

# Neuromuscular Responses to Incremental Caffeine Doses: Performance and Side Effects

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## ABSTRACT

PALLARÉS, J. G., V. E. FERNÁNDEZ-ELÍAS, J. F. ORTEGA, G. MUÑOZ, J. MUÑOZ-GUERRA, and R. MORA-RODRÍGUEZ. Neuromuscular Responses to Incremental Caffeine Doses: Performance and Side Effects. *Med. Sci. Sports Exerc.*, Vol. 45, No. 11, pp. 2184–2192, 2013. **Purpose:** The purpose of this study was to determine the oral dose of caffeine needed to increase muscle force and power output during all-out single multijoint movements. **Methods:** Thirteen resistance-trained men underwent a battery of muscle strength and power tests in a randomized, double-blind, crossover design, under four different conditions: (a) placebo ingestion (PLAC) or with caffeine ingestion at doses of (b) 3 mg·kg<sup>-1</sup> body weight (CAFF<sub>3mg</sub>), (c) 6 mg·kg<sup>-1</sup> (CAFF<sub>6mg</sub>), and (d) 9 mg·kg<sup>-1</sup> (CAFF<sub>9mg</sub>). The muscle strength and power tests consisted in the measurement of bar displacement velocity and muscle power output during free-weight full-squat (SQ) and bench press (BP) exercises against four incremental loads (25%, 50%, 75%, and 90% one-repetition maximum [1RM]). Cycling peak power output was measured using a 4-s inertial load test. Caffeine side effects were evaluated at the end of each trial and 24 h later. **Results:** Mean propulsive velocity at light loads (25%–50% 1RM) increased significantly above PLAC for all caffeine doses (5.4%–8.5%,  $P = 0.039$ – $0.003$ ). At the medium load (75% 1RM), CAFF<sub>3mg</sub> did not improve SQ or BP muscle power or BP velocity. CAFF<sub>9mg</sub> was needed to enhance BP velocity and SQ power at the heaviest load (90% 1RM) and cycling peak power output (6.8%–11.7%,  $P = 0.03$ – $0.05$ ). The CAFF<sub>9mg</sub> trial drastically increased the frequency of the adverse side effects (15%–62%). **Conclusions:** The ergogenic dose of caffeine required to enhance neuromuscular performance during a single all-out contraction depends on the magnitude of load used. A dose of 3 mg·kg<sup>-1</sup> is enough to improve high-velocity muscle actions against low loads, whereas a higher caffeine dose (9 mg·kg<sup>-1</sup>) is necessary against high loads, despite the appearance of adverse side effects. **Key Words:** ERGOGENIC AIDS, NEUROMUSCULAR EFFECTS, MUSCLE STRENGTH, MUSCLE POWER, LOAD-POWER RELATIONSHIP

The ergogenic effect of caffeine (1,3,7-trimethylxanthine) on endurance performance is well recognized and has been analyzed at length (7). In contrast, it is uncertain if caffeine ingestion is ergogenic during short-term high-intensity exercises. One plausible reason for the disagreement between studies is the duration/intensity of the effort undertaken. Controversial findings have been reported for exercise performance durations >1 min to the point of muscle failure (1,3,6,16,19,38), efforts lasting <1 min such as the Wingate test and 20-m sprints (6,12,13,17), and single maximal isometric (22,25,27,35), isokinetic (4,5,20), or isoinertial contractions (3,6,29) lasting only a few seconds. Differences in the muscle groups tested (6,14,37), doses of caffeine ranging from 2 to 10 mg·kg<sup>-1</sup>, and disparity of samples used that ranged from moderately active subjects to resistance-trained athletes may have also contributed to the

observed differences between studies. In a recent meta-analysis, Astorino and Roberson (2) reported caffeine ergogenic effects when testing muscle endurance (increased number of repetitions to failure) but little evidence to sustain caffeine ergogenic effects on maximum strength (one-repetition maximum [1RM]). The effects of caffeine on a single forceful action should precede the study of several fatiguing repetitions where metabolite accumulation may hinder the ergogenic effect of caffeine. The present study attempts to address the effects of caffeine on single all-out muscle contractions.

We have recently reported increases in maximum muscle strength and power output with caffeine ingestion in resistance-trained men (29), whereas others found similar results in women (14). In contrast, other studies found no effect when administering comparable caffeine doses (3–6 mg·kg<sup>-1</sup> body weight) in similarly trained subjects (3,38) or in collegiate football players (40). This uncertainty is unfortunate because performance in many sports depends on brief contractions that require a maximum rate of force development. Even an ergogenic effect of caffeine on muscle power as low as 5% (29) could influence performance in these short actions. It thus seems relevant to clarify this issue because world-class athletes of sports disciplines that require high muscle strength and power (e.g., track cycling, Olympic weightlifting, or volleyball) are among the ones with the highest caffeine consumption (36).

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Submitted for publication February 2013.

Accepted for publication May 2013.

0195-9131/13/4511-2184/0

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DOI: 10.1249/MSS.0b013e31829a6672

The minimal caffeine dose needed to enhance endurance performance was first established in the classical study of Graham and Spriet (15) ( $3 \text{ mg}\cdot\text{kg}^{-1}$ ) and later confirmed by Kovacs et al. (24) ( $3.2 \text{ mg}\cdot\text{kg}^{-1}$ ) and other recent studies (21) ( $2 \text{ mg}\cdot\text{kg}^{-1}$ ). During prolonged exercise, a delay in central nervous system fatigue could be behind the ergogenic effect of caffeine on endurance performance. In contrast, caffeine effects on neuromuscular performance may occur through a different mechanism involving improved muscle excitation–contraction coupling (27,28). Because caffeine could be acting through a different mechanism of action for endurance than for strength–power performance, the dose of caffeine required to activate the mechanism could also differ. Some studies suggest that a high caffeine dose ( $5\text{--}7 \text{ mg}\cdot\text{kg}^{-1}$ ) is needed to elicit performance effects on isokinetic strength (4,20). To our knowledge, no study has addressed the dose of caffeine needed to improve strength and power during isoinertial contractions of large muscle groups. It is possible that the caffeine dose needed to obtain an ergogenic effect may depend on the magnitude of the resistance that the musculature has to overcome.

