

Relationship between creatine kinase activity and muscle damage induced by running following cold-water immersion in 10-km runners: secondary analysis of randomized controlled trial

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Abstract:

10-km street run is a highly popular and accessible sport, yet can result in exercise-induced muscle damage for runners. Ensuring a positive continuation of sports practice after the recovery process from running performance becomes essential. While several therapeutics modalities have been employed for accelerate performance recovery, Cold-Water Immersion (CWI) notably stands out among them. In addition, although Creatine Kinase concentration ([CK]) has been used to monitor the recovery status, its relationship with other muscle damage indirect markers following exercise remains inconclusive. Thus, this study aimed to investigate the relationships between creatine kinase concentration ([CK]) and pain, and functional and neuromuscular muscle damage markers after a 10-km street run following cold-water immersion (CWI).

Key Words: Athletic performance; Muscle damage; Recovery; Cryotherapy

Introduction

The street run is a very popular sport, accessible to amateur and recreational athletes, and can be performed over a wide range of distances (Del Coso et al., 2013). Although the 10-km street run has been growing exponentially due to multiple benefits (Ishida et al., 2013), the combination of weight-bearing activity (i.e., concentric and eccentric actions of the lower limbs) and prolonged duration leads to exercise-induced muscle damage (EIMD) (Coso et al., 2012) that is manifested as muscle soreness, swelling, prolonged muscle strength impairment, and intracellular protein leakage into the bloodstream (Brancaccio et al., 2007; Magal et al., 2010). Also, muscle performance may be reduced after a 10-km run; however, its origin remains elusive (Coso et al., 2012).

In this context, the performance recovery process becomes essential to alleviate the deleterious effects of a 10-km run and ensure positive bioadaptation and continuation of sports practice (Wiewelhove Id et al., 2018). Cold-water immersion (CWI) is a popular recovery method among endurance runners (Stenson et al., 2017), probably due to the combined action of hydrostatic pressure and reduced muscle tissue temperature and metabolism, thus accelerating the recovery process (Ihsan et al., 2016).

Few data have been published regarding CWI in runners, and inconsistent findings were reported. Some studies observed improvements only on muscle soreness and perceived recovery (both measured subjectively) following CWI (Wiewelhove Id et al., 2018), while other studies reported no effects on muscle soreness, range of motion, perceived exertion, running performance (Dantas et al., 2019; Stenson et al., 2017), and functional recovery (Dantas et al., 2019; Wilson et al., 2018). These inconsistencies may also be related to different study protocols and recovery markers, which hinders the assessment of both the muscle damage and the recovery process (Micheletti et al., 2019).

Although plasma creatine kinase concentration ([CK]) has been used to monitor the recovery status (Baird et al., 2012), its relationship with muscle damage markers following exercise remains inconclusive. The increase in [CK] was related to decreased running pace (Del Coso et al., 2013), jump performance (Coso et al., 2012), and strength in elite-level soccer games (Owen et al., 2015) and following eccentric exercise (Kim & Lee, 2015). In contrast, studies (Bouzid et al., 2018; Magal et al., 2010) observed no relationships between increased [CK] levels and jumps, maximum voluntary contraction, sprints, and soreness. Recent review raised the discussion of the use of [CK] for workload management within sports medicine, but factors such as [CK] release mechanisms and measurement methods, differences in the analyzed populations and methodological quality of the studies, make it difficult to data interpretation (Haller et al., 2023).

Besides, randomized clinical trials investigating the potential effectiveness of CWI during the recovery process and its relationships with muscle damage markers in street runners have not been investigated. Therefore, this study aimed to analyze the relationships between [CK] and clinical, functional and neuromuscular performance markers after a 10-km run following CWI. We hypothesized that increased [CK]

was related to increased muscle soreness and decreased functional and neuromuscular performance long-run and that this relationship would be reversed after CWI.

Material & methods

Experimental design

This is a three-arm parallel-group randomized controlled trial (ClinicalTrials.gov NCT03094689) designed to investigate the relationship between muscle damage indirect markers following CWI after 10-km running and conducted according to the Consolidated Standards of Reporting Trials (CONSORT) (Boutron et al., 2017). The study was approved by the Research Ethics Committee of Federal University of Rio Grande do Norte (number 1.441.252) according the Resolution 466/12 of the National Health Council, and the Declaration of Helsinki.

