J Appl Physiol 124: 583–591, 2018.
First published September 28, 2017; doi:10.1152/japplphysiol.00411.2017.

RESEARCH ARTICLE

Evidence of a greater functional sympatholysis in habitually aerobic trained postmenopausal women

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Submitted 5 May 2017; accepted in final form 22 September 2017

Kruse NT, Hughes WE, Hanada S, Ueda K, Bock JM, Iwamoto E, Casey DP. Evidence of a greater functional sympatholysis in habitually aerobic trained postmenopausal women. *J Appl Physiol* 124: 583–591, 2018. First published September 28, 2017; doi: 10.1152/japplphysiol.00411.2017.—Habitual aerobic exercise attenuates elevated vasoconstriction during acute exercise (functional sympatholysis) in older men; however, this effect remains unknown in postmenopausal women (PMW). This study tested the hypothesis that PMW who participate in habitual aerobic exercise demonstrate a greater functional sympatholysis compared with their untrained counterparts. Nineteen PMW (untrained $n = 9$ vs. trained $n = 10$) performed 5 min of steady-state (SS) forearm exercise at relative [10% and 20% of maximum voluntary contraction (MVC)] and absolute (5 kg) contraction intensities. Lower-body negative pressure (LBNP) was used to increase sympathetic vasoconstriction during rest and forearm exercise. Brachial artery diameter and blood velocities (via Doppler ultrasound) determined forearm blood flow (FBF; ml/min). Forearm muscle oxygen consumption ($\dot{V}O_{2m}$; ml/min) and arteriovenous oxygen difference (a-vO_{2diff}) were estimated during SS-exercise and SS-exercise with LBNP. Forearm vascular conductance (FVC; ml·min^{-1}·100 mmHg^{-1}) was calculated from FBF and mean arterial pressure (MAP; mmHg). Vasoconstrictor responsiveness was determined as the %change in FVC during LBNP. The reduction in FVC (% change FVC) during LBNP was lower in trained compared with untrained PMW at 10% MVC ($-7.3 \pm 1.2\%$ vs. $-13.0 \pm 1.1\%$; $P < 0.05$), 20% MVC ($-4.4 \pm 0.8\%$ vs. $-8.6 \pm 1.4\%$; $P < 0.05$), and 5 kg ($-5.3 \pm 0.8\%$ vs. $-8.9 \pm 1.4\%$; $P < 0.05$) conditions, whereas there were no differences at rest ($-32.7 \pm 4.4\%$ vs. $-33.7 \pm 4.0\%$). Peripheral (FVC, FBF, and $\dot{V}O_{2m}$) and the magnitude change in systemic hemodynamics (heart rate and MAP) did not differ between groups during exercise. Collectively, the findings present the first evidence suggesting that PMW who participate in aerobic exercise demonstrate a greater functional sympatholysis compared with untrained PMW during mild to moderate forearm exercise.

NEW & NOTEWORTHY Habitual aerobic exercise attenuates the elevated sympathetic nervous system-induced vasoconstriction during an acute bout of exercise (improved functional sympatholysis) in aging men; however, this effect remains unknown in postmenopausal women (PMW). The novel findings of this study suggest that habitual aerobic exercise results in an enhanced functional sympatholysis in PMW. Conversely, habitual aerobic exercise does not alter blood flow and oxygen utilization during acute forearm exercise compared with PMW who do not habitually exercise.

aging; exercise; postmenopausal women; vasoconstrictor tone

INTRODUCTION

During exercise, vascular tone, and hence skeletal muscle blood flow, is modulated by a balance between sympathetic nervous system (SNS)-mediated vasoconstriction and local concentrations of vasodilatory metabolites released from the endothelium, circulating erythrocytes, and the active skeletal muscle (i.e., ATP, prostaglandins, nitric oxide, etc.) (13, 42). Such evidence indicates that vasodilatory metabolites and metabolic substances override the enhanced sympathetic vasoconstriction, with the net effect of directing flow to metabolically active skeletal muscle tissue during exercise; this physiological phenomenon has come to be known as functional sympatholysis (41). Thus it is believed that functional sympatholysis reflects the ability of active muscle beds to release sympatholytic factors to locally attenuate the sympathetic vasoconstrictor response associated with exercise, leading to an optimal tissue metabolism-perfusion matching.

Advancing age is associated with a progressive increase in SNS activity and plasma norepinephrine concentrations, acting to increase peripheral vascular resistance and thereby enhance vasoconstriction at rest and during exercise (2, 13, 31, 43, 44). One manifestation of advancing age is impaired functional sympatholysis and reduced perfusion to the active skeletal muscle tissue (6–8, 13). Emerging evidence obtained from both longitudinal (16, 28, 29) and cross-sectional (29) studies suggests that age-associated impairments in functional sympatholysis appear to be attenuated or even abolished when chronic endurance exercise training is performed at moderate- to high-intensity efforts, at least in males. For example, Mortensen et al. (28) showed that when compared with their sedentary counterparts, trained older men demonstrated a significant increase in femoral arterial blood flow and muscle O_2 consumption during knee-extensor exercise in response to postjunctional alpha-adrenergic vasoconstriction via tyramine infusion. These findings support the contention that habitual aerobic exercise in older males enhances functional sympatholysis leading to an improved metabolism-perfusion matching.

