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Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers

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Bell, Douglas G., and Tom M. McLellan. Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. *J Appl Physiol* 93: 1227–1234, 2002. First published May 17, 2002; 10.1152/japplphysiol.00187.2002.—The purpose of the present study was to examine the duration of caffeine's ergogenic effect and whether it differs between users and nonusers of the drug. Twenty-one subjects (13 caffeine users and 8 nonusers) completed six randomized exercise rides to exhaustion at 80% of maximal oxygen consumption after ingesting either a placebo or 5 mg/kg of caffeine. Exercise to exhaustion was completed once per week at either 1, 3, or 6 h after placebo or drug ingestion. Exercise time to exhaustion differed between users and nonusers with the ergogenic effect being greater and lasting longer in nonusers. For the nonusers, exercise times 1, 3, and 6 h after caffeine ingestion were 32.7 ± 8.4, 32.1 ± 8.6, and 31.7 ± 12.0 min, respectively, and these values were each significantly greater than the corresponding placebo values of 24.2 ± 6.4, 25.8 ± 9.0, and 23.2 ± 7.1 min. For caffeine users, exercise times 1, 3, and 6 h after caffeine ingestion were 27.4 ± 7.2, 28.1 ± 7.8, and 24.5 ± 7.6 min, respectively. Only exercise times 1 and 3 h after drug ingestion were significantly greater than the respective placebo trials of 23.3 ± 6.5, 23.2 ± 7.1, and 23.5 ± 5.7 min. In conclusion, both the duration and magnitude of the ergogenic effect that followed a 5 mg/kg dose of caffeine were greater in the nonusers compared with the users.

time to exhaustion; ergogenic aid; drug sensitivity

THERE HAVE BEEN NUMEROUS STUDIES and reviews indicating that caffeine ingested before exercise causes rapid and significant improvements in performance, especially in aerobic exercise capacity (6, 8, 16, 20, 28, 30). The dose of caffeine studied has ranged from 1 to 15 mg/kg of body mass. The optimal dose has not been determined because it may vary according to the sensitivity of the individual to caffeine. However, doses between 3 and 6 mg/kg produce an equivalent ergogenic effect to higher doses (5, 29), and this has led Graham et al. (17) to suggest that the optimal dose thus lies in this lower range.

Even though caffeine has a half-life of 4–6 h that implies high levels of caffeine will be in the blood for up to 3–4 h after ingestion, most studies have focused on exercise performance ~1 h after ingestion. The assumption is that the ergogenic effect is related to the circulating level of the drug in the blood. Thus maximal effects are assumed to occur ~1 h after ingestion, when peak blood concentrations are observed (2, 14). Some studies (27, 35) have suggested that waiting 3 h may be more optimal because the caffeine-induced effect on lipolysis is greater than at earlier times after ingestion. However, the hypothesis that the ergogenic effect from caffeine is due to an enhanced free fatty acid mobilization and tissue utilization has not found much support in the recent literature (16, 17, 29).

For sustained operations, as is quite common in the military, or for athletes who might be faced with unplanned delays in competition, it would seem critical not only to know when a particular drug should be taken to produce its effect, but also it would seem important to understand for how long that ergogenic effect may last. Military operations or athletic events may be delayed or cancelled at the last minute, and information about the time course of the effect of a drug would assist in the planning and subsequent rescheduling of activities.

Caffeine acts as an A_1 and A_{2a} adenosine receptor antagonist (13, 14). Regular consumption of caffeine is associated with an upregulation of the number of these adenosine receptors in the vascular and neural tissues of the brain (13, 14). One might expect, therefore, that users and nonusers of caffeine would respond differently to the same dose of the drug because it is known that some individuals are more sensitive than others to caffeine (1, 9, 11, 26). Others have compared users and nonusers of caffeine during an incremental exercise test to maximum (7) or during 1 h of submaximal exercise at 50% of maximal oxygen consumption ($\dot{V}O_{2\,max}$) (35). To our knowledge, however, a comparison of the ergogenic effect of caffeine between users and nonusers of the drug has not been studied during a submaximal exercise test to exhaustion. Furthermore, it is unknown whether the duration of the ergogenic effect that follows caffeine ingestion will be different between users and nonusers of the drug.

Thus it was the purpose of this study to clarify whether the ergogenic effect after the ingestion of a 5 mg/kg dose of caffeine was related to the circulating

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concentration of the drug; to determine the duration of the ergogenic effect after the ingestion of this dose of caffeine; and to determine whether these effects are different for users and nonusers of caffeine.

METHODS

Subjects. Nineteen civilian and two military (15 male and 6 female) subjects with mean ± SD values for age 32 ± 7 yr, height 175 ± 9.5 cm, and body mass 74.8 ± 12.6 kg participated in this study. None of the six women was using oral contraceptives. All subjects were regularly active in aerobic activities and had a cycle ergometer $\dot{V}O_{2\,max}$ of 51 ± 8 $ml \cdot kg^{-1} \cdot min^{-1}$. There were 13 regular caffeine users (ingesting ≥300 mg caffeine/day) and 8 nonusers (ingesting <50 mg caffeine/day), as categorized by their response to a questionnaire on caffeine use administered at the beginning of the study. Caffeine was predominantly ingested in the form of coffee; however, other caffeine products were also ingested, i.e., tea, colas, and chocolate candy bars. The subjects were fully informed of the details, discomforts, and risks associated with the experimental protocol, and written, informed consent was obtained. The subjects were asked to refrain from heavy exercise and alcohol for 24 h and to refrain from caffeine or products containing caffeine for 12 h before each trial. This study was granted approval by the human ethics committee of the Defence R&D Canada-Toronto.

