Published in final edited form as:

Med Sci Sports Exerc. 2016 August ; 48(8): 1548–1557. doi:10.1249/MSS.0000000000000936.

The Effect of Physical Activity on Passive Leg Movement-Induced Vasodilation with Age

H. Jonathan Groot^{1,2}, Matthew J. Rossman^{1,2}, Ryan S. Garten³, Eivind Wang^{4,5}, Jan Hoff^{5,6}, Jan Helgerud^{5,7,8}, and Russell S. Richardson^{1,2,4}

¹Geriatric Research, Education, and Clinical Center Salt Lake City VAMC, UT

²Department of Exercise and Sport Science University of Utah, Salt Lake City, UT

³Department of Kinesiology and Health Sciences, Virginia Commonwealth University, Richmond, VA

⁴Department of Internal Medicine, University of Utah, Salt Lake City, UT

⁵Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

⁶Department of Physical Medicine and Rehabilitation, St. Olavs University Hospital, Trondheim, Norway

⁷Hokksund Medical Rehabilitation Center, Hokksund, Norway

⁸Department of Sports and Outdoor Life Studies, Telemark University College, Bø, Norway

Abstract

Introduction—Due to reduced nitric oxide (NO) bioavailability with age, passive leg movement (PLM)-induced vasodilation is attenuated in older sedentary subjects and, unlike the young, cannot be augmented by posture-induced elevations in femoral perfusion pressure. However, whether vasodilator function assessed with PLM, and therefore NO bioavailability, is preserved in older individuals with greater physical activity and fitness is unknown.

Methods—PLM was performed on four subject groups (young sedentary (Y, 23±1 yrs, n = 12); old sedentary (OS, 73±2 yrs, n = 12); old active (OA, 71±2 yrs, n = 10); old endurance trained (OT, 72±1 yrs, n = 10)) in the supine and upright-seated posture. Hemodynamics were measured utilizing ultrasound Doppler and finger photoplethysmography.

Results—In the supine posture, PLM-induced peak change in leg vascular conductance (LVC_{peak}) was significantly attenuated in the OS compared to the young (OS: 4.9±0.5, Y: 6.9±0.7 ml/min/mmHg), but was not different from the young in the OA and OT (OA: 5.9±1.0, OT: 5.4±0.4 ml/min/mmHg). The upright-seated posture significantly augmented LVC_{peak} in all but the OS (OS: 4.9±0.5, Y: 11.8±1.3, OA: 7.3±0.8, OT: 8.1±0.8 ml/min/mmHg), revealing a

Correspondence: Russell S. Richardson, r.richardson@hsc.utah.edu, Tel: 801-582-1565 ext 4344, Fax: 801-584-5658, Address: VA Medical Center, Bldg 2, Rm 1D25, 500 Foothill Dr., Salt Lake City, Utah 84148.

Competing Interest

None of the authors has any conflicts of interest.

significant vasodilatory reserve capacity in the other groups (Y: 4.92 ± 1.18 , OA: 1.37 ± 0.55 , OT: 2.76 ± 0.95 ml/min/mmHg).

Conclusions—As PLM predominantly reflects NO-mediated vasodilation, these findings support the idea that augmenting physical activity and fitness can protect NO bioavailability, attenuating the deleterious effects of advancing age on vascular function.

Keywords

PLM; endothelium; exercise; vasodilatory reserve; vascular function

Introduction

An increased risk of cardiovascular disease (CVD) is a hallmark of advancing age. Attenuated vasodilator function, prior to overt signs of CVD, is an independent predictor of future CVD risk (22, 39) and is likely a consequence of diminished endothelium-mediated vasodilation. Indeed, in sedentary older humans, endothelium dependent vasodilator function is attenuated compared to young controls, whether assessed by the PLM technique (15, 16, 25, 46), intra-arterial infusion of the vasodilator acetylcholine (ACh) (2, 7, 28, 43), or brachial artery flow mediated dilation (FMD) (4, 6, 9, 29). Specifically, it appears that the endothelium derived vasodilator NO, which possesses antiatherogenic properties and is therefore an important factor in human aging (19, 24, 26, 33), is reduced in sedentary older subjects (43). However, whether this reduction in NO-dependent vasodilator function is the result of primary aging, or a secondary effect of reduced physical activity and fitness in the old is still unclear.

