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## Caffeine Attenuates Delayed-Onset Muscle Pain and Force Loss Following Eccentric Exercise

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**Abstract:** This double-blind, placebo-controlled, repeated-measures experiment examined the effects of a  $5 \text{ mg} \cdot \text{kg}^{-1}$  body weight dose of caffeine on delayed-onset muscle pain intensity and force loss in response to 64 eccentric actions of the dominant quadriceps induced by electrical stimulation. Low caffeine-consuming college-aged females ( $n = 9$ ) ingested caffeine or placebo 24 and 48 hours following electrically stimulated eccentric exercise of the quadriceps. One hour after ingestion, maximal voluntary isometric contractions (MVIC) and submaximal voluntary eccentric actions were used to determine force loss during activation of damaged quadriceps and whether caffeine attenuates muscle pain intensity. Pain intensity was measured using a 0 to 100 visual analog scale. Caffeine produced a large (12.7 raw visual analog scale [VAS] units;  $-48\%$ ; Cohen's  $d$  effect size =  $-0.88$ ), statistically significant hypoalgesia during the MVIC ( $t = -2.52$ ;  $df = 8$ ;  $P = .036$ ). The reduction in pain scores during submaximal voluntary eccentric movements was smaller (7.8 raw VAS units;  $-26\%$ ,  $d = -0.34$ ), as was the increase in MVIC force ( $4.4\%$ ;  $d = 0.13$ ).

**Perspective:** Eccentric exercise occurs when skeletal muscles produce force while being lengthened. For example, the biceps brachii muscles act eccentrically when a cup of coffee is lowered from the mouth to a tabletop. This experiment found that caffeine (equal to  $\sim 2$  cups of brewed coffee) could produce a large reduction in pain resulting from eccentric exercise-induced, delayed-onset muscle injury. This finding may improve the quality of life of individuals who experience skeletal muscle pain after engaging in unaccustomed, eccentrically biased exercise.

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**Key words:** Adenosine antagonist, DOMS, muscle damage, electrical stimulation, soreness.

Dozens of experiments have tested the effectiveness of pharmacological (eg, nonsteroidal anti-inflammatory medications), physical (eg, massage, stretching), and other potential therapies (eg, antioxidants, ultrasound) for reducing delayed-onset muscle pain caused by eccentric exercise. In general, these treatments have been inconsistent in attenuating delayed onset muscle pain or had small or no effect.<sup>7</sup>

Investigators have not reported the results of experiments aimed at determining the role of caffeine or adenosine in delayed-onset muscle pain. Adenosine is an algesic known to be involved in inflammation.<sup>20</sup> Adenosine receptors are located in numerous neural tis-

ues involved in nociception and pain processing, including peripheral afferent nerves,<sup>21</sup> the dorsal horn of the spinal cord, and higher brain areas.<sup>31</sup>

Caffeine is a competitive, nonselective adenosine receptor antagonist primarily acting on high-affinity adenosine  $A_1$  and  $A_{2A}$  receptors.<sup>10</sup> Orally ingested caffeine by humans has effects on both the peripheral and the central nervous system because caffeine crosses the blood-brain barrier. Habituation and withdrawal effects occur with chronic use and disuse of caffeine, and these effects are associated with upregulation and downregulation of adenosine receptors.<sup>16</sup>

Caffeine has documented exercise-related hypoalgesic effects. Caffeine significantly increases the exercise test duration to onset of angina<sup>26</sup> and reduces experimentally induced ischemic forearm muscle pain<sup>23</sup> as well as quadriceps muscle pain that occurs naturally during cycling exercise.<sup>22,24</sup> Because it has been hypothesized that delayed-onset muscle pain is caused in part by increased sensitization of nociceptors via an accumulation of inflammation-related algesics,<sup>6</sup> it is plausible that caffeine

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also could reduce delayed-onset muscle pain. This possibility has not been tested empirically.

Caffeine in doses above  $3 \text{ mg} \cdot \text{kg}^{-1}$  body weight also has been shown repeatedly to improve endurance performance,<sup>12</sup> but less attention has been given to whether caffeine ingestion has ergogenic effects on muscular strength. Caffeine doses of approximately 4 to  $7 \text{ mg} \cdot \text{kg}^{-1}$  taken 60 minutes prior to testing resulted in small improvements in maximal voluntary strength in five of six studies that used lower body strength measures.<sup>2,14,15,17,18,27</sup> The overall increase in mean strength in the five studies with positive results was 4.4%; however, the test-retest reliability of the strength measures was not reported. No studies have reported on the effect of caffeine on the strength loss that follows muscle injury induced by eccentric exercise.