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Current evidence suggests that sex differences in the modulatory effect of fitness and/or physical activity on the aging cardiovascular system in humans is heterogeneous to specific cardiovascular outcomes and vasodilator pathways (11, 12, 24, 26, 34–36). Specifically, with regard to postmenopausal women (PMW), the enhanced decline in vascular function is accelerated during the postmenopausal period, which may be one reason that this population experiences more functional impairment, higher prevalence of hypertension, and overall cardiovascular morbidity and mortality than age-matched males (4). In line with this notion, Parker and colleagues (36) confirmed evidence of an age-sex interaction regarding vasoconstrictor tone and regulation of peripheral vascular resistance by demonstrating that older women, but not men, exhibit blunted hyperemic and vasodilator responses to graded exercise relative to their young counterparts. In addition, Fadel et al. (9) identified a reduced ability of handgrip exercise to blunt sympathetic vasoconstriction (as based on near-infrared spectroscopy oxygenation indexes) during acute SNS stimulation (via lower-body negative pressure) in the exercising forearm of young vs. older estrogen-deficient PMW. However, this study was not specifically designed to investigate whether blood flow, vascular conductance, and O_2 utilization is indeed altered during acute exercise under sympathetic stimulation (i.e., functional sympatholysis) in PMW. Furthermore, it remains unknown whether PMW who are aerobically exercise-trained have a greater functional sympatholysis relative to their untrained, age-matched counterparts.

With this information as background, the present study sought to explore *1*) whether PMW who participate in habitual aerobic exercise exhibit a greater functional sympatholysis relative to PMW who do not habitually exercise; and *2*) whether steady-state blood flow and muscle O_2 consumption/O_2 extraction are improved in habitually aerobic exercised PMW. We hypothesized that PMW who participate in habitual aerobic exercise would demonstrate a greater ability to offset SNS-mediated vasoconstriction in contracting skeletal muscle relative to untrained older women. Furthermore, it was hypothesized that steady-state blood flow and/or skeletal muscle O_2 consumption/O_2 extraction will be augmented in PMW who participate in habitual aerobic exercise during conditions with and without elevated SNS activity.

METHODS

A total of 20 PMW (untrained $n = 10$ vs. trained $n = 10$) participated in this cross-sectional investigation. All PMW enrolled in the study were not receiving hormone replacement therapy, were free of any cardiovascular, metabolic, autonomic, or musculoskeletal disorders, and were not taking medications that may alter blood pressure responses. Postmenopausal status was defined as >12 mo since last menstrual period (13, 15) and none were labeled as obese (body mass index >30 kg/m^2). Participants were characterized as untrained (U-PMW) if they did not engage in regular and rigorous physical activity programs (>30 min in duration and >2 times per week), whereas exercise trained PMW (T-PMW) were labeled as those having been active in aerobic or high intensity interval training (running, cycling, swimming, rowing, etc.) for at least 2 yr before the study (>45 min in duration and >4 days per week) as determined per physical activity/exercise questionnaire form. Studies were performed in the morning after an overnight fast, and subjects refrained from exercise, alcohol, and caffeine for 24 h before reporting to the laboratory. The nature, risks, and benefits of all study procedures were explained to volunteers, and their written, informed consent was obtained before participation in the study. All procedures were reviewed and approved by the Institutional Review Board at the University of Iowa.

Experimental Overview

Subjects were studied while lying supine, with the left arm perpendicular to the body (~80°) and in a dependent position (just above heart level) to avoid gravitational influences on blood flow at rest and during exercise. Each subject performed three separate 5-min forearm hand-gripping exercise protocols, using two different relative contraction intensities and an additional absolute contraction intensity, which were randomized within each subject. After 3 min of steady-state (SS) forearm exercise, lower-body negative pressure (LBNP) was applied for the remaining 2 min of exercise. Measures of forearm blood flow (FBF), mean arterial pressure (MAP), and heart rate (HR) were continuously recorded in a period of 1-min before and during each 5-min exercise protocol.

Experimental procedures. Figure 1 depicts the design and timeline of each experimental condition. After a preliminary testing and familiarization session (conducted on a separate day), subjects per-

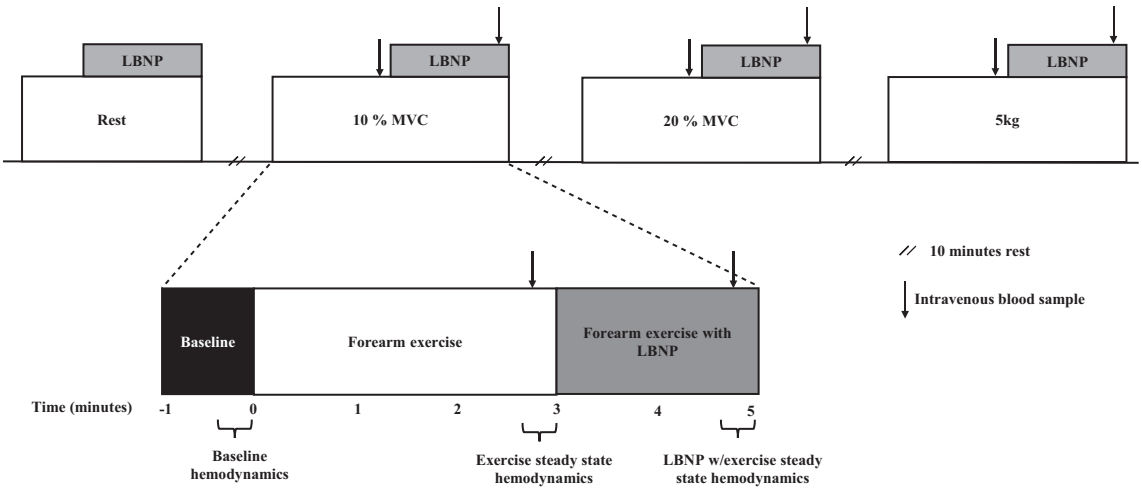

Fig. 1. Experimental design and timeline representing a rest condition with lower body negative pressure (LBNP) and three different contraction handgrip exercise trials during steady-state (SS) exercise and exercise with LBNP. The 10% and 20% maximal voluntary contraction (MVC) trials represent the relative contraction intensities whereas the 5-kg condition represents the absolute workload in which every participant performed this exact forearm workload.

formed the experimental testing session, consisting of one rest and three exercise trials. The rest trial always preceded the exercise conditions, and at least 10 min of rest was provided between experimental trials.

