

Comparison of Blood Pressure and Vascular Health in Physically Active Late Pre- and Early Postmenopausal Females

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ABSTRACT

DEBRAY, A., C. ENEA, N. RAVANELLI, G. K. CHASELING, H. GRAVEL, L. BOSQUET, L. BHERER, and D. GAGNON. Comparison of Blood Pressure and Vascular Health in Physically Active Late Pre- and Early Postmenopausal Females. *Med. Sci. Sports Exerc.*, Vol. 54, No. 7, pp. 1066–1075, 2022. **Purpose:** The benefits of exercise on vascular health are inconsistent in postmenopausal females. We investigated if blood pressure and markers of vascular function differ between physically active early post- and late premenopausal females. **Methods:** We performed a cross-sectional comparison of 24-h blood pressure, brachial artery flow-mediated dilation, microvascular reactivity (reactive hyperemia), carotid–femoral pulse wave velocity, and cardiac baroreflex sensitivity between physically active late premenopausal ($n = 16$, 48 ± 2 yr) and early postmenopausal ($n = 14$, 53 ± 2 yr) females. **Results:** Physical activity level was similar between premenopausal (490 ± 214 min·wk⁻¹) and postmenopausal (550 ± 303 min·wk⁻¹) females ($P = 0.868$). Brachial artery flow-mediated dilation (pre, 4.6 ± 3.9 , vs post, $4.7\% \pm 2.2\%$; $P = 0.724$), 24-h systolic ($+5$ mm Hg, 95% confidence interval [CI] = -1 to $+10$, $P = 0.972$) and diastolic ($+4$ mm Hg, 95% CI = -1 to $+9$, $P = 0.655$) blood pressures, total reactive hyperemia (pre, 1.2 ± 0.5 , vs post, 1.0 ± 0.5 mL·mm Hg⁻¹; $P = 0.479$), carotid–femoral pulse wave velocity (pre, 7.9 ± 1.7 , vs post, 8.1 ± 1.8 m·s⁻¹; $P = 0.477$), and cardiac baroreflex sensitivity (-8 ms·mm Hg⁻¹, 95% CI = -20.55 to 4.62 , $P = 0.249$) did not differ between groups. By contrast, peak reactive hyperemia (-0.36 mL·min⁻¹·mm Hg⁻¹, 95% CI = -0.87 to $+0.15$, $P = 0.009$) was lower in postmenopausal females. **Conclusions:** These results suggest that blood pressure and markers of vascular function do not differ between physically active late pre- and early postmenopausal females. **Key Words:** ARTERIAL STIFFNESS, CARDIOVASCULAR, ENDOTHELIAL FUNCTION, EXERCISE, WOMEN'S HEALTH

Cardiovascular diseases (CVD) are the leading cause of mortality in postmenopausal females, and the prevalence of CVD within this population is estimated at 19% (1). Cardiovascular risk after menopause is partly attributed to a greater prevalence of hypertension (1). As highlighted by evidence in females with early ovarian failure (2), the greater risk of hypertension is largely explained by the consequences of estrogen deficiency on blood pressure regulation.

Different mechanisms have been suggested to underlie this observation. First, cross-sectional studies have demonstrated that the transition from pre- to postmenopause is associated with endothelial dysfunction (3,4) and greater central arterial stiffness (5). Both of these physiological markers predict the risk of CVD and hypertension in postmenopausal females (6,7). Second, greater cardiac baroreflex sensitivity (cBRS) has been observed in postmenopausal females treated with estrogen compared with untreated age-matched counterparts (8). Together, these results suggest that vascular aging and alterations in cBRS may constitute targets for the prevention of hypertension and cardiovascular risk after menopause.

Aerobic exercise, sometimes combined with resistance exercise, is associated with a lower risk of hypertension and CVD in postmenopausal females (9,10). Aerobic exercise notably activates signaling pathways (MAPK and PGC1 α) within endothelial cells that are also triggered by estrogens and that lead to the synthesis of nitric oxide (11). Therefore, aerobic exercise should be an effective strategy to counteract the deleterious effects of estrogen loss on vascular health. However, the benefits of aerobic exercise for vascular health

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remain unclear in postmenopausal females (12,13). In terms of arterial stiffness, the effect of aerobic exercise is consistently protective (5,14). By contrast, the effects of aerobic exercise on endothelial function are mixed. Initial studies did not observe a benefit of 8- to 12-wk aerobic exercise interventions on endothelial function in females at a late stage (~9 yr) of menopause (15,16). Furthermore, cross-sectional studies have shown that endurance-trained females at a late stage of menopause (~6 to 8 yr) do not demonstrate improved endothelial function relative to their inactive peers (16,17). By contrast, a more recent study observed that 12 wk of aerobic exercise improves endothelial function in previously inactive females who are within an early stage (~1 to 3 yr) of menopause (18). Taken together, these previous studies support the “exercise timing hypothesis,” stating that aerobic exercise may be more effective at improving endothelial function if it is initiated before, during, or shortly after the onset of menopause rather than 5 to 10 yr later (11). Despite these observations, it remains unclear if females who are physically active before menopause can offset the deleterious changes in vascular health associated with the menopausal transition. Previous intervention studies recruited inactive females (15,16,18), whereas cross-sectional studies compared females at a late stage of menopause to relatively young (18–36 yr of age) premenopausal females (16,17). Lastly, it should be noted that studies demonstrating alterations in blood pressure and/or markers of vascular health with menopause recruited relatively inactive females (3,4).

The overall objective of this study was to determine, with the use of a cross-sectional design, if blood pressure and vascular function differ between physically active late pre- and early postmenopausal females. The primary hypothesis was that blood pressure would not differ between physically active early post- and late premenopausal females. The secondary hypothesis was that endothelial function, central arterial stiffness, and cBRS would not differ between physically active early post- and late premenopausal menopausal females. Finally, we explored the possibility that endothelial function is modulated by physical activity levels within these populations by testing the hypothesis that a positive correlation exists between physical activity levels and endothelial function.

