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Effects of blood flow restriction in nervous conduction velocity

Dissertação elaborada com vista à obtenção de Grau de Mestre em Treino de Alto Rendimento

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“Do not pray for an easy life, pray for the strength to endure a difficult one”

Bruce Lee

Acknowledgments (Português)

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Abbreviations

αMN – alpha motoneuron

1RM – one-repetition maximum

AOP – arterial occlusion pressure

BFR – blood flow restriction

CMAP – compound muscle action potential

DOMS – delay onset muscle soreness

EMG - electromyography

GH – growth hormone

H-reflex – hoffman reflex

HI – high intensity

LAT DIFF – difference between the M- and H-latency

LI – low intensity

LI BFR – low intensity blood flow restricted exercise

M_{max} – maximal M-wave

MNCV – motor nerve conduction velocity

MVC – maximal voluntary contraction

NCV – nerve conduction velocity

PO_{bf} – blood flow changes post-exercise

REP - repetition

SBP – systolic blood pressure

SNAP – sensory nerve action potential

SNCV – sensory nerve conduction velocity

Units of measure

µV - microvolts

cm – centimeters

h – hours

Hz - hertz

kg – kilograms

kg/m^2 – kilograms per square meter

mA - milliamps

min - min

mmHg – millimeters of mercury

ms – milliseconds

mV – millivolts

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Abstract

Purpose: In the last two decades, low intensity blood flow restricted (LI BFR) exercise has been increasingly used by individuals focused in hypertrophy gains. The practice of this type of training not following the procedures advanced in the literature, and neglecting factors such as: cuff pressure, wideness and placement as well as time of blood flow restriction might cause nerve damage. There are reports of individuals feeling numbness in the extremity of their limbs after enduring exercise with blood flow restriction (BFR). Thus, we explored whether BFR might affect peripheral nerve integrity both at resting and exercise conditions.

Methods: Thirteen healthy young male participants (age: 22.0 ± 1.7 years, height: 175.2 ± 3.9 cm, body mass: 68.4 ± 5.4 kg and body mass index: 22.3 ± 1.5 kg/m^2) were included in this study. Participants visited the laboratory on two different occasions (BFR and LIBFR at 60% arterial occlusion pressure (AOP) vs BFR and LI BFR at 80% AOP). The latency and amplitude of the M-wave and H-reflex were evaluated at 3 different moments (before, during and after BFR) at resting and exercise conditions. The stimulation of the posterior tibial nerve was performed in the popliteal fossae and the response was recorded on the soleus muscle. Both waves were elicited at 30% M_{max}.

Results: Overall, BFR had no impact on changing the amplitude or latency of either waveform. The latency difference between the M and H wave was unaffected by each condition (60 or 80%) ($p > 0.05$). Similar findings were also obtained for the interaction between BFR and Li exercise. Concerning the amplitude of both waveforms M-wave/H-wave, BFR (either 60 or 80%) had no effect altering the absolute or relative values of this specific variable with or without exercise ($p > 0.05$).

Conclusions: Performing BFR at 60 or 80% AOP, for a period slightly > 5 min does not exert a negative impact on peripheral nerve function (unchanged amplitude and latency of evoked potential). Thus, we provide preliminary evidence that peripheral nerve conduction is not altered by BFR during resting or exercise conditions. Therefore, from a neurological standpoint, LI BFR exercise may be regarded as a safe mode of resistance training within the general population.

Keywords: KAATSU, blood flow restriction, low-intensity exercise combined with blood flow restriction, hoffman reflex, arterial occlusion pressure, electromyography, soleus, nerve conduction velocity, electrical stimulation, tibial nerve.

Resumo (Português)

Objetivos: Nas duas últimas décadas, o treino de força de baixa intensidade com restrição vascular (LI BFR), tem sido utilizado por indivíduos focados em ganhos hipertróficos. A prática desta modalidade de treino, negligenciando os processos descritos na literatura, tais como: pressão do *cuff*, largura e local de aplicação tal como duração do tempo de restrição, poderão causar lesões no nervo. Inclusive, alguns sujeitos reportaram sensações de dormência nas extremidades dos membros após praticarem exercício com restrição vascular (BFR). Atendendo a estas ocorrências, exploramos se a BFR poderia afetar a integridade dos nervos periféricos, em condições de exercício e repouso.

Métodos: Treze jovens saudáveis do sexo masculino (idade: 22.0 ± 1.7 anos; altura: 175.2 ± 3.9 cm; peso: 68.4 ± 5.4 kg e índice de massa corporal: 22.3 ± 1.5 kg/m^2) foram incluídos neste estudo. Os participantes visitaram o laboratório em duas ocasiões diferentes (BFR e LI BFR a 60% pressão de oclusão arterial (AOP) vs BFR e LI BFR a 80% AOP). A latência e amplitude da onda-M e reflexo-H foram avaliadas em 3 momentos diferentes (antes, durante e após BFR) com e sem a presença de exercício. A estimulação do nervo tibial posterior foi feita na fossa poplítea e a resposta muscular foi registada no solear. Ambas as ondas foram solicitadas a 30% da M_{max}.

Resultados: No geral, BFR não teve impacto quer na amplitude quer na latência de nenhuma onda. A diferença de latências entre as ondas M e H não foi afetada por qualquer condição (60 ou 80%) ($p > 0.05$). Obtemos resultados semelhantes para a interação entre BFR e LI BFR. Relativamente à amplitude das duas ondas onda-M/onda-H, BFR (quer 60 quer 80%) não teve qualquer efeito na alteração dos valores absolutos ou relativos desta variável específica com ou sem exercício ($p > 0.05$).

Conclusões: Realizar BFR a 60 ou 80% AOP, por um período ligeiramente superior a 5 minutos não tem um impacto negativo na função dos nervos periféricos (amplitude e latência do potencial evocado inalterados). Deste modo, apresentamos evidências preliminares de que a condução nervosa periférica não é alterada pela BFR durante as condições de repouso ou exercício. Assim sendo, de um ponto de vista neurológico, exercício LI BFR pode ser considerado um modo seguro de treino de força para a população geral.

Palavras-chave: KAATSU, restrição vascular, treino de força com restrição vascular, reflexo de Hoffmann, pressão de oclusão arterial, eletromiografia, solear, velocidade de condução nervosa, estimulação elétrica, nervo tibial.

I. Literature review

KAATSU

KAATSU (added pressure) is the designation commonly used to refer to a low intensity resistance training with blood flow restriction (LI BFR). This type of training began in Japan and its precursor was the Professor Yoshiaki Sato. After spending a considerable amount of time kneeling, with his back straight while attending a Buddhist memorial, Yoshiaki Sato felt his legs numb. Then, he also noticed that the calf area was larger than before and that the experienced discomfort was similar to the sensation felt after strenuous sets of calf-raise exercise. He attributed this swelling to venous pooling in the lower limbs (Sato, 2005). Subsequently, he tested several methods to induce BFR to the exercising limbs, and near 10 years later, after self-experimenting different types of BFR pressure, Yoshiaki Sato was able to design a safe and effective exercise prescription. Another 10 years later (1983), and after following up several hundred thousand students, who had completed a year of KAATSU training, the methods of this type of training were made available for public use (Sato, 2005).

The KAATSU approach focuses on inducing moderate restriction of arterial blood flow to the exercised segment and not on total vascular occlusion. As importantly, this technique seeks to evoke absolute venous restriction, thus eliciting a pool of venous blood in the segment targeted for training purposes.

Low-intensity blood flow restricted exercise training

LI BFR is an acronym commonly used to describe KAATSU training. Despite being prescribed at low relative intensities, this type of training aims at increasing muscle mass (i.e. muscle hypertrophy) and strength. Training for muscle hypertrophy is typically done using high intensity (HI) resistance training. This classic approach consists of performing 8-12 repetitions (reps) corresponding to 60-80% of one-repetition maximum (1RM), with novice trainees performing more reps at the lower end of this interval. Conversely, experienced exercisers generally perform less reps at the upper end of this training zone (Garber et al., 2011; Ratamess et al., 2009).

