,184	<0,001	0,003
	POST	501 (±123) #	433 (±132) # *			
VA (%)	PRE	90 (±7)	92 (±8)	0,153	<0,001	0,026
	POST	84 (±11)	74 (±13) # *			
LFF (A.U.)	PRE	0,57 (±0,08)	0,57 (±013)	0,029	<0,001	0,015
	POST	0,43 (±011) #	0,33 (±0,13) # *			
Db100Hz (N·m)	PRE	260 (±46)	267 (±36)	0,055	<0,001	0,003
	POST	254 (±48)	200 (±59) # *			
Db10Hz (N·m)	PRE	147 (±38)	151 (±37)	0,042	<0,001	0,004
	POST	111 (±35) #	71 (±42) # *			
Single Twitch (N·m)	PRE	140 (±37)	142 (±40)	0,001	<0,001	<0,001
	POST	105 (±36)	64 (±41) # *			
ST-RFD (N·m·s^{-1})	PRE	2539 (±903)	2680 (±764)	0,004	0,619	<0,001
	POST	3330(±848) #	1642 (±992) # *			
ST-½RRT (N·m·s^{-1})	PRE	-1524(±504)	-1531 (±589)	0,002	0,191	0,001
	POST	-2344 (±742) #	-1114 (±848) # *			

MVC maximal voluntary contraction, VA voluntary activation, LFF low frequency fatigue index Db100Hz double electrical pulse at 100Hz, Db10Hz double electrical pulse at 10Hz, Single Twitch single electrical pulse, ST-RFD Rate of force development of single twitch, ST-½RRT Rate of relaxation of single twitch, CS cluster set configuration, TS traditional set configuration.* Significant differences between set configurations. # Significant differences compared with PRE values.

Single twitch

Both set configurations lead to a reduction of the Single Twitch Torque (Table 1). However, this reduction was significant in the TS configuration ($P < 0.001$), while the CS configuration only showed a tendency for a reduction ($P = 0.053$). In addition, the post-exercise Single Twitch Torque values were significantly lower in the traditional in comparison with the CS configuration ($P < 0.001$) (Fig 2c). The analysis for ST-RFD revealed that while the traditional set configuration induced a significant decrease for the ST-RFD ($P = 0.008$), the CS configuration lead to an increase of this parameter ($P = 0.016$). Finally, ST- ½RRT increased significantly only in the CS configuration (P =

0.001) and these values post-exercise were significantly higher for CS in comparison with TS configuration ($P < 0.001$).

The analysis of the M-Wave for the Rectus Femoris (Fig 13d) showed a significant effect for the time ($F_{1,10} = 17.091$, $P = 0.002$) but no main effect for set configuration ($F_{1,10} = 0.234$, $P = 0.639$), nor a set configuration x time interaction ($F_{1,10} = 0.020$, $P = 0.890$) (Fig 12d).

Low frequency fatigue

The analysis of the LFF revealed that LFF ratio decreased significantly after each exercise configuration ($P < 0.001$ for TS and CS configurations) (Table 1). In addition, LFF ratio post-exercise was significantly lower in the traditional compared with the CS configuration ($P = 0.003$) (Fig 2d). While similar results were found for the Db10Hz component of the LFF, this was not the case for the high frequency component measured with Db100Hz. The Db10Hz decreased significantly for both set configurations ($P < 0.001$) and the values post-exercise were significantly lower in TS compared with CS ($P = 0.003$). However, Db100Hz values decreased significantly only in the TS configuration ($P = 0.001$) and these post-exercise values were significantly lower for the TS in comparison with the CS configuration ($P = 0.007$).

Voluntary activation

The analysis of the Voluntary Activation showed a significant reduction of this parameter in the traditional ($P < 0.001$) but not in the CS configuration (Fig 12b and table 1).

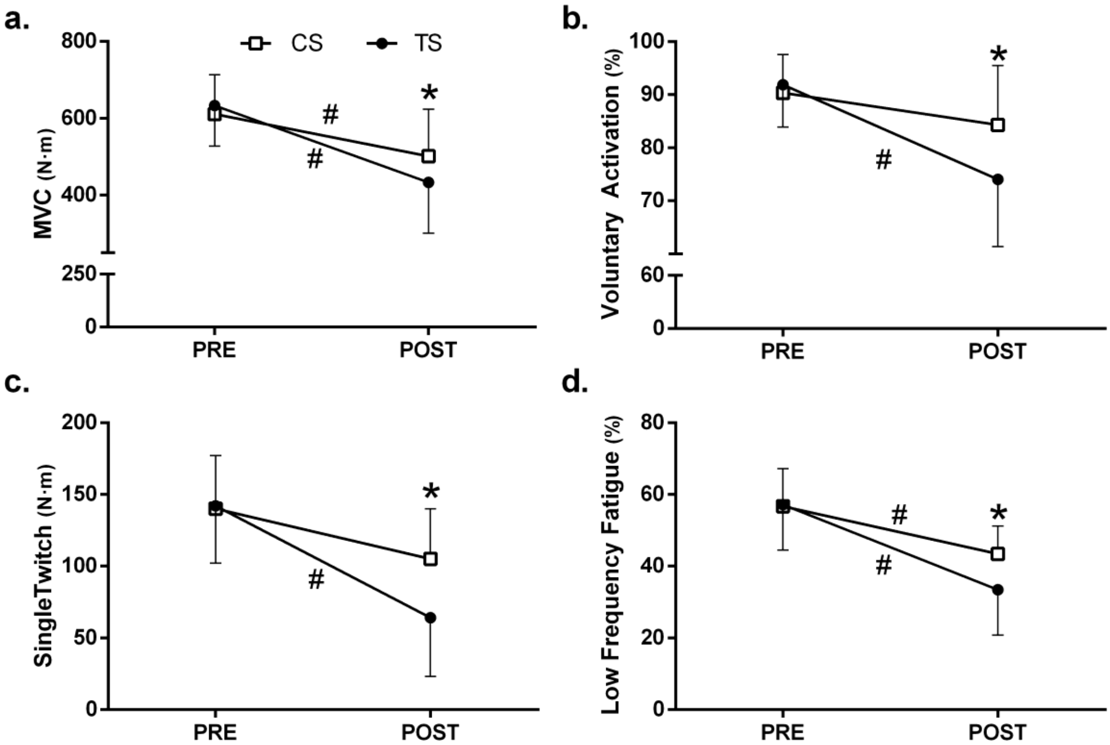


*Figure 12 Changes in maximal voluntary contraction (a), voluntary activation (b), single twitch (c), low frequency fatigue (d) after the performance of traditional set (black circles) and cluster set configuration (white squares). Mean and SD values are displayed. *Significant differences between set configurations. #Significant differences between with PRE and POST values.*

Transcranial magnetic stimulation

The analysis of the MEP amplitude normalized with the M-wave (Fig 13a) showed a decrease in MEP amplitude after exercise for both set configurations (50% and 75% reduction for CS and TS, respectively). This reduction was only significantly for the TS configuration (P = 0.031) although a tendency to significance was found for the CS configuration (P = 0.053). The differences in the MEP amplitudes post-exercise between set configurations were statistically significant (P = 0.034). The analysis of SICI values revealed higher post-exercise values for the TS configuration compared with baseline (ΔTS = 46%, P = 0.049) and CS (ΔCS = 8%, P = 0.516), indicating less intracortical inhibition for the latter although no statistical differences were found between groups after exercise (P = 0.109). There were no significant differences in the ICF values between or after the exercise set configurations (Fig 13b).

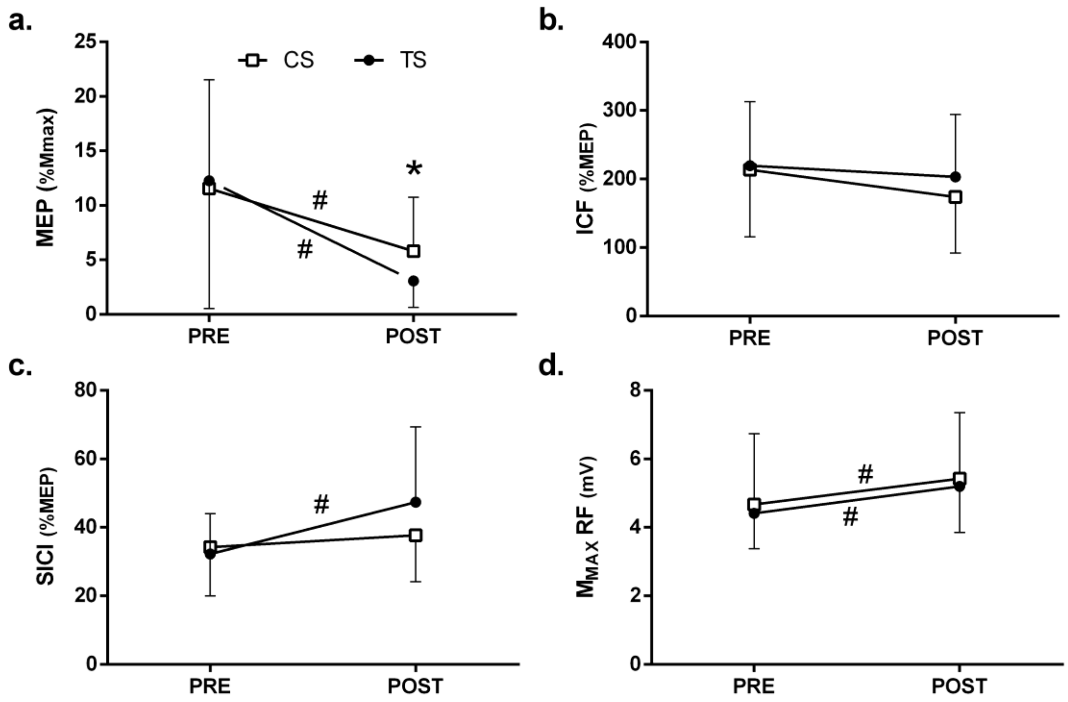


Figure 13 Changes in motor evoked potentials (a), intracortical facilitation (b), short intracortical inhibition (c) maximal wave of rectus femoris (d) after the performance of traditional set (black circles) and cluster set configuration (white

squares). Mean and SD values are displayed. *Significant differences between set configurations. #Significant differences between PRE and post values.

Cardiovascular response during exercise

The analysis for the HR_{mean} showed that the baseline values of both set configurations had a significant increase during exercise ($P \leq 0.003$) returning to baseline values in CS but not in TS after exercise ($P = 0.003$). Traditional set configuration lead to higher HR values during and after exercise compared with CS ($P < 0.001$ and $P = 0.001$) (see table 2). The HR_{max} remains elevated during and after exercise ($P \leq 0.001$ and $P = 0.013$, respectively). Post-hoc analysis showed higher values for TS during ($P \leq 0.001$) and after exercise ($P = 0.001$) with respect to CS configuration.

Table 2. mean, SD and P values of the mean cardiovascular response before, during and after exercise

		CS	TS		ANOVA	
VARIABLE (units)	MOMENT	MEAN (±SD)	MEAN (±SD)	SET	MOMENT	INTERACTION
HR_{mean} (bpm)	PRE	66(±14)	66(±13)	<0,001	<0,001	<0,001
	DUR	88 (±15) # ¥	108(±14) # ¥ *			
	POST	66(±13)	75(±12) # *			
MAP_{mean} (mmHg)	PRE	85(±6)	90(±5)	0,084	<0,001	0,283
	DUR	103(±14)	116(±16)			
	POST	90(±8)	90(±17)			
SBP_{mean} (mmHg)	PRE	113(±7)	118(±8)	0,114	0,007	0,358
	DUR	130(±21)	144(±21)			
	POST	121(±6)	120(±21)			
DBP_{mean} (mmHg)	PRE	67(±7)	72(±5)	0,136	<0,001	0,305
	DUR	84(±12)	98(±14)			
	POST	70(±10)	72(±18)			
RPP (mmHg·bpm)	PRE	5629(±1411)	5928(±1233)	<0,001	<0,001	0,01
	DUR	9007(±1739) #	12425(±1841) # ¥ *			
	POST	5957(±1155)	6835(±1827)			

HR_{mean} mean heart rate, *MAP_{mean}* mean value of mean arterial pressure, *SBP_{mean}* mean systolic blood pressure, *DBP_{mean}* mean diastolic blood pressure, *RPP* rate pressure product, *CS* cluster set configuration, *TS* traditional set configuration.* Significant differences between set configurations. # Significant differences compared to PRE values. ¥ Significant differences compared to POST values

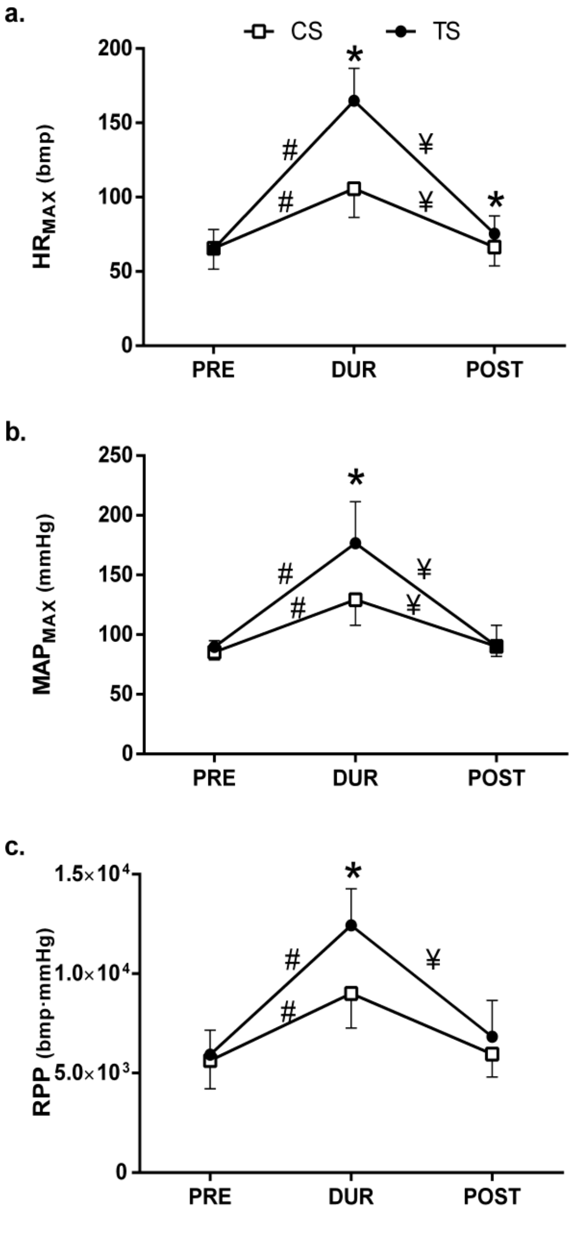


Figure 14. Cardiovascular Response to set configuration

For the MAP_{mean}, the analysis revealed higher values for MAP during exercise compared with baseline values and after exercise (P < 0.001 and P = 0.003, respectively) and no differences before and after exercise (P > 0.05). The MAP_{max} analysis showed higher values for TS during exercise (P = 0.001) compared with CS.

The analysis for the SBP_{mean} revealed higher SBP values for SBP during exercise compared with values at baseline and after exercise (P = 0.006 and P = 0.005, respectively) and no differences before and after exercise (P > 0.05). The SBP_{max} showed higher values for TS during exercise (P = 0.003) compared with CS.

