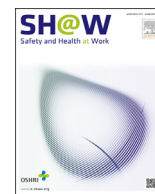


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Original Article

Effects of Low-Dose Aspirin Therapy on Thermoregulation in Firefighters



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ABSTRACT

Background: Heart attack is the most common cause of line-of-duty death in the fire service. Daily aspirin therapy is a preventative measure used to reduce the morbidity of heart attacks but may decrease the ability to dissipate heat by reducing skin blood flow.

Methods: In this double-blind, placebo-controlled, crossover study, firefighters were randomized to receive 14 days of therapy (81-mg aspirin or placebo) before performing treadmill exercise in thermal-protective clothing in a hot room [$38.8 \pm 2.1^\circ\text{C}$, $24.9 \pm 9.1\%$ relative humidity (RH)]. Three weeks without therapy was provided before crossing to the other arm. Firefighters completed a baseline skin blood-flow assessment via laser Doppler flowmetry; skin was heated to 44°C to achieve maximal cutaneous vasodilation. Skin blood flow was measured before and after exercise in a hot room, and at 0 minutes, 10 minutes, 20 minutes, and 30 minutes of recovery under temperature conditions ($25.3 \pm 1.2^\circ\text{C}$, $40.3 \pm 13.7\%$ RH). Platelet clotting time was assessed before drug administration, and before and after exercise.

Results: Fifteen firefighters completed the study. Aspirin increased clotting time before and after exercise compared with placebo ($p = 0.003$). There were no differences in absolute skin blood flow between groups ($p = 0.35$). Following exercise, cutaneous vascular conductance (CVC) was $85 \pm 42\%$ of maximum in the aspirin and $76 \pm 37\%$ in the placebo groups. The percentage of maximal CVC did not differ by treatment before or after recovery. Neither maximal core body temperature nor heart rate responses to exercise differed between trials.

Conclusion: There were no differences in skin blood flow during uncompensable heat stress following exercise after aspirin or placebo therapy.

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1. Introduction

Firefighters have the highest occurrence of line-of-duty death in the United States [1]. Over half of these deaths are cardiovascular events directly related to fire-suppression activities [2–4]. Continuous heavy work in thermal-protective clothing and repetitive upper body tool use characteristic of structural fire suppression impose significant cardiovascular strain by increasing myocardial oxygen demand and decreasing myocardial oxygen

supply [5,6]. The physical strain combined with uncompensable heat stress provides triggers for ischemic events (i.e., myocardial infarction, stroke) [7–9].

Heart rate and core body temperature rise rapidly in response to increased physical work and environmental heat stress, which activates coagulation and causes vasoconstriction and endothelial dysfunction [7–9]. In addition, shift work, lifestyle factors, and exposure to smoke and chemicals during fire suppression may further predispose firefighters to earlier onset heart disease by

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amplifying inflammation and endothelial dysfunction, a precursor to atherosclerosis [10–13].

Our laboratory has completed a clinical trial investigating the effects of low-dose aspirin therapy on firefighter physiology, platelet activation, and vascular function during and following uncompensable heat stress (clinicaltrials.gov NCT01066923). Aspirin has been shown to reduce cardiac events in individuals of the general population who have cardiovascular disease (CVD) risk factors [14] and may decrease the overall prothrombotic state resulting from exertional heat stress during fire suppression. Data from our laboratory have demonstrated that aspirin therapy blunts heat-induced platelet activation and did not adversely affect core body temperature during work in an uncompensable heat stress environment [15]. However, other reports have suggested that systemic platelet inhibition by aspirin with standard therapeutic doses subsequently inhibited reflex cutaneous vasodilation [16–18]. Specifically, anticoagulation therapy inhibits the release of vasodilator substances from activated platelets [19–21], decreases the shear stimulus on the cutaneous microvasculature [17], and/or alters the internal temperature threshold for heat dissipation [16,17], eventually resulting in decreased dry heat loss capacity and increased thermal strain.

