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TITLE

Thermal Regulation in the Heat During Exercise After Caffeine and Ephedrine Ingestion

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ORIGINAL RESEARCH

Thermal Regulation in the Heat During Exercise After Caffeine and Ephedrine Ingestion

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Background: Ingesting a combination of caffeine and ephedrine (C+E) has been shown to raise metabolic heat production and body temperature. This side effect of C+E ingestion may be positive during a cold stress scenario, however, during heat stress it could prove to be detrimental. Thus, the purpose of this study was to clarify the effect of C+E ingestion on body temperature regulation during moderate exercise in a hot dry environment. ***Methods:*** Ten, healthy, non heat acclimated, males exercised at 50% $\dot{V}O_{2peak}$ in a 40°C and 30% RH environment until rectal temperature reached 39.3°C; heart rate (HR) remained at 95% of peak value or greater for 3 min, dizziness or nausea precluded further exercise, or 3 h had elapsed. They did this four times at weekly intervals: familiarization (Fam), control (Cont), placebo, and C+E (5 mg · kg^{-1} caffeine + 1 mg · kg^{-1} ephedrine) trials. The Fam and Cont treatments were done first and sequentially while the placebo and C+E treatments were balanced and double-blind. Tolerance times, mean skin temperature ($\bar{T}_{sk}$), rectal temperature (T_{re}), $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, sweat rate (SR), HR, and sensation of thermal comfort were measured. ***Results:*** Tolerance times (mean ± SD in minutes) were similar for the placebo (120.0 ± 28.4) and C+E (121.3 ± 33.9) trials and both times were significantly longer than Cont (106.6 ± 24.0) trial. C+E did not affect $\bar{T}_{sk}$, initial T_{re}, ΔT_{re}, SR or the sensation of thermal comfort. $\dot{V}O_2$ and $\dot{V}_E$, were significantly increased by C+E. HR was elevated by C+E compared with the other trials, but only during the initial 20 min of exercise. ***Conclusion:*** Although the metabolic rate was slightly increased with C+E treatment, it was sufficiently offset by increased heat loss mechanisms so that internal body temperature was not increased during moderate exercise in a hot, dry environment.

Keywords: ergogenic, methylxanthine, sympathomimetic, heat stress, metabolism.

THE INGESTION OF A combination of caffeine and ephedrine (C+E) was reported to prolong time to exhaustion by about 38% during exercise at 85% of maximal aerobic power (3), and to increase the average running velocity during a military field test consisting of a 3.2 km cross-country run (4). Such increases in physical work capacity suggest that C+E might be an effective tool to consider for certain military operations where enhanced high intensity performance would be advantageous.

A concern that must be addressed, however, is that C+E might affect heat tolerance. This concern is based on the report that C+E increases metabolic rate (1) and the associated heat production in resting subjects during a 3 h cold exposure to 10°C (19). Unless the increased metabolic rate associated with C+E ingestion is matched by an increased evaporative and/or connective rate of heat loss, there would be a more rapid increase in internal body temperature which could be expected to compromise tolerance of hard physical work in a hot environment. Thus, it was the purpose of this study to clarify the influence of C+E ingestion on body temperature regulation during exercise in the heat. It was hypothesised that the ingestion of C+E before exercise would result in a decreased tolerance time of exercise in a hot environment.

METHODS

Subjects

Following approval from this institute's human ethics committee, 10 healthy males volunteered to participate in this study. Their mean ± SD age, height, weight, and peak aerobic power ($\dot{V}O_{2peak}$) during treadmill exercise were 39 ± 8 yr, 1.77 ± 0.05 m, 81.9 ± 11.2 kg, and 50.4 ± 6.4 ml · kg^{-1} · min^{-1}, respectively. All subjects consumed caffeine in one form or another i.e., coffee, tea, colas with mean ± SD cups · day^{-1} of 4.8 ± 2.9. Subjects were fully informed of the details, discomforts and risks associated with the experimental protocol, and written informed consent was obtained.

