

Are electrically induced muscle cramps able to increase the cramp threshold frequency, when induced once a week?

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Abstract

The cramp threshold frequency (CTF) is known to be positively correlated with the individual cramp susceptibility. Here we assessed CTF changes after two bouts of electrically induced muscle cramps (EIMCs). The EIMCs (6×5 sec) were unilaterally induced twice (separated by one week) in the gastrocnemius of an intervention group (n=8), while 5 participants served as control. The CTF increased from 25.1±4.6 Hz at baseline to 31.4±9.0 Hz and 31.7±8.5 Hz 24 h after bout 1 and 2 (P<0.05). Thereafter, the CTF declined following both bouts to reach values of 28.0±6.7 Hz and 29.1±7.7 Hz after 72 h after bout 1 and 2. Creatine kinase (CK) activity and perceived discomfort during cramps was lower after bout 2 (P<0.05). CTF, CK, and discomfort did not change in CG. That is, a single bout of EIMCs induces a 24 h CTF increment and a second bout sustains this effect, while perceived discomfort and muscle damage decreases. This short term effect may help athletes to reduce the cramp susceptibility for an important match.

Introduction

Skeletal muscle cramps are defined as sudden, involuntary, and painful contractions.¹ Though cramps commonly represent a self-limiting condition that clears up after a few seconds, affected people usually instinctively stretch their cramping muscles immediately to relieve the pain. While this acute treatment may effectively stop cramps in most cases, there is still a lack of evidence about non-drug therapies to prevent muscle cramps.² This unsatisfactory situation results from the fact that the underlying mechanisms of this phenomenon are still poorly understood.

Pathologies that are known to be associated with an increased prevalence of muscle cramps include diseases of the lower motor neuron, some metabolic disorders, an acute

depletion of the extracellular volume, medications, hereditary disorders, and antibodies against voltage-gated potassium channels.³ Additionally, it is not uncommon for young and healthy subjects to suffer from muscle cramps without any apparent cause. These idiopathic cramps often occur during prolonged intense contractile activity and are therefore commonly denominated as exercise-associated muscle cramps (EAMC).⁴ Despite a potential overlap with the aforementioned acute depletion of the extracellular volume due to extensive sweating, it has been reported that 69% of the EAMCs occur in subjects that were well hydrated and sufficiently supplemented with electrolytes.⁵ Therefore, it seems questionable if those factors are capable of explaining the development of EAMCs. However, dehydration and electrolyte imbalance have been reported to be the most frequently assumed mechanism for EAMCs among athletic trainers.⁶ Interestingly, a recently published Cochrane review on magnesium supplementation concluded that there is no randomized controlled trial to date that has evaluated the effects of magnesium on EAMCs.⁷ This sharply contradicts its reputed benefits and the widespread use in praxis.⁷ By contrast, more and higher level scientific evidence is available for the theory of an altered neuromuscular control, as reviewed elsewhere.⁸ In short, proponents of this theory state that a reduced inhibitory input to the alpha motoneuron from the Golgi tendon organs (GTOs) in concert with an increased excitatory input from the muscle spindles (MSPs) are responsible for the development of EAMCs.⁹ This imbalance is particularly present in a shortened muscle position, where the GTO signal is largely depressed, accompanied by a reduced excitation threshold of motor-endplates.¹⁰ The latter likely explains the observation that skeletal muscles cramps develop almost exclusively in shortened muscles,¹¹ and that stretching is an effective method to terminate muscle cramps, as it increases the inhibitory drive from GTOs.⁸ Further, it has been shown in animal models that skeletal muscle fatigue goes along with an increased firing rate of MSPs and a reduced firing rate of GTOs, which may explain the association of EAMCs with prolonged and intense contractile activities.^{12,13}

In a previously published study, it has been reported that the cramp threshold frequency (CTF), defined as the lowest stimulation frequency required to elicit a muscle cramp, was fundamentally increased from 23.3±5.7 Hz to 33.3±6.9 Hz at 96 h after a six-week training protocol, consisting of electrically induced muscle cramps (EIMCs).¹⁴ The authors suggested that the chronically applied EIMCs resulted in a rebalancing of the excitatory and inhibitory input to the alpha motoneurons. Against the background that this threshold has

