Journal of Thermal Biology 84 (2019) 266–273

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

Exercise heat acclimation causes post-exercise hypotension and favorable improvements in lipid and immune profiles: A crossover randomized controlled trial

Eric Rivas[a,b,*], Craig G. Crandall[c], Oscar E. Suman[d], Naima Moustaid-Moussa[b,e], Vic Ben-Ezra[f]

[a] Exercise & Thermal Integrative Physiology Laboratory, Department of Kinesiology & Sport Management, Texas Tech University, Lubbock, TX, USA
[b] Obesity Research Institute, Texas Tech University, Lubbock, TX, USA
[c] Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital of Dallas, University of Texas Southwestern Medical Center, Dallas, TX, USA
[d] Department of Surgery, University of Texas Medical Branch Galveston, TX, USA
[e] Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA
[f] Department of Kinesiology, Texas Woman's University, Denton, TX, USA

ARTICLE INFO

Keywords:
Hyperthermia
Blood pressure
Exercise heat therapy
Thermal stress

ABSTRACT

Background: Passive hyperthermic exposure causes an acute hypotensive response following the cessation of heat stress. Chronic heat stress is well documented in animal studies to instigate metabolic and lipid alterations. However, it is unknown if exercise-heat acclimation also causes favorable chronic blood pressure, lipid, and immune responses in humans.

Purpose: This project tested the hypothesis that 10-day exercise-heat acclimation (HA) would cause greater post-exercise reductions in arterial blood pressure and favorable metabolic, lipid, and immune responses compared to 10-day exercise under neutral conditions (CON).

Methods: Thirteen healthy sedentary participants (8M/5F, 28 ± 6y, 78 ± 17 kg), completed a 10-day (90 min/day exercise bout) clamped hyperthermia HA (increase internal temperature 1.5 °C, in 42 °C, 28% R*h*) and control (CON: 23 °C, 42% R*h*) protocols in a counterbalanced design with a 2 month washout. Pre- and post-exercise HA/CON blood pressures were taken 1-h post-exercise on exercise days 1 and 10. Metabolic, lipid and immune panels were taken pre-post HA/CON.

Results: Exercise under heat stress had greater post-exercise hypotension (systolic; -6 mmHg, diastolic; -8 mmHg; and mean arterial pressure; -7 mmHg) on both days 1 and 10 compared to exercise under neutral conditions (main effect for condition, $P \leq 0.004$). Only from pre-to-post HA, total cholesterol (168 ± 19 to 157 ± 15; $P < 0.03$) and triglycerides (137 ± 45 to 111 ± 30; $P < 0.03$) were reduced, while absolute lymphocytes (−26%), monocytes (−22%), and basophils (−49%) significantly decreased (each $P \leq 0.04$). Relative values of neutrophils increased (18%) and lymphocytes decreased (−20%) only after HA ($P \leq 0.04$).

Conclusion: These data indicate that exercise in the heat (regardless of acclimation status) causes a profound post-exercise hypotensive response, while HA causes favorable lipid, and immune profile changes. Further examination of exercise-heat acclimation on vascular, metabolic, and immune responses will offer insight for benefits in other clinical populations with vascular, metabolic and immune dysfunction.

1. Introduction

Post-exercise hypotension (PEH) is a well-documented response following an acute bout of exercise (Kenney and Seals, 1993). Notably, PEH is characterized as reduced systolic and/or diastolic arterial blood pressure below resting pre-exercise values after a one session of exercise that is commonly reported in young and middle-aged normotensive, borderline hypertension, and patients with established essential hypertension (Halliwill et al., 2013; Kenney and Seals, 1993). Most importantly, post-exercise hypotension can persist upwards to 13 h post-exercise (Kenney and Seals, 1993). Passive heat stress may be beneficial similar to exercise for improving vascular endothelial function (Green et al., 2010; Naylor et al., 2011). Mechanistically, both exercise and passive heat exposure cause hemodynamic alterations of cyclical strain that increase shear stress on the vessel wall distention (by transmural pressure) and increase blood flow induced frictional force

* Corresponding author. Texas Tech University, Lubbock, TX, USA.
E-mail address: eric.rivas@ttu.edu (E. Rivas).

https://doi.org/10.1016/j.jtherbio.2019.07.017
Received 24 May 2019; Received in revised form 17 June 2019; Accepted 11 July 2019
Available online 13 July 2019
0306-4565/

(Ballermann et al., 1998). This blood flow induces stress on the vessel and activates signal transduction in endothelial cells that release nitric oxide and prostacyclin (Ballermann et al., 1998).

Under resting passive conditions, while exposed to heat stress causes severe cardiovascular strain for the purpose of thermoregulation adjustments (Wilson and Crandall, 2011). In addition, the accompanying redistribution of blood flow directed to the skin also causes profound augmented vasodilation via shear stress and endothelial function in the micro and microvasculature. (Green et al., 2010; Markos et al., 2013; Naylor et al., 2011; Thijssen et al., 2011; Tinken et al., 2010). Thus, hyperthermia exposures may provide a novel use for improving cardiovascular health. Consistent with that hypothesis, we and others report cardiovascular benefits of passive heat exposure (Hooper, 1999; Rivas et al., 2016b). Via hot water immersion, also term "heat therapy," offer vascular health benefits of increased blood flow (Song, 1984) that are found in healthy (Becker, 2009; Nagasawa et al., 2001), cardiovascular disease populations such as hypertension, heart failure, coronary artery disease, and aging (Allison et al., 1993; Gruner Svealv et al., 2009; Shin et al., 2003; Ueno et al., 2005). We previously reported that during whole body hot water immersion, for each 1 °C increase in body temperature, mean arterial pressure was reduced by 9 ± 6 mmHg in adults with type 2 diabetes and 11 ± 7 mmHg in non-diabetics that were primarily affected by a reduction in diastolic blood pressure (1 °C reduced diastolic blood pressure by 14 ± 7 and 17 ± 10 mmHg) (Rivas et al., 2016a).

Exercise also improves metabolic and immune function. The immune system's complex role as the defense system of the human body detects and protects against a wide variety of known pathogens and diseases. Chronic low-grade inflammation is a significant contributor to macrophage infiltration in obese insulin-resistant populations (Qatanani and Lazar, 2007; Weisberg et al., 2003). This unbalanced-proinflammatory state is likely initiated by other dysregulated organs caused by either obesity-induced lipotoxicity and/or impaired hormonal regulation of uncontrolled glycemia (Han et al., 2013; Harford et al., 2011). Notably, exercise can cause hormonal responses that play key roles in growth, development, functional adaptation, immunity, and metabolism. Dependent on exercise intensity, an acute inflammatory response initiates cellular and molecular events that lead to repair, rejuvenation, and remodeling. In fact, exercise induces an anti-inflammatory effect that can reduce pro-inflammatory cytokines in populations with low-grade inflammation such as obesity and diabetes (Belotto et al., 2010; Gielen et al., 2003; Petersen and Pedersen, 2006; Teixeira de Lemos et al., 2009). Passive heat exposure, or exercise combined with heat stress on immune function, has not been extensively studied. However, heat exposures during exercise increases catecholamines and cortisol responses (Jimenez et al., 2007; Starkie et al., 2005) and attenuate the inflammatory response in vitro and in vivo (Brenner et al., 1997, 1998; Cross et al., 1996; Starkie et al., 2005).