The DBP_{mean} analysis showed higher DBP values during exercise compared with values at baseline and after exercise (P ≤ 0.001 and P = 0.002 respectively) and no differences before and after exercise (P > 0.05). In addition, TS induced higher values compared with CS (P=0.048). The DBP_{max} showed higher values for TS during exercise (P = 0.001) compared with CS.

The rate-pressure product increased during exercise compared with baseline ($P < 0.001$) with significant differences between CS and TS ($P < 0.001$). Significantly higher values were observed for TS compared with CS during exercise ($P = 0.001$) and returning to baseline values after exercise ($P = 0.063$).

The HF spectral component of the heart rate variability decreased significantly only in the traditional set configuration ($P = 0.013$) and these post-exercise values were lower for the TS in comparison with the CS configuration ($P = 0.023$) (see table 3). The analysis for LF revealed that TS post-exercise values had a tendency to decrease ($P = 0.051$). Post exercise values for TS were significantly lower compared with CS ($P = 0.012$).

The Total Power for TS showed a significant reduction after exercise ($P = 0.019$) while CS showed no significant differences ($P = 0.066$). TS values were lower compared with CS values ($P = 0.002$).

Baroreflex activation (BRS-Up) analysis revealed a significant decrease for the TS ($P= 0.002$) but not for the CS configuration. The BRS-Up after the TS configuration was significantly higher compared with CS ($P= 0.002$). The baroreflex inhibition (BRS-Down) post exercise was significantly lower for the traditional set configuration ($P \leq 0.001$). Differences between set configurations were found ($P= 0.020$) indicating an impaired baroreflex sensitivity for TS configuration.

Table 3. mean, SD and P value of heart rate variability and baroreflex sensitivity before and after exercise

		CS	TS		ANOVA	
VARIABLE (unit)	MOMENT	MEAN	MEAN	SET	MOMENT	INTERACTION
ln-HF (ms^2)	PRE	6,48 (±1,11)	6,62(±1,13)	0,221	0,268	0,005
	POST	6,79(±1,21)	5,87(±0,95) # *			
ln-LF (ms^2)	PRE	6,91(±0,64)	7,06(±0,90)	0,258	0,702	0,015
	POST	7,28(±0,89)	6,80(±0,71) *			
ln-TP (ms^2)	PRE	7,73(±0,76)	8,05(±0,98)	0,304	0,519	<0,001
	POST	8,11(±0,86)	7,42(±0,71) # *			
ln-BRS-Up (ms.mmHg)	PRE	3,28 (±0,63)	3,00 (±0,52)	0,06	0,013	0,007
	POST	3,23(±0,70)	2,58(±0,46) # *			
ln-BRS-Down (ms.mmHg)	PRE	3,03 (±0,63)	2,83 (±0,55)	0,193	0,003	0,022
	POST	3,12(±0,41)	2,34(±0,43) # *			

Ln-HF Natural logarithm of high frequency band, *Ln-LF* Natural logarithm of low frequency band, *Ln-TP* Natural logarithm of total spectrum power, *Ln-BRS-Up* Natural logarithm of ascending sequences of baroreflex sensitivity, *Ln-BRS-Down* Natural logarithm of descending sequences of baroreflex sensitivity *CS* cluster set configuration, *TS* traditional set configuration.* Significant differences between set configurations. # Significant differences compared with PRE values.

Perception of effort.

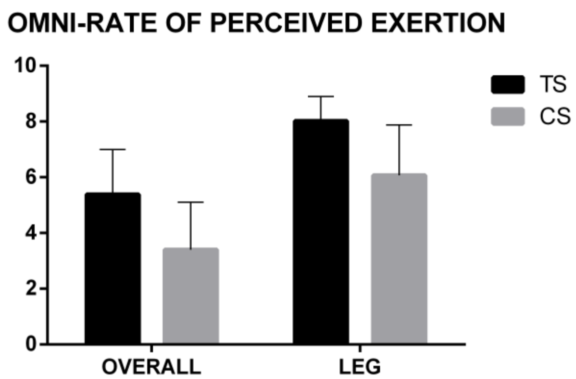


Figure 15.. Central and peripheral perceptual responses to set configuration

The comparison of RPE-Overall between set configurations revealed significant differences (t = -4.1, P = 0.002). When the subjects were asked to distinguish peripheral sensations (RPE-Leg), significant differences were found (t = -4.378, P = 0.001) between set configurations.

Correlations.

The increase in Rate-Pressure Product (RPP), from pre to during exercise values, correlated significantly and negatively with the change in the Voluntary Activation post-exercise for the TS configuration session (r = -0.85, P < 0.001) (Fig 16).

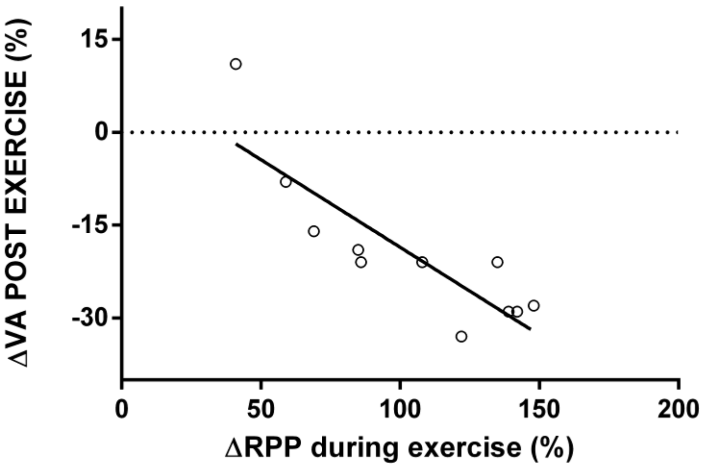


Figure 16. Correlation between cardiovascular and central fatigue responses in traditional set configuration

The increase in the MAP, from pre to during exercise values, showed a significant and negative correlation with the change in VA for the TS configuration session (r = -0.65, P = 0.03). In addition, the decrease in the SICI values correlated significantly and negatively with the change in the BRS-Down for the TS configuration (r = -0.71, P = 0.014). There were no correlations between these variables for the CS configuration session.

The value of RPE-Leg in traditional training had a strong negative correlation with the change in the Low Frequency Fatigue index (r = -0.75, P = 0.008). The RPE-Leg also showed a strong negative relationship with the change of low frequency doublet pulse, Db10 Hz (r = -0.75, P = 0.008). Finally, the change in the high frequency electrical evoked pulse (Db100 Hz) showed a significant positive correlation with the LF spectral component of HRV (r = 0.65, P = 0.030).

D. Discussion

The aim of this study was to explore and compare the neurophysiological, mechanical and hemodynamic acute responses of traditional and cluster set configurations with equal volume, intensity and work-to-rest ratios. Our main findings show that CS configuration is associated with lower levels of central and peripheral fatigue, as well as lower hemodynamic and cardiovascular stress, in comparison with a traditional set configuration. Interestingly, central fatigue was associated with cardiovascular stress during the traditional resistance exercise configuration but not during the cluster set configuration, suggesting that central fatigue processes are linked with the intensity of the cardiovascular responses. Therefore, the current findings suggest that the set configuration has a key role in determining the levels of fatigue and cardiovascular effects that are induced by resistance exercises.

Set configuration effects on muscle function

The cluster set configuration resulted in a loss of MVC of 18%, whereas TS configuration induced a greater decrement (32%). Previous studies have shown that CS is associated with a superior mechanical performance compared with that of TS configuration (Iglesias-Soler et al., 2015, 2012). Our results expand on these findings and show this for isometric exercises as well.

The traditional set but not the CS configuration lead to peripheral fatigue, since the rate of force development and the rate of relaxation time of the evoked torque twitches were impaired after the TS configuration whereas the CS lead to an improvement of these variables. These opposite responses to a single twitch may be explained by the coexistence of fatigue and potentiation mechanisms that occur immediately after exercise

(Enoka and Stuart, 1992; Gandevia, 2001; Gruet et al., 2013; Morris et al., 2012). The M-wave amplitude increases that were observed after both set configurations suggest that there is a post-activation potentiation effect. However, our findings suggest that only the CS, and not the TS configuration, benefited from this potentiation effect. It is plausible that the TS configuration lead to a reduction in Na^{+}-K^{+} ATPase activity (Aughey et al., 2007) and impair sarcoplasmic reticulum Ca^{2+} release and uptake (Leppik et al., 2004), as a result of the longer relative contraction times in comparison with the CS configuration. Although, the total muscle contraction time was identical for both configurations, the TS was characterized by 4 periods of long contractions in comparison with the 16 periods of short contractions in the CS configuration. Longer muscle contraction periods may have a greater impact on the metabolic profile of the excitation-contraction coupling (Schott et al., 1995). Furthermore, both set configurations induced low frequency fatigue, although this fatigue was more intense after TS than after CS. However, the nature of these changes was different for each configuration. While the TS configuration induced lower twitches at 10 and 100 Hz, the CS configuration only lead to a reduction of the twitch at 10 Hz. Thus, TS induced a proportionately greater loss of force at low stimulation frequency (10 Hz) compared with high stimulation frequency (100 Hz). Low frequency fatigue results from increases in intracellular free Ca^{2+} ($[Ca^{2+}i]$) during fatigue and these elevations in $[Ca^{2+}i]$ activate processes which lead to a failure of excitation-contraction (E-C) coupling and Ca^{2+} release (Chin and Allen, 2006). It is possible that TS induced a high failure of Ca^{2+} release that could affect the shape of the force-Ca^{2+} curve for both low and high frequencies. In contrast, CS configuration may affect the steep part of the force-Ca^{2+} curve, where moderate falls in the Ca^{2+} release produce a greater loss of tension at low frequencies (Westerblad et al., 1993). In summary, using peripheral measurements, the current study demonstrates that CS is associated with less impairment in the muscle contraction properties compared with the TS configuration.

Our voluntary activation findings demonstrate that TS, but not CS, induced an impairment in the voluntary neural drive to the knee extensors, even though the work-to-rest ratios were equated for both configurations. In addition, the TS configuration induced a significant reduction in the MEP amplitude (normalized to M-wave), suggesting a lower corticospinal excitability after the TS compared with CS configuration. Moreover, the SICI reduction suggests that mechanisms acting at the cortical level may contribute to the central fatigue that is induced by the TS configuration. These mechanisms are likely to involve cortical $GABA_A$ circuits, since SICI is related to activity in intracortical inhibitory circuits that use $GABA_A$ as neurotransmitters (Kujirai et al., 1993) and is mediated at cortical rather than subcortical structures (Kujirai et al., 1993). The observed reduction of the SICI may reflect compensatory mechanisms in response to the impairment in the central neural drive (Gruet et al., 2013; Maruyama et al., 2006). In order to maintain the target force, the brain plasticity induces an expansion of the motor areas by reducing the interneurons inhibitory activity, thus increasing the neural drive to the muscles (Maruyama et al., 2006).

The voluntary activation for the CS configuration decreased from 90% to 84%. Although, this decrease was not significant, it is possible that central fatigue played a minor role in the MVC decrease, as indicated by the reduction of the MEP amplitude. In addition, the absence of changes in the SICI after the CS configuration could be due to a fast recovery of the SICI circuit as a result of a less fatiguing protocol. This is supported by other findings showing that recovery times of SICI values between 5 – 10 minutes are associated with fatiguing isometric contractions (Maruyama et al., 2006).

The ICF values after both set configurations remained unaffected. Although, the effect of exhaustive exercise on ICF is not clear, our results support previous findings suggesting that muscle fatigue does not affect cortical glutamatergic circuits (Maruyama et al., 2006).

Finally, although, MEP changes should be interpreted with caution (Gruet et al., 2013), both our MEP and voluntary activation findings demonstrate that the distribution between effort and rest during a training session has a different impact on the central nervous system, with CS having a lower impact on the central muscle fatigue mechanisms compared with TS.

Muscle fatigue and cardiovascular response

During the performance of both set configurations, the mean and maximal values of the blood pressure parameters (MAP, SBP and DBP) increased significantly in comparison with pre-exercise values. These parameters returned to baseline values 10 minutes after the exercise. The maximal values of these parameters during the exercise were significantly lower for the CS compared with the TS configuration. In addition, the CS configuration induced lower HR_{mean}, HR_{max} and RPP values in comparison with the TS. These findings are in agreement with a previous study using dynamic contractions (Iglesias-Soler et al., 2015) and confirm that the cluster set configuration induces lower cardiovascular responses compared with a traditional set configuration.

This increase in the HR in the traditional set-configuration is likely the result of a parasympathetic withdrawal, as suggested by the strong high frequency (HF) power density decrease after exercise, while the low frequency band (LF) demonstrated a more moderate power density decrease (Stanley et al., 2013). These changes were accompanied by an impairment of the baroreflex mechanism during the TR configuration, suggesting higher cardiovascular stress for the TR in comparison with the CS configuration. Reductions in the HF and LF together with a baroreflex impairment has been associated with high intensity resistance training (Niemelä et al., 2008). However, since the intensity for both set configurations was identical (50% of MVC) other factors related with the distribution of the effort may explain the observed differential RPP modulation.

The relative periods of muscle contraction may explain not only the differences in neuromuscular fatigue but also the differential cardiovascular responses between the configurations. The increases in RPP and MAP in response to the TS configuration were associated with a decrease in the voluntary activation. In addition, after the performance of the TS configuration a decrease of the HF twitch correlated with a decrease of the LF. This neuromuscular and cardiovascular modulation induced by the traditional set may be mediated by central and peripheral mechanisms. This is supported by higher perceived effort that was reported by the subjects during the traditional set compared with CS. These findings may be related to the central command that is sent to the muscles in order to maintain the force during the relative longer muscle contraction periods. A direct relationship between the perception of effort and the central command sent to the muscles has been previously reported (DeMorree et al., 2012). Moreover, it has been suggested that the increase in blood pressure and heart rate during time to task failure of a low force contraction is due to the contribution of the central command (Mitchell, 2013). Our results of the intracortical inhibition as measured by pair pulse TMS (SICI) support the role of the central command for the cardiovascular regulation. The reduction in the SICI after the TS configuration correlated with a decrease in the sensitivity of the baroreflex response. To the best of our knowledge, only one other study found a significant correlation between SICI and BRS (Buharin et al., 2014). The authors postulated that the unloading of the baroreceptor enhanced the cortical excitability due to increased noradrenergic, dopaminergic, and serotonergic function within the motor cortex, leading to a decrease in SICI mechanisms.

Peripheral mechanisms may also have an impact on the perceived effort. This is supported by our finding that peripheral fatigue (LFF and DB10Hz) is associated with a higher local perceived effort (RPE-leg). We suggest that longer muscle contraction periods may induce prolonged periods of restricted blood flow and of muscular ischemia. Muscle ischemia activates the exercise pressor reflex response via mechanical and metabolic stimulation (i.e. III/IV afferents), leading to excitation-coupling failure in muscle fibers, affecting their contractibility (Enoka and Stuart, 1992; Gandevia, 2001; Gruet et al., 2013). In addition, the III/IV muscle afferents may limit the circuits that generate motor cortical output (Taylor and Gandevia, 2008) causing a suboptimal firing of the motoneurons. The afferent signals from the musculature reach superior centers such as the Nucleus Tractus Solitarii (NTS), which plays a role as an integration center in the cardiovascular response receiving inputs from musculature, baroreceptors and the central command, modulating the vagal tone and the subsequent cardiovascular response (Fisher and White, 2004).