To our knowledge, this is the first study to comprehensively examine the effects of low-dose aspirin therapy on multiple indices of thermoregulation, inflammation, and physiological responses to exertion in the heat while wearing thermal-protective clothing. Previous studies demonstrating an attenuation in skin blood-flow responses were primarily done under passive heat stress conditions in middle-aged and older adults [16,17], with large doses of aspirin [22], or using anodal current-induced vasodilation [18,22], none of which is reflective of the environmental conditions or exertional loads that firefighters are exposed to. In addition, doing exercise in the heat leads to total body water and plasma volume losses, which further reduce blood flow to the gut [23]. Hypoperfusion of the gut leads to mucosal damage and the invasion of endotoxins into the blood. Low-dose aspirin has also been reported to damage the gut mucosa [24,25]. Elevated endotoxin levels can lead to fever, shivering, dizziness, nausea, vomiting, and diarrhea, all of which have been reported in endurance athletes [26–28]. The level of plasma tumor necrosis factor- α (TNF- α) is significantly increased in response to endotoxin [29]. Endotoxin and cytokine release may be indicative of poor thermal compensation. Understanding the impact of aspirin therapy on endotoxin release and the subsequent cytokine response is vital with regard to the safety profile of aspirin use during exertion under uncompensable heat stress conditions.

This is important given that firefighters may use daily aspirin therapy as primary prevention against heart attacks as well as to treat minor pain; therefore, information on the effect of aspirin during uncompensable heat stress is needed to make educated decisions about preventative treatment of CVD. If aspirin is detrimental to some aspect of thermoregulation, then this can guide physicians to treat the risk factors of CVD with other therapies and provide critical information about the risk/benefit ratio for aspirin therapy in firefighters whether used in an occupational context or for the management of CVD risk. This examination of the thermoregulatory, inflammatory, and physiological responses to low-dose aspirin therapy in firefighters during and following exertion under uncompensable heat stress conditions offers a more in-depth assessment of the safety of its use in this occupational cohort.

2. Materials and methods

We conducted a double-blind, placebo-controlled, crossover study to determine the additional effects of aspirin therapy on reflex cutaneous vasodilation, core body temperature, and heart rate

responses under uncompensable heat stress conditions. Participants were volunteers and career firefighters from fire departments and emergency service agencies from Western Pennsylvania. All participants had no history of CVD, did not use medications expected to blunt the physiologic response to treadmill exercise or those with the known side effect of impaired thermoregulation, medications or supplements known to alter endothelial function (i.e., arginine, omega 3 fatty acids, nonsteroidal anti-inflammatory drugs, tobacco), or had no known history of platelet dysfunction, aspirin allergy/intolerance, or iodine allergy. The University of Pittsburgh Institutional Review Board approved the study and all participants provided written informed consent prior to participation.

2.1. Screening

All participants received a physical examination from a study physician including a 12-lead electrocardiogram (ECG) and a treadmill exercise stress test. Height was determined using a stadiometer, weight was recorded on a digital scale accurate to 0.5 g (KERN & SOHN GmbH, Balingen, Germany), and body fat was measured using three-site skinfold measurements [30]. Exclusion criteria included hypertension during screening and a resting ECG depicting the presence or history of CVD.

A Bruce protocol treadmill test was used to determine aerobic capacity (VO_{2max}) with open-circuit spirometry (TrueOne 2400; Parvo Medics, Sandy, UT, USA) measuring respiratory rate and maximal oxygen consumption (VO_{2peak}). Test results were interpreted by a board-certified cardiologist.

After meeting all inclusion criteria, a venous blood sample was obtained from each participant for estimating baseline platelet closure time. The sample was stored for future assay for detecting levels of endotoxin, interleukin-6 (IL-6), and TNF- α . Epinephrine-induced platelet aggregability (platelet closure time) was determined in whole-blood samples using a platelet function analyzer (PFA-100, Siemens, Malvern, PA, USA). A timeline of study visits is presented in Table 1.