Given the reported independent benefits of heat therapy and exercise on blood pressure and immune profiles, the combination of both stimuli may offer a synergistic benefit. No human randomized controlled trials have investigated the influence of exercise-heat acclimation on post-exercise hypotension, metabolic, lipid and immune profiles. Thus, the purpose of this study was to investigate an acute and post 10-day exercise-heat acclimation in comparison to exercise under neutral conditions on post-exercise blood pressure, metabolic, lipid, and immune changes.

2. Material and methods

2.1. Participants

Thirteen healthy sedentary participants (8M/5F, 28 ± 6y, 77.9 ± 17 kg) completed this study. The subject characteristics are presented in Table 1. Exclusion criteria included known cardiovascular or metabolic diseases or taking medications known to affect the cardiovascular system and/or heat dissipation. Females completed all exercise trials during the start of the early follicular phase. Prescreening was obtained after informed written consent, that included a health and physical activity readiness questionnaire (PAR-Q, (Pescatello and American College of Sports Medicine, 2014)), and weight and height assessments. Following the consent, a familiarization was provided of all experimental procedures. No participants were involved in an exercise training program, nor were they heat acclimated prior to testing. Each subject maintained their sedentary activity levels while enrolled throughout the study. Texas Woman's University Institutional Review Board approved this study. This study was in agreement with the *Declaration of Helsinki*.

2.2. Experimental design

The study design was a randomized controlled repeated measures counterbalanced design. See Fig. 1 for the study design. We have previously published this study design protocol (Rivas et al., 2017). This data was obtained concurrently from that project. Briefly, the 10-day (90 min/day exercise bout) hyperthermia clamp-controlled heat acclimation (HA) protocol and the control (CON) protocol entailed having participants exercise at identical external work rates on day one and ten. On days two through nine, external work rate was increased to maintain a 1.5 °C increase in internal body temperature. Participants were euhydrated (confirmed via urine specific gravity: 1.015 ± 0.008) prior to exercise on each study day. Participants refrained from exercise, alcohol or caffeine 48 h prior to each visit. Participants fasted 10–12 h prior to day 1 and 10 visits. Once instrumented, participants rested in a supine position for 30 min and resting baseline heart rate, core and mean skin temperatures, and blood pressure was recorded. The environmental ambient temperature was set to 42 °C, 28% relative humidity R*h* (HA) or a thermoneutral environment of 23 °C, 42% R*h* (CON). Participants were told to wear similar clothing and shoes each day. Following 90 min of walking exercise on a treadmill, participants dried off, we recorded nude body weight, and then rested in supine position for 1-h for the post-exercise measurements of blood pressure, skin, internal, and mean body temperatures. Water intake was provided ad libitum during exercise for all visits.

2.3. Instrumentation and physiological measurements

Weight (Tanita, Arlington Heights, IL), body composition (DXA, General Electric, Lunar Prodigy Promo, Madison, WI), and exercise capacity (VO_2peak) were obtained prior to day 1 and after day 10 exercise for each condition. Internal body temperature was measured via a rectal thermistor. Participants inserted a general-purpose rectal thermocouple (Mon-a-therm, Mallinckrodt Medical, Inc., St. Louis, MO, USA) ~10 cm past the anal sphincter. Mean skin temperature was measured with thermocouples (Omega Engineering, Stamford, CT) and taped (Transpore, 3M Health Care, Neuss, Germany) on the right side of the body. The calculation for mean skin temperature used a weighted coefficient from six sites (chest, shoulder, lower back, abdomen, thigh, and calf) (Taylor et al., 1984). Calibration of thermocouples used a standard thermometer in a water bath. A standard 12-lead ECG (Quinton Q-Stress System, Cardiac Science, Waukesha, WI) recorded heart rate. Arterial blood pressure was obtained on the left arm (brachial) at heart level with an automated auscultation electrosphygmomanometry (Tango+, SunTech, Raleigh, NC, USA) using standard measurement techniques (2–3 measures taken with 1 min interval) used by the American Heart Association (Pickering et al., 2005). The calculation of mean arterial pressure was [diastolic + 1/3(systolic-diastolic)].

2.4. Peak exercise capacity test

Maximal oxygen consumption (VO_2peak) was determined by a

Table 1
Descriptive characteristics of the participants for pre and post conditions.

	PreHA	PostHA	PreCON	PostCON	ANOVA
Weight (kg)	78 ± 15.5	77.6 ± 15.2	77.4 ± 15.2	76.6 ± 15.1	0.06
Body surface area (m^2)	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	0.49
Body mass index	27.5 ± 4.6	27.4 ± 4.5	27.3 ± 4.5	27.0 ± 4.5*	**0.04**
Fat mass (kg)	25.5 ± 9.7	25.0 ± 9.2	24.7 ± 9.6	24.6 ± 9.4+	**0.02**
Lean mass (kg)	50.6 ± 10.9	50.6 ± 10.9	50.4 ± 10.6	50.1 ± 10.8	0.44
Body fat (%)	33.3 ± 8.7	32.9 ± 8.4	32.5 ± 8.7	32.7 ± 8.7	0.09
Gynoid fat (kg)	16.2 ± 4.8	15.8 ± 4.4	16.0 ± 5.0	15.6 ± 4.4	0.41
Android fat (kg)	17.2 ± 4.8	17.1 ± 4.8	16.6 ± 4.8	16.7 ± 5.2	0.06

Results are expressed as means ± SD. * indicates statistical difference from pre-HA, + indicates statistical difference from postHA.

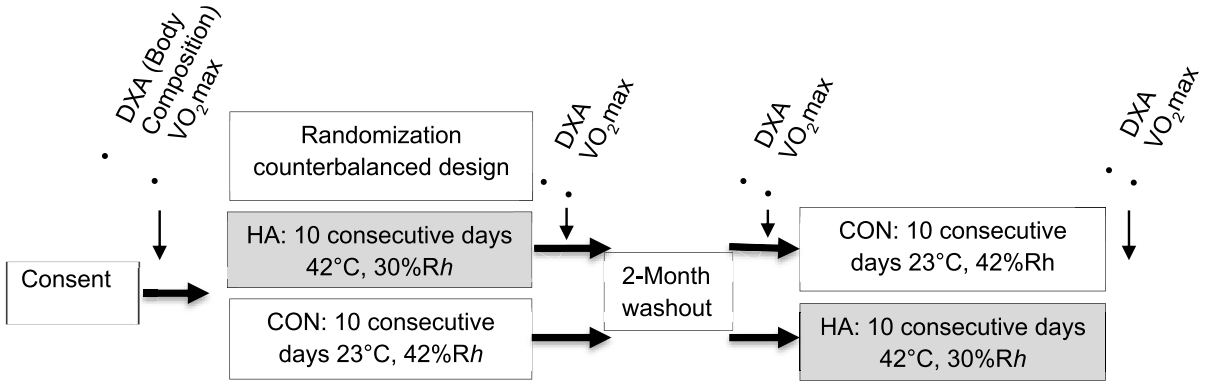

Fig. 1. Randomize control repeated measures study design. Fasting blood sample for metabolic, lipid and immune profiles obtained on days 1 and 10 prior to the acute exercise bout on those days. Pre- and post-exercise blood pressures were obtained after 30 min of quiet rest both before exercise and post-exercise, with measurements obtained for 60 min thereafter.