Importantly, the above described correlations were not observed for the CS configuration. This may be since CS did not induce sufficient fatigue levels in order to induce a modulation in the central command, unlike the TS configuration.

To the best of our knowledge this is the first study that found correlations between neuromuscular and cardiovascular modulations in response to resistance exercise training, further studies are needed in order to understand the nature of these relationships.

Limitations

Despite the strong correlations reported in this study between voluntary activation and cardiovascular responses, our results are limited to an isometric contraction regime. There is evidence that isometric contractions induce higher blood pressure compared with dynamic contractions (Millar et al., 2014). Thus, it is of importance to ascertain whether the correlations observed in the current study generalize to non-isometric contractions. Previous studies using CS and TS configurations during dynamic contractions (Iglesias-Soler et al., 2015) have reported modulations in the cardiovascular responses similar to those observed in the current study and thus, it is likely that the association between voluntary activation and cardiovascular responses is not limited to isometric contractions. Moreover, it is possible that isometric training using higher intensities (greater than 50% of MVC used in the current study) may induce stronger cardiovascular responses, specifically in the CS configuration.

Another limitation is related to the TMS measures that were utilized. The TMS measures were not obtained immediately after completion of the exercise, and it is known that MEP and SICI recover quickly after exercise (Maruyama et al., 2006). However, after the TS configuration, both of these parameters (obtained 7 minutes post-exercise) remained significantly low, suggesting a bigger impact on the central muscle fatigue mechanisms compared with the CS configuration.

Significance

The current study demonstrates that the set configuration has a key role in the modulation of the cardiovascular response and fatigue effects in resistance training. An CS configuration has an advantage over TS since subjects are able to complete the same amount of work in the same time but with lower cardiovascular stress, lower neuromuscular impairment and a lower perceived effort compared with a traditional set configuration. This finding is of importance for clinicians and trainers, who would like to avoid an unnecessary elevation of blood pressure and heart rate in healthy adults during the performance of resistance exercise. A recent review pointed out the relevance of the use of isometric resistance training as a treatment for cardiovascular diseases (Millar et al., 2014). In addition, a recent study has reported similar increments of thigh circumference after both TR and CS configurations training (Iglesias-Soler et al., 2016). Together with our current findings we suggest that training protocols, such as CS, result in a reduction of the cardiovascular impact of the exercise, while preserving muscle growth. This could be of relevance for elderly people that suffer from chronic conditions associated with old age such as muscle sarcopenia and cardiovascular disease (i.e. hypertension, heart failure). However, more studies must be conducted to further explore differences in muscle and cardiovascular adaptations between TR and CS configuration training in elderly and young subjects.

E. Conclusions

Our study supports the hypothesis that there is a relationship between central fatigue and hemodynamic responses, such that the greater the central fatigue, the larger the hemodynamic response. Our findings show that this relationship is modulated by the set configuration. A cluster set configuration is associated with lower central and peripheral fatigue with subsequent lower loss in maximal force values as well as lower cardiovascular stress in comparison with a traditional set configuration with equal work, rest and work-rest ratio. The greater hemodynamic response in traditional set configuration seems to be related to the magnitude of the exercise pressor reflex response, the baroreflex modulation and the central command. These changes are associated with a lower voluntary activation, suggesting a relationship between central fatigue and cardiac stress. To our knowledge this is the first study that compared the central and peripheral fatigue, in combination with hemodynamic and cardiovascular measures, of two resistance exercise set configurations with equal work to rest ratios. The findings provide further insight into the physiological mechanisms underlying set configuration and its relevance in managing the effects of resistance exercise.

VI. STUDY II

Modulation of quadriceps motor cortex excitability by femoral nerve stimulation

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A. Introduction

Complex motor activities require appropriate inputs from muscular and cutaneous afferents. The integration of the sensory input with the motor output is of importance for an appropriate control of movement. The functionality of this sensoriomotor integration varies according to the muscle involved in the motor action. For instance, blockage of sensory inputs from finger muscles lead to a loss of finger coordination and appropriate grip force (Brochier et al., 1999), while anaesthesia of the plantar sole of a foot can affect the recovery from a forward fall (Thoumie and Do, 1996).

The circuitry underlying sensoriomotor integration can be tested using paired pulse paradigms, where an electrical stimulus given to a peripheral nerve is followed by a transcranial magnetic stimulation (TMS) pulse on the motor cortex (Deletis et al., 1992; Kasai et al., 1992). This paradigm has been mostly used in upper limb muscles, to explore the time course of the modulation that the somatosensory inputs exert on the motor output (Chen et al., 1999; Tokimura et al., 2000). Typically, a conditioning electrical stimulus applied to a mixed nerve (most often the median or digital nerve of the wrist) has an inhibitory effect on motor cortex excitability. These effects, more evident at inter-stimulus intervals of around 20 ms and 200 ms, have been described as short and long latency afferent inhibition, respectively (Tokimura et al., 2000).

Several studies have shown that peripheral nerve stimulation can also modulate the cortical excitability of lower limb muscles, with a main focus on the tibial and soleus muscles (Deletis et al., 1992; Kasai et al., 1992; F. Roy and Gorassini, 2008; Simonetta-Moreau et al., 1999). Only a couple of studies explored the effects of peripheral nerve stimulation on MEPs in quadriceps muscle (Deletis et al., 1992; Simonetta-Moreau et al., 1999). These studies showed that a peripheral electrical stimulus induced an increase in the amplitude of the motor response evoked by a TMS pulse at several inter-stimulus intervals. However, the stimulated nerves were the common peroneal, gastrocnemius medialis and tibial nerves. Therefore, it remains unknown whether an electrical pulse of the femoral nerve, which supplies innervation to the quadriceps, is able to modulate the cortical response of this muscle. This is of relevance since the quadriceps muscle is one of the most important lower limb muscles for a wide range of physical functions (Stevens-Lapsley et al., 2013), and the sensory inputs from this muscle may play an important role in its spinal and cortical control. For instance, poor peripheral nerve function has been associated with low and fast declining quadriceps strength in older adults (Ward et al., 2015), which may lead to impairments in balance (Moxley Scarborough et al., 1999), gait (Fukagawa et al., 1995) and an increased risk of falls (Moreland et al., 2004).

In summary, the study of the sensoriomotor integration of the quadriceps muscle can provide new insight in to the role of the sensory inputs in the control of this muscle. In the current study we conducted a series of experiments in order to explore the conditioning effect of a percutaneous electrical pulse of the femoral nerve on cortical motor evoked responses in the rectus femoris muscle. In addition, we examined the time course of this modulation.

B. Methods

Subjects and general procedure

A total of sixteen neurological healthy subjects (9 males, 7 females, 19-21 years of age) participated in the study. Some subjects took part in more than one experiment. Written informed consent was obtained from all subjects. Experimental procedures conformed to the declaration of Helsinki and were approved by the Local Ethics Committee of the University of A Coruña. Subjects were screened for contraindications to TMS (Wassermann, 1998). None of the subjects reported any neurological (including a past medical history of head injury or seizures), psychiatric or other significant medical problems. Prior to the experimental sessions, subjects were familiarized with the general procedure of the transcranial magnetic and percutaneous electrical stimulation.

During the experiments the subjects were comfortably seated in a reclining armchair; with the hips flexed at 90°, the right knee flexed at 90° and the ankles were at 110° of a plantar flexion, with the feet resting on a foot support. Subjects kept their eyes open and were asked not to engage in conversation during the experiment.

Surface electromyography (EMG) recording

Electromyographic (EMG) signals were recorded using bipolar self-adhesive Ag/AgCl electrodes of 10-mm diameter in a bipolar configuration of the rectus femoris (RF), vastus lateralis, vastus medialis and biceps femoris, following the SENIAM recommendations (Hermens et al., 2000), with an inter-electrode distance of 25 mm and with the reference electrode located on the patella. The position of the electrodes was marked on the skin so that these were used in the subsequent session. The recording sites were shaved, abraded and cleaned with isopropyl alcohol to obtain low impedance (Z ,5kΩ). EMG signals were amplified and filtered with a bandwidth frequency ranging from 10 Hz to 1 kHz (gain =

1,000). The EMG signals were simultaneously digitized using an acquisition card at a sampling rate of 5 kHz per channel (Digitimer D360, Welwyn Garden City, UK) and stored for later analysis on a computer with a custom built Signal Software script [Cambridge Electronics Design (CED), Cambridge, UK].

Femoral nerve stimulation (FNS)

Electrical stimulation was used to activate the femoral nerve of the right leg. A cathode, a circular self-adhesive electrode of 1 cm diameter (Cefar-Compex Scandinavia AB, Sweden), was positioned on the femoral triangle, 3-5cm below the inguinal ligament. The anode, a 130×80mm self-adhesive electrode, was applied to the gluteal fold. Square-wave pulses with a width of 1 ms, at a maximal voltage of 400 V from a constant current stimulator (Digitimer DS7A, Welwyn Garden City, UK), were delivered to the resting muscle.

Transcranial magnetic stimulation (TMS)

Single TMS pulses of 1-ms duration Magstim BiStim 2002, The Magstim Company, Dyfed, UK) were delivered via a concave double-cone coil (diameter: 110 mm; maximum output: 1.4 T). The handle of the TMS coil was positioned over the vertex of the head and held tangential to the skull in an anterior–posterior orientation. The coil was positioned over the left motor cortex and the orientation of the coil was determined by localizing the largest motor evoked potential (MEP) in the right RF muscle, with the lowest motor response in the biceps femoris muscle. The optimal stimulation site was marked with an indelible red marker to ensure reproducibility of the stimulus conditions for each subject throughout the sessions. The resting motor threshold (RMT) was determined as the minimum stimulus intensity required to elicit an MEP in the RF, of at least 50 µV, in 3 of 5 consecutive trials.

Main experiment. Effects of FNS on corticospinal excitability

Fourteen subjects participated in the main experiment. To explore the effects of peripheral sensory stimulation on corticospinal excitability, a single TMS pulse (test stimulus, TS) was preceded by an electrical femoral nerve stimulus (conditioning stimulus, CTS) at twelve inter-stimulus intervals: 10 (CTS_{10}), 25 (CTS_{25}), 50 (CTS_{50}), 75 (CTS_{75}), 100 (CTS_{100}), 125 (CTS_{125}), 150 (CTS_{150}), 175 (CTS_{175}), 200 (CTS_{200}), 225 (CTS_{225}), 250 (CTS_{250}) and 275 (CTS_{275}) ms. TMS intensity was adjusted to 120% of the RMT. However, in some cases the intensity was increased in order to obtain a more stable MEP. The electrical femoral nerve stimulation was adjusted to the individual motor threshold, and was defined as the minimum intensity able to evoke a visible twitch in the RF.

Since MEP amplitudes (induced by magnetic cortical stimulation) have a large variability, partly due to the liability of the attention level (Péréon and Guihéneuc, 1995), we distributed TS and CTS trials in 4 blocks as follows: (TS, CTS_{10}, CTS_{100}, CTS_{200}); (TS, CTS_{25}, CTS_{125}, CTS_{225}); (TS, CTS_{50}, CTS_{150}, CTS_{250}) and (TS, CTS_{75}, CTS_{175}, CTS_{275}). The order of the blocks was randomized across subjects. Each block included 12 TS trials and 12 CTS trials at three different intervals making a total of 48 trials. The order of the trials was randomized in each block and the time between the trials was set at 7 seconds with a 10% variation. Between blocks subjects rested for 5 minutes, remaining seated in the same position.

Complementary experiment 1: Effects of different FNS intensities on corticospinal excitability

To explore whether the intensity of the FNS affects the modulation of the TMS pulse, we tested eleven subjects using two different FNS intensities, while the TMS pulse intensity remained constant. The TMS intensity was adjusted to 120% of the RMT. FNS intensities were adjusted to the motor threshold, as in the main experiment, or to 2 times the sensory threshold. We only evaluated the conditioned MEP at 25 and 150 ms intervals since these intervals showed a significant effect on corticospinal excitability in the main experiment. One block of 60 trials was recorded (12 TS, 12 CTS_{25} and 12 CTS_{150} at motor threshold intensity, 12 CTS_{25} and 12 CTS_{150} at sensory threshold intensity). The order of the trials was randomized and the time between trials was set at 7 seconds with a 10% variation.

Complementary experiment 2. Effects of different TMS intensities on the peripheral modulation on corticospinal excitability

To explore whether the modulation observed at 25 ms and 150 ms stimulus intervals are affected by the TMS intensity, we tested ten subjects using two different TMS intensities, while the FNS intensity remained constant. The FNS intensity was adjusted to the motor threshold. TMS intensities were delivered at 120% and 150% of the RMT. One block, consisting of 36 trials, was recorded for each TMS intensity. Each block consisted of 12 TS, 12 CTS_{25} and 12 CTS_{150} trials. The order of the trials was randomized in each block and the time between trials was set at 7 seconds with a 10% variation. Between blocks subjects rested for 5 minutes, remaining seated in the same position.

Complementary experiment 3. Effects of two FNS pulses on the M wave.

Six subjects participated in experiment 3. This complementary experiment explored whether the motor response (M wave) induced by the electrical femoral nerve stimulus is modulated by a conditioning electrical stimulus applied to the same nerve. The objective of this experiment was to ensure that the corticospinal modulation that was observed in the main experiment was not due to the mechanical contraction evoked by the fermoral nerve stimulus.

The test femoral nerve stimulus was delivered at an intensity that induced M wave amplitudes, similar to the MEP amplitudes evoked by TMS in the main experiment (~ 0.4 mV). The conditioning electrical pulse was adjusted to the motor threshold. We evaluated two inter-stimulus intervals: 45 ms ($CT_{\sim 45}$) and 170 ms ($CT_{\sim 170}$). These intervals corresponded to the FNS-TMS inter-stimulus intervals of 25 ms and 150 ms but were adjusted to the individual latencies of the descending cortical volleys (~ 20 ms). Each block consisted of 12 TS, 12 $CT_{\sim 45}$ and 12 $CTS_{\sim 170}$ trials. The order of the trials was randomized and the time between trials was set at 7 seconds with a 10% variation.

Data analysis

For the main and complementary experiments 1 and 2, the peak-to-peak amplitude of the RF MEP was measured offline. The conditioned MEP amplitudes were expressed as percentages of the mean MEP amplitude obtained with TS alone in the same block. For complementary experiment 3, the amplitude of the M wave was recorded.

Statistical analysis

None of the data violated the normality assumption necessary to conduct parametric statistical tests. Statistical analysis was conducted using SPSS software version 15.0 (SPSS, Chicago, IL). Statistical significance was set at $P \leq 0.05$.

Main Experiment.

To test the stability of the baseline corticospinal excitability a repeated measurements analysis of variance (ANOVA) was conducted comparing the absolute MEP amplitudes of the TS trials across the four blocks. . To test the effects of the conditioning femoral nerve on MEP amplitudes, separate ANOVAs were performed comparing the absolute MEP amplitudes in each block with Condition as factor (TS and three CTS intervals). When a main effect was detected, each CTS interval was compared with the TS using post-hoc analysis. This statistical procedure was chosen in order to minimize statistical errors type I and II.