LI BFR resistance training induces similar hypertrophic gains as HI, but using considerably less load (Kim & Sherk, 2012; Vechin et al., 2015). Past research has shown that exercise intensities as low as 20% 1RM, performed at a frequency of 2-3 days per

week, are particularly effective for increasing muscle strength and size (Jeremy P. Loenneke, Wilson, Marín, Zourdos, & Bemben, 2012). This makes LI BFR very appealing to both athletes, recovering from injuries, and frail individuals (elderly), who might benefit from resistance training without the negative risks involved in HI (Hughes, Paton, Rosenblatt, Gissane, & Patterson, 2017).

LI BFR training can be adjusted by setting different combinations of: 1) volume (sets and reps), 2) relative intensity, 3) level of BFR pressure. Data on how to manipulate these three variables most effectively is widely available, but not always consistent.

Volume The most widely used training volume consists of 75 reps, divided along four sets (i.e. 30:15:15:15) (Christopher Roy Brandner, Warmington, & Kidgell, 2015; Colomer-Poveda, Romero-Arenas, Vera-Ibáñez, Viñuela-García, & Márquez, 2017; Fatela, Reis, Mendonca, Avela, & Mil-Homens, 2016; Martín-Hernández et al., 2013; Scott, Loenneke, Slattery, & Dascombe, 2015; Vanwye, Weatherholt, & Mikesky, 2017; Yasuda, Brechue, Fujita, Sato, & Abe, 2008; Yasuda, Loenneke, Thiebaud, & Abe, 2012). While the optimal protocol for LI BFR resistance training has not yet been firmly established, this repetition scheme has been demonstrated to aid in recovery from knee injury (Jeremy P. Loenneke, Young, Wilson, & Andersen, 2013). It has also proved effective for enhancing muscle activation, strength and size, without muscle damage (Wilson, Lowery, Joy, Loenneke, & Naimo, 2013).

Intensity As with volume, different intensities have been used in past reports. The range of intensities used in these studies range from a minimal of 15% of maximal voluntary contraction (MVC) (Kacin & Strazar, 2011), up to 80% of 1RM (Laurentino et al., 2008). There is compelling evidence that, when training with multiple sets, a load of 20% 1RM combined with continuous BFR (i.e. maintained during the inter-set rest periods) results in a metabolic stimulus similar to that seen following multiple sets of HI resistance exercise (Scott et al., 2015). Vanwye & colleagues, also recommend training at 20% 1RM because it has been shown that this intensity is particularly effective for improving muscle strength and size (Vanwye et al., 2017).

Level of BFR pressure, the available literature is particularly inconsistent for the level of BFR pressure used for training purposes. Given its importance within the context of LI BFR exercise, this topic will be more extensively described in the next subsection.

Blood Flow Restriction

There are four main approaches to BFR described in the existent literature. First, with a more practical approach, Lowery & colleagues designed a study in which the participants whore elastic straps in their limbs and BFR pressure was adjusted based on the perception of pain in a scale from 0-10. Exercise was performed at a pain intensity level of 6/7 (Lowery et al., 2014). Second, using an alternative approach, other authors prescribed an arbitrary value of pressure and all participants exercised at the same absolute intensity of restriction, independently of their limb circumference or blood pressure values (Shinohara, Kouzaki, Yoshihisa, & Fukunaga, 1997). The values chosen for inducing BFR varied between 100 (Yasuda et al., 2012) and 220 mmHg (Layne et al., 2017). Normally, lower values have been used when training the upper body, ranging from 100 to 160 mmHg (Takarada et al., 2000; Yasuda et al., 2008, 2012, 2011). Conversely, higher values, ranging from 110 to 220 mmHg, have been used when training the lower body (Layne et al., 2017; Martín-Hernández et al., 2013; Næss-Schmidt, Morthorst, Pedersen, Nielsen, & Stubbs, 2016; Takarada, Sato, & Ishii, 2002). Third, and more recently, some studies have focused on adjusting BFR to a percent value of the arterial occlusion pressure (AOP). In this method, a Doppler probe is placed over the radial or tibial artery (depending on training the upper or lower body, respectively) so that the pulsatile element can be acoustically traced. Then, the BFR pressure is progressively risen until the pulse is no longer audible. Afterwards, a percent value of AOP is prescribed for training (varying from 40 to 90% AOP) (Fatela et al., 2016; Scott et al., 2015; Sousa et al., 2017; Vanwye et al., 2017). Fourth, in another set of studies, BFR pressure was adjusted to systolic blood pressure (SBP) and/or limb circumference. BFR values used in these designs ranged from 80 to 130% of SBP (Christopher Roy Brandner et al., 2015; Suga et al., 2012; Yasuda et al., 2011). Absolute pressure values between 150 and 210 mmHg have also been used, depending on the thigh circumference of each participant (Colomer-Poveda et al., 2017).

The aim of BFR, within the context of LI resistance exercise, is to promote the accumulation of metabolites (e.g. lactate, H^+, prostaglandins). This metabolic accumulation increases serum growth hormone (GH) concentration, thus promoting collagen synthesis for tissue repair and recovery (Manini & Clark, 2009). A surge in GH also stimulates insulin-like growth factor-1 (IGF-1) production (Hawke & Garry, 2001),

a protein related with muscle growth that has powerful anabolic effects by enhancing satellite cell proliferation (Vanwye et al., 2017).

The restrictive pressure used during LI exercise must be applied to the most proximal area of the exercised segment. For safety reasons, the cuff should not be placed around the elbow or knee joints. The superficiality of the underlying nervous structures, with origin in brachial plex (superior limb) and of the sciatic or femoral nerve (inferior limb) implies, in the context of LI BFR exercise, a considerable risk towards neurapraxia or even mononeuropathy (nerve paralysis) (Mil-Homens, Correia, & Mendonça, 2015).

Safety and KAATSU exercise

LI BFR training allows the exerciser to train using lighter loads (less physical stress to the limbs), and have similar hypertrophic gains as high resistance exercise (Kim & Sherk, 2012; Vechin et al., 2015). Nevertheless, the increased pressure applied to the exercising limb might exert negative effects in the circulatory, musculoskeletal and nervous system. The following paragraphs describe how each can be affected by BFR training.

Vascular congestion and distension, following LI BFR exercise, could potentially damage or impair the functioning of venous valves due to the additional blood pooling. Patterson and Ferguson reported that, after 4 weeks of plantar flexion exercise with BFR, the participants enhanced their PO_{bf} (blood flow changes post- exercise) compared to the resistance training without BFR (Patterson & Ferguson, 2010). Takano and colleagues, revealed that while total peripheral resistance was not affected, systolic volume decreased during KAATSU exercise due to the inhibition of venous return (i.e. lower cardiac preload) (Takano et al., 2005).

Muscle damage symptomatology (i.e. delayed onset muscle soreness - DOMS) is particularly exacerbated during post-exercise recovery. There is compelling evidence that the extent of muscle damage varies as a function of the load lifted during each exercise session (Warren, Lowe, & Armstrong, 1999). Brandner and Warmington reported that DOMS was significantly greater and persistent post- LI BFR exercise (either continuous or intermittent protocol) than after HI or LI exercise without BFR (Christopher R. Brandner & Warmington, 2017). In another study, comparing DOMS from two legs that endured the same exercise paradigm (knee extension task) both with and without BFR, it

was found that the BFR-exercised leg exhibited an increased sensitivity to pressure and a loss of muscle strength 24-h post-exercise of 14%. In contrast, the control leg (non-BFR LI) was minimally affected (Umbel et al., 2009). Finally, Nakajima et al. (2006) completed a health survey on 105 facilities using LI BFR training. Numbness was found to be occasionally reported by some users during training. Nevertheless, it should be emphasized that numbness was reported only in 1.6% of 30000 exercise sessions. Irrespectively, due to its possible relationship with nerve damage, all these findings raised questions about an eventual negative impact of BFR exercise on nerve conduction (Nakajima et al., 2006).