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been shown to correlate with the individual cramp susceptibility,¹⁵ these findings may help athletes prevent muscle cramping during training and/or competitions. However, from the available data it remains unclear how many stimuli are necessary to significantly increase the CTF and how long the respective effects will last. That is, from a practical point of view, it would be beneficial if only a single EIMC training would be needed to induce the desired effects and that repeated bouts at large time intervals would be sufficient to maintain the achieved effects. Therefore, the present study was planned to achieve a better understanding about the precise time course of CTF changes induced by a single bout of EIMCs. Further, a second bout was applied one week later to investigate if stimulation effects are additive in terms of a further increase in CTF. The CTF measurements were supplemented by blood analyses to estimate the amount of stimulation induced muscle damage. We hypothesized that the first bout of EIMCs will increase both, the CTF and CK values, while the second bout will similarly affect the CTF with only blunted damage marker responses in the blood, in terms of a repeated bout effect.¹⁶

Materials and Methods

Subjects

A total of 13 healthy male subjects were randomly assigned to an intervention group (IG; $n=8$) and a control (CG; $n=5$) group. A coin was tossed to determine from which leg the CTF was measured. In the IG this was also the leg that underwent the stimulation protocol. The methods and procedures applied in the present study were approved by the local ethics board of the German Sport University Cologne and the study was conducted in accordance with the Declaration of Helsinki. Prior to enrollment, written informed consent was obtained from participants. Baseline characteristics of participants are displayed in Table 1. The percent body fat and the impedance of the stimulated leg was measured by using the body composition analyzer BC-418 (Tanita, Arlington Heights, IL, USA). Exclusion criteria were defined as any cardiovascular, metabolic, or orthopedic disorder. Further, chronic medication was defined as exclusion criterion.

Cramp threshold frequency

In the IG, the CTF was measured prior to (pre), and on 3 consecutive days after the stimulation protocol. CTF measurement time points were the same for the CG, but no stimulation protocol was applied between pre and post. To minimize potential circadian rhythm effects on the CTF, all follow-up measurements were conducted at the same time of day as the pre-measurements were performed. The CTF was determined according to a previously published protocol.¹⁴ In brief, 5 s impulse trains (impulse width 400 μ s) were applied to the m. gastrocnemius medialis using a battery powered muscle stimulator (Stim-Pro X9, Axion GmbH, Weissenhorn, Germany) and two self-adhesive gel electrodes (Axion) while subjects were lying prone on an examination bench, ankle joints flexed at $\sim 120^\circ$. One of the two electrodes was placed on the motor point of the muscle belly while the other was placed on the proximal muscle portion just below the popliteal cavity. Electric prospection of MPs were performed by scanning the skin with a pen electrode (motor point pen, Cefar Compex, Compex Médical SA, Ecublens, VD, Swiss) using a continuous stimulus of 30 Hz and 2 mA. Each stimulation train was followed by a rest period of 55 s before the next train was applied. Starting at 12 Hz for the initial stimulation train, the frequency was gradually increased by 2 Hz from one train to the next until subjects reported a cramp.

Apart from subject feedback, cramps were verified by visual inspection, by palpation of the calf muscle, by evidence of a sustained plantar flexion of the foot, and by increased

electromyography (EMG) activity. If the cramp was not self-limiting within 5 s, the subjects were allowed to stretch their calf muscles to end the cramp. The electrical activity of the induced muscle cramps was assessed by surface electromyography (sEMG), using the TeleMyo™ 2400T G2 (Noraxon USA, Inc., Scottsdale, AZ, USA) and disposable electrodes (Ambu Blue Sensor P, Ambu A/S, Ballerup, Denmark). EMG electrodes were placed between the stimulation electrodes. To improve electrode contact, the respective skin areas were shaved and cleaned with skin disinfectant prior to the electrode placement. A sampling rate of 3000 Hz was used to record the sEMG data and the software MyoResearch XP (Version 1.08 Master Edition, Noraxon US, Inc) was used afterwards to analyze the recorded data.