Endurance exercise-training creates an antiatherogenic arterial blood flow profile characterized by predominantly antegrade blood flow and low oscillatory shear rate (18, 20, 40, 44, 51). This beneficial flow pattern acutely increases endothelial NO synthase (eNOS) phosphorylation (12, 17), and chronically increases eNOS protein expression (17, 30), likely leading to greater NO bioavailability. However, while the current literature demonstrates a positive effect of increasing physical activity and fitness in terms of maintaining NO bioavailability with advancing age (7, 9, 21, 28, 38, 42), these conclusions are based exclusively on measurements made in the arm. Therefore, although providing important insight into vascular aging, these studies may not reflect changes in NO bioavailability in the potentially more important locomotor muscles of the lower limbs, which have a predisposition to develop vascular disease (8, 28, 55).

The vasodilatory response to PLM, a novel assessment of vasodilator function performed in the lower limb, has been documented to be predominantly (~80%) NO-mediated in the young (27, 48), while in the old, who possess a significantly attenuated PLM-induced vasodilation (16, 25), NO seems to play little to no role (15, 46). Moreover, during posture-induced alterations in femoral perfusion pressure (FPP), the contribution of NO to the PLM-induced vasodilation is augmented in the young, with no change in the old, thus revealing a vasodilatory reserve capacity (LVC_{peak} from supine to upright-seated) that has been demonstrated to further characterize the NO-mediated portion of the PLM response with age (15). These findings, in addition to recent questions about the validity of brachial artery

FMD as a measure of NO-bioavailability (36, 49, 55), evidence that the lower limbs of humans age in a different manner than the upper limbs (8, 28, 53), and the invasiveness of intra-arterial drug infusions, suggest that the PLM model may be a more appropriate test of vasodilator function. However, while the validity of the PLM model to detect reductions in NO bioavailability and vasodilator function with age is clear, the effect of varying activity and fitness levels in older subjects on PLM-induced vasodilation is unknown.

Therefore, the purpose of this investigation was to determine the effect of increasing levels of physical activity and fitness in older individuals on PLM-induced vasodilation in the supine and upright-seated posture in young sedentary, old sedentary, old active, and old endurance exercise-trained subjects. We hypothesized that 1) vasodilator function would be attenuated in the old sedentary compared to the young sedentary group, and 2) that increases in physical activity and fitness in the old would lead to enhanced vasodilator function, such that the old active group would have augmented vasodilator function compared to the older sedentary, and 3) the old endurance trained would have a restoration of vasodilator function, demonstrating augmented vasodilation compared to both the old sedentary and old active groups, with no difference compared to the young sedentary.

Methods

Subjects

Subjects were included in this research study based on the following criteria: 1) an absence of cardiovascular or metabolic disease, as assessed by a health history questionnaire; 2) aged 18–25 yrs for the young, and greater than 65 yrs for the old; and 3) sedentary/low physical activity for the young, and three levels of physical activity in the old (sedentary/low, active, endurance trained). The old subjects were initially separated into groups based on their responses to a modified physical activity level (PAL) questionnaire (32). Placement in the appropriate group was then confirmed by accelerometry, utilizing a combination of the average steps per day and average activity counts per minute, and $\text{VO}_{2\text{peak}}$ attained during a cycle exercise test. Forty-four healthy men met the inclusion criteria for this research study (young sedentary $n = 12$, old sedentary $n = 12$, old active $n = 10$, and old endurance trained $n = 10$). All procedures were approved by the Institutional Review Boards of the University of Utah and the Salt Lake City VA Medical Center, and written informed consent was obtained from each participant prior to inclusion in the study. The study conformed to the standards set by the Declaration of Helsinki.

Experimental Protocol

Subjects reported to the laboratory on two separate experimental days. On the first experimental day, subjects arrived at the laboratory after a light meal. They then performed a graded exercise test on a cycle ergometer to volitional exhaustion, during which expiratory gasses were collected to determine peak volume of oxygen consumption ($\text{VO}_{2\text{peak}}$). Prior to departure from the laboratory the subjects were given an accelerometer and instructed on proper operating procedures. All subjects wore the accelerometers for a minimum of seven consecutive days, and returned them on the second experimental day.