KAATSU and Nerve Conduction

To induce BFR, a pneumatic cuff is paced around the exercised segment. BFR should be performed at a level compatible with venous outflow blockade. It is possible that the compression applied to the limb is enough to affect the nervous structures, thus altering their function (Hofmeijer et al. 2013; Uttal, 1967). In previous studies, it was found that slight pressures (50 mm Hg) applied for 30 min decreased the nervous conduction velocity (NCV) to about 95% of pre-BFR values, and if maintained it could diminish to about 70% after 2 hours (Rydevik & Nordborg, 1980). Another study revealed that at 200 mm Hg both amplitude and velocity of fast component nerve fibers completely abolished after ~ 23 min of BFR and did not recover soon after pressure release (Dahlin, Shyu, Danielsen, & Andersson, 1989). Both studies were performed in animals, where the nerve was isolated and directly compressed; which is not the case with BFR exercise. Conversely, previous research, focusing on effects of compression and devascularization on nerve function, also showed that compressing a monkey's limb with a pneumatic cuff at 250 mm Hg for 25 min did not alter nerve conduction velocity or amplitude (Ogata, Shimon, Owen, & Manske, 1991). In humans, there is available data showing that peripheral sensory axons are more vulnerable to ischemia than motor axons, with faster inexcitability during ischemia. Moreover, it was shown that, while the amplitude of compound motor and sensitive action potentials only decreased significantly after 10-20 min of ischemia, this was not the case for nerve conduction latencies (immediately affected post-5-10 min of ischemia) (Hofmeijer et al. 2013). These data are well supported by one other report showing that the latency of action potential is particularly sensitive to the impact of ischemia (more than its amplitude) (Uttal, 1967). Finally, Clark et al. investigated the general integrity of the sensory-motor nerves conduction by measuring

the H-reflex response latency. The latency of the H reflex did not change after 4 weeks of low intensity resistance training (30% 1RM) with blood flow restriction (130% systolic blood pressure) (Clark et al., 2011).

H-Reflex

The H reflex is an estimate of alpha motoneuron (αMN) excitability and can be used to assess the response of the nervous system to various neurologic conditions (Palmieri, Ingersoll, & Hoffman, 2004). Described by Paul Hoffmann in 1910 and later given his name, the H reflex is an electrically induced reflex, very similar to the myotatic reflex (Hoffmann, 1910). The main differences between both lays on the triggering of the reflex mechanism. The H reflex is elicited via electrostimulation of a peripheral nerve that activates afferent Ia pathway all the way up to the spinal cord (Burke, 2016; Palmieri et al., 2004; Scaglioni et al., 2002; Schimsheimer, Ongerboer de Visser, Kemp, & Bour, 1987). In contrast, the myotatic reflex follows the same neural circuits as the H reflex, however, the stimulus is originated at the muscle level, due to the stretching of the intrafusal muscle spindle fibers (Palmieri et al., 2004).

The oligosynaptic nature of the H reflex makes it an appealing tool for research and clinical neurophysiology. Amplitude changes in the reflex can be explained by at least three possibilities: 1) alteration in the excitability of the motoneurons; 2) variation in the amount of neurotransmitter released by the afferent terminals; 3) variation in the intrinsic properties of the motoneurons (Misiaszek, 2003). The following paragraphs will briefly describe each possibility.

Alterations in the excitability of the motoneuron: The activity level of the muscles can be monitored through surface EMG recordings and estimates its motoneuron pool activation (Zehr, 2002). Increasing the pool of motoneurons available will enable the recruitment of additional αMN, thus eliciting greater H-reflex amplitudes.

Variation in the amount of neurotransmitter released by the afferent terminals: The main factors responsible for this variation are the presynaptic inhibition of the Ia afferents and the post-activation depression. The first can be affected by a series of direct and indirect factors such as supraspinal sources, limb motion and heteronymous afferent activation, affecting transmission in H-reflex arc (Rudomin & Schmidt, 1999). The second deals with frequency-related control of neurotransmitter release, any previous

activation of the Ia afferent can lead to reduction of neurotransmitter availability in the Ia afferent terminals, increases in the frequency of activation can lead to insufficient replenishment of neurotransmitter stores, resulting in post-activation depression and a decrease in the H-reflex amplitude (Hultborn et al., 1996).

Variation in the intrinsic properties of the motoneurons: Disorders disrupting the descending activity such as spinal trauma, athletic training or operant conditions have been proved to produce changes in motoneuron firing threshold and axonal conduction velocity, and in synaptic terminals on motoneurons (Wolpaw & Tennissen, 2001). These changes are associated with functional and structural plasticity in the spinal cord.

When the tibial nerve is stimulated percutaneously by a short-lasting low-intensity electrical current, action potentials are elicited only in the axons of the sensory Ia afferents due to their larger axon caliber. The evoked action potentials spread to the spinal cord, where they originate excitatory postsynaptic potentials, then eliciting action potentials, which travel in the αMN axons toward the muscle. Subsequently, with a latency of 30–40 ms, the volley of efferent action potentials is recorded in the muscle as an H-reflex. Increasing the stimulus intensity will cause action potentials to occur also in the thinner axons of the αMN, traveling to the muscle as a direct motor response (M wave). At the same time, action potentials propagate antidromically in the αMN axons toward the spinal cord to collide with action potentials of the evoked reflex response, resulting in a partial cancellation of the reflex response. In consequence, the M wave directly increases with the stimulus intensity while at the same time the H-reflex amplitude gradually decreases due to the increase in antidromic collision. At a given stimulus intensity, an elevated H-reflex response will indicate the excitability of α-motoneurons to have increased (and/or presynaptic inhibition to have decreased). At very high (i.e., supramaximal) stimulus intensity, orthodromic and antidromic action potentials will occur in all motoneuron axons, the former giving rise to a maximal M-wave (M_{max}), whereas the latter cause a complete cancellation of the H-reflex volley due to antidromic collision occurring in all axon fibers (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002).

The latency of the H-reflex represents the time needed to the conduction through the axon of Ia sensory afferent from the stimulus point (popliteal fossae) to the spinal cord, synaptic delay at the motoneuron and conduction through efferent motor nerve to the EMG recording site (Clark et al., 2011). The M-wave latency represents the time

needed for the peripheric nervous conduction from the stimulus point through the motor axon ramifications and through the neuromuscular junction (Clark, Cook, & Ploutz-Snyder, 2007). When taken together, these two latencies represent a global index of neuromuscular action potential conduction velocity that is sensitive in detecting marginal changes in both sensory and motor conduction (Scaglioni et al., 2002; Troni, Cantello, & Rainero, 1983)

Nerve Conduction Velocity

Nerve conduction velocity (NCV) can be used in clinical neurophysiology to monitor peripheral nerve function (Troni et al., 1983). As it is well known, NCV is altered by fiber diameter (Waxman, 1980) and myelin sheath thickness (Pasquale et al., 2015; Seidl, 2014; Waxman, 1980). The internode distance (distance between nodes of Ranvier) also influences the NCV, although the relationship has a fairly broad maximum (Simpson et al., 2013; Wu, Williams, Delaney, Sherman, & Brophy, 2012).

The NCV is measured accordingly to the type of nerve fiber studied. Therefore, the literature displays values for sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity (MNCV) (Palve & Palve, 2018). The most widely used method for measuring MNCV implicates the determination of the compound muscle action potential (CMAP) (M-wave) latency (Herrera, Sandoval, Camargo, & Salvini, 2010; Hodes, Larrabee, & German, 1948; Ikeda & Oka, 2012; Lori et al., 2018; Pasquale et al., 2015; Vasconcelos, Escoda, Vasconcellos, & Neves, 2003; Vecchierini-Blineau & Guiheneuc, 1979). To do this, a proximal and a distal stimulation must be performed (in the inferior limb it is common to use the sciatic nerve at the hip and the tibial nerve at the ankle). Then, the distance between cathode sites is divided by the difference in M-wave latency to determine the MNCV (Higashimori, Whetzel, Mahmood, & Carlsen, 2005).