2.2. Baseline skin blood flow

Following the screening visit, all participants returned to our laboratory for skin blood-flow measurements to establish baseline

Table 1
Timeline of study visits

Study visit 1	Screening	Informed consent, demographics, screening, and exercise stress test
Study visit 2	Baseline and maximal SBF, ASG	Resting LDF in heated room (37.5–40°C) Iodine paper test for sweat gland activation
Study drug No. 1 (14 d)		
Study visit 3	Protocol 1	1. Baseline measurements and preparation 2. Pre-exercise LDF, ASG 3. 45-min hot exercise 4. Postexercise LDF, ASG 5. 30-min recovery period
3-wk washout period before beginning second study medication		
Study drug No. 2 (14 d)		
Study visit 4	Protocol 2	1. Baseline measurements and preparation 2. Pre-exercise LDF, ASG 3. 45-min hot exercise 4. Postexercise LDF, ASG 5. 30-min recovery period

ASG, activated sweat gland; LDF, laser Doppler flowmetry; SBF, skin blood flow.

and maximal values. To obtain an index of skin blood flow, cutaneous red blood cell flux was measured using an integrated laser-Doppler flowmeter (LDF) (PeriFlux System 5020; Perimed AB, Stockholm, Sweden) placed on the volar aspect of the forearm. The LDF measurements are specific to the skin and are not influenced by underlying skeletal muscle blood flow [31]. Blood pressure was recorded on the contralateral arm. Cutaneous vascular conductance (CVC) was indexed as $LDF (V)/\text{mean arterial pressure (mmHg)}$. Participants were dressed in shorts and a t-shirt and seated in a semireclined position in a heated room [$38.6 \pm 2.3^\circ\text{C}$; $20.0 \pm 6.3\%$ relative humidity (RH)]. Oral temperature was taken to ensure all participants were afebrile ($<37.5^\circ\text{C}$). Following 5 minutes of steady-state resting measurement, the skin was heated from 36°C to 44°C , with a steady-state 3-minute interval at each degree. Participants were informed about the importance of remaining still and not moving during the testing.

Prior to and immediately after obtaining the LDF measurements, starch-impregnated paper was placed onto iodine-prepared skin proximal to the LDF probe for assessment of the number of activated sweat glands (ASGs). The carbohydrates in sweat combine with iodine to create a dark dot, which indicates an active sweat gland. Four, 1-cm^2 squares were counted and the average number of ASGs was obtained [32–34]. Skin saturated with sweat was wiped dry prior to paper placement. Measurements were also obtained on both exercise protocol days.

Participants were randomized to receive low-dose aspirin (81 mg) and placebo for 2 weeks in a double-blind, crossover fashion. The UPMC Investigational Drug Service prepared the study drugs by placing aspirin tablets into an opaque capsule with an additional binder or by filling identical capsules with binder alone. The masked drug was then dispensed to the research technicians based on unique participant identification codes. Participants were given 15 capsules of the study drug and instructed to take one capsule each day with water. A study coordinator contacted each participant by phone or text message with reminders to take the study drug. Participants returned the pill bottle at each protocol visit to verify the number of pills taken.

2.3. Protocol visits

Protocol visits were scheduled 13–15 days after beginning the study drug. Participants took an ingestible pill with a radio receiver (HQ Inc, Palmetto, FL, USA) the night before the protocol for measurement of core body temperature and to minimize the confounding effects of food or fluid in the gastrointestinal tract. Fig. 1 depicts the timeline of events and data collection for the protocol visits. Participants provided a urine sample for determination of urine-specific gravity via a handheld refractometer (ATAGO U.S.A., Inc., Bellevue, WA, USA). If the value was >1.025 , an additional 500 mL of water was consumed and participants rested quietly for 30 minutes prior to continuing with the protocol. A fasting venous

blood sample was provided for assessment of platelet closure time and detection of endotoxin, IL-6, and TNF- α levels. A weight-based standardized meal (PowerBar, Glendale, CA, USA; Clif Bar, Berkeley, CA, USA) and 400–600 mL of water were provided to ensure similar pre-exercise nutrition prior to exercise. Participants were then weighed nude.

