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Caffeine increases endurance and attenuates force sensation during submaximal isometric contractions

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Plaskett, C. J., and E. Cafarelli. Caffeine increases endurance and attenuates force sensation during submaximal isometric contractions. *J Appl Physiol* 91: 1535–1544, 2001.—Caffeine has known ergogenic effects, some of which have been observed during submaximal isometric contractions. We used 15 subjects in a randomized, double-blind, repeated-measures experiment to determine caffeine's ergogenic effects on neuromuscular variables that would contribute to increased endurance capacity. Subjects performed repeated submaximal (50% maximal voluntary contraction) isometric contractions of the right quadriceps to the limit of endurance (T_{lim}) 1 h after oral caffeine administration (6 mg/kg). Time to reach T_{lim} increased by 17 ± 5.25% ($P < 0.02$) after caffeine administration compared with the placebo trial. The changes in contractile properties, motor unit activation, and M-wave amplitude that occurred as the quadriceps reached T_{lim} could not account for the prolonged performance after caffeine ingestion. In a separate experiment with the same subjects, we used a constant-sensation technique to determine whether caffeine influenced force sensation during 100 s of an isometric contraction of the quadriceps. The results of this experiment showed that caffeine reduced force sensation during the first 10–20 s of the contraction. The rapidity of this effect suggests that caffeine exerts its effects neurally. Based on these data, the caffeine-induced increase in T_{lim} may have been caused by a willingness to maintain near-maximal activation longer because of alterations in muscle sensory processes.

neuromuscular; fatigue

CAFFEINE HAS THE POTENTIAL to influence human neuromuscular performance through its effects on central and peripheral events along the motor pathway. The drug has central stimulatory effects by blocking the inhibitory effects of adenosine (5), and it is well established that it potentiates contractile force in skeletal muscle preparations and in humans (19, 29, 45). Despite the evidence that caffeine may affect performance, there are only a few studies available that have investigated its effects on endurance during isometric contractions (8, 24, 27, 50). For example, Lopes et al. (27) found that three of their five subjects increased endurance time of a sustained contraction of the adductor pollicis after ingestion of 500 mg of caffeine. There was a mean increase in endurance time of 12% in the caffeine trial; however, this was not significantly different from the placebo trial. Kalmar and Cafarelli (24) found that fatigue was significantly delayed in submaximal contraction of the quadriceps. Conflicting results from other investigations (8, 46, 50) are likely because of variability in methodologies, subject selection, caffeine doses, and individual sensitivities to an acute dose of caffeine.

The sensation of force that accompanies a contraction is an important component in the quality of the motor performance. When producing a muscular contraction at a constant force, there is a continual buildup of force sensation (9, 43). The ergogenic properties of caffeine during aerobic activities have frequently been associated with an attenuation in exercise sensory processes (12, 13), and a hypoalgesic effect with caffeine has also been observed during ischemic muscle contractions (33). These reports have mainly used category rating scales after the activity to determine single time-point assessment of the influence of caffeine on these measurements. It is, therefore, possible that the attenuation of force sensation may contribute to the increased endurance capacity of a sustained, submaximal, isometric contraction. This has not previously been investigated.

The studies by Kalmar and Cafarelli (24) and Lopes and colleagues (27) indicate that caffeine has performance-enhancing effects on the neuromuscular system; however, the mechanisms responsible for these effects are not clear. The purposes of this investigation were *1*) to determine where, along the motor pathway, caffeine exerts its effect on the voluntary activation of skeletal muscle during a fatigue protocol and *2*) to determine whether caffeine alters force sensation during a submaximal isometric contraction.

METHODS

Subjects

Fifteen men (age 22.6 ± 0.6 yr, weight 77.1 ± .2.3 kg, and height 178.3 ± 1.9 cm), who were all nonsmokers and noncaffeine users, were paid volunteer subjects for the present investigation. Noncaffeine users were classified as those who

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consumed <200 mg of caffeine/wk based on a survey of daily intake of foods and beverages. All subjects were provided with a list of caffeinated foods, drugs, and beverages to avoid for a minimum of 5 days before their first experimental session and throughout their participation in the study. In response to an acute dose of caffeine, habituated caffeine users show a dampened rise in plasma epinephrine and smaller increases in blood pressure and heart rate (3, 38). However, these responses can be potentiated after 4 days of withdrawal. Van Soeren and Graham (47) observed an ergogenic effect after an acute dose of caffeine in habituated caffeine users, regardless of the duration of a withdrawal period. This indicates that an ergogenic influence is obtainable in habituated caffeine users and a withdrawal period is not necessary.

Experimental Protocols

All techniques were approved by the York University Human Participants Review Committee. Two different protocols were used in the study: *1*) an endurance protocol to identify the central or peripheral neuromuscular alterations that enable caffeine to increase the endurance of an isometric contraction and *2*) a sensory protocol to determine whether caffeine alters force sensation during an isometric contraction. A double-blind, repeated-measures design, with randomized experimental and placebo trials, was used over 4 separate test days. A "no-capsule control" group was not used because a previous study found no significant difference between placebo and no-capsule groups in a similar experimental protocol (24).

All experiments were conducted at least 3 days apart to control for fatigue, muscle soreness, and habituation to caffeine and were performed at approximately the same time in the morning to control for circadian rhythms and to minimize sleeplessness. Subjects were instructed to refrain from physical activity and caffeine and to eat the same meal before each experimental session. Compliance was monitored with verbal self-report before each experiment. A preliminary session was conducted to familiarize the subjects with the experimental procedures. After each experiment, subjects were asked if they could identify whether they had received caffeine or the placebo and to describe the basis of that decision.

Before starting the experiment, the subjects rested quietly in the apparatus for 10 min. We then recorded control measurements of resting heart rate and blood pressure, maximum potentiated evoked twitch (Tw_{max}), maximal voluntary contraction (MVC) force of the right quadriceps, maximal surface electromyogram (EMG), and percent voluntary activation. MVCs were repeated until three contractions that were within 10% of each other were obtained. Subjects were then given a capsule containing either caffeine or flour. Control measures were repeated 1 h after ingestion of caffeine or the placebo (20, 47). This was followed by either the endurance or sensory protocol.

Endurance protocol. Five minutes after the second set of control measurements, subjects performed one MVC and then immediately commenced the endurance protocol. Isometric contractions at 50% MVC for 15 s were repeated with the target force displayed on a computer monitor. Every 15 s the right quadriceps was relaxed for the time needed to evoke a Tw_{max} (~1.5 s). Electrical stimulation was also administered in the middle of every isometric contraction to determine the degree of activation required to achieve the target force. The protocol was terminated when force declined to <45% of MVC for longer than 2 s.