There is limited information regarding the side effects of the caffeine doses usually ingested for improving sports performance ( $3\text{--}9 \text{ mg}\cdot\text{kg}^{-1}$ ). A review suggests that caffeine ingestion of doses higher than  $9 \text{ mg}\cdot\text{kg}^{-1}$  can lead to adverse effects such as anxiety, restlessness, and headaches, which could negatively affect endurance performance (2). In addition, sleep deprivation due to caffeine ingestion could impair athletic performance when the competition extends over several consecutive days (31). We propose to study the neuromuscular performance effects of caffeine by increasing the dose while observing the side effects in the same subjects. This analysis would identify the oral caffeine dose that, while increasing neuromuscular performance, would not result in undesirable side effects that may undermine caffeine's ergogenic potential.

Therefore, the purpose of this study was to find the oral dose of caffeine that improves the voluntary contraction and power of large muscle groups in resistance-trained athletes. Different submaximal loads were used to investigate which dose of caffeine enhances either slow-velocity high-resistance contractions or high-velocity low-resistance contractions. Second, we examined the side effects associated with a complete range of caffeine doses and their possible implications for the athletes' performance. We hypothesized that a high caffeine dose ( $>6 \text{ mg}\cdot\text{kg}^{-1}$ ) will be needed to obtain an ergogenic effect on slow-velocity high-resistance contractions, whereas lower caffeine doses ( $<6 \text{ mg}\cdot\text{kg}^{-1}$ ) will be ergogenic in high-velocity low-resistance contractions.

## METHODS

**Subjects.** Thirteen highly resistance-trained men volunteered to participate in this study (age,  $21.9 \pm 2.9$  yr; body mass,  $76.5 \pm 8.5$  kg; height,  $172.7 \pm 5.4$  cm; body fat,  $12.4\% \pm 2.7\%$ ; resistance training experience,  $7.1 \pm 3.5$  yr). Their 1RM

strength for the free-weight full-squat (SQ) and bench press (BP) exercises was  $112.5 \pm 12.6$  and  $121.0 \pm 22.7$  kg, respectively, which accounted for  $1.47 \pm 0.16$  and  $1.58 \pm 0.19$  when normalized per kilogram of body mass. Most of the subjects were resident in the sports performance center of the Region of Murcia (Spain). The subjects were informed in detail about the experimental procedures and the possible risks and benefits of the project. The study complied with the Declaration of Helsinki and was approved by the Bioethics Commission of the University of Murcia. Before participation, written informed consent was obtained from each athlete, and subjects were informed that they could resign from participation at any time. All subjects were light caffeine consumers ( $\leq 70 \text{ mg}\cdot\text{d}^{-1}$  from caffeinated soda or lyophilized coffee in milk).

**Experimental design.** A randomized, double-blind, crossover, placebo-controlled experimental design was used, with all subjects serving as their own controls. Participants underwent the same battery of neuromuscular and biochemical assessments under four different conditions: (a) placebo trial (PLAC) and three doses of caffeine ingestion: (b)  $3 \text{ mg}\cdot\text{kg}^{-1}$  trial (CAFF<sub>3mg</sub>), (c)  $6 \text{ mg}\cdot\text{kg}^{-1}$  trial (CAFF<sub>6mg</sub>), and (d)  $9 \text{ mg}\cdot\text{kg}^{-1}$  trial (CAFF<sub>9mg</sub>). Trials were separated by 48 h to avoid any possible fatigue and to allow caffeine washout (23). All trials began at 8:00 a.m. to control the circadian rhythms effects (29). Caffeine (Durvitan, Seid, Spain) was provided in gelatin capsules to deliver doses of 3, 6, and  $9 \text{ mg}\cdot\text{kg}^{-1}$  body mass, respectively. The capsules were ingested 60 min before the trial to allow peak blood caffeine concentration (10) (Fig. 1). In the trial without caffeine ingestion (PLAC trial), subjects ingested placebo capsules filled with the same amount of dextrose to avoid identification. The amount of additional energy provided by the dextrose ( $\sim 2$  kcal) was deemed negligible.

**Familiarization.** All subjects had previously participated in experiments involving all the muscle strength and power tests performed in this study. Nevertheless, participants underwent seven familiarization sessions before the start of the experimental trials to avoid the bias of progressive learning. The last familiarization session, performed in the morning (8:00 a.m.) of the third day before the beginning of the study, included the determination of the individual load (kg) corresponding to 25%, 50%, 75%, and 90% of 1RM in the BP and SQ exercises for each subject. To carry out that assessment, the initial load was set at 20 kg for all subjects and was increased in 10-kg increments until the attained mean propulsive velocity (MPV) was less than  $0.5 \text{ m}\cdot\text{s}^{-1}$  in the BP or less than  $0.8 \text{ m}\cdot\text{s}^{-1}$  in the SQ because those velocities indicate proximity to 1RM (32). Thereafter, the load was adjusted with smaller increments so that 1RM could be precisely determined. The heaviest load that each subject could properly lift while completing the full range of motion was considered to be his 1RM.

**Experimental protocol.** The day before and during the 7 d that the experiment lasted, the subjects lived at the sports performance center where they slept and ate all meals. They

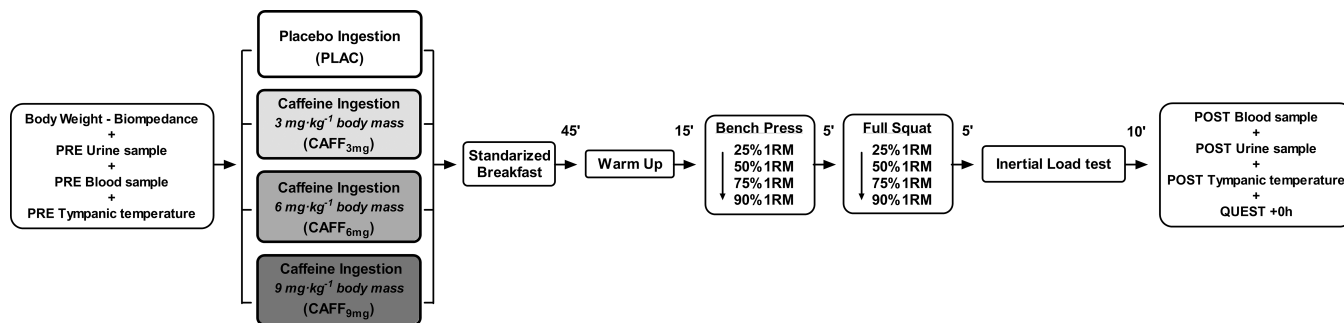


FIGURE 1—Experimental protocol.