The second experimental day took place 7 days after the initial trial. Subjects arrived on the second experimental day fasted and having refrained from caffeine and exercise for 24 hours prior to the initiation of data collection. Accelerometers were turned in and blood was collected from the antecubital vein to assess blood lipids, fasting glucose, and hemoglobin.

Subjects were then assigned to begin assessments in either the supine or upright-seated posture using a counterbalanced design. Subjects rested for a minimum of 20 minutes after instrumentation and prior to the PLM protocol. The PLM protocol was performed as previously described (15, 16). Briefly, hemodynamic measurements were then collected during 1 min of baseline with the leg held at a constant 180° knee joint angle, followed by 1 min of passive knee flexion-extension through a 90° range of motion (180–90°) at 1 Hz, performed by a member of the research team. The protocol was then repeated in the opposing body posture (supine or upright-seated) after a rest period of at least 20 min in the new posture.

Measurements

Central hemodynamics—Heart rate (HR) was determined using an electrocardiogram (ECG), and mean arterial pressure (MAP) was determined by finger photoplethysmography with a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) positioned at heart level. Stroke volume (SV) was automatically calculated using the Modelflow method (Beatscope, version 1.1; Finapres Medical Systems), with cardiac output (CO) calculated as the product of SV and HR.

Peripheral hemodynamics—Measurements of blood velocity in the common femoral artery (CFA) and vessel diameter were performed in the passively moved leg distal to the inguinal ligament and proximal to the bifurcation of the superficial and deep femoral artery using a Logic 7 ultrasound system (General Electric Medical Systems, Milwaukee, WI, USA). The Logic 7 was equipped with a linear array transducer operating at an imaging frequency of 14 MHz. CFA diameter was determined at a perpendicular angle along the central axis of the scanned area, and blood velocity was measured using the same transducer with a frequency of 5 MHz. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insonation angle of 60 degrees or less. The sample volume was maximized according to vessel size and was centered within the vessel based on real-time ultrasound visualization. Using CFA diameter and mean velocity (V_{mean}) (angle corrected, and intensity weighted) leg blood flow (LBF) was automatically calculated by commercially available software (Logic 7) as $V_{\text{mean}}\pi(\text{vessel diameter}/2)^2 \times 60$, where blood flow is in milliliters per minute. The PLM-induced peak change in leg blood flow ($\Delta \text{LBF}_{\text{peak}}$) was calculated as peak LBF minus baseline LBF. Leg vascular conductance (LVC) was calculated as LBF divided by MAP. Rapid vasodilation was interpreted as the slope of increasing LVC over time for the first 9 s of PLM. Vasodilatory reserve capacity was calculated as upright-seated LVC_{peak} minus supine LVC_{peak} . The rapid vasodilatory reserve capacity was calculated as the upright-seated LVC slope minus the supine LVC slope. Both the vasodilatory reserve capacity and the rapid vasodilatory reserve capacity have previously been reported to reflect NO-mediated vasodilatory mechanisms (15).

Knee joint angle—During each PLM protocol, knee joint angle of the passively moved leg was continuously recorded using a Vishay Spectrol 360 degree Smart Position Sensor (Vishay Intertechnology Inc., Malvern, PA, USA) mounted on a BREG X2K knee brace (BREG Inc., Vista, CA, USA) worn by the participants.

Anthropometrics—Body mass and height were recorded and used to calculate body mass index (BMI) as $BMI = \text{body mass} \times \text{height}^2$, where body mass is measured in kilograms and height is measured in meters. Thigh volume of the passively moved leg was calculated, as previously described (23), using three measurements of thigh circumference (proximal, middle, and distal), thigh length, and skinfold measurements.

