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Exercise training reduces the frequency of menopausal hot flushes by improving thermoregulatory control

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Abstract

Objective: Postmenopausal hot flushes occur due to a reduction in estrogen production causing thermoregulatory and vascular dysfunction. Exercise training enhances thermoregulatory control of sweating, skin and brain blood flow. We aimed to determine if improving thermoregulatory control and vascular function with exercise training alleviated hot flushes.

Methods: Twenty-one symptomatic women completed a 7-day hot flush questionnaire and underwent brachial artery flow-mediated dilation and a cardiorespiratory fitness test. Sweat rate and skin blood flow temperature thresholds and sensitivities, and middle cerebral artery velocity (MCA*v*) were measured during passive heating. Women performed 16 weeks of supervised exercise training or control, and measurements were repeated.

Results: There was a greater improvement in cardiorespiratory fitness (4.45 mL/kg/min [95% CI: 1.87, 8.16]; $P = 0.04$) and reduced hot flush frequency (48 hot flushes/wk [39, 56]; $P < 0.001$) after exercise compared with control. Exercise reduced basal core temperature (0.14°C [0.01, 0.27]; $P = 0.03$) and increased basal MCA*v* (2.8 cm/s [1.0, 5.2]; $P = 0.04$) compared with control. Sweat rate and skin blood flow thresholds occurred approximately 0.19°C and 0.17°C earlier, alongside improved sweating sensitivity with exercise. MCA*v* decreased during heating ($P < 0.005$), but was maintained 4.5 cm/s (3.6, 5.5; $P < 0.005$) higher during heating after exercise compared with control (0.6 cm/s [−0.4, 1.4]).

Conclusions: Exercise training that improves cardiorespiratory fitness reduces self-reported hot flushes. Improvements are likely mediated through greater thermoregulatory control in response to increases in core temperature and enhanced vascular function in the cutaneous and cerebral circulations.

Key Words: Brain blood flow – Exercise training – Hot flushes – Thermoregulation – Vascular function.

Hot flushes are experienced by the vast majority of postmenopausal women and are associated with increased cardiovascular disease risk.[1] Menopausal hot flushes can seriously disrupt the lives of symptomatic women[2] with approximately 70% of women experiencing hot flushes 1 to 5 years after the onset of menopause.[3] A hot flush is typically defined as the subjective sudden intense sensation of heat causing cutaneous vasodilation and profuse sweating.[4] Hormone therapy (HT) is an effective treatment for hot flushes and can reduce hot flush frequency by 50% to 72%,[5,6] but has poor uptake.[7] Furthermore, not all women can be prescribed HT due to time since menopause and a history of cardiovascular disease or breast cancer.[8] The current alternatives are limited, but one nonpharmacological option is exercise training.

The mechanisms causing hot flushes are not completely understood, yet it is thought that the reduction in estrogen due to ovarian failure causes thermoregulatory and vascular dysfunction, leading to the occurrence of hot flushes.[9] An elevation in basal core body temperature and a narrowed thermoneutral zone are thought to be primary explanations,[2] with a reduced skin vascular reactivity to increases in core body temperature also proposed as a mediator.[9,10] No research study to date has simultaneously investigated the impact of exercise training on thermoregulatory and vascular dysfunction observed in symptomatic postmenopausal women and the effect of improvements in these systems on hot flush symptomology.

A number of research studies, but not all, have shown that exercise training can reduce the frequency of self-reported hot flushes[11-17] and improve other nonvasomotor symptoms including depression, anxiety, and insomnia.[14,18,19] Nevertheless, these studies have solely relied on subjective questionnaires as the primary outcome. It is also important to highlight that the most recent randomized control trial

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investigating the impact of exercise training (home based and general advice) using subjective frequency of hot flushes reported a lack of impact of exercise training despite finding a 22% decrease in weekly hot flushes compared with control.[17]

It is well established that exercise training can improve the thermoregulatory control system by decreasing core body temperature, and by changing both the temperature threshold for the onset, and sensitivity of sweating and cutaneous vasodilation in premenopausal women.[20] Although HT reduces hot flushes, it also affects thermoregulatory control mechanisms via lowering core body temperature and altering the threshold at which cutaneous vasodilation and sweating responses are initiated.[21,22] If the thermoregulatory control system can be altered with exercise training in symptomatic postmenopausal women, this may also reduce the frequency of hot flushes. Moreover, exercise training improves endothelial function in the cutaneous and conduit vessels in postmenopausal women,[23-25] and cerebral blood flow (CBF) in older individuals.[26,27] Endothelial dysfunction is associated with hot flush severity,[28] suggesting that if endothelial function is improved with exercise training this may contribute to a reduction in the occurrence and severity of hot flushes. Therefore, the aim of this study was to determine whether improving thermoregulatory control and systemic vascular function with exercise training alleviates the frequency and severity of menopausal hot flushes. We hypothesized that exercise training reduces the frequency and severity of hot flushes via improving sweat rate and skin blood flow responses to increases in core body temperature.

METHODS

Participants

Twenty-one symptomatic postmenopausal women were recruited from the gynecology and reproductive medicine clinic at Liverpool Women's Hospital, local GP practices, and via local advertisement. Participants were 1 to 4 years since their last menstrual period and suffered more than 4 hot flushes over a 24-hour period. All participants had no history of diabetes, cardiovascular or respiratory disease, were nonsmokers, drank less than 14 units of alcohol per week, and had no contraindications to exercise. Participants who had used HT, metformin, vasoactive, or BP lowering medications within the last 6 months were excluded from the study. Similarly, women who were currently taking part in regular exercise (>2 h/wk based on a self-reported questionnaire) were also excluded. Participants were informed of the methods verbally and in writing before providing written informed consent. The study conformed to the Declaration of Helsinki and was approved by the local research ethics committee.