A heart rate monitor was placed around the chest, and skin temperature probes were placed over the sternal head of the pectoralis major, supraspinatus, midpoint of the triceps brachii, and the midpoint of the quadriceps femoris muscles. Mean skin temperature (Tsk) was calculated as follows: $Tsk = \text{chest} (0.25) + \text{back} (0.25) + \text{thigh} (0.3) + \text{arm} (0.2)$ [35]. The skin of the right forearm was cleaned with deionized water and an LDF probe holder was secured to the volar aspect. Next to the probe holder, iodine was smeared onto the skin and allowed to dry for later ASG measurement. Following instrumentation, participants donned station duty pants, a cotton short-sleeve t-shirt, and thermal-protective clothing for structural firefighting consisting of turnout pants (Body-Guard, Lion Apparel, Dayton, OH, USA) and steel-toed rubber boots (Servus Products, Rock Island, IL, USA).

The participants then entered the hot room ($38.8 \pm 2.1^\circ\text{C}$; $24.9 \pm 9.1\%$ RH) and sat in a semireclined position for 10 minutes to obtain LDF measurements. ASG assessment was carried out immediately prior to obtaining skin blood-flow measurement. Following LDF, participants donned their thermal-protective coat (Body-Guard, Lion Apparel), nomex hood (Majestic Fire Apparel, Inc., Lehighton, PA, USA), polycarbonate helmet (Paul Conway, Dayton, OH, USA), and leather gloves. They walked on a level treadmill in the heated room for 45 minutes at 6.4 km/h (4.0 mi/h). Heart rate, core body temperature, and skin temperature were recorded every 5 minutes during exercise. Ratings of perceived exertion, comfort, sweating, and thermal stress were also recorded every 5 minutes during exercise using previously validated scales [36]. Standardized instructions were provided prior to exercise including examples of how to use the scales. Exercise ended when participants completed the 45-minute protocol or when they reached one of the following termination criteria: (1) participant request; (2) heart rate exceeding $220 - \text{age} + 10$ bpm; (3) body core temperature exceeding 39.5°C ; or (4) unsteady gait while walking on the treadmill. Immediately following exercise, participants removed their gloves, helmet, hood, and coat and sat in a semireclined position for 10 minutes for LDF measurement and ASG assessment.

The participant then exited the hot room to begin a 30-minute recovery period in a temperate climate ($25.3 \pm 1.2^\circ\text{C}$; $40.3 \pm 13.7\%$ RH). A venous blood sample was drawn for assessment of platelet closure time and future endotoxin detection. Skin blood flow, heart rate, blood pressure, core body, and skin temperature were recorded every 5 minutes of the recovery period. Participants were given 100 mL of water at 5 minutes, 15 minutes, and 25 minutes of recovery. ASG assessment was carried out prior to and



Fig. 1. Timeline of events during each protocol. ASG, activated sweat gland; HR, heart rate; LDF, laser Doppler flowmetry.

immediately after the recovery period. Protective clothing was then removed and a nude weight was obtained. Sweat loss was calculated the change in body mass.

A 3-week washout period followed the first drug protocol. After the washout period, participants were given the other study drug and instructed to follow the same procedures as before. Upon completing the second study drug, participants returned to the laboratory and repeated the aforementioned protocol.

2.4. Blood samples and assays

All blood samples were drawn using aseptic technique by trained technicians. All blood samples, with the exception of the platelet closure time sample, were placed immediately on ice for 10 minutes, and then centrifuged for 15–20 minutes at 3,500 rpm at 4°C. The sample obtained to assess platelet closure time was allowed to stand at room temperature for 10 minutes before obtaining measurements. The endotoxin level was measured using a sensitive and rapid chromogenic *Limulus* assay (*Limulus* amoebocyte lysate; QCL-100, Lonza, Walkersville, MD, USA). Levels of IL-6 and TNF- α were analyzed using a commercially available enzyme-linked immunoassay (R&D Systems, Minneapolis, MN, USA).

