Journal of Electromyography and Kinesiology 48 (2019) 37–43

Contents lists available at ScienceDirect

Journal of Electromyography and Kinesiology

journal homepage: www.elsevier.com/locate/jelekin

Effects of ischemic conditioning on maximal voluntary plantar flexion contractions

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ARTICLE INFO

Keywords:
Vascular occlusion
Dynamometric performance
Force generation
Interference sEMG signals
Skeletal muscle

ABSTRACT

Intermittent blood flow restriction to local or remote vascular beds induces endogenous protection against ischemia-reperfusion injury in several tissues and organs. When applied non-invasively by placing occlusion cuffs on the limbs, this ischemic conditioning has been shown to elicit an acute ergogenic response. However, the underlying mechanisms behind this phenomenon remain unknown. Prior research suggest that ischemic conditioning may operate via improved motor discharges from the central nervous system, thus enhancing the electrochemical activation and force generation of agonist muscles. Here we show that, for healthy individuals performing maximal voluntary contractions of the plantar flexors, the acute benefit elicited by ischemic conditioning on maximal isometric ankle torque production is largely explained by parallel gains in the surface myoelectrical activity of the triceps surae. However, the magnitude of this response appears to vary between individuals. These findings indicate that enhanced levels of agonist activity contribute to the ergogenic effect of ischemic conditioning during maximal efforts, thereby enabling more direct assessments of neural output following the procedure.

1. Introduction

Ischemic conditioning (IC) consists of a procedure known to induce endogenous protection against ischemia-reperfusion injury in several tissues and organs (Tapuria et al., 2008; Lim and Hausenloy, 2012). Curiously, when applied non-invasively on the limbs, the IC stimulus has been shown to elicit an acute ergogenic response of relevant magnitude (Lisbôa et al., 2017). However, the pathways underlying this effect remain unknown. From previous papers (Cruz et al., 2015, 2016), we have elaborated an introductory model to study the ergogenic mechanisms of IC (Cruz et al., 2017). Briefly, this initial template predicts that IC reduces sensory feedback from small-diameter nerve fibres (particularly the high-threshold metabo-nociceptor subtype), thereby enabling a greater neural output to the muscles and improving contractile force production. If limb IC can enhance the recruitment and/or discharge rates of agonist motor unit pools, individuals subjected to the manoeuvre should display a greater ability to fully activate their muscles during maximal efforts. Furthermore, such neuromuscular responses must be linked to simultaneous increases in volitional torque. Therefore, making these measurements during single-joint contractions could be relevant to investigate the potential neurological origin of IC.

Although the primary focus of IC studies has been usually to estimate the mean performance enhancement, it is important to know whether individual responses are present. Incognito et al. (2016) suggested the existence of responders and non-responders to IC, which could partially account for the variability in between-study responsiveness. However, appropriate statistical methods to investigate this hypothesis have not yet been implemented. If participants eventually differ in their dynamometric responses to the procedure, this heterogeneity could be estimated in a pre-post crossover design (Hopkins, 2015). Specifically, individual responses should manifest as a larger standard deviation of the change scores in the IC condition compared to those in response to a low-pressure sham intervention (LP), typically used to approximate a control condition. In addition, in the event of these potential individual responses being neurally mediated, they should be proportionally reduced when the corresponding electromyographic amplitudes of working muscles are included as covariates in the analysis.

To investigate these issues, an experiment comprised by series of maximal voluntary contractions (MVCs) of the plantar flexors was set. It

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https://doi.org/10.1016/j.jelekin.2019.06.004
Received 13 April 2019; Received in revised form 5 June 2019; Accepted 11 June 2019

involved only static contractions, as neural mechanisms can be delineated more easily for them (Gandevia, 2001), combined with measures of surface electromyography (sEMG), which can indirectly describe neural inputs to muscles (Farina et al., 2010). Its primary aim was to determinate whether IC enables exercising muscles to be "extra" activated by volition. We hypothesized that acute IC of the lower limbs would increase maximal voluntary torque (MVT), which would be associated to higher amplitudes of sEMG potentials for the triceps surae. The secondary aim was to explore for the presence of individual ergogenic responses to limb IC. We hypothesized that eventual heterogeneities in the effect of IC on ankle torque production would be related to concomitant heterogeneities in sEMG amplitudes.