Physical activity and fitness levels—PAL was assessed using both a modified subjective recall questionnaire (32) and objective accelerometer data. The PAL questionnaire garnered information regarding the average type, frequency, intensity, and duration of physical activity in any given week. After receiving standardized operating instructions, subjects wore an accelerometer (GT1M; Actigraph, Pensacola, FL, USA) on their left hip for a minimum of seven continuous days, with adherence automatically assessed by the device. Average total daily physical activity was expressed as both average steps per day, and average total accelerometer counts per minute. The later assessment was separated into sedentary, low, moderate, high and very high intensity categories using device specific software (Actilife, Pensacola, FL, USA). Previous research has documented the validity and reliability of the Actigraph GT1M in the estimation of daily physical activity (1, 52). Classification of the subjects' level of physical activity was based on a validated step-determined scale (sedentary: <5000 steps/day, low active: 5000–7499 steps/day, somewhat active: 7500–9999 steps/day, active: 10,000–12,499 steps/day, and highly active: 12,500 steps/day) (37, 50), as well as total accelerometer counts per minute.

Fitness level was determined by a cycling $VO_{2\text{peak}}$ test performed on an electronically braked cycle ergometer (Lode, Groningen, The Netherlands), and pulmonary VO_2 was measured continuously throughout the test (Parvomedics, Sandy, UT). The $VO_{2\text{peak}}$ protocol consisted of a 1 min warm-up at 25 watts followed by an incremental increase of 25 watts each minute until volitional exhaustion (3). Criteria for successful attainment of $VO_{2\text{peak}}$ were a respiratory exchange ratio of >1.1, and the achievement of a maximal HR within 10 beats/min of the predicted value ($220 - \text{age}$). $VO_{2\text{peak}}$ was considered the highest 30 s average prior to cessation of exercise.

Data Acquisition and Statistical Analysis

Throughout each protocol ECG, SV, CO, MAP, and knee joint angle signals underwent analog-to-digital conversion and were simultaneously acquired (200 Hz) using commercially available data acquisition software (AcqKnowledge, Biopac Systems Inc., Goleta, CA, USA). CFA diameter and V_{mean} were acquired on the ultrasound system (GE Logic 7). Baseline was analyzed using the average of the 60 s prior to the initiation of PLM. All variables were analyzed second-by-second for the 60 s of passive movement, and data were smoothed using a 3 s rolling average prior to final data analysis. Multiple 2×4 repeated measures ANOVA were used to determine significant differences in baseline and the

absolute change from baseline to peak for HR, SV, CO, MAP, LBF, LVC, and LVC slope, and Tukey's HSD was used for post hoc analysis. A one-way ANOVA (1×4) was used to determine group differences in vasodilatory and rapid vasodilatory reserve capacity. Student's t-tests were used for subject characteristics and significance was set at an α -level of 0.05. Data are presented as mean $\pm$ SEM.

Results

Subjects

The differences in the subject characteristics between groups, displayed in Table 1, were anticipated based on their respective physical activity and fitness levels.

Physical activity and fitness comparisons are displayed in Figure 1. Total daily physical activity, as assessed by both accelerometer counts/min and steps/day, was not different between young and old sedentary subjects (Figure 1, A and B). As previously reported (16), the similar total daily physical activity between these two groups was achieved in differing ways. Old sedentary subjects spent more time engaged in low intensity physical activity (~ 60 min/day), while young subjects spent more time in the moderate intensity category (~ 20 min/day). In contrast, both absolute and relative $\text{VO}_{2\text{peak}}$ were attenuated in the old compared to the young sedentary subjects (Figure 1, C and D). The old active subjects had greater activity counts/min and steps/day compared to both the young and old sedentary (Figure 1, A and B), greater time spent in the moderate and vigorous intensity categories compared to old sedentary (~ 30 min/day and ~ 8 min/day, respectively), and a higher $\text{VO}_{2\text{peak}}$ than the old sedentary, but still demonstrated attenuated absolute and relative $\text{VO}_{2\text{peak}}$ compared to the young sedentary subjects (Figure 1, C and D). The old endurance trained group had significantly greater activity counts/min, steps/day, time spent in the moderate and vigorous intensity categories (~ 45 min/day and ~ 20 min/day, respectively), and absolute and relative $\text{VO}_{2\text{peak}}$ compared to both the young and old sedentary subjects. While the old active and old endurance trained groups took a similar number of steps/day, the old endurance trained group tended to spend more time in the vigorous intensity category compared to the old active (21 ± 4 vs. 9 ± 4 min/day, respectively; $p = 0.06$), resulting in greater activity counts/min, and an augmented absolute and relative $\text{VO}_{2\text{peak}}$ compared to the old active (Figure 1, B, C and D). (See Table, Supplemental Digital Content 1, for direct comparison of physical activity intensities across groups.)