all consumed a diet of 2800–3000 kcal·d<sup>-1</sup>, composed of 55% energy intake from carbohydrates, 25% from fat, and 20% from protein, evenly distributed across three meals each day (breakfast at 7:00 a.m., lunch at 13:30 p.m., and dinner at 20:00 p.m.). Subjects refrained from physical activity other than that required by the experimental trials and withdrew from alcohol, tobacco, and any kind of caffeine intake 10 d before testing and while the experiment lasted. The day before the onset of the experiment, height was measured in the morning to the nearest 0.5 cm during a maximal inhalation using a wall-mounted stadiometer (Seca 202; Seca Ltd., Hamburg, Germany).

In every trial, upon arrival to the testing facility at 6:30 a.m. in a fasted state (PRE), a urine sample (15 mL) was obtained. Urine specimens were measured in duplicate for urine-specific gravity ( $U_{SG}$ ; Uricon-NE, Atago, Japan), and the rest of the sample was immediately frozen at  $-20^{\circ}\text{C}$  for future analysis. Then, the subject's body weight was determined and body water estimated using a four-contact electrode body composition bioimpedance analyzer (Tanita TBF-300A; Tanita Corp., Tokyo, Japan) to obtain a percentage of body fat and fat-free mass. Following this, tympanic temperature (Thermoscan, Braun, Germany) was measured in triplicate after the removal of earwax when needed. Next, a 5-mL blood sample was withdrawn from an antecubital vein without stasis. A small portion of the whole blood was used to determine hematocrit by triplicate using non-heparinized capillary tubes (70  $\mu\text{L}$ ; Hirschmann Laborgerate, Germany) and a microcentrifuge (Biocen, Arlesa, Spain). The serum and plasma obtained after centrifugation (3000g) was immediately stored at  $-70^{\circ}\text{C}$ . Then, subjects ingested the capsules containing their individualized-randomized caffeine dose (3, 6, or 9  $\text{mg}\cdot\text{kg}^{-1}$ ) or placebo with 330 mL of a fruit milkshake (168 kcal) and a pastry (456 kcal) that served as a standardized breakfast (total of 624 kcal and 68 g of carbohydrate).

After a standardized warm-up that consisted of 10 min of jogging at 10  $\text{km}\cdot\text{h}^{-1}$  and 10 min of static stretches and joint mobilization exercises, the subjects entered the laboratory to start the neuromuscular test battery assessments under a paced schedule (see Fig. 1). These tests consisted of the measurement of bar displacement velocity and muscle power output against four incremental loads (25%, 50%,

75%, and 90% of 1RM) for upper and lower body musculature (BP and SQ). Those step measures allowed a continuous representation of the load–velocity and load–power curves to study the interaction between load and caffeine dose on neuromuscular performance. Cycling peak power output (PPO) was assessed next using a nonfatiguing inertial load test of 4-s duration. Subjects remained blinded to the results during the whole experiment. Instructions before lifting were standardized and always delivered by the same experimenter.

Upon completion of the test battery (~60 min from the beginning of the neuromuscular assessments), a second urine and blood sample were collected (POST). Then, subjects filled out a questionnaire (QUEST + 0 h) aimed to address whether side effects of caffeine were present during the trial. Subjects were then discharged and reminded about their schedule for the next trial. Blood and urine caffeine concentration was evaluated at the beginning (PRE) and immediately at the end (POST) of each trial.  $U_{SG}$  and blood hematocrit were also determined PRE and POST each trial.

**Load–velocity and load–power relationships.** We used a graded loading test in a Smith machine (Multipower Fitness Line, Peroga, Spain) with a linear encoder and its associated software (T-Force System; Ergotech, Murcia, Spain; 0.25% accuracy) attached to the bar by a light retractable metal cable. There were two Smith machines, each one dedicated to a given exercise (SQ or BP). Both encoders were cross validated before the test with agreement of  $r = 0.999$ . A detailed description of the validity and reliability data of the dynamic measurement system (ICC = 1.00, CV = 0.57%) has recently been reported (32). At the individually determined 25%, 50%, 75%, and 90% of 1RM (see Familiarization section), changes in bar displacement velocity and power output were measured after the ingestion of different caffeine doses. MPV and mean propulsive power (MPP) were calculated as the average velocity and power output values, respectively, measured only during the propulsive phase, defined as that portion of the concentric action during which the acceleration is greater than acceleration because of gravity (33). In each trial, three attempts were executed for light (25% RM), two for medium (50% RM), and only one for the heaviest (75% and 90% RM) loads interspersed with 5 min of passive rests. Only the best

repetition at each load, according to the criteria of fastest MPV, was considered for subsequent analysis.

The individual range of movement during the BP and SQ exercises was carefully replicated in each trial with the help of two telescopic bar holders with a precision of  $\pm 1.0$  cm. In the BP, the bar holders were positioned to allow the bar to descend to 1 cm above each subject's chest. In the SQ, the bar holders were set at each subject's lowest squat depth defined as that position in which the back of the thighs and upper calves made contact with each other. Subjects were instructed to perform the eccentric phase of both exercises in a slow and controlled manner, to pause for 2 s at the bar holders, momentarily releasing the weight, and thereafter to perform a purely concentric action pushing back up at maximal intended velocity. The momentary pause imposed between the eccentric and the concentric actions was designed to minimize the contribution of the stretch-shortening cycle (i.e., rebound effect) and to allow for more reliable and consistent measurements. Pilot data collected during the previous familiarization revealed significant reductions in the intrasubject coefficient of variation when using the described technique compared with a nonstop technique involving the stretch-shortening cycle (i.e., 3.5% vs 2.4% for BP and 3.7% vs 2.7% for SQ exercise, both  $P < 0.05$ ).