Research design

Participants reported to the laboratory on two separate occasions, and were asked to fast overnight, refrain from alcohol and exercise for 24 hours and caffeine for 12 hours before each visit. Visit 1 included anthropometric measurements, assessment of brachial artery endothelial function using flow-mediated dilation (FMD), and a cardiorespiratory test ($\dot{V}O_{2peak}$). Visit 2 consisted of a fasting blood sample and a passive heat stress challenge to assess thermoregulatory, hemodynamic, and cerebrovascular responses to increases in core body temperature. Both visits were completed within 7 days of each other with assessments conducted in a temperature-controlled laboratory (24°C ± 1°C). Participants then underwent a supervised exercise training intervention or a no-exercise control that was based on participant choice. Fourteen (n = 14, 52 ± 4 y, body mass index [BMI] 21.1-41.8 kg/m^2) symptomatic women received a 16-week program of supervised moderate-intensity aerobic exercise training, whereas seven (n = 7, 52 ± 6 y, BMI 21.1-41.3 kg/m^2) symptomatic women comprised the no-exercise control group. After each intervention, all measurements were repeated.

Measurements

Hot flush frequency and severity questionnaire

Participants completed a 7-day hot flush frequency and severity diary[29] before and after the 16-week intervention period. Participants recorded on a daily basis how many hot flushes they experienced as well as information regarding the severity of each hot flush on a scale of 1 to 4 (1 being mild, 2 moderate, 3 severe, and 4 very severe). From this, a 7-day sum of hot flushes provided a weekly hot flush score. A daily severity score was calculated by the sum of hot flushes recorded into each severity rating, that is [(3 × 1 (mild))+(4× × 2 (moderate))+(1× 3 (severe))+(0× 4 (very severe))- = daily severity score of 14]. A hot flush severity index was then calculated by the total sum of daily severity scores over the 7-day period. The use of subjective diaries is established as a valid approach to obtaining data on subjective hot flushes when reporting participant symptoms and perceptions[29] and in a number of hot flush research studies.[11,12,16,30]

Cardiorespiratory assessment for peak oxygen consumption

A fitness test (peak oxygen uptake; $\dot{V}O_{2peak}$) was performed on a treadmill after a modified Bruce protocol. After a 2-minute warm-up at 2.2 km/h on a flat gradient, the initial workload was set at 2.7 km/h at a 5° gradient. Thereafter, stepwise increments in speed and gradient were performed each minute until volitional exhaustion. Heart rate (12-lead electrocardiogram) and rate of perceived exertion were monitored throughout. Peak oxygen uptake was calculated from expired gas fraction (Oxycon Pro, Jaegar, Hochberg, Germany) as the highest consecutive 15-second period of data in the final minute before volitional exhaustion.

Brachial artery endothelial-dependent vasodilation

Brachial artery endothelium-dependent function was measured using the FMD technique.[31] Measurements were performed in the supine position after 20 minutes of rest and are described in detail elsewhere.[31] After a 1-min recording period of resting diameter and flow, a rapid inflation pneumatic cuff (D.E. Hokanson, Bellevue, UK), positioned on the forearm immediately distal to the olecranon process, was

inflated (>200 mm Hg) for 5 minutes to provide a stimulus for forearm ischemia. Diameter and flow recordings resumed 30 seconds before cuff deflation and continued for 3 minutes thereafter, in accordance with recent technical specifications.[32,33]

Analysis of brachial artery diameter was performed using custom-designed edge-detection and wall-tracking software, which is largely independent of investigator bias. Recent articles contain detailed descriptions of the analysis approach.[31,32] From synchronized diameter and velocity data, blood flow (the product of lumen cross-sectional area and Doppler velocity) were calculated at 30 Hz. Shear rate (an estimate of shear stress without viscosity) was calculated as 4 times mean blood velocity/vessel diameter. Reproducibility of diameter measurements using this semiautomated software is significantly better than manual methods, reduces observer error significantly, and possesses an intraobserver coefficient of variation of 6.7%.[34] We also controlled for the baseline diameter measured before the introduction of hyperemia in each test of FMD. This allometric approach is more accurate for scaling changes in diameter than simple percentage change, which makes implicit assumptions about the relationship between baseline diameter and peak diameter.[35]

Passive heat stress challenge

Participants were placed in a tube-lined jacket and trousers (Med-Eng, Ottawa, Canada), which covered the entire body except for the head, feet, and the right forearm. Participants rested quietly in a semirecumbent position, although water (34°C) was perfused through the suit for a 15-minute baseline period. Participants were then exposed to a moderate heat stress by perfusing water at 48°C through the suit for 60 minutes or until a rise of approximately 1°C in core body temperature. The following measurements were taken during the baseline and heating periods.