2.5. Statistical analysis

Absolute maximal CVC was calculated as the average of a 3-minute stable plateau in laser Doppler flux following local heating of the skin to 44°C with the CVC calculated and represented as the percentage of maximum (%CVC_{max}). Two-way analysis of variance with repeated measures were conducted to determine differences between trials in absolute CVC, %CVC_{max}, core temperature, heart rate, skin temperature, activated sweat gland count, endotoxin levels, and platelet clotting time. Paired *t* tests were conducted to determine differences in the accelerometer data, treadmill time, treadmill distance, and body mass lost. Level of significance was set at $\alpha = 0.05$. All data are reported as mean \pm standard deviation.

3. Results

Eighteen male firefighters were enrolled in the study. Two were excluded from participation for medical reasons and one dropped out due to a nonstudy-related illness (Table 2).

3.1. Skin blood-flow assessment

During the baseline skin blood-flow assessment and prior to skin heating, absolute resting CVC was 0.26 ± 0.27 V/mmHg, which increased to a maximum of 2.44 ± 0.57 V/mmHg. During the exercise protocols, absolute CVC demonstrated significant and expected changes in both the aspirin and placebo trials, however, these changes were not different between groups ($p = 0.35$). There were significant changes over time in both the aspirin and placebo groups in the percentage of maximal CVC achieved. Before exercise,

Table 2
Demographics of the participants

Age (y)	30.5 \pm 9.3
Height (cm)	179.8 \pm 5.8
Weight (kg)	90.7 \pm 14.0
Body mass index (kg/m ²)	27.9 \pm 3.7
Body fat (%)	15.7 \pm 5.3
VO _{2max} (mL/kg/min)	46.6 \pm 7.0

All values are reported as mean \pm standard deviation.

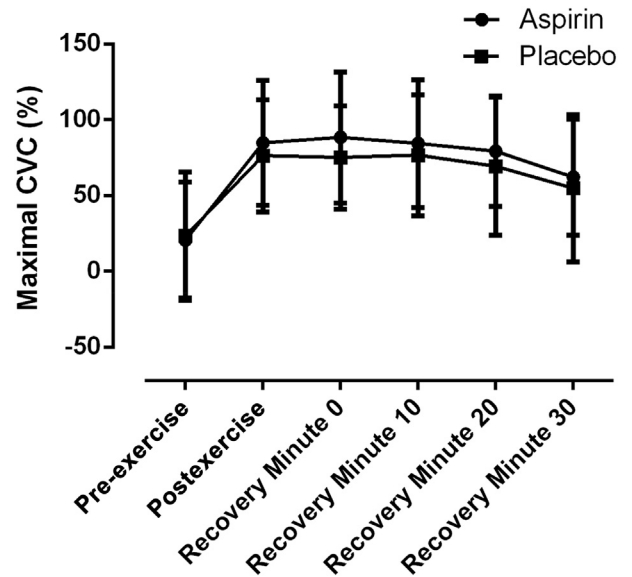


Fig. 2. Skin blood flow as a percentage of maximal cutaneous vasculature conductance (CVC).

skin blood flow in the aspirin trial was $20 \pm 38\%$ of maximal CVC and $23 \pm 42\%$ of maximal CVC in the placebo trial. After exercise, CVC was $85 \pm 42\%$ of maximum in the aspirin trial and $76 \pm 37\%$ in the placebo trial. The percentage of maximal CVC did not differ before the start of the recovery period in either the aspirin ($88 \pm 43\%$) or placebo ($75 \pm 34\%$) trial. At the end of the 30-minute recovery period, CVC was $62 \pm 38\%$ of maximum in the aspirin trial and $55 \pm 49\%$ of maximum in the placebo trial ($p = 0.28$; Fig. 2).