**Cycling peak power test.** Cycling PPO was measured using the previously described isoinertial load test (26). In brief, we measured the power needed to overcome the inertial load of a heavy (21.5 kg) cycle-ergometer flywheel (Monark-818, Varberg, Sweden). This cycling PPO assessment lasts only 4 s; however, a complete power-velocity spectrum curve is generated using an absolute encoder (ASM 2000 ppr; Unterhaching, Germany; 1000 Hz) connected to the cycle ergometer flywheel. Subjects sat on the cycle ergometer after the handlebars and saddle had been adjusted to fit their individual's body dimensions. After a 3-min warm-up (100 W at 90 rpm interspersed with two short (2–3 s) bouts of maximal acceleration), subjects performed two maximal sprints interspersed by 180 s of active recovery (50 W). The test started from a complete stop with the pedal of the dominant leg placed at  $45^\circ$  from the vertical. The test-retest intraclass correlation coefficient was 0.85 (0.60–0.95), and the coefficient of variation was  $3.9\% \pm 1.3\%$ . The average value of the two PPO sprints was recorded for data analysis.

**Urine and plasma analysis.** Blood samples (5 mL) were mixed with ethylenediaminetetraacetic acid in plastic tubes and plasma immediately separated by centrifugation (MPW-350R; MedInstruments, Poland). The plasma samples were stored at  $-80^\circ\text{C}$  for future analysis. At a later date, urine and plasma samples were analyzed for caffeine concentrations and related metabolites using an Agilent Technologies HPLC 1200 system (Santa Clara, CA) coupled to a triple quadrupole/ion trap mass spectrometer (MS; API 4000, Q TRAP, AB SCIEX, Framingham, MA US). Methylxanthine internal standards were purchased from Cerilliant (Round Rock, TX). Aliquots of urine sample (100  $\mu\text{L}$ ) were filtered (VWR, Barcelona, Spain) and transferred into a liquid chromatography

vial containing 900  $\mu\text{L}$  of mobile phase (aqueous solution of 0.1% acetic acid). Subsequently, 20  $\mu\text{L}$  of internal standard working solution (caffeine  $^{13}\text{C}_3$  5  $\mu\text{g}\cdot\text{mL}^{-1}$ ) was added and mixed. Ten microliters of the sample was then directly applied to the HPLC-MS system. For blood, 20  $\mu\text{L}$  of the internal standard working solution was added to the aliquots of plasma sample (100  $\mu\text{L}$ ). The sample was vortex mixed for 10 s, then 20  $\mu\text{L}$  of 20% perchloric acid was added, and the sample was vortex mixed for 10 s and centrifuged at 3500 rpm for 10 min. One hundred microliters of the supernatant was transferred into a liquid chromatography vial containing 900  $\mu\text{L}$  of mobile phase and mixed. Then the sample was filtered through 0.2  $\mu\text{m}$  of cellulose acetate membrane, 25-mm syringe filters, and 10  $\mu\text{L}$  was then directly applied to the HPLC-MS system. To calibrate the system, aqueous solutions of caffeine (ranging from 0.25 to 12  $\mu\text{g}\cdot\text{mL}^{-1}$ ) were used for each batch of samples. The lower limit for the accurate quantization of these methylxanthines was 0.25  $\mu\text{g}\cdot\text{mL}^{-1}$ .

**Side effects evaluation.** Immediately after each neuromuscular test battery (QUEST + 0 h) and 24 h later (QUEST + 24 h), participants answered a questionnaire. The QUEST + 0 h was designed to evaluate the physical fatigue, the perceived performance, and the side effects (e.g., urine output, gastrointestinal problems, tachycardia, or headache) felt by the participants during the neuromuscular test battery. QUEST + 24 h was designed to evaluate physical fatigue and side effects (e.g., sleep quality, gastrointestinal problems, tachycardia, muscle soreness, or headache) perceived by participants during the 24 h after the caffeine dose was ingested. These surveys included eight items on a yes/no scale and were based on previous publications about side effects derived from the ingestion of caffeine (8,11).

**Statistical analysis.** The Shapiro-Wilk test was used to assess normal distribution of data. Pretesting conditions, the cycling isoinertial load power test and the caffeine levels data were analyzed using one-way ANOVA for repeated measures (doses of caffeine). The load-velocity and load-power relationships were analyzed using two-way (caffeine dose  $\times$  load) ANOVA for repeated measures. The Greenhouse-Geisser adjustment for sphericity was calculated. After a significant  $F$ -test, differences among means were identified using pairwise comparisons with Bonferroni's adjustment. The significance level was set at  $P \leq 0.05$ . Cohen's formula for effect size (ES) was used, and the results were based on the following criteria:  $>0.70$  large effect, 0.30–0.69 moderate effect, and  $\leq 0.30$  small effect (9). Reported side effects in the questionnaires were not normally distributed, and a non-parametric statistical technique was used.

## RESULTS

**Pretesting conditions, hydration status.** Before the four experimental trials (PRE), body mass (range between  $76.4 \pm 8.5$  and  $76.9 \pm 8.2$  kg) and body bioimpedance (range between  $462 \pm 46$  and  $475 \pm 54$   $\Omega$ ) were not different between

TABLE 1. Side effects reported by participants immediately after the conclusion of each neuromuscular test battery (QUEST + 0 h) and 24 h later (QUEST + 24 h).

	PLAC		CAFF <sub>3mg</sub>		CAFF <sub>6mg</sub>		CAFF <sub>9mg</sub>	
	+0 h	+24 h	+0 h	+24 h	+0 h	+24 h	+0 h	+24 h
Muscle soreness	15	8	8	8	8	31	15	38
Increased urine output	8	8	15	8	15	23	62	54
Tachycardia and heart palpitations	8	0	15	0	15	0	23	23
Anxiety or nervousness	8	0	8	0	15	0	31	23
Headache	8	0	0	8	8	23	15	38
Gastrointestinal problems	0	8	8	8	8	8	31	38
Insomnia	—	0	—	0	—	8	—	54
Increased vigor/activeness	8	0	38	0	46	8	54	23
Perception of performance improvement	8	—	54	—	54	—	62	—

Data are presented as the percentage of prevalence.