Central and Peripheral Hemodynamics at Rest and During PLM

Central hemodynamics—At rest, MAP, CO, SV, and HR were similar between groups and body postures (Table 2). In response to PLM, the old trained group had less of an increase in HR in both the supine and upright-seated postures compared to the old sedentary. All other central hemodynamic responses to PLM were similar between groups and body postures.

Peripheral hemodynamics—At rest, the old sedentary group had lower LBF and LVC compared to the young in both the supine and upright-seated postures (Table 2). In response to PLM, the LBF_{peak} in the supine posture was not different between these groups,

although tending to be lower in the old sedentary compared to the young subjects ($p = 0.11$, Table 2). Similarly, the LVC_{peak} was not different between the three old groups, or when comparing the young to the old active and old endurance trained groups, but was significantly lower in the old sedentary compared to the young (Table 2, Figure 2C). The upright-seated posture augmented the PLM response (LBF_{peak} and LVC_{peak}) in the young, old active, and old endurance trained groups, with no effect in the old sedentary ($p = 0.93$ and $p = 0.73$, respectively), such that LBF_{peak} and LVC_{peak} were significantly greater in the young, old active, and old endurance trained compared to the old sedentary (Table 2, Figure 2D). However, while the old active and old endurance trained groups displayed an upright-seated posture-induced increase in the PLM response, the LBF_{peak} and LVC_{peak} remained attenuated compared to the young sedentary subjects. Although not reported here, it should be noted that area under the curve was also calculated for both LBF and LVC in response to PLM and yielded nearly identical results to that of LBF_{peak} and LVC_{peak} .

The young, old active, and old endurance trained groups all demonstrated a significant vasodilatory reserve capacity (young sedentary: 4.92 ± 1.18 , old active: 1.37 ± 0.55 , old endurance trained: 2.76 ± 0.95 ml/min/mmHg; $p < 0.05$), while the old sedentary group was unable to take advantage of the posture-induced increase in FPP in terms of vasodilation (old sedentary: -0.34 ± 0.41 ; $p = 0.73$; Figure 3). Compared to the young, the old sedentary and old active groups displayed an attenuated vasodilatory reserve capacity, while the old endurance trained group's response was not significantly different from the young ($p = 0.27$). Due to the complete lack of a vasodilatory reserve capacity in the old sedentary group, both the old active and old endurance trained groups had a significantly greater vasodilatory reserve capacity compared to the old sedentary.

The rapid vasodilatory response in the supine posture was attenuated in the old sedentary compared to the young (young sedentary: 0.69 ± 0.08 , old sedentary: 0.38 ± 0.06 ml/min/mmHg/s; $p < 0.05$; Figure 4A), with no other differences between groups (old active: 0.55 ± 0.10 , old endurance trained: 0.50 ± 0.06 ml/min/mmHg/s; $p > 0.05$). Moving from the supine to the upright-seated posture significantly augmented the rapid vasodilation in the young, old active, and old endurance trained (1.08 ± 0.14 , 0.75 ± 0.10 , 0.86 ± 0.13 ml/min/mmHg/s, respectively; $p < 0.05$ for all), with no change in the old sedentary group (0.42 ± 0.06 ml/min/mmHg/s; $p = 0.44$), such that the rapid vasodilation in the upright-seated posture in the old sedentary was attenuated compared to all three groups (Figure 4B). Despite the posture-induced increase in rapid vasodilation in the old active, the response in the young was of a greater magnitude, leading to a significant difference between these two groups. However, there was no difference in the rapid vasodilation between the young sedentary and old endurance trained while in the upright-seated posture ($p = 0.17$). When comparing the posture-induced increase in the LVC slope between groups (rapid vasodilatory reserve capacity, Figure 4C), a similar qualitative pattern was observed as that for the vasodilatory reserve capacity. While there were no significant differences between the groups, both the young and old endurance trained tended to display a greater rapid vasodilatory reserve capacity compared to the old sedentary ($p = 0.10$ and $p = 0.11$, respectively).