Procedures

Each subject visited the laboratory on five occasions. During visit 1, the subject was medically screened and then proceeded to the exercise laboratory where his peak aerobic power ($\dot{V}O_{2peak}$) was determined on a motor driven treadmill using open-circuit spirometry described below. Following 2 min of running at a self-selected pace at 0% grade, the treadmill grade was increased 1% · min^{-1} until the subject was running at

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10% grade. Thereafter, treadmill speed was increased 0.22 $m \cdot s^{-1}$ each minute until the subject could no longer continue. $\dot{V}O_{2peak}$ was defined as the highest oxygen consumption ($\dot{V}O_2$) observed during the incremental test. Heart rate (HR) was monitored throughout the incremental test and the value recorded at the end of the test was defined as the individual's peak HR.

Subjects then completed four heat stress trials. The first trial was a familiarization session where subjects were exposed to all of the test conditions and procedures i.e., treadmill walking at 50%$\dot{V}O_{2peak}$ under controlled climatic conditions of 40°C, 30% relative humidity and a wind speed of less than 0.1 $m \cdot s^{-1}$, the wearing of the temperature thermistors, the insertion of the rectal probe and the sampling of blood. Termination criteria were identical to those described below. The next visit represented the control trial, while the last two represented the experimental trials, i.e., either ingestion of gelatin capsules containing caffeine (5 $mg \cdot kg^{-1}$) + ephedrine (1 $mg \cdot kg^{-1}$), or a placebo (dietary fiber, Metamucil®) 1.5 h before exercise in the heat. The order of the placebo and C+E trials was balanced among the subjects and presented in a double-blind fashion. All trials involved treadmill walking at 50% $\dot{V}O_{2peak}$ under controlled climatic conditions of 40°C, 30% relative humidity and a wind speed of less than 0.1 $m \cdot s^{-1}$.

Subjects refrained from participating in heavy exercise for 24 h before each trial. They also abstained from ingesting any food substance containing caffeine for 12 h and refrained from drinking alcoholic beverages for 48 h prior to the trials. On the day of the trial, each subject arrived at the laboratory and first took his drugs. They then rested in an air-conditioned room temperature (23°C) for 1 h after which they started dressing for the trial. They first inserted a rectal thermistor 0.15 m beyond the anal sphincter. After the probe was in place, nude weight was recorded. Shorts were then put on, a heart rate transmitter was strapped around each subject's chest and 12 skin thermistors were taped on the subject. The subject then completed dressing by putting on his socks and running shoes. Next, a 5-ml venous blood sample was taken from an antecubital vein. Dressed weight was then recorded. The subject next entered the hot chamber and commenced walking on a treadmill. Treadmill speed and inclination were adjusted so that the individual was walking at a load equivalent to 50% $\dot{V}O_{2peak}$. Time elapsed from the commencement of dressing and entering the chamber was 30 min. Once the subject started dressing and for the duration of the hot exposure, water ingestion was not allowed. Exercise ceased when any of the following criteria were met: rectal temperature (T_{re}) reached a level of 39.3°C, HR remained at 95% of peak value or greater for 3 min, dizziness or nausea precluded further exercise, the subject or experimenter terminated the trial, or 3 h had elapsed. Immediately on exiting the chamber, dress weight was recorded. The subject was then undressed, toweled dry and nude weight was next recorded. Then a rating of thermal comfort was obtained. After this, the subject was rehydrated with a sport drink and water, and allowed to go to the showers once his rectal temperature had decreased by 0.5°C.

Measurements

Open-circuit spirometry was used to measure $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ during the heat stress and $\dot{V}O_{2peak}$ trials. During heat stress, values were averaged over 2 min, taken once every 15 min. During the incremental test to determine $\dot{V}O_{2peak}$ values were calculated every 30 s. For all trials, subjects breathed through a Hans-Rudolph valve. Expired air was directed into a 5-L mixing box and through a ventilation module (VMM 110 Series Interface Associates, Aliso Viejo, CA) for determination of $\dot{V}E$. A sampling line directed dried gases from the mixing box to the O_2 and CO_2 analyzers (OCM-2 AMETECK, Pittsburgh, PA). The gas analyzers were calibrated before each collection period with a precision-analyzed gas while the ventilation module was calibrated with a syringe of known volume.

HR during the heat stress trials was recorded every 5 min (Vantage XL Polar System, Port Washington, NY). During $\dot{V}O_{2peak}$ determination, HR was monitored continuously with the same system.

T_{re} was measured with a rectal thermistor (400 Series rectal/esophageal probe Baxter Healthcare Corp., Valencia, CA). The 12 skin temperatures (forehead, chest, upper and lower back, abdomen, forearm, hand, front and rear thigh, front and rear calf and foot) were measured with bead thermistors (Series 44004 bead thermistors Yellow Springs, Yellow Springs, OH). The T_{re} and weighted mean skin temperature ($\bar{T}_{sk}$) (20) were displayed, printed and recorded every minute during the heat exposure.