2. Methods

2.1. Participants

This study was in accordance with the Declaration of Helsinki and approved by the local ethics committee (65107517.0.0000.0118). Nineteen physically active men (27 ± 5 years, 176 ± 5 cm, 79 ± 10 kg; mean ± standard deviation) were recruited. They were fully informed of the potential risks and discomforts associated with the experiment before giving their written informed consent. Only individuals regularly practicing physical activity were considered for selection, provided they were not under medication or have had any type of musculoskeletal or neural injury/disorder compromising their ability to perform MVCs of the plantar flexors. The participants were instructed not to perform vigorous exercise (especially those involving the calf muscles) in the 48 h preceding each visit and to abstain from alcohol on the day before each session. They were also asked to maintain the same dietary pattern throughout the experiment and to refrain from caffeine or any other stimulants on the day of testing.

2.2. Design and overview

This experiment was designed as a pre-post crossover trial. Altogether, the recruited volunteers attended three laboratory sessions over a two-week period, always at the same time of day. All sessions were 3–7 days apart to allow for any effect of the previous session to wash out. Specifically, participants underwent an initial visit to determine eligibility as well as to be prepared for the various procedures involved in this study, including extensive familiarization with isometric MVCs of the plantar flexors after carrying a full IC protocol. On the following session, participants were submitted twice to an identical exercise protocol held on a Biodex dynamometer (System 4 Pro™, Biodex Medical Systems Inc., Shirley, NY, USA), with the randomly selected and counterbalanced cuff inflation procedure (IC or LP) interposed in between (Fig. 1A). The exercise protocol, composed by a series of ten MVCs, was initially applied for the acquisition of baseline measures for the dependent variables, followed thereafter by the intended cuff inflation procedure. We acknowledge that the mechanical performance of a muscle can be altered by preceding contractile activity (Hamada et al., 2003). However, the inclusion of additional MVCs reduces the typical error of measurement by a factor of $1/\sqrt{n}$, where n is the number of contractions, thus improving the signal-to-noise ratio (Hopkins, 2000). After the end of the IC or LP protocols, that is, 5 min after the last cuff deflation, a 45-min resting period was observed and then participants were asked, once again, to perform for post-intervention measurements. The last (third) visit was the same as the second visit described above, with the clear exception of the pressure on the cuffs. During the exercise protocol, the analog signal outputs for torque readings (update rate of 2 kHz) and sEMG of the calf muscles were sent to a 16-channel telemetric EMG system (TeleMyo 2400T G2™, Noraxon U.S.A. Inc., Scottsdale, AZ, USA). There, the multiple signals (properly synchronized) were analog-to-digital converted with a 16-bit resolution at a sampling rate of 3 kHz, and then transmitted wirelessly to a personal computer for processing and storage.

2.2.1. sEMG

The electrical activity emanating from contracting soleus, gastrocnemius medialis and gastrocnemius lateralis were acquired by means of sEMG sensors. The skin over the muscles were initially shaved, sandpapered, and cleaned with cotton and 70% ethanol. Disposable 1-cm-diameter Ag-AgCl electrodes (Kendall™ 100 Series, Covidien llc, Mansfield, MA, USA) were carefully tapped to the belly of each muscle using a bipolar configuration, in the direction of the muscle fibres, with an interelectrode distance of 2 cm. For the soleus muscle, the recording electrodes were placed along the mid-dorsal line of the leg, about 5 cm distal from where the two heads of the gastrocnemius join the Achilles tendon (Guette et al., 2006). For the gastrocnemius muscles, electrodes were fixed in accordance with standard recommendations (Hermens et al., 2000), while the reference electrode was placed over the medial malleolus. Skin impedance between pairs of electrodes was checked with a regular multimeter (< 5 kΩ). Electrode positioning was marked with indelible ink during the second visit to ensure that they were placed in the same location at the third visit. Active leads were subsequently applied to the electrodes. The performance characteristics of these sEMG leads were as follows: a baseline noise < 1 uV RMS, an input range of ± 3.5 mV, an input impedance > 100 MOhm, a common mode rejection ratio > 100 dB, and a base gain of 500. After signal quality checking, cables were secured in place with the aid of an elastic strap wrapped in the subject's leg. During data acquisition, the signal was conditioned by two hard-ware filters prior to digitalization: all sEMG leads had first order high pass filters set to 10 Hz ± 10% cut-off and all channels had low pass anti-alias filters set to 1500 Hz.