Discussion

Utilizing the novel PLM assessment, we sought to elucidate the impact of increased physical activity and fitness on vasodilator function with advancing age. Among the old subjects, elevated levels of physical activity and fitness had a positive effect on PLM-induced vasodilation in the upright-seated posture. Furthermore, the vasodilatory reserve capacity and rapid vasodilatory reserve capacity appear to be affected in a dose dependent manner by physical activity and fitness, resulting in significantly improved vasodilator function in the old active and old endurance trained, compared to their sedentary peers. Finally, while the upright-seated LVC_{peak} in the old endurance trained was not completely restored to the level of the young, both the vasodilatory reserve capacity and rapid vasodilatory reserve capacity, reported to be highly NO-dependent, were similar between these two groups. Consequently, utilizing the novel PLM assessment, these findings suggest that increasing levels of physical activity and fitness can improve NO bioavailability and reduce the deleterious effects of advancing age on vasodilator function.

Age and Attenuated NO-Mediated Vasodilator Function

NO is an endothelium derived vasodilator that is synthesized in response to a number of stimuli, including endothelial cell deformation and luminal shear forces (10, 11, 41). In addition to its role as a vasodilator, NO prevents atherogenesis by inhibiting platelet aggregation, white blood cell adhesion, and vascular smooth muscle cell migration and proliferation (24, 26). Therefore, NO is a critically important molecule in limiting the progression of CVD, suggesting that measuring NO bioavailability may provide insight into CVD risk across the human lifespan.

A preponderance of evidence collected in the human arm demonstrates that healthy aging is associated with reduced NO-mediated vasodilator function (2, 7, 27, 30, 42, 43, 46). Indeed, when the endothelium and NO-dependent vasodilator ACh is infused into the brachial artery of young and old sedentary subjects, the vasodilatory response is attenuated in the old (7, 42, 43). In contrast, infusion of sodium nitroprusside, an endothelium and NO-independent vasodilator, results in similar levels of vasodilation in both young and old subjects, indicating that the attenuated vasodilation with age is a consequence of diminished endothelial NO bioavailability (7, 42, 43). Seemingly in agreement with these findings, the percent dilation of the brachial artery in response to post occlusion-induced increases in wall shear stress (FMD), demonstrate that the vasodilatory response is attenuated with age (6, 9, 29). However, brachial artery remodeling with age leads to increased lumen diameter in old subjects (4, 14), which confounds the calculation of FMD as a percentage change from baseline and reduces endothelial shear forces that cause the brachial artery to dilate. Indeed, when brachial artery dilation is normalized for the shear stimulus, the difference between young and old frequently disappears (29, 54), which would suggest that vasodilator function is preserved with age, a finding that contradicts data from investigations using ACh infusions. Furthermore, the current literature questions the role of brachial artery FMD as a marker of NO-mediated vasodilation (36, 49, 55), and indicates that the lower limbs, which are more susceptible to age related vascular dysfunction, may be a more appropriate site to study alterations in NO bioavailability with age (8, 28, 53).

PLM, a leg movement model essentially devoid of increases in metabolism and therefore metabolically mediated vasodilation, causes a robust vasodilation-induced increase in LBF and LVC, the magnitude of which is attenuated with age (16, 25). When the eNOS inhibitor *N*^G-monomethyl-L-arginine (L-NMMA) is infused into the common femoral artery during PLM, the vasodilatory response is reduced by ~80% in the young, indicating that the PLM-induced vasodilation is predominantly NO-mediated (15, 27, 48). Furthermore, eNOS inhibition has little effect on the already attenuated PLM response in old sedentary subjects, suggesting that reduced NO bioavailability is largely responsible for the age related decrease in vasodilator function assessed by this novel approach (15, 48). The current investigation once again supports this previous work by demonstrating an age-associated attenuation in the PLM-induced LBF_{peak} and LVC_{peak} in the old sedentary men while in the supine posture (Table 2, Figure 2, A and C). Additionally, in the current study PLM was performed in the upright-seated posture, which has previously been documented to elevate FPP and lead to an increased contribution of NO to PLM-induced vasodilation in young, but not old subjects. As anticipated, the young sedentary individuals displayed a significant increase in PLM-induced LBF_{peak} and LVC_{peak} (Figure 2, B and D), revealing a vasodilatory reserve capacity that was not present in the old sedentary (Figure 3). Similarly, the rapid vasodilatory response to PLM, an additional indicator of NO-mediated vasodilation, was significantly augmented by the upright-seated posture in the young subjects, but not in the old sedentary subjects, revealing a rapid vasodilatory reserve capacity in the young that was absent in the old sedentary (Figure 4). Therefore, the vasodilatory reserve capacity and the rapid vasodilatory reserve capacity, both of which are suggested to be primarily NO-dependent (15), provide additional evidence that the attenuated PLM response with age is due to reduced NO bioavailability. However, whether the PLM-induced vasodilation is protected in older individuals who maintain a greater level of physical activity and fitness has not previously been investigated.