The purpose of this double-blind, placebo-controlled, repeated-measures experiment was to test whether a  $5 \text{ mg} \cdot \text{kg}^{-1}$  body weight dose of caffeine attenuates either muscle pain or maximal isometric force loss following eccentric exercise.

## Methods

### Participants

University of Georgia female undergraduates were recruited. Volunteers were offered the opportunity to earn extra credit for a class by participating as a test subject in one of several experiments or reviewing primary research papers on exercise-related topics. Eligibility required one to be: (a) nonpregnant, (b) a non-smoker, (c) not overweight, defined as a body mass index  $<25$ , (d) not involved in any lower body resistance exercise program that included knee extensions or flexions more than once per week to reduce the likelihood of a protective effect, (e) not currently training for any competitive athletic event, (f) a low daily caffeine consumer ( $<100 \text{ mg} \cdot \text{day}^{-1}$ ), (g) free from known hypersensitivity to caffeine consumption and sensitivity based on a self-reported caffeine history questionnaire and 7-day recall, (h) not taking any prescription medicine or over-the-counter stimulants, (i) free from medical contraindication for performing leg exercises, and (j) without a pre-existing knee injury. Participants were informed of risks associated with the project, and each provided written informed consent, using a document that had been approved by the Institutional Review Board at the University of Georgia. Ten volunteers completed testing.

### Procedures

#### Day 1

Potential participants completed four questionnaires to establish eligibility: an exercise history and injury questionnaire, a medical history questionnaire, a 7-day caffeine recall, and a caffeine sensitivity questionnaire.

Participants were measured for height and weight, using a calibrated DETECTO scale. Next, maximal voluntary isometric contraction (MVIC) strength of the dominant

quadriceps was assessed. Subjects were seated in a custom-built chair with the hip and knee secured at  $\sim 70^\circ$  of flexion. The leg was firmly secured to a rigid lever arm with an inelastic strap fastened at the ankle to ensure that the knee extensors could only perform isometric contractions. Participants were instructed to hold themselves down on the chair and activate only their quadriceps. Isometric mode contractions were used to minimize the potential for skeletal muscle injury. The moment arm was established by placing a load cell (model 2000A; Rice Lake Weighing Systems, Rice Lake, WI) parallel to the line of pull and perpendicular to the lever arm. Torque was recorded from the load cell by using a MacLab analog-to-digital converter (model ML 400; AD Instruments, Milford, MA) sampling at 100 Hz and interfaced with a portable Macintosh computer (Apple Computer, Cupertino, CA). Peak torque was calculated in Newton-meters, using a standardized lever length (0.304 meters). Three MVICs, separated by 1 minute, were performed. Participants were instructed to perform each MVIC as quickly and explosively as possible, and the average of the 3 trials was used as the criterion MVIC. These instructions and methods were used for all subsequent tests of MVIC strength. Participants next were fitted to and familiarized with the Kin-Com dynamometer (Isokinetic International, Harrison, TN). The dominant leg was attached to the Kin-Com lever arm at the ankle and positioned so the axis of rotation was aligned with the knee joint. The length of the lever arm was measured for each individual and maintained during all subsequent testing.

#### Day 2

Participants underwent an electrically induced, lengthening protocol designed to produce moderate levels of muscle injury and delayed-onset muscle pain of the quadriceps. Two  $6.98 \times 10.16$ -cm electrodes were placed distally on the vastus medialis and proximally on the vastus lateralis of the dominant quadriceps. A Rich-Marr TheraMINI electrical stimulator was used to elicit 8 sets of 8 eccentric actions of the dominant quadriceps while participants were positioned in the Kin-Com dynamometer. The electrical stimulus consisted of a biphasic sinusoidal wave with a 0.450-ms pulse duration elicited at 100 Hz. The absolute current applied varied among participants, but each received a current that resulted in force produced of  $\sim 50\%$  MVIC. Fifty percent of MVIC was selected to adequately activate and damage skeletal muscle fibers but not harm joint or soft tissue during the eccentric actions and because of high success in eliciting delayed onset muscle soreness of the quadriceps using this protocol in the past.<sup>8</sup>