Complementary experiment 1.

Normalized MEP values were compared using an ANOVA with Intensity (motor vs sensory) and CTS (CTS_{25}, CTS_{150}) as factors.

Complementary experiment 2.

Normalized MEP values were compared using an ANOVA with Intensity (120% RMT vs 150% RMT) and CTS (CTS_{25}, CTS_{150}) as factors.

Complementary experiment 3.

Absolute M wave amplitudes were compared using an ANOVA with Condition as factor (TS, $CT_{\sim 45}$ and $CT_{\sim 170}$).

C. Results

Effects of FNS on corticospinal excitability.

Table 4 demonstrates the absolute MEP values for TS and CTS trials. The ANOVA did not show significant differences across blocks for the TS trials. This confirms that the corticospinal excitability for the non-conditioning trials were similar across the four blocks.

Table 4. Absolute MEP values

	TS	CTS_{10}	CTS_{100}	CTS_{200}
MEP amplitude (mV)	0.42 ± 0.14	0.44 ± 0.18	0.40 ± 0.16	0.51 ± 0.22
	TS	CTS_{25}	CTS_{125}	CTS_{175}
MEP amplitude (mV)	0.38 ± 0.14	0.30 ± 0.13	0.41± 0.15	0.39 ± 0.16
	TS	CTS_{50}	CTS_{150}	CTS_{250}
MEP amplitude (mV)	0.42 ± 0.22	0. 44 ± 0.24	0.59 ± 0.35	0.52 ± 0.29
	TS	CTS_{75}	CTS_{175}	CTS_{275}
MEP amplitude (mV)	0.44 ± 0.23	0.37 ±0.20	0.56 ± 0.23	0.46 ± 0.21

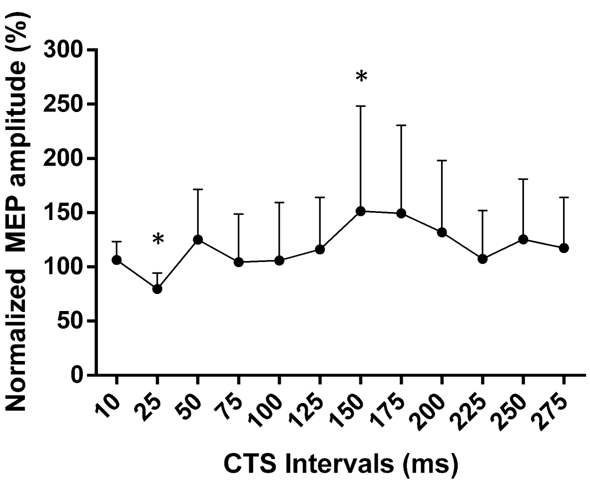

*Figure 17. Conditioned MEP amplitudes. * Indicates the inter-stimulus intervals that showed significant absolute MEP differences relative to TS alone.*

The time course of the corticospinal excitability following femoral nerve stimulation (contralateral to TMS) is shown in figure 17, and examples of single trials from one subject are shown in figure 18. There was a significant main effect for Condition in the following blocks: TS, CTS_{25}, CTS_{125}, CTS_{225} ($F = 10.84$ $P = 0.001$);

TS, CTS_{50}, CTS_{150}, CTS_{250} ($F = 5.67$ $P = 0.004$) and TS, CTS_{75}, CTS_{175}, CTS_{275} ($F = 4.19$ $P = 0.02$). Post-hoc analysis revealed significantly smaller MEP amplitudes at CT_{25} ($P < 0.0001$) and larger amplitudes at CT_{150} ($P = 0.038$) in comparison with TS. At CT_{175} there was also a tendency for a significant increase of the MEP amplitude ($P = 0.06$) in comparison with TS.

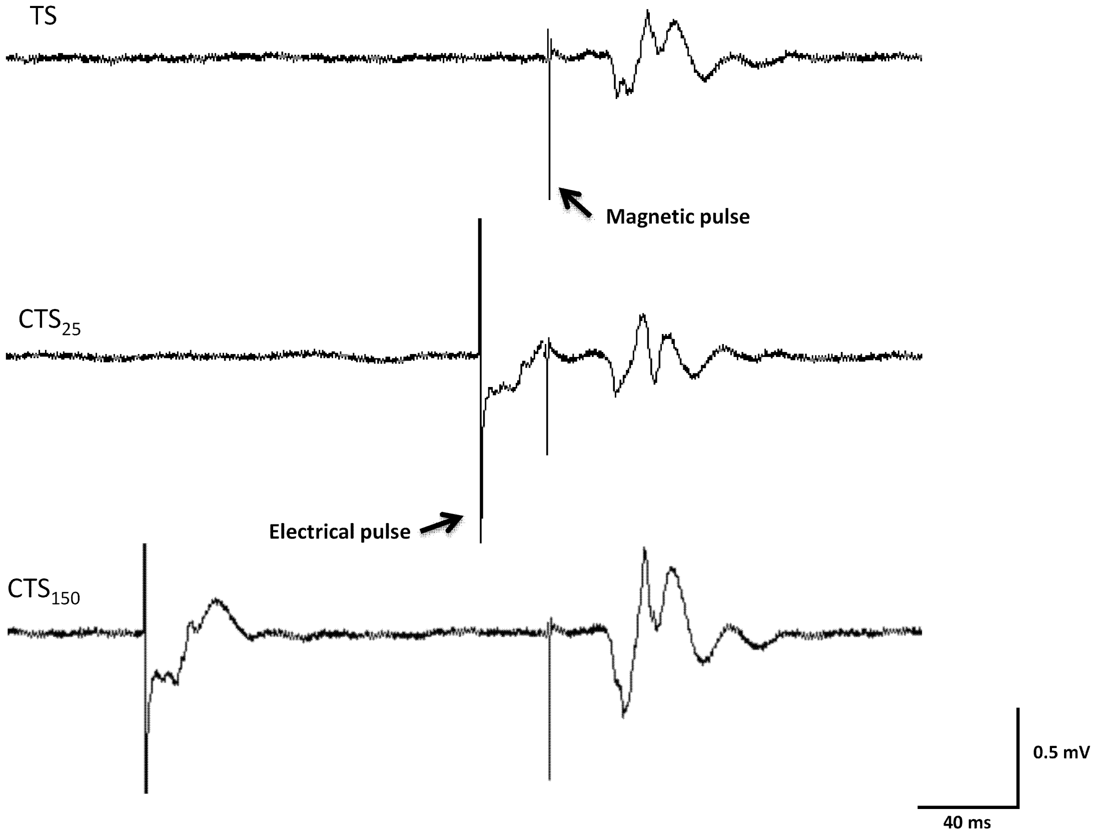

Figure 18. Examples of single trials in one subject. Recordings from the rectus femoris muscle. TS.- single transcranial magnetic pulse; CT25.- electrical femoral nerve pulse is delivered 25ms before the TMS pulse; CT150.- electrical femoral nerve pulse is delivered 150ms before the TMS pulse. The first waves in B–D are due to median nerve stimulation. MEP amplitudes was decreased at CT25 and was increased at CT150.

Complementary experiment 1

The analysis of the normalized MEP showed a significant CTS effect (F = 6.65 P = 0.03) and a significant CTS x Intensity interaction (F = 5.20 P = 0.04). There was no significant main effect for Intensity. Post hoc analysis revealed a significant reduction in the MEP amplitude at CTS_{150} (P = 0.04) when the electrical intensity pulse was adjusted to two times the sensory threshold in comparison with the motor threshold intensity. No differences were found at CTS_{25} (Fig 19).

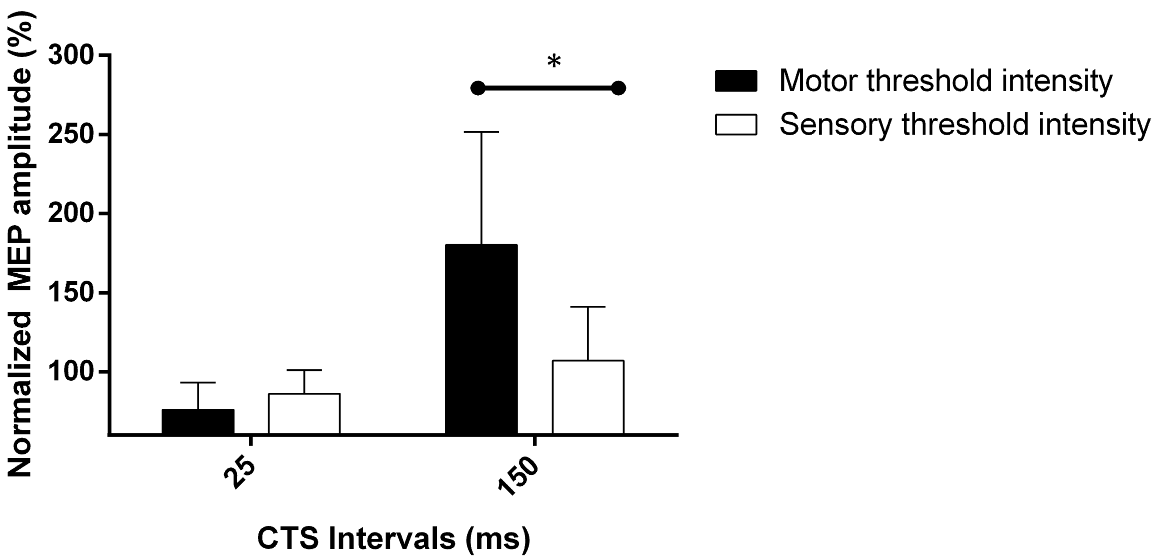

Figure 19. Effects of different FNS intensities on corticospinal excitability.

Complimentary experiment 2

The analysis of the normalized MEP showed a significant CTS effect (F = 6.84 P = 0.03) and a significant CTS x Intensity interaction (F = 6.46 P = 0.04). There was no significant main effect for Intensity. Post hoc analysis revealed significantly larger MEP amplitudes at CTS_{25} (P = 0.03) when a TMS intensity of 150% was used compared to 120% RMS. No differences were found at CTS_{150} (figure 20).

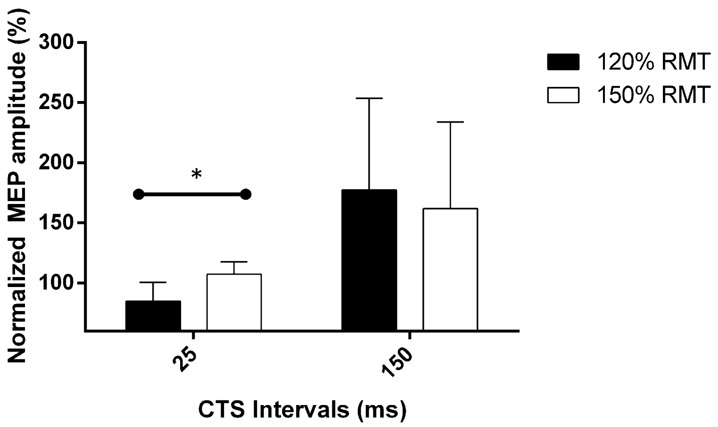

Figure 20. Effects of different TMS intensities on corticospinal excitability.

Complimentary experiment 3

The ANOVA did not show a significant main effect for condition, indicating that there were no differences between TS, $CT_{\sim 45}$ and $CT_{\sim 170}$ (figure 21).

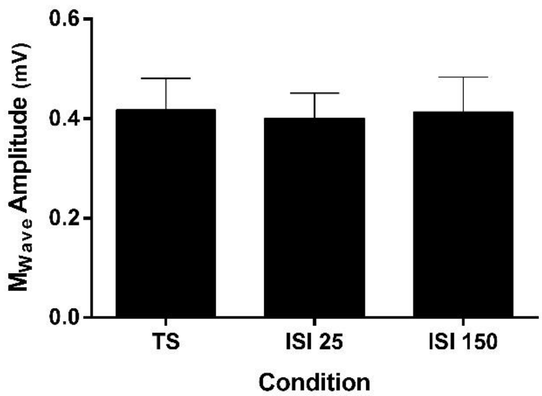

Figure 21. Effects of two FNS pulses on the M wave

D. Discussion

The goal of the current study was to determine the time course of MEP modulation in the rectus femoris muscle following percutaneous electrical stimulation of the femoral nerve. The main findings can be summarized as follows: i) inhibition and facilitation of the quadriceps motor evoked potentials were induced by a previous electrical pulse delivered at inter-stimulus intervals of 25 and 150 ms, respectively; ii) the facilitation at 150 ms was reduced when low electrical intensity was used, while the inhibition at 25 ms decreased with high TMS intensity.

Our study shows that afferent inputs from femoral stimulation were able to modulate the responses elicited by TMS of the contralateral quadriceps motor cortex. These results are in agreement with previous studies that showed both a suppression and an increase in the MEP responses in lower limb muscles by a preceding sensory stimulus at different conditioning-test intervals (Deletis et al., 1992; Kasai et al., 1992; Péréon and Guihéneuc, 1995; F. Roy and Gorassini, 2008). However, to the best of our knowledge, the current study is the first to evaluate the TMS response in quadriceps muscle using femoral nerve stimulation. The MEP inhibition found in the quadriceps at an inter-stimulus interval of 25 ms possibly corresponds with the short latency afferent inhibition (SAI) previously observed in upper limb muscles (Delwaide and Olivier, 1990; Tokimura et al., 2000). Only two other studies have shown an MEP modulation in quadriceps muscles using peripheral nerve stimulation (Deletis et al., 1992; Marchand-Pauvert et al., 1999). However, the nerves that were stimulated in these studies were not that of the femoral nerve, thus making any comparison with our study difficult. In addition to the short latency inhibition, there was also a clear period of facilitation at longer inter-stimulus intervals. This was evident at inter-stimulus intervals between 125 ms and 200 ms, although significant differences were only observed at 150 ms, probably due to the high inter-individual variability of the responses at these intervals. Both the facilitation and inhibition reported in our study reinforce the idea that the responses to cortical stimulation can be modulated by afferent inputs, even in proximal lower limb muscles.

The modulation that is induced by the electrical nerve stimulation may be due to effects occurring at spinal and/or cortical levels, since the MEP amplitude provides a quantification of cortico-spinal excitability (Rothwell, 1997)). A simple way of evaluating whether the inhibition or facilitation induced by femoral nerve stimulation is of spinal or cortical origin is to compare the MEPs and H-reflexes amplitudes. However, we were unable to evaluate the H-reflex in the quadriceps at rest due to factors such as branching of the femoral nerve, varying amounts of subcutaneous tissue, and differing size ratios of efferent to afferent fibers (Hopkins et al., 2001). Nevertheless, the current study was designed to determine the time course of afferent modulation on quadriceps corticospinal excitability rather than to determine the specific site or afferents responsible for this modulation.