Nude and dressed weight were measured to the nearest 0.01 kg on an electronic scale (Super Count Setra Systems Inc., Markham, Ont., Canada). The amount of sweat produced was calculated from the pre-trial minus the post-trial nude weight and corrected for respiratory water loss (14) and metabolic weight loss (17).

The rate of metabolic heat production (15), $\dot{M}$, was determined from the measured $\dot{V}O_2$, and the respiratory exchange ratio, RER, as

$$\dot{M} = 352(0.23 \cdot RER + 0.77)(\dot{V}O_2) \quad (15)$$

Respiratory evaporative heat loss, $\dot{E}_{resp}$, and connective heat gain, $\dot{C}_{resp}$, were calculated from the chamber vapor pressure, P_A, of 2.21 kPa for 40°C and 30% relative humidity, and the respired vapor pressure, P_{resp}, of 5.32 kPa which assumes 100% saturation of expired air at a mouth temperature, T_{resp}, of 34°C for the chamber conditions (11), as

$$\dot{E}_{resp} = 0.0173 \cdot \dot{M} \cdot (P_{resp} - P_A) \quad \text{and}$$
$$\dot{C}_{resp} = 0.0014 \cdot \dot{M} \cdot (40 - T_{resp}) \quad (6)$$

The net respiratory heat loss was calculated as $\dot{E}_{resp} - \dot{C}_{resp}$.

Serum osmolality was determined from measured values of glucose, sodium and blood urea nitrogen (Stat Profile, Utra Nova Biomedical, Waltham, MA) (18). Hematocrit was determined by micro centrifugation (model 575, Autocrit Utra3, Clay Adams, Franklin Lakes, NJ). Caffeine and ephedrine concentrations were deter-

TABLE I. TREATMENT EFFECT.

	Control	Placebo	C+E
Tolerance time (min)	106.6*† ±24.0	120.0 ±28.4	121.3 ±33.9
Initial T_{re} (°C)	37.044 ±0.214	36.951 ±0.160	36.995 ±0.327
Sweat rate ($kg \cdot h^{-1}$)	1.2033 ±0.344	1.203 ±0.364	1.291 ±0.376
Respiratory heat loss (W)	31.3 ±5.0	30.6† ±5.1	32.6 ±5.4
Thermal sensation	9.9 ±1.2	10.2 ±1.3	9.4 ±1.7

Values are Mean ± SD.
* Significantly different from Placebo; † Significantly different from C+E.

mined by gas chromatograph-mass spectrometry electron impact single ion monitoring (model MSD 5970a, Hewlett Packard, Palo Alto, CA).

Perception of thermal comfort was obtained from the McGinnis Thermal Scale that ranged from 1 to 13, with 1 meaning "I am so cold I am helpless," 7 meaning "I am comfortable," and 13 meaning "I am so hot I am sick and nauseated" (9).

Data Analyses

A one-factor repeated-measures Analysis of Variance (ANOVA) was used to compare the time to exhaustion for the treatment trials, initial T_{re}, sweat rate, respiratory heat loss, sensation of thermal comfort, osmolality and hematocrit. A two-factor (trial × time) repeated-measures ANOVA was used to analyze the change in T_{re}, $\bar{T}_{sk}$, HR, $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$, during the first 75 min of exercise, as this is the longest duration for which complete data for each trial were obtained for all subjects. When the ANOVA yielded a significant F-ratio, then a post hoc comparison of means was done (7); Huynh-Feldt epsilon factors were used to adjust degrees of freedom for multiple comparisons. Dependent measures were also analyzed for an order effect with the inclusion of the familiarization session as week 1. Statistical significance was accepted at the $p \leq 0.05$.