The eccentric actions were performed from  $10^\circ$  to  $80^\circ$  below horizontal ( $70^\circ$  range of motion). The start force at  $10^\circ$  was set at the Kin-Com's default of 50 Newtons to ensure that the participants could efficiently initiate each eccentric movement even as force decreased throughout the protocol. The eccentric actions were performed at a constant angular velocity of  $120^\circ \cdot \text{sec}^{-1}$ . Electrical stimulation of the quadriceps was elicited by using a 1-second "on," 1-second "off" protocol. One re-

searcher controlled the stimulation pattern for all participants. The stimulator wire was plugged in to elicit each eccentric movement and then unplugged once the 70° range of motion was completed. After each eccentric movement, the researcher returned the lever arm back to 10° below horizontal starting position at a controlled rate of  $200^\circ \cdot \text{sec}^{-1}$  for each movement. Each set was separated by 1 minute.

Following the eccentric exercise protocol, participants walked from the Kin Com to the custom-built chair to assess the force lost immediately following the eccentric exercise protocol. Participants performed three maximal voluntary isometric contractions, each separated by 1 minute. The time from the end of the eccentric exercise to MVICs was ~2 minutes.

### Days 3 and 4

Participants again reported for testing at 24 and 48 hours after the eccentric exercise protocol. The procedures were identical on these days except that on one day caffeine was ingested and the other a placebo was ingested.

Three MVICs were completed, both to determine maximal force and to stimulate muscle pain. Immediately after the 3 exercises were completed, the participants were asked to report the highest pain intensity experienced during the 3 MVICs.

Two subsequent submaximal eccentric actions also were used to stimulate pain. The participants twice voluntarily activated the Kin-Com from 10° to 80° below horizontal at a speed of  $90^\circ \cdot \text{sec}^{-1}$ . The participants needed to overcome the Kin-Com default setting of 50 N of preset load force to initiate these eccentric actions and were instructed to resist against the load cell throughout the entire range of motion. The low preset load of 50 N was chosen because of the participants' decreased ability to generate force at 24 and 48 hours following a damaging eccentric exercise protocol and at the start angle of 10° below horizontal. Immediately after the second eccentric action, the participant reported the highest pain intensity experienced during the 2 exercises. Next, the participants consumed either a caffeine pill or a placebo pill. One hour after pill ingestion, the MVIC and submaximal eccentric tests were repeated and the associated pain ratings were obtained.

The order in which caffeine or placebo was received was counterbalanced and randomly assigned. Twenty-four hours after eccentric exercise, 5 of the participants ingested  $5 \text{ mg} \cdot \text{kg}^{-1}$  of caffeine (Caffeine Anhydrous, USP; Meridian, Decatur, AL) and the other five participants received placebo (flour). Caffeine and placebo were delivered in gelatin capsules (No. 0; NOW Foods, Bloomington, IL). Forty-eight hours after eccentric exercise, those who previously consumed caffeine received placebo and those who had consumed placebo received caffeine. All participants consumed caffeine or placebo with 500 mL of water and then sat and read quietly in a sound-dampened, thermoneutral environmental chamber maintained at  $23^\circ \pm 2^\circ$  (Celsius) and ~50% relative humidity.

Substantial evidence supports the validity of scores using a visual analog scale (VAS) as a measure of pain intensity.<sup>29</sup> Quadriceps muscle pain intensity ratings were obtained by participants placing a vertical mark with a pen on a 10-cm horizontal VAS. The left and right ends of the scale were anchored with the phrases "no pain" and "most intense pain imaginable," respectively. Pain intensity was scored from 0 to 100, measured in millimeters from the left end of the scale.

### Statistical Analysis

Raw data were entered into the Statistical Program for Social Sciences (SPSS version 13.0 for Windows; SPSS, Chicago, IL), which was used for data analysis.

### Preliminary Analyses

One participant completed only 16 of 64 eccentric muscle actions because of equipment failure. Her data were included in the analysis because the delayed force loss (ranging from 3.5% to 8.5%) and muscle pain intensity responses (VAS scores ranging from 9 to 14) observed prior to caffeine or placebo ingestion were adequate to test the experimental hypotheses.