The subjects were randomized into three groups: cold-water immersion group (CWIG), immersion group (IG), or control group (CG) (see CONSORT flow chart in the supplementary material). An offsite randomization schedule was prepared by an independent researcher to ensure allocation concealment (#1). Other independent researchers were responsible for the supervised intervention (#2), while another blinded researcher (#3) conducted all clinical, biochemical, functional, and neuromuscular assessments (baseline, post-running, post-intervention and 24h post-intervention). To guarantee the blindness of researcher #3, the participants were instructed not to reveal the group they belonged.

Statistical analysis was planned to investigate the impact of muscle damage, the possible effects induced by the recovery interventions in muscle damage markers and to determinate whether there is a relationship between change of these markers in time. Δ_1 was defined by mean change of dependent variable value (e.g.: Pain, CK) from T0 to T1 (Δ_{T1-T0}); Δ_2 : mean change of values from T1 to T2 (Δ_{T2-T1}); Δ_3 : mean change of values from T2 to T3 (Δ_{T3-T2}).

Participants

30 recreational self-reported healthy male runners who had never performed a 10-km but were practicing street-running for at least six months, two times per week, with neither pain in the lower limbs nor cardiac, musculoskeletal, orthopedic, or neurological diseases, were included in the study (Table 1). Those with hypersensitivity or allergy to cryotherapy, who did not finish the 10-km run, or failed to perform any study procedures, were excluded. Sample size was estimated based on Pearson's correlation coefficients between CK concentration and functional performance ($r = 0.54$) observed in the study of Del Coso *et al.* (Coso et al., 2012). Thus, considering a statistical power of 0.8 and a significance level of 5%, the optimal number was estimated as 25 participants.

Table 1 – Demographic characteristics of the subjects and dependents variables at baseline assessment.

	Control n = 10	Immersion n = 10	Cold Water Immersion n = 10	p Value
Age (years)	33.00 ± 4.84	31.71 ± 5.43	30.28 ± 6.10	0.637
Body mass (kg)	76.87 ± 7.97	76.85 ± 8.25	78.40 ± 5.91	0.762
Stature (cm)	173.62 ± 5.60	174.14 ± 5.55	177.57 ± 6.85	0.415
BMI (kg/m ²)	25.96 ± 1.31	25.56 ± 0.93	26.03 ± 1.05	0.697
EVA (mm)	0	0	0	0
CK (U/L)	258.90 ± 223.54	218.70 ± 95.34	217.50 ± 112.74	0.794
20m ST (s)	5.20 ± 0.17	5.39 ± 0.26	5.22 ± 0.22	0.512
TW _{Ext}	1057.98 ± 140.13	1067.39 ± 190.10	1075.12 ± 201.16	0.977

Legend: BMI: Body Index Mass; CK: Creatine Kinase; 20m ST: Modified 20 meters sprint test; TW_{Ext}: Extensor total work. ANOVA *One-Way* test between-groups.

All participants involved received verbal information about purpose and potential risks of procedures and signed an informed consent form.

Procedures

The experimental design of this study (Figure 1) was characterized by four evaluations: baseline (T0), post-running (T1), post-intervention (T2) and 24h post-intervention (T3) assessments. The baseline assessment (T0) immediately before the 10-km run, except for the isokinetic evaluation that was performed 48h before the run to avoid bias. The assessment of pain, CK concentration, and time during the modified 20-m ST were performed 10 minutes before the run.

Immediately after the 10-km run, performed on a pre-established circuit around the University, a second assessment (T1) was performed and Heart rate (HR – cardiac monitor Beurer model PM25) and perceived exertion (Borg Scale 6-20) were also evaluated immediately after the run. According randomization, immediately after T1 the participants were allocated to the interventions. After interventions, the third assessment (T2) was conducted and fourth assessment (T3) was performed 24h post-intervention (Figure 1).