Forearm contraction protocol. Prior to the first exercise bout, maximal voluntary contraction (MVC) of the left hand was measured by having subjects squeeze a handgrip dynamometer (Stoelting, Chicago, IL) at maximal effort three separate times and averaging the values that were within 2 kg of each other. The MVC was then used to calculate the relative workload corresponding to 10% and 20% MVC for the forearm exercise trials. In addition, an absolute work load (5 kg) was used, as evidence suggests that inhibition of sympathetic adrenergic vasoconstriction in the exercising muscle may be more closely associated with the mechanical cost of contractions (absolute work) performed and, therefore, related to the rate of oxidative metabolism, as opposed to other confounding factors (i.e., relative workload contraction, age, sex, training status) (3, 46, 47).

Rhythmic forearm exercise was conducted by squeezing and releasing two handles together (4 cm apart) on a custom-built, handgrip device effectively raising and lowering a given weight attached via a simple pulley system. Forearm contractions were completed at 20 contractions/min, which were controlled by a metronome (1:2 s duty cycle). Subjects were cued to contract at the sound of the beat on the metronome and release the weight (without the intent to contract upon descent) when the metronome went silent during the relaxation phase.

Lower-body negative pressure. LBNP was used to unload the cardiopulmonary baroreceptors and reflexively increase sympathetic vasoconstriction during acute exercise. The lower body of each subject was sealed in an airtight box just above the level of the iliac crests. The box, attached to a vacuum source, allowed for rapid reductions in air pressure (−30 mmHg) within ~10 s and lasted for the remaining 2 min of each exercise trial (*minutes 3–5*; Fig. 1). This LBNP stimulus has been previously reported to be sufficient at increasing muscle SNS activity without significant changes in systemic blood pressure (32).

Prior to the exercise trials, LBNP was also applied at rest as a separate trial (Fig. 1) for 2 min to account for the sympathetic response at rest as well as to be compared against each exercise condition. This consisted of a 1-min baseline period leading into 2 min of LBNP.

Experimental Measurements

Central hemodynamic measurements. Heart rate was monitored by three-lead electrocardiography (ECG). Brachial artery pressure was measured in duplicate using an automated cuff (Cardiocap/5, Datex-Ohmeda, Louisville, CO) following 20 min of rest, before beginning experimental testing. During each experimental rest or exercise sequence beat-by-beat arterial pressure was measured by placing a finger cuff around the middle phalanx of the third finger on the nonexercising hand via finger plethysmography (Nexfin; Edward Lifesciences, Irvine, CA).

Deep vein catheterization and blood gas measurements. A 3-cm, 20-gauge catheter (BD Insyte Autogard; Beckton+ Dickinson Infusion Therapy Systems, Sandy, UT) was inserted in retrograde fashion into a deep vein in the antecubital fossa of the exercising arm. Confirmation that the selected vein drained the active forearm muscle was obtained via ultrasound imaging before catheterization by skilled anesthesiologists, ensuring the catheter was threaded into a deep vein from the exercising forearm. Saline was continuously infused through the catheter at a rate of ~1–2 ml/min for the duration of the study to keep the catheter patent. During each experimental exercise sequence, a single blood sample (~3 ml) was taken during the last 30 s of SS-exercise and SS-exercise with LBNP (Fig. 1). A blood-gas analyzer (RadiometerLive, ABL 80 FLEX CO-OX, Brønshøj, Denmark) was used to immediately analyze the following: partial pressures of venous carbon dioxide (Pv_{CO_2}) and oxygen (Pv_{O_2}), venous oxygen content (Ctv_{O_2}), venous hemoglobin content (Ctv_{Hb}), and oxygen saturation (Sv_{O_2}).

Measurement of forearm blood flow. Brachial artery diameter and blood velocity were determined with a 12-MHz linear-array Doppler probe (model M12L; Vivid 7, General Electric, Milwaukee, WI) with a probe insonation angle of 60°. Velocity waveforms were synchronized to a data-acquisition system (WinDaq; DATAQ Instruments, Akron, OH) through a Doppler audio transformer (15). End-diastolic brachial artery diameter measurements were obtained at rest and at the end of SS-exercise and SS-exercise with LBNP.