Procedures. The subjects visited the laboratory on nine occasions. During the initial visit, subjects were medically screened and had their $\dot{V}O_{2\,max}$ determined on an electrically braked cycle ergometer (Ergometrics 800, SensorMedics). Men began pedaling at a power output of 75 W, and this was increased 50 W every 4 min for four submaximal power outputs. Thereafter, the work rate was increased 30 W every minute until exhaustion. Women started at 60 W, and the work rate was increased 30 W every 4 min. After the fourth work rate, the power output was increased 25 W every minute until exhaustion. Open-circuit spirometry was used to determine oxygen consumption ($\dot{V}O_2$) every 30 s, and the highest value obtained was defined as the $\dot{V}O_{2\,max}$. Heart rate (HR) was monitored every minute by using a transmitter/telemetry unit (Vantage XL Polar System, Port Washington, NY). The relationship between $\dot{V}O_2$ and power output was also derived from this test, and from that relationship the power output equivalent of 50 and 80% $\dot{V}O_{2\,max}$ was used during the subsequent trials on the same ergometer.

Before *visit 2*, subjects were asked to record all food and caffeinated beverages consumed for a 2-day period. Subjects were then instructed to attempt to replicate this diet for the 2-day period before each of the remaining trials.

During the next eight visits, which were scheduled once a week, the subject performed the exhaustion ride (ER). The ER consisted of two phases. The first phase involved 5 min of cycling at 50% $\dot{V}O_{2\,max}$ with a pedal frequency that was self-selected between 60 and 100 revolutions/min but constant for a given subject. Immediately thereafter, the second phase began, which consisted of a ride to exhaustion at 80% $\dot{V}O_{2\,max}$ at the same pedaling frequency.

The first two trials, *visits 2* and *3*, were a familiarization to the procedures and followed the 1-h treatment-trial time line, as shown in Fig. 1, except no capsules were ingested. The other six rides were the treatment trials, also shown in Fig. 1 and explained below. The subject arrived 1, 3, or 6 h before the ER depending on which trial was scheduled for that day. Because there were six possible treatment orders that varied the time after ingestion of the drug or placebo, both users and nonusers of caffeine were randomly allocated to one of these orders. Within any particular order, a subject performed both the drug and placebo trials for a specific time (1, 3, or 6 h after ingestion) before continuing on to perform the subsequent trials. The dose of caffeine (5 mg/kg) or placebo was administered in a double-blind manner.

Immediately after the subject's arrival, a catheter was inserted into an antecubital vein and an initial 4-ml blood sample was taken. After this, blood samples were taken just before the ER, after 10 min of riding at 80% $\dot{V}O_{2\,max}$, and at exhaustion. After the initial blood sample, either caffeine or placebo capsules were ingested. For the 1-h trials, the capsules were ingested with Gatorade equivalent to 5 mg/kg. For the 3- and 6-h trials, the capsules were ingested with water, and later a similar amount of Gatorade, described above, was ingested 1 h before the ER. Recent evidence has suggested that the ergogenic effect associated with the ingestion of large amounts of carbohydrate before endurance exercise is not increased with the addition of caffeine (23). Although the use of Gatorade to ensure hydration before beginning the exercise trials may have represented a confounding factor

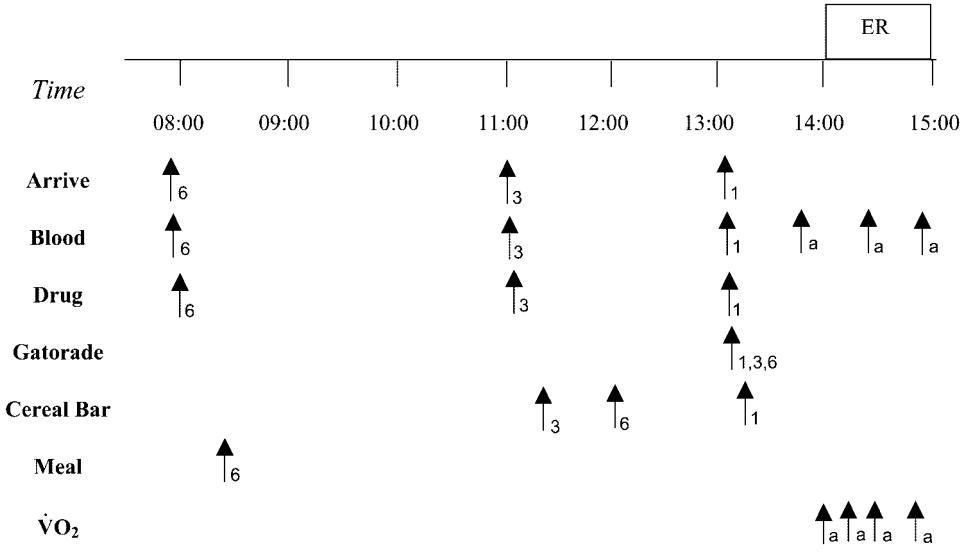

Fig. 1. Time line for arriving, blood sampling, delivery of Gatorade, cereal bar, meal, and measurement of oxygen consumption ($\dot{V}O_2$) during the treatment trials. ER, exercise ride to exhaustion interval; 1, 3, and 6, 1-h trial, 3-h trial and 6-h trial, respectively. [a]Procedure was done at this time for all trials.