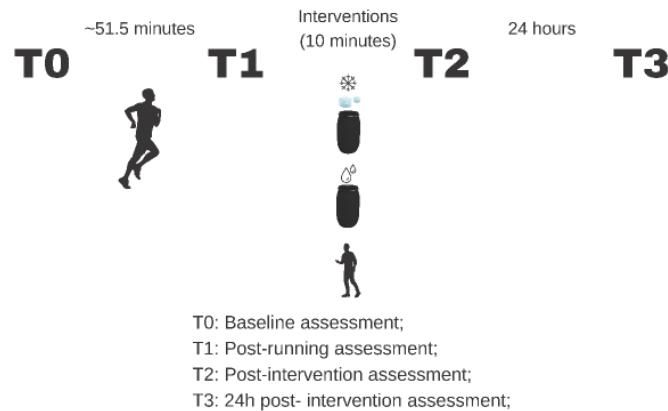


Figure 1 – Experimental design of the study protocol.

Outcomes

All participants were instructed to avoid caffeine-containing beverages, alcohol, high intensity trainings, and maintain the physical routine and eating habits at least one week before and during all experimental period.

Clinical markers. Muscle soreness in the anterior thigh (quadriceps) was assessed using the Visual Analogic Scale (VAS - 0 to 100mm), in which “no pain” was indicated on the left side (0mm) and “maximum pain” (100mm) on the right side.

Biochemical analysis. Venous blood was collected by an experienced pharmaceutical team, placed in anticoagulant tubes (10ml), and protected from the light. To examine blood CK levels (ELISA, Abcam, Cambridge, UK), samples were centrifuged in the laboratory (3000 rpm/10min) using a semi-automatic analyzer (CV = 0.6%).

Functional performance. Two cones and one digital chronometer was used to perform the Modified 20-m Sprint Test (20-m ST) (Nimphius et al., 2018). The first cone (indicating the starting point) was positioned 10-m apart from the second cone (indicating the turning point). The runners were instructed to initiate the test with the non-dominant limb positioned before the starting line point, run the first 10 meters as fast possible, turn around the cone, and return to the starting line (20 m total) (Nimphius et al., 2018). One blinded researcher was positioned at the starting line to measure the time spent to perform the test (in seconds) with a digital chronometer. Before the test, the participants performed two trials for familiarization, with a 2-minute interval in between. Three sets were conducted and the fastest run was included in data analysis.

Neuromuscular performance. The extensor total work (TW_{Ext}) was measured using an isokinetic dynamometer (Biodex Multi-Joint System 3, Biodex Biomedical System Inc, New York, USA) in the dominant limb, identified through kicking and/or hopping on a single leg (2). Three submaximal repetitions were conducted before the test (familiarization) and, then, five maximum voluntary knee flexion/extension concentric contractions were performed at a speed of 60°/second and a total range of motion of 85° (Dvir, 2004). No visual feedback was allowed for the participants during the isokinetic dynamometer test.

Recovery protocols

Cold Water Immersion. Runners were immersed in an ice bath ($10^{\circ}\text{C} \pm 0.35^{\circ}\text{C}$) up to the anterior superior iliac spine level for 10 minutes (Abaídia et al., 2017; Roberts et al., 2014). A digital thermometer (Salvterm® 1200K, Brazil) was placed in the ice bath to monitor the temperature during the entire immersion time. If necessary, ice or cold water was added to ensure the temperature at 10° .

Immersion group. Subjects were immersed in a bath with water at room temperature ($29.8^{\circ}\text{C} \pm 0.66^{\circ}\text{C}$ - local humidity and temperature conditions) to the same depth and immersion time of the CWI group. A thermometer also was placed in the bath to monitor the water temperature.

Control group. The participants were instructed to rest quietly in a standing position for 10 minutes after the running.

Statistical analysis

The Shapiro-Wilk and Levene tests were used to assess data distribution and homogeneity of variances, respectively. The Mauchly’s test was performed to assess sphericity, while the Greenhouse-Geisser test was used to perform corrections, if necessary (i.e., sphericity violation). Descriptive statistics were presented as the mean \pm standard deviation (SD) and 95% confidence interval (CI95%). Analysis of Variance (ANOVA) three-way followed by Tukey’s post-hoc test was used to analyze time/group interaction between the dependent variables. To avoid type II error, effect-sizes (Cohen’s f statistic) were calculated and interpreted as small (>0.10), moderate (between 0.25 and 0.40), and large (<0.40). Relationships between mean changes (Δ ; i.e., Δ_{T1-T0} , Δ_{T2-T1} , Δ_{T3-T2}) in [CK] and pain, TW_{Ext} and 20m ST time were assessed using Pearson’s correlation coefficients (r) and interpreted as: very large ($r \geq 0.7$), large ($0.7 > r \geq 0.5$), moderate ($0.5 > r \geq 0.3$), and small ($0.3 > r \geq 0.1$) (Hopkins et al., 2009).