Stimulation protocol

Except for the higher impulse width used in the present investigation (400 μ s vs. 150 μ s), the stimulation protocol equaled that of our previous study.¹⁴ The modification was made to avoid automatic impulse width changes of the used battery-powered myostimulator (Cefar Compex, Compex 3 Professional). These occur at submaximal impulse width settings (<400 μ s), when the maximal available current of 120 mA is reached, to further increase the total charge. The stimulation protocol consisted of three sets of biphasic rectangular-wave pulsed currents, with 6 \times 5 s contractions each, separated by 10 s breaks (duty cycle of 0.33). The stimulation frequency was set to 30 Hz above the predetermined CTF and the applied current was set to 85% of the maximal tolerated intensity. Self-adhesive gel electrodes (Dura-Stick plus, Cefar Compex,) were placed on the motor points (MPs) of the m. gastrocnemius medialis and lateralis and two reference electrodes were placed on the proximal portion of both muscle bellies, immediately below the popliteal cavity.

Muscle damage marker

To assess the muscle damage induced by the cramp protocol, the muscle damage marker (MDM) creatine kinase (CK) was measured pre, post, 2 h, 24 h, 48 h, and 72 h after the stimulation protocol. CK measurement time points were the same for the CG, but no stimulation protocol was applied between pre and post. Blood was collected from the antecubital fossa by venipuncture with an evacuated tube system (Vacutainer®, Becton-Dickinson, Plymouth, UK) into Serum Separation Tubes™ (SST). The blood was then centrifuged for 10 minutes at 1861 g and 4°C (Rotixa 50, Hettich Zentrifugen, Mühlheim, Germany) after allowing it to clot for 30 min at room temperature. Afterwards, the serum was separated and stored at -80°C until analyses

for CK was performed. CK activity was assessed spectrophotometrically (Advia 1800, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany).

Perceived discomfort

A visual analogue scale, ranging from *no pain* (0 mm) to *unbearable pain* (100 mm) was used to assess the perceived discomfort. Subjects were asked to mark the level of discomfort of each CTF measurement.

Statistics

A two-way repeated measures analysis of variance (ANOVA) was used to assess significant main effects (group, bout, time) and interactions. The Levene's test revealed that the assumption of homogeneity of variances between both groups was violated only in two cases (24 h CK measurements). Nevertheless, the Tukey-Kramer method was used for pairwise comparisons between IG and CG to control for potential effects of the unequal sample sizes between both groups. The strength of association between continuous variables was assessed by calculating the Pearson's correlation coefficient. The level of significance was set to <0.05 for all analyses and means with respective standard deviations are used to present data in tables and in the running text. Vertical bars in figures represent 95% confidence intervals. All statistical analyses were performed with the statistics software package Statistica (Version 7.0 for Windows, Statsoft, Tulsa, OK, USA).

Results

The attendance rate for both training sessions (IG) and for all follow-up measurements (IG and CG) was 100%. No injuries resulted from the applied training and testing procedures. Prior to the intervention, IG and CG did not differ significantly in any of the assessed physical characteristics (Table 1).

Cramp threshold frequency

Prior to the first training session, the CTF for the IG and CG were 25.0 ± 4.28 Hz and 22.8 ± 5.22 Hz, respectively, with no significant difference between both groups. Besides a significant main effect for time, the overall ANOVA revealed a significant group \times time but no bout \times group \times time interaction (Figure 1). Following bout 1, the CTF of the IG significantly increased from the pre-training level by 25.6% and gradually decreased thereafter (Figure 1). No CTF changes, by contrast, were observed in the CG group. Prior to bout 2, there was still a small but insignificant difference between both groups. Starting from this slight-

ly elevated CTF value, the second bout induced a further CTF increase (28%) in the IG 24 h after bout 2. Similarly to bout 1, the CTF values declined after the 24 h peak. Again, the CTF remained virtually unchanged in the CG.

Muscle damage marker

Baseline activity for CK, measured prior to bout 1, did not significantly differ between IG (193.4±131.7 U/L) and CG (221±98.2 U/L). Besides a significant main effect for time, the overall ANOVA revealed a significant group × time and bout × time but no bout × group × time interaction (Figure 2). CK activity in blood differed from pre-test at 24 h, 48 h, and 72 h following bout 1. By contrast, following bout 2 only the 24 h activity was significantly CG, different from the respective pre-value. In the CK, the activities did not significantly vary at any of the assessed time points.