To measure SNCV, two methods are generally available in the literature: 1) H-reflex latency or 2) the sensory nerve action potential (SNAP). The H-reflex can be used as the CMAP, with the SNCV representing the distance between cathodes divided by the difference in H-reflex latency (Higashimori et al., 2005; Vecchierini-Blineau & Guiheneuc, 1979). The SNAP is the sum of action potentials from individual sensory nerve fibers (Crone & Krarup, 2013). The maximal SNCV is obtained from the latency between the site of stimulation and the site of recording (distal SNCV) (Krarup, 2004). At more proximal sites SNCV is measured from conduction times between recording sites

at orthodromic conduction; if antidromic conduction is recorded, conduction times and SNCV are obtained between stimulation sites similar to MNCV (Lori et al., 2018; Palve & Palve, 2018).

Troni & colleagues proposed a mixed index of sensorimotor conduction velocity using the H wave pathway (Troni et al., 1983). The velocity was calculated by: twice the distance from the stimulus point to the processus spinosus of the 11^{th} thoracic vertebra divided by the difference between the M and H latencies. To account for the central synaptic delay 1 ms was subtracted from the denominator.

Tanenbaum and Jabre, developed another approach to measuring NCV - the F-wave (Tanenbaum & Jabre, 1991). The F-wave is a late latency resultant of a antidromic activation of one or small number of motoneurons following peripheral nerve electrical stimulation (Ohgaki et al., 1998; Panayiotopoulos & Chroni, 1996; Tanenbaum & Jabre, 1991). In this study, the authors described a simple method to calculate a wave conduction velocity using F-wave latency and limb length. Demonstrating that it was a valid estimate of MNCV.

II. Purpose and Goals

This study aimed at exploring whether BFR alters the latencies and amplitudes of M and H wave measured taken at the level of the restricted limb. It also sought to determine if the impact of BFR on NCV might depend on the magnitude of BFR (BFR: 60 vs. 80% AOP). Additionally, we tested if the impact of BFR on NCV might be further aggravated in the context of LI exercise (NCV in response to BFR with vs. without LI exercise). Lastly, we intended to disclose whether such effect might be reversed during post-BFR recovery. Three hypotheses were drawn:

1. BFR at 80% AOP would have a greater impact in the amplitude and latency comparing to the BFR at 60%;
2. LI BFR exercise would also have a greater impact in the amplitude and latency comparing to BFR alone;
3. Time needed to recover would vary as a function of BFR (80% > 60%) and the presence of low intensity exercise (LI BFR exercise > BFR alone).

III. Methods

Participants

A total of 13 healthy young male participants (age: 22.0 ± 1.7 years, height: 175.2 ± 3.9 cm, body mass: 68.4 ± 5.4 kg and body mass index: 22.3 ± 1.5 kg/m^2) with normal blood pressure (systolic and diastolic values repeatedly < 122/68 mmHg) were included in this study. Participants were recruited via word-to-mouth from the Faculty of Human Kinetics and surroundings. Each participant was instructed to visit the laboratory on two different occasions (within 1 week), each lasting ~ 150 min. The risks of participation were carefully explained to every participant and written informed consent was obtained before testing. This study complied with the principles set forth in the Declaration of Helsinki and was approved by the Faculty's Ethics Committee (CEFMH Nº 4/2017). In the first visit, the effects of BFR and LI BFR at 60% AOP were tested unilaterally in the lower limb. During the second visit, the contralateral lower limb was tested at 80% of AOP with and without exercise (randomized lower limb selection).

Inclusion Criteria

1) Healthy status (obtained through a medical questionnaire). Participants that reported any symptom, disease or active medication were excluded at this stage.
2) Male sex, to avoid possible changes in the nerve velocity conduction due to the female menstrual cycle.
3) Age between 18 and 30 years old.
4) Participants showing a normal response to the peripheral stimulation of the tibial nerve (M wave preceding the H-reflex; gradual increase in the H-reflex amplitude following an increase in stimulus intensity and after reaching maximus, a reduction of the same followed by appearance of the M wave) and without muscle tremor.

Sample Size

The sample size was calculated from a pilot study with 6 participants, in which nerve conduction velocity was compared between baseline and LI BFR at 80% of AOP. This pilot study was conducted using the same experimental approach as described below. G*Power software (Version 3.1, Dusseldorf University, Germany) was used to determine

the sample size compatible 95% power of correctly rejecting the null hypothesis (13 participants).

Experimental Protocol – Procedures

In the first visit, after arriving to the laboratory, each participant provided informed consent for participation via written signature. Then, they filled a physical activity questionnaire to characterize the participants' levels of physical fitness at study entry. Finally, each participant also filled a medical questionnaire to discriminate medical conditions, active medication, past injury and life habits that might affect the outcome of this study. Then, blood pressure measurements were taken more than once and weight as well as height were taken.

Participants preparation

The soleus muscle EMG activity was recorded. The EMG electrode was placed in the posterior part of the medial posterior face of the leg. Lengthwise, it was placed in the zone comprised between the third quarter and the last third of the tibia length (66- 75%), following a proximal to distal direction (Botter & Vieira, 2017; Rainoldi, Melchiorri, & Caruso, 2004). The hair was removed and the skin was abraded with a sterile swab and alcohol to remove the skin corneal layer. Then, the electrodes were placed parallel to the muscle fiber orientation. Electrode placement was satisfactory whenever the baseline EMG peak-to-peak amplitude was < 30 μV. If such condition was not met, the skin was again abraded and the site of recording was altered. A ground electrode was placed around the right ankle.

The surface EMG recordings were performed using EMG differential sensors (DE – 2.1, Delsys, Inc.). The EMG signal was collected at a sample rate of 1000 Hz, using a Delsys Bagnoli-8 Amplifier. Mr. Finally, Kick III software (Knud Larsen, SMI, Aalborg University) was used for data collection and analyses of both EMG signal and torque.

Baseline data collection

After preparing the participants for EMG data collection, they sat on the chair of a Biodex dinamometer (Biodex System, Biodex Medical Systems, Shirley, NY). They remained seated throughout the entire duration of the experiments. They were also asked to wear a pneumatic cuff (SC12L Tourniquet cuff, D.E. Hokanson, Inc., Bellevue, WA)

in the upper thigh. As recommended in past research, we used a wide cuff for BFR induction (12 x 124 cm) (Jeremy P. Loenneke, Fahs, et al., 2012). Once sat, the angle of the foot pedal and the position of the chair were carefully adjusted to an angle of 120º at the knee joint and 110º at the ankle joint (Vila-Cha, Falla, Correia, & Farina, 2012). The foot plate was adjusted, making sure that the lateral malleolus was aligned with the motor axis of the dynamometer. Subsequently, AOP was tested twice (2 min of pause between measurements). AOP was taken with a fetal probe Doppler (ULTPD1CV8) that was placed on the tibial artery to determine the cuff pressure compatible with total vascular occlusion (E20 Rapid Cuff Inflator, D.E. Hokanson, Inc. Bellevue, WA). AOP was measured exactly in the same position as used for exercise to ensure that the pressure values were maintained throughout the experiments; therefore allowing a better control of the physiological effects of BFR (Sieljacks, Knudsen, Wernbom, & Vissing, 2018).

Once AOP was determined, the participants were strapped to the chair of the Biodex and warmed-up while performing 20 plantar flexions with a gradual increased in torque applied to the foot plate. The participants were instructed to perform the last two repetitions as hard and fast as possible. Then, after resting, the participants were instructed to perform 3 maximal voluntary contractions (MVC) as fast and hard as possible for four seconds. One minute of rest was given between each MVC to allow recovery between repetitions.