progressive, incremental graded treadmill (Quinton ST 65 Treadmill, Quinton Instruments Company, Bothell, WA.) exercise stress test to volitional exhaustion. The test was administered one week prior to and one day after the 10 days of exercise-heat acclimation and control protocols to confirm fitness did not change. The protocol entailed at an initial speed of 3.5 mph and 8% grade, which then increased by 1 mph and a 2% grade every 3 min until volitional fatigue. Respiratory O2 and CO2 gas and air flow were calibrated prior to use (known gases and a 3-L syringe) using the ParvoMedics Truemax 2400 metabolic cart (Consentius Technologies, Sandy, UT). Perceived exertion was recorded using a standard scale (RPE, Borg scale 6–20). A 12-lead electrocardiography (EKG) (Quinton Q-Stress System, Cardiac Science, Waukesha, WI) recorded heart rate and rhythm. The criteria for maximal exertion was determined if three of the following were observed: once participant signaled to stop exercise due to volitional fatigue, blood capillary finger-prick lactate samples (Lactate Scout, SensLab GmbH, Germany) greater than 8 Mm, a respiratory exchange ratio (RER) of ≥1.10, a leveling off in VO_2 with increasing workloads, exercise heart rate that was within 10 beats of the age-predicted maximal heart rate (220-age). All participants met three of the listed criteria. (Howley et al., 1995).

2.5. Perceptual and strain index measurements

Subjective thermal perception utilized the 13-point McGinnis categorical scale in which 1 “so cold I am helpless,” 7 as “comfortable” and 13 as “so hot I am sick and nauseated” and have previously been validated (Lee et al., 2010). Perceived exercise exertion used the standard Borg's ratings of perceived exertion (RPE) (from 6 to 20). For all scales, participants were shown the scales and asked to report a number that best represented his/her whole-body thermal sensation or exertion at that time.

2.6. Blood sampling

Participants rested in a supine position followed by placement of a catheter in an antecubital vein. A catheter was used to measure blood samples pre, during, and post. Venous blood samples were collected in K2-EDTA and sodium heparin treated vacutainer tubes and immediately centrifuged (3000g, 10 min, 10 °C). Plasma samples were aliquoted into a 5 mL plastic screw-cap vials. Whole blood and plasma samples were placed on ice packs and analyzed by Quest Diagnostics Testing Services in Denton TX for metabolic, lipid, and immune profiles.

2.7. Statistical analysis

Pre and post HA/CON peak exercise test and participant characteristics were analyzed using a one-way repeated measures analysis of variance. Pre-HA/CON resting blood pressure, metabolic, lipid and immune profiles and the change from pre to post were analyzed using a dependent *t*-test. Thermal variables were analyzed by a two-way repeated measures design for interactions (Condition [HA/CON] x Day [day1/day10]) and main effects. The recovery thermal, and heart rate, from postHA and postCON, were analyzed using a three-way repeated measures analysis of variance (Condition [HA/CON] x Day [Day1/Day10] x Time [minute]) and main effects. Blood pressure was measured every 10 min with means of 2–3 measures over 60 min of recovery. A trapezoidal model for the incremental area under the curve was used to analyze the total 60 min during recovery for change in blood pressure (systolic, diastolic and mean arterial pressures) and analyzed with a two-way repeated measures analysis of variance (Condition [HA/CON] x Day [day1/day10]) and main effects. The description for each analysis is as follows: Condition is HA and CON; Time is each 10-min post exercise; and Day is day 1 and day 10. preHA/CON is day 1, postHA/CON is day 10. For each ANOVA analysis where appropriate, utilized the *post hoc Holm-Sidak's multiple* comparison test and

Greenhouse-Geisser corrections for violations of sphericity. Data were analyzed by GraphPad statistical software (Prism for Windows 64-bit, version 8.0.2, San Diego, CA, USA) with significance set at $P < 0.05$. All data reported as mean ± SD.

3. Results

3.1. Exercise-heat acclimation did not change body composition or peak exercise characteristics

Participant characteristics are presented in Table 1. HA or CON exercise did not change body composition. PostCON was different than PostHA for body mass index and fat mass ($P < 0.05$). HA or CON did not change peak VO_2 or any characteristic for this exercise capacity test ($P < 0.05$). The change in pre-post fluid loss was not different between pre to post conditions (HA day1: 0.7 ± 1.4%; HA day10: 0.5 ± 0.8%; CON day1: 0.5 ± 0.8%; CON day10: 0.0 ± 0.4%; $P > 0.5$).

3.2. Exercise-heat acclimation did not change resting blood pressures but changed lipid and immune markers

The comparison for blood pressure, metabolic, lipid, immune characteristics during preHA/CON-condition and pre-to-post changes after HA and CON on days 1 and 10 are presented in Table 2. During preHA/CON trials, absolute values were similar for blood pressure, metabolic, lipid and immune profiles. Only pre-to-post HA changes resulted in reductions in cholesterol, triglycerides, white blood cell count, hemoglobin, and hematocrit (each $P \leq 0.03$). HA also resulted in reductions in immune markers (absolute lymphocytes, monocytes, neutrophils, basophils, and relative values of neutrophils, lymphocytes, and basophils; $P \leq 0.04$).

3.3. Exercise-heat acclimation during exercise lowered final internal and mean body temperatures and heart rate responses

The pre-to-post heat acclimation responses from internal, mean skin, and mean body temperature, heart rate, and thermal perception are presented in Fig. 2. Mean skin temperature was greater during HA than CON (Main Effect for Condition, $P < 0.0001$). Internal and mean body temperatures were lower at day 10 HA, (Condition × Day Interaction, $P = 0.008$). HA reduced heart rate on day 10 compared to day 1 (Condition × Day Interaction, $P = 0.005$). Thermal perception was greater during HA compared to CON (Main Effect for Condition, $P < 0.0001$) and was reduced on day 10 of both conditions (Main Effect for Day, $P < 0.01$).

3.4. The recovery from HA and CON condition were different for internal body temperature and heart rate

Mean skin, internal body, and mean body temperatures, and heart rate responses pre/postHA and pre/postCON conditions are presented in Fig. 3. Mean skin, internal body and mean temperatures during recovery in CON was different than other HA conditions (Day × Time Interaction, $P < 0.001$). Similarly, the internal temperature was reduced compared to the preHA condition (Condition × Time Interaction, $P < 0.0001$). Heart rate recovery was lower in the pre and postCON compared to the preHA condition and slightly attenuated during the postHA condition (Condition × Time Interactions, $P < 0.0001$).

3.5. Post-exercise hypotension is greater after HA compared to CON exercise

The change and area under the curve blood pressure response post HA and CON conditions are reported in Fig. 4. Systolic blood pressure was attenuated after one bout and ten consecutive days of exercise during HA and CON conditions (Condition x Day × Time Interaction, $P = 0.046$). The magnitude of post-exercise hypotension for systolic was greater after Day 10 HA compared to Day 1 CON (minute 20–60). The examined area under the curve changes found both days 1 and 10 HA to be greater than CON days 1 and 10 (Main Effect for Condition, $P \leq 0.03$). Similarly, diastolic and mean arterial pressures were reduced after one and ten bouts of consecutive HA and CON exercise (Time × Condition Interaction, $P \leq 0.025$). Days 1 and 10 HA were both lower across 60 min recover compared to day 1 CON ($P \leq 0.001$). The magnitude of change in AUC blood pressure was greater after HA compared to CON exercise (Main Effect for Condition, $P \leq 0.004$).