One participant who completed the study and whose data were included in the primary analysis reported a knee injury. Whether the injury was caused by the exercise protocol, an unrecognized preexisting condition, or physical activities performed outside the laboratory was unclear. There was nothing remarkable about this participant's reduction in MVIC force (ranging from 2% to 16%) or quadriceps pain intensity ratings (VAS score ranging from 3 to 30) at either 24 or 48 hours after eccentric exercise that would suggest the injury biased the outcome of this study.

One participant experienced no delayed-onset muscle pain 24 to 48 hours after eccentric exercise, and her data were excluded from the primary analysis.

Preliminary analyses ( $n = 9$ ) were performed to determine the trial-to-trial reliability of the MVIC force measures. The associated means for each trial were day 1 baseline = 183.4, 185.1, 188.0 Nm; day 2 immediately after eccentric exercise = 153.0, 154.3, 154.9 Nm; 24 hours before ingestion = 159.2, 159.0, 158.2 Nm; 24 hours after ingestion = 157.4, 161.1, 160.3 Nm; 48 hours before ingestion = 155.9, 161.2, 164.7 Nm; and 48 hours after ingestion = 159.8, 166.4, 166.7 Nm. The intraclass correlation (ICC) reliability model used was a one-way (3 trials) random-effects model. The ICC model also used consistency as the type of agreement and the single-measures option. High ICC reliability was found for each of the 6 sets of 3 MVIC force assessments, with day 1 baseline = 0.980; day 2 after eccentric exercise = 0.995; 24 hours before ingestion = 0.986; 24 hours after ingestion = 0.986; 48 hours before ingestion = 0.985; and 48 hours after ingestion = 0.990. These preliminary analyses supported the use of the average of 3 MVICs as the criterion measure of maximal isometric force in the primary analysis.

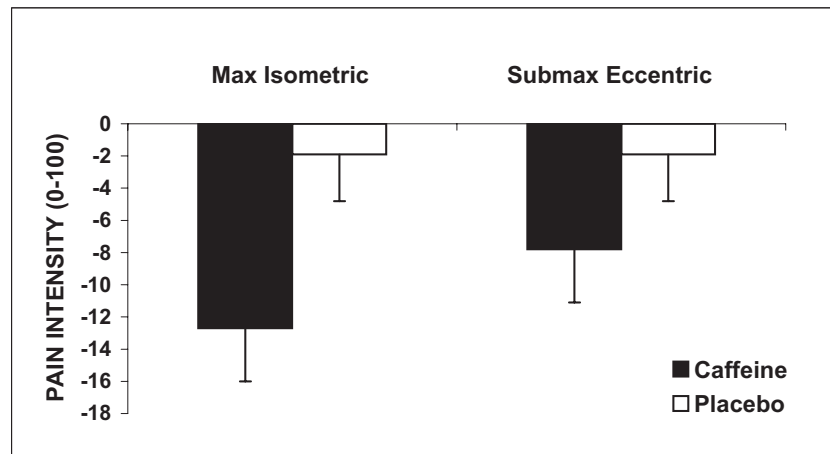


Figure 1. Pain intensity change scores.

### Primary Analyses

Descriptive data are reported as means and standard deviations in text and tables. Means and standard errors are used in Fig 1. Effect size calculations were made by using Cohen's *d*; that is, the difference in 2 means divided by the pooled standard deviation. Dependent *t* tests using pre- to post-ingestion change scores comparing the caffeine and placebo conditions were used to test the hypotheses.

Preliminary analyses showed that caffeine attenuated pain and force loss at both the 24- and 48-hour testing periods. Consequently, data from the 24- and 48-hour tests were combined.

### Results

Selected characteristics of the 9 participants are presented in Table 1.

#### Force Loss After Eccentric Exercise

Baseline (day 1) MVIC torque was  $185.4 \pm 48.1$  Nm. Following eccentric exercise on day 2, MVIC force was lower than baseline by 31.4 Nm (~17%; Cohen's *d* effect size =  $0.59 SD_{pooled}$ ). The reduction in force was significantly different than baseline ( $t = 4.77$ ;  $df = 7$ ;  $P = .001$ ).