Heart rate was obtained from a 3-lead electrocardiogram (PowerLab; ADInstruments, Oxford, UK), alongside continuous beat-by-beat finger arterial blood pressure (BP) (Finapress, Amsterdam, the Netherlands). Stroke volume and cardiac output were calculated using the BP waveform using the Modelflow method, incorporating age, height, sex, and weight (Beatscope 1.0 software; TNO, Biomedical Instruments, Amsterdam, the Netherlands). To verify continuous BP measured at the finger, an automated BP (Dinamap, Germany) reading was collected at regular intervals. Mean skin temperature was obtained from the weighted average of 4 regional temperatures measured from thermocouples (iButtons data logger; Maxim Integrated, San Jose, CA) secured to the lateral calf, lateral thigh, upper arm, and chest.[36] Core body temperature was measured from an ingestible pill telemetry system taken approximately 5 hours before data collection began (CoreTemp, HQ Inc, Palmetto, FL), with the ingestion time recorded and repeated for each participant's pre- and post-trials. Mean body temperature was calculated using the weighted product of core and mean skin temperatures.[37]

Local sweat rate was recorded continuously from the dorsal forearm and the mid-sternum (not covered by the water-perfused suit) using capacitance hygrometry. Dry 100% nitrogen gas was supplied through acrylic capsules (surface area = 2.32 cm^2) attached to the skin's surface at a flow rate of 300 mL/min, with the humidity of the gas flowing out of the capsules measured by the capacitance hygrometer (Viasala HMP155, Helsinki, Finland). Local skin blood flow was also measured at the chest and the forearm, using laser-Doppler flowmetry (Periflux System 5001; Perimed AB, Stockholm, Sweden). Laser-Doppler flow probes were affixed with an adhesive heating ring in close proximity to the ventilated sweat rate capsule. Cutaneous vascular conductance (CVC) was calculated as the ratio of laser-Doppler flux units to mean arterial pressure (MAP) and expressed as both CVC and a percentage of maximum CVC (%CVC_{max}).

Middle cerebral artery blood velocity (MCA*v*; 1 cm distal to the MCA-anterior cerebral artery bifurcation) was measured continuously through the temporal window using transcranial Doppler ultrasonography. A 2-MHz Doppler probe (Spencer Technologies, Seattle WA) was adjusted until an optimal signal was identified, as described in detail previously,[38-40] and held in place using a headband strap to prevent subtle movement of the Doppler probe and maintain insonation angle accuracy. Once the optimal MCA signal was attained in the temporal window, the probe location and machine settings (depth, gain, and power) were recorded to identify the same imaging site during postintervention assessments. Using these guidelines this technique is a valid and reliable index of CBF.[38] Participants were instrumented with a two-way valve-breathing mouthpiece from which peak end tidal CO_2 ($P_{ET}CO_2$) was measured every 5 minutes and at each 0.1°C increase in core body temperature. An index of cerebrovascular conductance (CBVC) was calculated from the ratio of MCA*v* to MAP. All data were calculated as 60-second averages at every 0.1°C increase in core temperature during heating. All data during the heat stress challenge were sampled at 50 Hz with a data acquisition system (PowerLab; ADInstruments).

After the passive heat stress, local skin heating was performed simultaneously at the chest and forearm laser-Doppler flowmetry sites to assess maximal cutaneous blood flow. Temperature of the local heating units was increased at a rate of 1°C every 5 seconds to a temperature of 42°C. This resulted in an increase in skin temperature to approximately 42°C at the heating probe-skin surface interface. The protocol was complete once flux at both sites had reached a stable plateau (~30 min).

Data reduction

The temperature thresholds for the onset of sweating (mean body temperature) and cutaneous vasodilation (core body temperature) were calculated in a blinded fashion by the same analyst.[41] The sensitivity of the sweating responses was estimated from the slope of the relationships between sweat rate per unit change in mean body temperature beyond the

mean body temperature threshold, and any sweat rate plateau, or increase during a hot flush episode, were excluded from the slope calculation. Skin blood flow sensitivity was estimated in the same way, instead using the rate of CVC per unit change in core temperature.

Supervised exercise training intervention

Before commencing the exercise intervention, all participants attended a thorough familiarization session. Participants were required to attend the university gym on a weekly basis during which time they wore a heart rate monitor (Polar Fitness, Polar Electro Oy, Finland) and were provided with full exercise supervision and guidance from a trained exercise physiologist. During these sessions, participants were issued with a weekly progressive exercise program that was specific to their own rate of progression.[42,43] On the basis of individual fitness level, participants underwent 30 minutes of moderate-intensity aerobic exercise 3 times per week (30% heart rate reserve), which progressed weekly based on HR responses and included treadmill walking/running, cycling, cross-training, and rowing. At week 12, participants were exercising 4 to 5 times per week for 45 minutes at 60% heart rate reserve. To facilitate compliance throughout the 16-week intervention, participants were monitored via the Wellness Key system, a software program that enables remote and accurate tracking of exercise activity. A moderate-intensity program was used in line with National Health Service (NHS) guidelines and our previous studies that have shown improvements in cardiorespiratory fitness.[23,42-44]

Control intervention

After consent and physiological flush assessment, women who opted for the control group had little contact with the research team throughout the 16 weeks. The research team did not influence life-style during the 16-week period. This type of control intervention reflects current convention care for nonpharmacological hot flush treatment in the UK.

Statistical analyses

For comparison of exercise versus control, delta changes (Δ) from preintervention were calculated for each group and entered as the dependent variable in a linear mixed model (ANCOVA), with preintervention data entered as a covariate, this allows all differences between changes to be covariate-adjusted for the preintervention values.[45] This analysis approach is more statistically precise and adjusts properly for any study group imbalances at preintervention. Ultimately, this analysis provides 1 P value for the effect of intervention, which is adjusted for the preintervention values. Data are presented in the text for intervention-adjusted effects as mean and 95% CIs. Data in the tables are absolute values (point estimates) for pre- and postintervention and are presented as mean (SD). Correlations between the Δ intervention changes in hot flush frequency and SR and CVC thresholds were quantified using Pearson's correlation coefficient (r).