trials (PLAC, CAFF<sub>3mg</sub>, CAFF<sub>6mg</sub>, and CAFF<sub>9mg</sub>). No significant differences were detected between treatments in PRE testing conditions for tympanic temperature, blood hematocrit, or urine  $U_{SG}$ . POST tympanic temperature values in all trials (PLAC, CAFF<sub>3mg</sub>, CAFF<sub>6mg</sub>, and CAFF<sub>9mg</sub>) were significantly elevated (range of increase = 1.5%–2.2%,  $P = 0.000$ – $0.041$ ,  $ES = 1.10$ – $1.70$ ) when compared with their respective PRE value. No significant differences were detected for hematocrit or urine  $U_{SG}$  values between PRE and POST conditions at any dose, except in the CAFF<sub>9mg</sub> trial where hematocrit was significantly higher (from  $45.4\% \pm 3.7\%$  to  $47.0\% \pm 3.9\%$ ,  $P = 0.031$ ,  $ES = 0.42$ ), and urine  $U_{SG}$  was significantly lower (from  $1.024 \pm 0.005$  to  $1.016 \pm 0.007$ ,  $P = 0.003$ ,  $ES = 1.40$ ) in the POST testing conditions.

**Caffeine side effects.** Immediately after the PLAC trial, subjects reported a very low frequency of side effects (0%–8%; QUEST + 0 h). The CAFF<sub>3mg</sub> and the CAFF<sub>6mg</sub> treatments produced very similar side effects, with a limited increase in the sensations of tachycardia and heart palpitations, self-reported urine output, and gastrointestinal problems (8% of the subjects) compared with the PLAC trial. On the other hand, the subject's perception of performance and vigor increased five to seven times above PLAC during the CAFF<sub>3mg</sub> and CAFF<sub>6mg</sub> trials (38% and 54% of the subjects, respectively). Finally, the CAFF<sub>9mg</sub> trial produced a drastic increase in the reported frequency of side effects (Table 1). It is particularly relevant that 62% and 31% of participants reported an increase in the estimates of urine output and gastrointestinal problems, respectively. The perception of performance and vigor or activeness also rose in 62% and 54% of the participants, respectively (Table 1).

The following morning of each experimental trial (QUEST + 24 h), very few participants (8%) reported that PLAC treatment produced residual side effects such as muscle soreness, increase in the estimates of urine output, and gastrointestinal problems. The CAFF<sub>3mg</sub> trial produced very similar side effects to PLAC, with an additional 8% of participants reporting a headache. The CAFF<sub>6mg</sub> trial tended to increase the frequency of muscle soreness and headaches and the estimates of urine output in comparison with the PLAC and CAFF<sub>3mg</sub> treatments, although still with a frequency lower than 31% of the subjects. In addition, CAFF<sub>6mg</sub> produced symptoms of increased vigor and sleep problems, although with a very low incidence (8%). Finally,

CAFF<sub>9mg</sub> increased the frequency of all adverse side effects, with a frequency of appearance from 23% to 54%. Of note, 23% of participants reported tachycardia and anxiety or nervousness, 38% with gastrointestinal problems, and 54% with insomnia or sleep disturbances (Table 1).

**Load-velocity and load-power relationship.** MPV attained against the two lower loads (25% and 50% 1RM) in the BP and SQ exercises significantly increased with all caffeine doses (CAFF<sub>3mg</sub>, CAFF<sub>6mg</sub> and CAFF<sub>9mg</sub>) compared with the placebo treatment (PLAC) (range of increase = 5.4%–8.5%,  $P = 0.039$ – $0.000$ ,  $ES = 0.76$ – $1.28$ ; Fig. 2). Similarly, MPV at 75% 1RM was significantly increased in all caffeine trials in the BP and SQ exercises compared with the placebo treatment (PLAC) (range

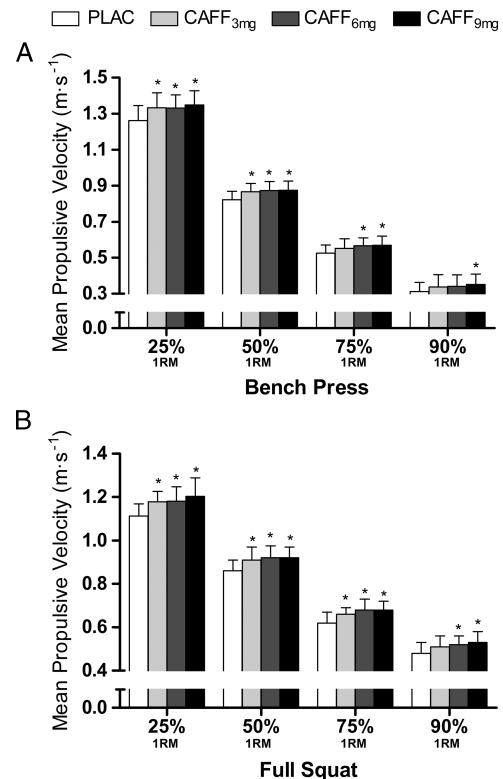
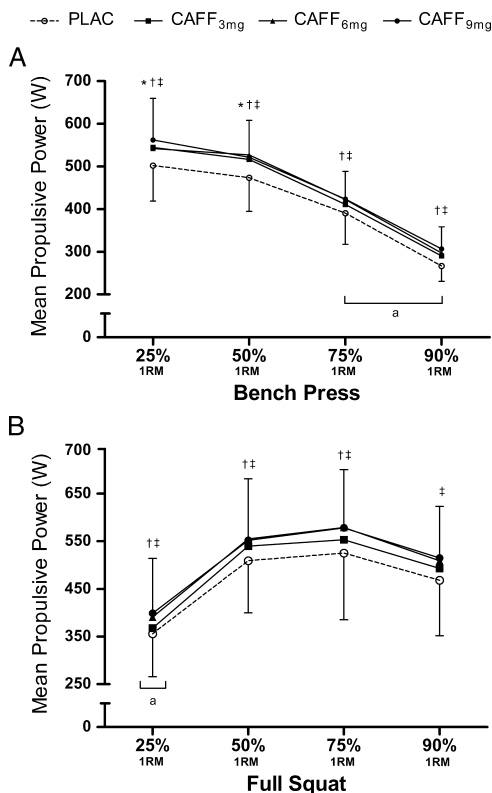