3.2. Physiological variables

Core body temperature was not different between trials at any time ($p = 0.69$). After exercise, core temperature reached $39.0 \pm 0.7^\circ\text{C}$ in the aspirin trial and $39.1 \pm 0.6^\circ\text{C}$ in the placebo trial. Core temperature continued to rise following exercise and reached maximum values at the start of the recovery period in both the aspirin ($39.3 \pm 0.5^\circ\text{C}$) and placebo ($39.4 \pm 0.6^\circ\text{C}$) trials. Core body

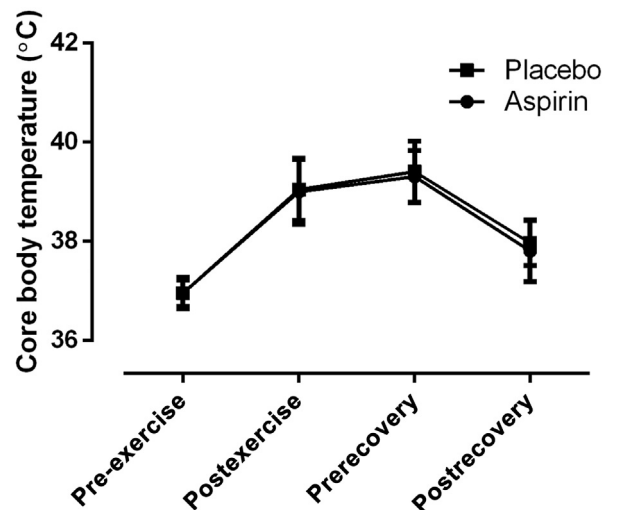


Fig. 3. Core body temperature responses.

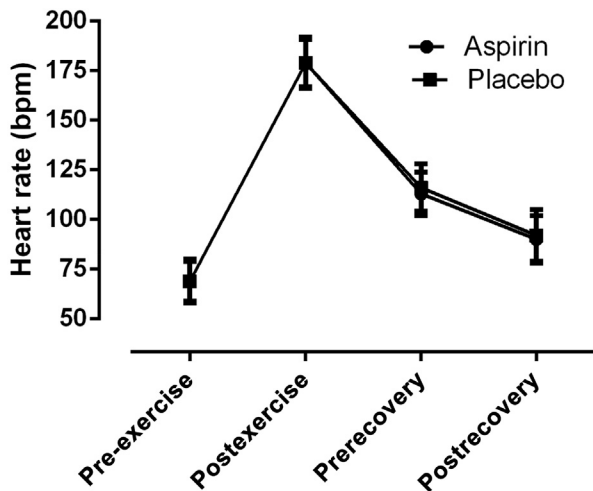


Fig. 4. Heart rate responses.

temperature remained elevated above pre-exercise values at the end of the 30-minute recovery period in both groups (Fig. 3).

Changes in heart rate over time were seen in both groups; however, there were no group differences. Near-maximal heart rates were achieved in both the aspirin (179 ± 13 bpm) and placebo (179 ± 12 bpm) trials. Heart rate remained elevated in both groups at the end of the recovery period (Fig. 4). There were no differences in mean skin temperature between trials at any time point (Fig. 5).

Mass loss due to sweating was similar between the aspirin (1.6 ± 0.3 kg) and placebo (1.6 ± 0.5 kg) trials. In addition, the number of activated sweat glands during exercise was not different between trials (Table 3). Total treadmill time and distance completed were similar between trials. Similarly, accelerometer data revealed that total calories expended, total metabolic equivalents, and total steps were not different between trials (Table 4). Participants did not report differences in perceptual ratings of whole-body exertion, comfort, thermal sensation, or sweating during exercise.

3.3. Blood markers

Platelet closure time increased after 14 days of aspirin therapy, but did not change in the placebo trial. After exercise, platelet

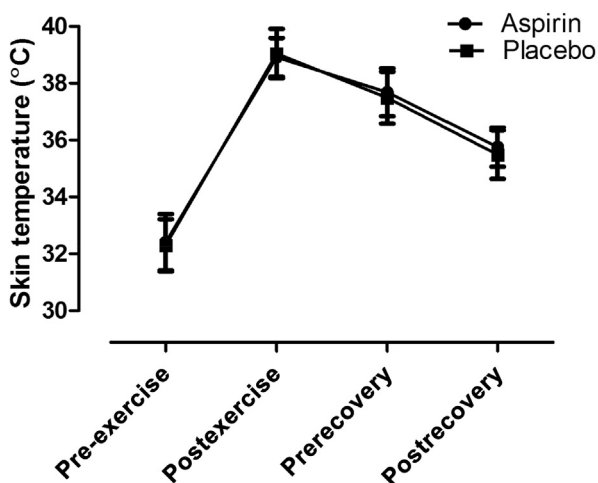


Fig. 5. Skin temperature responses.