2.2.2. MVCs

Prior to each session, a calibration verification procedure was performed on the dynamometer according to the manufacturer's specifications. After the sEMG sensors were placed, participants were comfortably seated in the positioning chair, with the seatback tilt set at 70°. A limb support pad was placed under the distal femur of the subject's right limb, which was firmly secured by a Velcro strap. Also, pelvic and shoulder stabilization straps were buckled until tight but not uncomfortable for the subject. Subsequently, the chair and dynamometer settings were carefully adjusted until the foot was placed in the equipment's ankle attachment, with the knee angle maintained at 90°. The joint's anatomical axis of rotation (predefined as the fibular malleolus) was then aligned with the dynamometer shaft and fine tuning was performed to ensure proper subject positioning. Once all adjustments had been completed, range of motion limits were established, and the ankle was placed in its neutral position. Only then the subject's foot was tightly fastened to the equipment. The settings were noted during the first session and reproduced on subsequent tests.

Prior and after the cuff inflation procedures, subjects were asked to perform a series of ten isometric (5-s) MVCs interspersed with 4 min of passive recovery. After a 30-s count-down (every 5 s), an audible signal was triggered, clearing the subject to execute the contraction. Usually after a brief pause, often including a deep breath, the participant started the MVC. Subjects were repeatedly instructed to contract "as fast and hard as possible" throughout each attempt, from a fully relaxed state, until 10 acceptable trials have been measured (never more than 12). To be considered valid, the torque-time curve should have presented a visually stable baseline, as well as being a clear maximal explosive effort, reaching an identifiable plateau after a few seconds (Fig. 1B). Failure to meet one of these requirements culminated in the rejection of the curve, whereas subjects were also allowed to reject efforts that they did not regarded as truly "maximal" (Gandevia, 2001). To maximize motivation, verbal encouragement was given, always by the same two investigators. In addition, real-time visual feedback was available, but varying torque gain so the participant stayed unaware of the magnitude of his performance.