Data analysis. Data were collected at 250 Hz, stored on a computer, and analyzed off-line with signal processing software (WinDaq; DATAQ Instruments). MAP was determined from the finger arterial pressure waveforms and HR was determined from the ECG recordings. Cardiac output (l/min) was estimated from the Nexfin device using an automated pulse contour waveform analysis via a three-element windkessel model that incorporates the influence of arterial pressure wave form and subject's characteristics on aortic properties (10). Forearm blood flow (FBF, ml/min) was calculated as the product of mean blood velocity (cm/s) and brachial artery cross-sectional area (cm^2). Forearm vascular conductance (FVC, $ml \cdot min^{-1} \cdot 100\ mmHg^{-1}$) was calculated using the quotient of FBF and MAP. All hemodynamic measurements for rest, SS-exercise, and SS-exercise with LBNP for each trial were determined by averaging values during the last 30 s of rest, last 30 s of SS exercise (during the 3rd minute of exercise), and last 30 s of SS-exercise with LBNP (the 5th minute of exercise).

The degree of vasoconstriction (% change in FVC; % ΔFVC) that occurred during LBNP relative to rest or SS exercise among trials was calculated as [% ΔFVC = FVC (LBNP) − FVC (SS)/FVC (SS)] × 100. Percent reduction in FVC was used as the standard index to compare vasoconstrictor responses to LBNP-induced vasoconstriction across trials in accordance with previous research (8).

Venous blood gas measurements of Pv_{O_2}, Ctv_{O_2}, and Sv_{O_2} were collected from the exercising arm and used to estimate the arterial-venous O_2 difference ($a\text{-}vO_{2diff}$). Estimation of $a\text{-}vO_{2diff}$ was based on *1*) unpublished findings in our laboratory showing arterial O_2 content to be ~16 ml/dl (range 14–18 ml/dl; $n = 8$) in healthy sedentary PMW and *2*) the available evidence demonstrating that arterial O_2 content does not typically change during mild to moderate forearm (handgrip) exercise in humans (5). From $a\text{-}vO_{2diff}$ and FBF, muscle O_2 consumption across the exercising forearm ($\dot{V}O_{2m}$) was estimated using the Fick equation.

Statistical analysis. All values are expressed as means ± SE unless stated otherwise. The main dependent variables are FBF and FVC which are represented as absolute values during SS-exercise and LBNP conditions. A two-way repeated-measures ANOVA (1 factor repetition) was used to assess a group (trained vs. untrained) × condition (10% vs. 20% vs. 5 kg) interaction on FBF and FVC. In addition, a two-way repeated-measures ANOVA was used to test significance between the trained and untrained subjects in the vasoconstrictor effects (% change FVC) within and between trials. Tukey's post hoc test was conducted to assess main effects (within- and between-group differences) when applicable. In addition, all systemic hemodynamic (MAP, CO, SV, and HR) and metabolic ($a\text{-}vO_{2diff}$ and $\dot{V}O_{2m}$) variables were compared via repeated-measures (1 factor) ANOVA to detect differences between responses for each contraction trial during SS-exercise and LBNP, respectively. All statistical analyses were performed using SigmaPlot software version 11.0 (Systat Software, San Jose, CA). Statistical difference was set a priori at $P < 0.05$.

RESULTS

Subject Characteristics

Table 1 represents the subject characteristics for U-PMW vs. T-PMW. Due to technical constraints during a study visit for

Table 1. *Subject characteristics*

Variable	Trained	Untrained
Age, yr	61 ± 5	64 ± 4
Years postmenopause	10 ± 6	12 ± 5
Height, cm	170 ± 4	170 ± 4
Weight, kg	58 ± 9*	67 ± 9
BMI, kg/m^2	21 ± 3*	25 ± 3
MVC, kg	27 ± 5	25 ± 6
MAP, mmHg	83 ± 9*	91 ± 7
Total volume exercise, h/wk	11 ± 4*	2 ± 1
Moderate- to high-intensity exercise, h/wk	9 ± 2*	1 ± 1

Values are means ± SD. MVC, maximal voluntary contraction; MAP, mean arterial pressure; BMI, body mass index. *$P < 0.05$ vs. untrained postmenopausal women

one U-PMW individual, data for this particular subject were removed from the statistical analysis. Therefore, all hemodynamic data were compared and represented as U-PMW ($n = 9$) and T-PMW ($n = 10$).

Age, height, and number of years postmenopausal were not different between U-PMW vs. and T-PMW; however, T-PMW had a lower body weight, body mass index (BMI), and resting BP compared with U-PMW (all $P < 0.05$). With regard to exercise regimens, T-PMW performed a greater total volume of aerobic exercise ($P < 0.05$) as well as time spent performing moderate- to high-intensity aerobic exercise ($P < 0.05$) relative to U-PMW. In addition, almost all (9/10) T-PMW reported engaging in upper-body exercise, such as rowing, swimming, tennis, and racquetball, in addition to their lower-body aerobic exercise regimens.

Forearm Blood Flow, Vascular Conductance, and Muscle Oxygen Consumption

Figure 2 represents the FBF (Fig. 2*A*) and FVC (Fig. 2*B*) responses between groups across each condition. At rest with and without LBNP, there were no differences in FBF and FVC among groups. Within each exercise work condition among groups, LBNP reduced FBF and FVC compared with SS-exercise ($P < 0.05$). The 10% MVC trial exhibited a lower FBF and FVC response compared with 20% MVC and 5 kg work conditions ($P < 0.05$). In addition, there were no differences in FBF and FVC during SS-exercise and SS-exercise with LBNP between groups.

Table 2 represents forearm $\dot{V}_{O_{2m}}$ and a-vO_{2diff} during SS-exercise and during SS-exercise with LBNP. Acute sympathetic stimulation via LBNP resulted in a lower ($P < 0.05$) $\dot{V}_{O_{2m}}$ in each exercise condition. The lower $\dot{V}_{O_{2m}}$ was likely explained by a reduced FBF (Fig. 2*A*), as no differences in a-vO_{2diff} were evident between groups across each condition.