Table 2
Blood pressure, metabolic, and immune panel prior to each HA and CON (PreHA/CON) conditions and the changes from pre to post HA/CON conditions.

	PreHA	PreCON	*P* value	Δ pre-postHA	*P* value	Δ pre-postCON	*P* value
Systolic blood pressure (mmHg)	115.7 ± 8.7	112.6 ± 6.3	0.17	−0.6 ± 7.2	0.78	1.7 ± 4.7	0.22
Diastolic blood pressure (mmHg)	72.1 ± 7.7	68.9 ± 6.8	0.10	−1.8 ± 5.9	0.29	2.7 ± 4.9	0.07
Mean arterial pressure (mmHg)	86.6 ± 7.6	83.5 ± 5.9	0.10	−1.4 ± 5.8	0.40	2.4 ± 4.6	0.09
Cholesterol Total (mg/dL)	161.4 ± 22.1	168.4 ± 30.7	0.08	−40.4 ± 57.8	**0.03**	4.7 ± 20.6	0.21
HDL Cholesterol (mg/dL)	48.4 ± 13.7	47.7 ± 15.2	0.35	−12.6 ± 24.0	0.38	−0.6 ± 3.0	0.20
Triglycerides (mg/dL)	124.5 ± 50.4	131.6 ± 77.6	0.31	−39.0 ± 47.3	**0.03**	−4.8 ± 59.9	0.44
LDL Cholesterol (mg/dL)	88.1 ± 22.2	94.3 ± 31.2	0.11	−20.2 ± 32.5	0.19	6.3 ± 20.4	0.22
Glucose (mg/dL)	86.4 ± 6.0	89.3 ± 6.4	0.11	−23.2 ± 42.9	0.22	−22 ± 5.2	0.20
HBA 1C (% of total Hgb)	5.4 ± 0.3	5.7 ± 0.8	0.10	−0.9 ± 0.13	0.13	0.3 ± 0.8	0.09
White blood cell count (Thousand/uL)	6.8 ± 1.1	7.1 ± 1.5	0.22	−0.27 ± 1.9	0.38	0.7 ± 1.6	0.11
Red blood cell count (M illion/uL)	4.6 ± 0.5	5.6 ± 3.1	0.13	−0.6 ± 1.1	**0.00**	1.36 ± 3.3	0.12
Hemoglobin (g/dL)	15.3 ± 7.2	16.3 ± 9.0	0.38	−1.8 ± 3.6	**0.00**	3.4 ± 8.6	0.09
Hematocrit (%)	43.8 ± 14.7	44.4 ± 13.1	0.46	−5.2 ± 10.4	**0.00**	8.6 ± 12.9	0.09
Platlet count (Thousand/uL)	239.5 ± 52.0	308.4 ± 208.2	0.15	−34.0 ± 70.7	0.07	89.7 ± 237.4	0.11
Abs Neutrophils (cells/uL)	3526.5 ± 470.1	3929.2 ± 923	0.10	154.5 ± 460.9	0.16	356.8 ± 1111.7	0.21
Abs Lymphocytes (cells/uL)	2970 ± 356.6	2556.9 ± 783.4	0.12	−759.8 ± 549.7	**0.01**	363.6 ± 526.8	0.17
Abs Monocytes (cells/uL)	519.3 ± 89.3	560.4 ± 170.5	0.23	−114.7 ± 130.1	**0.03**	118.2 ± 125.5	0.14
Abs Eosinophils (cells/uL)	176 ± 98.5	1829 ± 113.9	0.41	17.8 ± 59.2	0.23	−90.7 ± 126.2	0.17
Abs Basophils (cells/uL)	33.3 ± 17.5	31.6 ± 9.5	0.40	−13.8 ± 17.9	**0.04**	11.04 ± 6.3	0.19
Neutrophils (%)	48.6 ± 3.7	524 ± 4.7	0.05	9.0 ± 6.5	**0.01**	−1.6 ± 5.6	0.40
Lymphocytes (%)	41.1 ± 4.0	33.8 ± 5.1	**0.01**	−8.3 ± 5.3	**0.00**	−1.6 ± 4.4	0.30
Monocytes (%)	7.4 ± 1.6	7.5 ± 1.7	0.42	−1.0 ± 1.6	0.07	−0.4 ± 0.9	0.23
Eosinophils (%)	26 ± 1.6	24 ± 1.3	0.37	0.5 ± 0.7	0.06	−20 ± 1.6	0.13
Basophils (%)	0.5 ± 0.2	0.3 ± 0.2	0.16	−0.8 ± 0.3	0.06	−0.13 ± 0.1	0.17