Table 1. *Subject characteristics*

	Nonusers (n = 8)	Users (n = 13)	P Value
Age, yr	29.1 ± 6.4	34.0 ± 7.7	0.15
Height, cm	173.5 ± 11.7	176.1 ± 8.1	0.55
Body mass, kg	70.8 ± 13.3	77.3 ± 11.9	0.26
$\dot{V}O_{2max}$, l/min	3.57 ± 0.8	3.94 ± 0.9	0.32
$\dot{V}O_{2max}$, ml·kg^{-1}·min^{-1}	50.7 ± 8.4	51.2 ± 7.4	0.90
Maximal heart rate, beats/min*	190 ± 10	180 ± 7	0.007

Values are means ± SD. $\dot{V}O_{2max}$, maximal oxygen consumption. *Nonusers > users.

with the ingestion of caffeine, the administration was consistent across trials and should not have affected the comparisons between groups or among trials. However, the magnitude of the ergogenic effect may have been compromised. The subject was also given a cereal bar to eat to reduce the possibility of nausea. For the 1- and 3-h trials, the cereal bar was ingested 15 min after the drug. For the 6-h trial, the cereal bar was given 4 h after the drug. Also for the 6-h trial, the subject arrived at the laboratory in a fasted state and was give a meal similar to his/her normal breakfast, half an hour after drug ingestion. For the 1- and 3-h trials, the subject ate a normal breakfast 1 h before coming to the laboratory.

During the ER, open-circuit spirometry was used to determine $\dot{V}O_2$ during the first 5 min of warm-up, after 5 and 15 min at 80% $\dot{V}O_{2\,max}$, and at 15-min intervals thereafter. A whole-body rating of perceived exertion (RPE) using the Borg scale (3) and HR were recorded every 5 min.

Subjects performed the ER dressed in running shoes, shorts, and a T-shirt. The ER was conducted in a climatic suite where the temperature of the room was controlled at 18°C and 40% relative humidity.

Measurements. For the experimental trials, plasma was assayed for free fatty acid (FFA; NEFA C Kit, Wako) (coefficient of variation 2.4%) and for caffeine concentration by using gas chromatograph-mass spectrometry electron impact single-ion monitoring (model MSD 5970a, Hewlett-Packard, Palo Alto, CA). Another aliquot of each blood sample was immediately deproteinized and subsequently assayed for glucose (GOD-PAP, Roche Diagnostics) (coefficient of variation 3.3%) and lactate (25) (coefficient of variation 6.0%). Serum osmolality was measured with freezing-point depression (Advanced Micro-Osmometer model 3300, Advanced Instruments, Norwood, MA).

Statistics. A repeated-measures ANOVA with two within (time after ingestion × drug) factors and one between factor (caffeine use) was used to compare the times to exhaustion during ER and rest concentrations of lactate, glucose, and FFA. For all other variables, a repeated-measures ANOVA with three within (time after ingestion × drug × time during exercise) factors and one between factor (caffeine use) was used to compare the dependent measures. To correct for the violation of the sphericity assumption with the repeated factors, a Huynh-Feldt correction was applied to the F-ratio. When the ANOVA yielded a significant F-ratio, a post hoc comparison of means was done with a means-comparison contrast technique (15). Statistical significance was accepted at the $P \leq 0.05$ level.

RESULTS

Subjects. Although the nonusers tended to be younger, lighter, and smaller, these differences between groups were not significant (Table 1).

Time to exhaustion. Figure 2 presents time to exhaustion for the ER for the different treatments. For all subjects, caffeine significantly improved time to exhaustion from 24.0 ± 6.5 min during the placebo trials to 28.8 ± 8.6 min. However, as shown in Fig. 2, this improvement was greater for the nonusers. Furthermore, the effect of caffeine in the nonusers was still evident 6 h after ingestion of the drug, whereas in the users this was not the case.

$\dot{V}O_2$. As shown in Table 2, $\dot{V}O_2$ was similar for all treatments during the 5-min warm-up period at 50% $\dot{V}O_{2\,max}$. During ER, caffeine produced a small but significant increase in $\dot{V}O_2$ after 15 min of exercise for both users and nonusers.