METHODS

Ethical approval. This study was performed as a collaboration between the Montreal Heart Institute (MHI, Canada) and the Laboratory of Mobility, Aging and Exercise of Poitiers (MOVE, France). The study was approved by the MHI Ethics Board (ICM no. 2019-2524) and the French national ethics committee for noninterventional research (CERSTAPS no. 2018-21-09-26). Written informed consent was obtained from all participants before their participation in the study.

Participants. Of 112 participants who were assessed for eligibility, 16 premenopausal (48 ± 2 yr) and 14 postmenopausal (53 ± 2 yr) females completed the study (see Appendix, Fig. S1, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). Twenty of the participants (11 premenopausal

and 9 postmenopausal) were recruited at the MHI, whereas the remaining 10 participants (5 premenopausal and 5 postmenopausal) were recruited at the laboratory MOVE. To be eligible for the study, participants had to be between 45 and 55 yr of age and be physically active (≥ 150 min·wk⁻¹ of moderate-intensity physical activity or ≥ 75 min·wk⁻¹ of vigorous-intensity physical activity). Participants also had to be free of any disease or risk factors for CVD, nonsmoker, nonobese, and not taking any medication that could alter cardiovascular function. Menopausal status was characterized according to the STRAW+10 classification (19). Premenopausal females were recruited only if they had regular menstrual cycles and were not using oral contraceptives, and postmenopausal females were recruited if they were ≥ 1 -yr postmenorrhoea and not taking hormone replacement therapy within the previous 12 months.

Study design. Eligibility was determined during a screening visit during which a review of medical records and lifestyle habits was performed, and measurements of body height, weight, as well as a resting ECG and blood pressure were taken. Body composition was assessed by bioelectrical impedance analysis (BC-418; Tanita, Arlington Heights, IL). At the end of the visit, participants were provided with an accelerometer (wGT3X-BT; ActiGraph, Pensacola, FL) to quantify physical activity level for seven consecutive days on the dominant hip. Participants were asked to remove the device at bedtime and during bathing activities (shower, bath, and swimming) and to complete a log to note the type of physical activity completed during the week. Participants were asked to maintain their normal lifestyle habits over the 7-d measurement period. Then participants volunteered for two laboratory visits (see Appendix, Fig. S2, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). For both visits, participants were advised to avoid strenuous exercise at least 24 h prior, alongside caffeine and alcohol 12 h prior. For the first laboratory visit during which blood sample was obtained and brachial artery flow-mediated dilation (FMD), central arterial stiffness, and cBRS were assessed, participants were also required to arrive fasted (12 h), and premenopausal females performed this visit within the first 7 d after the onset of their menses.

Upon arrival for laboratory visit no. 1, a blood sample was obtained. Participants were subsequently instrumented and rested in the supine position for 10 min in a quiet, thermoneutral (~21°C) laboratory with the lights dimmed. At the end of this resting period, blood pressure was measured in triplicate. Then endothelial function was assessed by brachial artery FMD, followed by central arterial stiffness as carotid–femoral pulse wave velocity (cf-PWV) and lastly cBRS during 5 min of spontaneous breathing in supine position. At the end of the visit, participants underwent ambulatory blood pressure monitoring for 24 h (Mobil-O-Graph; IEM GmbH, Aachen, Germany). Blood pressure was measured every 30 min during the day (from 7:00 AM to 10:00 PM) and once per hour during the night. Participants filled out a log to note awake and sleep times, and activities. Upon arrival for laboratory visit no. 2, participants were instrumented and rested in the supine position

for 10 min after which a resting 12-lead ECG and blood pressure measurement was performed. The participants subsequently performed a cardiopulmonary exercise test on a treadmill with continuous measurements of gas exchange.

Measurements. All blood samples were obtained after a 12-h fast and analyzed by clinical biochemistry laboratories (MHI: Hematology and Biochemistry Laboratory; MOVE: BIO 86 Medical Analysis and Biology Laboratory) for serum glucose, glycated hemoglobin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, 17 β -estradiol, luteinizing hormone, and follicle-stimulating hormone. Heart rate was obtained from lead II of a 5-lead ECG (MHI: Solar i8000, GE Healthcare, Chicago, IL; MOVE: Physioflow Enduro, Cortex Medical, Leipzig, Germany). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by automated auscultation of the brachial artery (MHI: Tango M2, SunTech Medical, Morrisville, NC; MOVE: Omron M3, Healthcare).

FMD was measured according to expert guidelines (20) by a single trained operator. Brachial artery diameter and blood velocity were measured simultaneously by high-resolution Doppler ultrasound (MHI: uSmart3300, Terason, Burlington, MA; MOVE: CX-50, Phillips, Amsterdam, The Netherlands), equipped with a 4- to 15-MHz linear array transducer maintained at an insonation angle of 60°. A rapid inflation/deflation pneumatic cuff (SC5; Hokanson, Bellevue, WA) was placed immediately distal to the antecubital fossa. The ultrasound probe was placed 5–15 cm proximal to the antecubital fossa, where an optimal B-mode image could be obtained. Brachial artery diameter and blood velocity were recorded for 1 min after which the forearm cuff was inflated to 250 mm Hg for 5 min by a rapid cuff inflator (MHI: E20, Hokanson) or by an aneroid sphygmomanometer (MOVE: DS 400, Hokanson). After cuff pressure release, brachial artery diameter and velocity measurements continued for 3 min postocclusion. Ultrasound recordings were sent to a remote computer using a frame grabber (DVIUSB 3.0; Epiphan, Ottawa, ON, Canada) and were video captured and analyzed using edge-detection and wall-tracking software (Cardiovascular Suite v.3; Quipu SRL, Pisa, Italy). This method provided measurements of arterial diameter and time-averaged positive (antegrade)/negative (retrograde) blood velocities based on the Doppler envelope, at a sampling rate of 30 Hz. cf-PWV was measured using applanation tonometry according to expert guidelines (21). Pressure waveforms were obtained from the common carotid and femoral arteries with a pencil tip tonometer (MHI: SPT-301 and PCU-2000; Millar Instruments, Houston, TX) or by the Sphygmocor device (MOVE: SphygmoCor v8.0; AtCor Medical, Naperville, IL). Transit time between the foot of the carotid and the femoral waveforms was determined using a continuously recorded ECG signal. The pressure waveforms were recorded for a minimum of 10 consecutive cardiac cycles. Distance traveled by the pulse wave was measured, in triplicate, as the direct distance between the two measurement sites with a correction factor of 0.8 (21). cf-PWV was calculated as distance traveled (m) divided by transit time (s). Spontaneous cBRS was calculated by the Finapres monitoring