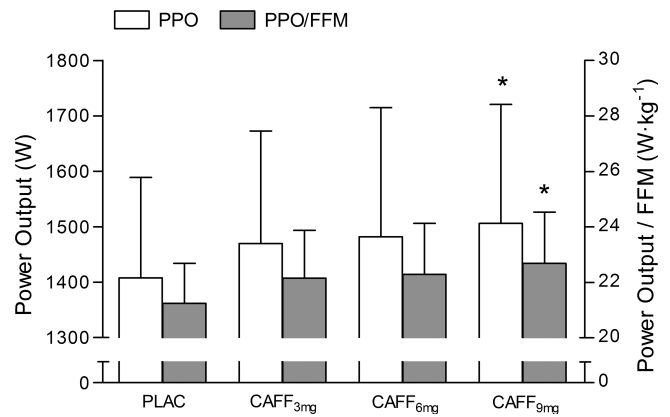
FIGURE 2—Dose-response effects of caffeine ingestion on load-velocity relationship for bench press (A) and full squat (B) exercises. Data are means  $\pm$  SD. \*Significant differences ( $P \leq 0.05$ ) compared with the PLAC trial within each load.

of increase = 6.3%–8.9%,  $P = 0.046$ – $0.014$ ,  $ES = 0.91$ – $1.21$ ; Fig. 2). The only exception was for the  $CAFF_{3mg}$  trial in the BP exercise ( $P = 0.15$ ). Finally, MPV at the heaviest load (90% 1RM) was significantly enhanced with the  $CAFF_{9mg}$  compared with placebo in both exercises (BP: 13.1%,  $P = 0.031$ ,  $ES = 0.74$ ; SQ: 10.4%,  $P = 0.046$ ,  $ES = 1.03$ ). During SQ at 90% 1RM, a caffeine dose of  $CAFF_{6mg}$  was also enough to increase MPV above PLAC (8.3%,  $P = 0.029$ ,  $ES = 0.90$ ; Fig. 2B).

MPP at the two light loads (25% and 50% 1RM) in the BP and SQ exercises was significantly increased with all caffeine doses ( $CAFF_{3mg}$ ,  $CAFF_{6mg}$  and  $CAFF_{9mg}$ ) compared with PLAC (range of increase = 8.1%–12.0%,  $P = 0.022$ – $0.000$ ,  $ES = 0.36$ – $0.68$ ), except for the  $CAFF_{3mg}$  treatment in the SQ exercise ( $P = 0.18$ – $0.09$ ). At 75% 1RM, MPP in the BP and SQ was also significantly increased in the  $CAFF_{6mg}$  and  $CAFF_{9mg}$  trials compared with PLAC (range of increase = 8.3%–10.2%,  $P = 0.037$ – $0.010$ ,  $ES = 0.36$ – $0.48$ ). Finally, MPP at 90% 1RM was significantly enhanced in the  $CAFF_{9mg}$  trial for BP and SQ (11.7%–15.0%,  $P = 0.031$ – $0.014$ ,  $ES = 0.47$ – $0.92$ ) and with the  $CAFF_{6mg}$  dose for the BP exercise (11.4%,  $P = 0.021$ ,  $ES = 0.71$ ) compared with PLAC (Fig. 3A and B). The peak in mean power in the BP exercise occurred at 25%



**FIGURE 3**—Dose–response effects of caffeine ingestion on load–power relationship for bench press (A) and full squat (B) exercises. Data are means  $\pm$  SD. \*Significant difference ( $P \leq 0.05$ ) between  $CAFF_{3mg}$  and PLAC. †Significant difference ( $P \leq 0.05$ ) between  $CAFF_{6mg}$  and PLAC. ‡Significant difference ( $P \leq 0.05$ ) between  $CAFF_{9mg}$  and PLAC. <sup>a</sup>Significantly lower ( $P \leq 0.05$ ) than the peak power (25% 1RM for BP and 75% for full squat) for each exercise.



**FIGURE 4**—Dose–response effects of caffeine ingestion on cycling PPO using a 4-s inertial load test in absolute and fat-free mass normalized values. Data are means  $\pm$  SD. \*Significantly different ( $P \leq 0.05$ ) than PLAC.

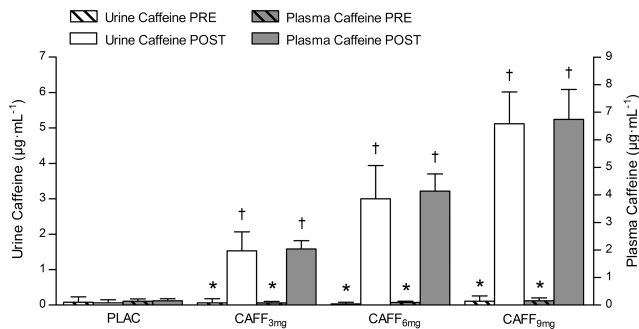
1RM, independently of the caffeine dose ingested (range = 501–562 W), and was significantly lower at 75% and 90% 1RM loads (range 267–423 W,  $P < 0.001$ ; Fig. 3A). The peak in mean power for SQ occurred at 75% 1RM in all trials (range = 525–579 W) and was significantly lower at 25% 1RM (range 356–400 W,  $P < 0.001$ ; Fig. 3B).

**Cycling PPO test.** No significant differences were detected in cycling PPO in absolute (W) or normalized per kilogram of FFM ( $W \cdot kg^{-1}$ ) values between PLAC,  $CAFF_{3mg}$ , and  $CAFF_{6mg}$  trials. However, a significantly 7.0% higher PPO was detected in the  $CAFF_{9mg}$  trial ( $1506 \pm 225$  W) compared with PLAC ( $1408 \pm 189$  W,  $P = 0.040$ ,  $ES = 0.47$ ). Likewise, a significantly 6.9% higher PPO/FFM was detected in the  $CAFF_{9mg}$  trial ( $22.7 \pm 1.8$   $W \cdot kg^{-1}$ ) compared with the PLAC trial ( $21.2 \pm 1.4$   $W \cdot kg^{-1}$ ,  $P = 0.036$ ,  $ES = 0.88$ ; Fig. 4).

