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SHORT REPORT

Nicotine exacerbates exertional heat strain in trained men: a randomized, placebo-controlled, double-blind study

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Abstract

To determine whether using nicotine exacerbates exertional heat strain through an increased metabolic heat production (H_{prod}) or decreased skin blood flow (SkBF), 10 nicotine-naïve trained males [37 ± 12 yr; peak oxygen consumption ($\dot{V}O_{2peak}$): 66 ± 10 mL·min^{-1}·kg^{-1}] completed four trials at 20°C and 30°C following overnight transdermal nicotine (7 mg·24 h^{-1}) and placebo use in a crossover, double-blind design. They cycled for 60 min (55% $\dot{V}O_{2peak}$) followed by a time trial (~75% $\dot{V}O_{2peak}$) during which measures of gastrointestinal (T_{gi}) and mean weighted skin ($\bar{T}_{sk}$) temperatures, SkBF, H_{prod}, and mean arterial pressure (MAP) were made. The difference in ΔT_{gi} between nicotine and placebo trials was greater during 30°C (0.4 ± 0.5°C) than 20°C (0.1 ± 0.7°C), with $\bar{T}_{sk}$ higher during nicotine than placebo trials (0.5 ± 0.5°C, $P = 0.02$). SkBF became progressively lower during nicotine than placebo trials ($P = 0.01$) and progressively higher during 30°C than 20°C trials ($P < 0.01$); MAP increased from baseline ($P < 0.01$) and remained elevated in all trials. The difference in H_{prod} between 30°C and 20°C trials was lower during nicotine than placebo ($P = 0.01$) and became progressively higher during 30°C than 20°C trials with exercise duration ($P = 0.03$). Mean power output during the time trial was lower during 30°C than 20°C trials (24 ± 25 W, $P = 0.02$), and although no effect of nicotine was observed ($P > 0.59$), two participants (20%) were unable to complete their 30°C nicotine trials as one reached the ethical limit for T_{gi} (40.0°C), whereas the other withdrew due to "nausea and chills" ($T_{gi} = 39.7$°C). These results demonstrate that nicotine use increases thermal strain and risk of exertional heat exhaustion by reducing SkBF.

NEW & NOTEWORTHY In naïve participants, acute nicotine use exerts a hyperthermic effect that increases the risk of heat exhaustion during exertional heat strain, which is driven by a blunted skin blood flow response. This has implications for *1*) populations that face exertional heat strain and demonstrate high nicotine use (e.g., athletes and military, 25%–50%) and *2*) study design whereby screening and exclusion for nicotine use or standardization of prior use (e.g., overnight abstinence) is encouraged.

exercise; heat stress; metabolic heat production; nicotine; skin blood flow

INTRODUCTION

After caffeine, nicotine use is globally the most prevalent in terms of psychoactive substances (1). Common forms include smoked (e.g., cigarettes) and smokeless (e.g., snus) tobacco, a range of products normally marketed as tobacco-replacement therapies, and more recently, e-cigarette "vaping." Worldwide, the use of nicotine exceeds 20% in the general population (2), whereas in athletes—varying from recreational to elite—self-report (25%–35%) and anti-doping urinalysis (23%–36%) data indicate a similar or higher prevalence (3). This is supported by practitioner reports (4) and the most comprehensive antidoping urinalysis account to date, whereby one in four athletes tested positive for its use (5).

Centrally, nicotine elicits neurotransmitter release (e.g., dopamine, serotonin, and catecholamines), which is critical to its addictive properties, whereas peripherally its sympathoadrenal effects increase cardiac rate and contractility, vascular resistance, blood pressure, and circulating catecholamines (3). However, during physical activity, its physiological consequences are less remarkable. For example, we have

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previously observed no effects of a 7 mg·24 h^{-1} transdermal nicotine patch during cycling exercise in a temperate environment on cardiorespiratory measures, energy substrate metabolism, acid-base balance, or body core temperature (T_{core}), which led us to conclude that when sympathetic output is already high during prolonged or high-intensity exercise, the peripheral effects of nicotine are attenuated (6, 7).

Whether nicotine alters exercise thermoregulation beyond a change in T_{core} (e.g., thermoeffectors) has not been investigated. This is despite nicotine being a potent vasoconstrictor known to reduce skin blood flow (SkBF) and, therefore, skin temperature and increase metabolic rate of a magnitude that is enhanced by exercise intensity and duration (8–11). Thus, in conditions where metabolic heat production (H_{prod}) is increased and heat dissipation is decreased—such as physical activity with increased thermal stress—greater heat strain could ensue when using nicotine, leading to heat injury. Druyan et al. (12) performed a heat tolerance test (2-h treadmill walking at 5 km·h^{-1} in 40°C) on healthy smokers following no nicotine exposure, nicotine exposure (2 mg nicotine lozenge), and after smoking two cigarettes and observed that both nicotine and smoking increased final T_{core} by ~0.2°C compared with no nicotine, speculating that this was due to a combination of increased H_{prod} and decreased SkBF. However, neither of these were measured.