The 25 ms interval used in the current study corresponds to the onset latency of the somatosensory evoked potential after a stretch of the knee extensors (Larsen et al., 2006). In addition, it takes at least 25 ms for the common peroneal group I volley to reach the motor cortex: 11 ms of peripheral conduction time plus 14 ms from L4 to the cortex (Marchand-Pauvert et al., 1999). Thus, 25 ms would be a reasonable time period for the femoral afferent volleys to reach the motor cortex and modify the cortical excitability at the time of the TMS pulse. Our results showing that high TMS intensity abolishes the inhibition at this interval further support this proposition. High TMS intensity may have recruited more corticospinal neurons, thus overcoming the inhibition of these neurons via afferent input (Cash et al., 2015). Moreover, when two electrical nerve stimuli were applied, the conditioning electrical stimulus did not affect the amplitude of the M wave that was induced by the electrical test stimulus (the conditioning-test interval was adjusted to the latency of the descending corticospinal volleys). This finding indicates that the source of the inhibition observed in the current study is not mediated through peripheral feedback that may result from the mechanical contraction. Therefore, our results suggest that the inhibition at 25 ms is of a cortical origin. This is in line with the assumption that SAI, at least in hand muscles, occur through supraspinal mechanisms (Tokimura et al., 2000) and are most likely due to corticocortical connections from sensory cortices (Chen et al., 1999). Nevertheless, and in the absence of any spinal measurements, we can not rule out a possible spinal contribution to the inhibition we observed, overall when it has been suggested that for lower leg muscles SAI may be mediated by spinal circuits (F. Roy and Gorassini, 2008). The mechanisms involved in the facilitatory effect at 150 ms are more difficult to elucidate due to the relatively long latency of this facilitation. Several studies have suggested that the facilitation, induced by peripheral electrical stimulation, which is observed in the lower limbs at long latencies, may involve superimposed integration of circuits at different levels (Deletis et al., 1992; Kasai et al., 1992; Péréon and Guihéneuc, 1995; Wolfe and Hayes, 1995). However, given the paucity of data from femoral nerve stimulation, the precise pathways involved in the conditioning effects reported in our study remain to be explored in future studies.

The electrical stimulation intensity that was used in the main experiment, i.e. the minimum intensity able to evoke a visible twitch, likely activated both muscle and cutaneous afferents but not nociceptive afferents (group III and IV). The activation of A-δ fibers via the lateral femoral cutaneous nerve requires intensities higher than that used in our study (Tataroglu et al., 2005). Thus, it is unlikely that the inhibition that we observed is induced by nociceptive afferents. Furthermore, we demonstrated that the inhibition observed at 25 ms was maintained even when the electrical pulse intensity was decreased to the sensory threshold, although the facilitatory effect disappeared at 150 ms. These findings suggest that different afferent types are modulated across different time intervals. For example, cutaneous afferents may be responsible for the short latency inhibition observed in the current study. This is in line with several studies that have reported inhibition at similar intervals using mixed or cutaneous nerve stimulations of the hand (Cash et al., 2015; Classen et al., 2000; Tamburin et al., 2005) and lower limb muscles (Kasai et al., 1992; F. Roy and Gorassini, 2008). On the other hand, our finding showing a lack of facilitation, when a lower electrical stimulation intensity was used, suggests that muscle afferents from group I are responsible for the increase of the MEP amplitudes at 150 ms. This is in agreement with previous findings that showed no facilitatory effects using peripheral stimulus intensities at or below sensory threshold (Deletis et al., 1992), but is in contrast with other studies that have found MEP amplitude increases in lower limbs as a result of cutaneous stimulation (Marchand-Pauvert et al., 1999; Nielsen et al., 1997; Wolfe and Hayes, 1995). This discrepancy between the studies may be due to the inherent complexity associated with the study of cortical excitability in response to percutaneous electrical nerve stimulation, where peripheral nerve stimulation could stimulate a mixed populations of nerve fibers such as muscle, cutaneous, joint afferents and motor efferents (Reis et al., 2008).

E. Conclusions

The functional significance of the modulatory effect of the quadriceps reported in our study may be viewed in the context of postural control. For instance, the facilitatory effect observed at an inter-stimulus interval of 150 ms seems to mimic the onset of the activation of the quadriceps in anticipatory postural adjustments (Badke et al., 1987) and during reactive balance responses (Sundermier et al., 2001). The short latency inhibition on the other hand may indicate a reflex effect through segmental pathways (Kasai et al., 1992). Whether these modulatory effects have any clinical application remains to be established.

In summary, electrical stimulation of the femoral nerve induced a short latency inhibition and long latency facilitation of the motor responses evoked in the rectus femoris by TMS. These responses indicate sensoriomotor integration of proximal lower limb muscles that may be mediated via different types of afferents. This could be of relevance for studies that explore the role of lower limb muscles in postural control and balance.

Acknowledgments

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VII. STUDY III

Sensorimotor integration is affected by set configuration

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Sent for Peer Review Process

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A. Introduction

The motor system continuously elaborates sensory afferents in order to prepare for motor tasks and to enhance the execution of fine motor activities in a process called sensorimotor integration (SMI) (Tamburin et al., 2005). Short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI) reflects this function, where the sensory and motor paths are required. Afferent inhibition is the phenomena by which a sensory afferent volley inhibits the motor response in a given muscle and is typically studied by combining non-invasive electrical nerve stimulation with transcranial magnetic stimulation over primary motor area (Turco et al., 2017).

SAI and LAI have been used as tools to probe changes in sensorimotor function in disease and following neurological injury to advance the understanding of sensorimotor control. The majority of studies were carried out in the upper limb (i.e. hand muscles) (Dubbioso et al., 2017b). However, some studies were developed in order to test if this function were present also in the lower limb. Some studies tested the latencies of the SAI in the tibialis anterior and gastrocnemius (Roy & Gorassini 2008; Geertsen et al. 2011; Bikmullina et al. 2009), but there´s only one which studied this integration in the quadriceps muscle (Río-Rodríguez et al., 2016a).

Though, our current understanding of the physiological factor that may influence SAI/LAI is far from enough. LAI is significantly understudied compared to SAI and the neural circuitries underlying these phenomena are unclear. There are existing gaps in knowledge that, if filled, will yield significant advance in the use of SAI and LAI as reliable tools to better understand human nervous system function. Both SAI/LAI may be considered as measures to quantify physiological changes. Further, future research should establish whether SAI/LAI could serve as biomarkers of functional recovery (Turco et al., 2017).

In order to explore whether this modulatory effect occurs with fatigue, we proposed two previously tested models of exercise that causes different amounts and types of fatigue (Río-Rodríguez et al., 2016b). The traditional training set configuration and the cluster set training. These ways of training were well established in the scientific literature in the last years (Iglesias-Soler et al., 2016, 2012; Mayo et al., 2014; Tufano et al., 2017a) in order to better understand the factors that the set configuration modulates. The fact that these two models of exercise cause different fatigue response is an opportunity to test if this modulation also occurs during fatigue. So, the primary objective of this study was to describe the effects of the lower limb modulation during two equated training configurations in the rectus femoris muscle.

B. Methods

Participants

A total of 12 healthy sport science students voluntarily participated in the study. Means (SD) of age, stature, and body mass were 20 (2.3) yrs, 172 (9.1) cm, and 72 (7.2) kg, respectively. Before any data collection, participants gave written informed consent using procedures approved by Local Ethics Committee of the University of A Coruña according to the declaration of Helsinki (The World Medical Association, 2013). None of the participants reported any neurological (including a past medical history of head injury or seizures), psychiatric or other significant medical problems.

Experimental procedure

Pre and Post-exercise data were obtained during recovery following exercise protocols described in detail earlier (Río-Rodríguez et al., 2016b). Briefly, a repeated measures design was used, in which participants completed four sessions, including two initial familiarizations, maximal voluntary force (MVC) and time to failure (TTF) practice and test sessions and two subsequent training sessions. Each session was separated by at least three days, to minimize carryover effects due to residual. Participants performed intermittent isometric exertions at their 50%MVC in two conditions involving different set configurations: cluster set configuration (16 efforts of the 20%TTF with 36 seconds of rest) and traditional set configuration (4 efforts of the 80%TTF with 180 seconds of rest between sets). This training scheme comprised equal proportions of work and rest, and the order of exposure to the two conditions was balanced across participants equated in intensity and work to rest ratio.

Set Up

During the experiments the subjects were comfortably seated in a reclining armchair; with the hips flexed at 90°, the right knee flexed at 90° and the ankles were at 110° of a plantar flexion, with the feet resting on a foot support. Subjects kept their eyes open and were asked not to engage in conversation during the experiment.

Surface electromyography (EMG) recording

Electromyographic (EMG) signals were recorded using bipolar self-adhesive Ag/AgCl electrodes of 10-mm diameter in a bipolar configuration of the rectus femoris (RF), vastus lateralis (VL), vastus medialis and biceps femoris, following the SENIAM recommendations (Hermens et al., 2000), with an inter-electrode distance of 25 mm and with the reference electrode located on the patella. The position of the electrodes was marked on the skin so that these were used in the subsequent session. The recording sites were shaved, abraded and cleaned with isopropyl alcohol to obtain low impedance (Z ,5kΩ). EMG signals were amplified and filtered with a bandwidth frequency ranging from 10 Hz to 1 kHz (gain = 1,000). The EMG signals were simultaneously digitized using an acquisition card at a sampling rate of 5 kHz per channel (Digitimer D360, Welwyn Garden City, UK) and stored for later analysis on a computer with a custom-built Signal Software script [Cambridge Electronics Design (CED), Cambridge, UK].

Femoral nerve stimulation (FNS)

Electrical stimulation was used to activate the femoral nerve of the right leg. A cathode, a circular self-adhesive electrode of 1 cm diameter (Cefar-Compex Scandinavia AB, Sweden), was positioned on the femoral triangle, 3-5cm below the inguinal ligament. The anode, a 130×80mm self-adhesive electrode, was applied to the gluteal fold. Square-wave pulses with a width of 1 ms, at a maximal voltage of 400 V from a constant current stimulator (Digitimer DS7A, Welwyn Garden City, UK), were delivered to the resting muscle.

Transcranial magnetic stimulation (TMS)

Single TMS pulses of 1-ms duration MagstimBiStim 2002, The Magstim Company, Dyfed, UK) were delivered via a concave double-cone coil (diameter: 110 mm; maximum output: 1.4 T). The handle of the TMS coil was positioned over the vertex of the head and held tangential to the skull in an anterior–posterior orientation. The coil was positioned over the left motor cortex and the orientation of the coil was determined by localizing the largest motor evoked potential (MEP) in the right RF muscle, with the lowest motor response in the biceps femoris muscle. The optimal stimulation site was marked with an indelible red marker to ensure reproducibility of the stimulus conditions for each subject throughout the sessions. The resting motor threshold (RMT) was determined as the minimum stimulus intensity required to elicit an MEP in the RF, of at least 50 µV, in 3 of 5 consecutive trials.

Short and Long Afferent Inhibition of the Lower Limb

In a previous experiment this research group found a consistent pattern of SAI and LAI applying a percutaneous conditioning stimulus with 25 and 150 ms respectively, to explore the sensory modulation. The conditioning FNS intensity was adjusted to the motor threshold and to the individual latencies of the participants. TMS intensities were delivered at 120%/150% of the RMT After exercise and adjustment only of the TMS intensity where employed to ensure the measurement of the response. Before and after exercise one TMS block was recorded with SAI and LAI conditioning stimulus, consisting of 45 trials. Each block has 15 test stimulus (MEP), 15 SAI and LAI stimulus plus the individual latencies. The order of the trials was randomized in each block and the time between trials was set at 7 seconds with a 10% variation.

Central and Peripheral fatigue

Voluntary activation, maximal M-wave and twitch evoked force were measured in this study as previously described (Río-Rodríguez et al., 2016b).

Data analysis

TMS. The peak-to-peak amplitude of the MEP was measured offline. The MEP measured on the RF was normalized to Mmax (Gruet et al., 2013). SAI and LAI values were also expressed as percentages of the mean Mmax amplitude obtained in the RF before the TMS block.

Electrical stimulation. The amplitude of the Mmax evoked during a single supramaximal electrical stimulus was recorded. Peak force response of the single twitch were measured using femoral nerve stimulation. Maximal voluntary activation was quantified using the twitch interpolation technique using doublets (Oskouei et al., 2003). Briefly, the force produced by a superimposed twitch delivered during the MVC was compared with the force produced by a twitch delivered during relaxation 2 s after the MVC: Voluntary activation (%) = [1 – (superimposed doublet 100Hz /control doublet 100Hz)]×100.

Statistical analysis

None of the data violated the normality assumption necessary to conduct parametric statistical tests. ANOVAs of repeated measurements with time (before vs. after the exercise) and set configuration (TSC vs. CSC) as main factor were performed for the following variables: MEP, SAI, LAI, MVC, Mmax, VA and ST. Post-hoc analyses were conducted using Siddak correction. Normal distribution was checked by using a Shapiro-Wilk test of normality. Statistical analysis was conducted with SPSS software version 15.0 (SPSS, Chicago, IL). Statistical significance was set at P = 0.05.

C. Results

A general summary of fatigue data and SMI are presented in Figure 22 and Figure 23 respectively. All the subjects completed all the experimental procedures and sessions.. No significant differences were found in the baselines values between set configurations for all the variables recorded (P-values ranged from 0.122 to 0.957).

Muscular performance, Central and Peripheral Fatigue

As previously reported by this laboratory these two equated training set configurations provided different types and amounts of fatigue. Again there was main effects for, time, set and time x set interactions. The results of the MVC are displayed in Fig 19. There was a significant decrease in the MVC in both SC ($P < 0.001$). The MVC post-exercise was significantly lower for the TSC in comparison with the CS configuration ($P = 0.001$) indicating an acussed decrease in MVC for TSC compared with CS. The analysis of the Voluntary Activation showed a significant decrease of this parameter in the traditional ($P = 0.004$) but not in the CS configuration (Fig 22). Both set configurations lead to a significant reduction of the Single Twitch Torque ($P<0.023$). Thus, the post-exercise Single Twitch Torque values were significantly inferior in the traditional in comparison with the CS ($P<0.001$) (Fig 19). The analysis of the M-Wave for the Rectus Femoris (Fig 19) only showed a significant reduction on the amplitude for the TS configuration with no differences in the CS configuration.