Sensory protocol. The sensory protocol commenced 5 min after the second set of control measurements. Visual feedback of a horizontal cursor was displayed on a computer monitor to obtain a target of 50% MVC of the knee extensors. When the target force was achieved, visual feedback was removed, and the instructions were to maintain force sensation constant by adjusting the force output. No further verbal commands or encouragement were provided once visual feedback was removed. Each trial lasted 100 s because this is the approximate time it takes to reach the time limit of endurance (T_{lim}) under these conditions (24). Four trials were performed with 3 min between each (Fig. 1*A*).

An advantage of using this constant-sensation technique is that the measurements do not require the interpretation of numbers or categories. The technique also provides continuous data during these contractions that would not have been possible with a self-report rating scale. Finally, the technique has proven to be sensitive to experimental manipulation (10, 40).

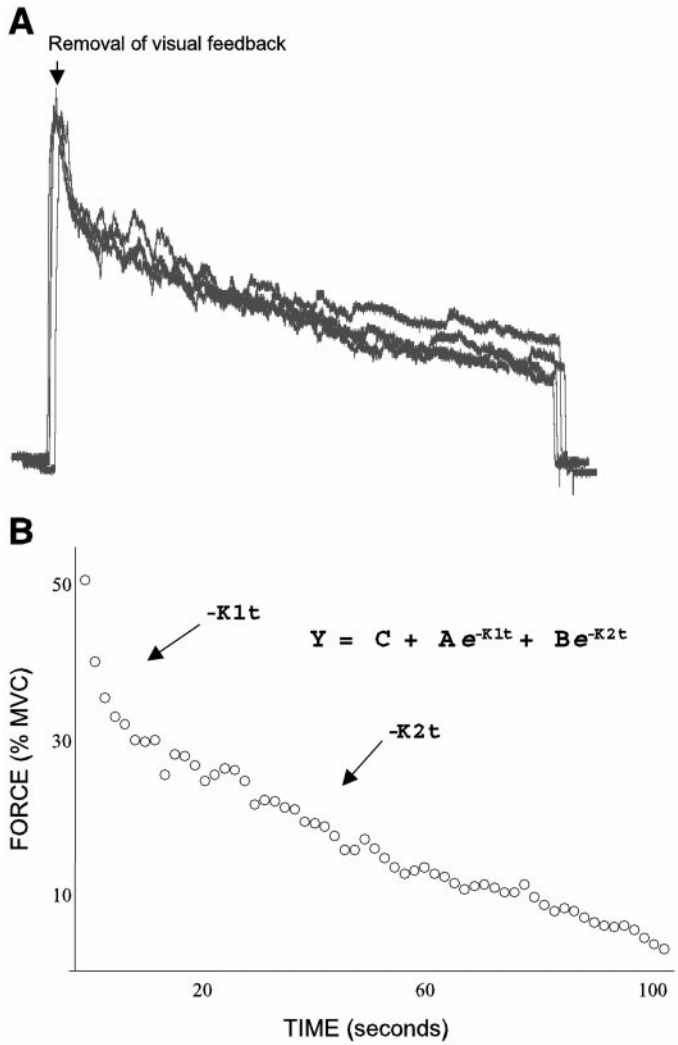

Fig. 1. *A*: four force tracings from the sensory protocol performed by 1 subject. *B*: average of the 4 tracings shown in *A* were smoothed and then fit to a double-exponential equation of the form shown. The terms $-K1t$ and $-K2t$ are rate constants, Y is force, t is time, A and B are the values of the exponential processes, and C is the asymptote. MVC, maximal voluntary contraction.

Procedures

Dosage. One hour before the experimental trials, 6 mg/kg of USP grade caffeine (A&C American Chemicals, Montreal, Quebec) or all-purpose flour in gelatin capsules was administered. Dosage was based on similar experimental protocols that have elicited an ergogenic effect (22, 24, 47).

Tw_{max} and electrical stimulation. Two stimulating electrodes (12.5 × 7 cm) were used to depolarize the right femoral nerve and activate the right knee extensors. The anode was placed in the inguinal crease, and the cathode was placed midway between the superior aspect of the greater trochanter and inferior border of the iliac crest. Shocks were applied in 200-μs square-wave pulses from a Digitimer (model DS7A, Hertfordshire, UK) constant-voltage (270 V), high-intensity stimulator triggered from Spike2 software (version 3.0, CED, Cambridge, UK). Tw_{max} was achieved when an increase in current produced no further increase in twitch force. The current was then increased by 15 mA to administer a supramaximal stimulation.

MVC. Brief voluntary submaximal isometric contractions were performed as a warm-up before the first attempt at a MVC for the control measures. With verbal encouragement, subjects were instructed to produce an isometric MVC of their right quadriceps as fast and as forcefully as possible. A single supramaximal shock was administered to the femoral nerve at the peak of the MVC and another immediately after it to determine the degree of voluntary activation with the method of Allen et al. (2).

Force. The isometric force produced by the quadriceps was measured in a dynamometer, which was adjustable to accommodate each subject. The seat of the dynamometer was equipped with full back and head support, and an adjustable lap belt was used to stabilize the hips in 90° of flexion. The entire unit was tilted back 45°, and the subject's arms were folded over his chest during all leg contractions. The right knee joint was positioned in 90° of flexion, and a cast aluminum cuff attached to a force transducer was clamped 2 cm above the lateral malleolus.

EMG. A bipolar silver-silver chloride surface electrode (EQ, Chalfont, PA) with an interelectrode distance of 2 cm was used to record electrical activity from the right vastus lateralis. The electrode was positioned ~10 cm proximal to the patella in the center of the vastus lateralis muscle belly. The skin surface was shaved and cleaned with 70% alcohol. The EMG signal was preamplified at the surface electrode and passed through a variable-gain second-stage amplifier, before being stored on magnetic tape. A strap electrode soaked in water and covered with plastic wrap to prevent evaporation was wrapped around the right upper thigh to serve as a ground.

Signal Processing

Force and EMG signals recorded on tape (VCR model 500D, PCM model 4000A; Vetter, Rebersberg, PA) were analyzed off-line using Spike2. Force signals for Tw_{max}, MVC, and the muscle endurance protocol were sampled at a rate of 1,000 Hz and smoothed using a Spike2 script that calculated a moving average of every 25 points to eliminate high-frequency noise. Surface EMG was sampled at 5,000 Hz and rectified before the determination of the root-mean-square (RMS) amplitude.