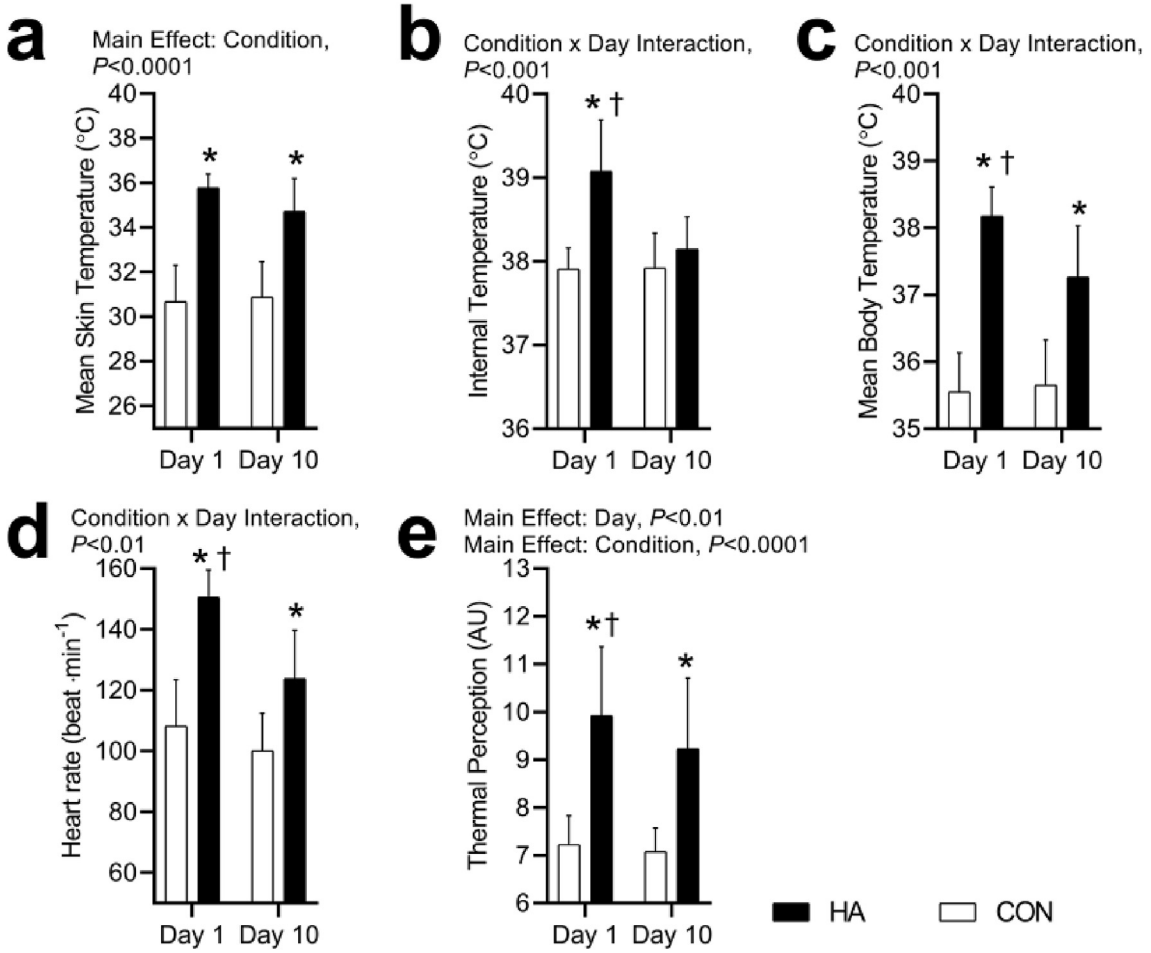

Fig. 2. End of exercise pre and post heat acclimation (HA, black bar) and control (CON, open bar) for mean skin temperature (a), internal body temperature (b), mean body temperature (c), heart rate (d), and thermal perception (e). * indicates statistical difference between HA and CON; † indicates statistical difference on Day 1 HA vs Day 10 HA and Day 10 CON. Results are expressed as means ± SD.

4. Discussion

To our knowledge, this is the first study to utilize randomized controlled repeated measures cross-over design to examine the effect of a hyperthermia clamp HA and compared work matched CON conditions on post-exercise hypotension. The main finding of this study suggests that exercise in the HA protocol caused a robust reduction in acute blood pressure (1-h post-exercise) after both a single session and ten consecutive days of HA in young healthy adults. However, the chronic effect (10 days of repeated heat-exposure) did not last longer than 24 h, as resting blood pressures were not different during the morning before exercise of days 1 from 10. The second major finding was that HA caused significant reductions in lipid, and immune profiles whereas CON conditions did not.

We are the first to report reductions in cholesterol and triglycerides from exercise HA. Exercise alters acute and chronic plasma lipid and lipoprotein concentrations, while triglyceride reductions from exercise after eating a meal is reported to occur acutely and the exercise lowering cholesterol effect occurs by chronic exercise training (Halverstadt et al., 2007; Haskell, 1984). The beneficial effects of exercise training also involve fat mass reduction that can improve lipid profiles (Nordmann et al., 2006). We found no changes in body composition and likewise no lipid profile changes after 10 days of exercise in the CON condition. Similarly, fat mass was not reduced after HA; however, lipid profiles were improved, suggesting that heat exposure played a role. Others have reported an increase in free fatty acids after a single and repeated bouts of passive heat exposures in healthy young individuals (Lee and Kim, 2014, 2015) which may suggest an increase in hyperthermia-induced lipolysis. Recently, it was reported that passive heat exposure (42 °C) at rest for 120 min and during exercise for 30 min increased non-esterified fatty acid concentrations (O'Hearn et al., 2016). Low-intensity exercise during hot exposures may offer a novel approach to improve lipid profiles and improve cardiovascular risk factors in populations at risk for cardiovascular disease.

Heat exposures during exercise alter catecholamines and cortisol responses (Starkie et al., 2005), which may play a major role in the immune response to exercise-heat stress (Jimenez et al., 2007). Further, the combination of heat stress while exercising attenuates the release of hormones, cytokines, leukocytes and inflammatory proteins such as TNFα and IL-1α (Brenner et al., 1997, 1998; Starkie et al., 2005). Cross et al. (1996) first reported that endurance exercise at 65% VO_2peak in 39 °C conditions increased leukocytes originating from both exercise and increases in body temperature (Cross et al., 1996). The immune changes post HA are in agreement with Brenner et al. (1998) and Starkie et al. (2005), as we found an attenuation in absolute lymphocytes, monocytes, and basophils in addition to reductions in relative lymphocytes after HA. In populations having diseases such as cardiovascular disease and obesity, where low-grade inflammation plays a major role in the etiology of the disease (Maurizi et al., 2018), low-intensity exercise heat exposure may reduce immune cell activation and inflammatory profiles.

Much of the thermoregulatory and cardiovascular adaptations of HA occur after 5–8 days of heat exposure while full acclimation is obtained after 14 days (Armstrong and Maresh, 1991; Pandolf, 1979). Our

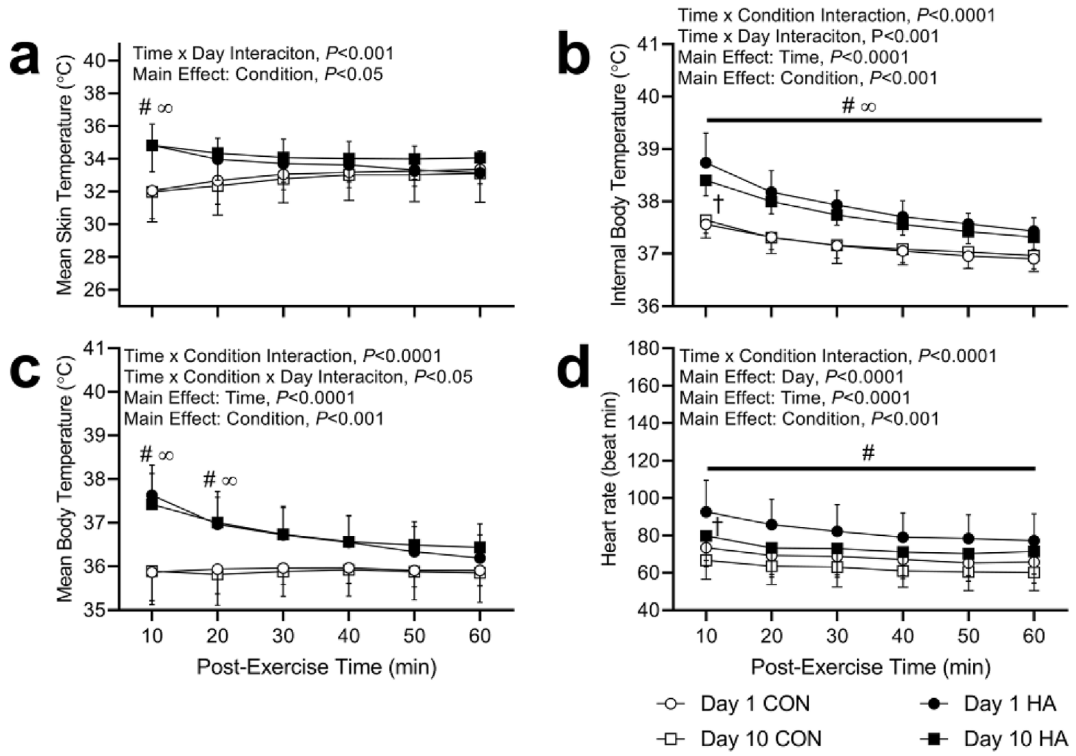

Fig. 3. Mean skin temperature (a), internal body temperature (b), mean body temperature (c), heart rate (d) during recovery from pre (circle) and post (box) heat acclimation (HA, black) and control (CON, open) conditions. # indicates statistically difference between Day 1 HA vs Day 1 CON; ∞ indicates statistical difference between Day 10 HA vs Day 1 CON; † indicates statistical difference on Day 1 HA vs Day 10 HA. Results are expressed as means ± SD.