system (MOVE: NOVA; Finapres Medical Systems, Enschede, The Netherlands) or Labchart software (MHI: LabChart Pro v8; ADInstruments, Colorado Springs, CO) using the sequence method of beat-to-beat time series of SBP and R-R intervals (22) during 5 min at rest in a supine position.

A modified Balke incremental exercise treadmill protocol (23) was used to determine maximal oxygen consumption. Speed and inclination were set between 5.0 and 5.3 km·h⁻¹ and 0%, respectively, for the first minute. Subsequently, inclination increased to 6% for the second minute and by 2% every minute thereafter until participants were unable to continue or when signs or symptoms indicated the exercise test should be terminated. Continuous 12-lead ECG monitoring was performed during exercise, and blood pressure was measured by auscultation every 2 min. RPE (Borg scale) was determined every 2 min and at peak exercise. Expired gases were continuously measured and analyzed with calibrated gas analyzers (MHI: Quark, Cosmed, Rome, Italy; MOVE: Metalyzer 3B, Cortex Biophysik GmbH, Leipzig, Germany). For the test to be considered maximal, one of the following primary criteria had to be attained: a plateau of oxygen consumption despite an increase in exercise intensity and/or a respiratory exchange ratio >1.10 in addition to two of the following secondary criteria: attainment of 95% of age-predicted maximal heart rate, inability to maintain exercise intensity, and/or exhaustion with cessation caused by fatigue and/or other clinical symptoms (dyspnea, abnormal blood pressure responses) or ECG abnormalities that required exercise cessation.

Data analyses. Baseline brachial artery diameter was defined as the average diameter during the 1-min baseline recording. Peak brachial artery diameter was defined as the maximal 1-s average during the postocclusion period. FMD was calculated as the percentage change in brachial artery diameter from baseline to peak. Shear rate ($4 \times$ mean blood velocity/diameter) area under the curve (SR_{AUC}) up to peak diameter was considered the stimulus for FMD. Antegrade and retrograde shear rates were calculated using positive and negative mean blood velocity, respectively. Microvascular reactivity was quantified as peak and AUC forearm vascular conductance (FVC = forearm blood flow/mean arterial pressure) during the 3-min postocclusion period. For cBRS, sequences of at least three consecutive cardiac cycles were identified during which changes in SBP and R-R interval were in the same direction (i.e., consecutive up or down sequences). Parameters were set to detect sequences when changes in SBP were ≥ 1 mm Hg and the variation in R-R interval was ≥ 5 ms (24). Linear regression analyses were applied to each potential sequence, and the R^2 value was calculated. Acceptable baroreflex sequences were determined when R^2 was ≥ 0.85 . Spontaneous cBRS was calculated separately for up and down sequences, and overall cBRS was calculated as the average for up and down sequences. During ambulatory blood pressure monitoring, mean daytime (awake), nighttime (sleep), and 24-h values of SBP, DBP, mean, and pulse (PP) pressures were computed. Nocturnal blood pressure decline was calculated as the difference between mean diurnal and mean nocturnal blood pressure divided by the mean diurnal

blood pressure (25). Nondippers were defined by a <10% reduction in blood pressure from day to night, whereas individuals with $\geq 10\%$ reduction in blood pressure were considered as dippers.

Statistics. The study was powered based on a previous study (17) demonstrating that SBP is lower in physically active postmenopausal females (mean \pm SD, 105 ± 8 mm Hg) compared with sedentary postmenopausal females (mean \pm SD, 118 ± 15 mm Hg). An *a priori* power calculation determined that 15 participants per group (pre- and postmenopause) were required to detect a similar effect size ($d = 1.08$) with 80% power and a two-tailed alpha of 0.05. Data were analyzed using SPSS software (SPSS Statistics, IMB), and figures were created using GraphPad software (GraphPad, Prism v8). A Shapiro–Wilk test was performed to assess the distribution of normality. An ANCOVA was used to compare dependent variables between pre- and postmenopausal females with age as a covariate. For the analysis of brachial artery FMD, values were analyzed using unadjusted values and values adjusted for baseline diameter after allometric scaling (26). A Spearman correlation was used to evaluate the association between physical activity level and brachial artery FMD. The significance level for all analyses was set at $P < 0.05$. The effect size for analyses of covariance was assessed with partial eta squared (η^2) and classified as small ($\eta^2 = 0.01$), medium ($\eta^2 = 0.06$), or large ($\eta^2 > 0.14$). All values are reported as mean \pm SD, except for between-group differences (post minus pre) that are presented as mean with 95% confidence intervals.

RESULTS

Participant characteristics. Participant characteristics are reported in Tables 1 and 2, and dietary habits are reported in the supplementary file (see Appendix, Table S1, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). All postmenopausal females experienced a natural menopause and were at an average of 4 ± 3 yr postmenopause (13 females ≤ 5 yr, 1 female at 7 yr). Body mass index, fat and lean body mass, triglycerides, moderate to vigorous physical activity levels,

TABLE 1. Participant characteristics.