Endurance protocol. The T_{lim} was defined as the point when force fell <45% MVC for ≥2 s. If force fell <45% MVC and recovered back to the target force in <2 s, the target force needed to be maintained for 2 s or longer to continue with the protocol. T_{lim} was calculated from the beginning of the first 50% isometric contraction until the target force could no longer be maintained. The changes in muscle contractile properties during the endurance protocol were analyzed from Tw_{max} evoked every 15 s. The measurements consisted of peak twitch amplitude (Tw_{amp}) and the maximum instantaneous ascending and descending slopes [maximum instantaneous rate of tension development and relaxation (+dF/dt and −dF/dt, respectively)]. Voluntary activation of the vastus lateralis was assessed from the RMS amplitude of the surface EMG and from the superimposed twitch technique. The EMG was measured in 2-s epochs from each isometric contraction, excluding the superimposed shock. Voluntary activation of the motor unit pool was determined from the superimposed shock administered in the middle of each isometric contraction. The force increase caused by the electrical stimulation during the 50% MVC was compared with the force elicited by the electrical stimulation in the immediately following inactive period. Percent activation was determined by using the following equation (2)

$$\text{percent voluntary activation} = \left(1 - \frac{\text{superimposed } Tw_{amp}}{\text{potentiated } Tw_{amp}}\right) \times 100$$

The peak-to-peak amplitude of the M wave produced from electrical stimulation was used to assess the efficacy of neuromuscular transmission and action potential propagation along the sarcolemma.

Sensory protocol. In this technique, the reciprocal of the force recording is the analog of force sensation. To maintain force sensation constant from its initial level, force is typically reduced in a nonlinear manner (11). A sharp reduction in force occurs within the first few seconds and then declines less rapidly over the duration of the contraction. The time course of the force recording is highly reproducible and can be best fit to the following double-exponential function

$$Y = C + Ae^{-K1t} + Be^{-K2t}$$

where Y is force, t is time, A and B are the values of the exponential processes, C is asymptote, and $K1$ and $K2$ are rate constants (10, 11, 36).

An average of the four sensory trials was calculated using a Spike2 script that averaged each trial from the point at which visual feedback was withdrawn until 100 s had elapsed (Fig. 1*A*). The averaged force tracing was transposed as numerical values into Excel 97 (Microsoft, Chicago, IL), and an arithmetic formula was used to obtain an average of every 50 points (Fig. 1*B*). This procedure was chosen to smooth the curve and still maintain enough data points so that the image of the force tracing was not altered. The averaged force tracing values from Excel were transposed into SigmaPlot 2000 for Windows (SPSS, Chicago, IL) and fit with the double-exponential decay equation using an iteration process to produce the nonlinear regression (Fig. 1*B*).

MVCs and maximal EMG. MVCs performed for the control measures were averaged among the three highest trials that were within 10% force of each other. The RMS of the EMG signal during each contraction was measured for 1 s at the peak of the contraction before the stimulus artifact and also averaged. Voluntary activation, M wave, and twitch were measured as described in the endurance protocol.

Statistical Analysis

Statistics were performed with Statistica (release 5.1, Statsoft, Tulsa, OK). Control measurements were expressed as the ratio between post- to precapsule and compared be-

tween placebo and caffeine conditions using a one-way repeated-measures ANOVA.

The dependent variables for the sensory protocol (final force, rate constant *K1*, and rate constant *K2*) were analyzed using a one-way repeated-measures ANOVA between conditions. All of the dependent variables measured during the endurance protocol (Tw_{max}, $+dF/dt$, $-dF/dt$, EMG, percent voluntary activation, and M-wave amplitude) for each subject were individually fit to a linear regression using SigmaPlot. The slopes were compared between placebo and caffeine conditions for each variable with a one-way repeated-measures ANOVA. For all endurance protocol statistical analyses, the dependent variables were expressed as a percentage of the first measurement obtained during the endurance protocol (%initial), and the time for both conditions was normalized to placebo T_{lim}.

Each dependent variable in the endurance protocol was compared between the caffeine and placebo trial at three different time points: *1*) at placebo T_{lim}, *2*) at the time point in the caffeine trial corresponding to placebo T_{lim}, and *3*) at caffeine T_{lim} using a one-way repeated-measures ANOVA with a Tukey post hoc when needed (see Fig. 5). As with other fatigue protocols, difficulty in the statistical analysis arises because of individual differences in endurance time. In the present experiment, there was considerable variability in the time to T_{lim} among subjects as well as between conditions for individual subjects. Because a few subjects had a decreased T_{lim} in the caffeine condition, there were no data points at the time corresponding to placebo T_{lim}. To perform a matched repeated-measures one-way ANOVA for each dependent variable at three time points, these missing data were replaced with data assessed at caffeine T_{lim}. This analysis was selected because it is the most conservative and actually underestimates the ergogenic effects that were observed with caffeine.

RESULTS

Contractile properties of the knee-extensor muscles and electrical activity of vastus lateralis during voluntary and evoked contractions along with systemic cardiovascular responses to the two treatments are shown in Table 1. These data were obtained immediately before and 1 h after capsule ingestion in all experiments and were intended to assess the effects of caffeine in the rested state.

Systolic ($P < 0.01$) and diastolic ($P < 0.01$) blood pressure increased significantly 1 h after caffeine ingestion, but there was no change in heart rate, which is consistent with previous findings (14, 38). MVC increased significantly ($P < 0.01$) by 5 ± 2% in the caffeine condition, and voluntary activation also increased ($P < 0.01$) by 2 ± 0.3%.

A total of 60 experimental sessions were conducted on 15 subjects. After each experimental session, subjects correctly identified which treatment they had received 77% of the time. They most often described feelings of alertness and restlessness associated with caffeine.

Endurance Protocol

Figure 2 is an example of the recordings obtained from one subject during a complete endurance protocol. These are consistent with the pattern of fatigue associated with repeated submaximal isometric contractions (6). As T_{lim} approached, there was a reduction in force-generating capacity and slowing of the muscle as seen by the decrease in MVC (Fig. 2*A*), and Tw_{amp}, $+dF/dt$, and $-dF/dt$ (Fig. 2*B*). Central drive increased throughout the endurance protocol, which is seen in the increase in surface EMG (Fig. 2*C*). Neuromuscular transmission was preserved throughout the protocol, as indicated by the constancy of the M-wave shape and amplitude (Fig. 2*D*).

T_{lim}. Figure 3 shows the range of individual subject changes in T_{lim} with caffeine compared with the placebo trial. In the caffeine trial, 9 of the 15 subjects increased T_{lim}, 4 had no change (plus or minus <5%), and 2 subjects decreased their T_{lim}. The mean T_{lim} was 85.9 ± 4.5 s for placebo and 98.4 ± 5.3 s for the caffeine trial ($P < 0.02$).