hyperthermia clamp exercise protocol reduced internal body and mean body temperatures and heart rate on the final day of exercise HA. Passive and exercise heat exposures cause an increase in cardiac output via elevations in heart rate, a slight increase in stroke volume and reductions in central venous pressure (Rowell et al., 1969; Weston et al., 1987). A decreased systolic and diastolic pressure has also been found during whole body passive heat stress (> 1.0 °C) which results in cutaneous vasodilation for heat dissipation (Craig and Dvorak, 1966; Crandall et al., 2008). Passive heat therapy improves vascular endothelial function (measured by flow-mediated dilation techniques) via shear stress mechanisms (Green et al., 2010; Naylor et al., 2011), mitochondrial biogenesis (cell cultures) (Liu and Brooks, 2012) and myocardial function (in rats) (Donnelly et al., 1992; Gowda et al., 1998). Our previous work showed that one session of hot water immersion (i.e., heat therapy) reduced post-heat therapy arterial pressure by 15–19% in adults with type 2 diabetes (Rivas et al., 2016a, 2016b). In humans, two weeks of sauna therapy (60 °C for 15 min) altered endothelial function and reduced body weight, blood pressure, and fasting plasma glucose in patients with obesity and hypertension (Biro et al., 2003). We report in this study that a 10-day HA caused similar post-exercise hypotension responses including both after a single and after 10 days of heat exposure compared to CON thermoneutral exercise. However, note that even exercising in neutral conditions increases internal body temperature by ~0.8 °C above baseline and that may contribute to the post-exercise cardiovascular benefits. Another human pilot study of 30 min hot tub therapy for 3 weeks significantly decreased fasting plasma glucose and glycosylated hemoglobin levels in adults with type 2 diabetes (Hooper, 1999). In addition, we reported that this may be due to upregulation of intracellular heat shock proteins that are involved with improving insulin signaling in type 2 diabetes animal models, see review (Hooper et al., 2014). In this review we highlight the role of heat shock proteins mediating the improvments in insulin signaling in diabetes. We add to this literature that possibly the immune system itself may mediate the beneficial effects of improving glucose and lipid metabolism; however, this requires further understanding. Notably, we had one adult with obesity and type 2 diabetes (fasting glucose value of 343 mg/dL, HbA1c of 12.7%) also complete the 10-day HA and CON protocol and we found post HA a 1.2% reduction in his HbA1c, reduced fasting glucose, and total and LDL-cholesterol (data not reported). This is clinically relevant, as less than 1% reduction in A1c reduces cardiovascular risk by 45% (Eeg-Olofsson et al., 2010). Further work should examine low-intensity exercise HA protocols in clinical populations.

A limitation of this study is the confounding influence of plasma volume changes that are associated with HA. Calculations of plasma changes are commonly used by the Dill and Costill calculations, however, this is utilized after acute dehydration protocols (Dill and Costill, 1974) and may not be appropriate after chronic exercise training and a positive increase in plasma volume.

5. Conclusions

In conclusion, our findings suggest one bout of low intensity exercise heat exposure and HA exercise results in greater hypotensive responses compared to work matched in CON conditions. We also found beneficial changes in lipid and immune profiles. The lack of chronic reductions in blood pressure may be due to the study population being healthy young adults. The alterations via immune response may provide mechanistic insight into improvements in populations with metabolic dysfunction. Further study should examine low-intensity exercise HA as a therapy in populations with cardiovascular disease.

Conflicts of interest

The authors declare that they have no conflict of interest.