	Premenopause (<i>n</i> = 16)	Postmenopause (<i>n</i> = 14)	<i>P</i>
Age (yr)	48 \pm 2	53 \pm 2	<0.001
BMI (kg·m ⁻²)	23.8 \pm 3.5	22.2 \pm 2.8	0.187
Body mass (kg)	63.5 \pm 9.7	59.9 \pm 8.8	0.520
Fat mass (kg)	18.9 \pm 6.0	17.3 \pm 6.4	0.502
Lean body mass (kg)	44.7 \pm 4.9	42.6 \pm 3.6	0.197
VO _{2max} (mL·kg ⁻¹ ·min ⁻¹)	35.8 \pm 6.0	34.0 \pm 6.1	0.184
Glycemia (mmol·L ⁻¹)	4.7 \pm 0.3	5.1 \pm 0.4	0.004
HbA1c (%)	5.1 \pm 0.4	5.5 \pm 0.2	0.003
Total cholesterol (mmol·L ⁻¹)	4.8 \pm 0.7	6.2 \pm 1.6	0.004
LDL (mmol·L ⁻¹)	2.5 \pm 0.6	3.5 \pm 1.3	0.010
HDL (mmol·L ⁻¹)	1.9 \pm 0.3	2.3 \pm 0.4	0.018
Triglycerides (mmol·L ⁻¹)	0.9 \pm 0.3	0.8 \pm 0.3	0.643
17 β -estradiol (pg·mL ⁻¹)	72.7 \pm 48.8	<12.0	<0.001
LH (U·L ⁻¹)	7.8 \pm 8.1	29.3 \pm 8.4	<0.001
FSH (U·L ⁻¹)	12.0 \pm 13.3	82.8 \pm 23.8	<0.001

Data are presented as mean \pm SD. *P* value is for an independent samples *t*-test. BMI, body mass index; VO_{2max}, maximal oxygen consumption; HbA1c, hemoglobin A1c; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

TABLE 2. Physical activity history.

Physical Activity Levels	Premenopause (<i>n</i> = 16)	Postmenopause (<i>n</i> = 14)	<i>P</i>
MVPA (min·wk ⁻¹)	490 \pm 214	550 \pm 303	0.868
Sedentary time (min·d ⁻¹)	582 \pm 383	580 \pm 307	0.408
Years of physical activity	7 \pm 8	8 \pm 13	0.450
Type of Physical Activity Characteristics	Aerobic	Resistance	Combined
Participants, <i>n</i> (%)	14 (47)	5 (17)	11 (37)
Frequency (d·wk ⁻¹)	3 \pm 2	2 \pm 1	3 \pm 1
Duration (min·wk ⁻¹)	75 \pm 53	51 \pm 42	55 \pm 23

Data are presented as mean \pm SD. *P* value is for an ANCOVA with age as a covariate. MVPA, moderate to vigorous physical activity.

sedentary time, and maximal oxygen consumption did not differ between groups. The postmenopausal group was older ($P < 0.001$) and had greater levels of fasting glucose ($P = 0.004$), glycated hemoglobin ($P = 0.003$), total cholesterol ($P = 0.004$), HDL and LDL (both $P = 0.010$), luteinizing hormone ($P < 0.001$), and follicle-stimulating hormone ($P < 0.001$). 17 β -estradiol level was greater in pre- compared with postmenopausal females ($P < 0.001$).

24-h ambulatory blood pressure. The 24-h SBP (+5 mm Hg, 95% confidence interval [CI] = -1 to $+10$, $P = 0.972$, $\eta^2 < 0.01$), DBP (+4 mm Hg, 95% CI = -1 to $+9$, $P = 0.655$, $\eta^2 < 0.01$), mean blood pressure (+4 mm Hg, 95% CI = 0 to $+9$, $P = 0.789$, $\eta^2 < 0.01$), and PP (+1 mm Hg, 95% CI = -4 to $+5$, $P = 0.596$, $\eta^2 = 0.01$) did not differ between groups (Fig. 1). There were no differences in day or nighttime SBP, DBP, mean blood pressure, and PP between groups (see Appendix, Figs. S3 and S4, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). There were no differences in the proportion of participants who were classified as nighttime dippers ($n = 5$ premenopause and $n = 4$ postmenopause, +2.1%, 95% CI = -7.2 to $+11.6$, $P = 0.183$, $\eta^2 = 0.06$).

Markers of vascular health. Brachial artery FMD variables are reported in Table 3. Data were not useable for one premenopausal female and were excluded. Baseline SBP ($P = 0.692$, $\eta^2 < 0.01$), DBP ($P = 0.062$, $\eta^2 = 0.13$), brachial artery diameter ($P = 0.077$, $\eta^2 = 0.12$), antegrade shear rate ($P = 0.696$, $\eta^2 < 0.01$), and retrograde shear rate ($P = 0.062$, $\eta^2 = 0.06$) did not differ between groups. Unadjusted (+0.04%, 95% CI = -2.38 to $+2.47$, $P = 0.724$, $\eta^2 = 0.04$) and adjusted ($P = 0.750$, $\eta^2 < 0.01$) brachial artery FMD did not differ between groups. SR_{AUC} ($P = 0.657$, $\eta^2 < 0.01$) and time to peak dilation ($P = 0.844$, $\eta^2 < 0.01$) also did not differ between groups. Baseline forearm blood flow ($P = 0.629$, $\eta^2 < 0.01$) and FVC ($P = 0.582$, $\eta^2 = 0.01$) were not different between groups. Reactive hyperemia expressed as FVC_{AUC} (-0.15 mL·mm Hg⁻¹, 95% CI = -0.54 to 0.25 , $P = 0.479$, $\eta^2 = 0.02$) did not differ between post- and premenopausal females (Fig. 2). By contrast, reactive hyperemia quantified as FVC peak was lower in post- compared with premenopausal females (-0.36 mL·min⁻¹·mm Hg⁻¹, 95% CI = -0.87 to $+0.15$, $P = 0.009$, $\eta^2 = 0.23$). cf-PWV did not differ between groups (+0.29 m·s⁻¹, 95% CI = -1.03 to 1.62 , $P = 0.477$, $\eta^2 = 0.02$).