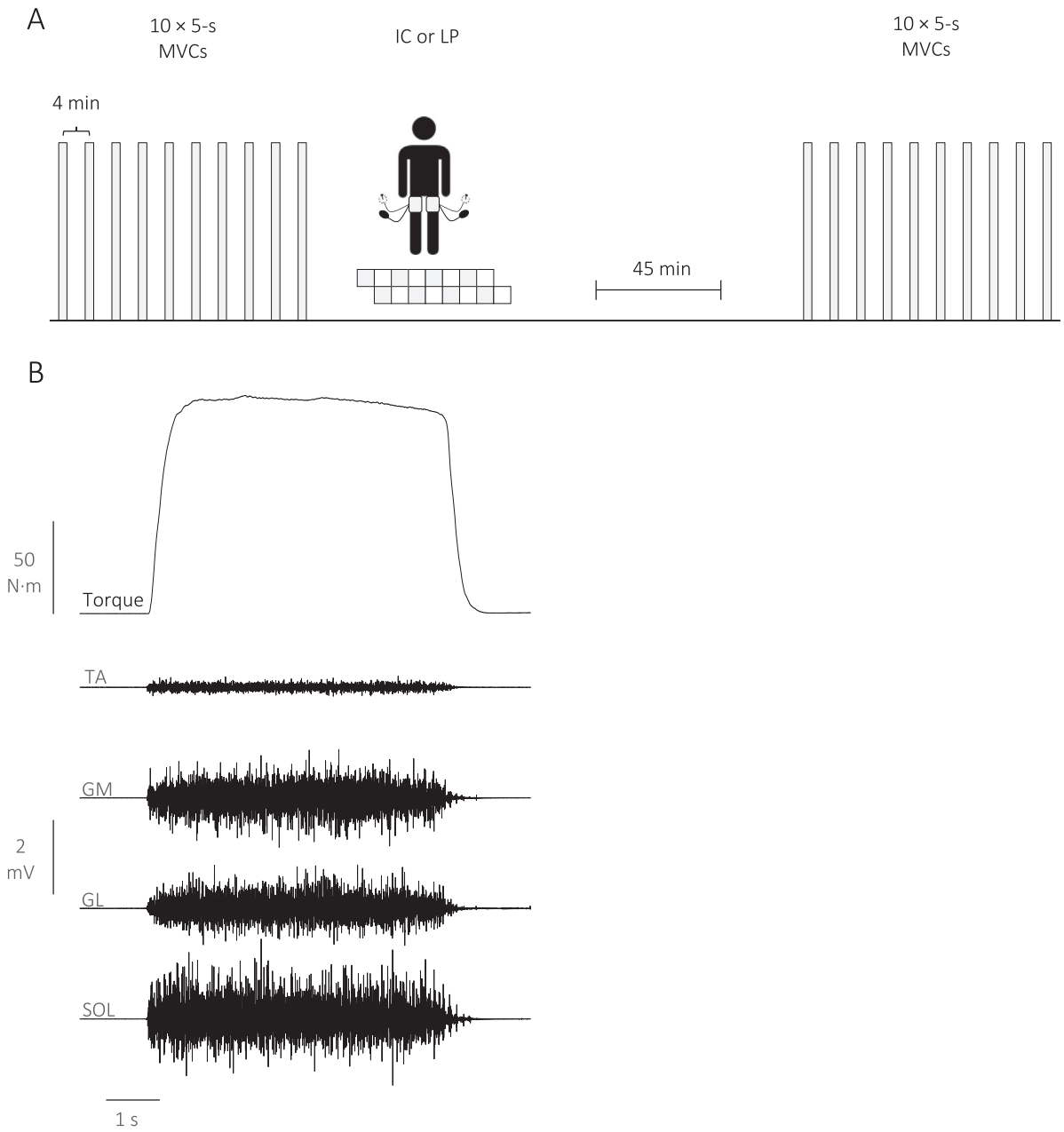

Fig. 1. Experimental overview (A). A series of ten maximal voluntary contractions lasting 5 s (grey bars; MVCs) was initially performed (interspersed with a 4-min passive recovery) to record pre-intervention measures for the dependent variables. Participants were then submitted to the selected cuff inflation protocol (IC or LP) and rested for 45 min. After this period, they were asked to perform once again for post-intervention measurements. Representative torque and electromyographic responses to a maximal voluntary plantar flexion contraction (B). Note the sharp rise and the subsequent plateau in the torque signal.

Table 1
Dynamometric and electromyographic responses.

	Ischemic Conditioning		Low-Pressure Protocol	
	Post	Pre	Post	Pre
Maximal voluntary torque, N·m	154 ± 33	152 ± 38	150 ± 32	154 ± 33
Overall sEMG amplitude, uV	258 ± 132	236 ± 113	235 ± 126	235 ± 105
Low frequency, uV	144 ± 90	130 ± 75	130 ± 84	126 ± 64
Middle frequency, uV	205 ± 98	188 ± 85	188 ± 95	189 ± 81
High frequency, uV	58 ± 26	55 ± 25	53 ± 24	58 ± 28

Data are means and standard deviations.

2.2.3. Cuff inflation procedures

Acute IC was evoked by intermittently restricting the arterial blood inflow to the lower limbs (alternately), while the subjects lay comfortably supine on a horizontal examining table. Two 13-cm-wide pneumatic cuffs were positioned proximally around the upper thighs and automatically inflated to 220 mmHg by a custom-made, computer-controlled device. Each ischemic procedure lasted for five minutes and was repeated four times in each limb, always separated by 5 min of full cuff deflation (i.e., the reperfusion period). This protocol was chosen as it has been found to be safe, well tolerated, and was successfully applied in previous studies investigating the ergogenic effects of IC. On LP condition, participants followed an identical protocol, but, instead, cuffs were inflated only to 20 mmHg (Cruz et al., 2015, 2016; Turnes et al., 2018). To minimize psychogenic responses, participants were not informed about the study rationale.

Table 2
Fixed and random effects.