RER. Regardless of the trial, respiratory exchange ratio (RER) was similar during the 5 min at 50% $\dot{V}O_{2max}$ and averaged 0.97 ± 0.05, 0.97 ± 0.05, and 0.97 ± 0.5 for the 1-, 3-, and 6-h trials, respectively. RER during the 5 min at 50% $\dot{V}O_{2max}$ also was not affected by caffeine ingestion. During exercise at 80% $\dot{V}O_{2max}$, RER significantly decreased from 1.08 ± 0.04 at 5 min to 1.02 ± 0.03 after 15 min. Again, RER was similar among trials and not influenced by the ingestion of caffeine (1.05 ± 0.04 vs. 1.05 ± 0.05 for the caffeine and placebo trials, respectively). RER also was not different between the users and nonusers of caffeine.

HR. The HR response throughout the trials is presented in Table 3. HR was higher for the nonusers compared with the users at both the 50% and 80% $\dot{V}O_{2\,max}$ power outputs. HR increased over time, and values were further increased after caffeine ingestion throughout the ER.

RPE. Table 4 shows that RPE was similar for all trials during the 5-min warm-up period. During ER,

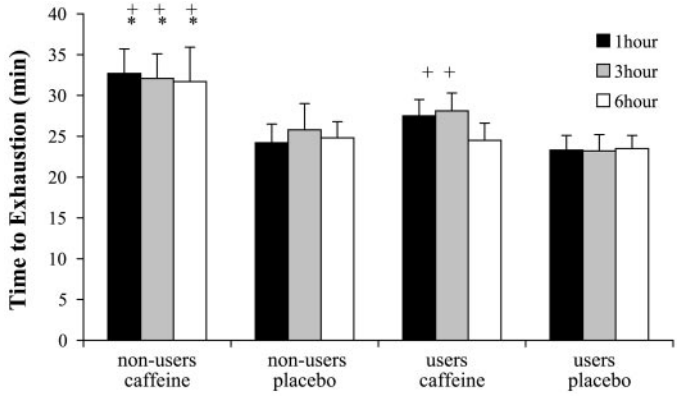

Fig. 2. Time to exhaustion at 80% maximal $\dot{V}O_2$ in caffeine users and nonusers 1, 3, and 6 h after caffeine ingestion. *Nonusers > users. $^+$Caffeine > placebo.

Table 2. *$\dot{V}O_2$ during exercise at 50 and 80% of $\dot{V}O_{2max}$ 1, 3, and 6 h after caffeine or placebo ingestion*

	1 h		3 h		6 h	
Time	Caffeine	Placebo	Caffeine	Placebo	Caffeine	Placebo
Nonusers (n = 8)						
5 min 50% $\dot{V}O_{2max}$	1.72 ± 0.38	1.66 ± 0.29	1.75 ± 0.32	1.78 ± 0.34	1.76 ± 0.38	1.71 ± 0.38
5 min 80% $\dot{V}O_{2max}$	2.85 ± 0.69	2.80 ± 0.63	2.88 ± 0.66	2.93 ± 0.67	2.83 ± 0.62	2.84 ± 0.68
15 min 80% $\dot{V}O_{2max}$	3.10 ± 0.90*	3.01 ± 0.73	3.08 ± 0.76*	3.06 ± 0.78	3.12 ± 0.88*	3.04 ± 0.81
Users (n = 13)						
5 min 50% $\dot{V}O_{2max}$	1.86 ± 0.36	1.88 ± 0.37	1.88 ± 0.37	1.85 ± 0.29	1.90 ± 0.37	1.83 ± 0.34
5 min 80% $\dot{V}O_{2max}$	3.19 ± 0.73	3.21 ± 0.79	3.21 ± 0.72	3.15 ± 0.71	3.18 ± 0.70	3.19 ± 0.73
15 min 80% $\dot{V}O_{2max}$	3.44 ± 0.71*	3.39 ± 0.75	3.42 ± 0.76*	3.36 ± 0.71	3.43 ± 0.75*	3.37 ± 0.75

Values are means ± SD (in l/min). *After 15 min at 80% $\dot{V}O_{2max}$, caffeine produced a slight but significant increase in oxygen consumption ($\dot{V}O_2$).

however, RPE was reduced after caffeine ingestion for both users and nonusers. The lower RPE occurred later during ER for the nonusers, with the significant changes not being evident until after 10 min of exercise.

Blood measures. Blood sampling was not successful for two users during one of their exercise rides. As a result, data are presented for 11 users for Tables 5–7.

Lactate. The blood lactate response before and during the exercise tests is shown in Table 5. Caffeine ingestion increased lactate concentrations before exercise, and this increase was greatest for trials conducted 1 h after ingestion of the drug. Caffeine ingestion also increased blood lactate levels during ER for the users of the drug and during the 1-h trial for nonusers of the drug. At exhaustion, lactate levels were higher after caffeine ingestion compared with placebo for all trials.

Glucose. As shown in Table 6, nonusers before exercise had higher glucose levels than users. During exercise, caffeine produced a slight but significant increase in glucose, and this was increased even further at the end of exercise.

FFA. Regardless of the trial, FFA were similar at rest and averaged 0.20 ± 0.11, 0.19 ± 0.11, and 0.23 ± 0.12 mmol/l for the 1-, 3-, and 6-h trials, respectively. Similarly, FFA were similar at rest for the caffeine (0.21 ± 0.13 mmol/l) and placebo (0.20 ± 0.10 mmol/l) trials. During exercise, FFA levels increased significantly from 0.22 ± 0.11 mmol/l after 5 min to 0.28 ± 0.12 mmol/l at the end of ER. There was no difference among trials or between the caffeine and placebo trials for the FFA response during exercise.