#### Delayed-Onset Muscle Pain at 24 and 48 Hours

Mean pain intensity ratings prior to pill ingestion during MVIC at 24 and 48 hours were  $24.3 \pm 14.09$  and  $20.44 \pm 13.85$ , respectively. Mean pain intensity ratings prior to ingestion during submaximal voluntary eccentric actions at 24 and 48 hours were  $27.89 \pm 11.19$  and  $30.33 \pm 11.98$ , respectively.

#### Effect of Caffeine on Pain

Pain data in the caffeine and placebo conditions are presented in Table 2. Fig 1 shows the data consistent with the *t* test analysis. One hour after caffeine ingestion, pain intensity during the maximal voluntary isometric contractions was decreased by 12.7 raw VAS units

(-47.7%, Cohen's *d* effect size =  $-0.88 SD_{pooled}$ ). This reduction in pain intensity was statistically significantly greater than the 1.9 VAS score decrease found after placebo ingestion ( $t = -2.52$ ;  $df = 8$ ;  $P = .036$ ). Eight of 9 participants reported larger decreased MVIC pain scores following caffeine ingestion compared with placebo, compared with pre-ingestion.

One hour after caffeine ingestion, pain intensity stimulated by voluntary lengthening of the quadriceps during submaximal eccentric actions decreased by 7.8 raw VAS units (-26%, Cohen's *d* effect size =  $-0.34 SD_{pooled}$ ). Six of the 9 participants reported larger decreased pain scores following caffeine ingestion compared with placebo during submaximal eccentric actions. Two participants reported no change in pain scores. This reduction in pain intensity was not statistically greater than the 1.9 VAS score decrease found after placebo consumption ( $t = -.975$ ;  $df = 8$ ;  $P = .368$ ).

#### Effect of Caffeine on Force

Descriptive MVIC force data are presented in Table 2. One hour after caffeine ingestion, force increased by a small magnitude compared with before ingestion (4.4%; Cohen's *d* effect size =  $0.12 SD_{pooled}$ ). Five of 9 participants reported an increase in force production following caffeine ingestion compared with placebo. One participant experienced no change in force. This increase in force was not statistically significantly greater than the 1.5% reduction in force found after placebo ingestion ( $t = 1.43$ ;  $df = 8$ ;  $P = .19$ ).

Table 1. Characteristics of the Nine Female Participants

Age (y)	$21.3 \pm 1.6$
Height (cm)	$169 \pm 6.0$
Mass (kg)	$59.8 \pm 6.9$
Daily caffeine consumption (mg day <sup>-1</sup> )	$55.1 \pm 30.9$
Body mass index	$20.9 \pm 1.8$
Caffeine dose	$298.9 \pm 34$

NOTE. Values are mean  $\pm$  SD.

**Table 2. Pain Intensity Ratings and Maximal Voluntary Isometric Contraction Torque**

	<i>MVIC pain (0-100)</i>		<i>SVEA pain (0-100)</i>		<i>MVIC torque (Nm)</i>	
	<i>Placebo</i>	<i>Caffeine</i>	<i>Placebo</i>	<i>Caffeine</i>	<i>Placebo</i>	<i>Caffeine</i>
Before ingestion	18.2 ± 10.8	26.6 ± 15.6	28.1 ± 11.3	30.1 ± 11.9	162.8 ± 58.7	156.9 ± 51.9
After ingestion	16.3 ± 8.9	13.9 ± 13.1*	26.2 ± 9.9	22.3 ± 16.8	160.4 ± 54.6	163.4 ± 56.9
Effect size d	-0.19	-0.88	-0.12	-0.34	-0.04	0.12
Average % change	-10.4	-47.7	-6.8	-25.9	-1.5	4.4

Abbreviations: MVIC, Maximal voluntary isometric contraction; SVEA, submaximal voluntary eccentric action.

NOTE. Values are mean ± SD.

\*Statistically different change versus placebo ( $P < .05$ ).