	Change Scores				Net effects		Individual Responses			Typical errors	
	ΔIC ± 95% CL	p	ΔLP ± 95% CL	p	ΔIC-ΔLP ± 95% CL	p	SD and 95% CI		p	SD and 95% CI	
Maximal voluntary torque, N·m	1.8 ± 4.9	0.445	−4.4 ± 4.0	0.034*	6.2 ± 6.2	0.048*	6.1	(−6.7 to 10.9)	0.381	5.9	(4.2–8.1)
Overall sEMG amplitude, %	9.9 ± 9.7	0.046*	−2.8 ± 8.4	0.493	12.7 ± 12.4	0.045*	10.0	(−15.2 to 20.8)	0.554	12.4	(8.9–17.1)
Low frequency, %	10.9 ± 11.6	0.064†	−1.6 ± 10.2	0.740	12.5 ± 14.9	0.097†	11.5	(−18.6 to 24.7)	0.584	14.9	(10.8–20.7)
Middle frequency, %	9.7 ± 9.3	0.043*	−3.3 ± 8.0	0.398	13.0 ± 11.9	0.033*	10.0	(−14.3 to 20.1)	0.518	11.7	(8.5–16.3)
High frequency, %	7.6 ± 9.8	0.121	−7.6 ± 5.5	0.009*	15.2 ± 10.9	0.008*	16.8	(−0.6 to 23.8)	0.050†	8.1	(5.8–11.2)
Reanalysis of maximal voluntary torque controlling by changes in sEMG amplitudes											
Overall, N·m	−1.1 ± 4.7	0.638	−3.8 ± 3.8	0.051†	2.8 ± 5.8	0.343	3.6	(−7.2 to 8.8)	0.689	5.5	(4.0–7.8)
Low frequency, N·m	−0.3 ± 5.0	0.900	−4.0 ± 3.5	0.027*	3.7 ± 5.9	0.210	6.0	(−5.7 to 10.2)	0.307	5.1	(3.6–7.1)
Middle frequency, N·m	−1.3 ± 4.6	0.559	−3.8 ± 4.0	0.059†	2.5 ± 5.8	0.386	2.4	(−7.7 to 8.3)	0.865	5.7	(4.1–8.0)
High frequency, N·m	−0.4 ± 4.5	0.866	−3.9 ± 5.0	0.121	3.5 ± 6.5	0.280	1.6	(−8.2 to 8.5)	0.939	6.0	(4.3–8.4)

Effects are deltas (Δ) or standard deviations (SD) and uncertainties are 95% confidence limits (CL) or intervals (CI). IC; ischemic conditioning; LP, low-pressure protocol; sEMG, surface electromyography.

* $P < 0.05$.

† $P < 0.10$.

2.3. Data processing and analysis

The digitalized data were exported to ASCII files and imported into Matlab (R2011a™, Math-works Inc. Natick, MA, USA), where the set of files from each individual was processed for analysis with a custom algorithm containing a loop function. The continuous torque signals were initially filtered using a low-pass, fourth-order Butterworth filter with cut-off frequency of 20 Hz. Subsequently, two dynamometric variables were extracted from each MVC. (1) The baseline torque was the mean torque value of a "silent" period, manually delimited from a plot containing 30 s prior to contraction onset. (2) The uncorrected MVT was computed as the highest value of the filtered signal during each contraction. The resulting dataset was exported to Excel spreadsheets, where the MVT values were corrected by the mean baseline torque of the day. The intensities of the corresponding myoelectric signals (the last 0.5 s prior to each MVT) were resolved into time/frequency space using a maximal overlap discrete wavelet transform algorithm. Briefly, the detrended signals were decomposed into several sub-oscillations with different frequency bands, using the Daubechies-4 wavelet function as the mother wavelet (Wei et al., 2012). To remove noise components, frequency bands with energy predominating below 20 Hz and above 750 Hz were excluded. The RMS values of the remaining components (all of which presenting acceptable signal-to-noise ratios) were then agglutinated into the overall response of each muscle, as well as into high (> 400 Hz, HF), middle (MF) and low (< 100 Hz, LF) frequency amplitudes of the sEMG power-density spectrum. As for torque variables, data was exported to Excel spreadsheets and the values from different muscles were averaged to provide a representative response of triceps surae activation. For each individual, the computed values from the ten MVCs were averaged to provide a single pre- and post-intervention measure per condition. Subsequently, the MVT and sEMG amplitudes were converted into absolute and relative change scores, respectively.