As with much of the literature, results may be confounded by recruiting participants who are habitual nicotine/tobacco users, as chronic nicotine use develops tolerance and affects sensitivity to nicotine, thereby moderating the physiological response (3), especially with regard to cardiovascular (dys) function toward a pathological state (13). Thus, we have successfully developed a model to study the exercise response to nicotine-naïve participants (6, 7), which was used in the current study to test the hypothesis that nicotine would exacerbate thermal strain (only) during exercise in a warm environment and determine the causal mechanism(s), i.e., increased H_{prod} and/or decreased SkBF.

MATERIALS AND METHODS

Ethical Approval

The Massey University Human Ethics Committee: Southern A (10/73) approved this study. The study conformed to the standards set by the latest revision of the Declaration of Helsinki, except for registration in a database, with each participant providing informed, written consent.

Participants

Ten well-trained male cyclists/triathletes volunteered to participate in this study. All participants were competing at a club or national level on a regular basis and maintained a weekly cycling volume of more than 200 km. Their means ± SD characteristics were age, 37 ± 12 yr; stature, 1.78 ± 0.07 m; mass, 76 ± 9 kg; body surface area, 1.94 ± 0.15 m^2; body fat 8 ± 2%; peak O_2 uptake ($\dot{V}O_{2peak}$), 66 ± 10 mL·min^{-1}·kg^{-1}; and peak aerobic power, 348 ± 22 W. All participants were nonsmokers and did not habitually use any form of nicotine. Our decision to recruit only men for this initial study was guided by the fact that *1*) even in trained women, hormonal differences brought about by differing menstrual phases and oral contraceptive pill use cause differences in T_{core}, forearm blood flow (FBF), and forearm vascular conductance (FVC), all primary outcome measures of the current study, that interact with exercise intensity, duration, and environmental heat stress (14, 15) and *2*) women metabolize nicotine faster than men, and this is further accelerated in those taking estrogen-containing oral contraception (16).

Experimental Overview

All participants attended the laboratory on six occasions: *1*) preliminary submaximal and maximal aerobic capacity test, *2*) experimental familiarization, *3*–*6*) experimental trials. The four experimental trials were completed in a randomized, crossover, double-blind design. All visits were separated by 7 days, conducted at the same time of day (±1 h), following >24 h of dietary and exercise control. All exercise was done using an electromagnetically braked cycle ergometer (Lode Excalibur, The Netherlands) with participant-specific setup for the seat, handlebars, and pedals, which was maintained constant for each trial within a participant, and a fan generating airflow of 19 km·h^{-1} facing participants. For experimental trials, two were conducted at an ambient temperature of 20°C and two at 30°C, and at each ambient temperature, they were administered either a placebo or nicotine via transdermal patch.

Exercise and Ambient Temperature Parameters

Concerning the combination of exercise protocol (intensity/duration) and ambient conditions (ambient temperature/humidity), our decision-making was guided by earlier investigations that successfully demonstrated increased heat strain using other psychoactive agents, namely bupropion (17) and methylphenidate (18). Both studies used a cycling protocol consisting of a work-dependent time trial (~75% $\dot{V}O_{2peak}$) preloaded by 60-min steady-state exercise at 55% $\dot{V}O_{2peak}$ that was completed in 18°C and 30°C. Therefore, we replicated this design in ambient conditions of 19.9 ± 1.5°C (T_{db}), 17.4 ± 2.3°C (T_{wb}), 60.3 ± 4.7% (relative humidity) and 30.4 ± 0.5°C (T_{db}), 26.4 ± 1.9°C (T_{wb}), 61.2 ± 3.8% (relative humidity). Data collection was conducted excluding the southern hemisphere summer (March–November) where the average daily temperature did not exceed 22°C, nor had participants spent any time in a warmer climate for at least 1 mo prior to the study.

Preliminary Testing and Familiarization

Following anthropometric measurements (stature, mass, and composition), a 20-min steady-state submaximal exercise test was conducted in a temperate laboratory environment (18°C–22°C). The submaximal exercise test consisted of four consecutive 5-min stages with power outputs of 100 W, 150 W, 200 W, and 250 W at a self-selected but constant cadence. Following a 5-min active recovery and a 5-min inactive recovery, a ramp protocol was used to determine $\dot{V}O_{2peak}$. Work rate began at 100 W and consisted of a linear increase at 40 W·min^{-1} until volitional fatigue. Expired gases were collected continuously for the determination of ventilation and gas exchange. Following this, a linear relationship between the mean rate of oxygen consumption ($\dot{V}O_2$) during the last 2 min of each submaximal stage and power output

was determined and used to calculate a power output, which would elicit 55% (steady state) and 75% (time trial) of $\dot{V}O_{2peak}$ for each participant for the remaining trials.