Caffeine concentration. Plasma caffeine concentrations are shown in Table 7. As expected, caffeine ingestion significantly elevated plasma concentrations above values measured during the placebo trials. Users had significantly higher caffeine levels than the nonusers during all trials, but these differences were attributed to the higher baseline levels. The change in caffeine concentration above the baseline value was similar for users and nonusers after ingestion of the drug. For the 1-h trial, caffeine concentration increased significantly throughout exercise, whereas caffeine levels remained constant for trials conducted 3 and 6 h after ingestion. Caffeine concentrations determined 1 and 3 h after caffeine ingestion were greater than for the trial conducted 6 h after ingestion.

Serum osmolality. Osmolality was not different among the trials and averaged 289.7 ± 3.4 mosmol/kgH_2O.

DISCUSSION

In the present study, we report novel findings that document a greater and longer lasting ergogenic effect for nonusers compared with users of caffeine after a 5

Table 3. *Heart rate during exercise at 50 and 80% $\dot{V}O_{2max}$ 1, 3, and 6 h after caffeine or placebo ingestion*

	1 h		3 h		6 h	
Time	Caffeine	Placebo	Caffeine	Placebo	Caffeine	Placebo
Nonusers* (n = 8)						
5 min 50% $\dot{V}O_{2max}$	125 ± 8	122 ± 8	125 ± 12	124 ± 7	128 ± 12	124 ± 10
5 min§ 80% $\dot{V}O_{2max}$	164 ± 7†	162 ± 9	168 ± 11†	164 ± 8	167 ± 10†	162 ± 8
10 min§ 80% $\dot{V}O_{2max}$	170 ± 8†	168 ± 9	174 ± 11†	171 ± 10	174 ± 11†	170 ± 9
15 min§ 80%max	174 ± 8†	172 ± 10	177 ± 10†	174 ± 10	178 ± 11†	175 ± 10
Exhaustion§ 80% $\dot{V}O_{2max}$	180 ± 8†	174 ± 14	183 ± 11†	177 ± 11	182 ± 12†	177 ± 12
Users (n = 13)						
5 min 50% $\dot{V}O_{2max}$	110 ± 9	116 ± 9	113 ± 11	110 ± 10	113 ± 11	115 ± 14
5 min§ 80% $\dot{V}O_{2max}$	154 ± 9†	155 ± 9	154 ± 12†	152 ± 11	155 ± 11†	152 ± 10
10 min§ 80% $\dot{V}O_{2max}$	164 ± 10†	163 ± 7	164 ± 11†	161 ± 11	162 ± 11†	159 ± 10
15 min§ 80% $\dot{V}O_{2max}$	169 ± 10†	167 ± 8	168 ± 9†	165 ± 10	166 ± 12†	164 ± 10
Exhaustion§ 80% $\dot{V}O_{2max}$	173 ± 10†	170 ± 7	171 ± 10†	168 ± 10	170 ± 12†	166 ± 10

Values are means ± SD (in beats/min). *Nonuser at 50% and at 80% $\dot{V}O_{2max}$ > user. †Caffeine at 80% $\dot{V}O_{2max}$ > placebo at 80% $\dot{V}O_{2max}$. §Heart rate increased with time.

Table 4. *Rating of perceived exertion during exercise at 50 and 80% $\dot{V}O_{2max}$ 1, 3, and 6 h after caffeine or placebo ingestion*

Time	1 h		3 h		6 h	
	Caffeine	Placebo	Caffeine	Placebo	Caffeine	Placebo
Nonusers (n = 8)						
5 min 50% $\dot{V}O_{2max}$	9.6 ± 1.3	8.8 ± 1.3	9.1 ± 1.6	9.1 ± 1.6	9.0 ± 1.3	8.8 ± 1.8
5 min 80% $\dot{V}O_{2max}$	12.3 ± 1.0	12.1 ± 0.8	13.1 ± 1.7	13.4 ± 1.5	12.5 ± 1.2	13.1 ± 1.0
10 min 80% $\dot{V}O_{2max}$	13.9 ± 1.3*	14.6 ± 0.5	14.7 ± 1.7*	15.1 ± 1.0	14.8 ± 1.2*	15.2 ± 1.4
15 min 80% $\dot{V}O_{2max}$	15.4 ± 1.3*	16.8 ± 0.8	15.9 ± 1.6*	17.1 ± 1.2	16.3 ± 1.1*	16.9 ± 1.4
Exhaustion 80% $\dot{V}O_{2max}$	18.3 ± 1.6	18.6 ± 1.1	19.3 ± 0.6	18.5 ± 1.2	18.8 ± 1.0	18.4 ± 1.3
Users (n = 13)						
5 min 50% $\dot{V}O_{2max}$	8.2 ± 1.1	8.4 ± 1.2	8.1 ± 1.3	8.8 ± 1.7	8.6 ± 1.2	8.0 ± 1.3
5 min 80% $\dot{V}O_{2max}$	12.2 ± 1.4*	13.0 ± 1.4	12.2 ± 1.6*	13.2 ± 1.7	12.8 ± 1.4*	13.3 ± 1.4
10 min 80% $\dot{V}O_{2max}$	14.5 ± 1.2*	15.4 ± 2.1	14.7 ± 1.7*	15.2 ± 1.8	15.0 ± 1.9*	15.5 ± 1.5
15 min 80% $\dot{V}O_{2max}$	16.2 ± 1.4*	17.0 ± 2.0	16.2 ± 2.3*	17.0 ± 2.0	16.7 ± 1.9*	17.4 ± 1.8
Exhaustion 80% $\dot{V}O_{2max}$	18.3 ± 1.4	18.6 ± 1.0	18.8 ± 1.5	18.6 ± 0.9	18.7 ± 1.3	18.7 ± 1.5