The posterior tibial nerve was stimulated with a constant-current an isolated stimulator (STIMSOLA, Biopac Systems, Inc., CA, US). The self-adhesive cathode (8 mm diameter, Ag-AgCl) was placed on the popliteal fossa and the anode (5 x 10 Compex, Medical SA) was placed proximal to the patella. Each participant was initially familiarized with a range of electrical stimuli (1-40 mA) over a period of ~ 5 min. Before defining the final placement of the cathode electrode, the optimal position was identified using a handheld cathode ball electrode (0.5-cm diameter). Once the position eliciting the greatest response with the minimum stimulus intensity was determined, the stimulation electrode was firmly fixed to this site with rigid straps and taping.

The motor response (M-wave) was elicited while each participant maintained a low-level tonic contraction of the plantar flexors (10 % MVC). Participants were provided with online visual feedback of the torque exerted, which was displayed on a computer monitor. Testing procedures and recordings started by progressively increasing the

current intensity by 5 mA (STIMSOLA, Biopac Systems, Inc., CA) from 0 until there was no further increase in peak twitch torque, nor in concomitant peak-to-peak M-wave amplitudes. Three stimuli were delivered at each intensity level at 3-s intervals. Then, at each current intensity, the preceding M-wave peak-to-peak amplitude was compared with the new M-wave peak-to-peak amplitude. Once the preceding and new M-wave peak-to-peak amplitude reached a plateau over the three stimulations, the current intensity of the previous stimulation was defined as the maximum current intensity.

Nerve conduction velocity

For H-reflex measurements, most authors recommend a stimulation intensity between 10-20% (Palmieri et al., 2004; Zehr, 2002) of M_{max}. Intensities of greater magnitude may be compatible with antidromic collision and cancelation of the evoked reflex response; thus affecting H-reflex amplitude. Based on our pilot study, we found that such intensities produce an unclear M-wave. Moreover, we determined that 30% M_{max} was the lowest intensity that allowed a clear determination of both H-reflex and M-wave latencies. Data collection can be schemed as following:

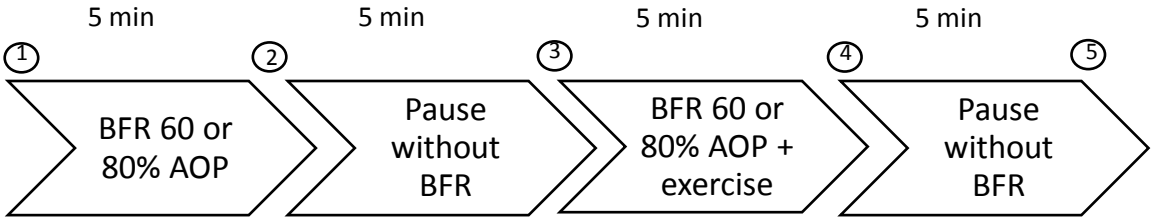

Figure 1. Study schematic representation. Circled numbers represent evaluations of NCV. Arrows (left to right) represent periods of: blood flow restriction (BFR) at 60 or 80% AOP (arterial occlusion pressure), rest, BFR at 60 or 80% AOP and exercise, rest.

The circles represent evaluations (16 stimuli) of the H-reflex and M-wave obtained at 30% of M_{max} peak-to-peak amplitude. Each participant sustained a continuous plantar flexion during the entire duration of data collection (10% of the MVC). This was done to avoid the onset of post-activation depression (Burke, 2016). In the 1st, 3rd and 5th time points, the stimulation was performed without BFR. Conversely, in the 2nd and 4th time points, stimulation was done with BFR. Briefly, the experimental procedure included two distinct studies: (1) exploring the effects of BFR per se on the NCV (time points #1 to 3) and (2) exploring the effects of LI BFR on the NVC (time points #3 to 5).

Additionally, for each experimental condition (BFR with and without exercise), we also designed a pre-condition time point (baseline - without BFR) and a post-condition time point (post - without BFR). This was done to test whether the effects of BFR (with and without exercise) on NVC might be reversed towards baseline with reperfusion of the lower limb.

LI BFR was performed at the 3rd time point depicted in figure 1. It corresponded to the most commonly used LI BFR exercise protocol: 75 reps, divided along four sets (30:15:15:15), with 30 seconds of rest between sets (Christopher Roy Brandner et al., 2015; Colomer-Poveda et al., 2017; Fatela et al., 2016; Martín-Hernández et al., 2013; Scott et al., 2015; Vanwye et al., 2017; Yasuda et al., 2008, 2012). As the participants exercised isometrically, each duty cycle corresponded to 2 s of contraction (20% of the MVC) and 1 s of relaxation. To monitor these timings, a metronome was used with different audio signals to inform the participant when to produce force and when to stop. Taken together, exercise was performed by each participant for a total of 5 min. Per session, the participants experienced a total of 12 min with BFR.

In this study, BFR was set to 60 and 80% AOP. Generally, LI BFR is performed at 40% to 90% AOP (Vanwye et al., 2017). Each testing session was preceded by a structured protocol designed to expose the exercising limb to the desired level of BFR on a progressive fashion. Thus, before inflating the pneumatic cuff to the target pressure, an adaptive cycle of cuff inflation/deflation was performed, with inflations of 30 s and deflations of 10 s executed gradually at 25, 50, and 75% of each target point.

Data Analysis

NVC was set as the primary dependent variable. We therefore explored changes in its values resulting from two levels of BFR with and without exercise. NVC was estimated using the difference between the latency (in ms) of the H-reflex and M-wave. The beginning of each wave was determined as described in past research (Burke, 2016). Briefly, the latency of each waveform was taken as the time for the onset of the first deflection from baseline post-stimulation of the tibial nerve within the popliteal fossa (figure 2). All 16 sweeps (1/stimulus) obtained per time point were visually analyzed and selected or excluded.

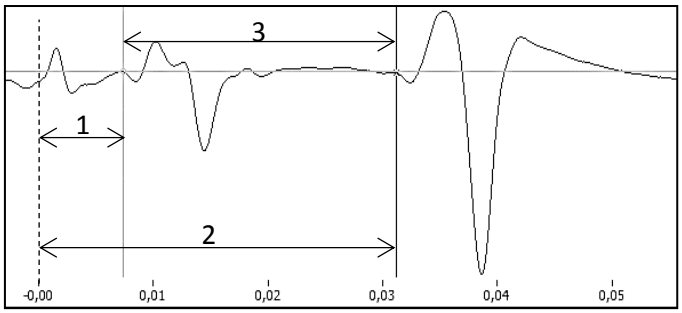

Figure 2. Representative example of the soleus M wave and H reflex. ***Legend****: dashed line – onset stimulus; gray line – M-wave beginning; black line – H-reflex beginning; 1- M-wave latency; 2- H-reflex latency; 3- latency difference.*

Afterwards, the mean latency and standard deviation obtained for each time point was calculated and the sweeps containing a variation greater than 2 standard deviations were eliminated. Then, the new mean for the remaining sweeps was defined as the reference value for that specific time points. Additionally, we also computed the M- and H-wave peak-to-peak amplitude at all time points.

Statistical Analysis

All data were tested for normality and homoscedasticity with the Kolmogorov–Smirnov and Levene's test, respectively. Standard descriptive statistics were used to summarize the data. A two-way analysis of variance with repeated measures was computed to test for the effect of condition (60 vs. 80% BFR) and time (pre-BFR vs. BFR vs. post-BFR) and condition-by-time interaction. This analysis was repeated for the experiments involving LI exercise. Post hoc t tests, with Bonferroni's adjustment, were used for all repeated measures analyses when significant effects were detected. All statistical analysis were computed using SPSS (version 24.0, SPSS Inc., Chicago, IL) and significance was set at $p < 0.05$. All data are reported as means ± SD, unless otherwise specified.

IV. Results

Table 1 compares the absolute and M_{max} normalized values of peak-to-peak amplitudes for the M- and H-wave before, during and after BFR, at 60 and 80% AOP, with and without LI exercise. BFR (either 60 or 80%) had no effect on changing the amplitude of both waveforms M-wave/H-wave (condition main effect, F=0.163/0.106; time main effect, F=1.032/1.097; interaction main effect, F=0.009/0.026; p>0.05). For LI BFR (either 60 or 80%) the same was seen, without any effect on changing the amplitude of both waveforms (condition main effect, F=0.002/0.354; time main effect, F=0.425/0.303; interaction main effect, F=0.224/0.166; p>0.05).