Following at least 24 h rest from the preliminary session, a familiarization trial was undertaken to ensure participants were accustomed to the experimental procedures and to minimize learning effects. This trial replicated entirely the experimental trial, outlined below in *Experimental Trial Procedure,* at an ambient temperature of 20°C.

Dietary and Exercise Control

Participants were asked to refrain from exercise between 24 and 48 h prior to each experimental trial. Twenty-four hours prior to each experimental trial, participants attended the laboratory to complete a standardized training ride of 60 min in duration at a power output that elicited 65% maximal heart rate, i.e., 120 ± 5 beats·min^{-1}. Participants were then provided with a standardized snack (Sanitarium UP&GO, New Zealand: 823 kJ providing 30.3 g carbohydrate, 8.3 g protein, and 3.8 g fat) and recorded their diet during the 24-h period prior to the first experimental trial. This diet was replicated for each subsequent experimental trial, and to further minimize variation in pretrial metabolic state, a standardized meal (Sanitarium UP&GO as earlier, and One Square Meal, New Zealand: 1,450 kJ providing 45.1 g carbohydrate, 8.4 g protein, and 11.7 g fat) was consumed 3 h prior to arriving at the laboratory for the experimental trial, after which no food was consumed. Fluid was encouraged and ad libitum until 3 h prior to the experimental trial. A euhydrated state was further ensured by instructing participants to drink a premeasured bolus of water (5 mL·kg^{-1} body wt) 2 h prior to each trial.

The day of and prior to any experimental trial was marked by abstinence from alcohol and only habitual caffeine use, as abstinence would confound results from withdrawal effects.

Treatment and Temperature Pill Administration

Approximately 10 h prior to each experimental trial, a staff member not involved with the research project placed a patch on the participant between the right shoulder blade and the spine. The patch was either a nicotine patch (7 mg·24·h^{-1}, Habitrol, Novartis, New Zealand) or a placebo patch (orthoptic eye patch 63.5 mm × 45.7 mm, Nexcare, 3 M, New Zealand). Participants were also given a factory-calibrated temperature-sensing radio pill (CorTemp, HQ Inc; accurate to 0.1°C) to ingest at this time as an index of T_{core}. For most, this occurred ~1 h before each participant went to bed. Participants were not aware of the research hypotheses and were informed that the purpose of the study was to investigate the detection of nicotine in athletes (19); hence, in some trials, they would receive nicotine, whereas in others, they would not. Following the final experimental trial, participants were fully debriefed. The independent staff member was only aware that they were administering *intervention A* (20°C placebo), *B* (20°C nicotine), *C* (30°C placebo), or *D* (30°C nicotine) with results remaining blinded to the authors until data collection was complete, after which disclosure was made.

Experimental Trial Procedure

Following the dietary and exercise control described earlier, participants arrived at the laboratory, where they were checked to see whether they still had the temperature pill in their gastrointestinal tract and provided a midstream urine sample to confirm hydration status via urine-specific gravity <1.020 (1.009 ± 0.006; 20). A blood sample was obtained from an antecubital vein, following which participants provided their nude body mass before changing into their cycling shorts and top, shoes, and socks before entering the environmental chamber. Participants were seated at rest on the cycle ergometer for 20 min, during which they were instrumented, and baseline measurements were recorded. Participants then cycled for 60 min at the predetermined power output that was estimated to elicit 55% $\dot{V}O_{2peak}$ (187 ± 19 W) with the ergometer set in the cadence-independent mode. Tap water was provided to drink at room temperature ad libitum in aliquots of 3 mL·kg^{-1} body wt either at 15-min intervals or when requested to minimize dehydration. Immediately on completion of the 60-min steady-state period, the ergometer was set to linear mode, based on the formula of Jeukendrup et al. (21), and participants were asked to complete an individualized set amount of work (458 ± 43 kJ) as quickly as possible, which was calculated as the equivalent of 30 min of cycling at 75% $\dot{V}O_{2peak}$. Following completion of the time trial, participants performed a low-intensity cooldown for 5 min, where recovery was monitored before exiting the environmental chamber. Finally, nude body mass was measured after toweling dry.

Measurements

Anthropometric.

Participant stature and mass were measured using a stadiometer (Seca, Germany; accurate to 0.1 cm) and scale (Jadever, Taiwan; accurate to 0.01 kg), from which surface area was estimated (22). Seven-site skinfold thickness was determined using a Harpenden skinfold caliper (Baty International, UK) at the chest, axilla, triceps, subscapula, abdomen, suprailliac, and thigh. Percent body fat (23) was estimated from body density, calculated from the sum of seven skinfolds using published relationships (24).

Respiratory.