2.4. Statistical analysis

The fixed and random effects of IC on the dependent variables were assessed with the mixed linear modelling procedure of the IBM SPSS statistics™ (Version 20, IBM Corporation, Armonk, New York, USA). The condition was included as the fixed factor of interest, while the random effect representing individual responses was set by combining a dummy variable with the identity of the subjects. The typical error of measurement was calculated from the residual term. The contribution of myoelectrical responses to the torque outcome was estimated by including the sEMG change scores in the model as covariates. Pearson product-moment correlations were also presented to indicate the strength of linear associations. Uncertainties in the effects and errors were expressed as 95% confidence limits (CL) or intervals (CI). All tests were analysed at an alpha level of 5%.

3. Results

Data were expressed as means and standard deviations in Table 1. A summary of statistical results is reported in Table 2. Limb IC improved MVT mainly by preventing the decrease observed at post-intervention contractions. The overall agonist activity was also enhanced by the procedure, but mostly by promoting an overshoot in post-conditioning values. The MF subband of the power spectrum significantly contributed to this response, while the LF component presented larger errors of measurement and only tended to do so. The net advantage in agonist activation could be also partially attributed to changes in HF amplitudes, but rather by the maintenance of baseline values. Despite the considerably greater variance in the change scores of the IC trial (Fig. 2), individual MVT responses to IC were not clear. A similar outcome was noticed for the overall sEMG responses, as well as for the LF and MF subbands. On the other hand, participants tended to respond differently in their HF amplitudes with IC.

When included as a covariate in the model, the overall sEMG amplitude explained about half of the benefit elicited by IC on MVT (3.4 N·m, CL of ± 2.2 N·m, p = .004), primarily via reductions in the change scores of the IC trial (2.9 N·m, CL of ± 2.1 N·m, p = .010). The LF and MF components were also able to attenuate the net effect of IC in a similar fashion, respectively by 2.5 N·m (CL of ± 2.1 N·m, p = .024) and 3.7 N·m (CL of ± 2.2 N·m, p = .002), whereas a statistical trend toward significance was found for the HF subband (2.7 N·m, CL of ± 3.2 N·m, p = .091). The SD representing individual torque responses tended to be compressed when adjusted by the changes in the overall agonist amplitude (p = .071). Further spectral analysis revealed that the MF (p = .012) and HF (p = .006) subbands could explain a significant portion of these individual differences, while the LF could not (p = .962). Finally, the individual net effects of MVT were strongly correlated with the net change scores in the LF (r = 0.52, p = .022), MF (r = 0.64, p = .003), and HF (r = 0.65, p = .003) subcomponents, as well as those from the overall sEMG amplitude (r = 0.61, p = .006).

4. Discussion

The major findings of the present investigation include the following. (1) IC improved isometric torque during maximal voluntary plantar flexion contractions. This benefit was partially explained by parallel enhancements in the activation of the calf muscles, probably manifested in all frequency components of the sEMG spectrum. These