Table 3
Activated sweat glands

	Pre-exercise	Postexercise	Prerecovery	Postrecovery
Placebo	1 ± 1	71 ± 62	56 ± 79	14 ± 23
Aspirin	2 ± 3	63 ± 68	57 ± 56	10 ± 22

All values are reported as mean ± standard deviation.

closure time decreased to 114 ± 24 seconds in the placebo trial and to 210 ± 82 seconds in the aspirin trial, demonstrating that low-dose aspirin therapy partially attenuates exertional and heat stress-related platelet activation. Compared with pre-exercise levels, plasma endotoxin levels were increased after the exercise; however, these levels were not different between the placebo or aspirin trial. Hemoglobin level before exercise was higher in the placebo trial compared with the aspirin trial ($p = 0.022$); however, there were no differences between groups after exercise. There were no differences in hematocrit level before or after exercise or between trials ($p = 0.749$). Lactate levels after exercise were significantly increased compared with levels obtained before exercise in both drug trials ($p = 0.001$; Table 5). The TNF- α and IL-6 levels were undetectable by immunoassay.

4. Discussion

Fourteen days of low-dose aspirin therapy blunts platelet activation under uncompensable heat stress condition. In this group of young, healthy firefighters, there were no differences in skin blood-flow responses following exertion while wearing thermal-protective clothing after aspirin therapy. Firefighters reached near-maximal heart rates, and their core body and skin temperature exceeded 39.0°C at the end of exertion, which is similar to what our laboratory has reported following live fire exercises [37,38].

Bruning et al [39] reported that core temperature was elevated after passive heat stress and remained elevated following an exercise bout after 7 days of low-dose aspirin. However, there were no differences in the rate of rise in core body temperature or subjective perception of effort between the aspirin and placebo trials. This is in agreement with our results that there were no significant differences in core body temperature, with both groups reaching temperatures above 39.0°C . Bruning et al [39] also reported a reduction in CVC_{max} of approximately 10% and a rightward shift in the threshold for the onset of reflex vasodilation following aspirin therapy. We did not find this to be true in our experiment. This may be due to differences in the mode of exercise (cycle vs. treadmill), higher exercise intensity resulting in higher maximal heart rates and core body temperature during exercise, and uncompensable heat stress conditions in our report.

We speculate that the uncompensable heat stress environment created by thermal-protective clothing and the hot environmental conditions in both treatment trials was the cause of the lack of differences in skin blood-flow response between groups in this study. Encapsulation resulted in significant sweat losses (>1 -kg mass lost) without body cooling, leading to a rise in core body

Table 4
Exercise test results

	Exercise interval (min)	Total distance (km)	Calories expended (kcal)	Metabolic equivalents achieved	Total steps
Placebo	38.6 ± 5.9	4.0 ± 0.7	386.8 ± 94.3	6.2 ± 1.2	$4,267 \pm 908$
Aspirin	36.3 ± 6.9	3.9 ± 0.8	367.3 ± 77.8	4.6 ± 1.8	$4,586 \pm 776$

All values are reported as mean ± standard deviation.