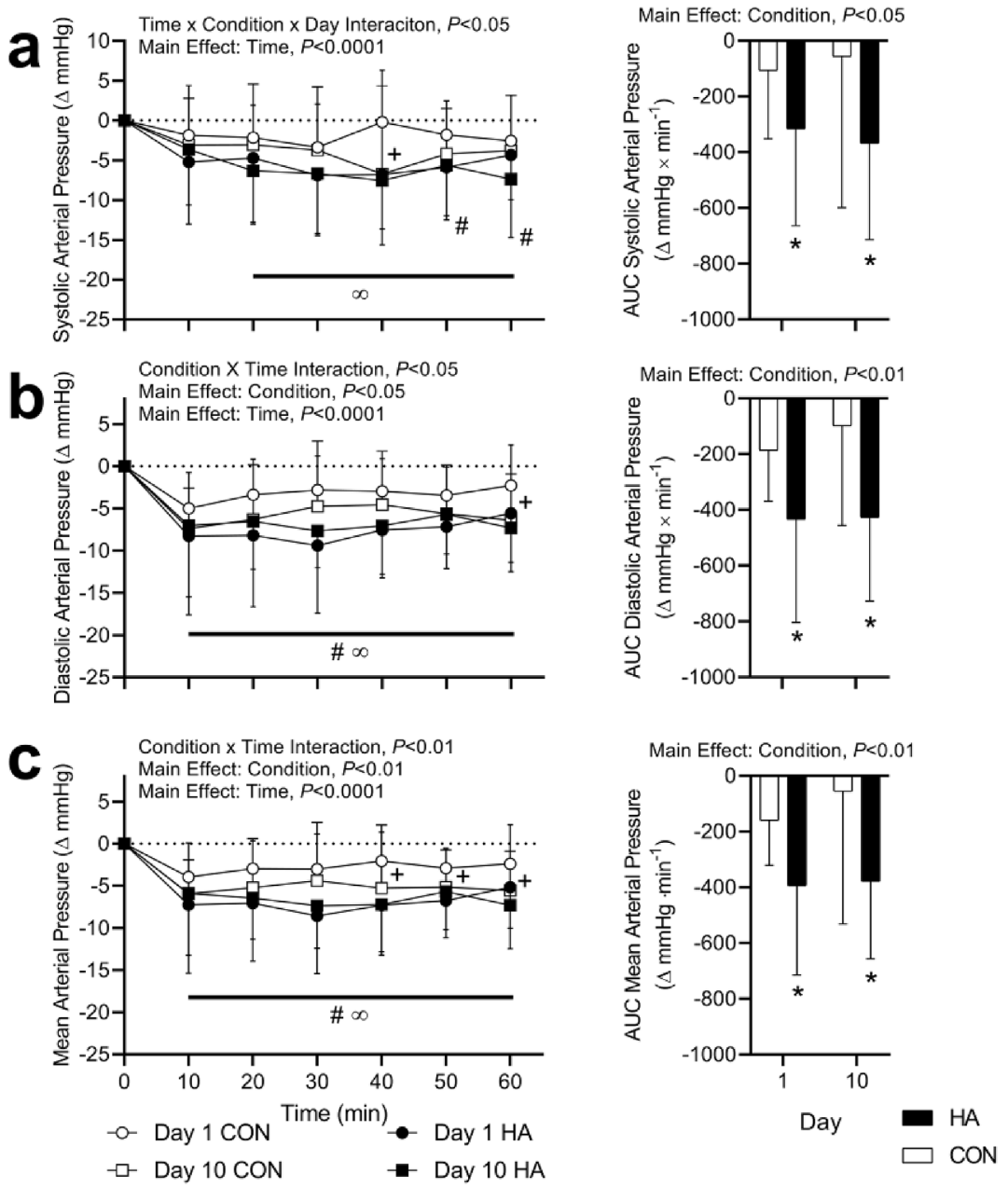

Fig. 4. Post-exercise systolic (a), diastolic (b), mean (c) arterial blood pressures during recovery from pre (circle) and post (box) heat acclimation (HA, black) and control (CON, open) conditions. # indicates statistically difference between Day 1 HA vs Day 1 CON; ∞ indicates statistical difference between Day 10 HA vs Day 1 CON; + indicates statistically difference between Day 10 CON vs Day 1 CON. Area under the curve (AUC) for each are to the right of each, * indicates statistical difference between HA and CON. Results are expressed as means ± SD.

Acknowledgments

The authors acknowledge the financial support from The American Heart Association Predoctoral Fellowship, SouthWest Affiliate, United States and the National Swimming Pool Foundation, United States, Grants to E.R.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtherbio.2019.07.017.

References

Allison, T.G., Miller, T.D., Squires, R.W., Gau, G.T., 1993. Cardiovascular responses to immersion in a hot tub in comparison with exercise in male subjects with coronary artery disease. Mayo Clin. Proc. 68, 19–25.

Armstrong, L.E., Maresh, C.M., 1991. The induction and decay of heat acclimatisation in trained athletes. Sport. Med. 12, 302–312.

Ballermann, B.J., Dardik, A., Eng, E., Liu, A., 1998. Shear stress and the endothelium. Kidney Int. Supplement 67, S100–S108.

Becker, B.E., 2009. Aquatic therapy: Scientific foundations and clinical rehabilitation applications. PM & R : J. Inj. Funct. Rehabil. 1, 859–872.

Belotto, M.F., Magdalon, J., Rodrigues, H.G., Vinolo, M.A., Curi, R., Pithon-Curi, T.C., Hatanaka, E., 2010. Moderate exercise improves leucocyte function and decreases inflammation in diabetes. Clin. Exp. Immunol. 162, 237–243.

Biro, S., Masuda, A., Kihara, T., Tei, C., 2003. Clinical implications of thermal therapy in lifestyle-related diseases. Exp. Biol. Med. 228, 1245–1249.

Brenner, I., Shek, P.N., Zamecnik, J., Shephard, R.J., 1998. Stress hormones and the immunological responses to heat and exercise. Int. J. Sports Med. 19, 130–143.

Brenner, I.K., Zamecnik, J., Shek, P.N., Shephard, R.J., 1997. The impact of heat exposure and repeated exercise on circulating stress hormones. Eur. J. Appl. Physiol. Occup. Physiol. 76, 445–454.

Craig Jr., A.B., Dvorak, M., 1966. Thermal regulation during water immersion. J. Appl.