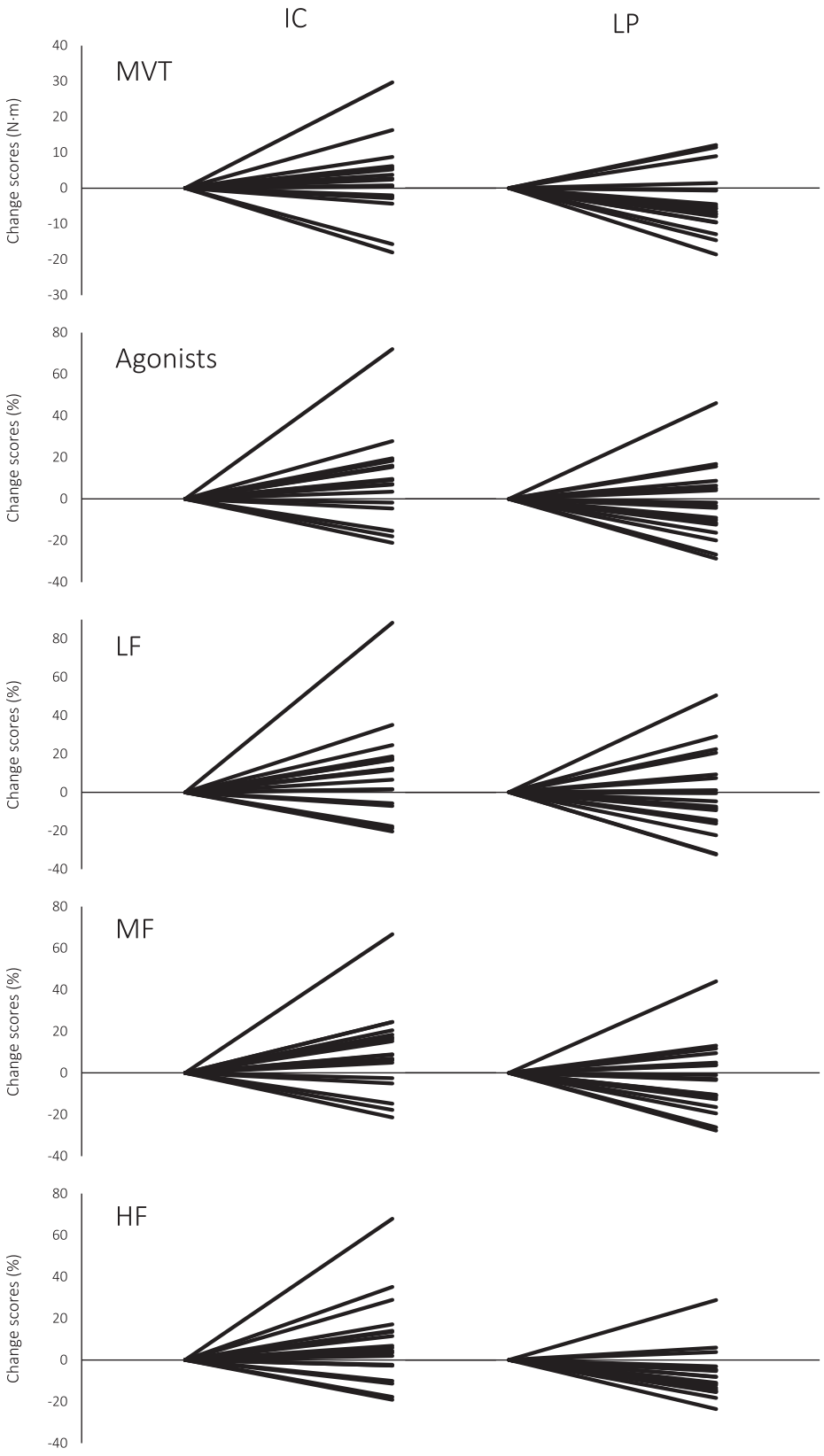

Fig. 2. Individual changes after the IC and LP protocols. Each line represents a different participant (n = 19). LF, MF and HF represents low, middle and high frequency amplitudes of the sEMG power-density spectrum, respectively.

results are in accordance with earlier findings suggesting an increased neuromuscular activation as one of the main effectors of IC on performance (Cruz et al., 2015, 2016; Hyngstrom et al., 2018). However, when combined with the unexpected decrease in force generation at post-intervention measurements, the inability of sEMG amplitudes to explain more than half of the torque benefit may be suggesting an additional post-conditioning effect at the muscular level. (2) Notwithstanding the lack of precision to detect heterogeneous torque responses

with IC, individual net effects of MVT were highly correlated with those from sEMG variables. Furthermore, gradually lower measurement errors at the higher frequency bands evidenced the capacity of the sEMG signal to account for the magnitude of the benefit evoked in different participants, while also contributed to glimpse different sEMG activities in the upper spectral frequencies. Together, these findings suggest that neural factors might be also randomly modulating the extent of the gain obtained with IC on volitional torque, strengthening prior speculations on responders and non-responders to the procedure (Incognito et al., 2016).