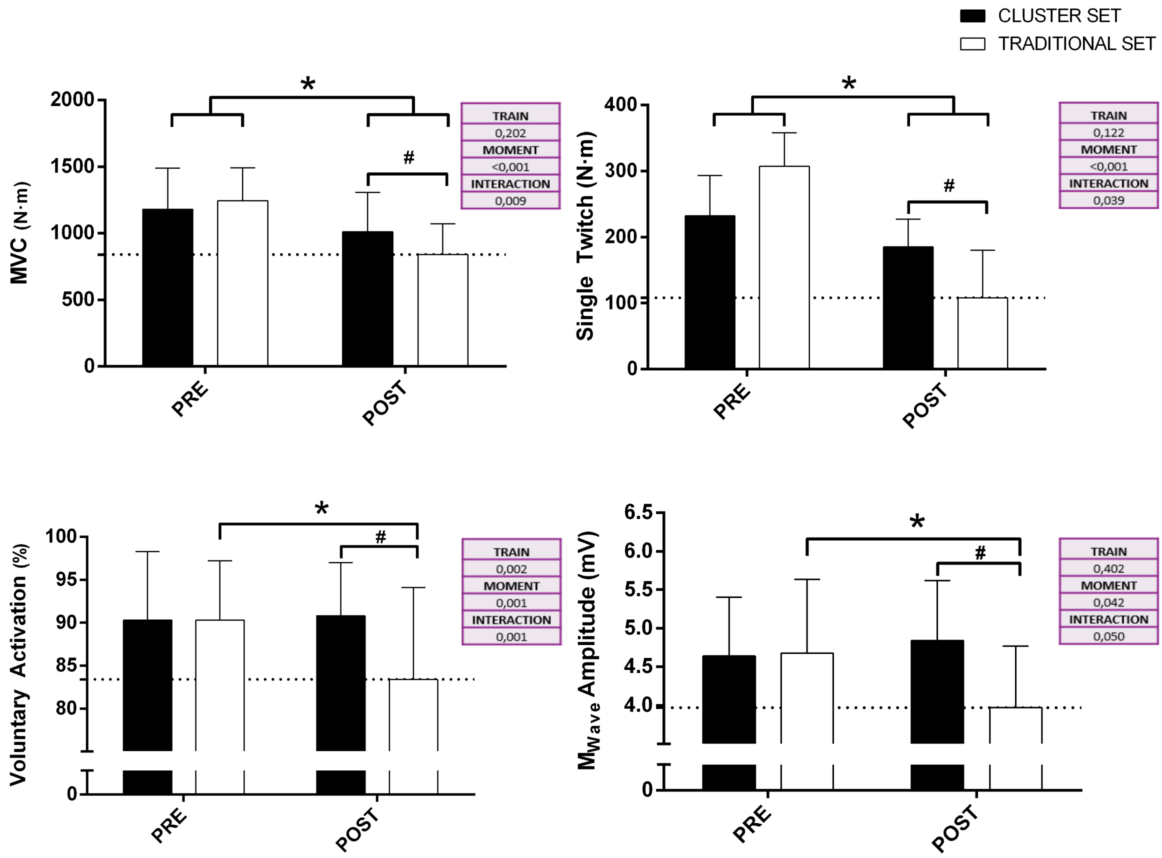

*Figure 22. Changes in maximal voluntary contraction (a), voluntary activation (b), single twitch (c), M-Wave Amplitude (d) after the performance of cluster set (black bars) and traditional set configuration (white bars). Mean and SD values are displayed. # Significant differences between set configurations. * Significant differences between with PRE and POST values.*

Sensory and Motor Integration

The analysis of the MEP amplitude normalized with the M-wave (Fig 23) showed a significant diminution in MEP amplitude after exercise for both SC (P > 0.003). This reduction was similar for both set configurations, 43-52%. The analysis of SAI and LAI values revealed a proportionate similar post-exercise behavior for both training set configurations with a significant time effect (P ≤ 0,001) but not time x set interaction (P > 0,05).

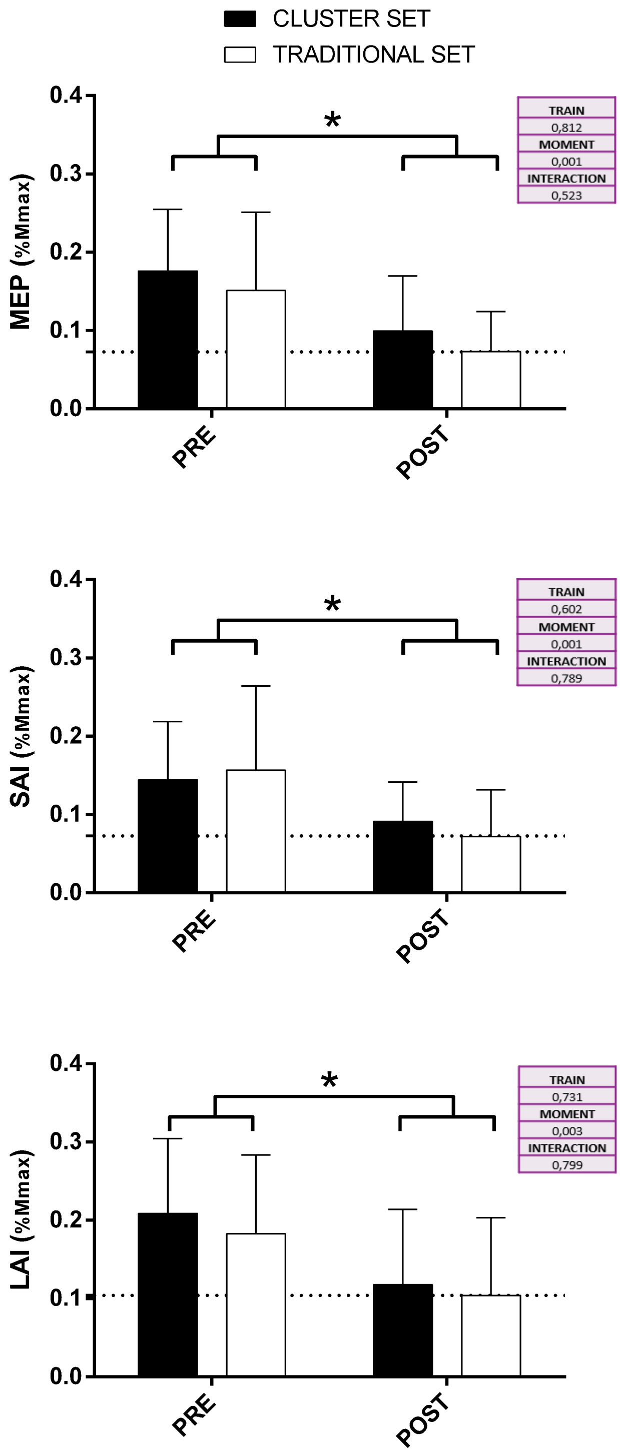

*Figure 23. Changes in motor evoked potentials (a), short afferent inhibition (b), long afferent inhibition inhibition (c) after the performance of cluster set (black bars) and traditional set configuration (white bars). Mean and SD values are displayed. # Significant differences between set configurations. * Significant differences between with PRE and POST values.*

D. Discussion

This study aimed to explore and describe the effects of the lower limb modulation in response to different amounts of fatigue evoked by two different training set configurations. LAI and SAI parameters were tested before and after traditional and cluster training set configurations in the isometric leg extension exercise. The main outcome of this research is that the long and short afferent inhibition processes are sensitive to fatigue provoked by an intense muscular effort. However, these LAI and SAI parameters were not able to detect differences in the type (peripheral or central) or amount of fatigue. So, its relevance might be limited to the exploration of sensorimotor control and postural assessment.

Sensory and Motor Integration

A consistent reduction (~40%) was found in the corticospinal activity (MEP) and the sensorimotor integration (SAI/LAI) despite of the training set configuration performed. The fall on the MEP values in both trainings highlighted the intense effort that participants underwent. SAI and LAI values followed the same reduction patterns showed by the MEP. This is of relevance since to the best of the authors knowledge there is no studies that explored the SMI after fatiguing tasks. Sensory afferents influence M1 either directly through the intracortical connections between the primary sensory cortex (S1) and M1 or through thalamocortical pathways that reach M1 (Chakrabarti et al., 2008; Rocco-Donovan et al., 2011). As such, SAI and LAI have been used as tools to probe changes in sensorimotor function in disease and following neurological injury to advance our understanding of sensorimotor control. Different mechanisms probably mediate LAI and SAI. At short latencies (less than 40 ms) the contralateral S1 and secondary somatosensory cortex (S2) are primarily activated, while at longer latencies (more than 40 ms) there is more widespread activation of sensory areas, including S1, bilateral S2, and the contralateral posterior parietal cortex (Chen, 2004). SAI reflects the direct effect of the sensory stimulus on the motor cortex, LAI probably concerns the basal ganglia or cortical association areas (Matur and Öge, 2017; Sailer et al., 2003).

Differences in the response of the SAI and LAI could be expected due to the stated different inhibition periods between the proposed neural underlying mechanisms. It is essential to take account that the intense and maintained muscular effort comprises both potentiation and inhibition effects from muscle spindles and afferents (i.e. group I-IV) (Boyas and Guével, 2011; Gandevia, 2001; Marque et al., 1996). This could be a confounding factor that surpasses the subtle changes that could be occurring due to SAI/LAI. However, the maintained muscular effort could generate some discomfort sensations (i.e pain). A pain-induced reduction of afferent inhibition may be a protective response, as less inhibition to the muscle may allow the restoration of motor function (Burns et al., 2016). LAI is also reduced in complex regional pain syndrome (Morgante et al., 2017), suggesting an association with the sensory feature of pain processing. Therefore, intense muscular work intensities that elicit pain may decrease SAI and LAI. (Turco et al., 2018)

Muscular Performance, Central and Peripheral Fatigue

Voluntary force, central and peripheral fatigue variables were differently affected by set configuration in this study. These results replicate a previous study from the same laboratory (Río-Rodríguez et al., 2016b). Cluster set configuration or, commonly named, cluster training stands as a stimulating form of training in order to avoid the setbacks of fatigue of the classic traditional resistance training. Importantly, if the aim is to improve explosive movements such as high and long jumps, some studies confirmed its utility (Asadi and Ramírez-Campillo, 2016; Mora-Custodio et al., 2018; Morales-Artacho et al., 2017). Not only CS configuration offer advantages to power training but also offers an interesting alternative to traditional set configurations for people with cardiovascular impairments (Millar et al., 2014).

Limitations

A study should be interpreted at the light of its limitations. To test a known model of resistance training and confirm previous evidence seems to be a right decision in order to incorporate new variables to the study. However, one of the possible reasons to cannot find any differences in the long and short afferent inhibition could be the time under tension. Previous studies showed that if the work-to-rest ratio is equated and the intensity is the same, the outcomes should be no different as it has been obtained (Iglesias-Soler et al., 2016).

E. Conclusions

Long and short afferent inhibition processes are sensitive to fatigue provoked by two different resistance training sessions with intense muscular effort. Nevertheless, to detect related differences in LAI and SAI parameters between set configurations were not possible despite sound differences were detected in central and peripheral fatigue responses. However, it is possible to found no differences in some parameters when work and rest ratios are equated. Thus,it is importat to stress the sensitivity of this LAI/SAI paradigm and try to explore it in no equated work-to-rest ratio studies. The sensorymotor integration stands as a new opportunity to explore neuromuscular adaptations to exercise and fatigue.

VIII. General Discussion

The main findings of this dissertation were that: I) set configuration determines the fatigue response both central, peripheral and cardiovascular as well as the perception of the effort. II) central fatigue response is linked to cardiovascular stress. III) sensory-motor integration is present in the lower limb. IV) LAI and SAI are sensitive to fatigue but there is still a need to clarify its application.

Despite performing the same amount of work and having the same time of rest in each set configuration, the fatigue responses were entirely different as revealed studies I and III. Since the time under tension is one of the main factors in the strength and fatigue response (Tran et al., 2006), the origin of the differences observed in our studies must be other than muscular tension. So, this strengthens the idea that the relative continuous time under tension remains as a more critical factor in the fatigue response in the human physiology. The SC manages this period under tension and divides them into clusters of repetitions of fractions of time (Haff et al., 2008). Understanding the SC as a critical factor, it is easy to explain the observed results in both central, peripheral, cardiovascular and perceived fatigue responses as discussed in the study I.

The neural control of the cardiovascular system and its interactions is a topic of heated debate between physiologists (Amann et al., 2015; DeMorree et al., 2012; Mitchell, 2013; Noakes, 2011; Shephard, 2009). Evidence for or against one model or another is released in each article. However, there is a question that remains true, and it is the complexity of the interactions between physiological systems. The changes observed in the voluntary activation as a paramount of the central fatigue (Shield and Zhou, 2004) and the correlation with the cardiovascular response in TS configuration seems to be related to the magnitude of the exercise pressor reflex response, the baroreflex modulation and the central command. In other words, the larger the central fatigue, the bigger cardiovascular response is observed. As fatigue processes starts the group III and IV afferent sent signals to brain to adjust the neural drive to muscles at the same time that the baroreflexes are stimulated resulting in elevation of heart rate and blood pressure to ensure the blood perfusion to muscles. The rise of the cardiovascular response is linked to the perception of effort and the latter with the central fatigue (DeMorree et al., 2012).

The methodological study II provided a new meassurement of the lower limb sensorimotor integration with the LAI and SAI parameters showing that afferent inputs from femoral stimulation were able to modulate the responses elicited by TMS of the contralateral quadriceps. Long and short afferent inhibition processes are sensitive to fatigue provoked by two different resistance training sessions with intense muscular effort. The sensorimotor integration stands as a new opportunity to explore neuromuscular adaptations to exercise and fatigue.

The study III applied the knowledge adquired in study II about the sensorimotor integration variables and it applied to the CS and TS configuration. This provided a refutation of previous results in corticospinal and mechanical variables and expanded the information of the sensorimotor integration processes that set configuration modulated. Surprinsingly, the LAI and SAI vaiables reacted in the same proportion and direction in response to the CS and TS configurations suggesting the idea that if the total time under tension is the same, the sensorimotor response could also be the same.

Limitations of each study were highlighted separately at the discussion section of each one. However a whole picture of the entire dissertation must be considered before the consclusions section. The novelty of the methodology used, where the online cardiovascular response, force recordings and the corticospinal were measured, brought associated problems the use of an isometric contraction regime display makes the generalization of the results of this dissertation should be taken with caution. However, this regime is optimal for the fatigue measurements in the field of neuromuscular fatigue, maximal strength, cortical excitability, baroreflex, variability and beat to beat pressure measures. In this line, the order of the measurements after fatigue could affected the total response of fatigue obtained in these studies since it is known that corticospinal manifestations of fatigue recovers fast (Carroll et al., 2017). Despite of that a consistent corticospinal impairment were detected as well as cardiovascular after effects.

IX. General Conclusions

To investigate differences in the neurophysiological, mechanical and cardiovascular acute responses of TS and CS configurations matched for volume, intensity, and work-to-rest ratio.

- A large reduction in the corticospinal excitability was provided by the traditional set suggesting a bigger impact on the central muscle fatigue mechanisms compared with the cluster set configuration
- Short-intracortical inhibition were negatively affected by a traditional set configuration suggesting compensatory mechanisms in response to the impairment in the central neural drive., the brain plasticity induces an expansion of the motor areas in order to maintain the target force by reducing the interneurons inhibitory activity, thus increasing the neural drive to the muscles.
- Central fatigue played a minor role in the maximal force decline decrease, as indicated by the reduction of the MEP amplitude and voluntary activation in the cluster set configuration.
- A traditional set configuration produced a 43% greater drop in maximal voluntary force values than the cluster method as well as greater central and peripheral fatigue.
- The coexistence of fatigue and potentiation mechanisms that occur immediately after exercise favored to the cluster set configuration obtaining an increase in the M-Wave and RFD parameters of twitch evoked force.
- Longer relative contraction times in comparison of the traditional set compared with the cluster accounted for a greater impact on the metabolic profile of the excitation-contraction coupling as reflected the Low frequency fatigue values.
- Lower hemodynamic stress was provided by the cluster set configuration.

- The greater hemodynamic response in traditional set configuration seems to be related to the magnitude of the exercise pressor reflex response, the baroreflex modulation and the central command. These changes are associated with a lower voluntary activation, suggesting a relationship between central fatigue and cardiac stress.
- Reductions in the HF and LF together with a baroreflex impairment has been associated with high-intensity resistance training but this effects only stands in the traditional but not in the cluster set configuration.
- Strong correlations linking the cardiovascular response with the neurophysiological fatigue and the perception were found with an inverse correlation between voluntary activation and rate pressure product and a positive correlation of blood pressure and perception of effort expanding results of previous experiments on the field of psycophysiology.
- Set configuration plays a key role in managing the deleterious effects of fatigue in all the body systems during resistance exercise.