Table 5
Blood markers

Variable	Time point	Placebo	Aspirin	Group (p)	Time (p)	Group × Time (p)
PCT (s)	Baseline	151 ± 71	151 ± 71	0.001	0.005	0.003
	Pre-exercise	151 ± 65	250 ± 74			
	Postexercise	114 ± 24	210 ± 82			
Hb (g/dL)	Pre-exercise	17.2 ± 1.9	16.1 ± 1.5	0.022	0.644	0.219
	Postexercise	16.7 ± 1.4	16.3 ± 1.1			
Hct (%)	Pre-exercise	46.3 ± 3.1	45.3 ± 2.5	0.442	0.227	0.749
	Postexercise	47.0 ± 3.6	46.5 ± 3.7			
La (mmol/L)	Pre-exercise	1.0 ± 0.4	1.0 ± 0.4	0.597	0.001	0.609
	Postexercise	1.5 ± 0.5	1.6 ± 0.8			
Endotoxin (UE/mL)	Baseline	2.5 ± 0.9	2.5 ± 0.9	0.637	0.011	0.835
	Pre-exercise	2.3 ± 0.7	2.1 ± 0.9			
	Postexercise	2.7 ± 0.8	2.7 ± 0.8			

All values are presented as means ± standard deviation.
Hb, hemoglobin; Hct, hematocrit; La, lactate; PCT, platelet closure time.

temperature of >2°C. High core body and skin temperatures (>39°C) coupled with encapsulation likely reduced the evaporative capacity of the skin and further reduced the gradient for heat dissipation between the core, skin, and outside environment. After exercise, both groups only reached approximately 80% of CVC_{max}. Upright exercise in the heat has been previously reported to attenuate skin blood flow as core body temperature approaches 38°C and that at high core body temperature, skin blood-flow levels are not maximal [40–43]. In addition, the reduced blood volume from sweat loss further restricts skin blood flow during exercise in the heat [44,45]. The reduction in skin blood flow in both groups is more likely due to exercise in the uncompensable heat stress environment than the result of the aspirin therapy.

Both dehydration and aspirin have been reported to cause mucosal damage to the gut leading to endotoxin release and subsequent increases in plasma TNF-α levels [23–25,29]. In our study, endotoxin levels increased after the exercise in both the aspirin and placebo trials. However, we do not believe that this is clinically significant or indicative of increased gut permeability following exertion in the heat or related to the administration of aspirin as none of the firefighters reported any adverse symptoms. This is further supported by the nondetectable TNF-α levels in our study.

There are a few limitations to this study. First, our participants were young, healthy, male firefighters. Previous reports showing reductions in skin blood flow were done in middle-aged men and women, primarily aged >55 years [16,17,38]. To determine whether age- or sex-related differences in skin blood-flow responses under uncompensable heat stress conditions following aspirin therapy exist, this study should be repeated with older firefighters. Second, we believe that uncompensable heat stress, rather than aspirin therapy, is the major strain driving thermoregulatory changes during work while wearing thermal-protective clothing. Additional studies of an identical workload under compensable heat stress conditions with and without aspirin therapy would allow us to fully understand the thermoregulatory consequences of both aspirin therapy and work under uncompensable heat stress conditions.

Finally, there is not a reliable system for real-time measurement of skin blood flow during exercise or while working under thermal-protective clothing. Laser Doppler flowmetry is a good measurement of skin blood flow because it is localized and specific to the skin, allows measurements from multiple sites, and has a great deal of agreement with other skin blood-flow measurement instruments [46]. However, it does have its limitations in that it is

highly sensitive to motion and cannot be used during exercise and is unable to measure absolute flow. For this study, skin blood flow was measured at rest before exercise and immediately after exercise, which we feel were adequate time points for this study. In addition, the thermal-protective clothing would have made the placement of the flow probes on the forearms next to impossible during the exercise phase. In this study, skin blood flow was normalized to the values attained during maximal vasodilation, which has been determined to be a valid measurement technique [46,47]. Despite these limitations, we feel that this method was appropriate and accurate for this study.

Aspirin blunts platelet activation during uncompensable heat stress. In this group of young, healthy, male firefighters, there were no differences in skin blood flow following exertion after 14 days of aspirin therapy. We speculate that this may be due to the thermal-protective clothing worn and uncompensable heat stress causing severe thermoregulatory strain that supersedes any deleterious effects of aspirin. These current data suggest that the effect of aspirin on thermoregulation is not sufficient to recommend against its use among firefighters when indicated. However, more research is needed to fully understand the mechanisms related to thermoregulation while wearing thermal-protective clothing during uncompensable heat stress conditions.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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