Expired respiratory gases were collected every 15 min and analyzed to calculate $\dot{V}O_2$ and carbon dioxide elimination ($\dot{V}CO_2$), ventilation ($\dot{V}E$), and respiratory exchange ratio (RER), using an online, breath-by-breath system (VacuMed Vista Turbofit) using a 60-s average. The system was calibrated before each trial using a zero and β-standard gas concentrations and a 3-L syringe (VacuMed). H_{prod}, normalized to Dubois surface area (A_D, W/m^2), was estimated using partitional calorimetry (25) as the difference between metabolic rate (M) and external work rate from $\dot{V}O_2$, RER, and the caloric equivalents for carbohydrate (21.13 kJ·L^{-1} of O_2) and fat (19.62 kJ·L^{-1} of O_2) oxidation:

$$M = \dot{V}O_2 \cdot \frac{\left[\left(\frac{RER-0.7}{0.3}\right) \times 21.13\right] + \left[\left(\frac{1.0-RER}{0.3}\right) \times 19.62\right]}{60} \times 1,000 \times A_D$$

Cardiovascular.

Blood pressures were measured every 15 min using a stethoscope and a sphygmomanometer over the right brachial artery, in duplicate, and by the same experienced operator.

Mean arterial pressure (MAP) was calculated as diastolic blood pressure +1/3 pulse pressure. As an index of SkBF, FBF was measured every 15 min in triplicate (mean values reported) using venous occlusion plethysmography (26) with a mercury-in-silastic strain-gauge on the widest part of the forearm supported at heart level. The voltage output was acquired (PowerLab, ADInstruments, New Zealand) and displayed (Labchart Pro, ADInstruments) in real time and for offline analysis. The venous occlusion pressure was 50 mmHg, and the cycle duration was ≤10 s. To account for changes in vasomotor tone, FVC was calculated as FBF/MAP (27).

Body temperatures.

The T_{core} was indexed from gastrointestinal temperature (T_{gi}) every 15 min, given its similar reading to rectal temperature during a design like the current study and with better participant acceptance (28). Twelve calibrated wireless surface thermistors (iButtons, Maxim Integrated Products Inc., accurate to 0.1°C) were secured using surgical tape (3 M Healthcare) to the forehead, forearm, hand, foot, shin, calf, quadriceps, hamstrings, chest, abdomen, scapula, and lower back on the right side of the body for determination of mean weighted skin temperature every 15 min ($\bar{T}_{sk}$; 29). The $T_{core} - \bar{T}_{sk}$ gradient was calculated as this influences SkBF requirements (30).

Sweat loss.

Local sweat rate (LSR) was measured using the technical absorbent method (31) for a 5-min duration beginning at the 30- and 55-min time points using a 36-cm^2 square patch (#2164 laminated Airlaid, Technical Absorbents, North East Lincolnshire, UK) centered 6 cm distal to the antecubital fossa on the ventral surface of the forearm, as described previously (31). Whole body sweat loss (WBSL) was estimated from body mass loss and corrected for fluid consumed and respiratory and metabolic fluid losses (32).

Blood sampling and analyses.

Venous blood samples were obtained from an antecubital vein into a 4-mL vacutainer tube (Becton Dickinson, Plymouth, UK) containing clot activator. Following inversion, the tube was allowed to clot at room temperature for 30–60 min before being centrifuged (Eppendorf, Hamburg, Germany) at 4°C for 10 min at 805 *g*. Serum was removed, aspirated into 500 μL aliquots, and frozen at −80°C for later analyses using high-performance liquid chromatography (HPLC). Due to nicotine's tendency to fluctuate and short half-life, cotinine, its major metabolite with a longer retention time, was preferred (3, 19). Sample preparation, extraction, and analysis by HPLC were based on previous methodology (33) and performed in duplicate. The HPLC system (Shimadzu Prominence 20 Series) consisted of a DGU-20AS Prominence degasser, SIL-20AC Autosampler, SPD-M20A Diode array detector and a CTA-20A column oven with a Phenomenex Luna 5 μ C18 (2) 100 Å 150 × 4.6 mm column attached. Operating conditions were as per the method used by Massadeh et al. (33) except for the column, with a limit of detection for cotinine of 7.8 $ng \cdot mL^{-1}$.

Statistical analyses.

Using T_{core} as the primary outcome measure, an a priori power analysis determined that based on conventional α (0.05) and β (0.80) values, and *d* of 1–1.3 as in previous investigations using psychoactive agents using similar exercise and environmental parameters and cohort (17, 18), a minimum of 5–8 participants was required. All statistical analyses were performed with SPSS software for windows (IBM SPSS Statistics 28, New York). Descriptive values were obtained and reported as means ± SD. Levene's test was used to ensure data did not differ from a normal distribution. Data were analyzed by three-way (treatment × environment × time) ANOVA for repeated measures. Sphericity was assessed and where the assumption of sphericity could not be assumed, adjustments to the degrees of freedom were made ($\varepsilon > 0.75$ = Huynh–Feldt; $\varepsilon < 0.75$ = Greenhouse–Geisser). Where interaction effects occurred, main effects are not reported, and post hoc pairwise analyses were performed using a paired samples *t* test (Bonferroni correction where relevant), with statistical significance set at $P < 0.05$. Partial eta-squared (η_p^2) is reported as a measure of effect size, with demarcations of small (<0.09), medium (≥0.09 and ≤0.25), and large (>0.25) effects, respectively (34). Given that blood nicotine may relate to the decline in SkBF and $\bar{T}_{sk}$ (9), we sought to determine whether [cotinine] was related to body mass and the primary outcome measures of T_{gi}, FBF, and H_{prod} by describing the form and strength of bivariate association using Pearson's correlation coefficient.