Impact of Physical Activity and Fitness on Vasodilator Function with Age

Aging is associated with increased formation of atherosclerotic plaques, which may result, in part, from alterations in the arterial blood flow profile towards a proatherogenic state (5, 31, 47, 56). This proatherogenic blood flow profile is characterized by lower anterograde flow, higher retrograde flow, and greater endothelial oscillatory shear forces, all of which lead to attenuated NO bioavailability and impaired endothelium dependent vasodilation (20, 40, 45, 51). An acute bout of endurance exercise increases anterograde blood flow, decreases retrograde blood flow, and decreases oscillatory shear both during and directly after the exercise bout (18, 44). Therefore, endurance exercise creates an antiatherogenic blood flow pattern that has been documented to acutely increase eNOS phosphorylation and chronically increase eNOS protein expression, leading to greater NO bioavailability (10, 14, 17, 30). Indeed, the forearm vascular conductance response to doubling doses of ACh is very similar between old endurance trained and young sedentary men (7, 28, 42), and 3 months of exercise training in previously sedentary old men can restore their ACh response to that of young sedentary and old endurance trained men (7). However, results in terms of the effect of endurance exercise training in the old on brachial artery FMD are mixed, with some reporting improved vasodilation (9, 34), and others reporting no change (4, 35). These contradictory findings may be due to the confounding effects of arterial remodeling in

response to chronic exercise training that results in a greater baseline luminal diameter (13, 14). Indeed, in the current investigation, the old endurance trained tended to have a larger CFA diameter compared to their sedentary peers ($p = 0.07$, Table 1), but as PLM does not rely upon changes in CFA diameter, per se, to assess vasodilator function, this is not a confounding issue in the current study.

Utilizing the PLM model, the impact of physical activity and fitness on vasodilator function is clear. Both the active and endurance trained old groups exhibited significantly augmented PLM-induced LVC_{peak} , vasodilatory reserve, and upright-seated rapid vasodilation compared to the old sedentary (Figures 2, 3 and 4, respectively). Furthermore, to our knowledge this is the first study to assess two different levels of physically active old subjects, allowing the assessment of a physical activity and fitness “dose response”. In this regard, in terms of the PLM-induced LVC_{peak} , it would appear that higher levels of physical activity and fitness in the old endurance trained group had no additional benefit on vasodilator function above and beyond that exhibited by the old active group (Figure 2). However, the vasodilatory reserve capacity, which remained attenuated in the old active compared to the young, was improved in the old endurance trained to the point that this group’s vasodilatory reserve capacity was no longer different from the young, suggesting that there is some additional augmentation of NO-mediated vasodilation with greater physical activity and fitness in the old (Figure 3).

Further evidence from the assessment of the rapid vasodilatory response supports the restorative or protective role of greater levels of physical activity and fitness in the old. Specifically, while both the old active and old endurance trained displayed a posture-induced augmentation of the rapid vasodilatory response, this response was only similar in the young and old endurance trained (Figure 4B). Furthermore, analysis of the rapid vasodilatory reserve capacity provides an additional examination of the effect of posture on vasodilatory function (Figure 4C). While this method of analysis created additional variance, resulting in no statistically significant differences between groups, it appears that there is a stepwise increase in the rapid vasodilatory reserve capacity with greater levels of physical activity and fitness among the old groups, such that the response in the old endurance trained tended to be greater than the old sedentary, and was very similar to the young.