Contractile properties. Figure 4 shows the average data points and linear regression line fit to the Tw_{amp} for the placebo ($r = 0.99$, $Y = 114.8 - 0.94x$) and caffeine ($r = 0.99$, $Y = 113.7 - 0.95x$) trials through the progression of the endurance protocol to T_{lim}. The data points represent the averages from all subjects at the

Table 1. *Effects of caffeine and placebo ingestion on control measurements*

Variable	Placebo			Caffeine		
	Pre	Post	Ratio	Pre	Post	Ratio
HR, beats/min	69.6 ± 2.7	63.2 ± 2.5	0.90 ± 0.02	67.6 ± 2.6	62.7 ± 2.5	0.93 ± 0.03
SBP, mmHg	120.0 ± 1.8	119.6 ± 1.9	1.00 ± 0.01	118.8 ± 1.8	126.4 ± 1.8	1.06 ± 0.01*
DBP, mmHg	78.3 ± 0.9	78.2 ± 0.5	1.00 ± 0.01	78.1 ± 1.0	81.4 ± 1.2	1.04 ± 0.01*
MVC, N	514.9 ± 37.0	501.8 ± 35.6	0.98 ± 0.01	490.9 ± 30.8	513.4 ± 33.8	1.05 ± 0.02*
%Act	97.1 ± 0.5	97.4 ± 0.5	1.00 ± 0.003	96.1 ± 0.5	97.9 ± 0.5	1.02 ± 0.003*
EMG_{max}, V	0.24 ± 0.03	0.25 ± 0.03	1.05 ± 0.02	0.24 ± 0.04	0.26 ± 0.03	1.09 ± 0.03
Tw_{amp}, N	99.2 ± 4.9	100.9 ± 4.7	1.02 ± 0.01	98.2 ± 5.8	103.5 ± 6.2	1.05 ± 0.01
$+dF/dt$, N/s	1,631.9 ± 109.6	1,607.2 ± 106.5	0.99 ± 0.02	1,589.7 ± 90.5	1,602.4 ± 86.7	1.01 ± 0.02
$-dF/dt$, N/s	−905.3 ± 59.4	−904.2 ± 57.6	1.00 ± 0.02	−878.5 ± 43.7	−905.1 ± 51.8	1.03 ± 0.02
M_{amp}, V	3.8 ± 0.4	3.8 ± 0.4	0.99 ± 0.02	3.8 ± 0.4	3.7 ± 0.3	1.00 ± 0.02

Values are means ± SE. Ratio values are post-to-precapsule ingestion. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MVC, maximum voluntary contraction; %Act, %voluntary activation; EMG_{max}, maximum EMG root mean square; Tw_{amp}, maximum potentiated twitch amplitude; $+dF/dt$, maximum instantaneous rate of tension development; $-dF/dt$, maximum instantaneous rate of tension relaxation; M_{amp}, peak-to-peak M-wave amplitude. *Significantly different from placebo ($P < 0.01$).

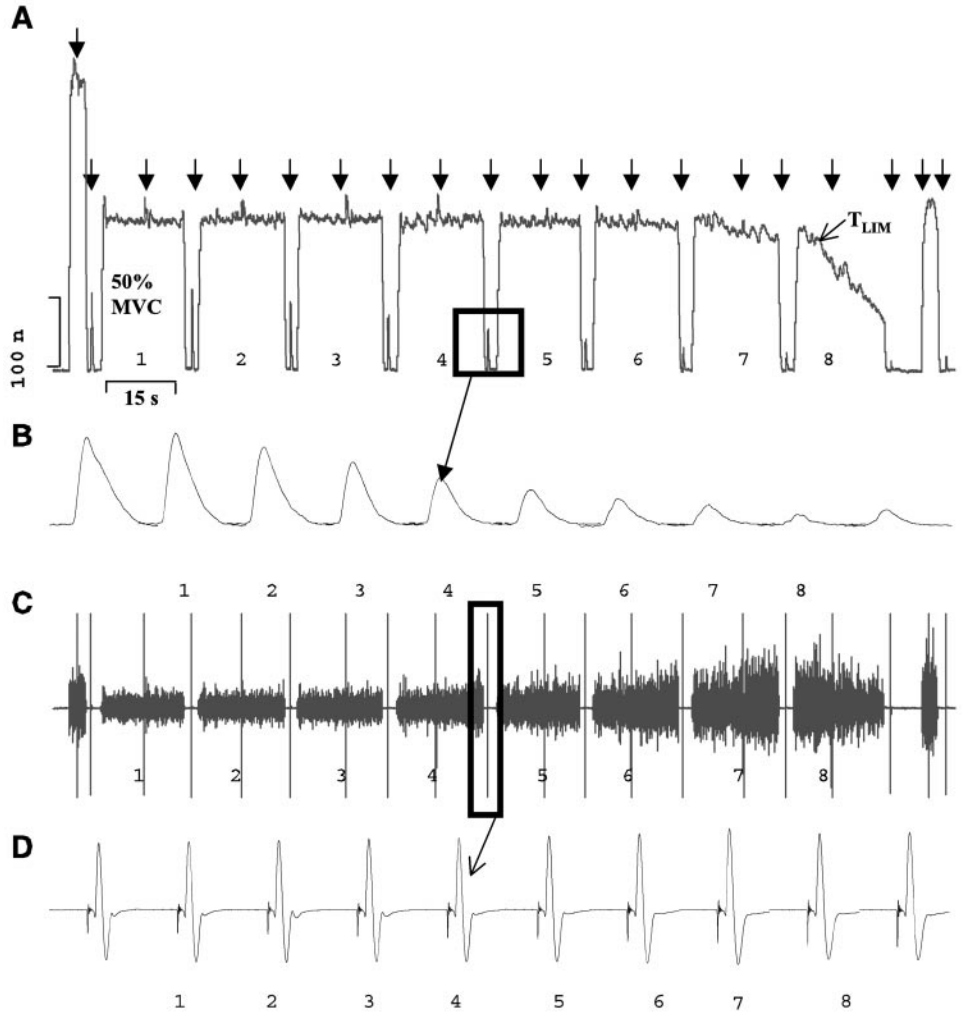

Fig. 2. Example of the endurance protocol (EP) performed by 1 subject. *A*: repeated isometric contractions at 50% MVC for 15 s were performed until force dropped <45% MVC for >2 s [time limit of endurance (T_{lim})]. A MVC was performed before and after the EP. Arrows indicate supramaximal stimuli. *B*: twitches extracted from period between contractions. Approaching T_{lim}, twitch amplitude (Tw_{amp}), maximum instantaneous rate of tension development ($+dF/dt$), and maximum instantaneous rate of tension relaxation ($-dF/dt$) decreased. *C*: electromyogram (EMG) associated with isometric contractions. Electrical activity increased approaching T_{lim}. *D*: M waves extracted from EMG recording. No changes were observed in M waves throughout the EP.