Perceived discomfort

There was a visible trend for perceived discomfort to be slightly lower at follow-up CTF measurements of bout 2, when compared to bout 1. However, this trend was not statistically significant.

Discussion

The main outcome of the present study was that a single bout of EIMCs significantly increased the CTF for 24 h and that CTF values tended to remain elevated for one week. Further, a similar response pattern was observed following the second bout of EIMCs, which was applied one week later. That is, the CTF peaked one day after both bouts, followed by a continuous decline in CTF. By contrast, the CK response was blunted following the second bout of EIMCs and the perceived discomfort of EIMCs during CTF-measurements tended to decrease over time. Therefore, the present data not only supports the previous observation that EIMCs result in a CTF elevation,¹⁴ but also provide a deeper understanding about the time course of the CTF response to a single and a repeated bout of EIMCs. As outlined introductorily, the CTF has been reported to be correlated with the individual cramp susceptibility.¹⁵ Thus, increasing the CTF by a single bout of EIMCs, as shown in the present study, may be a practical method to prevent cramping. Apart from the study that investigated the effect of EIMCs on the CTF in healthy subjects,¹⁶ to date only a few data are available on the adaptability of the individual CTF. These data include a CTF elevation as a consequence of muscle fatigue and muscle cooling via ice bag applications.^{17,18} Further it could be shown that the ingestion of pickle juice reduces the

duration of electrically induced muscle cramps.¹⁹ However, all of these data are acute effects, assessed immediately after the respective treatment. By contrast, no other study to date investigated the time course of CTF changes following two bouts of EIMCs.

Clinical relevance

Though the phenomenon of skeletal muscle cramps must be known since time immemorial, and the prevalence of these sudden, involuntary, and painful contractions is high,²⁰⁻²² a previously published Cochrane review concluded that there is still a lack of effective non-drug therapies.² Furthermore, there are significant concerns about the risk-benefit ratio of the widely used alkaloid quinine, as it only moderately prevents muscle cramps but can result in fatal hypersensitivity reactions.²³ Against this background, the present findings may be of great importance for the prevention of this neuromuscular phenomenon. Of course it can be justifiably questioned if inducing muscle cramps makes any sense in the context of cramp prevention, as both EIMCs and spontaneous muscle cramps are painful. However, in some cases this may be judged differently. For example, athletes who regularly suffer from cramps during strenuous physical activity may benefit from the presented EIMC protocol, if it is applied one day prior to an important competition. Further, it has been reported that there are individuals that suffer greatly from multiple muscle cramps per night, resulting in severe sleep disorders.²⁴⁻²⁶ In these individuals, the EIMCs may provide a suitable method to improve the sleep quality and their quality of life. In addition, it needs to be taken into account that the applied protocol showed a repeated bout effect for muscle damage measured by the CK activity. This effect describes the phenomenon that muscle damage symptoms are markedly reduced, when the same exercise is repeated within a certain period of time, which is interpreted as a protective effect.¹⁶ Additionally, there was a trend of decreasing discomfort during the CTF measurements. Thus, the ratio between achieved CTF levels and perceived muscle pain likely increases with prolonged interventions. These

results are consistent with our previous finding that the stimulation intensity during the EIMCs could be continuously increased from the first to the last of 12 training session,¹⁴ indicating an improved tolerability. Though the previously reported correlation between the applied stimulation intensity and the induced CTF gains in that study was high ($r=0.92$, $r^2=0.85$, $n=8$, $P<0.001$), it remains unclear to what extent the CTF would increase if the stimulation intensity is held constant throughout a cramp training intervention.