RESULTS

Serum [cotinine] was not detected in any placebo samples/trials, whereas [cotinine] was detected in all nicotine samples/trials measuring 35 ± 29 $ng \cdot mL^{-1}$ (range: 9–110 $ng \cdot mL^{-1}$). Of the 10 participants, *1*) six (60%) reported not knowing which treatment they were on, *2*) one (10%) incorrectly identified the treatment, and *3*) three (30%) correctly identified the treatment, indicating successful blinding for a majority (7/10) of participants. Two participants reported side effects following nicotine treatment (one with headache and one with disrupted sleep), whereas a third reported nausea following placebo treatment.

The T_{gi} response to exercise can be seen in Fig. 1*A*. Treatment × time ($P = 0.04$, $\eta_p = 0.23$) and environment × time ($P < 0.01$, $\eta_p = 0.49$) interactions were observed, whereby the rise in T_{gi} during exercise was greater during nicotine than placebo trials (2.3 ± 0.5°C vs. 2.0 ± 0.5°C) and greater during 30°C than 20°C trials (2.4 ± 0.6°C vs. 1.8 ± 0.5°C), respectively. For clarity, the T_{gi} response as change (Δ) from baseline can be seen in Fig. 1*B* with changes of 1.8 ± 0.8°C (20°C placebo), 1.8 ± 0.4°C (20°C nicotine), 2.2 ± 0.5°C (30°C placebo), and 2.6 ± 0.7°C (30°C nicotine). The $\bar{T}_{sk}$ response to exercise can be seen in Fig. 1*C*. An effect of treatment ($P = 0.02$, $\eta_p = 0.45$) and environment × time interaction ($P = 0.02$, $\eta_p = 0.31$) was observed such that $\bar{T}_{sk}$ was higher during nicotine than placebo trials (32.4 ± 1.0°C vs. 32.0 ± 1.2°C), and whereas $\bar{T}_{sk}$ did not change over time in 20°C trials, it increased until 30 min before plateauing in 30°C trials. The $T_{core} - \bar{T}_{sk}$ response to exercise can be seen in Fig. 1*D*. Effects of treatment ($P = 0.01$, $\eta_p = 0.53$), environment ($P < 0.01$, $\eta_p = 0.97$), and time ($P < 0.01$, $\eta_p = 0.56$) were observed such that $T_{core} - \bar{T}_{sk}$ was lower in nicotine than placebo trials (5.5 ± 0.9°C vs. 6.0 ± 1.1°C), lower in 30°C