We recently proposed that limb IC operates via central processing of sensory nociceptive inputs, leading to increased excitatory drive and/or more excitable α-motoneuron pools (Cruz et al., 2017). Evidently, the present study does not provide any evidence on participation of afferent fibres, but it seems consistent with greater motor efferent discharges from the spinal cord. The sEMG signal represents the sum of the action potentials generated by active motor units and filtered by the volume conductor (Farina et al., 2010). Even though the resultant signal also depends on the properties of the muscle fibre membranes and is subject to some important drawbacks, including amplitude cancelation, its energy in the time domain represents a crude measure of changes in neuromuscular activation (Farina et al., 2014). Therefore, the fact that the overall sEMG amplitude was increased in conditioned muscles suggest that IC can boost maximum neural output above ordinary levels, although the effects of IC on the amplitude and duration of sarcolemmal transmembrane potential remain unknown. This notion is additionally supported by a new study showing concomitant increases in maximal isometric strength and vastus lateralis activation after IC in chronic stroke survivors performing MVCs of knee extensors, which also showed decreases in motor unit force recruitment thresholds during submaximal contractions (Hyngstrom et al., 2018). Future research could delve into testing the excitability of human motoneuron pools after IC, perhaps by electrically evoking single compound muscle action potentials and spinal reflexes at rest and during isometric MVCs.

Estimation of individual responses to a given intervention with enough precision frequently requires impractically large sample sizes (Hopkins, 2015). To overcome this limitation, it has been advised the inclusion in the analysis of participant characteristics possibly accounting for such unequal responses, as their effects can often be characterized satisfactorily with realistic samples (Hopkins et al., 2009). Therefore, perhaps the most interesting finding of the present study was that the large inter-individual variation in joint torque with IC, albeit not statistically significant, was closely related to likely different amplitude responses at higher spectral frequencies. Specifically, the variance summarizing individual differences in the ergogenic effect of IC was practically abolished (a 93% reduction) when controlled by changes in the HF subband. The physiological meaning of this relationship is not easy to interpret. However, sEMG signals has been often resolved in the frequency space to provide some insight into muscle recruitment patterns for a given activity (Wakeling et al., 2002). Theory predicts that the greater conduction velocities of fast-twitch fibres translate into higher-frequency oscillations in the surface electromyogram (Farina et al., 2002; Del Vecchio et al., 2017). We are not sure the extent to which the smoothing properties of the volume conductor influenced such relationship (Farina et al., 2002). Nevertheless, it can be speculated from the present findings that distinct changes in motor unit recruitment and/or rate coding with IC may be eliciting non-uniform dynamometric responses between individuals, even within a group that was set to be homogeneous. Unfortunately, the influence of participant's personal beliefs on this deviation was not assessed, but these results certainly help explaining the large variability on performance enhancement noticed among different IC studies (Incognito et al., 2016; Salvador et al., 2016).

The systematic reduction of MVT values after the LP protocol was mostly unrelated to changes in sEMG amplitudes and was probably caused by the first round of contractions. This fact suggests that local protective mechanisms of IC may have also acted to preserve the ability of the joint tissues to generate/transmit force. As our investigation was specifically intended to delimit if IC permits the utilization of a higher portion of the individual's functional reserve, the findings presented here cannot contribute to this topic. However, there is solid evidence demonstrating that IC can attenuate markers of exercise-induced muscle damage (Page et al., 2017; Williams et al., 2018). Apart from this unforeseen phenomenon, we believe the evidence provided in the present work supports the following conclusions. (1) An improved activation of calf muscles contributes for the mild benefit elicited by limb IC on voluntary torque during maximal plantar flexion contractions, warranting more direct assessments of neural drive/output following the procedure. (2) Individual muscular activation responses seem to evoke a meaningful deviation from this mean benefit. Discovering the source(s) of this random variation could help identifying the phenotype more susceptible to take advantage from IC.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgements

This study was financially supported in part by the following Brazilian institutions: Coordination for the Improvement of Higher Education Personnel (CAPES; finance code 001), Santa Catarina Research Foundation (FAPESC; grant TO 2017TR816) and São Paulo Research Foundation (FAPESP; grant #2018/17245-0).

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