Inferential analyses were performed using the Statistical Package for the Social Sciences, version 23.0 (IMB Corp. USA). The significance level for all analyzes was set at $p < 0.05$ (2-sided).

Results

Runners demonstrated similar conditions after the run (T1), reaching high perceived exertion and heart rate levels without significant differences between groups (Table 2).

Table 2 – Training characteristics and runners' condition after running.

	Control n = 10	Immersion n = 10	Cold Water Immersion n = 10	p Value
Practice Time (Months)	13.25 ± 1.48	13.14 ± 1.57	12.28 ± 1.97	0.503
Frequency of Practice (Weekly)	2.87 ± 0.64	2.85 ± 0.89	2.71 ± 0.75	0.999
Borg Scale	17.40 ± 0.51	17.70 ± 0.82	18.50 ± 1.08	0.276
HR _{Max} (%)	96.40 ± 8.55	93.83 ± 3.65	98.50 ± 4.42	0.233
Running time (min)*	50.80 ± 3.15	52.00 ± 3.26	51.90 ± 3.84	0.690

Legend: HR_{Max}: Máximum Heart Rate. Borg Scale and HR_{Max} was collected immediately after run. *Running duration was similar to the mean duration reached by American recreation runners (Vickers & Vertosick. 2016). ANOVA *One-Way* test between-groups.

No time-group interaction was observed between the dependent variables analyzed (Figure 2). The 10-km run effect was similar between groups and characterized by low-magnitude muscle damage since no pain was observed during the T1 assessment. A mean increase of 32.46% in [CK] (CI95%: 23.86 – 41.01) and 4.94% in the 20m sprint time (mean difference: 0.25 sec; CI95%: 0.13 – 0.38), and a mean decrease of 12.06% in TW_{Ext} (mean difference: 128.55 J; CI95%: 59.82 – 197.28) was found (Figure 2). In all groups, no significant correlations were observed between the Δ_{T1-T0} [CK] and changes in pain, 20m sprint time or TW_{Ext} (Table 3).

After interventions (T2) positive correlations were observed between the Δ_{T2-T1} [CK] and TW_{Ext} in the IG (Table 3). A mean increase of 87.70% in [CK%] 24h after interventions (T3) induced by 10-km running (CI95%: 34.45 – 140.94) was found between groups. Furthermore, even without between-group differences, both the IG and CWIG reduced 49.25% of the CK overflow compared with CG at T3, while the CWIG improved the 20m sprint time by 5.24% compared with T2 (mean difference: 0.28 sec; CI95%: 0.02 – 0.55). Negative correlations were observed between Δ_{T3-T2} [CK] and TW_{Ext} in the CG (Table 3).