Electrical activity of muscle cramps

Stone *et al.*²⁷ used the electrical activity of the muscles after the stimulation to define a muscle cramp. According to these authors an increase of the average root mean square amplitude (aRMSA) of the 2 s after the stimulation to two standard deviations (SDs) above the 1 s baseline aRMSA characterizes a muscle cramp. Other authors adapted this definition.¹⁵ However, in the present study this threshold seems to be inapplicable as it was crossed by all subjects at low frequencies without developing a muscle cramp, as evident by visual inspection, palpation or cramp sensation. When the individual CTF was reached, the aRMSA was ~26 SDs above the baseline values (Figure 3), and significantly differed from the preceding test frequency (CTF-2 Hz). This largely differs from the previously suggested definition which likely reflects the fact that Stone *et al.*²⁷ investigated EIMCs in a much smaller muscle (m. flexor hallucis brevis) when compared to the m. gastrocnemius medialis.

Underlying mechanisms

Though the purpose of the investigation was not to investigate the underlying mechanisms, some potential mechanisms are listed here. As speculated previously,¹⁴ the underlying mechanisms for this CTF adaptation may be an increased inhibitory feedback of the GTO and/or a decreased muscle spindle activity during contractions at short muscle lengths. That is, the cramp training may have adapted the proprioceptive sensors to forceful contractions in a shortened position, avoiding an imbalance between the inhibitory and excitatory drive –

Table 1. Baseline physical characteristics for both groups.

	IG (n=8)	CG (n=5)
Age, years	22.6±0.5	23.8±3.5
Height, m	1.84±6.7	1.82±3.0
Body mass, kg	80.2±8.7	80.5±7.0
Body fat, %	13.2±3.3	9.0±4.3
Impedance of stimulated leg, Ω	247.8±34.9	220.4±9.9

None of the physical characteristics significantly differed between groups. IG, intervention group; CG, control group.

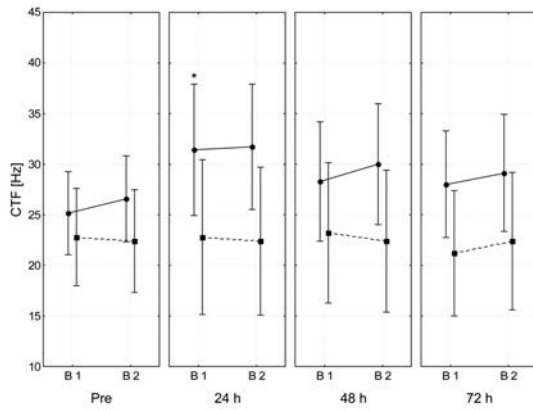


Figure 1. Mean cramp threshold frequency (CTF) response to bout 1 (B1) and bout 2 (B2) in the IG (circles) and the CG (squares). Vertical bars denote 0.95 confidence intervals. Asterisks indicate significant differences at $P < 0.05$ from pre values within the respective bout.

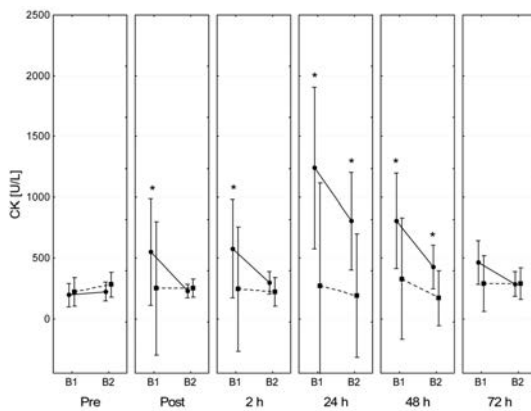


Figure 2. Mean creatine kinase (CK) response to bout 1 (B1) and bout 2 (B2) in the IG (circles) and the CG (squares). Vertical bars denote 0.95 confidence intervals. Asterisks indicate significant differences at $P < 0.05$ from pre values within the respective bout.