For comparison of exercise versus control during the passive heat stress, a three-factor [(group $\times$ 0.1°C increase) $\times$ time(pre/postintervention)] linear mixed model was used for the analysis of the CBF and $P_{ET}CO_2$ responses to each 0.1°C increase in core body temperature. If any hot flushes occurred during heat stress, the CBF and $P_{ET}CO_2$ data during such episodes were excluded from the CBF and $P_{ET}CO_2$ data analyses. Owing to variable individual increments in core body temperature during the passive heat stress, data up to an increase of 0.6°C were used for the CBF and $P_{ET}CO_2$ analyses. Statistically significant interactions were followed up with the least significant difference approach to multiple comparisons.[46]

RESULTS

Participants undertaking the exercise intervention demonstrated 93% compliance to the exercise sessions. After adjustment for baseline values, the body mass normalized change in $\dot{V}O_{2peak}$ was 4.5 (1.9, 8.2) mL/kg/min greater in the exercise group versus control ($P = 0.04$). The absolute change was 21.0 (0.4, 41.5) mL/min greater in the exercise group versus control ($P = 0.05$). The mean frequency of hot flushes per week was 48 (39, 56) events lower after the exercise intervention versus control ($P < 0.001$). The hot flush severity index was 109 (80, 121) arbitrary units lower after exercise training versus control ($P < 0.001$).

Conduit brachial artery endothelial function

FMD was 2.3% (0.3, 4.9) greater after exercise training versus control, but this did not reach statistical significance ($P = 0.08$; Table 1). Baseline and peak diameter did not change with either intervention.

Resting measurements

Hemodynamics

Heart rate was 4 (2, 5) beats/min lower after exercise training versus control ($P = 0.003$; Table 2). There were negligible differences in MAP, cardiac output, or stroke volume with the interventions.

Thermoregulatory

Basal core body temperature was 0.14 (0.01, 0.27)°C lower after exercise training versus control in ($P = 0.03$; Table 2). There were negligible differences between interventions for basal skin blood flow (Table 2). Maximal skin blood flow (CVC_{max}) at the arm was 1.2 (0.1, 2.4) arbitrary units/mm Hg greater after exercise training versus control ($P = 0.05$; Table 2). This difference was not evident at the chest CVC_{max}.

CBF

Basal MCAv was 2.8 (1.0, 5.2) cm/s greater after exercise training versus control ($P = 0.04$; Table 2). This improvement was reduced when accounting for BP, with CBVC 0.05 (−0.02, 0.13) cm/s higher after exercise training versus control, but this did not reach statistical significance ($P = 0.09$; Table 2).

TABLE 1. *Anthropometric, hot flush, and vascular function data after exercise training or control*

Variable	Pre-exercise	Postexercise	Precontrol	Postcontrol	*P*
Weight, kg	77.9 (18.3)	73.5 (16.5)	75.5 (19.9)	75.2 (20.4)	0.02[a]
BMI, kg/m^2	29 (5.8)	27 (4.5)	28 (7.2)	28 (7.0)	0.03[a]
Systolic, mm Hg	128 (5)	126 (7)	127 (10)	128 (8)	0.25
Diastolic, mm Hg	78 (8)	75 (7)	77 (11)	77 (9)	0.58
$\dot{V}O_{2peak}$, mL/kg/min	22.5 (3.3)	27.3 (4.1)	23.2 (2.4)	22.6 (3.1)	0.04[a]
$\dot{V}O_{2peak}$, L/min	1.7 (0.4)	2.0 (0.3)	1.7 (0.3)	1.6 (0.4)	0.05[a]
Hot flushes					
Frequency, hot flushes/wk	64 (20)	23 (13)	45 (21)	49 (36)	<0.001[a]
Severity index, AU	137 (49)	37 (22)	91 (49)	102 (70)	<0.001[a]
Vascular measurements					
FMD, %	5.0 (1.2)	7.4 (1.5)	5.6 (1.9)	5.5 (1.8)	0.08
Baseline diameter, mm	0.37 (0.03)	0.37 (0.05)	0.36 (0.04)	0.35 (0.04)	0.97
Peak diameter, mm	0.39 (0.04)	0.40 (0.04)	0.38 (0.04)	0.37 (0.04)	0.86
Shear rate$_{AUC}$, $s^{-1} \times 10^3$	16.3 (8.6)	17.8 (10.4)	21.5 (13.9)	20.4 (12.8)	0.95
Time to peak, s	69.7 (32.5)	54.2 (34.6)	70.5 (33.2)	76.7 (35.6)	0.19

Data are presented as mean (SD).
AU, arbitrary units; BMI, body mass index; FMD, flow-mediated dilation.
[a]Significant difference between change Δ in exercise and Δ in control values ($P < 0.05$).

Measurements during the heat stress challenge

Hemodynamics

Heart rate during heat stress was 5 (1, 10) beats/min lower after exercise training versus control, but this did not reach statistical significance ($P = 0.08$; Table 2).

Thermoregulatory

There were no differences in the changes in core body temperature (0.07 [−0.09, 0.24]°C; $P = 0.40$) or weighted mean skin temperature at the end of heating after the interventions (0.06 [−0.57, 0.66]°C; $P = 0.88$; Table 2).

Sweat rate

Mean body temperature for chest sweating was 0.19 (0.04, 0.34)°C lower after exercise training versus control ($P = 0.01$; Fig. 1A). Similarly, mean body temperature for the onset of arm sweating was 0.19 (0.05, 0.36)°C lower after exercise training versus control ($P = 0.01$; Fig. 1B). Mean body temperature onset of sweating at the chest ($r = 0.688$; $P = 0.006$) and the forearm ($r = 0.688$; $P = 0.006$) after the exercise intervention were correlated with the frequency of self-reported hot flushes.