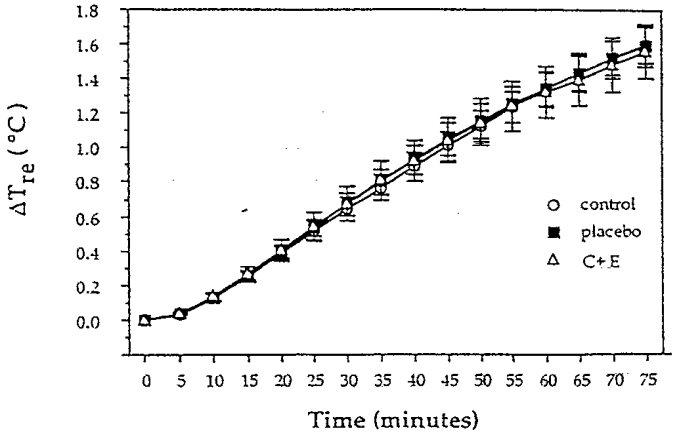

Fig. 1. Change in rectal temperature (ΔT_{re}) (mean ± SEM) during exercise at 40°C and 30% relative humidity.

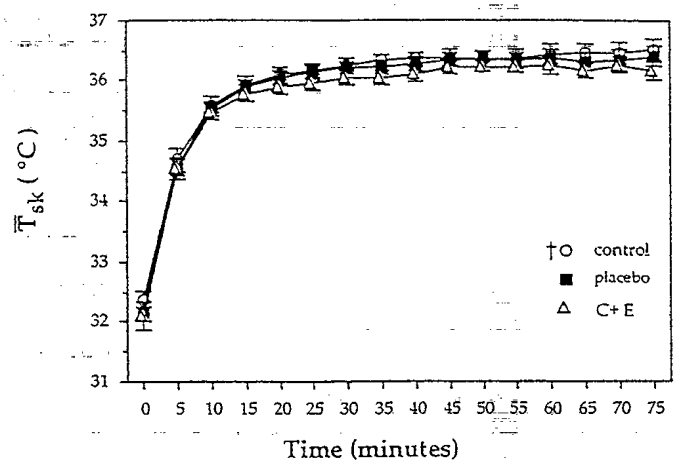

Fig. 2. Change in mean skin temperature ($\bar{T}_{sk}$) (mean ± SEM) during exercise at 40°C and 30% relative humidity. Main effect; † significantly different from C+E.

RESULTS

Tolerance Time

C+E ingestion did not significantly change tolerance time when compared with the placebo trial. Both of these trials were significantly longer when compared with the control trials (Table I).

Thermogregulatory Variables

Initial T_{re} did not differ among trials (Table I). The ΔT_{re} was not affected by C+E ingestion (Fig. 1). Although sweat rate tended to be higher in the C+E trial this was not significant (Table I). The analysis of $\bar{T}_{sk}$ (Fig. 2) showed that there was a main effect of treatment, but this effect was not because of any differences between the placebo and C+E trials which were similar; rather C+E was lower than Cont. The sensation of thermal comfort was similar for the control and experimental trials (Table I).

Metabolic Rate

Although the 7.5% increase in $\dot{V}O_2$ for the C+E trial was significantly higher than the placebo trial (Table II), C+E was similar to Cont. $\dot{V}CO_2$ and RER were similar for all trials. $\dot{V}E$ (Table III) showed a time by treatment effect, with C+E being greater than placebo at all time intervals and greater than control at all intervals with the exception of the minute 75. Further, Cont was significantly greater than placebo from the

TABLE II. OXYGEN CONSUMPTION.

Time (min)	Control ($L \cdot min^{-1}$)	Placebo ($L \cdot min^{-1}$)	C+E* ($L \cdot min^{-1}$)
15	1.952 ± 0.264	1.894 ± 0.338	2.004 ± 0.347
30	1.961 ± 0.306	1.946 ± 0.336	2.052 ± 0.374
45	2.014 ± 0.331	1.935 ± 0.319	2.097 ± 0.344
60	2.058 ± 0.336	1.961 ± 0.338	2.111 ± 0.354
75	2.078 ± 0.385	2.026 ± 0.353	2.127 ± 0.393

Values are Mean ± SD. Main effect: * significantly different from Placebo.

TABLE III. VENTILATION.

Time (min)	Control ($L \cdot min^{-1}$)	Placebo ($L \cdot min^{-1}$)	C+E ($L \cdot min^{-1}$)
15	48.8† ± 9.2	48.8±7.9	54.5*± 7.8
30	50.2† ± 9.0	50.2±8.2	54.8*± 9.0
45	51.2* ± 9.3	49.6±8.3	56.4*±10.0
60	52.6*†±10.7	50.7±8.2	55.6*± 9.5
75	54.8* ±11.0	51.9±8.9	56.1*±10.6

Values are Mean ± SD. Time by treatment interaction: * significantly different from Placebo; † significantly different from C+E.