Values are means ± SD. *Caffeine at 80% $\dot{V}O_{2max}$ < placebo at 80% $\dot{V}O_{2max}$.

mg/kg dose of the drug. To our knowledge, we are the first to systematically study the effects of caffeine ingestion at specific time intervals after ingestion of the drug for both users and nonusers. For military operations or for athletic competition, inclement weather or a change in scheduling may prevent the ingestion of the drug and subsequent peak blood concentrations coinciding with the onset of physical activity. The findings from the present study, therefore, will be of added benefit in these situations.

Others have compared users and nonusers of caffeine at rest and during an incremental exercise test to exhaustion after a 3 or 5 mg/kg dose of the drug (7) or during 1 h of submaximal exercise at 50% $\dot{V}O_{2\,max}$ after a 5 mg/kg dose (34). For both of these studies, exercise began 1 h after the ingestion of the drug and there was no impact of caffeine on the cardiorespiratory response during exercise. Van Soeren et al. (34) did report that the metabolism of caffeine differed between the users and nonusers of the drug and that caffeine ingestion had a greater impact on the epinephrine response during exercise for nonusers. Neither of these studies (7, 34), however, studied the impact of caffeine ingestion on time to exhaustion during submaximal exercise.

In the present study, all subjects received the same dose of caffeine relative to their body mass, and yet the magnitude and duration of the ergogenic effect was different between users and nonusers of the drug. Caffeine acts as an A_1 and A_{2a} adenosine receptor antagonist (13, 14), and regular consumption of caffeine is associated with an upregulation of the number of these adenosine receptors in the vascular and neural tissues of the brain (14, 21, 22, 26). The resultant cascade of cellular events that follow adenosine receptor blockade, including increased dopamine and noradrenaline release (14), have been proposed as key regulatory mechanisms to explain the ergogenic effect of the drug. Thus the same concentration of caffeine might be expected to block a greater percentage of the adenosine receptors for nonusers and lead to a greater response and ergogenic effect. Similarly, one might expect that higher blood concentrations of caffeine would be necessary to block the same percentage of adenosine receptors for users of the drug. However, this rationale is complicated by individual differences in sensitivity to the drug and the associated side effects such as nausea, tremor, anxiety, and confusion that develop when high doses of the drug are ingested.

The present data would suggest that a 5 mg/kg dose of caffeine would be closer to optimal for nonusers than for users of the drug. Others have reported an ergogenic effect with doses of caffeine between 3 and 9 mg/kg for subjects with varied caffeine consumption

Table 5. *Blood lactate before, during, and at the end of exercise at 80% $\dot{V}O_{2max}$ 1, 3, and 6 h after caffeine or placebo ingestion*

Time	1 h		3 h		6 h	
	Caffeine	Placebo	Caffeine	Placebo	Caffeine	Placebo
Nonusers (n = 8)						
Before exercise	1.2 ± 0.3§†	0.9 ± 0.3	1.1 ± 0.4†	0.9 ± 0.3	1.0 ± 0.4†	0.8 ± 0.3
10 min 80% $\dot{V}O_{2max}$	5.7 ± 1.8*	4.6 ± 1.7	5.0 ± 1.6	5.2 ± 1.8	5.2 ± 1.4	5.2 ± 1.8
Exhaustion 80% $\dot{V}O_{2max}$	7.3 ± 3.1‡	5.4 ± 2.7	6.8 ± 2.4‡	6.5 ± 2.7	6.5 ± 2.5‡	6.2 ± 2.5
Users (n = 11)						
Before exercise	1.2 ± 0.4§†	0.8 ± 0.2	0.9 ± 0.4†	0.6 ± 0.3	0.7 ± 0.2†	0.6 ± 0.2
10 min 80% $\dot{V}O_{2max}$	5.4 ± 1.2*	5.3 ± 1.7	5.5 ± 1.3*	5.3 ± 1.4	5.6 ± 1.6*	5.1 ± 1.5
Exhaustion 80% $\dot{V}O_{2max}$	7.3 ± 1.2‡	6.4 ± 1.6	7.2 ± 1.5‡	6.8 ± 1.7	7.2 ± 1.7‡	5.7 ± 1.4

Values are means ± SD (in mmol/l). *Caffeine at 80% $\dot{V}O_{2max}$ > placebo at 80% $\dot{V}O_{2max}$. †Before exercise with caffeine > placebo. ‡Caffeine exhaustion 80% $\dot{V}O_{2max}$ > placebo exhaustion 80% $\dot{V}O_{2max}$. §Before exercise at 1 h >3 h and 6 h.