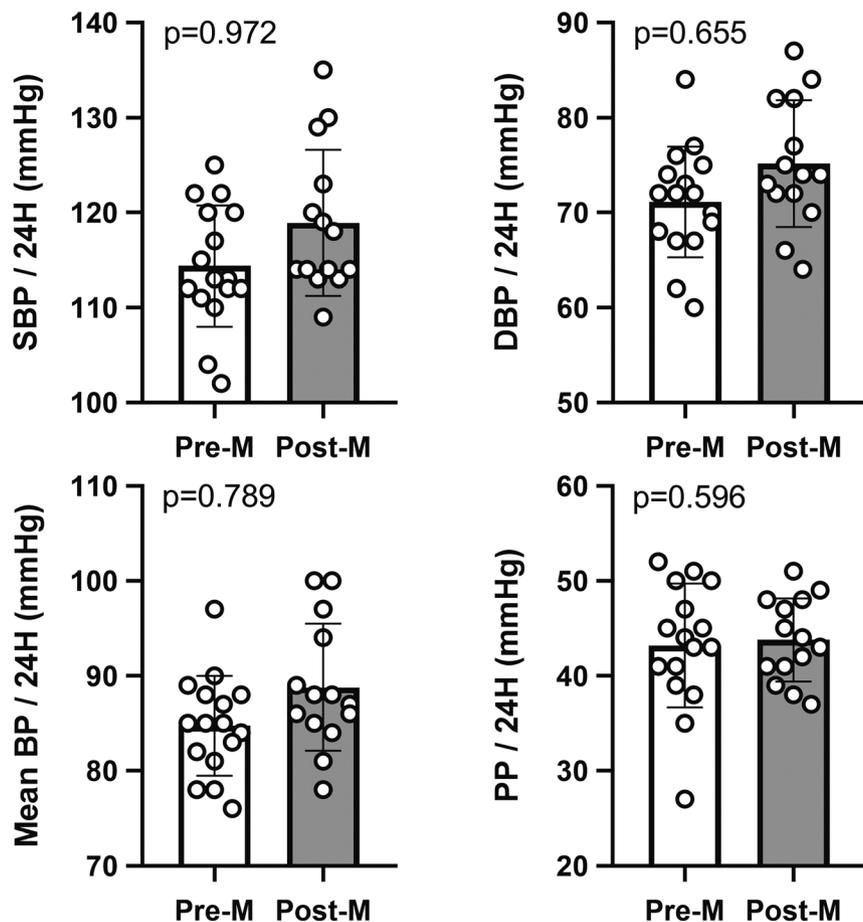


FIGURE 1—24-h ambulatory blood pressure in physically active premenopausal (Pre-M, white) and postmenopausal (Post-M, gray) females. SBP (top left panel); DBP (top right panel); mean BP (bottom left panel); PP, pulse pressure (bottom right panel). Data are presented as mean \pm SD with individual values for 16 pre- and 14 postmenopausal females. *P* value is for an ANCOVA with age as a covariate.

Relation between physical activity levels and brachial artery FMD. There was no association between brachial artery FMD and total physical activity level in the combined group ($r = -0.08$, $P = 0.634$) and when performing the analysis separately for premenopausal ($r = 0.04$, $P = 0.873$) and postmenopausal ($r = -0.38$, $P = 0.079$) females (Fig. 3). A negative correlation was observed between brachial artery FMD and moderate to vigorous physical activity level in the combined group ($r = -0.48$, $P = 0.007$). When the analysis was performed separately for each group, this relationship was significant in postmenopausal ($r = -0.83$, $P < 0.001$) but not premenopausal ($r = -0.23$, $P = 0.392$) females (Fig. 4).

cBRS. Because of technical difficulties, cBRS could only be measured in nine pre- and nine postmenopausal females. cBRS during spontaneous breathing did not differ between groups ($-8 \text{ ms}\cdot\text{mm Hg}^{-1}$, 95% CI = -20.55 to 4.62 , $P = 0.249$, $\eta^2 = 0.09$).

DISCUSSION

This study compared blood pressure, markers of vascular health, and cBRS between physically active late pre- and early postmenopausal females. The findings show that 24-h blood pressure, endothelial function, total reactive hyperemia, central

arterial stiffness, and spontaneous baroreflex sensitivity do not differ between physically active late pre- and early postmenopausal females. By contrast, peak reactive hyperemia was lower in postmenopausal females.

Blood pressure, physical activity, and menopause.

Blood pressure is altered with menopause (27,28), and postmenopausal females have a higher prevalence of hypertension (1). The rise in blood pressure after menopause has been evaluated in several studies, and the specific effect of menopause is debated (29). Cross-sectional studies show that SBP and DBP

TABLE 3. Brachial artery FMD variables.

Variable	Premenopause (n = 15)	Postmenopause (n = 14)	P
SBP (mm Hg)	108 \pm 5	114 \pm 12	0.692
DBP (mm Hg)	71 \pm 5	77 \pm 7	0.062
Baseline artery diameter (mm)	3.56 \pm 0.27	3.42 \pm 0.38	0.077
Baseline FBF (mL·min ⁻¹)	24 \pm 16	29 \pm 17	0.629
Baseline FVC (mL·min ⁻¹ ·mm Hg ⁻¹)	0.28 \pm 0.18	0.32 \pm 0.16	0.582
Baseline antegrade SR (s ⁻¹)	64 \pm 25	72 \pm 39	0.696
Baseline retrograde SR (s ⁻¹)	-16 \pm 14	-11 \pm 12	0.062
Peak dilation (mm)	0.16 \pm 0.13	0.15 \pm 0.08	0.540
Time to peak dilation (s)	44 \pm 25	47 \pm 20	0.844
SR _{AUC} to peak (a.u.)	7620 \pm 4090	7634 \pm 2919	0.657
Dbase-adjusted FMD (%)	4.39 \pm 3.94	4.92 \pm 3.81	0.750

Data are presented as mean \pm SD. *P* value is for an ANCOVA with age as a covariate. FBF, forearm blood flow. Dbase, baseline brachial artery diameter.