## Discussion

The primary novel finding from this study was the large pain reduction during maximal voluntary isometric contraction following caffeine ingestion. Because the release of adenosine, a potent algic agent, is increased during inflammation following injury<sup>20</sup> and caffeine is an adenosine antagonist, it is plausible that the findings resulted from caffeine attenuating nociceptive activity induced by adenosine in the periphery. Indeed, 4 to 8 hours following eccentric exercise, the expression of the gene for the adenosine A<sub>1</sub> receptor is increased by nearly 6 times in human skeletal muscle.<sup>5</sup> Also, adenosine A<sub>1</sub> receptors have been implicated in the peripheral algic effects of adenosine in humans.<sup>11,32</sup> The precise mechanism for the reduction in pain found in this experiment is uncertain because caffeine is a nonselective adenosine receptor antagonist with high affinity for both A<sub>1</sub> and A<sub>2A</sub> receptors.<sup>32</sup> Also, the locus within the nervous system for the antinociceptive effect is uncertain because of the widespread location of adenosine receptors and the complexity of adenosine effects. Adenosine receptors are present in, and caffeine has access to, nociceptive afferent fibers, the dorsal horn of the spinal cord, and brain areas involved in pain such as primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices.<sup>1,31</sup> The effects of adenosine vary depending on the tissue and species. For example, although adenosine A<sub>1</sub> receptors have been implicated in the peripheral algic effects of adenosine in humans, A<sub>2A</sub> receptors have been implicated in rodents.<sup>11,32</sup>

The magnitude of the hypoalgesic effect (12.7 VAS units and 48%) of caffeine during MVICs is greater than what has been previously reported in experiments testing other treatments for delayed-onset muscle pain. Naproxen doses of 500 mg twice daily or 220 mg · day<sup>-1</sup> produced a 22% and 30% reduction in muscle soreness, respectively (approximately -0.46 and -0.60 SD, respectively), and ketoprofen produced a 10% and 17% reduction in muscle soreness with doses of 25 and 100 mg in participants reporting high pre-drug pain intensity scores of 40 to 77 on a 100-mm visual analog scale.<sup>8,19,33</sup> A study examining topical ketoprofen, with mean pre-drug pain intensities similar to those in the present study, found a 33% reduction in muscle pain (0.71 SD).<sup>4</sup> A 25% reduction in pain following 2600 mg of aspirin has been reported,<sup>9</sup> though no placebo

group was used. In addition, inconsistent results from ibuprofen have been reported with a wide range of doses (1200 to 2400 mg) and treatment periods (5 days before damage to 10 days after damage).<sup>7</sup> The efficacy of nonsteroidal anti-inflammatory agents in reducing delayed-onset muscle pain has been inconsistent.

The hypoalgesic effect of caffeine in response to MVICs was observed despite relatively low pre-ingestion pain scores. Prior studies examining therapeutic interventions for delayed-onset muscle pain often have used methods that result in higher mean VAS pain ratings,<sup>8,19,33</sup> and some investigators contend that therapeutic interventions cannot be tested validly without moderate or higher (> 40 on a 0 to 100 scale) pain intensity ratings.<sup>1</sup> The present findings show the inaccuracy of that contention, at least with caffeine. Moreover, it is possible that the failure to find treatments that consistently reduce delayed-onset muscle pain may be due in part to the severity of past eccentric protocols causing pain too intense to be effectively treated with a single, readily available intervention (eg, over-the-counter medicine). In the present study, the hypoalgesic effects of caffeine were revealed at relatively low mean pain intensities that may be more consistent with the delayed-onset muscle pain intensity experienced by most individuals performing activities of daily living outside of a laboratory environment including gardening, yard work, and sporadic participation in sports such as hunting, softball, or basketball.

In addition to adenosine receptor antagonism, several alternative explanations for the results exist that cannot be ruled out, based on the design of the present investigation, including differences in pre-treatment pain scores and blood pressure responses to caffeine. Mean MVIC pain scores prior to caffeine ingestion were ~8 raw VAS units higher than pre-placebo ingestion. It is well known that the magnitude of change in many physiological variables is dependent in part on the initial values, and, by analogy, this might have occurred for the MVIC pain results. This possibility is discounted by the smaller decrease in pain ratings with the submaximal eccentric actions despite higher mean pre-caffeine ingestion pain scores in that condition compared with the MVIC condition (ie, 30.1 vs 26.6). With regard to blood pressure, caffeine increases blood pressure, and increased systolic blood pressure can be hypoalgesic.<sup>3</sup>

Blood pressure was not assessed here; however, a weak correlation between blood pressure and delayed-onset muscle pain has been found.<sup>28</sup>