Table 6. *Blood glucose before, during, and at the end of exercise at 80% $\dot{V}O_{2max}$ 1, 3, and 6 h after caffeine or placebo ingestion*

Time	1 h		3 h		6 h	
	Caffeine	Placebo	Caffeine	Placebo	Caffeine	Placebo
Nonusers (n = 8)						
Before* exercise	4.0 ± 1.0	3.5 ± 0.5	4.1 ± 0.2	3.9 ± 0.5	4.4 ± 0.6	3.5 ± 0.6
10 min 80% $\dot{V}O_{2max}$	4.0 ± 0.5†	3.3 ± 0.3	3.7 ± 0.3†	3.7 ± 0.6	3.8 ± 0.5†	3.4 ± 0.3
Exhasution 80% $\dot{V}O_{2max}$	4.7 ± 1.0†	3.9 ± 0.6	4.7 ± 0.7†	4.2 ± 0.6	4.4 ± 0.7†	4.1 ± 0.6
Users (n = 11)						
Before exercise	3.4 ± 1.1	3.5 ± 1.4	3.4 ± 0.6	3.4 ± 0.7	3.5 ± 0.4	3.5 ± 0.4
10 min 80% $\dot{V}O_{2max}$	3.1 ± 0.5†	3.2 ± 0.7	3.5 ± 0.5†	3.3 ± 0.5	3.7 ± 0.5†	3.4 ± 0.7
Exhaustion† 80% $\dot{V}O_{2max}$	4.3 ± 1.3†	3.6 ± 0.9	4.7 ± 1.3†	4.1 ± 0.8	4.2 ± 1.2†	3.9 ± 1.1

Values are means ± SD (in mmol/l). *Nonusers before exercise > users. †Caffeine at 80% $\dot{V}O_{2max}$ > placebo at 80% $\dot{V}O_{2max}$.

habits (5, 8, 12, 19, 28, 32). Two studies from the same laboratory report equivocal findings after a 9 mg/kg dose of caffeine (19, 32), and Graham and Spriet (19) have suggested that these inconsistent effects reflect the different proportions of users and nonusers or light consumers of caffeine in their subject groups. These authors also state that, although there was no direct relationship between caffeine habits and the ergogenic response to the 9 mg/kg dose of the drug, those subjects who were lightest users of caffeine tended to have their poorest response after this high dose and complained of confusion (19). Bell et al. (1) have also documented a greater ergogenic response during exercise to exhaustion at 80% $\dot{V}O_{2\,max}$ for users compared with nonusers of caffeine after the ingestion of the combined stimulants of caffeine (4 mg/kg) and ephedrine (0.8 mg/kg). Thus one might expect that the ergogenic response would be greater for users compared with nonusers of caffeine after the ingestion of higher doses of caffeine. However, the dose-response relationship between caffeine and exercise performance has yet to be clarified for users and nonusers of the drug.

There are other factors involved in the design of this study that could influence the comparisons between the users and nonusers of caffeine. First, blood concentrations of caffeine were higher for users compared with nonusers of the drug throughout the trials, and these differences could be attributed to the elevated baseline levels of caffeine present for the users of the drug. The resultant change in the blood caffeine profile was similar between users and nonusers of the drug when the baseline levels were subtracted from the subsequent concentrations determined 1, 3, or 6 h after the ingestion of the drug. Nevertheless, Graham et al. (18) have reported that elevated blood concentrations of caffeine derived from coffee consumption do not produce an ergogenic effect during a treadmill exercise test to exhaustion. In contrast, the same concentrations of caffeine that followed the ingestion of anhydrous caffeine were associated with a 30% improvement in performance time. Thus other ingredients in coffee, as yet unidentified, might negate the ergogenic effect that follows the ingestion of anhydrous caffeine. In the present study, we cannot discount the possibility that the small elevations in baseline blood caffeine levels remaining from the previous consumption of coffee or other caffeine-containing beverages in our users reduced the ergogenic impact of the 5 mg/kg dose of anhydrous caffeine. More definitive studies are required to address whether the ingestion of caffeinated beverages such as coffee, tea, and some sodas reduces the ergogenic effect associated with the ingestion of anhydrous caffeine. Studies that address this issue are necessary before the use of a certain dose of anhydrous caffeine to enhance physical and/or cognitive function

Table 7. *Caffeine concentration predrug and before, during, and at the end of exercise at 80% $\dot{V}O_{2max}$ 1, 3, and 6 h after caffeine or placebo ingestion*