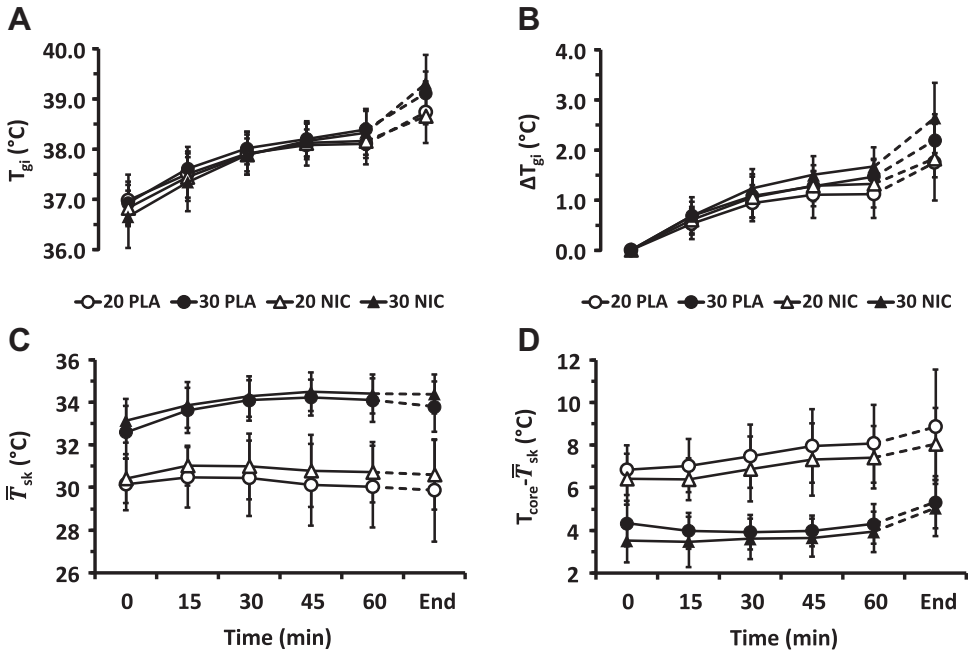

Figure 1. Means ± SD participant responses ($n = 10$) to exercise in 20°C and 30°C following overnight placebo (PLA) or nicotine (NIC) use for absolute (*A*) and change from baseline (Δ, *B*) gastrointestinal (T_{gi}) and mean weighted skin ($\bar{T}_{sk}$, *C*) temperatures and the $T_{core} - \bar{T}_{sk}$ gradient (*D*). Dashed lines represent duration of time trial.

than 20°C trials (4.1 ± 0.9°C vs. 7.4 ± 1.2°C), and had increased by the end of exercise (1.6 ± 1.1°C).

The FBF response to exercise can be seen in Fig. 2*A*. Treatment × time ($P = 0.01$, $\eta_p = 0.45$) and environment × time ($P < 0.01$, $\eta_p = 0.50$) interactions were observed whereby FBF became progressively lower during nicotine than placebo trials with exercise duration (mean difference: 0 min, 1.1 ± 2.4 vs. 60 min, 7.1 ± 5.9 mL·dL^{-1}·min^{-1}) and became progressively higher during 30°C than 20°C trials (mean difference: 0 min, 1.9 ± 2.0 vs. 60 min, 8.8 ± 7.1 mL·dL^{-1}·min^{-1}). The H_{prod} response to exercise can be seen in Fig. 2*B*. Treatment × environment ($P = 0.01$, $\eta_p = 0.53$) and environment × time ($P = 0.03$, $\eta_p = 0.27$) interactions were observed whereby the difference in H_{prod} between 30°C and 20°C trials was lower during nicotine than placebo (61 ± 25 vs. 94 ± 25 W/m^2) trials and became progressively higher during 30°C than 20°C trials with exercise duration (mean difference: 15 min, 66 ± 17 vs. 60 min, 82 ± 20 W/m^2). The MAP response to exercise can be seen in Fig. 2*C*. An effect of time ($P < 0.01$, $\eta_p = 0.75$) was observed such that values during exercise increased from baseline (98 ± 4 mmHg) and remained elevated. The FVC response to exercise can be seen in Fig. 2*D*. Treatment × time ($P < 0.01$, $\eta_p = 0.48$) and environment × time ($P < 0.01$, $\eta_p = 0.40$) interactions were

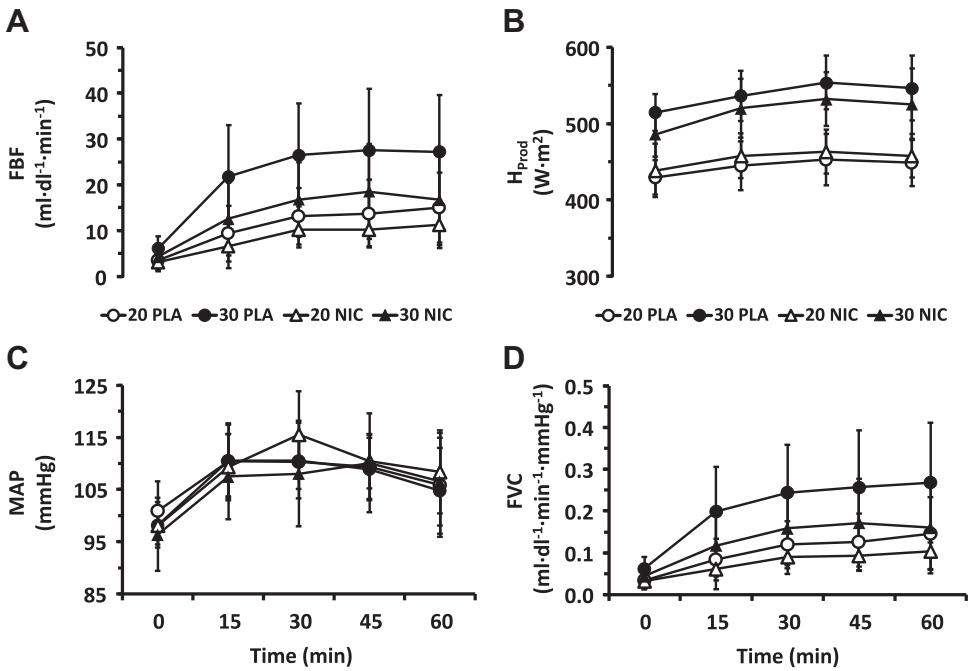

Figure 2. Means ± SD participant responses ($n = 10$) to exercise in 20°C and 30°C following overnight placebo (PLA) or nicotine (NIC) use for forearm blood flow (FBF, *A*), metabolic heat production (H_{prod}, *B*), mean arterial pressure (MAP, *C*), and forearm vascular conductance (FVC, *D*). For H_{prod} time points range is 15–60 min.

observed whereby FVC became progressively lower during nicotine than placebo trials with exercise duration (mean difference: 0 min, 0.01 ± 0.02 vs. 60 min, 0.07 ± 0.06 $mL \cdot dL^{-1} \cdot min^{-1} \cdot mmHg^{-1}$) and became progressively higher during 30°C than 20°C trials (mean difference: 0 min, 0.02 ± 0.02 vs. 60 min, 0.09 ± 0.08 $mL \cdot dL^{-1} \cdot min^{-1} \cdot mmHg^{-1}$).