A second novel finding from this study was that pain reduction varied as a function of the pain stimuli; submaximal eccentric movements resulted in less pain reduction compared with the MVIC stimulated pain. Because the order of the exercises used to elicit the delayed-onset muscle pain was not randomized in this study, it can be argued that an order effect could have affected pain responses via post-exercise analgesia. The most closely related literature, which has not involved delayed-onset muscle pain, has reported hyperalgesia, hypoalgesia, or no effect of exercise on post-exercise pain intensity.<sup>25</sup> In addition, some of these studies have shown no effect of exercise and differing pain intensity, whereas others have shown a pain increase following exercise.<sup>25</sup>

It is not clear why the hypoalgesic effects of caffeine would differ between these 2 movements, but there are several possible explanations, including small sample bias and differing physiological responses to the 2 types of movements. Compared with the submaximal eccentric actions, maximal exercise (MVICs) probably would be associated with higher intramuscular adenosine and pressure. Both these effects may have resulted in caffeine having a larger hypoalgesic effect; the high intramuscular pressure hypothesis is based on reduced blood flow in the maximally contracting muscle contributing to a higher concentration of adenosine. It is possible that larger hypoalgesic treatment effects are revealed when maximal exercise is used as the noxious stimulus. To date, few muscle injury studies have used maximal exercise as a noxious stimulus.

The third new finding in this study was the 4.4% increase in MVIC force after caffeine ingestion. The magnitude of this effect is consistent with prior research examining the influence of caffeine on voluntary muscle strength in non-fatigued human subjects. Six studies are most directly comparable to the present investigation because their designs did not confound the voluntary strength results, the investigations all used lower body strength, and the caffeine dose ( $\sim 4$  to  $7 \text{ mg} \cdot \text{kg}^{-1}$ ), timing (60 minutes prior to testing), and recent history of use (low caffeine consumption) were similar. Five of these 6 studies resulted in small improvements in maximal voluntary strength.<sup>2,14,15,17,18,27</sup> The overall increase in mean strength in the 5 studies with positive results was 4.4%, with a range of 3.5% to 5.8%.

There are mixed findings concerning force generation and muscle function on days following damaging eccentric

exercise. It has been suggested that muscle function and force are affected by muscle pain, and a recent investigation examined participants' ability to perceptually match and maintain maximal force following damaging eccentric exercise.<sup>30</sup> The large errors reported indicate that participants may be attempting to match effort rather than force, suggesting that nociceptive input has a central action that reduces motor cortical excitability.<sup>30</sup> However, most of the evidence supports the idea that damaged muscles can be fully activated regardless of the existence of muscle pain.<sup>6</sup> The in vivo administration of caffeine in rodents can cause calcium release from the sarcoplasmic reticulum through the ryanodine/SR calcium release channel and increase force.<sup>13</sup> However, in humans, the caffeine dose needed to produce a similar effect would be toxic.<sup>17</sup> Therefore, in humans, it may be the case that the ergogenic effects of caffeine occur by acting on the nervous system rather than directly on skeletal muscle excitation-contraction mechanisms.

There are several limitations of the results of the present investigation. A small sample of young, healthy, low caffeine-consuming women was tested. A larger sample would have increased the likelihood of statistical significance, extending to the hypoalgesia with the submaximal eccentric pain stimulus and the attenuated MVIC force loss after eccentric muscle damage. The hypoalgesic effect observed with the  $5 \text{ mg} \cdot \text{kg}^{-1}$  dose used here may not generalize to other samples (ie, groups with above-average caffeine consumption). This probably is because many of the effects of an acute dose of caffeine are attenuated with chronic caffeine consumption.<sup>16</sup> The magnitude of the hypoalgesic effect also may be dependent on the caffeine dose. It is unknown whether smaller or larger caffeine doses would produce smaller, similar, or larger effects on delayed-onset muscle pain ratings. Studies involving smaller caffeine doses might eliminate one of the potential limitations of the present investigation. That is, despite the double-blind nature of the caffeine administration, all the participants were able to accurately discern the day on which they consumed caffeine. This observation was not unexpected, given the caffeine dose, the prior caffeine consumption history of the study participants, and the known psychophysiological effects of caffeine. A smaller dose might be less discernible by the participants and also produce a hypoalgesia. Despite the limitations, the results suggest that caffeine can produce large reductions in pain resulting from eccentric exercise-induced, delayed-onset muscle injury.

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