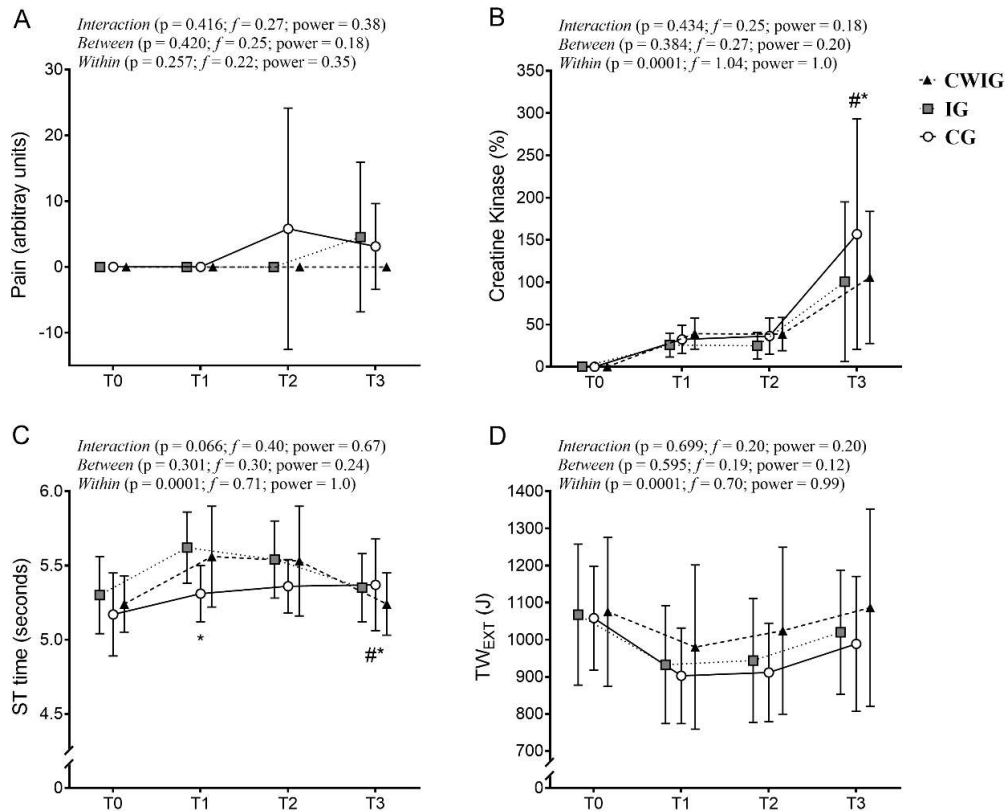


Figure 2 – Muscle damage indirect markers: Pain (A); Creatine kinase concentration normalized by baseline values (B); Time of 20 meters sprint test (C); Isokinetic Extensor total work (D); Values recorded at baseline (T0); post-running (T1); post-intervention (T2) and 24h post-intervention (T3) assessments. Values are means and standard deviations.

CWIG: cold-water immersion group; IG: immersion group; CG: control group.

*p < 0.05, compared with T0 (to all groups); #p < 0.05, compared with T2 (only to CG in B and only to CWIG in C).

Table 3 – Correlations between mean changes of CK concentration, pain, time of ST and TW_{Ext} during study period.

	ΔCK					
	CG (n=10)		IG (n=10)		CWIG (n=10)	
	<i>r</i>	P value	<i>r</i>	P value	<i>r</i>	P value
Δ_{T1-T0} Pain	-	-	-	-	-	-
Δ_{T1-T0} ST	-0.245	0.494	-0.224	0.534	-0.084	0.818
Δ_{T1-T0} TW	0.400	0.252	0.389	0.267	-0.350	0.322
Δ_{T2-T1} Pain	0.182	0.616	-	-	-	-
Δ_{T2-T1} ST	0.374	0.287	0.108	0.766	-0.114	0.755
Δ_{T2-T1} TW	-0.232	0.520	0.671	0.034*	-0.130	0.719
Δ_{T3-T2} Pain	0.145	0.690	-0.366	0.298	-	-
Δ_{T3-T2} ST	0.254	0.479	-0.471	0.169	0.623	0.054
Δ_{T3-T2} TW	-0.658	0.038*	-0.007	0.985	-0.290	0.417

Legend: Δ_{T1-T0} : mean change of dependent variable value (e.g.: Pain, CK) from T0 to T1 (i.e.: T1-T0); Δ_{T2-T1} : change value from T1 to T2 (i.e.: T2-T1); Δ_{T3-T2} : change value from T2 to T3 (i.e.: T3-T2); ST: Modified 20m Sprint Test; TW: Extensor Total Work.

* $p < 0.05$ (significant correlation).

Discussion

This is the first study investigating the relationships between [CK] and functional and neuromuscular performance markers after a 10-km run following CWI. The main findings were that changes in [CK] were not related to changes in others muscle damage indirect markers, and CWI did not improve recovery after a 10-km run. The hypothesis that the increase in CK concentration after exercise would be related to increased pain and decreased functional and neuromuscular performance as previously described in the literature (Epstein et al., 2006; Oxendale et al., 2016) was rejected. The increase in [CK] is related to the worsening of pain after muscle damage induced by eccentric contractions, and anaerobic performance reduction after endurance exercise (Epstein et al., 2006). In elite rugby players after matches, the increase in game's duration, high intensity runs and the number of collisions correlated with reduced upper limb functional performance and increased [CK] levels (Oxendale et al., 2016).