**Urine and blood analysis.** Upon arrival to the laboratory (PRE), plasma ( $<0.13 \pm 0.08$   $\mu g \cdot mL^{-1}$ ) and urine ( $<0.12 \pm 0.15$   $\mu g \cdot mL^{-1}$ ) caffeine concentrations were negligible in all subjects, confirming the complete caffeine washout before trials. At the end of the test battery (i.e., POST: 2 h after the caffeine or placebo ingestion), urine and plasma caffeine concentrations in all caffeine trials ( $CAFF_{3mg}$ ,  $CAFF_{6mg}$ , and  $CAFF_{9mg}$ ) were significantly higher ( $P < 0.05$ ) than their respective basal values. The ingestion of the graded caffeine doses produced a significant parallel increase in plasma and urine caffeine concentrations at their respective POST values ( $P < 0.05$ ; Fig. 5).

## DISCUSSION

The main finding of this study is that caffeine significantly improves movement velocity under all loading conditions (from 25% to 90% 1RM) in both the upper (BP) and the lower body (SQ) musculature. The higher the load, and thus the longer time available to apply force, the higher the caffeine dose needed to achieve an ergogenic effect



**FIGURE 5—Dose–response effects of caffeine ingestion on urine and plasma caffeine concentrations at PRE and POST time points. Data are means  $\pm$  SD. \*Significantly different ( $P \leq 0.05$ ) when compared with their respective POST value. †Significantly different ( $P \leq 0.05$ ) when compared with their previous caffeine dose trial.**

(see Fig. 3). We have previously reported a  $\sim 5\%$  MPV improvement in BP and SQ exercises after ingestion of  $3 \text{ mg}\cdot\text{kg}^{-1}$  of caffeine against loads of  $75\%$  1RM (29). In the present study, we observe improvements between  $5.2\%$  and  $13.1\%$ , depending on the dose of caffeine ingested and the magnitude of the resistance to overcome. Interestingly, the ergogenic effect of caffeine against the lighter loads ( $25\%$ – $50\%$  of 1RM) was maximal with a low dose of caffeine ( $3 \text{ mg}\cdot\text{kg}^{-1}$ ). In contrast, higher caffeine doses were required to improve performance against higher loads ( $6 \text{ mg}\cdot\text{kg}^{-1}$  for  $75\%$  1RM and  $9 \text{ mg}\cdot\text{kg}^{-1}$  for  $90\%$  1RM load). This seems to suggest that the dose of caffeine recommended will depend on the resistance that athletes have to overcome. As we will discuss later, administering the minimal ergogenic dose would be recommended to avoid undesirable adverse side effects.

As observed in Figure 2, caffeine increased movement velocity in 20 of the 24 caffeine ingestion trials ( $83\%$  effectiveness). This consistency on the ergogenic effects of caffeine has no comparison in the literature that examines caffeine effects on resistance exercise. Some studies found no effect of caffeine on maximum strength measured as 1RM (1,3,38) or the number of repetitions to failure against a submaximal load (1,3,6,16,19,38–40). However, our data are not directly comparable with those studies addressing the effect of caffeine ingestion using the 1RM test. The reproducibility ( $\text{CV} = 2.9\%$ – $5.3\%$  [34]) and accuracy (usually  $2.5$ – $5.0 \text{ kg}$  at each side of the bar) for typical 1RM tests is lower than those reported using a linear velocity transducer ( $\text{CV} = 0.57\%$ , accuracy =  $0.25\%$ ,  $1000 \text{ Hz}$  [32]). These improvements in the quality of the measure allow us to detect small but significant effects of caffeine on performance (29). Others have reported an increased peak torque after caffeine ingestion using isokinetic or isometric devices. Astorino et al. (4) found that a  $5\text{-mg}\cdot\text{kg}^{-1}$  dose of caffeine improved isometric power whereas a lower  $2 \text{ mg}\cdot\text{kg}^{-1}$  had no effect. Jacobson et al. (20) reported that  $7 \text{ mg}\cdot\text{kg}^{-1}$  caffeine ingestion improved peak isometric torque at several angular velocities, findings that have been recently confirmed by Bazzucchi et al. (5). Our findings using isoinertial

loads and an accurate measure of bar velocity are comparable with those using isokinetic tests in that caffeine is ergogenic during single muscle actions against several external resistances.

We found that a high dose of caffeine ( $9 \text{ mg}\cdot\text{kg}^{-1}$ ) was needed to improve peak power in our highly reproducible ( $\text{CV} = 3.9\%$ ) and sensible (sampling frequency  $1000 \text{ Hz}$ ) inertial load cycling test (Fig. 4). In this test, subjects have to overcome the inertial load of a heavy ( $21.5 \text{ kg}$ ) cycle-ergometer flywheel. Thus, during the initial pedal strokes of the 4-s test, the leg musculature is required to develop a high percentage of their MVC (26). In agreement with the SQ data (Fig. 3B), only the highest dose of caffeine was ergogenic against the high inertial load. Our data are similar to those of Glaister et al. (13) in that we did not find an effect of caffeine on cycling sprint peak power with doses of  $3$  and  $6 \text{ mg}\cdot\text{kg}^{-1}$ . However, we found an ergogenic effect with  $9 \text{ mg}\cdot\text{kg}^{-1}$ , whereas they did not with doses of  $8$  or  $10 \text{ mg}\cdot\text{kg}^{-1}$ . However, Glaister et al. reported a tendency for a reduction in the time to peak power at the highest caffeine dose. Our tests differed in the length of the sprint; ours being less than half of the duration compared with that of Glaister et al. (i.e.,  $4$  vs  $10 \text{ s}$ ). It seems that the longer the duration of the sprint, the less likelihood of finding an effect of caffeine ingestion. In fact, studies using the regular 30-s Wingate test to investigate the effects of caffeine are inconclusive with either positive (39) or negative (6,17,38) findings. In summary, our results using repeated muscle contractions ( $4 \text{ s}$  cycling sprint against an inertial load; Fig. 4) confirm the results observed during single muscle actions (Fig. 3) in that a high dose of caffeine is needed when the resistance to overcome is high.