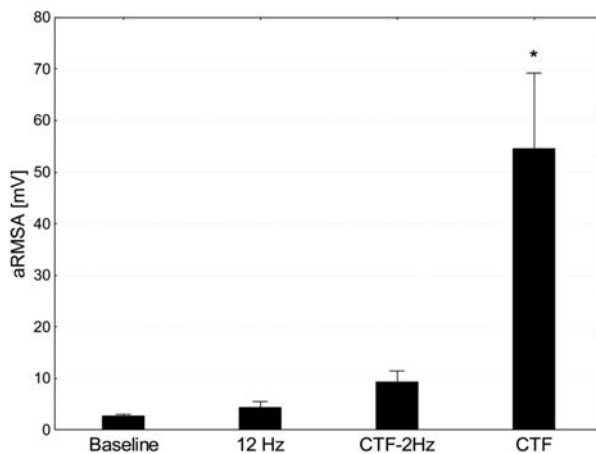


Figure 3. Mean average root mean square activity (aRMSA) of the *m. gastrocnemius medialis* at baseline and after the 12 Hz stimulation, the individual cramp threshold frequency (CTF), and the last frequency tested prior to the CTF (CTF-2 Hz). Vertical bars denote 0.95 confidence intervals. Asterisk indicates significant difference at $P < 0.001$ from 12 Hz values.

with pre-eminence of the latter. This would be in line with the neuromuscular theory of exercise induced muscle cramps proposed by Miller *et al.*⁴ According to this theory, muscle fatigue predisposes the muscle to cramp, as it further decreases the inhibitory drive of GTO and increases the excitatory drive from muscle spindles.

In addition to altered feedback from GTO and/or muscle spindles during contractions at short muscle lengths, one might speculate that spinal and/or supraspinal circuitries were modulated by the applied electrical stimulation. Some of the neurological adaptations in response to electrical stimulations have recently been reviewed by Hortobágyi and Maffiuletti.²⁸ These authors concluded that the increased afferent input to the motoneurons during the stimulation result in adaptations of the central nervous system. It is especially noteworthy, that electrical stimulation is thought to reduce the tone of spastic muscles by a negative feedback loop of Renshaw cells to the motoneurons in terms of a recurrent inhibition.²⁹ Furthermore, cutaneous afferents that are stimulated by surface electrical stimulation have been suggested to reduce the motoneuronal excitability via propriospinal interneurons or adaptations of spinal synaptic connections.³⁰ Long term effects on muscle spasticity have been reported and are thought to reflect the plasticity of spinal circuitries.³¹ The protocol in study consisted of 20 Hz stimulations with a pulse duration of 0.1 ms, a duration of 10 min, and an intensity that remained below the motor threshold. However, as presented previously,¹⁴ the CTF remained virtually constant if the calf muscles were stimulated equally but were hindered from cramping by fixing the ankle joint in a neutral position. Thus the stimulation itself is unlikely to explain the observed effects. Since EIMCs are associated with marked muscle pain, it is conceivable that the increased sensory input to motoneurons from activated nociceptors elicited the CTF increments. However, investigating the underlying mechanisms of the altered CTF is challenging and was beyond the scope of the present study. The microneurography technique, which allows the measurement of traffic in muscle mechanoreceptor afferents, would be needed to verify set-point changes of the proprioceptors.

Limitations

The present study is limited by the fact that the assumption of an increased CTF level to be effective in the prevention skeletal muscle cramps is exclusively based on the observation that the CTF is correlated with the cramp susceptibility.¹⁵ Therefore, it needs to be clarified by future studies if EIMC related CTF increases are actually able to prevent exercise induced and/or nocturnal muscle cramps.

Further, the observed variance of CTF and CK responses may partially be explained by the fact that we did not control for potential confounding factors like hydration or muscle temperature. Finally, the small sample size likely contributed to the fact that we missed a significant bout \times group \times time interaction for the CK and CTF response.

Conclusions

The data of the present study reveal that a single bout of EIMCs significantly increases the CTF. As this threshold remained elevated by trend for a period of one week, the applied stimulation protocol may provide a meaningful method to prevent muscle cramps in athletes or patients that severely suffer from nocturnal muscle cramps. It was further shown, that a second bout of the cramp training elicits an additional increase in the CTF, while the perceived muscle pain during the CTF measurements tended to decline and the CK response was blunted. Therefore, repeating the presented cramp training likely improves the ratio between perceived discomfort and muscle damage on the one side and potential benefits of the increased CTF on the other side. Future studies should focus on the perpetuity of the effects in terms of a dose-response relationship to clarify if the duration of CTF adaptations varies with the number of applied training sessions.

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