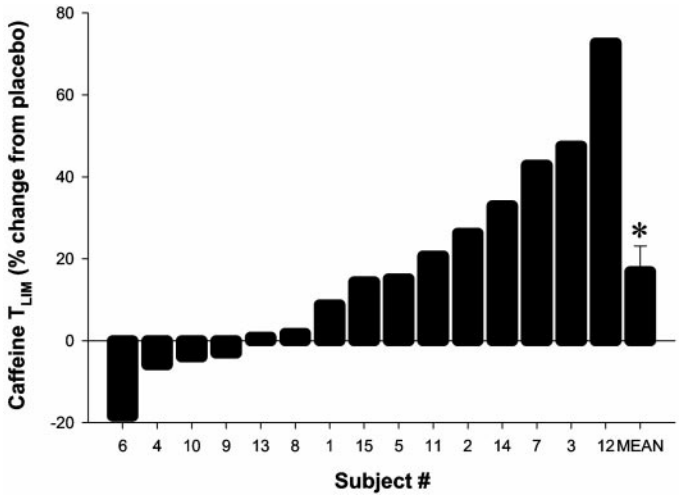

Fig. 3. T_{lim} for each subject. Positive values indicate a longer endurance time with caffeine. Nine subjects increased T_{lim}, 4 had no change (plus or minus <5%), and 2 subjects decreased T_{lim} with caffeine. Error bar, SE. $^*P < 0.02$.

closest times corresponding to 20, 50, 80, and 100% placebo T_{lim} and at caffeine T_{lim}. There was no difference in the slopes of the regression lines fit to every subject between conditions. Note that the Tw_{amp} continued to decline during the prolonged caffeine trials (open triangles).

Figure 5 illustrates the comparison of the contractile properties' end-point values in both conditions. During the caffeine trial at the time corresponding to placebo T_{lim}, there was no difference in the Tw_{amp}, $+dF/dt$, or $-dF/dt$ between the caffeine and placebo conditions. Tw_{amp} decreased to 29.8 ± 3.9% of the initial Tw_{amp} in the placebo trial and at the corresponding time in the caffeine trial to 26.3 ± 3.4% of the initial value. In the caffeine condition, the increased T_{lim} caused a further decrease in Tw_{amp} to 17.0 ± 2.5% of the initial Tw_{amp} value and slowing of the $+dF/dt$ to 20.4 ± 2.8% of the initial value. Both of these variables were significantly ($P < 0.01$) different from placebo T_{lim} and the corresponding time during the caffeine trial. There was no significant difference in $-dF/dt$ between conditions at these three time points.

Muscle activation. The data points displayed in Fig. 6 are the average EMG for all subjects in both condi-

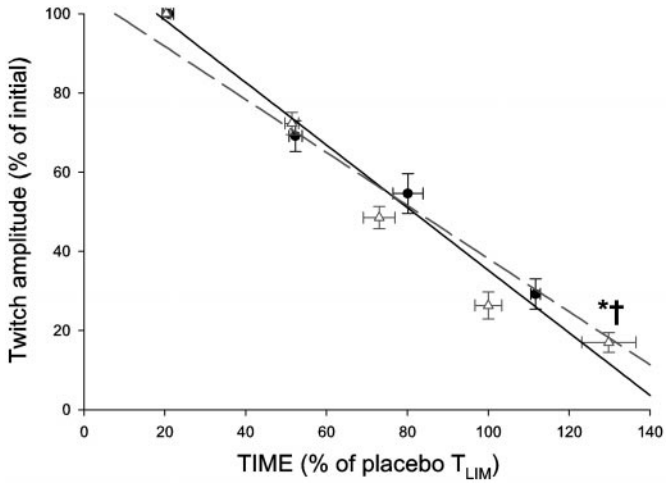

Fig. 4. Decline of Tw_{amp} during the placebo (●) and caffeine (△) conditions. Regression lines were calculated from all of the individual data and were not significantly different between the placebo ($r = 0.99$, $Y = 114.8 - 0.94x$; solid line) and caffeine ($r = 0.99$, $Y = 113.7 - 0.95x$; dashed line) conditions. Symbols are data (means ± SE) pooled across subjects as close to the same time point in each condition as possible and are intended to show actual values, but these were not used in the regression analysis. Tw_{amp} in the caffeine trial declined to a greater extent than in the placebo trial. *Significantly different from placebo T_{lim} (PL T_{lim}) value ($P < 0.01$). †Significantly different from time corresponding to PL T_{lim} in the caffeine trial ($P < 0.01$).

tions. Data were measured at the closest times corresponding to each 10% interval up to 100% of placebo T_{lim} and at caffeine T_{lim}. There was an increase in EMG for both conditions through the progression of the endurance protocol to T_{lim}. EMG had increased to 41.3 ± 13.2% of initial at T_{lim} in the placebo trial, and, at the same time point during the caffeine trial, it had increased to 47.5 ± 12.3%, which was not significantly different. However, at caffeine T_{lim}, EMG had further increased to 76.1% of initial ($P < 0.02$).

The voluntary activation of the vastus lateralis increased at T_{lim} from the initial contraction in both conditions. Figure 7 shows the data points that were averaged at the closest corresponding times to 10, 30, 60, and 100% of placebo T_{lim} and at caffeine T_{lim} through the endurance protocol and the regression lines for the placebo ($r = 0.69$, $Y = 77.2 + 0.13x$) and caffeine ($r = 0.73$, $Y = 76.4 + 0.16x$) trials. There was no difference between conditions in the rate of increase in voluntary activation or at any of the end time points. Of the nine subjects who increased T_{lim} with caffeine, eight achieved >90% activation of the vastus lateralis at placebo T_{lim}, and all but one subject maintained or increased this level of activation during the caffeine trial.

The M-wave amplitudes that were evoked in the rest period between isometric contractions were averaged among subjects for each condition at the closest corresponding times to 10, 30, 60, and 100% of placebo T_{lim} and at caffeine T_{lim}. Because the M-wave amplitudes did not change over time in each condition, the values were collapsed. Over the duration of the endurance protocol, the M-wave amplitudes changed an average of 4.4 ± 1.6% in the placebo trial and 3.7 ± 2.7% in the caffeine trial, from the initial measurement obtained at the onset of the endurance protocol.