45–75 min. Since respiratory heat loss (Table I) was calculated from metabolic rate, the differences among trials for this variable reflected the significant differences described above for $\dot{V}O_2$.

Heart Rate

Initially, HR for the C+E trials was elevated above the other trials; however, as exposure time continued this difference ceased to exist Fig. 3.

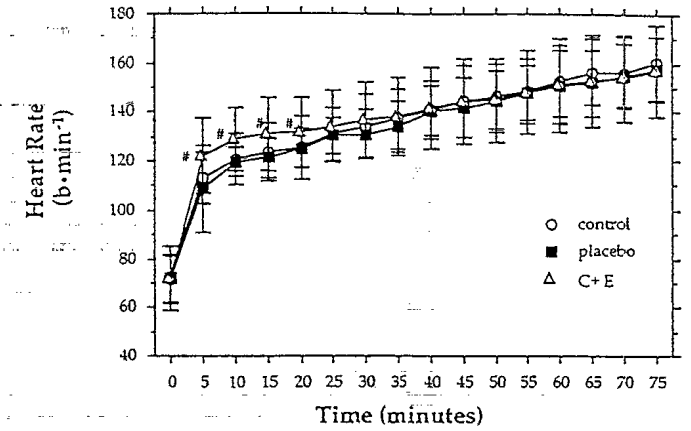

Fig. 3. HR (mean ± SEM) during exercise at 40°C and 30% relative humidity. Treatment by time interaction: #C+E > placebo and control from 5–20 min.

Blood

During the C+E trial, the levels of caffeine and ephedrine in the blood were 45.615 $\mu mol \cdot L^{-1}$ ± 4.254 and 0.756 $\mu mol \cdot L^{-1}$ ±0.071, respectively. During the placebo trial, ephedrine was not detectable while mean caffeine concentration was 6.5 $\mu mol \cdot L^{-1}$ ± 2.6. Osmolality was unaffected by drug ingestion as was hematocrit level, suggesting that hydration status prior to the trials did not change over the course of the study. Values for osmolality were 288.3 ± 4.2, 287.8 ± 2.2 and 289.3 ± 3.6 $mOsm \cdot kg\ H_2O^{-1}$ for control, placebo and C+E, respectively. Hematocrit levels were 46.2 ± 3.2, 46.2 ± 3.5 and 46.7 ± 3.4% for control, placebo and C+E, respectively.

DISCUSSION

Pre-exercise T_{re}, the rate of change of T_{re} during exercise in the heat, and $\bar{T}_{sk}$ were all similar during both the placebo and C+E trials. Thus, contrary to our hypothesis, C+E was not detrimental to body temperature regulation while exercising in this hot, dry environment, even though there was an associated slight but significant increase in $\dot{V}O_2$. The increase in $\dot{V}O_2$ agrees with others who reported an increased $\dot{V}O_2$ in resting subjects in thermally neutral conditions (1) and during cold stress (19). Contrasting with the results of the current study, the increased resting metabolic rate noted by Vallerand et al. (19) was associated with increased rectal and skin temperatures in the cold. This discrepancy can probably be attributed primarily to the additional avenue of heat loss in the current study which is not a factor during cold stress, i.e., evaporation of sweat. Respiratory heat loss was greater in the current study after C+E treatment and there was a trend for sweat rate to be increased. If the increased sweat rate was commensurate with an increased evaporation of sweat, then this would be consistent with the observation that $\bar{T}_{sk}$ was consistently lower during the C+E trials. The greater evaporative heat loss from the skin and respiration during the C+E trials could have balanced the increased heat production, accounting for the observation that heat storage and the ΔT_{re} were similar to the placebo trial. However, generalization of these findings during exercise in a relatively hot and dry environment to a hot and humid environment may not be warranted, particularly if the latter represents a situation which is physiologically uncompensable. For example, heat storage during exercise in environmental and/or clothing conditions that restrict evaporative heat loss have been shown to be primarily determined by the rate of heat production (12,13). In such a scenario, small differences in the metabolic rate due to C+E ingestion could have a significant negative impact on performance. For example, in the present study, the metabolic rate was increased approximately 140 $ml \cdot min^{-1}$ or about 50 W during the C+E trial. During light intensity exercise in the same environmental conditions but with the addition of wearing nearly impermeable protective clothing used against the threat of biological and chemical weapons, this increased rate of heat production would be predicted to decrease tolerance time from 2 h to 1.5 h (12,13).