Participants consumed more fluid (580 ± 93 vs. 457 ± 147 mL, $P = 0.03$, $\eta_p = 0.53$), and WBSL was greater (2.24 ± 0.58 vs. 1.65 ± 0.57 kg, $P < 0.01$, $\eta_p = 0.84$) during 30°C than 20°C trials, resulting in a greater percent body mass loss (−2.6 ± 0.8 vs. −2.0 ± 0.8%, $P < 0.01$, $\eta_p = 0.65$). Effects of time ($P < 0.01$, $\eta_p = 0.91$) and environment ($P < 0.01$, $\eta_p = 0.75$) were observed for LSR such that values increased from 30 to 55 min (0.94 ± 0.60 vs. 1.26 ± 0.57 $mg \cdot min^{-1} \cdot cm^{-2}$) and were greater during 30°C than 20°C (1.55 ± 0.85 vs. 0.65 ± 0.38 $mg \cdot min^{-1} \cdot cm^{-2}$) trials.

Performance data from the time trial can be seen in Table 1. All 10 participants completed the time trial for 20°C placebo, 20°C nicotine, and 30°C placebo trials (458 ± 43 kJ). However, two participants (20%) were unable to complete the full work during their 30°C nicotine trials such that only 84% of this trial was completed for both, resulting in a reduced work completed for this trial (442 ± 40 kJ). One participant had to be removed from the chamber due to reaching the ethical limit for T_{gi} (40.0°C), whereas the other withdrew himself due to "nausea and chills" (T_{gi} = 39.7°C). Therefore, based on an analysis of the eight that completed all four trials (Table 1), time to complete the individualized work was increased in the 30°C trials compared with 20°C trials by 4 ± 4 min ($P = 0.01$, $\eta_p = 0.61$) with no effect/interaction of treatment ($P > 0.44$, $\eta_p < 0.09$). Mean power output of work completed ($n = 10$) was 24 ± 25 W lower in the 30°C trials compared with 20°C trials ($P = 0.02$, $\eta_p = 0.50$) with no effect/interaction of treatment ($P > 0.59$, $\eta_p < 0.03$).

In absolute terms, body mass did not correlate with serum cotinine ($r = -0.16$, $P = 0.66$), nor did serum cotinine correlate with ΔT_{gi} ($r = 0.28$, $P = 0.43$), ΔFBF ($r = 0.08$, $P = 0.82$), or ΔH_{prod} ($r = -0.17$, $P = 0.64$).

DISCUSSION

The new and important findings from this investigation were that nicotine use increased thermal strain with increased T_{core} and $\bar{T}_{sk}$ and decreased $T_{core} - \bar{T}_{sk}$ during exercise in the heat. This was associated with a reduced SkBF rather than increased H_{prod} or altered sweat rate. Although nicotine did not have a detrimental effect on performance per se, it increased the risk of exertional heat injury, i.e., hyperthermia and heat exhaustion.

The current result of nicotine use increasing T_{core} during exercise in the heat by ∼0.4°C confirms the results of Druyan et al. (12) in smokers (chronic users) and extends this observation to nonsmokers (acute/naïve users). Interestingly, Druyan et al. (12) did not observe a significant increase in T_{core} in response to the heat tolerance test in the control group (nonsmokers) following ingestion of 2 mg nicotine lozenge, although no treatment verification was provided, i.e., blood/urine nicotine or cotinine. We have previously observed lower [cotinine] following oral (gum, ∼1.3–3.2 $ng \cdot mL^{-1}$) versus transdermal (patch, ∼38–44 $ng \cdot mL^{-1}$) nicotine delivery in a similar cohort as the current study (7), whereby absorption pharmacokinetics and bioavailability are known to be lower with buccal compared with transdermal administration due to nicotine-rich saliva being swallowed, with subsequent first-pass metabolism (3). As regular smokers maintain high blood concentrations of cotinine even following 12-h abstinence (e.g., ∼112 $ng \cdot mL^{-1}$;9), the current and previous results (12) indicate that a certain level/threshold of blood nicotine is required before hyperthermic effects are seen, although we did not observe a relationship between serum [cotinine] and ΔT_{gi}. For example, in the current study, 80% of serum [cotinine] samples were ≥18 $ng \cdot mL^{-1}$, which also corresponds to the number of participants that displayed an increased rise in T_{core} with nicotine in 30°C.