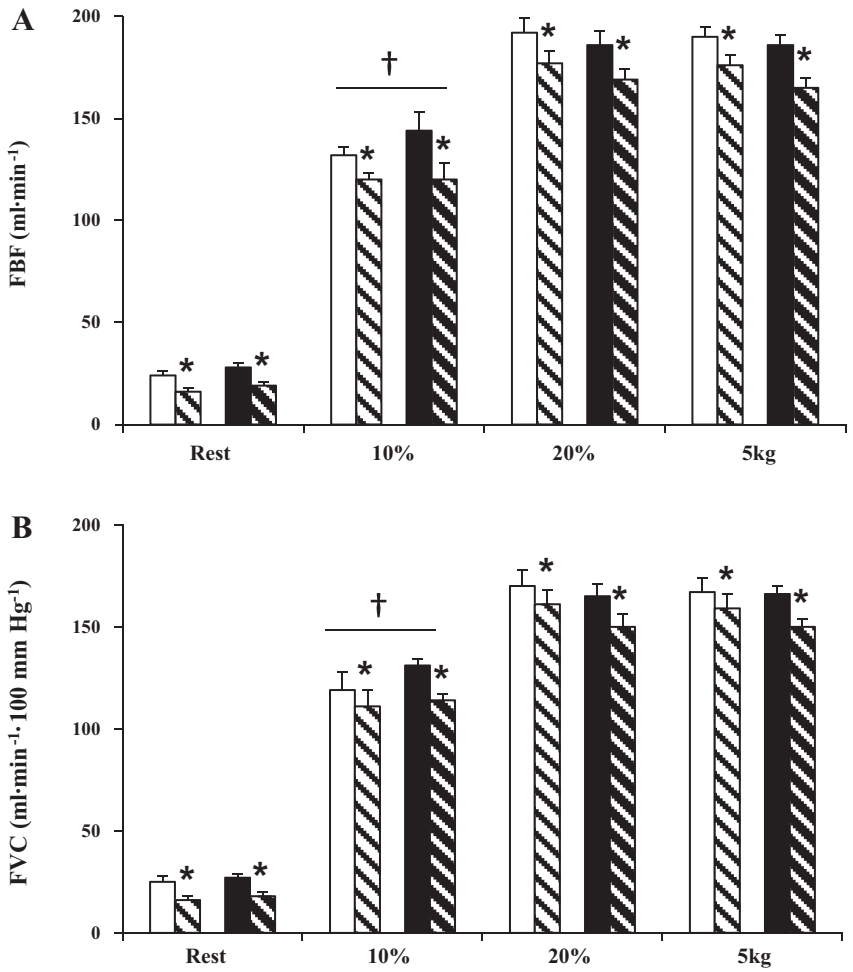

Fig. 2. Forearm hemodynamics at rest and during steady-state exercise at 10% and 20% of maximal and 5 kg in trained ($n = 10$; white bars) and untrained ($n = 9$; black bars) postmenopausal women. Hatched bars indicate lower-body negative pressure (LBNP) trial. LBNP resulted in a lower FBF (*A*) and FVC (*B*) response in each condition. †$P < 0.05$ vs. 20% and 5 kg, main effect of trial. *$P < 0.05$ vs. rest or SS-exercise, main effect of condition. Values are means ± SE.

Table 2. *Blood gas variables*

	Trained							Untrained						
	Pv_{CO_2}, mmHg	Pv_{O_2}, mmHg	ctHb, g/dl	Sv_{O_2}, %	Ctv_{O_2}, ml/l	a-vO_{2diff}, ml/min	$\dot{V}_{O_{2m}}$, ml/min	Pv_{CO_2}, mmHg	Pv_{O_2}. mmHg	ctHb, g/dl	Sv_{O_2}, %	Ctv_{O_2}, ml/l	a-vO_{2diff}, ml/min	$\dot{V}_{O_{2m}}$, ml/min
						SS-Exercise								
10%	50 ± 2	27 ± 3	12 ± 0.4	33 ± 5	5 ± 1	11 ± 1	15 ± 1	52 ± 3	25 ± 1	12 ± 0.3	30 ± 3	5 ± 0.1	11 ± 0.1	16 ± 2
20%	58 ± 2	30 ± 2	12 ± 0.3	38 ± 2	6 ± 0.3	10 ± 0.3	19 ± 2	57 ± 2	26 ± 1	12 ± 0.2	29 ± 3	5 ± 0.4	11 ± 0.4	20 ± 2
5 kg	59 ± 2	30 ± 3	12 ± 0.3	34 ± 3	6 ± 0.4	10 ± 0.4	20 ± 1	53 ± 1	26 ± 1	12 ± 0.3	31 ± 3	5 ± 0.4	11 ± 0.4	20 ± 1
						SS+LBNP								
10%	54 ± 1	23 ± 2	12 ± 0.2	29 ± 4	5 ± 1	11 ± 1	14 ± 1*	52 ± 4	24 ± 1	12 ± 0.4	30 ± 2	5 ± 0.4	11 ± 0.4	14 ± 2*
20%	56 ± 3	27 ± 2	12 ± 0.4	38 ± 4	6 ± 1	10 ± 1	18 ± 2*	57 ± 1	25 ± 2	12 ± 0.2	30 ± 3	5 ± 0.4	11 ± 0.4	19 ± 1*
5 kg	58 ± 2	26 ± 2	12 ± 0.3	34 ± 3	6 ± 1	10 ± 1	19 ± 1*	56 ± 2	23 ± 1	12 ± 0.2	26 ± 2	4 ± 0.3	12 ± 0.3	19 ± 1*

Values are means ± SE. Forearm muscle oxygen consumption ($\dot{V}_{O_{2m}}$) was decreased during acute sympathetic stimulation [lower-body negative pressure (LBNP)] in trained and untrained postmenopausal women (PMW) at each work intensity. There were no differences in arteriovenous oxygen difference (a-vO_{2diff}) and other blood gas variables during steady-state (SS) exercise and SS exercise with LBNP (SS+LBNP). *$P < 0.05$ vs. SS-exercise.