The results of the present study show a greater caffeine ergogenic effect on the lower compared with the upper body musculature, particularly at the higher resistances and caffeine doses (Fig. 2). These results are consistent with previous findings by Astorino et al. (1), who found an ergogenic effect of caffeine ingestion on repetitions to failure for leg press, but not for BP exercise. In a recent meta-analysis, Warren et al. (37) found more consistent effects of caffeine ingestion on improving 1RM knee extension than that in other muscle groups. In contrast, other researchers found enhanced 1RM strength (6) and number of repetitions to failure (39) in the BP but not in the leg press exercise, whereas others found no differences between muscle groups (3,19). These discrepancies could be due to (i) the order of the testing, because 1RM or repetitions to failure tests induce central fatigue that can influence the second muscle group tested as suggested by Astorino et al. (3), and (ii) the relatively low reliability of the muscle endurance tests. We have attempted to reduce the measurement variability by testing only single explosive actions with the velocity transducer and with our careful testing protocol. Our results allow us to suggest that caffeine has a larger ergogenic effect during lower body muscle contractions. Additional research is needed to identify the underlying mechanism responsible for these differences between upper and lower body

musculature. Warren et al. (37) argued that the muscle activation level during MVC may be lower for the knee extensors than for other smaller muscle groups. In these smaller groups, muscle activation without caffeine is already near 100%, and thus there is minimal room for caffeine to improve contraction force. This seems to us a very plausible explanation.

Although no subject reached the 2004 urinary caffeine threshold for doping ( $12 \mu\text{g}\cdot\text{mL}^{-1}$ ; Fig. 5), some of the doses produced side effects that remained 24 h after the trial. One of the findings of the present study was that the presence of negative side effects increased markedly with the  $9\text{-mg}\cdot\text{kg}^{-1}$  caffeine dose (Table 1). To our knowledge, these results are novel in the literature for a controlled, double-blind, crossover design where three incremental doses of caffeine are evaluated. In a descriptive cross-sectional study, Desbrow and Leveritt (11) associated habitual caffeine use by Ironman athletes with side effects and found very minor and infrequent adverse caffeine-related symptoms during this long distance endurance event. Their retrospective data did not allow them to analyze the dose–side effects relationship. In the present study, we found gastrointestinal problems, headaches, and insomnia appearing with doses at or higher than  $6 \text{mg}\cdot\text{kg}^{-1}$  (Table 1). In sport events lasting longer than half a day (morning or afternoon), these side effects generated by early caffeine ingestion could reduce cognitive and physical performance. The side effects data, together with the muscle strength and mechanical power output results, allow us to suggest that only in events where the sport success depends on force application against high loads, like Olympic weightlifting or the start and the first 1–5 cycles or strokes in sprints, would it be advisable to ingest caffeine doses higher than  $6 \text{mg}\cdot\text{kg}^{-1}$ .

Few studies have reported a wide range of load–power data in these basic resistance training exercises (BP, SQ). Figure 3 suggests that the shape of the load–power curve is not affected by caffeine ingestion. Furthermore, our data coincide with previous reports (18,33) in showing that muscle power output is very different in BP (25% 1RM) and SQ (75% 1RM) exercises, probably due to the biomechanics of the primary muscles recruited in each movement. Finally, no significant differences were observed in the power output developed against 25%–50% 1RM loads in BP, or against 50%–90% 1RM loads in SQ (Fig. 3). Attending to the load–power data (Fig. 3), it could be suggested that there is not one but a range of loads that maximize muscle power output (low loads for BP and moderate loads for SQ), and caffeine ingestion does improve power at all loads. In agreement with recent reports (33), these results make us wonder whether perhaps excessive attention has been paid to the question of identifying a single load for maximizing power output.

While delaying central nerve fatigue could be one of the mechanisms by which caffeine could improve repeated

sprint ability, it is less likely that it could improve single muscle actions or very short sprint performance (i.e., 4 s long) where fatigue is not limiting. In support for a local muscle mechanism, caffeine ingestion has been reported to increase the electrically evoked force of small (finger adductor [25]), medium (peroneus [35]), and large (quadriceps [29]) muscle mass when stimulated at a low frequency (20 Hz). In addition, several studies have failed to show increased motor unit activation with caffeine using electrostimulation superimposed into a maximal voluntary contraction (27,35). In contrast, others have found increased maximal activation using the twitch interpolation technique (22,30). As the motor unit recruitment and firing rate are likely larger during resistance than during endurance type activities, it could be hypothesized that caffeine could further benefit resistance exercise if a local effect is predominant. However, caffeine ingestion has not been shown to increase motor unit firing rates in nonfatigued muscle (22,30). Again, a bout of maximal contraction could be limited by the capacity to voluntarily activate motor units, which seems to be improved by caffeine ingestion (22). Thus, it is unclear by which mechanism (local or central) caffeine ingestion is improving force and power during single muscle actions.

In conclusion, in this study, we systematically raised caffeine dose while varying the load imposed to large muscle groups located in the upper and lower body (BP and SQ). The velocity of movement against those loads was improved in 83% of the trials with caffeine (4.3%–13.1%) and thus muscle power output. Importantly, as resistance increased toward 1RM, a higher dose of caffeine was needed to increase MPV (Fig. 2) and power (Fig. 3). Although no subject reached the 2004 urinary caffeine threshold for doping, the increase in dosage produced side effects like gastrointestinal problems, anxiety, and headaches that remained 24 h after the trial (Table 1). The practical application for sport nutrition and performance is that muscle contractions against heavy loads (75%–90% 1RM) also require a high caffeine dose ( $9 \text{mg}\cdot\text{kg}^{-1}$ ) to obtain an ergogenic effect. However, explosive, high-velocity low-resistance actions require a much lower caffeine dose ( $3 \text{mg}\cdot\text{kg}^{-1}$ ), thus avoiding the undesirable side effects.

The authors thank the collaboration of José María López Gullón, Ricardo Morán Navarro, Alvaro López Samanes, and Luis Sánchez Medina from the High-Performance Sports Center Infanta Cristina, University of Murcia, University of Castilla-La Mancha and Research and Sports Medicine Centre from the Government of Navarre, respectively. They also acknowledge the commitment and dedication to the testing of each of the 13 high-performance athletes that participated in this investigation.

No funding was received for this work. The authors report no conflicts of interest.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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