Druyan et al. (12) speculated that sympathetic activation caused by nicotine exposure was the cause of the increased T_{core} due to a combination of increased H_{prod} and decreased SkBF. This is supported by previous investigations demonstrating nicotine to reduce SkBF (8, 9) and increase H_{prod} with this thermogenic effect more than double during exercise and increasing with exercise duration (10, 11). Herein we demonstrate that H_{prod} was influenced by nicotine and ambient temperature (interaction/antagonistic effect), whereby H_{prod} with nicotine was lower at 30°C yet higher at 20°C. However, the overall effect on H_{prod} was much greater for ambient temperature than nicotine (∼80 vs. 20 W/m^2). Thus, our results confirm a reduced SkBF as the hyperthermic mechanism especially as our estimates of evaporative heat loss (WBSL and LSR) were unaffected by nicotine. This effect on the skin vasculature was independent of MAP and supports earlier human data at rest (8, 35, 36). Black et al. (35) used an isolated perfused human skin flap model to demonstrate that nicotine (10^{-7} M) amplified norepinephrine-induced skin vasoconstriction. Warner et al. (36) used local

Table 1. *Performance data from the time trial*

	20°C		30°C	
	Placebo	Nicotine	Placebo	Nicotine
Completion time ($n = 8$)*				
Means ± SD, min	29 ± 3	30 ± 2	34 ± 7	33 ± 5
Range, min	25–32	25–32	26–49	24–39
Mean power output ($n = 10$)*				
Means ± SD, W	257 ± 22	256 ± 23	231 ± 44	234 ± 35
Range, W	232–289	220–292	154–297	186–295

Values are means ± SD. Repeated-measures ANOVA (treatment × environment × time) was used for the analysis. *Significant difference between 20°C and 30°C, $P < 0.05$.

heating of the forearm (32°C–42°C) to demonstrate that acute nicotine exposure brought about by smoking one cigarette or 2 mg intranasal spray decreased the sustained vasodilatation and that this was dependent on local norepinephrine as bretylium inhibited this response.

Mean power output during the time trial was lower with heat stress, although completion time was not different between nicotine and placebo trials. This result supports our previous finding in trained cyclists (7) and much of the literature (3) that, in general, nicotine exerts neither an ergogenic nor an ergolytic effect. Nevertheless, 2 of the 10 participants were unable to complete their time trial and had 2 of the 3 highest end-exercise T_{core} when using nicotine in the heat. Taken together, with a hyperthermic effect of ~0.4°C during prolonged exercise in the heat, this result should raise concern for athletes, practitioners, and governing bodies. For example, the World Anti-Doping Agency currently has nicotine on its Monitoring Program alongside other stimulants that have been shown to be hyperthermic such as caffeine (37) and bupropion (17). This would appear to satisfy the criterion of "representing an actual or potential health risk to athletes"—one of three—that determines whether a substance is elevated to the List of Prohibited Substances (38) when exercise is performed with heat stress, especially alongside nicotine's other known health consequences (3).

Considerations

The observations herein are valid only for the current sample(s), protocol(s), and condition(s). Chronic nicotine/tobacco use precipitates cardiometabolic diseases and neurological disorders (3) that can lead to heat intolerance through impaired heat dissipation, especially SkBF (39). Therefore, it remains to be determined whether chronic use further exacerbates exertional heat strain, although previous results suggest this to be the case (12). Whether a differential response occurs between the sexes or due to changes in ovulatory/hormonal status should be investigated as females are more reliant on dry heat exchange (40), can display differences in SkBF between menstrual phases and with oral contraceptive use (14, 15), and are known to metabolize nicotine faster than men and at even faster rates with estrogen-containing oral contraceptives (16).

Perspectives and Significance

The findings from this study have two important implications. First, high nicotine-use populations, such as athletes (25%–50%; 3, 5) and military (38%; 41), that are regularly exposed to heat stressful conditions for sustained periods of time (i.e., >60 min) should be warned that nicotine use can be hyperthermic and increase the chance of heat exhaustion. Second, any future research(er), including a design with exertional heat strain and primary outcome measures of the thermoregulatory/cardiovascular systems (e.g., T_{core}, $\bar{T}_{sk}$, and SkBF), should consider their screening and exclusion procedures (i.e., nicotine use) or standardizing blood levels, i.e., a period of abstinence in current users.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.M. conceived and designed research; N.E.M., M.J.B., B.G.P., and T.M. performed experiments; T.M. analyzed data; T.M. interpreted results of experiments; T.M. prepared figures; T.M. drafted manuscript; N.E.M., M.J.B., B.G.P., N.F., T.A., N.K., and T.M. edited and revised manuscript; N.E.M., M.J.B., B.G.P., N.F., T.A., N.K., and T.M. approved final version of manuscript.

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