Maximum force-generating capacity. The mechanical and electrical measures obtained during the MVCs performed before and after the endurance protocol are shown in Table 2. There was a significant decrease in MVC force after the endurance protocol in both the placebo ($P < 0.01$) and caffeine ($P < 0.01$) conditions to values that were 66 ± 5 and 63 ± 4%, respectively, of the preendurance MVC force. There was no significant difference observed between conditions. Subjects maintained the same level of voluntary activation after the endurance protocol, with 13 of the 15 subjects in the placebo and 10 of the 15 in the caffeine condition achieving >95% recruitment of the vastus lateralis motor unit pool, which was not significantly different between conditions. EMG was maintained at the same levels before and after the endurance protocol and was not significantly different between caffeine and placebo. The potentiated twitches evoked after the MVCs maintained a significantly smaller amplitude ($P < 0.01$) and had a slower $+dF/dt$ ($P < 0.02$) and $-dF/dt$ ($P < 0.01$) in the caffeine trial compared with the placebo trial.

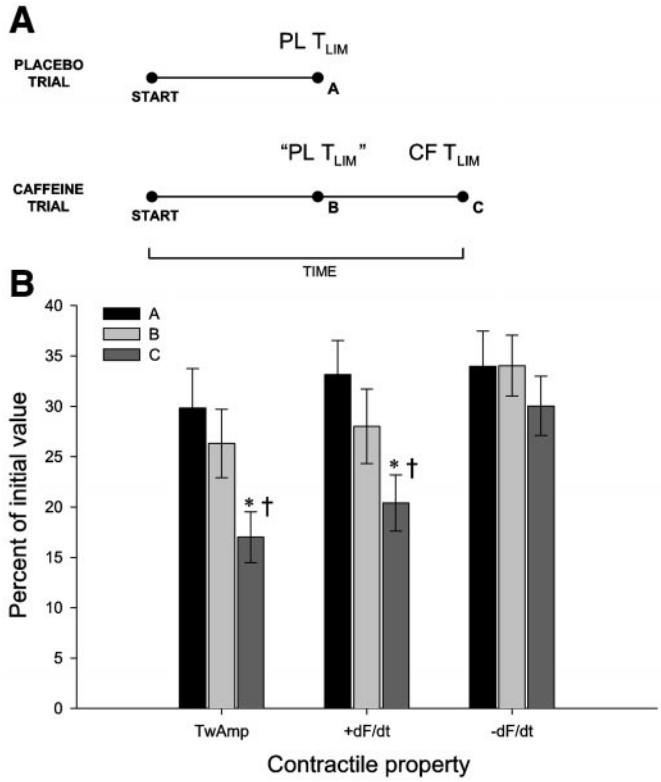

Fig. 5. *A*: each dependent variable for the EP was compared at 3 different time points: A) at PL T_{lim}, B) at the time point in the caffeine trial corresponding to PL T_{lim}, and C) at caffeine T_{lim} (CF T_{lim}). *B*: contractile properties at T_{lim}. Values are means ± SE. There was no significant difference among conditions at values corresponding to PL T_{lim} for any of the contractile properties. At CF T_{lim}, Tw_{amp} and $+dF/dt$ were significantly smaller than the values corresponding to PL T_{lim} in the placebo and caffeine trial. A, B, and C are as defined in *A*.*Significantly different from PL T_{lim} value ($P < 0.05$). †Significantly different from time corresponding to PL T_{lim} in the caffeine trial ($P < 0.01$).

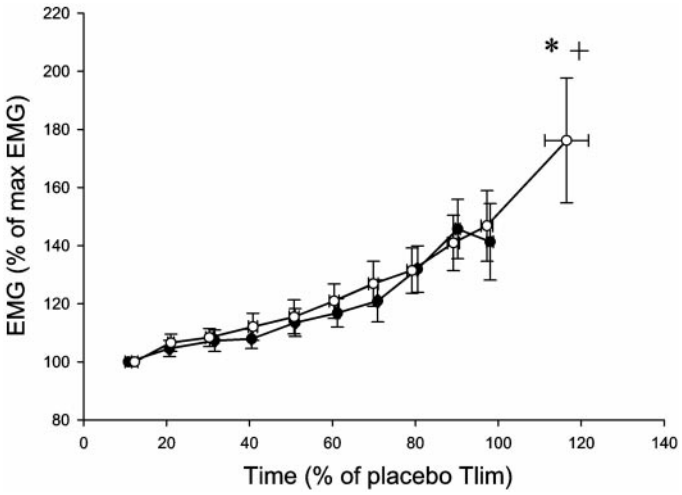

Fig. 6. EMG for the placebo (●) and caffeine (○) conditions at corresponding time points through the progression of the EP. Values are means ± SE. EMG was significantly higher at CF T_{lim} compared with EMG at PL T_{lim} and the time of PL T_{lim} in the caffeine trial. *Significantly different from PL T_{lim} value ($P < 0.02$). +Significantly different from time corresponding to PL T_{lim} in the caffeine trial ($P < 0.05$).

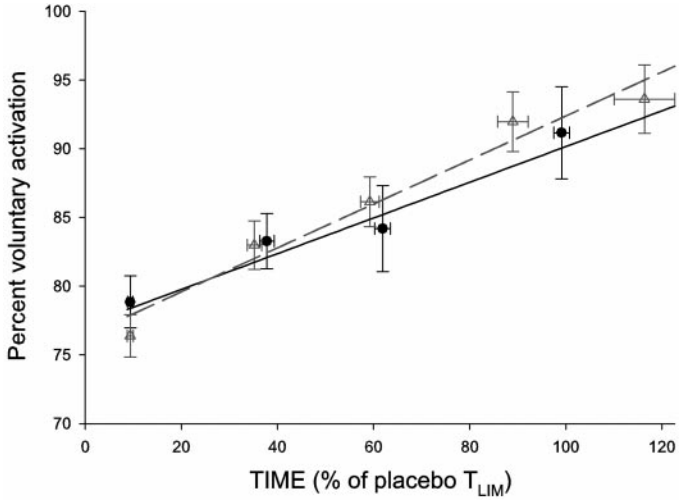

Fig. 7. Voluntary activation for the placebo (●) and caffeine (△) conditions at approximately corresponding time points through the progression of the EP. Values are means ± SE. The regression lines were not significantly different between the placebo ($r = 0.69$, $Y = 77.2 + 0.13x$; solid line) and caffeine ($r = 0.73$, $Y = 76.4 + 0.16x$; dashed line) conditions. Subjects achieved 91.2 ± 3.4% activation at PL T_{lim}, which was not significantly different from the achieved 91.9 ± 2.9% activation at the corresponding time in the caffeine trial. At CF T_{lim}, voluntary activation increased to 93.6 ± 2.5%, which was not significantly different from the voluntary activation at PL T_{lim} in both conditions.

Sensory Protocol

To maintain a constant-force sensation after withdrawal of visual feedback, there was an initial sharp reduction in force within the first few seconds and a less rapid decline over the remainder of the contraction. The decline in force was best fit with a double-exponential function that was similar to previous findings (10, 11) and was reproducible within the subject's four trials (Fig. 1*A*).