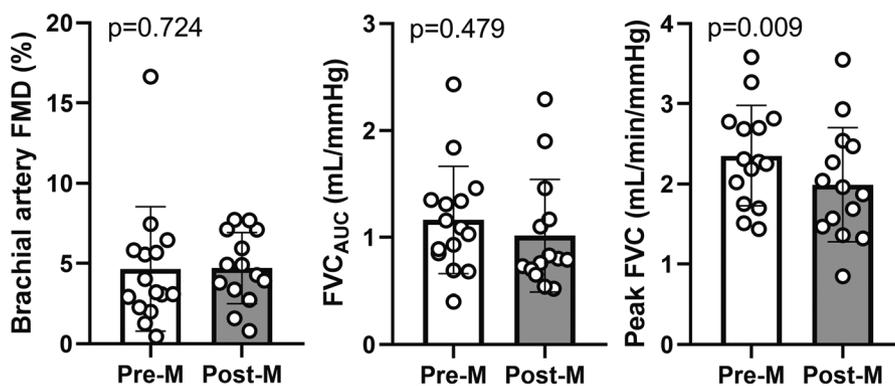


FIGURE 2—Markers of macro- and microvascular functions in physically active premenopausal (Pre-M, white) and postmenopausal (Post-M, gray) females. FMD, unadjusted flow-mediated dilation (*left panel*); FVC_{AUC} , forearm vascular conductance area under the curve (*middle panel*); Peak FVC, peak forearm vascular conductance (*right panel*). Data are presented as mean \pm SD with individual values for 15 pre- and 14 postmenopausal females. *P* value is for an ANCOVA with age as a covariate.

are 4 to 10 mm Hg and 3 to 6 mm Hg greater, respectively, in late post- compared with premenopausal females (27,30). In a prospective evaluation of ambulatory blood pressure measured during the menopausal transition, the rise in SBP was \sim 5 mm Hg greater per decade in post- compared with premenopausal females, whereas no difference was observed for DBP (30). The effect of physical activity on blood pressure in postmenopausal females has been evaluated in several cross-sectional (16,17,31) and longitudinal studies (10,32–34). Two cross-sectional studies did not observe a difference in SBP between sedentary and active postmenopausal females (16,31), whereas one study observed that SBP is lower in physically active postmenopausal females (\geq 6 yr) compared with sedentary peers and similar to a group of sedentary premenopausal females who were \sim 30 yr younger (17). The current study builds upon these previous studies by focusing on a relatively earlier stage of menopause (\sim 5 yr) and by narrowing the age gap between pre- and postmenopausal females to minimize potential differences attributable to aging. With this approach, 24-h blood pressure did not differ between physically active late pre- and early postmenopausal females.

Endothelial function, physical activity, and menopause. The menopausal transition is also associated with a reduction in brachial artery FMD (3), which is an independent predictor of hypertension and cardiovascular events in postmenopausal females (6,7). We observed that brachial artery FMD does not differ between groups of physically active late pre- and early postmenopausal females. Previous studies have observed inconsistent effects of aerobic exercise on endothelial function in postmenopausal females. Cross-sectional comparisons do not consistently observe a different brachial artery FMD in physically active postmenopausal females compared with sedentary peers (16,17). In addition, interventional studies (15,16) did not observe an effect of aerobic exercise (8 to 12 wk) on brachial artery FMD in postmenopausal females (35). The findings of the current study are difficult to reconcile with these previous observations. Notably, previous cross-sectional studies compared brachial artery FMD between late (6–10 yr) postmenopausal and relatively young (18–36 yr)

premenopausal females (16,17). Nonetheless, the current findings are consistent with the timing hypothesis (11), stating that aerobic exercise may be more effective at improving endothelial function if it is initiated before, or shortly after, the onset of menopause rather than many years later (5–10 yr).

Relation between physical activity level and brachial FMD. One aspect that has received less attention to explain the variable effect of aerobic exercise on brachial artery FMD in postmenopausal females is physical activity levels. Because we only set a lower limit of physical activity level as an inclusion criterion, we expected varying levels of physical activity between participants that would positively correlate with brachial artery FMD. Contrary to our hypothesis, we observed that greater levels of moderate to vigorous physical activity are associated with a lower brachial artery FMD in late pre- and early postmenopausal females. Furthermore, this relationship was primarily driven by the group of postmenopausal females. We explored (*a posteriori*) the possibility that differences in brachial artery diameter (36) and/or that the stimulus for FMD (37) explained this negative correlation. We observed a negative correlation between brachial artery FMD and baseline diameter in the combined group, but this relationship was driven by the premenopausal group (see Appendix, Fig. S5, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). For the FMD stimulus, we only observed a positive correlation between brachial artery FMD and SR_{AUC} within postmenopausal females (see Appendix, Fig. S6, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). Surprisingly, few studies have evaluated the relationship between physical activity level and brachial artery FMD. In children, habitual physical activity was positively correlated with brachial artery FMD (38), whereas leisure-time physical activity positively correlated with brachial artery FMD in teenage boys, but not teenage girls (39). It should be noted that these previous studies quantified self-reported physical activity levels using the Global Physical Activity Questionnaire (40), rather than by accelerometry in the current study. When we performed the correlation analyses with self-reported physical activity levels using the Global Physical Activity Questionnaire, we did not observe a correlation between