Vasoconstrictor Responsiveness

Figure 3 represents the vasoconstrictor responsiveness (% ΔFVC) to LBNP-induced sympathetic stimulation among and between each condition. There was a greater ($P < 0.05$) decrease in % ΔFVC during the rest trial compared with each exercise trial for both groups, respectively; however, no differences were evident between groups at rest (−33.7 ± 4.0% vs. −32.7 ± 4.4%). Among relative and absolute forearm workloads, the % ΔFVC was lower in T-PMW compared with U-PMW at 10% MVC (−7.3 ± 1.2% vs. −13.0 ± 1.1%), 20% MVC (−4.4 ± 0.8% vs. −8.6 ± 1.4%), and 5 kg (−5.3 ± 0.8% vs. −8.9 ± 1.4%) ($P < 0.05$ for all conditions).

Systemic Hemodynamics

Table 3 shows systemic hemodynamic responses at rest, during SS-exercise, and during SS-exercise with LBNP. There was no group-by-time interaction for any of the central hemodynamic variables. There was a main effect of time for HR, SV, and CO (all $P < 0.05$), whereas MAP was not different. There was a main effect of condition ($P < 0.05$) for CO where T-PMW exhibited a lower CO at rest and during each exercise trial as compared with U-PMW. Importantly, the effect of LBNP on HR, MAP, and SV did not differ between T-PMV and U-PMV.

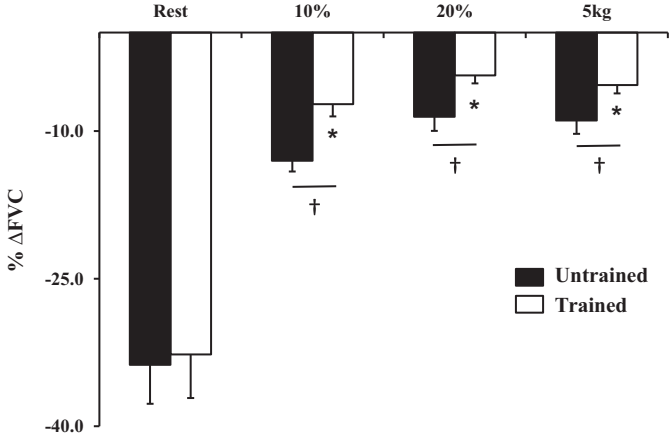

Fig. 3. Percent change in forearm vascular conductance (FVC) during sympathetic stimulation via lower-body negative pressure (LBNP). The reduction in FVC (% change FVC) during LBNP was greater during each workload in trained postmenopausal women ($n = 10$) compared with untrained postmenopausal women ($n = 9$). *$P < 0.05$ vs. untrained, main effect of trial. †$P < 0.05$ vs. rest, main effect of condition. Values are means ± SE.

DISCUSSION

The present study has provided novel evidence to suggest that PMW who regularly participate in aerobic exercise demonstrate a greater functional sympatholysis compared with healthy untrained PMW during mild to moderate dynamic forearm exercise. Furthermore, although functional sympatholysis was enhanced in T-PMW (Fig. 3), it was not inherently robust, as there were no significant differences in exercise hyperemia between T-PMW vs U-PMW for any exercise condition (Fig. 2). In addition, metabolic factors such as forearm $\dot{V}_{O_{2m}}$ and O_2 extraction (a-vO_{2diff}) did not differ between groups during relative or absolute forearm exercise. Collectively, these findings suggest that PMW who regularly participate in aerobic exercise demonstrate a greater functional sympatholysis, but does not statistically support the idea of an improved bulk blood flow and/or metabolic efficiency.

Exercise Training, Blood Flow, and Vasoconstrictor Responsiveness with Sex and Aging

Habitual aerobic exercise appears to result in an optimal blood flow distribution during exercise brought on by a more precise matching of O_2 delivery and oxidative metabolism (1, 17, 18, 45). This response has been extensively studied in healthy younger males and females as well as in older males (14); however, little information exists regarding PMW who participate in habitual aerobic exercise. It has recently been reported that habitual aerobic exercise can offset the age-associated decline in functional sympatholysis, leading to an improved skeletal muscle metabolism-perfusion matching, at least in older males (28, 29). Similar with prior work in older trained males (28, 29), the present study found that functional sympatholysis was greater in a group of PMW who participated in long-term endurance exercise compared with their healthy untrained counterparts. However, despite the greater functional sympatholysis in T-PMW, there were no notable improvements in blood flow, O_2 extraction, or $\dot{V}_{O_{2m}}$ during forearm exercise (Fig. 3). Although the present data report similar exercise vasodilatory (i.e., conduit) responses during SS-exercise between T-PMW and U-PMW, these findings are not surprising as they agree with most (20–22, 27, 33, 39) but not all exercise training studies (30).