The correlation coefficients for individual subjects for both conditions ranged from $r = 0.976$ to $r = 0.999$, showing that the double-exponential function fit the data extremely well. The first rate constant (*K1*) was significantly ($P < 0.01$) slower during the caffeine trial, but there was no difference in the second rate constant (*K2*) between conditions (Table 3). The average regression lines for the placebo ($Y = 4.83 + 19.62\ e^{-0.38t} + 26.85\ e^{-0.025t}$) and caffeine ($Y = 3.12 + 19.74\ e^{-0.22t} + 25.90\ e^{-0.019t}$) conditions are plotted in Fig. 8. Because there was a small, nonsignificant difference of 2.5% in the starting point of the caffeine trial, the caffeine curve was adjusted upward by that amount to better illustrate the difference in rate constants. However, curve fitting and statistical analyses were performed on the unadjusted data. The smaller initial rate constant in the caffeine condition indicates that force sensation increased at a slower rate during that trial (Fig. 8, *inset*). End-point force reached an average of 11.5 ± 2.2% MVC in the placebo condition and 10.3 ± 1.4% MVC with caffeine. These were not significantly different from each other.

DISCUSSION

The present investigation was conducted to examine how caffeine may alter neuromuscular functions that contribute to an increase in muscular endurance. Our results replicate previous findings showing the property of caffeine to increase maximum force-generating capacity and the endurance of submaximal isometric contractions of the quadriceps (24). However, the changes in contractile properties, motor unit activation, and junctional/sarcolemmal transmission that oc-

Table 2. *Maximal electrical and contractile characteristics before and after endurance protocol*

	Placebo			Caffeine		
Variable	Pre	Post	Ratio	Pre	Post	Ratio
MVC, N	501.8 ± 35.6	330.7 ± 35.6*	0.66 ± 0.05	513.4 ± 33.8	325.1 ± 35.0*	0.63 ± 0.04
%Act	97.4 ± 0.5	97.7 ± 1.0	1.00 ± 0.01	97.9 ± 0.5	95.0 ± 1.5	0.97 ± 0.01
EMG_{max}, V	0.25 ± 0.03	0.27 ± 0.03	1.12 ± 0.05	0.26 ± 0.03	0.30 ± 0.03	1.28 ± 0.09
Tw_{amp}, N	100.9 ± 4.7	35.4 ± 5.7*	0.34 ± 0.05	103.5 ± 6.2	21.3 ± 4.5*	0.23 ± 0.07†
+dF/d*t*, N/s	1,607.2 ± 106.5	530.0 ± 80.0*	0.32 ± 0.04	1,602.4 ± 86.7	392.8 ± 57.0*	0.26 ± 0.05†
−dF/d*t*, N/s	−904.2 ± 57.6	−327.1 ± 26.8*	0.37 ± 0.03	−905.1 ± 51.8	−264.9 ± 34.5*	0.30 ± 0.04†
M_{amp}, V	3.8 ± 0.4	4.1 ± 0.48	1.08 ± 0.06	3.7 ± 0.3	4.2 ± 0.41	1.13 ± 0.07

Values are means ± SE. Ratio values are post-to-preendurance protocol values. *Significantly different from preendurance protocol values ($P < 0.05$). †Significantly different from placebo ($P < 0.05$).

Table 3. *Parameters of double-exponential equation fit to sensory contractions*

	Placebo						Caffeine					
	r	*C*	*A*	*−K1*	*B*	*−K2*	*r*	*C*	*A*	*−K1*	*B*	*−K2*
Mean	0.99	4.83	19.62	0.38	26.86	0.025	0.99	3.12	19.74	0.22*	25.90	0.019
SE	0.002	1.18	1.50	0.08	2.00	0.004	0.002	1.70	3.10	0.04	2.71	0.004

$Y = C + Ae^{-K1t} + Be^{-K2t}$, where Y is force, t is time, A and B are values of exponential processes, C is asymptote, and $-K1$ and $-K2$ are rate constants. *Significantly different from placebo ($P < 0.05$).

curred as the quadriceps reached T_{lim} could not account for the prolonged performance. We also found that caffeine alters isometric force sensation very early in the contraction, an observation that has not been previously reported. This suggests that the increase in T_{lim} during the caffeine trial may have been caused by a willingness to maintain near-maximal activation because of a decrease in force sensation.

Effect of Caffeine on Muscle Endurance

Caffeine is a central nervous system stimulant (34) and is also known to increase the contractility of skeletal muscle (19, 29). Despite the evidence that the drug may influence neuromuscular performance, only a few studies are available that have investigated this possibility (8, 24, 27, 50). The results of these studies conflict with reports that say that caffeine is not ergogenic (8, 27, 46, 50). Disparities in methodologies, subject selection, and caffeine dosages make the interpretation of the data from these investigations difficult.

There is often a marked variability in the magnitude of physiological responses (17) and ergogenic influences (20, 22, 29) among subjects after an acute dose of caffeine. To control for these individual differences, we used a larger sample size ($n = 15$). We observed a mean increase of 17% in endurance time after caffeine ingestion, which agrees with previous observations (24) of a 26% increase in a sustained submaximal contraction of the quadriceps. Kalmar and Cafarelli (24) also used a larger sample size ($n = 11$) and controlled for caffeine habituation and other factors, such as smoking and obesity (25, 37). Moreover, only men were used as subjects because oral contraceptive use is known to alter caffeine pharmacokinetics (1). Lopes et al. (27) found no significant increase in the endurance of a sustained contraction of the adductor pollicis; however, the subject sample was small ($n = 5$), and there was an increase of 12% in endurance time during the caffeine trial. In that experiment, three of the five subjects increased their endurance time after caffeine consumption. Of the remaining two subjects, one maintained and the other decreased endurance time with caffeine. Similarly, Williams et al. (50) found no influence of caffeine on the endurance of handgrip contractions; however, they also used a small sample size ($n = 6$). The wide range of caffeine-related changes in T_{lim} emphasizes the necessity for adequate sample size when studying the ergogenic effects of caffeine.