Physiol. 21, 1577–1585.
Crandall, C.G., Wilson, T.E., Marving, J., Vogelsang, T.W., Kjaer, A., Hesse, B., Secher, N.H., 2008. Effects of passive heating on central blood volume and ventricular dimensions in humans. J. Physiol. 586, 293–301.
Cross, M.C., Radomski, M.W., VanHelder, W.P., Rhind, S.G., Shephard, R.J., 1996. Endurance exercise with and without a thermal clamp: Effects on leukocytes and leukocyte subsets. J. Appl. Physiol. 81 (1985), 822–829.
Dill, D.B., Costill, D.L., 1974. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. J. Appl. Physiol. 37, 247–248.
Donnelly, T.J., Sievers, R.E., Vissern, F.L., Welch, W.J., Wolfe, C.L., 1992. Heat shock protein induction in rat hearts. A role for improved myocardial salvage after ischemia and reperfusion? Circulation 85, 769–778.
Eeg-Olofsson, K., Cederholm, J., Nilsson, P.M., Zethelius, B., Svensson, A.M., Gudbjornsdottir, S., Eliasson, B., 2010. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: An observational study from the Swedish National Diabetes Register (NDR). J. Intern. Med. 268, 471–482.
Gielen, S., Adams, V., Mobius-Winkler, S., Linke, A., Erbs, S., Yu, J., Kempf, W., Schubert, A., Schuler, G., Hambrecht, R., 2003. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J. Am. Coll. Cardiol. 42, 861–868.
Gowda, A., Yang, C.J., Asimakis, G.K., Ruef, J., Rastegar, S., Runge, M.S., Motamedi, M., 1998. Cardioprotection by local heating: Improved myocardial salvage after ischemia and reperfusion. Ann. Thorac. Surg. 65, 1241–1247.
Green, D.J., Carter, H.H., Fitzsimons, M.G., Cable, N.T., Thijssen, D.H., Naylor, L.H., 2010. Obligatory role of hyperaemia and shear stress in microvascular adaptation to repeated heating in humans. J. Physiol. 588, 1571–1577.
Gruner Svealv, B., Cider, A., Tang, M.S., Angwald, E., Kardassis, D., Andersson, B., 2009. Benefit of warm water immersion on biventricular function in patients with chronic heart failure. Cardiovasc. Ultrasound 7, 33.
Halliwill, J.R., Buck, T.M., Lacewell, A.N., Romero, S.A., 2013. Postexercise hypotension and sustained postexercise vasodilatation: What happens after we exercise? Exp. Physiol. 98, 7–18.
Halverstadt, A., Phares, D.A., Wilund, K.R., Goldberg, A.P., Hagberg, J.M., 2007. Endurance exercise training raises high-density lipoprotein cholesterol and lowers small low-density lipoprotein and very low-density lipoprotein independent of body fat phenotypes in older men and women. Metabolism 56, 444–450.
Han, M.S., Jung, D.Y., Morel, C., Lakhani, S.A., Kim, J.K., Flavell, R.A., Davis, R.J., 2013. JNK expression by macrophages promotes obesity-induced insulin resistance and inflammation. Science 339, 218–222.
Harford, K.A., Reynolds, C.M., McGillicuddy, F.C., Roche, H.M., 2011. Fats, inflammation and insulin resistance: Insights to the role of macrophage and T-cell accumulation in adipose tissue. Proc. Nutr. Soc. 70, 408–417.
Haskell, W.L., 1984. The influence of exercise on the concentrations of triglyceride and cholesterol in human plasma. Exerc. Sport Sci. Rev. 12, 205–244.
Hooper, P.L., 1999. Hot-tub therapy for type 2 diabetes mellitus. N. Engl. J. Med. 341, 924–925.
Hooper, P.L., Balogh, G., Rivas, E., Kavanagh, K., Vigh, L., 2014. The importance of the cellular stress response in the pathogenesis and treatment of type 2 diabetes. Cell Stress Chaperones 19, 447–464.
Howley, E.T., Bassett Jr., D.R., Welch, H.G., 1995. Criteria for maximal oxygen uptake: Review and commentary. Med. Sci. Sport. Exerc. 27, 1292–1301.
Jimenez, C., Melin, B., Savourey, G., Launay, J.C., Alonso, A., Mathieu, J., 2007. Effects of passive hyperthermia versus exercise-induced hyperthermia on immune responses: Hormonal implications. Eur. Cytokine Netw. 18, 154–161.
Kenney, M.J., Seals, D.R., 1993. Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension 22, 653–664.
Lee, J.B., Kim, T.W., 2014. Passive heat loading links lipolysis and regulation of fibroblast growth factor-21 in humans. J. Therm. Biol. 45, 163–167.
Lee, J.B., Kim, T.W., 2015. Increased levels of FFA during passive heat loading after a 2-week repeated heat load in Koreans. Int. J. Biometeorol. 59, 473–475.
Lee, J.Y., Stone, E.A., Wakabayashi, H., Tochihara, Y., 2010. Issues in combining the categorical and visual analog scale for the assessment of perceived thermal sensation: Methodological and conceptual considerations. Appl. Ergon. 41, 282–290.
Liu, C.T., Brooks, G.A., 2012. Mild heat stress induces mitochondrial biogenesis in C2C12 myotubes. J. Appl. Physiol. 112, 354–361.
Markos, F., Ruane O'Hora, T., Noble, M.I., 2013. What is the mechanism of flow-mediated arterial dilatation. Clin. Exp. Pharmacol. Physiol. 40, 489–494.
Maurizi, G., Della Guardia, L., Maurizi, A., Poloni, A., 2018. Adipocytes properties and crosstalk with immune system in obesity-related inflammation. J. Cell. Physiol. 233, 88–97.
Nagasawa, Y., Komori, S., Sato, M., Tsuboi, Y., Umetani, K., Watanabe, Y., Tamura, K., 2001. Effects of hot bath immersion on autonomic activity and hemodynamics: Comparison of the elderly patient and the healthy young. Jpn. Circ. J. 65, 587–592.
Naylor, L.H., Carter, H., FitzSimons, M.G., Cable, N.T., Thijssen, D.H., Green, D.J., 2011. Repeated increases in blood flow, independent of exercise, enhance conduit artery vasodilator function in humans. Am. J. Physiol. Heart Circ. Physiol. 300, H664–H669.
Nordmann, A.J., Nordmann, A., Briel, M., Keller, U., Yancy Jr., W.S., Brehm, B.J., Bucher, H.C., 2006. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: A meta-analysis of randomized controlled trials. Arch. Intern. Med. 166, 285–293.
O'Hearn, K., Tingelstad, H.C., Blondin, D., Tang, V., Filion, L.G., Haman, F., 2016. Heat exposure increases circulating fatty acids but not lipid oxidation at rest and during exercise. J. Therm. Biol. 55, 39–46.
Pandolf, K.B., 1979. Effects of physical training and cardiorespiratory physical fitness on exercise-heat tolerance: Recent observations. Med. Sci. Sport. 11, 60–65.
Pescatello, L.S., American College of Sports Medicine, 2014. In: ACSM's Guidelines for Exercise Testing and Prescription, 9th ed. Wolters Kluwer/Lippincott Williams & Wilkins Health, Philadelphia.
Petersen, A.M., Pedersen, B.K., 2006. The role of IL-6 in mediating the anti-inflammatory effects of exercise. J. Physiol. Pharmacol. : Offi. J. Polish Physiol. Soc. 57 (Suppl. 10), 43–51.
Pickering, T.G., Hall, J.E., Appel, L.J., Falkner, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S.G., Roccella, E.J., 2005. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 111, 697–716.
Qatanani, M., Lazar, M.A., 2007. Mechanisms of obesity-associated insulin resistance: Many choices on the menu. Genes Dev. 21, 1443–1455.
Rivas, E., Newmire, D.E., Ben-Ezra, V., 2016a. Obese type 2 diabetics have a blunted hypotensive response to acute hyperthermia therapy that does not affect the perception of thermal stress or physiological strain compared to healthy adults. Physiol. Behav. 165, 374–382.
Rivas, E., Newmire, D.E., Crandall, C.G., Hooper, P.L., Ben-Ezra, V., 2016b. An acute bout of whole body passive hyperthermia increases plasma leptin, but does not alter glucose or insulin responses in obese type 2 diabetics and healthy adults. J. Therm. Biol. 59, 26–33.
Rivas, E., Rao, M., Castleberry, T., Ben-Ezra, V., 2017. The change in metabolic heat production is a primary mediator of heat acclimation in adults. J. Therm. Biol. 70, 69–79.
Rowell, L.B., Brengelmann, G.L., Murray, J.A., 1969. Cardiovascular responses to sustained high skin temperature in resting man. J. Appl. Physiol. 27, 673–680.
Shin, T.W., Wilson, M., Wilson, T.W., 2003. Are hot tubs safe for people with treated hypertension? CMAJ 169, 1265–1268 Canadian Medical Association journal = journal de l'Association medicale canadienne.
Song, C.W., 1984. Effect of local hyperthermia on blood flow and microenvironment: A review. Cancer Res. 44, 4721s–4730s.
Starkie, R.L., Hargreaves, M., Rolland, J., Febbraio, M.A., 2005. Heat stress, cytokines, and the immune response to exercise. Brain Behav. Immun. 19, 404–412.
Taylor, W.F., Johnson, J.M., O'Leary, D., Park, M.K., 1984. Effect of high local temperature on reflex cutaneous vasodilation. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 57, 191–196.
Teixeira de Lemos, E., Reis, F., Baptista, S., Pinto, R., Sepodes, B., Vala, H., Rocha-Pereira, P., Correia da Silva, G., Teixeira, N., Silva, A.S., Carvalho, L., Teixeira, F., Das, U.N., 2009. Exercise training decreases proinflammatory profile in Zucker diabetic (type 2) fatty rats. Nutrition 25, 330–339.
Thijssen, D.H., Dawson, E.A., van den Munckhof, I.C., Tinken, T.M., den Drijver, E., Hopkins, N., Cable, N.T., Green, D.J., 2011. Exercise-mediated changes in conduit artery wall thickness in humans: Role of shear stress. Am. J. Physiol. Heart Circ. Physiol. 301, H241–H246.
Tinken, T.M., Thijssen, D.H., Hopkins, N., Dawson, E.A., Cable, N.T., Green, D.J., 2010. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension 55, 312–318.
Ueno, L.M., Miyachi, M., Matsui, T., Takahashi, K., Yamazaki, K., Hayashi, K., Onodera, S., Moritani, T., 2005. Effect of aging on carotid artery stiffness and baroreflex sensitivity during head-out water immersion in man. Braz. J. Med. Biol. Res. 38, 629–637 Revista brasileira de pesquisas medicas e biologicas/Sociedade Brasileira de Biofisica ... [et al.].
Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R.L., Ferrante Jr., A.W., 2003. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Investig. 112, 1796–1808.
Weston, C.F., O'Hare, J.P., Evans, J.M., Corrall, R.J., 1987. Haemodynamic changes in man during immersion in water at different temperatures. Clin. Sci. 73, 613–616.
Wilson, T.E., Crandall, C.G., 2011. Effect of thermal stress on cardiac function. Exerc. Sport Sci. Rev. 39, 12–17.