Despite this, no correlations between [CK] and pain after running was observed in our study, corroborating the findings of Magal *et al.* (Magal et al., 2010) who investigated this relationship after muscle damage induced by an isokinetic dynamometer. These results can be justified by the magnitude of muscle damage produced since it has a greater influence on delayed onset muscle soreness (DOMS) and cellular response to EIMD (Baird et al., 2012). Nevertheless, even recruiting individuals with specific conditions and performing high effort levels, the induced muscle damage not produce DOMS and the increase [CK] levels was considered small. The lack of relationships between [CK] changes and functional and neuromuscular performance after running corroborated with Margaritis *et al.* (Margaritis et al., 1999) who found no correlations between [CK] and knee muscle strength in triathletes after a long-distance triathlon race. Our results suggest a small interference of muscle damage induced by the 10-km run on performance since a 4.94% increase in the modified 20-m sprint time and a 12.06% decrease in TW_{Ext} , together with a 32% increase in CK concentration was found. However, Del Coso et al. (Coso et al., 2012) (Del Coso et al., 2014) observed relationships between increased [CK] levels and both running time and jump performance after half-ironman triathlon, suggesting muscle breakdown as one of the causes for performance reduction.

CWI had no effects on recovery muscle damage markers between T1 and T2; however, the small increase in TW_{Ext} correlated with minimal CK levels decrease only in the IG. Thus, it seems that, even without any CWI effects, the neuromuscular recovery process started before [CK] reached its peak which impairs the association between CK levels and muscle damage markers.

Studies indicate that peak [CK] can be reached between 24 and 72h while other muscle damage markers are affected earlier (Baird et al., 2012; Dupuy et al., 2018). In the present study, the peak was reached 24h after the 10-km run in all groups, but the greater CK leakage was observed only in the control group, suggesting a possible effect of the CWI (Dantas et al., 2019). Nevertheless, the [CK] use as a performance recovery marker is still controversial (Bouzid et al., 2018; Coso et al., 2012; Del Coso et al., 2013; Kim & Lee, 2015). These conflicts increase when methods to accelerate the recovery of muscle damage markers are applied. Ascensão *et al.* showed a reduced [CK] leakage after CWI in soccer players (Ascensão et al., 2011), while other studies reported no CWI effects (Abaídia et al., 2017; Fonseca et al., 2016; Roberts et al., 2014). These inconclusive results would also be related to the muscle damage protocol. Also, the exercise intensity magnitude has a greater influence on cellular response to EIMD than the duration (Baird et al., 2012). Low-intensity (LI) exercise (50% of maximal isometric strength) induces less muscle damage and reduces muscle performance compared with maximal eccentric exercise (Baird et al., 2012).

Therefore, a higher number of muscle damage, and functional and neuromuscular markers should be considered for the analysis of performance recovery (e.g.: lactate, cortisol, stress, depression (KUSUMA et al., 2021), pain, sleep, or recovery perception) since only one isolated marker, such as CK, is not accurate as a

recovery performance marker. Monitoring the performance recovery process of athletes is still a major challenge for researchers, clinicians and runners. This becomes even more challenging when it involves techniques to accelerate the recovery of these athletes.

High-endurance athletes commonly train/compete multiple times within 24 hours and need quick recovery between exercise bouts. Thus, based on a biochemical, functional, and neuromuscular perspective, it is also possible that the 10-km street run caused muscle damage of low-magnitude. Some limitations must be acknowledged. The internal load during the 10-km street run was not assessed as well as sleep quality, perception of recovery, and nutritional control during the study period.

Conclusion

There are no relationships between [CK] and pain, functional and neuromuscular performance during the recovery process of street runners following CWI. Thus, after long-runs, the recovery process cannot be evaluated by isolated changes in CK concentration. In addition, CWI does not accelerate the recovery process of runners after a 10-km run.

From a practical point of view, monitoring the performance recovery process of athletes is still a major challenge for researchers, clinicians, coaches and runners. This becomes even more challenging when it involves techniques to accelerate the recovery of these athletes. Therefore, we tested the hypothesis that the CK concentration was related to clinical, functional, and neuromuscular muscle damage markers after CWI and whether CK could be used to monitor the recovery process. Our findings suggest no relationships between [CK] and pain, functional and neuromuscular performance during the recovery process of street runners following CWI. Thus, after long-runs, the recovery process cannot be evaluated by isolated changes in CK concentration.

Conflict of interest The authors declare that they have no competing interests.

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