Table 1. Peak-to-peak amplitude (mV) and normalization to M_{max} (%) before, during and after different levels of blood flow restriction (BFR) with and without low-intensity (LI) exercise.

		No-exercise		
		Pre-BFR	BFR	Post-BFR
60%	Amp M	1.7 ± 0.9	2.1 ± 1.7	1.9 ± 1.1
	Amp M norm.	36.8 ± 18.8	43.8 ± 30.2	43.0 ± 17.2
	Amp H	2.2 ± 1.1	1.9 ± 1.1	2.0 ± 1.1
	Amp H norm.	46.5 ± 20.2	43.2 ± 19.0	43.0 ± 17.2
80%	Amp M	1.8 ± 0.9	2.2 ± 2.4	2.1 ± 1.2
	Amp M norm.	31.9 ± 6.1	38.9 ± 28.8	37.1 ± 15.8
	Amp H	2.3 ± 1.5	2.0 ± 1.4	2.1 ± 1.2
	Amp H norm.	44.8 ± 21.7	40.3 ± 25.8	42.5 ± 21.5
		LI exercise		
		Pre-BFR	BFR	Post-BFR
60%	Amp M	1.9 ± 1.1	1.7 ± 1.4	2.0 ± 1.2
	Amp M norm.	43.0 ± 17.2	37.7 ± 28.4	41.0 ± 19.1
	Amp H	2.0 ± 1.1	2.0 ± 1.4	1.9 ± 0.9
	Amp H norm.	43.0 ± 17.2	44.3 ± 21.6	42.2 ± 17.6
80%	Amp M	2.1 ± 1.2	1.7 ± 1.8	1.8 ± 1.3
	Amp M norm.	37.1 ± 15.8	28.7 ± 22.4	30.3 ± 12.5
	Amp H	2.1 ± 1.2	2.4 ± 1.6	2.2 ± 1.3
	Amp H norm.	42.5 ± 21.5	44.3 ± 19.2	43.0 ± 19.2

Values are mean ± SD

Abbreviations: Amp M, M-wave peak-to-peak amplitude; Amp H, H-reflex peak-to-peak amplitude; norm, normalization to the M_{max}; BFR, blood flow restriction; LI, low intensity.

Table 2 compares the latencies of the M- and H-wave before, during and after BFR, at 60 and 80% AOP, with and without LI exercise. As can be seen, BFR (either 60 or 80%) had no effect on changing the latency of either waveform. More importantly, the difference between the M- and H-latency (Lat Diff) was also unaffected by each condition

over time (condition main effect: F=0.116; time main effect: F=1.748; interaction main effect: F=0.004; $p > 0.05$). Finally, as can be seen, these results were transversal to both exercise and non-exercise experiments. For LI BFR (condition main effect: F=0.004; time main effect: F=0.159; interaction main effect: F=0.288; $p > 0.05$).

Table 2. Time (ms) before, during and after different levels of blood flow restriction (BFR) with and without low-intensity (LI) exercise.

		No-exercise		
		Pre-BFR	BFR	Post-BFR
60%	Lat M	7.0 ± 1.0	7.1 ± 0.7	7.2 ± 1.0
	Lat H	31.4 ± 1.8	31.7 ± 1.7	31.8 ± 1.8
	Lat Diff	24.3 ± 1.4	24.6 ± 1.4	24.6 ± 1.4
80%	Lat M	7.5 ± 1.3	7.9 ± 1.4	7.6 ± 1.2
	Lat H	32.1 ± 1.5	32.7 ± 1.7	32.4 ± 1.5
	Lat Diff	24.5 ± 1.5	24.8 ± 1.1	24.8 ± 1.5
		LI exercise		
		Pre-BFR	BFR	Post-BFR
60%	Lat M	7.2 ± 1.0	7.3 ± 1.2	7.2 ± 0.8
	Lat H	31.8 ± 1.8	31.9 ± 1.8	31.8 ± 1.8
	Lat Diff	24.6 ± 1.4	24.6 ± 1.4	24.7 ± 1.5
80%	Lat M	7.2 ± 0.8	8.1 ± 1.2	7.8 ± 1.1
	Lat H	31.8 ± 1.8	32.7 ± 1.6	32.5 ± 1.6
	Lat Diff	24.7 ± 1.5	24.6 ± 1.5	24.7 ± 1.6

Values are mean ± SD**.**

Abbreviations: Lat M, M-wave latency; Lat H, H-reflex latency; Lat Diff, latency difference; BFR, blood flow restriction; LI, low intensity.

Figure 3 displays the percent change in Lat Diff from pre-BFR to BFR and post-BFR at resting conditions. Similarly, the percent change in Lat Diff between these specific time points is also depicted in figure 4 for the experiments involving LI exercise. White and dark bars represent BFR performed at 60 and 80% AOP, respectively. As can be seen, the influence of BFR (with and without exercise) on changing Latt Diff from resting values was virtually absent (< 1.5%).