To explore the conditioning effect of a percutaneous electrical pulse of the femoral nerve on cortical motor evoked responses in the rectus femoris muscle.

- Afferent inputs from a femoral electrical stimulus modulated the responses elicited by TMS of the contralateral quadriceps motor cortex.
- The MEP inhibition found in the quadriceps at an inter-stimulus interval of 25 ms possibly corresponds with the short latency afferent inhibition (SAI) previously observed in upper limb muscles and with cortical origin.
- Inhibition and facilitation of the quadriceps motor evoked potentials were induced by a previous electrical pulse delivered at inter-stimulus intervals of 25 and 150 ms, respectively.
- Whereas the facilitation at 150 ms was reduced when low electrical intensity was used the inhibition at 25 ms decreased with high TMS intensity.
- It is unlikely that the inhibition that we observed is induced by nociceptive afferents (Group III and IV). Muscle afferents from group I are responsible for the increase of the MEP amplitudes at 150 ms
- The responses to cortical stimulation can be modulated by afferent inputs, even in proximal lower limb muscles. Different types of afferents might be mediating the sensorimotor integration of proximal lower limb muscles.

To describe the effects of the lower limb modulation during two equated training configurations in the rectus femoris muscle.

- Long and short afferent inhibition processes are sensitive to fatigue provoked by two different resistance training sessions with intense muscular effort.
- A consistent reduction (~40%) was found in the corticospinal activity (MEP) and the sensorimotor integration (SAI/LAI) despite the training set configuration performed.
- Equating work and rest ratios could be of relevance to compare resistance training models but the mechanical stimuli for the muscle remains the same so it opens the possibility to could not detect subtle changes in parameters like LAI/SAI.
- The mechanical and neuromuscular effects of the each set configuration replicated the results of the first study of this dissertation providing strong support for the outcomes previously outlied and the crucial role of the set configuration in the management of the fatigue responses.

Hypotheses

The levels of muscle fatigue induced by different resistance exercise configurations account for the differences in the cardiovascular response.

This hypothesis has been accepted by the results of study I and refuted the mechanical and neuromuscular outcomes by study III. A strong relationship between cardiovascular response and central fatigue were found as well as the peripheral response effects on the cardiovascular stress.

An electrical pulse on the femoral nerve is able to modulate the cortical response of the rectus femoris muscle demonstrating that the sensorimotor integration processes are present in this musculature.

This supposition has been accepted by the results of the study II. A clear pattern of inhibition and facilitation of the quadriceps motor evoked potentials were shown at 25 and 150 ms after an electrical peripheral stimulus respectively.

The sensorimotor integration is affected by the amount of fatigue caused by different resistance set configurations.

This hypothesis has been rejected by the results of study III. The disproportionate changes observed in the fatigue responses for each set configuration did not account for the LAI and SAI parameters which showed the same reductions after resistance exercise.

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XI. APPENDIX A: Abstract of at least 3000 words in an official language (Spanish)

La intensidad y el volumen han sido las variables más estudiadas en el entrenamiento deportivo y la programación. Estas variables se utilizaron para aumentar, disminuir o ajustar la carga de entrenamiento. Esta visión corresponde a una forma tradicional de configurar el entrenamiento. Cuando el objetivo es manejar la fatiga del atleta, los entrenadores deben ser más específicos al diseñar sus programas de entrenamiento. En los últimos años, una variable más salió a la luz de la ciencia: la configuración de la serie. La configuración de la serie podría definirse como "la distribución de esfuerzo-tiempo" (Haff et al., 2008, 2003; Tufano et al., 2017a). Es diferente de la densidad o la pausa porque administra la relación entre el descanso y el trabajo durante el entrenamiento de resistencia (es decir, la relación trabajo-descanso) (Hansen et al. 2011; Mayo et al. 2014). Desde ahora, en este documento se denominará configuración de la serie (SC).

Los entrenadores e investigadores desarrollaron una nueva forma de entender la configuración de la serie, dividiendo las series tradicionales en pequeños grupos de repeticiones. Esto se denominó entrenamiento con descanso intra-serie de reposo o entrenamiento clúster (CS).Hay muchas formas de configurar la estructura de CS, como realizar repeticiones de uno, dos, tres, etc. y luego descansar, o redistribuir el tiempo total de entrenamiento para igualar la relación trabajo-descanso a una configuración de tradicional.

El rendimiento mecánico durante la serie es de gran importancia para aumentar la calidad del estímulo de entrenamiento. En la siguiente sección, una visión general de los efectos mecánicos en respuesta a la SC, desde la velocidad y la potencia hasta las adaptaciones a largo plazo. La velocidad y la potencia de cada repetición que se realizan son variables críticas para aumentar la calidad del estímulo de entrenamiento. Muchos estudios compararon el uso de la configuración clúster con el alto rendimiento en el deporte. Uno de los primeros estudios (Haff et al., 2003) sobre SC en el rendimiento de levantamiento de pesas exploró los factores que afectan a la velocidad y el desplazamiento de la barra. En esta investigación, parece que la configuración de la serie de un programa de entrenamiento de fuerza con un modelo clúster puede producir alteraciones específicas en ambos parámetros de rendimiento. Estas alteraciones tanto en la velocidad de la barra como en el desplazamiento pueden resultar en un mejor rendimiento debido a la relación de estas variables con el rendimiento de levantamiento de pesas. Basado en el concepto de velocidad y especificidad de movimiento, parece que la configuración clúster permite al atleta optimizar la velocidad del tirón y el desplazamiento (Haff et al., 2003). Un estudio con jugadores de rugby de élite que utilizaron diferentes configuraciones clúster en el rendimiento balístico (es decir, salto de sentadilla) comparó las estructuras de TS y CS. La configuración clúster mostrço una ventaja en el mantenimiento de la potencia durante la serie, pero no se encontraron diferencias entre los tipos de estructura clúster (Hansen et al., 2011).

Los efectos agudos de la configuración CS se compararon con la configuración TS en los párrafos anteriores, revelando mejores estímulos mecánicos proporcionados por el primero. Pero ¿son los estímulos mecánicos potenciados la condición necesaria para producir mejoras con CS? El influyente trabajo de Folland et al. en 2002 proporcionó un sólido argumento científico para evitar la fatiga máxima en cada entrenamiento. En otras palabras, no es necesario agotar todas las repeticiones en reserva para producir adaptaciones. Sin embargo, un estudio inicial de Rooney et al. (1994) en la estructura de CS que comparó el entrenamiento de flexores de codo al 6 RM 3 días a la semana durante 6 semanas con 42 participantes divididos en tres grupos: Con 30 segundos de descanso entre cada repetición, sin descanso y control. Después del período de entrenamiento, el grupo sin descanso mejoró un 56% con respecto al 41% del grupo de descanso (Rooney et al., 1994). Los autores señalan el hecho de que es necesaria una cantidad mínima de fatiga en el sistema neuromuscular para que se activen las adaptaciones.

En el párrafo anterior se proporcionó una descripción general de las características mecánicas de la configuración CS. Los intervalos de descanso entre series de entrenamiento son una de las variables más críticas que afectan los efectos agudos mecánicos y metabólicos del entrenamiento. La duración de los intervalos afecta el volumen total completado durante un entrenamiento y también la sostenibilidad de las repeticiones a lo largo de una sesión de entrenamiento (Iglesias-Soler et al., 2012). Para comprender mejor las causas que provocaron diferencias observadas con la configuración TS, es necesario explorar los mecanismos subyacentes que apoyan la mejora del rendimiento y la capacidad de la configuración de CS para controlar la fatiga.

Las variables estudiadas hasta ahora están relacionadas con la respuesta de fatiga de cada uno de los sistemas del organismo a la configuración de la serie. Muchas variables continúan sin explorar y es necesario saber más sobre la respuesta del resto de los sistemas para tener una visión multifactorial de los procesos de fatiga.

Para resumir, la configuración de la serie clúster:

- Reduce la pérdida de velocidad durante la serie.
- Permite completar la misma cantidad de trabajo con menos percepción de fatiga.
- Amortigua la respuesta cardiovascular y metabólica.

- Se presenta como una alternativa más segura a la configuración tradicional de entrenamiento de fuerza en poblaciones de riesgo (hipertensión, enfermedad coronaria, etc.)
- Tiene un efecto superior en los movimientos explosivos en el entrenamiento a largo plazo.
- Tiene efectos similares en las adaptaciones centrales y periféricas como la configuración TS en el corto plazo (5 semanas).

Explorar las relaciones de estas variables en el contexto del ejercicio de fuerza es interesante cuando la evidencia disponible se diluye en enfoques de un solo sistema. Por lo tanto, el estudio de la posible relación entre las variables mecánicas, cardiovasculares y perceptivas en la respuesta a la fatiga podría ofrecer una visión completa de los procesos que podrían estar ocurriendo en la fisiología humana.

La fatiga es un proceso multifactorial que podría surgir de los sistemas centrales o periféricos. Hay múltiples formas en que la fatiga tiene que manifestarse. La fatiga se define comúnmente como cualquier reducción en la capacidad máxima para generar fuerza (Vøllestad, 1997). Aunque la mayoría de las definiciones de fatiga se centran en la producción de fuerza, la fatiga no solo impide la capacidad de la fibra para la generación de fuerza máxima, sino también la velocidad máxima de acortamiento o alargamiento y, por lo tanto, la producción de potencia también se verá afectada (Gandevia, 2001; Gandevia et al. 1996). En las siguientes líneas, se expondrá una revisión de todo el proceso que subyace a la respuesta de fatiga. Aunque podría ser casi imposible identificar el factor limitante más importante de la fatiga, esto no debería disuadir a los científicos y clínicos de intentar resolver muchos de los problemas que confunden este concepto.

La fatiga central puede originarse en los lugares espinales y supraespinales. La regulación espinal implica principalmente el control de la actividad de las neuronas motoras alfa y gamma mediante algunos mecanismos. En resumen, las neuronas motoras espinales tienen una propiedad intrínseca para reducir su frecuencia de descarga natural con el tiempo que está regulada por las aferencias musculares (husos, órganos tendinosos de Golgi, y fibras de diámetro pequeño), interneuronas espinales e inhibición presináptica de entradas aferente de los centros propriospinales y supraespinales (Ranieri y Di Lazzaro, 2012).

Los cambios fisiológicos producidos en o distales a la unión neuromuscular se consideran fatiga periférica. En las siguientes líneas se ofrecerá una visión general de los procesos metabólicos dentro de la fibra muscular y la placa motora. De forma breve, H + y Pi contribuyen a la fatiga, principalmente tanto por sus efectos inhibidores sobre el puente cruzado como por la reducción de la sensibilidad de los miofilamentos al Ca2 +. De hecho, ahora está claro que las elevaciones en H + y Pi son los principales contribuyentes a la pérdida de fuerza y velocidad cuando se estudian en las fibras musculares in vitro, lo que demuestra que los subproductos metabólicos inhiben directamente la fuerza y la capacidad de movimiento del músculo durante la fatiga (Debold et al., 2016). Sin embargo, la evidencia experimental del músculo humano estudiada in vivo y las fibras musculares intactas aisladas hablan claramente contra la acidosis como un factor central que subyace a la función contráctil dañada en el músculo de mamíferos fatigados (Westerblad, 2016). En resumen, la acidosis como tal tiene solo efectos directos menores sobre la función contráctil del músculo de los mamíferos estudiado a temperaturas fisiológicas.

Los estímulos mecánicos y químicos inducidos por la contracción activan los receptores moleculares en el extremo terminal de las fibras nerviosas tanto mielinizadas (grupo III) como no mielinizadas (grupo IV) ubicadas dentro del músculo esquelético (Sidhu et al., 2017). Las aferencias del grupo muscular III y IV inervan las terminaciones nerviosas libres distribuidas ampliamente en todo el músculo. Estos receptores se mantienen silentes o mantienen bajas tasas de descarga basal mientras que responden a eventos mecánicos, bioquímicos y térmicos locales. Varios factores hacen que su descarga aumente durante las contracciones intensas y la fatiga, principalmente si la intensidad de la contracción es suficiente para afectar la perfusión muscular, lo que también depende del ejercicio específico que se realice.

En resumen, la configuración de la serie clúster proporciona una respuesta de fatiga menor con un rendimiento mecánico mejorado. Tomadas en conjunto, las respuestas mecánicas, cardiovasculares, metabólicas y perceptivas ofrecen una visión de los procesos que la configuración de la serie podría estar afectando. Por lo tanto, es de gran interés explorar si estas variables están relacionadas en la misma proporción en la respuesta de fatiga. Independientemente del modelo de fatiga, la misión principal al estudiar la respuesta de fatiga a un tipo de ejercicio, la intensidad o el parámetro de carga es la relación entre los factores neuromusculares (p. Ej., descarga neural), cardiovascular, metabólico y todos los mecanismos reguladores y sensoriales (aferencias musculares, barreflejos).

Por lo tanto, el propósito principal de esta tesis fue explorar las diferencias entre la configuración tradicional y la configuración de grupo en los sistemas neuromuscular, cardiovascular, de percepción y sensoriomotor y en un segundo orden para encontrar relaciones entre las manifestaciones de fatiga en cada sistema.

Así, se realizaron tres experimentos para buscar las respuestas a estos objetivos. En el primer estudio se exploraron las diferencias debidas a la configuración de la serie. En el segundo se desarrolló un estudio metodológico para establecer las propiedades de la integración sensoriomotora en la extremidad inferior. Finalmente, en el tercer experimento se buscó contrastar los resultados del primero al agregar las variables sensoriomotoras para verificar si la configuración de la serie podría afectar las propiedades sensoriomotoras de la extremidad inferior.

Los principales hallazgos de esta disertación fueron que: I) la configuración del conjunto determina la respuesta de fatiga central, periférica y cardiovascular, así como la percepción del esfuerzo. II) La respuesta de fatiga central está vinculada al estrés cardiovascular. III) La integración sensomotora está presente en la extremidad inferior. IV) LAI y SAI son sensibles a la fatiga, pero todavía es necesario aclarar su aplicación.

Nuestro primer estudio apoya la hipótesis de que existe una relación entre la fatiga central y las respuestas hemodinámicas, de modo que cuanto mayor es la fatiga central, mayor es la respuesta hemodinámica. Nuestros hallazgos muestran que esta relación está modulada por la configuración de la serie. Una configuración de la serie clúster se asocia con menor fatiga central y periférica, con una menor pérdida posterior en los valores de fuerza máxima, así como con un menor estrés cardiovascular en comparación con una configuración de la serie tradicional con igual trabajo, descanso y relación trabajo-pausa. La mayor respuesta hemodinámica en la configuración de la serie tradicional parece estar relacionada con la magnitud de la respuesta del reflejo presor del ejercicio, la modulación barorrefleja y el comando central. Estos cambios se asocian con una menor activación voluntaria, lo que sugiere una relación entre la fatiga central y el estrés cardiovascular. Por lo que sabemos, este es el primer estudio que comparó la fatiga central y periférica, en combinación con medidas hemodinámicas y cardiovasculares, de dos configuraciones de la serie en ejercicio de fuerza a igualdad de ratios de trabajo a reposo. Los hallazgos proporcionan información adicional sobre los mecanismos fisiológicos que subyacen a la configuración de la serie y su relevancia en el manejo de los efectos del ejercicio de resistencia.