The rate of chest sweating was 0.13 (0.05, 0.20) mg·min·cm^{-1}/°C greater after exercise training versus control ($P = 0.002$; Fig. 1C). The rate of forearm sweating was 0.19 (0.05, 0.34) mg·min·cm^{-1}/°C greater after exercise training versus control ($P = 0.01$; Fig. 1D).

Cutaneous blood flow

Mean body temperature onset of chest cutaneous vasodilation was a 0.17 (0.04, 0.29)°C lower after exercise training versus control ($P = 0.01$; Fig. 2A). Similarly, the mean body temperature onset of forearm cutaneous vasodilation was 0.15 (0.02, 0.28)°C lower after exercise training versus control ($P = 0.02$; Fig. 2B).

TABLE 2. *Resting and heating cardiovascular and thermoregulatory data before and after exercise training or control*

Variable	Pre-exercise	Postexercise	Precontrol	Postcontrol	*P*
Resting					
Heart rate, beats/min	64 (7)	60 (7)	66 (11)	65 (12)	0.003[a]
MAP, mm Hg	75 (7)	75 (5)	76 (4)	75 (6)	0.58
Stroke volume, mL	109 (16)	114 (27)	105 (18)	103 (16)	0.47
Cardiac output, L/min	7.2 (1.6)	7.6 (1.8)	7.1 (1.4)	7.3 (1.1)	0.69
Core temperature, °C	36.93 (0.19)	36.79 (0.21)	36.86 (0.31)	36.84 (0.27)	0.03[a]
Skin temperature, °C	32.2 (0.7)	32.9 (0.6)	32.8 (0.5)	32.9 (0.7)	0.10
MCA*v*, cm/s	51 (6)	54 (7)	51 (5)	51 (5)	0.05[a]
CBVC, cm/s/mm Hg	0.69 (0.11)	0.74 (0.13)	0.68 (0.06)	0.69 (0.04)	0.08
$P_{ET}CO_2$, Torr	42 (2)	42 (2)	41 (3)	42 (2)	0.36
CVC_{chest}, $\%CVC_{max}$	10.9 (5.0)	11.2 (6.9)	9.5 (4.5)	8.6 (3.2)	0.93
CVC_{arm}, $\%CVC_{max}$	9.7 (5.2)	10.2 (5.6)	8.8 (4.5)	9.5 (3.3)	0.13
Chest CVC_{max}, LDF/mm Hg	5.1 (1.6)	5.9 (1.4)	5.4 (1.1)	5.2 (1.4)	0.58
Arm CVC_{max}, LDF/mm Hg	2.9 (0.7)	3.9 (0.9)	3.3 (0.9)	3.4 (0.8)	0.05[a]
Heating					
Heart rate, beats/min	93 (10)	88 (12)	89 (9)	93 (9)	0.08
Core temperature, °C	37.75 (0.17)	37.71 (0.21)	37.63 (0.22)	37.58 (0.24)	0.40
Skin temperature, °C	37.3 (0.7)	37.2 (0.8)	36.9 (0.4)	36.9 (0.5)	0.88

Data are presented as mean (SD).
CBVC, cerebrovascular conductance; CVC, cutaneous vascular conductance; LDF, laser-Doppler flux; MAP, mean arterial pressure; MCA*v*, middle cerebral artery velocity; $P_{ET}CO_2$, peak end tidal CO_2.
[a]Significant difference between change Δ in exercise and Δ in control.

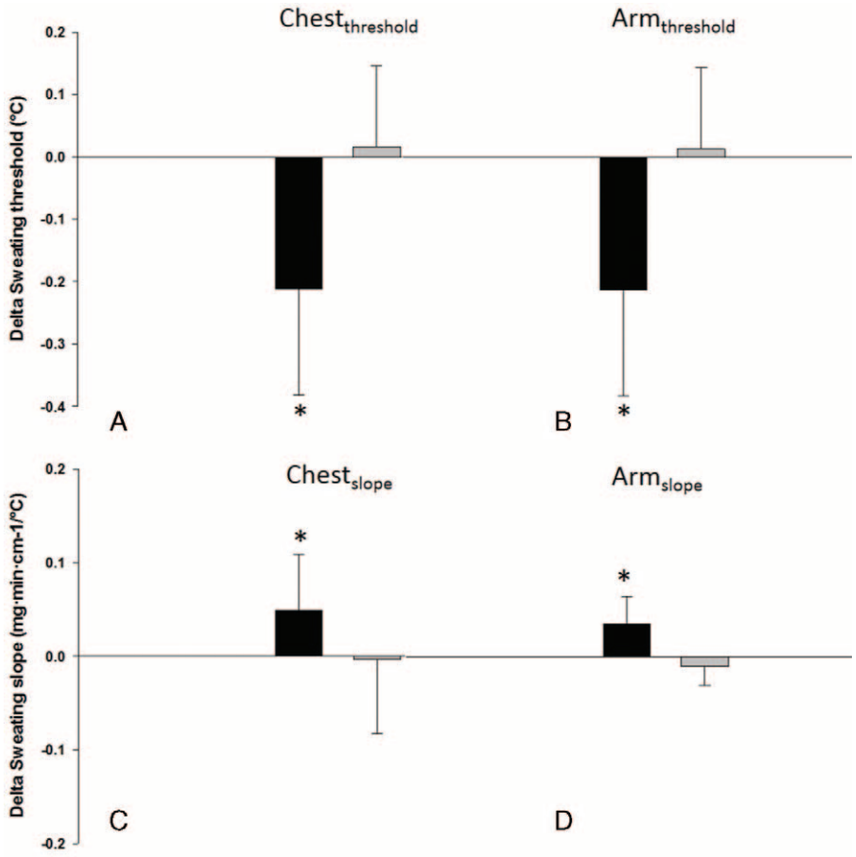

FIG. 1. Delta (Δ) change from pretraining in mean body temperature threshold for the onset of chest (**A**) and forearm (**B**) sweating. Delta (Δ) change from pretraining in sweat rate sensitivity (slope) at the chest (**C**) and forearm (**D**). Error bars are SD. *Significant difference between exercise black bars and control grey bars ($P < 0.05$).