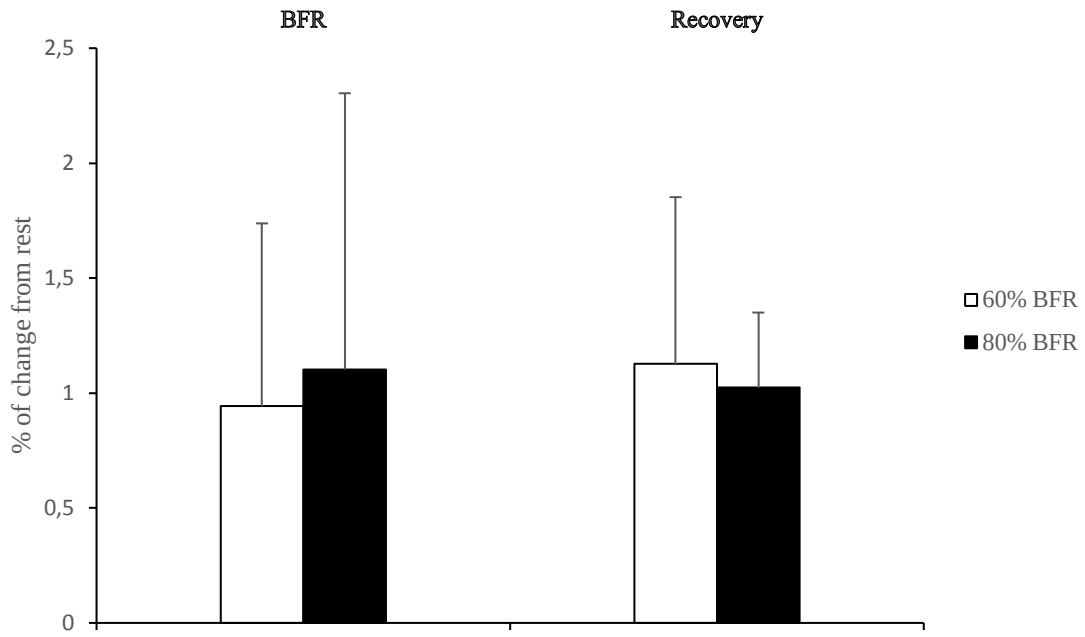

Figure 3. Percentage of latency difference from rest, no exercise condition

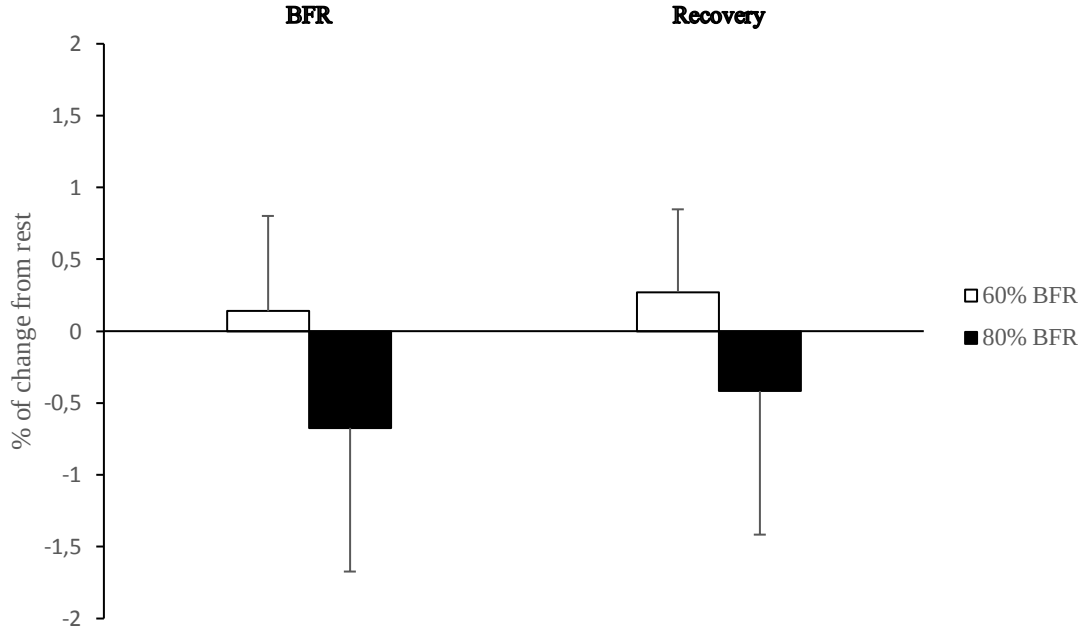

Figure 4. Percentage of latency difference from rest, low intensity exercise condition

Figures 5 and 6 are representative traces of EMG activity obtained in one participant in both conditions, at each time point. While figure 5 exhibits the impact of BFR on the latencies of each waveform in non-exercising conditions, figure 6 depicts the

influence of LIBFR exercise. As can be seen, the latencies of each waveform remain largely unchanged between time points and conditions.

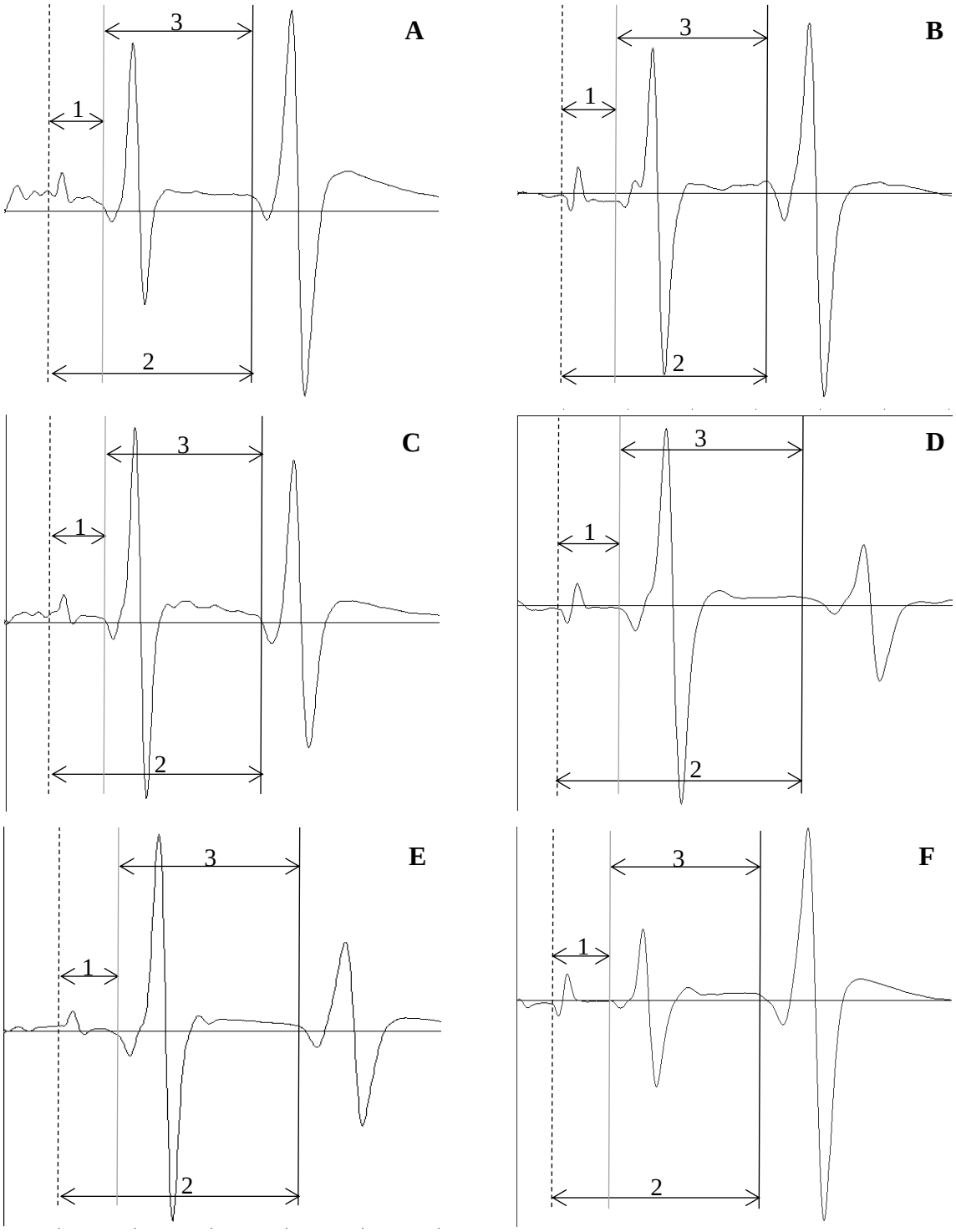

Figure 5. Soleus muscle M- and H-wave latencies obtained at different time points and levels of blood flow restriction (BFR) in one representative participant. ***Legend****: A – Pre-60% BFR; B – Pre-80% BFR; C - During 60% BFR; D – During 80% BFR; E – Post 60% BFR; F – Post 80% BFR. dashed line – onset stimulus; gray line – M-wave beginning; black line – H-reflex beginning; 1- M-wave latency; 2- H-wave latency; 3- difference between latencies.*