Table 3. *Central hemodynamics*

	Trained					Untrained				
	MAP, mmHg	HR, beats/min	SV, ml	CO, l/min	TPR, mmHg·min^{-1}·ml	MAP, mmHg	HR, beats/min	SV, ml	CO, l/min	TPR, mmHg·min^{-1}·ml
					SS-Exercise					
Rest	98 ± 3†	55 ± 2†	60 ± 2	3.4 ± 0.2†	30.4 ± 1.6	106 ± 4	63 ± 3	63 ± 3	4.0 ± 0.2	27.5 ± 2.0
10%	110 ± 4	59 ± 3	58 ± 2	3.4 ± 0.2†	33.4 ± 1.9	109 ± 5	63 ± 3	60 ± 4	3.8 ± 0.3	29.9 ± 2.9
20%	116 ± 4	62 ± 2	57 ± 2	3.5 ± 0.2†	34.3 ± 1.4	113 ± 5	66 ± 3	61 ± 4	4.0 ± 0.3	29.8 ± 3.2
5 kg	114 ± 5	61 ± 3	56 ± 2	3.5 ± 0.2†	34.2 ± 1.6	114 ± 5	66 ± 3	61 ± 4	4.0 ± 0.4	30.9 ± 4.2
					LBNP					
Rest	96 ± 3†	63 ± 2*	51 ± 2*	3.2 ± 0.2*†	31.1 ± 1.7	105 ± 5	66 ± 3*	56 ± 3*	3.6 ± 0.3*	31.8 ± 3.8
10%	109 ± 4	67 ± 3*	49 ± 2*	3.3 ± 0.2*†	34.2 ± 1.6	108 ± 5	69 ± 3*	52 ± 3*	3.6 ± 0.3*	31.3 ± 2.9
20%	115 ± 4	69 ± 3*	49 ± 1*	3.4 ± 0.2†	35.0 ± 1.1	114 ± 5	71 ± 3*	54 ± 4*	3.8 ± 0.3	32.5 ± 3.9
5 kg	112 ± 4	68 ± 3*	48 ± 2*	3.4 ± 0.2†	34.7 ± 1.6	112 ± 5	72 ± 4*	55 ± 3*	3.9 ± 0.3	30.9 ± 4.4

Values are means ± SE. HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; CO, cardiac output; SS, steady-state exercise; LBNP, lower body negative pressure; TPR, total peripheral resistance. *$P < 0.05$ vs. SS-exercise; †$P < 0.05$ vs. untrained.

The population being investigated, limb differences, exercise mode, and/or exercise intensity should be considered in the context of hemodynamic responses represented in the present study. For instance, during supine single-leg knee extension exercise, Parker et al. (35) found that the hyperemic response to exercise was greater in young women compared with young men at workloads 40% of maximal effort. Conversely, Limberg et al. (23) demonstrated no difference in vasodilator responses between men and women at forearm exercise workloads of 30% of maximal effort. Similar to Limberg et al. (23) the present study found no change in the hyperemic responses within the forearms of T-PMW at efforts that did not exceed 20% MVC. It has also been documented that the legs exhibit a more robust vasoconstrictor response compared with the forearms in aging humans (40, 48). Moreover, larger reductions in exercising vascular conductance in the leg after acute sympathetic stimulation are more robust in older compared with younger men and this is attributable to a greater alpha-adrenergic sensitivity relative to the forearm (37, 40, 48). Collectively, the findings of the present study coupled with previous evidence suggest that sex and age differences in the vasoconstrictor and hyperemic response to exercise may only become evident when a critical threshold intensity (and metabolic demand) is reached; however, limb-specific differences appear to account for the robustness in vascular reactivity with age and training status.

Improvements in brachial artery (upper extremity) endothelial function have been observed in older men who engage in lower-body endurance exercise, but appear diminished or absent in age-matched older women (25, 26, 38). In the present study, lower-body endurance exercise consisted of a large volume of exercise regimens performed in T-PMW; however, the majority (90%) of T-PMW also reported engaging in upper-body aerobic exercise (i.e., swimming and rowing). Therefore, one cannot make the tacit assumption that lower-body exercise results exclusively in a globalized (systemic) phenomenon involving the nonexercising (i.e., arms) musculature, at least in PMW. Collectively, our data support the implication of a greater sympatholysis in T-PMW vs. U-PMW, respectively.

Absolute vs. Relative Exercise Intensity: Influence of Oxidative Metabolism and Functional Sympatholysis in Postmenopausal Women

A strength of the current study was that we have addressed both relative and absolute exercise intensities in the upper extremities and their association with functional sympatholysis in a relatively overlooked population, as it is believed that distinct differences exist with regard to how "work" is performed when investigating vascular related variables (i.e., PMW) (47). As previously noted, attenuation of sympathetic vasoconstriction may be more dependent upon the absolute amount of work performed (47). Importantly, it is believed that this comparison offers the advantage of viewing alpha-adrenergic receptor sensitivity between groups in a condition where skeletal muscle performs a similar amount of external mechanical work and thus, a comparable metabolic cost (i.e., $\dot{V}O_{2m}$). In light of these observations, we found that under exercise conditions using the same absolute mechanical work (i.e., 5 kg), functional sympatholysis is greater in T-PMW vs. U-PMW. This result was similar when a relative exercise intensity was utilized (10% MVC and 20% MVC). Collectively, these findings are in agreement (29) and in contrast (47) with prior work.