The rate of cutaneous vasodilation was similar between interventions at the chest ($P = 0.62$; Fig. 2C) and forearm ($P = 0.31$; Fig. 2D).

CBF

CBF decreased during the heat stress ($P < 0.001$). There was an intervention × pre/postinteraction ($P < 0.001$), where the reduction in MCA*v* during heat stress was attenuated in the exercise group versus control (Table 3). MCA*v* was 4.5 cm/s (3.6, 5.5, $P < 0.001$) higher during heating after exercise training versus 0.7 (−0.3, 1.7) cm/s in control ($P = 0.27$). Similarly, CBVC decreased during the heat stress ($P < 0.001$). There was a significant intervention × pre/post-interaction ($P = 0.01$). CBVC was 0.07 (0.04, 0.09) cm/s/mm Hg higher during heat stress in the following exercise ($P < 0.001$) compared with 0.01 (−0.01, 0.03) cm/s/mm Hg in control ($P = 0.91$). $P_{ET}CO_2$ decreased during heat stress ($P < 0.001$), but there was no interaction (Table 3; $P < 0.05$).

DISCUSSION

The novel findings of the present study were that reductions in self-reported hot flush frequency and severity with exercise training coincided with improved thermoregulatory and vascular function in symptomatic postmenopausal women. These findings provide evidence that improving thermoregulatory and vascular function with moderate-intensity aerobic exercise training can be effective in the treatment of hot flushes in postmenopausal women.

Exercise training has been shown in a number of studies to improve the subjective ratings of self-reported hot flushes in postmenopausal women,[11-15] but the underlying physiological mechanisms responsible have not yet been investigated. The results of the current study suggest that the improvements in the occurrence of postmenopausal hot flushes after 16 weeks of moderate-intensity aerobic exercise training are linked to improvements in thermoregulatory control. We found that exercise training reduces thermoregulatory dysfunction via stabilization of central thermoregulatory control, that is, lowering core body temperature and improving heat dissipation thresholds, alongside improvements in peripheral mechanisms that allow for greater heat dissipation (sweating sensitivity). These adaptations likely include increases in the number of sweat expulsions per minute, sweat gland hypertrophy, increased nitric oxide (NO) availability, and/or enhanced sweat gland recruitment at a given internal temperature, or a combination of all of the above.[47] Importantly, these findings of improved thermoregulatory efficiency with exercise training support previous studies that suggest an

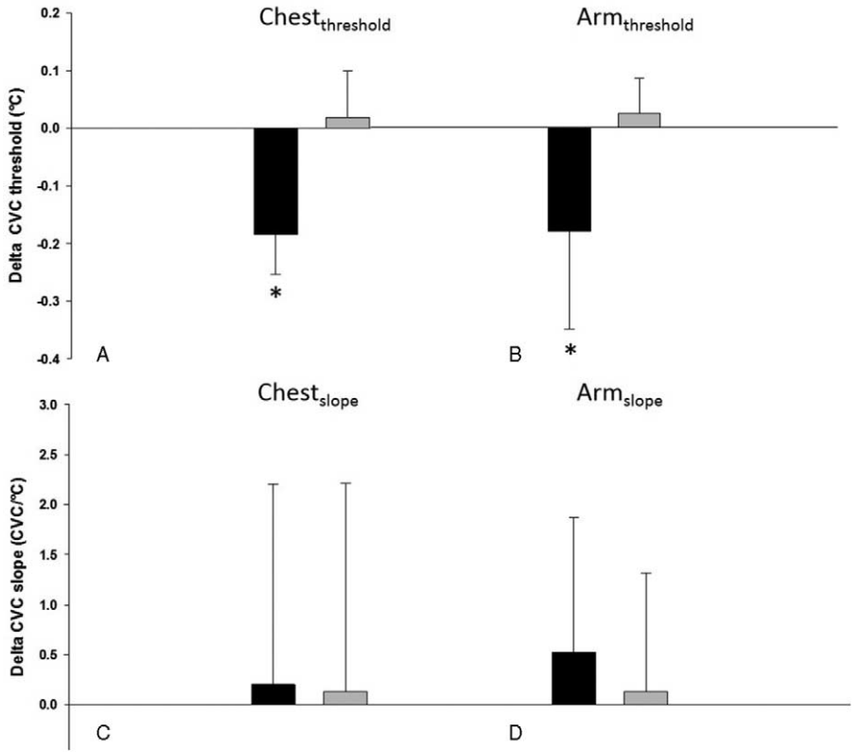

FIG. 2. Delta (Δ) change from pretraining in mean core body temperature threshold values for onset of chest (**A**) and forearm (**B**) cutaneous vasodilation. Delta (Δ) change from pretraining in cutaneous vascular conductance (CVC) sensitivity at the chest (**C**) and forearm (**D**). Error bars are SD. *Significant difference between exercise black bars and control grey bars ($P < 0.05$).

improvement in $\dot{V}O_{2peak}$ in the range of approximately 15% to 20% mediates positive adaptations to thermoregulatory function in premenopausal women.[20,48] This is the first study to demonstrate that postmenopausal women can improve thermoregulatory function with exercise training, and, importantly, that this contributes to alleviating the frequency and severity of hot flushes with exercise training.