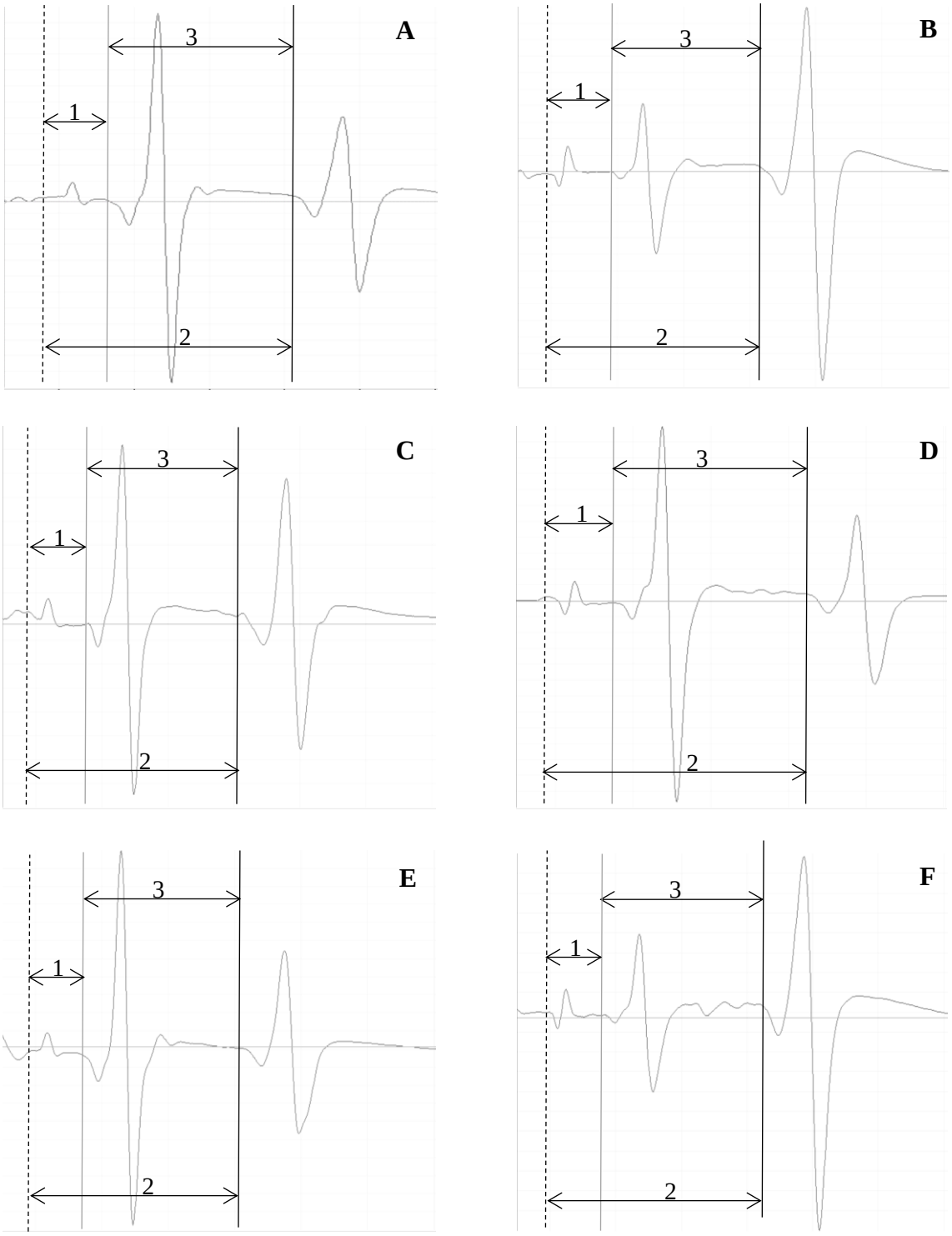

Figure 6 Soleus muscle M- and H-wave latencies obtained at different time points and levels of blood flow restriction (BFR) with low intensity exercise in one representative participant. ***Legend****: A – Pre-60% LI BFR; B – Pre-80% LI BFR; C - During 60% LI BFR; D – During 80% LI BFR; E – Post 60% LI BFR; F – Post 80% LI BFR. dashed line – onset stimulus; gray line – M-wave onset; black line – H-wave onset; 1- M-wave latency; 2- H-reflex latency; 3- difference between latencies.*

V. Discussion

The main purpose of this study was to explore whether the pressure exerted by the pneumatic cuff during BFR, at 60 and 80% AOP might exert a negative impact on NCV. This is important because past reports indicate the occasional occurrence of numbness in the extremities within the context of LIBFR exercise (Christopher R Brandner, May, Clarkson, & Warmington, 2018; Nakajima et al., 2006; Patterson, Brandner, & Patterson, 2018) and this may be secondary to peripheral nerve damage or ischemia (Lundborg, Gelberman, Minteer-Convery, Lee, & Hargens, 1982). The effects of BFR, with and without exercise, on NCV were determined using the Latdiff between the M-wave and the H-reflex, a mixed sensoriomotor index of conduction velocity in the entire length of the monosynaptic circuit. Our findings indicate that BFR has no effects on changing the amplitude nor latency of either waveform (H- and M-wave). Importantly, this was sustained for BFR elicited at 60 as well as 80% AOP and was unaffected by exercise conditions. Thus, our findings indicate that, when performed at a level < AOP, BFR pressure does not heighten the risk of nerve damage, either at rest or exercising conditions. It is likely that, under these conditions (submaximal pressure, applied to the thigh, avoiding zones of superficial nerves), cuff pressure is innocuous to the integrity of the sciatic nerve because tissue ischemia is effectively prevented.

Data from previous research demonstrate that pressure applied to a peripheral nerve decreases the amplitude and increases the latency of both the H- and M-wave (Dahlin et al., 1989; Hofmeijer, Franssen, Schelven, & Putten, 2013; Ogata et al., 1991; Pedowitz et al., 1992; Uttal, 1967)). However, in these experiments the pressure was directly applied to the previously isolated nerve and in some cases with pressure far above the ones we used in the limb (Dahlin et al., 1989; Ogata et al., 1991). Interestingly, the same effect has been shown in patients with polyneuropathy (a pathological condition compatible with nerve damage) (Panayiotopoulos & Lagos, 1980; Schimsheimer et al., 1987) and following peripheral nerve block induced by lidocaine and ketamine (Buffernoir et al. 2013).

The work of Nakajima et al. (Nakajima et al., 2006) reports a very low frequency of incidents (incidence of numbness < 2%). Furthermore, these symptoms tended to be experienced in cases of excessive cuff pressure, BFR time and inadequate cuff wideness. Accordingly to our data, from a neurologic standpoint, LI BFR exercise may be practiced

safely as long as the following conditions are respected: 1) 4 sets (30:15:15:15 reps) with 30 s of rest between sets; 2) individualized BFR pressure prescribed at 60 or 80% AOP value and 3) cuff with appropriate wideness in relation with limb circumference.

Despite focusing on an acute exercise paradigm, our results are consonant with those of past research showing that 4 weeks of BFR training do not affect H-wave latency of the trained limb (Clark et al., 2011). A different outcome was hypothesized because our assessments of nerve conduction were done while the leg of each participant remained subjugated to the effects of BFR. Instead of using H wave latency per se to estimate NCV as was done in that study, we use the difference between H and M latencies. Using the time difference between the latency of these waveforms, instead of the simple H latency has been, is more advantageous for comparisons of NCV between different conditions and times. Accordingly, this ensures that random H-latency changes, as seen in serial determinations in the same participant, are corrected by similar M latency variations (Troni et al. 1983).

Recent research, concerning the effects of 4 weeks of LI BFR training on the amplitude of the Soleus H reflex, also demonstrated no chronic impact of this regimen on affecting the maximal amplitude of either the H or M-wave (Colomer-Poveda et al., 2017). Again, based on our findings, we provide preliminary evidence that the amplitude of action potentials generated post-stimulation of the tibial nerve were not affected by BFR with or without acute LI exercise. This is relevant because it discards the possibility of BFR raising the risk of neuroapraxia as contended in past research (J. P. Loenneke, Wilson, Wilson, Pujol, & Bemben, 2011).

In conclusion, our data indicate that performing LI exercise with BFR set at 60 or 80% AOP does not exert a negative impact on peripheral nerve function (unchanged amplitude and latency of evoked potentials). Thus, we believe that, from a neurological standpoint, LI BFR exercise may be regarded as a safe mode of resistance training within the general population.

Limitations

Our study has two important limitations. First, the intensity selected to induce an H-reflex corresponding to 20% of the M_{max} was not compatible with a clearly defined M wave and this, in some cases, added some difficulties in determine the onset of this waveform. However, it should be mentioned that, when eliciting an H-reflex, a stimulus intensity > 20% of M_{max} should be avoided (Palmieri et al., 2004; Zehr, 2002). As it is well known, at intensities > 20% M_{max}, there is higher probability of antidromic collision. This reduces the reflex amplitude and could possibly affect its latency. Second, the period of data collection was too long, with the participants enduring almost one hour in the seated and immobilized position. Such factor induced high grades of individual discomfort.

VI. Conclusions

We can conclude that, performing BFR at 60 and 80% AOP, for a period slightly > 5 min does not increase the latency difference between the H-reflex and the M-wave. This means that NCV is not altered by BFR during resting or exercise conditions. Thus, data indicate that peripheral nerve integrity is not compromised by BFR.

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