Other factors may have influenced our findings. Even though the order of our drug and placebo trials was balanced among our subjects, an order effect for tolerance time was evident over the duration of the experiment (Table IV) implying that our subjects were becoming partially heat acclimated and/or experiencing a training effect. The latter possibility cannot be dis-

TABLE IV. ORDER EFFECT.

	Week 1	Week 2	Week 3	Week 4
Tolerance time (min)	101.3 ±20.5	106.6 ±24.0	117.1* ±32.1	124.2*† ±30.0
Sweat rate ($kg \cdot h^{-1}$)	1.104 ±0.388	1.2033 ±0.344	1.269 ±0.400	1.226 ±0.343
T_{re} initial (°C)	37.098 ±0.173	37.044 ±0.214	36.96 ±0.333	36.986 ±0.150

Values are Mean ± SD.
* Significantly different from week 1; † Significantly different from week 2.

TABLE V. NUMBER OF SUBJECTS AT THE DIFFERENT THERMAL EXHAUSTION CRITERIA.

	Week 1	Week 2	Week 3	Week 4
Volition	1	3	1	1
Heart Rate	2	2	2	2
T_{re}	7	5	6	6
Time	0	0	1	1

counted given that some of our subjects were not regularly active and that only a few exercise exposures are known to modify the cardiovascular response to submaximal exercise (8). However, the change in tolerance time is more consistent with the response that follows a heat acclimation program. The tendencies for an increased sweat rate (Table IV) and a decreased initial T_{re} (Table IV) and exercise $\dot{V}O_2$ (placebo values, Table II) are also supportive evidence that our subjects were becoming heat acclimated over the duration of the study (5,10). Further, the changes in tolerance time were not due to differences in the magnitude of discomfort that our subjects were willing to accept. Table V shows that the majority of subjects exited the chamber each week because they reached the same HR or T_{re} endpoint criteria. Others have claimed that 3 weekly exposures to exercise in a warm, humid environment is insufficient to induce signs of heat acclimation (2). However, in that study, only five subjects were tested, the exercise exposures lasted only 60 min and the subjects were regularly active with a $\dot{V}O_{2max}$ close to 60 mL · kg^{-1} · min^{-1}. Regular aerobic exercise has been shown to induce physiological changes in the response to heat stress similar to those observed following a heat acclimation program (16). Also, in addition to the heat exposures in the chamber, subjects were exposed to progressively warmer ambient temperatures since the present study was conducted during the late spring and early summer months. Thus, it is likely that the response of our subjects was influenced by a change in their heat acclimation status, in addition to C+E ingestion. It should be noted, however, that there were no differences in tolerance time, sweat rate or initial T_{re} between trials 3 and 4 (Table IV); this would suggest that extent of the heat acclimation did not change further over the last 2 wk of the study and, thus, this effect should not have confounded the interpretation of the placebo and C+E trials.

We have reported previously that C+E ingestion improves performance during exercise at 85–90% $\dot{V}O_{2max}$ leading to exhaustion in 15–30 min in a thermoneutral environment. Under such conditions, it is unlikely that heat storage and an increase in T_{re} would limit exercise performance. Since the focus of the present study was to examine the influence of C+E ingestion on temperature regulation, we chose an exercise intensity (50%$\dot{V}O_{2peak}$) and environmental conditions that would create a substantial increase in heat storage over a 2–3 h period. The metabolic rate, that approximated 700 W, would be classified by the military as heavy work and would be slightly greater than the metabolic demand of a forced march at 6.5 kph with a 30 kg backpack.

All subjects in this study were coffee drinkers and were asked to abstain from coffee consumption for 12 h before each trial. When they arrived at the laboratory to prepare for the trial, no withdrawal symptoms such as headache or fatigue were reported. Such symptoms could have affected their performance. Again, Table V shows that the majority of trials were terminated each week because subjects reached HR or T_{re} end-point criteria. Thus it is unlikely that caffeine withdrawal influenced our tolerance time data. In summary, the present study has found that C+E ingestion was not detrimental to the thermoregulatory and cardiovascular responses during moderate exercise in a hot, dry environment.

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