	1 h		3 h		6 h	
	Caffeine	Placebo	Caffeine	Placebo	Caffeine	Placebo
Nonusers* (n = 8)						
Predrug	0.4 ± 0.4	0.4 ± 0.4	0.5 ± 0.4	0.7 ± 0.7	0.6 ± 0.6	0.6 ± 0.6
Before exercise	26.2 ± 12.9†	0.4 ± 0.4	30.5 ± 5.3	0.3 ± 0.5	23.4 ± 7.1‡	0.5 ± 0.3
During exercise	30.1 ± 12.5	0.4 ± 0.3	30.1 ± 5.2	0.3 ± 0.5	23.2 ± 8.0‡	0.3 ± 0.3
Postexercise	32.3 ± 12.0	0.5 ± 0.9	30.7 ± 5.2	0.3 ± 0.4	22.1 ± 6.8‡	0.4 ± 0.3
Users (n = 11)						
Predrug	3.8 ± 2.8	3.4 ± 2.7	3.3 ± 4.2	3.2 ± 2.5	4.0 ± 2.7	4.1 ± 2.8
Before exercise	32.9 ± 10.1†	2.7 ± 2.3	33.1 ± 8.6	2.5 ± 1.9	26.9 ± 7.5‡	2.4 ± 1.6
During exercise	35.7 ± 8.4	2.5 ± 2.2	33.8 ± 6.4	2.3 ± 1.8	27.1 ± 5.3‡	2.1 ± 1.5
Postexercise	36.3 ± 7.4	2.5 ± 2.1	33.7 ± 6.4	2.4 ± 1.6	26.8 ± 7.8‡	2.0 ± 1.4

Values are means ± SD (in μmol/l). *Nonusers < users. †Caffeine 1 h before exercise < caffeine 1 h postexercise. ‡Caffeine 6 h < caffeine 1 and 3 h.

can be advocated for military personnel or workers involved in continuous operations.

Second, although users of caffeine were asked to refrain from caffeinated beverages for 12 h before reporting to the laboratory for each trial, the total duration of withdrawal from caffeine varied among the placebo trials. However, although some subjects complained of a headache while waiting for the exercise test to be performed 6 h after the placebo was ingested, there was no evidence that the variable withdrawal period influenced time to exhaustion or the metabolic response during the placebo tests. Thus we feel confident that the comparisons between the drug and placebo trials for the users reflect the time course of the ergogenic response after the ingestion of 5 mg/kg of caffeine and are not complicated by varying states of withdrawal during the placebo trials. Van Soeren and Graham (33) studied the impact of up to 4 days of withdrawal from caffeine on the ergogenic effect that followed the ingestion of 6 mg/kg of the drug. Interestingly, withdrawal from caffeine not only had no effect on the 30% improvement in cycle time to exhaustion at 80% $\dot{V}O_{2\,max}$, but cycle times to exhaustion during the placebo trials were also similar after 2 or 4 days of withdrawal from caffeine.

The findings from this study have also revealed that the relationship between the ergogenic effect that follows the ingestion of caffeine and the blood concentration of the drug is different for the users and nonusers. Clearly, for the users as blood concentrations of the drug began to decrease 6 h after ingestion so did performance. However, for the nonusers, the ergogenic effect at 6 h remained similar to trials conducted earlier despite a significant decrease in blood concentrations. Similarly, Kamimori et al. (24) have reported that choice reaction times and accuracy remain improved for 12 h after the ingestion of varying doses of caffeine in sleep-deprived subjects despite decreasing blood concentrations of caffeine over the last 9 h of data collection. Thus either the ergogenic and cognitive enhancement that follows caffeine ingestion is related to maintaining blood concentrations above a certain threshold level (which would be expected to be different for users and nonusers), or other secondary metabolites are more critical than the methylxanthine concentration in explaining the outcome effect.

The magnitude of the ergogenic effect seen in our subjects was 19% for the users and 28% for the nonusers. These improvements are comparable to those reported by others (6, 20, 28, 33) who have used a similar mode and intensity of exercise, as well as a similar dose of caffeine ingested 1–1.5 h before exercise. Furthermore, our findings 3 h after ingestion are consistent with a previous study by Flinn et al. (12). However, other inconsistent findings have been reported in the literature perhaps partially because of doses of the drug that have either been too low or exceedingly high (4, 31).

Weir et al. (35) have suggested that performance may be improved 3–4 h after the ingestion of caffeine as this time would correspond with elevated FFA levels. The preliminary theory put forward by Essig et al. (10) suggested that caffeine may exert its ergogenic effect by elevating FFA availability and thereby creating a sparing of glycogen within the muscle. In the present study, there was little evidence of an altered FFA and a very slight increase in glucose availability after drug ingestion that could account for the ergogenic effect of caffeine. Furthermore, the RER values were not affected by caffeine ingestion, implying that the metabolic fuel utilization was similar among trials. Thus the present findings confirm the work of Graham and co-workers (17, 29) that there is little evidence to suggest that caffeine mediates its ergogenic effect through increased FFA mobilization and sparing of muscle glycogen.

In conclusion, a 5 mg/kg dose of caffeine 1, 3, and 6 h before exercise produced quantitative differences in performance between caffeine users and nonusers. The ergogenic effect of caffeine was seen in both groups, but the improvements in exercise time to exhaustion were greater and lasted longer for the nonusers of the drug. Differences in sensitivity to caffeine were suggested as the main reason to account for the contrasting findings between users and nonusers of the drug.

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