The precise mechanisms underlying the pathophysiology of hot flushes is unclear; however, it is acknowledged that thermoregulatory dysfunction is a key contributing factor.[4,9,49] Elevated basal core body temperature and a narrowing of the thermoneutral zone (where shivering and sweating do not occur) are thought to be responsible for the large, rapid, and transient increases in skin blood flow, sweating, and flushing that characterize hot flushes.[2] This study suggests that improving the control, and stability, of the thermoregulatory system through lowering core body temperature and improving heat dissipation mechanisms per se reduces the occurrence of hot flushes.

The ability of the blood vessels (including the cutaneous, conduit, and cerebral vasculature) to vasodilate and thus deliver blood flow systemically is implicated in the pathophysiology of hot flushes and also contributes to thermoregulatory control. The reduction in estrogen associated with menopause causes endothelial dysfunction via decreased NO bioavailability[50] and/or increased reactive oxygen species scavenging NO.[51] Exercise increases endothelial NO synthase expression via similar mechanisms of transcriptional regulation to that of estrogen[52] and augments NO-mediated vasodilation.[53] We provide evidence (approaching statistical significance) for an improvement in NO-mediated conduit artery endothelial function, measured using FMD, after exercise training. Previous studies in postmenopausal women have not always observed exercise training-mediated increases in endothelial function using FMD,[24,25] but exercise training has been shown to enhance cutaneous endothelial function and microvascular reactivity in postmenopausal women.[23,54] One reason for the lack of statistical significance in FMD with exercise training maybe due to the vascular remodeling that occurs over the intervention period. Previous studies in young healthy males and type 2 diabetic individuals have been shown to improve function (increase in FMD) and then normalize due to changes in artery structure/remodelling.[55,56] Although the time course of changes in vascular function have not been investigated in postmenopausal women, this is the first investigation of exercise-mediated changes in endothelial function in symptomatic postmenopausal women. Recent research studies have suggested that menopausal hot flushes are associated with greater vascular impairments, including endothelial dysfunction,[1] with FMD a determinant of hot flush severity in early postmenopausal women.[28] Therefore, it is likely that symptomatic women have greater impairments in endothelial function and increased cardiovascular disease risk, a condition that exercise training in this study seems to ameliorate.

TABLE 3. *Cerebrovascular responses to 0.1°C increments in core temperature during passive heat stress before and after 16 weeks of exercise training or no-exercise control*

	Exercise training													
Variable	Pre						Post							
Core temperature, °C	Rest	0.1	0.2	0.3	0.4	0.5	0.6	Rest	0.1	0.2	0.3	0.4	0.5	0.6
MCAv, cm/s	51 (6)	50 (7)	47 (7)	45 (7)	43 (9)	43 (8)	42 (8)	54 (7)	54 (7)	51 (8)	50 (8)	49 (9)	48 (9)	48 (10)
CBVC, cm/s/mm Hg	0.69 (0.08)	0.67 (0.08)	0.65 (0.08)	0.63 (0.08)	0.60 (0.09)	0.60 (0.12)	0.59 (0.09)	0.74 (0.06)	0.74 (0.07)	0.70 (0.06)	0.69 (0.04)	0.68 (0.05)	0.67 (0.08)	0.68 (0.05)
$P_{ET}CO_2$, Torr	42 (4)	42 (5)	41 (5)	40 (6)	40 (6)	39 (5)	39 (5)	42 (3)	42 (4)	40 (6)	40 (5)	40 (4)	39 (3)	39 (5)
	Control													
	Pre							Post						
Core temperature, °C	Rest	0.1	0.2	0.3	0.4	0.5	0.6	Rest	0.1	0.2	0.3	0.4	0.5	0.6
MCAv, cm/s	51 (5)	50 (5)	49 (5)	48 (6)	47 (6)	44 (5)	41 (6)	51 (5)	50 (4)	48 (4)	46 (4)	44 (4)	44 (6)	43 (6)
CBVC, cm/s/mm Hg	0.68 (0.06)	0.68 (0.07)	0.67 (0.08)	0.66 (0.05)	0.64 (0.07)	0.61 (0.10)	0.60 (0.09)	0.69 (0.05)	0.68 (0.03)	0.66 (0.04)	0.65 (0.05)	0.64 (0.06)	0.62 (0.07)	0.61 (0.08)
$P_{ET}CO_2$, Torr	41 (5)	41 (6)	41 (6)	40 (8)	39 (6)	39 (5)	38 (6)	42 (5)	42 (5)	41 (5)	40 (7)	40 (5)	39 (5)	39 (5)

Data are presented as mean (SD). *P* values for MCAv (intervention $P = 0.83$, pre/post $P < 0.0001$, intervention × pre/postinteraction $P < 0.001$, intervention × pre/post × temp interaction $P = 0.52$), CBVC (intervention $P = 0.84$, pre/post $P < 0.0001$, intervention × pre/postinteraction $P < 0.05$, intervention × pre/post × temp interaction $P = 0.65$) and $P_{ET}CO_2$ (intervention $P = 0.79$, pre/post $P < 0.001$, intervention × pre/postinteraction $P = 0.47$, intervention × pre/post × temp interaction $P = 0.59$).
CBVC, cerebrovascular conductance; MCAv, middle cerebral artery velocity; $P_{ET}CO_2$, peak end tidal CO_2.