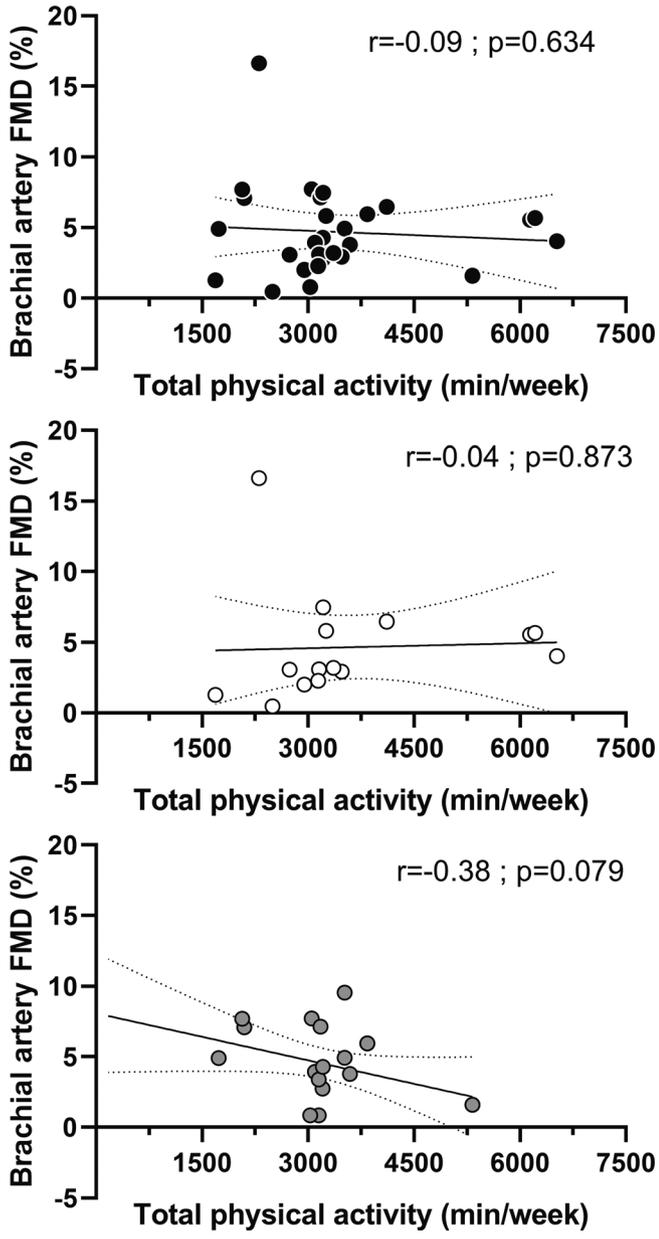


FIGURE 3—Relationship between brachial artery FMD and total physical activity level in pre- and postmenopausal females. *Top panel:* Premenopausal ($n = 15$) and postmenopausal ($n = 14$) females combined. *Middle panel:* Premenopausal females only. *(Bottom panel)* Postmenopausal females only. r and P values are for a Spearman correlation analysis.

brachial artery FMD and physical activity level (see Appendix, Fig. S7, Supplemental Digital Content, <http://links.lww.com/MSS/C516>). In adult females (44–60 yr), no association was observed between cardiorespiratory fitness and brachial artery FMD (41). In this same study (41), postmenopausal females with greater cardiorespiratory fitness had a lower FMD compared with postmenopausal females with lower cardiorespiratory fitness, suggesting that fitness does not attenuate the decline in FMD with aging after menopause. Future studies including larger samples sizes and a greater age range are needed confirm or refute the negative correlation between physical activity level and brachial artery FMD observed in the current study.

Physical activity, microvascular function, and menopause. In contrast to endothelial function, the effect of aerobic exercise on microvascular function in postmenopausal females has received less attention. This may be an important marker to consider in future studies considering that a decline in microvascular function may precede the decline in endothelial function and that markers of microvascular function independently predict the risk of cardiovascular events (42). Two previous cross-sectional studies have considered the effect of physical activity on microvascular reactivity in postmenopausal females. Santos-Parker et al. (17) first observed that the increase in forearm blood flow during intra-arterial acetylcholine

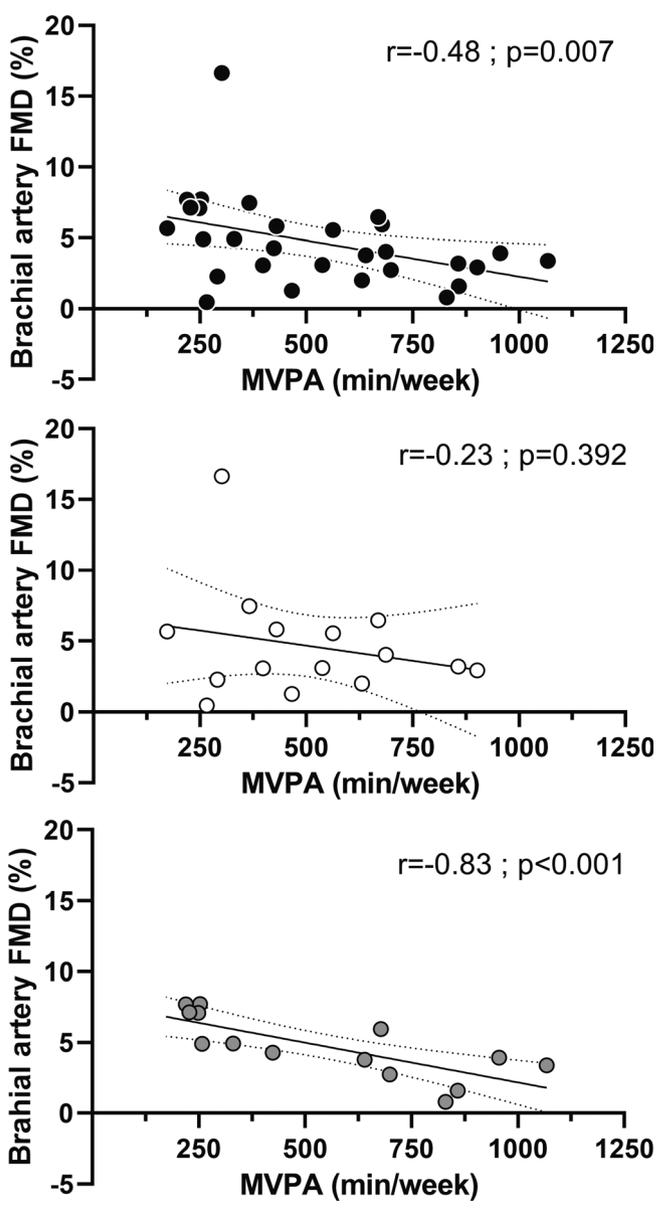


FIGURE 4—Relationship between brachial artery FMD and moderate to vigorous physical activity (MVPA) level in pre- and postmenopausal females. *Top panel:* Premenopausal ($n = 15$) and postmenopausal ($n = 14$) females combined. *Middle panel:* Premenopausal females only. *Bottom panel:* Postmenopausal females only. r and P values are for a Spearman correlation analysis.