El control neuronal del sistema cardiovascular y sus interacciones es un tema de acalorado debate entre fisiólogos (Amann et al., 2015; DeMorree et al., 2012; Mitchell, 2013; Noakes, 2011; Shephard, 2009). La evidencia a favor o en contra de un modelo u otro se publica en cada artículo. Sin embargo, hay una cuestión que sigue siendo cierta, y es la complejidad de las interacciones entre los sistemas fisiológicos. Los cambios observados en la activación voluntaria como un factor primordial de la fatiga central (Shield y Zhou, 2004) y la correlación con la respuesta cardiovascular en la configuración de TS parecen estar relacionados con la magnitud de la respuesta del reflejo presor del ejercicio, la modulación barorrefleja y el comando central En otras palabras, cuanto mayor es la fatiga central, mayor es la respuesta cardiovascular que se observa. A medida que comienzan los procesos de fatiga, las señales aferentes del grupo III y IV envían señales al cerebro para ajustar el impulso neural a los músculos al mismo tiempo que se estimulan los barorreflexos, lo que produce una elevación de la frecuencia cardíaca y la presión arterial para asegurar la perfusión de la sangre en los músculos. El aumento de la respuesta cardiovascular está vinculado a la percepción del esfuerzo y esta última a la fatiga central (DeMorree et al., 2012).

El estudio II, de cariz metodológico, proporcionó una nueva medición de la integración sensoriomotora del miembro inferior con los parámetros LAI y SAI, lo que demuestra que las entradas aferentes de la estimulación femoral pudieron modular las respuestas provocadas por la TMS en el cuádriceps contralateral. La importancia funcional del efecto modulador de las aferencias del cuádriceps reportados en nuestro estudio puede verse en el contexto del control postural. Por ejemplo, el efecto facilitador observado en un intervalo entre estímulos de 150 ms parece imitar el inicio de la activación del cuádriceps en los ajustes posturales anticipatorios (Badke et al., 1987) y durante las respuestas de equilibrio reactivo (Sundermier et al., 2001). La latencia de la inhibición corta, por otro lado, puede indicar un efecto reflejo a través de vías segmentarias (Kasai et al., 1992). Si estos efectos moduladores tienen alguna aplicación clínica aún no se ha establecido. En resumen, la estimulación eléctrica del nervio femoral indujo una inhibición de corta latencia y una facilitación de larga latencia de las respuestas motoras provocadas en el recto femoral por TMS. Estas respuestas indican la integración sensoriomotora de los músculos de las extremidades inferiores proximales que pueden mediarse a través de diferentes tipos de aferentes. Esto podría ser relevante para los estudios que exploran el papel de los músculos de las extremidades inferiores en el control y equilibrio postural.

El estudio III aplicó los conocimientos adquiridos en el estudio II sobre las variables de integración sensoriomotora y se aplicó a la configuración CS y TS. Esto proporcionó una refutación de resultados previos en variables corticoespinales y mecánicas y expandió la información de los procesos de integración sensoriomotor que modula la configuración de la serie. En este estudio se encontró que los procesos de inhibición aferente de larga y corta latencia son sensibles a la fatiga provocada por dos tipos de entrenamiento de fuerza diferentes sólo en la SC con un esfuerzo muscular intenso. Sin embargo, detectar diferencias relacionadas en los parámetros LAI y SAI entre las configuraciones establecidas no fue posible a pesar de que se detectaron diferencias notables en las respuestas de fatiga central y periférica. Sin embargo, es posible no encontrar diferencias en algunos parámetros cuando se equiparan las relaciones trabajo y descanso. Por lo tanto, es importante resaltar la sensibilidad de este paradigma de LAI / SAI y tratar de explorarlo en estudios de proporción trabajo-descanso no igualados. La integración sensoriomotora se presenta como una nueva oportunidad para explorar las adaptaciones neuromusculares al ejercicio y la fatiga.

Dado que el tiempo bajo tensión es uno de los factores principales en la respuesta de fuerza y fatiga (Tran et al., 2006), el origen de las diferencias observadas en nuestros estudios debe ser distinto de la tensión muscular. Entonces, esto fortalece la idea de que el tiempo continuo bajo tensión permanece como un factor más crítico en la respuesta de fatiga en la fisiología humana. La configuración de la serie gestiona este período bajo tensión y los divide en clúster de repeticiones o de fracciones de tiempo (Haff et al., 2008). Entendiendo el SC como un factor crítico, es fácil explicar los resultados observados en las respuestas de fatiga central, periférica, cardiovascular y percibida, como se discutió en el estudio I.

Las limitaciones de cada estudio se destacan por separado en la sección de discusión de cada uno de ellos. Sin embargo, una imagen completa de toda la tesis debe ser tomada en cuenta. La novedad de la metodología utilizada, donde se midieron la respuesta cardiovascular en línea, los registros de fuerza y el corticoespinal, trajo problemas asociados, el uso de un esfuerzo de régimen de contracción isométrica hace que la generalización de los resultados de esta tesis se tome con precaución. Sin embargo, este régimen es óptimo para las mediciones de fatiga en el campo de la fatiga neuromuscular, la fuerza máxima, la excitabilidad cortical, la barorrefleja, la variabilidad y las medidas de presión arterial latido a latido. En esta línea, el orden de las mediciones después de la fatiga podría afectar la respuesta total de la fatiga obtenida en estos estudios, ya que se sabe que las manifestaciones corticoespinales de la fatiga se recuperan rápidamente (Carroll et al., 2017). A pesar de ello, se detectó un deterioro corticoespinal constante y efectos secundarios cardiovasculares.

XII. APPENDIX B: informed consent

HOJA DE INFORMACIÓN AL PARTICIPANTE

TÍTULO: ***Respuestas de fatiga neurofisiológica y hemodinámica a la configuración de la serie en ejercicio de fuerza.***

INVESTIGADOR PRINCIPAL:

Este documento tiene por objeto ofrecerle información sobre un **estudio de investigación** en el que se le invita a participar. Este estudio se está realizando desde la Facultad de Ciencias do Deporte y la Educación Física (INEF Galicia), Universidade da Coruña.

Si decide participar en el mismo, debe recibir información personalizada del investigador, **leer antes este documento** y hacer todas las preguntas que necesite para comprender los detalles sobre el mismo. Si así lo desea, puede llevar el documento, consultarlo con otras personas, y tomarse el tiempo necesario para decidir si participar o no.

La participación en este estudio es completamente **voluntaria**. Vd. puede decidir no participar o, si acepta hacerlo, cambiar de opinión retirando el consentimiento en cualquier momento sin obligación de dar explicaciones.

¿Cuál es el propósito del estudio?

El objetivo de este estudio es comparar el efecto que genera sobre las variables de la fatiga la configuración de la serie en ejercicio de fuerza. Para ello se realizarán unas mediciones antes, durante y después de cada sesión, que permitirán determinar los cambios fisiológicos, metabólicos y neuromusculares que se generen en cada caso. El ejercicio a estudiar es la extensión isométrica de rodilla con una configuración tradicional VS configuración cluster.

¿Por qué me ofrecen participar a mí?

La selección de las personas invitadas a participar depende de unos criterios que están descritos en el protocolo de la investigación. Estos criterios sirven para seleccionar a la población en la que se responderá el interrogante de la investigación. Vd. es invitado a participar porque potencialmente cumple esos criterios, al ser una persona sana, mayor de edad y adaptada al entrenamiento de fuerza.

¿En qué consiste mi participación?

El estudio consistirá en 2 valoraciones previas más 2 sesiones de evaluaciones relacionadas con el objeto de estudio. Las valoraciones previas consisten en una sesión de familiarización con las medidas neurofisiológicas y otra sesión para obtener los valores de fuerza máxima y tiempo hasta la fatiga. De las 2 sesiones de evaluación una seguirá una metodología tradicional y otra cluster. Estas mediciones se harán en mediciones separadas 1 semana en la misma hora del día.

En todas las sesiones habrá una monitorización de diferentes variables a través de los siguientes parámetros:

- Parámetros cardiovasculares:

- Aportan información para analizar la respuesta integrada del organismo al ejercicio de fuerza.

- Parámetros mecánicos:

    - Se medirá la concentración de lactato en sangre.

- Parámetros neuromusculares:

- Se medirán a través de la estimulación percutánea del nervio femoral y a través de la estimluación magnética transcraneal del área motora correspondiente a la musculatura del cuádriceps.

Para garantizar unas condiciones experimentales adecuadas se deberá:

- Realizar todas las pruebas en la misma franja horaria según la disponibilidad individual
- No ingerir alimentos, alcohol, productos con cafeína ni tabaco en las 2-3 horas previas a cada intervención
- No modificar de manera significativa la alimentación de los días previos.
- No haber realizado un esfuerzo alto o inusual 24 horas antes, manteniendo el régimen habitual de actividad física en todo caso
- Llevar ropa y calzado adecuado y cómodo.

Es necesario que si Vd. decide participar en este estudio, se comprometa a asistir a las sesiones de toma de datos. En el momento en que la falta de asistencia sea repetida y provoque que no se cumplan los periodos de tiempo fijados, se decidirá a apartarle del estudio.

¿Qué riesgos o inconvenientes tiene?

La realización de las cargas de trabajo diseñadas puede generar fatiga y dolor muscular de aparición tardía (“agujetas”).. Para reducir cualquier riego de lesión, todas las valoraciones irán precedidas por un calentamiento específico diseñado y dirigido por un especialista. Las ejecuciones de los ejercicios serán supervisadas por al menos dos investigadores, que prestarán la ayuda necesaria al participante.

Si durante el transcurso del estudio se conociera información relevante que afecte a la relación entre el riesgo y el beneficio de la participación, se le transmitirá para que pueda decidir abandonar o continuar.

¿Obtendré algún beneficio por participar?

No se espera que Vd. obtenga beneficio directo por participar en el estudio. El único beneficio es valorar qué tipo de metodología de entrenamiento de fuerza proporciona un mejor estímulo para el entrenamiento y la mejora del rendimiento atendiendo a parámetros fisiológicos, metabólicos y neuromusculares.

¿Recibiré la información que se obtenga del estudio?

Si Vd. lo desea, se le facilitará un resumen de los resultados del estudio.

También podrá recibir los resultados de las pruebas que se le practiquen si así lo solicita. Estos resultados pueden no tener aplicación clínica ni una interpretación clara, por lo que, si quiere disponer de ellos, deberían ser comentados con el investigador principal del estudio.

¿Se publicarán los resultados de este estudio?

Los resultados de este estudio serán publicados en revistas científicas para su difusión, pero no se transmitirá ningún dato que pueda llevar a la identificación de los participantes.

¿Cómo se protegerá la confidencialidad de mis datos?

El tratamiento, comunicación y cesión de sus datos se hará conforme a lo dispuesto por el RGPD UE 2016/679 sobre de protección de datos de carácter personal. En todo momento, Vd. podrá acceder a sus datos, corregirlos o cancelarlos.

Sólo el equipo investigador tendrá acceso a todos los datos recogidos por el estudio. Se podrá transmitir a terceros información que no pueda ser identificada. En el caso de que alguna información sea transmitida a otros países, se realizará con un nivel de protección de los datos equivalente, como mínimo, al exigido por la normativa de nuestro país. La transmisión de datos a terceros tiene por finalidad el realizar un análisis más exhaustivo de algunos parámetros registrados que por razones técnicas no podrían ser analizados en nuestro laboratorio.

¿Existen intereses económicos en este estudio?

Vd. no será retribuido por participar.

Es posible que de los resultados del estudio se deriven productos comerciales o patentes. En este caso, Vd. no participará de los beneficios económicos originados.

Todas las mediciones se llevarán a cabo en las instalaciones de la Facultad de Ciencias del Deporte y la Educación Física de la Universidade da Coruña, por lo que en ningún caso se contempla el alquiler o arrendamiento de instalaciones.

¿Quién me puede dar más información?

Puede contactar con _______***en el teléfono*** __________ o ***dirección de correo*** ___________ para más información.

Muchas gracias por su colaboración.

DOCUMENTO DE CONSENTIMIENTO PARA LA PARTICIPACIÓN EN UN ESTUDIO DE INVESTIGACIÓN

TÍTULO: ***Respuestas de fatiga neurofisiológica y hemodinámica a la configuración de la serie en ejercicio de fuerza.***

Yo,

- He leído la hoja de información al participante del estudio arriba mencionado que se me entregó, he podido hablar con ***Investigador principal*** y hacerle todas las preguntas sobre el estudio necesarias para comprender sus condiciones y considero que he recibido suficiente información sobre el estudio. ☐
- Comprendo que mi participación es voluntaria, y que puedo retirarme del estudio cuando quiera, sin tener que dar explicaciones. ☐
- Accedo a que se utilicen mis datos en las condiciones detalladas en la hoja de información al participante. ☐
- Presto libremente mi conformidad para participar en el estudio. ☐

Respeto a la conservación y utilización futura de los datos y/o muestras detallada en la hoja de información al participante, ☐

NO accedo a que mis datos sean conservados una vez terminado el presente estudio ☐

Accedo a que mis datos se conserven una vez terminado el estudio, siempre y cuando sea imposible, incluso para los investigadores, identificarlos por ningún medio ☐

Accedo a que los datos se conserven para usos posteriores en líneas de investigación relacionadas con la presente, y en las condiciones mencionadas.

En cuanto a los resultados de las pruebas realizadas, ☐

DESEO conocer los resultados de mis pruebas ☐

NO DESEO conocer los resultados de mis pruebas ☐

El/la participante,	El/la investigador/a,
Fdo.:	Fdo.: investigador principal
Fecha:	Fecha:

XIII. APPENDIX C: Publications that led to the thesis

ARTICLES

1. *Set Configuration in Resistance Exercise: Muscle Fatigue and Cardiovascular Effects*
    - Published in PLoS One March 2016 after 2 rejections since 2014 and three minor revisions.
2. *Modulation of quadriceps corticospinal excitability by femoral nerve stimulation*
    - Published in Neuroscience Letters November 2016 after 1 rejection and 2 minor revisions.
3. The third study is in the peer review phase of the manuscript where the new paradigm on the involvement of sensitive afferents in fatigue developed in the second study (2) is explored for its application in the fatigue model studied in the main study (1) of the thesis.

CONFERENCE PROCEEDINGS

4. *Rate of perceived exertion as a measure of cardiovascular stress*
    - International NSCA Congress (Murcia, 2014)
5. *Traditional vs cluster set configuration neurophysiological and hemodynamic responses*
    - International NSCA Congress (Murcia, 2014)
6. *La configuración de la serie modula la respuesta hemodinámica en ejercicio resistido*
    - National congress of Sports Medicine (A Coruña, 2014)
7. *Is it central command related to central fatigue? A correlation study*
    - National congress of Sports Science (Cáceres, 2015)

8. Muscle fatigue, cardiovascular and hemodynamic responses induced by cluster resistance training configuration.
    - National congress of Sports Science (Cáceres, 2015)