Reductions in CBF are evident during a hot flush[57] and during a passive heat stress challenge,[58,59] and thus are implicated in thermoregulatory control via a reduction of blood flow to the thermoregulatory center (hypothalamus) in the brain. Improved basal blood flow to the cerebral circulation was observed with exercise training along with attenuation in the reduction of CBF typically observed with passive heat stress in the current study. Short-term exercise training improves cerebrovascular health across the lifespan[27] and our resting CBF data support this notion in postmenopausal women. No study to date has examined the exercise-mediated changes in CBF during passive heat stress; yet given that CBF reductions occur during a hot flush (which could be described as a heat stress response per se), it is plausible that an exercise-mediated attenuation in CBF decreases during heat stress may positively impact on cerebrovascular function during a hot flush and possibly other perturbations that challenge the maintenance of CBF. The mechanisms responsible for these adaptations could include an exercise-mediated increases in stroke volume,[60] plasma volume expansion,[61] and/or improved endothelial function as described above.[62]

An alternative, although not mutually exclusive explanation for the improvement in hot flush frequency and severity, could be related to the central sympathetic nervous system that influences the cutaneous, conduit, and cerebral vasculature by activating changes in blood flow via the noradrenergic and cholinergic systems.[63,64] Sympathetic noradrenergic nerve outflow increases after menopause[65] and elevates peripheral vascular resistance,[66] whereas sympathetic cholinergic nerve activity is also increased during hot flushes.[67] Moreover, muscle sympathetic nerve activity, an index of sympathetic nerve activity measured using microneuography, is reduced in postmenopausal women after 6 months of moderate-intensity cycling exercise alongside improvements in basal forearm blood flow.[68] Such a reduction in basal sympathetic nerve activity could have directly reduced the occurrence and/or severity of hot flushes in this study, or, indirectly, by reducing vascular resistance.

The impact of a reduction in body mass with exercise training on hot flushes also deserves consideration. Reductions in BMI were evident with exercise training in the current study in accordance with one previous study that reported lower BMI and hot flush symptoms after increases in self-reported physical activity.[69] Although the role of obesity on hot flush prevalence is unclear, observational studies have reported that women with low[70] and high[71] body fat are at increased risk of hot flushes. Although speculative, increased adiposity may increase hot flushes due to elevated insulation and/or affect vascular function via the release of adipokines and inflammatory markers from visceral adipose tissue, which could decrease with exercise training. It is also important to highlight that an intervention causing body mass reduction that did not involve exercise would not mediate the thermoregulatory and vascular function improvements observed in the current study.[72]

Despite the benefits of the exercise training intervention on reducing hot flushes, they were not completely abolished after exercise training (~62% reduction in weekly frequency). Using various indices, previous studies have reported reductions in hot flush frequency in the range of 8% to 33%[12,16] and severity in the range of 10% to 30%.[12-14,16] The reasons for the higher reductions in frequency and severity in the present study are likely due to differences in exercise training program design (eg, supervised vs unsupervised and/or program duration).[12] In a similar study to ours with supervision and high exercise adherence, Lindh et al reported similar reductions in hot flush frequency and severity with exercise training.[15] The frequency and severity responses of the present study mimic those observed (~50%-72% reduction in hot flushes) after HT administration (ie, usual clinical care) in symptomatic women over 12 weeks.[5] HT administration over 12 months further reduces hot flushes,[6,73] and thus the effects of exercise training may also further alleviate hot flushes in a similar dose-response manner. Despite a reduction in hot flushes with both HT and exercise training, it is currently unknown if the effects of exercise and HT act by the same mechanisms, via an increase in estrogen. Whether the combined effects of exercise training and HT further improve hot flushes and offset the increases in cardiovascular risk observed with HT is worth considering. Furthermore, whether the positive effects of exercise on reducing hot flushes remain after cessation of exercise training is currently unknown; however, it can be speculated that the positive effects may be transient in the absence of exercise training, that is approximately 4 weeks, in line with the reductions observed in thermoregulatory function after the cessation of exercise training in young women.[20] Nevertheless, the findings of the present study suggest that improving thermoregulatory function in symptomatic postmenopausal women is beneficial for hot flushes. Although exercise training clearly confers improvements in thermoregulatory function these findings also suggest that improving thermoregulatory function per se (eg, passive heat acclimation) may also be of benefit for symptomatic postmenopausal women.

One limitation of this study is that it was not a randomized controlled trial, with participants free to choose which treatment group they entered. Although this convenience sampling and small sample size limit generalizability, these findings are labeled preliminary and need to be confirmed in a larger randomized controlled trial, the reduction in hot flush frequency in the exercise group is similar to that observed in previous studies, and the hot flush frequency remained unchanged in the control group. Furthermore, thermoregulatory measurements are objective and cannot be influenced by the participant,[41] and were analyzed in a blinded fashion. Nonetheless, it is acknowledged that the current findings are specific to early postmenopausal women (1-4 y since last menstrual period) that were free of cardiovascular disease and not engaged in regular physical activity. The impact of exercise training in alleviating hot flushes in individuals with cardiovascular risk factors, or disease, or other populations who experience hot flushes (eg, cancer participants) warrants further research.

CONCLUSIONS

In summary, improvements in the occurrence of hot flushes with short-term exercise training are mediated via thermoregulatory and cardiovascular adaptation(s). This study provides mechanistic evidence that exercise training is indeed a useful nonpharmacological alternative intervention in the treatment of hot flushes. These findings suggest that targeting the thermoregulatory and cardiovascular systems with interventions may be useful in treating symptomatic postmenopausal women that suffer from hot flushes.

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