One key problem to recognize, which may explain discrepancies in our findings, is that in prior work (47) relative workloads were obtained from a "metabolic maximum" using an incremental exercise test to fatigue, whereas, in the present study, relative exercise intensities were determined from a single measurement of maximal force capacity (i.e., MVC). Given recent evidence suggesting that % peak force capacity (e.g., % MVC) and % peak aerobic capacity (e.g., metabolic maximum) may not be related (19), it is possible that our findings may not directly apply to studies in the legs in which relative work rates were obtained using % peak aerobic capacity. Another important aspect which may explain discrepancies is that the old vs. younger groups in the study by Wray et al. (47) differed markedly in terms of peak metabolic capacity. That is, the older group exhibited a much lower aerobic work capacity compared with their younger counterparts. As a result, the same % of maximum represented a considerably lower absolute work rate in older individuals. Thus, when the same absolute work rate is used for comparison between age groups,

a valid case can be made because the older individuals exhibited a much higher relative work rate. However, given that internal relative muscle work is proportional to metabolic cellular disturbances (H^+, P_i, etc.), and that the older group demonstrated a substantially reduced "metabolic max," it is not surprising that a higher submaximal intensity (via greater absolute workload) elicits a similar response. However, this would represent a less efficient sympatholysis. Last, it should be emphasized that the available evidence is not consistent, as our findings appear to support recent work using a metabolic max in the legs to examine workload (absolute vs. relative) differences in vasoconstrictor responsiveness in younger and older men (29). Given this quandary, future studies are needed to resolve whether absolute vs. relative exercise intensity, and/or whether the measurement of % peak aerobic capacity vs. % peak force capacity, is most appropriate when determining sympathetic vasoconstrictor tone during exercise.

Experimental Considerations

Despite strict inclusion criteria to reduce the confounding influences of age, postmenopausal status, cardiovascular related risk factors, medication, and supplementation use, the study's cross-sectional design may limit a comprehensive interpretation of our data. Therefore, while our data support the hypothesis that habitual aerobic exercise may be responsible for the greater sympatholysis in T-PMW, cause and effect toward this hypothesis remains to be directly tested. It should also be acknowledged that the lack of significant FBF values may be influenced by our small sample size. However, our primary outcome variable (% change FVC) yielded an adequate power (0.8) to detect an estimated 80% attenuation in the vasoconstrictor response to LBNP and with training status (T-PMW vs. U-PMW), respectively.

This study was not specifically designed to investigate whether there are differences between arterial O_2 content and venous O_2 content from the exercising skeletal muscle. Although we used unpublished data from healthy untrained PMW in our laboratory to provide an estimate of arterial O_2 content, it is possible that variations in arterial O_2 content in T-PMW alter the balance between O_2 delivery to O_2 utilization and therefore could account for the similarities in metabolism-perfusion matching among groups in the present investigation. In addition, the forearm venous sampling model employed in the present study may not have fully received all the venous effluent within the deep vein of the exercising forearm, as venous effluents are not an exact representation of the intravascular environment surrounding the active skeletal muscle. Therefore, some nonexercising effluent may have contributed to the observed lower $\dot{V}_{O_{2m}}$ values during LBNP within the present study.

It is also important to note that although the same mean relative workload value appeared to be nearly identical between T-PMW and U-PMW (Table 1), the wide range of MVCs (between 4 and 8 kg) and thus relative workloads employed still afforded us an opportunity to investigate absolute vs. relative workload on functional sympatholysis in the present study. Because of this and due to conflicting evidence in the available literature, we believe that this does not detract from the main important findings.

Last, our study did not directly quantify and compare sympathetic vasoconstriction in T-PMW vs. U-PMW, whether this is measured using MSNA recordings or norepinephrine spillover. It is possible that aerobic exercise might alter the SNS response to LBNP, and therefore the degree of forearm vasoconstriction might be different between groups. Additional studies involving the careful measurement and matching of the vasoconstrictor stimulus (e.g., MSNA, norepinephrine spillover) in younger and older subjects are required to determine if the absolute level of sympathetic vasoconstriction in exercising muscle increases with aging, sex, and training status.

Conclusions

In summary, the results from the present study have provided evidence of a greater functional sympatholysis in postmenopausal women who participate in habitual aerobic exercise compared with healthy PMW who do not partake in habitual aerobic exercise. However, it must be emphasized that despite the purported vasoconstrictor component involved in PMW who participate in habitual aerobic exercise, it is not inherently robust, as this did not modulate exercise O_2 consumption and blood flow, the latter likely being more important in the overall context of functional performance and physical fatigue during exercise.

ACKNOWLEDGMENTS

We are grateful for the subjects who volunteered to participate in this study. Extended appreciation goes out to A. Schneider and R. Hochstedler for valuable technical assistance during experimental data collection.

GRANTS

This research was supported by National Heart, Lung, and Blood Institute Research Grants HL-105467 (to D. P. Casey) and T32-HL-007121 (to N. T. Kruse).

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

N.T.K. and D.P.C. conceived and designed research; N.T.K., W.E.H., S.H., K.U., J.M.B., E.I., and D.P.C. performed experiments; N.T.K and D.P.C. analyzed data; N.T.K., W.E.H., J. B., E.I., and D.P.C. interpreted results of experiments; N.T.K. prepared figures; N.T.K. drafted manuscript; N.T.K., W.E.H., S.H., K.U., J.M.B., E.I., and D.P.C. edited and revised manuscript; N.T.K., W.E.H., S.H., K.U., J.M.B., E.I., and D.P.C. approved final version of manuscript.

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