infusion is lower in physically active post- compared with sedentary premenopausal females, but similar between physically active and sedentary postmenopausal females. A subsequent intervention study observed that microvascular function is improved after 12 wk of exercise training in early premenopausal females (18). Recently, Gliemann et al. (43) observed that the increase in femoral artery blood flow during intra-arterial acetylcholine infusion is greater in lifelong physically active postmenopausal females compared with moderately active and inactive peers. In the current study, total reactive hyperemia (FVC_{AUC}) was not different between groups, whereas peak reactive hyperemia was lower in postmenopausal females. The index of reactive hyperemia (FVC_{AUC} or peak FVC) that best reflects microvascular function is unclear (44), and it is therefore difficult to conclude whether physically active early postmenopausal females display preserved or reduced forearm microvascular function. However, it has been previously shown that inwardly rectifying potassium (K_{IR}) channels contribute to peak reactive hyperemia, whereas both the K_{IR} channels and the Na^+/K^+ -ATPase pump contribute to total reactive hyperemia in young healthy adults (45). It is therefore possible that the lower peak, but not total reactive hyperemia observed in early postmenopausal females, may reflect an alteration of K_{IR} channels, but future studies are needed to investigate this possibility.

Physical activity, central arterial stiffness, and menopause. Menopause accelerates the age-related increase in central arterial stiffness (5). We observed that carotid–femoral pulse wave velocity did not differ between groups, suggesting that physically active females may offset the increase in central arterial stiffness associated with the menopausal transition. Contrary to endothelial function, the effect of exercise on arterial stiffness in postmenopausal females is consistently protective as observed in cross-sectional (5,46) and interventional studies (47,48). Our results extend these previous findings to females within a relatively earlier stage of menopause (≤ 5 vs ~ 9 yr in previous studies).

Physical activity, cBRS, and menopause. cBRS did not differ between groups. In a recent cross-sectional study (49), cBRS was shown to be, on average, $4 \text{ ms} \cdot \text{mm Hg}^{-1}$ lower in early postmenopausal females (48 ± 3 yr, < 5 yr postmenopausal) relative to premenopausal females (43 ± 3 yr). Moreover, cBRS predicted prehypertension status after controlling for age in normotensive females at baseline (49). The current results suggest that physically active females may offset these changes associated with the menopausal transition. Such a possibility would be consistent with cross-sectional (50) and interventional (51) studies performed in males, demonstrating that aerobic exercise modulates the age-related decline in cBRS.

Limitations. When interpreting the results of this study, some limitations should be considered. First, we used a cross-sectional design, and as such, the differences (or lack thereof) between groups may not solely be due to menopausal status. We did observe a greater glycemia in postmenopausal females, but values are within the normoglycemic range. Furthermore, we minimized the influence of potential confounding variables such as age, body composition, physical activity level, and

fitness. Second, we did not include groups of sedentary pre- and postmenopausal females. This would have allowed us to more directly determine whether physically active females offset some of the physiological changes associated with the menopausal transition. Importantly, both groups of females were highly active, surpassing by three- to fourfold the currently recommended target of 150 min of moderate to vigorous physical activity time per week, which is not reflective of the general population. Third, the study was powered to detect an estimated effect size of 1.08 for a potential difference in SBP between groups. The actual effect size values for the difference in SBP ($d = 0.71$) and DBP ($d = 0.61$) were lower than this estimation. It is worth noting that the mean values of 24-h SBP (~ 5 mm Hg) and DBP (~ 4 mm Hg) were greater in postmenopausal females. Nonetheless, the mean values of blood pressure remained within the normotensive range in postmenopausal females. The current study cannot determine whether the observed mean differences are indicative of further increase in blood pressure that may occur with aging. Future studies are needed to determine whether physical exercise modulates the age-related increase in blood pressure within females, as has been observed in males (52).

Perspectives. In recent years, much attention has been drawn to the inconsistent effects of aerobic exercise on brachial artery FMD in postmenopausal females (13,53). An important consideration when interpreting this inconsistency is the fact that most studies recruited female participants at a relatively advanced stage of menopause (~ 9 yr). This led to the prevailing hypothesis that aerobic exercise training may be most beneficial at improving vascular function when it is initiated early after menopause (11). A recent study supports this “timing” hypothesis, as evidenced by improved leg endothelial function after 12 wk of exercise training in early premenopausal females (18). The current study adds to this emerging field of research by showing that physically active early postmenopausal females display preserved markers of vascular health, including brachial artery FMD, relative to physically active late postmenopausal females. These findings suggest that high levels of physical activity may attenuate the alterations in blood pressure and vascular health that normally accompany the menopausal transition (3). However, future studies are required to confirm this possibility and determine whether high levels of physical activity can provide protective effects for the long-term.

CONCLUSIONS

Using a cross-sectional study design, this study demonstrates that 24-h blood pressure, endothelial function, total reactive hyperemia, central arterial stiffness, and spontaneous baroreflex sensitivity do not differ between physically active late pre- and early postmenopausal females. By contrast, peak reactive hyperemia is lower in postmenopausal females. These results suggest that blood pressure and markers of vascular health do not differ between physically active late pre- and early postmenopausal females.

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