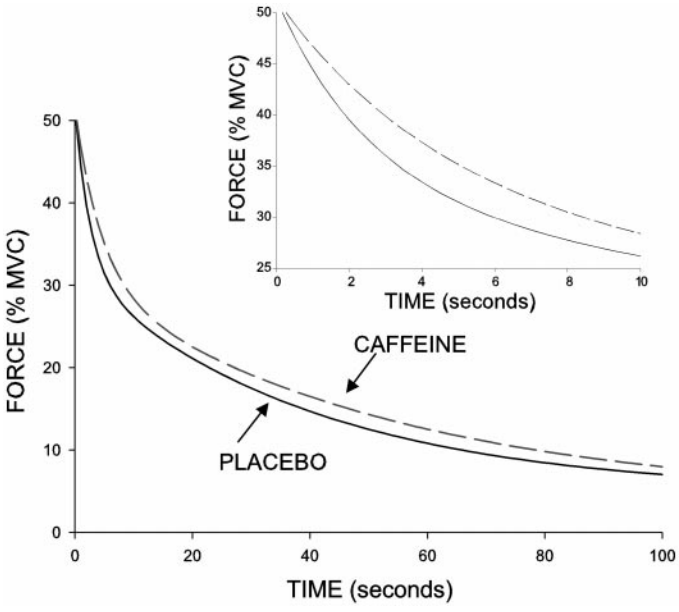

Fig. 8. Regression lines of placebo (solid) and caffeine (dashed) force tracings during the sensory protocols that were plotted from the average of the regression parameters fit to individual subject data. Force sensation was lower during the initial part of the contraction in the caffeine trial. To better illustrate this difference, the *inset* shows the first 10 s of the contraction on an expanded time scale.

The endurance of intermittent, submaximal, isometric contractions is not normally limited by substrate metabolism (6, 15). The length of performance is likely due to the failure of elements distal to the neuromuscular junction or the willingness to tolerate the discomfort associated with prolonged activity (4, 7). In highly motivated subjects, impairment of excitation-contraction coupling reduces force generation and limits endurance. Although it is well established from in vivo studies that caffeine affects calcium kinetics in skeletal muscle (19, 29), this occurs at concentrations that are toxic to humans. Nevertheless, Tarnopolsky et al. (45) found an increase in force generated by the tibialis anterior by 20-Hz stimulation of the peroneal nerve after consumption of 6 mg/kg of caffeine. Similarly, Lopes et al. (27) found an increase in tetanic force of the adductor pollicis produced by 20- to 50-Hz stimulation after a dose of 500 mg of caffeine. These data suggest an influence of caffeine on skeletal muscle that is independent of neural activation. However, it has yet to be shown that caffeine-induced alterations in calcium kinetics enhance human muscular endurance. In the studies by both Tarnopolsky et al. (46) and Lopes et al. (27), there were no data on the influence of caffeine on a single twitch. In those studies, increases in calcium flux induced by caffeine may have been slight, and intracellular Ca^{2+} concentration was only changed

sufficiently to alter performance after repetitive stimulation.

Although voluntary activation increased by 2% from the time corresponding to placebo T_{lim} to caffeine T_{lim}, this was not sufficient to account for the 28.6% increase in EMG, which is a reflection of both rate coding and recruitment. Thus the increase that we observed could be explained on the basis of a more rapid frequency of motor unit discharge, spontaneous bursts in the EMG signal, or an increase in motor unit synchronization (41, 52).

Kalmar and Cafarelli (24) found no effect of caffeine on motor unit firing rates during various levels of brief, nonfatigued submaximal contractions. It is, therefore, unlikely that an increase in firing rates caused the increase in EMG at the end of the caffeine trial. Another possibility is that the increase in EMG may have been caused by spontaneous bursts in the EMG recording. This type of EMG patterning has been observed during prolonged endurance contractions of the elbow flexors (41) and of the plantar flexors (44). However, these reports are from long-duration contractions at force levels <40% MVC (18, 41, 44). We are inclined to discard this explanation because visual analysis of the EMG recordings showed no evidence of bursts. Alternatively, an increase in the synchronization of motor unit firing may account for the large increase in EMG seen in the present study (52). Toward the end of an exhaustive isometric contraction, an increase in surface EMG and decrease in mean power frequency of the EMG signal have been associated with the occurrence of force tremors (28, 48). Force tremors are due to motor-unit synchronization that occurs at low frequencies (21, 30). Thus it is possible that the increase in EMG during the prolonged performance in the caffeine trial was the result of motor unit synchronization.

An acute dose of caffeine has a wide variety of effects on cardiovascular function, which include an influence on heart rate and blood pressure (14, 38) and a reduction in blood flow to a number of vascular beds (35, 42, 51). The few studies that have investigated the effects of caffeine on cardiovascular dynamics (14, 16) during exercise provide little evidence that caffeine will have ergogenic effects on cardiovascular function. It is unlikely that blood flow played a significant ergogenic role, because the interval between contractions in our endurance protocol was brief (1.5 s) and the muscle was not completely relaxed because of the Tw_{max} that was evoked. This was likely too little time to reverse the substrate depletion and metabolite buildup caused by the occluded blood flow during the contraction.

Caffeine and Force Sensation

The ergogenic properties of caffeine have been associated with an attenuation in sensory processes during aerobic activity (12, 13). Typically, category scales have been used to assess the influence of caffeine after an exhaustive bout of physical activity (12, 13, 49). We chose to use the constant-sensation technique because it does not require the interpretation of category scales (10, 11), it provides a continuous measurement of force sensation, it is highly repeatable within individual trials, and it can be experimentally manipulated (10, 40). The instructions during this protocol were to maintain force sensation constant after visual feedback of a target force had been removed. There was likely some variability in the interpretation of these instructions arising from the subject's ability to attend to both centrifugal motor commands and muscular tension associated with a contraction (31, 39). Because the change in the first rate constant associated with caffeine ingestion occurred in the first few seconds of the sensory protocol, we assume that the mechanism involved is neural.

There are at least three possible explanations of how caffeine may alter muscle sensory processes. The first is that it may cause changes in the chemical composition of the muscle's environment. Because the initial force was 50% MVC and falling, any feedback contributing to force sensation in the first 10 s of contraction would not likely be associated with significant changes in metabolite concentrations or increases in temperature. It is more likely that feedback from mechanoreceptors, such as Golgi tendon organs (23) and class III or IV muscle afferents (26, 32) that are sensitive to increases in tension or pressure, was influenced by caffeine. A second possibility is that caffeine may alter feedforward information. This is the central outflow to the sensory cortex sent simultaneously with the signal to the motoneuron pool. A third possibility is that caffeine may alter how information from either feedforward or feedback is processed centrally. Presently, there are no data available in the literature that would provide insight into this problem.

In summary, we found that caffeine increases the endurance of repeated voluntary submaximal isometric contractions of the quadriceps. There was no indication that caffeine preserved the function of the contractile apparatus as the muscle progressed to T_{lim} or that caffeine protected junctional and sarcolemmal transmission. Central activation of motor units was maintained at near-maximal levels longer with caffeine, which is likely the result of the willingness to prolong endurance. The caffeine-induced increase in T_{lim} may stem from alterations in muscle sensory processes.

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