Together, these findings indicate that the reduction in NO bioavailability with age can be mitigated in older populations who possess greater levels physical activity and fitness. Additionally, the PLM assessment of vasodilator function, which is not confounded by age and chronic exercise-induced changes in arterial structure, is capable of detecting alterations in vasodilator function among old individuals of varying physical activity and fitness levels.

Conclusion

Utilizing the novel PLM assessment of vasodilator function, the results of the current investigation support previous findings that aging has a deleterious effect on vasodilator function in otherwise healthy, sedentary humans. Furthermore, this study adds to the literature by demonstrating that higher levels of physical activity and fitness can partially restore or protect against this age-associated decrease in PLM-induced vasodilation. The observation that the upright-seated LVC_{peak} , PLM-induced vasodilatory reserve capacity,

and rapid vasodilatory reserve capacity are predominantly NO dependent in the young suggests that the reduced vasodilator function with age is due primarily to decreased NO bioavailability, which can be protected by elevated levels of physical activity and fitness with advancing age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grants

The work was supported by National Institutes of Health Grant P01-H1-091830 (to R.S. Richardson), Veterans Affairs Rehabilitation Research and Development Service Merit Grant E6910-R (to R.S. Richardson), Merit Grant E1697-R (to R.S. Richardson), and SPiRe Grant E1433-P (to R.S. Richardson).

We would like to express our appreciation to the subjects who partook in this research, and thank Runar Unhjem for his help in coordinating the participants. The results of the present study do not constitute endorsement by ACSM.

References

1. Abel MG, Hannon JC, Sell K, Lillie T, Conlin G, Anderson D. Validation of the Kenz Lifecorder EX and ActiGraph GT1M accelerometers for walking and running in adults. *Appl Physiol Nutr Metab*. 2008; 33(6):1155–64. [PubMed: 19088773]
2. Al-Shaer MH, Choueiri NE, Correia ML, Sinkey CA, Barenz TA, Haynes WG. Effects of aging and atherosclerosis on endothelial and vascular smooth muscle function in humans. *Int J Cardiol*. 2006; 109(2):201–206. [PubMed: 16054252]
3. Amann M, Subudhi A, Foster C. Influence of testing protocol on ventilatory thresholds and cycling performance. *Medicine and science in sports and exercise*. 2004; 36(4):613–22. [PubMed: 15064589]
4. Black MA, Cable NT, Thijssen DH, Green DJ. Impact of age, sex, and exercise on brachial artery flow-mediated dilatation. *Am J Physiol Heart Circ Physiol*. 2009; 297(3):H1109–16. [PubMed: 19633208]
5. Casey DP, Padilla J, Joyner MJ. alpha-adrenergic vasoconstriction contributes to the age-related increase in conduit artery retrograde and oscillatory shear. *Hypertension*. 2012; 60(4):1016–22. [PubMed: 22949528]
6. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *J Am Coll Cardiol*. 1994; 24(2):471–476. [PubMed: 8034885]
7. DeSouza CA, Shapiro LF, Clevenger CM, Dinunno FA, Monahan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation*. 2000; 102(12):1351–57. [PubMed: 10993851]
8. Donato AJ, Uberti A, Wray DW, Nishiyama S, Lawrenson L, Richardson RS. Differential effects of aging on limb blood flow in humans. *Am J Physiol Heart Circ Physiol*. 2006; 290(1):H272–78. [PubMed: 16183733]
9. Eskurza I, Monahan KD, Robinson JA, Seals DR. Effect of acute and chronic ascorbic acid on flow-mediated dilatation with sedentary and physically active human ageing. *J Physiol*. 2004; 556(1): 315–24. [PubMed: 14754992]
10. Fisslthaler B, Dimmeler S, Hermann C, Busse R, Fleming I. Phosphorylation and activation of the endothelial nitric oxide synthase by fluid shear stress. *Acta physiologica Scandinavica*. 2000; 168(1):81–8. [PubMed: 10691783]

11. Fleming I, Busse R. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. *American journal of physiology Regulatory, integrative and comparative physiology*. 2003; 284(1):R1–12.
12. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *The Journal of physiology*. 2004; 561(1):1–25. [PubMed: 15375191]
13. Green DJ, Rowley N, Spence A, Carter H, Whyte G, George K, Naylor LH, Cable NT, Dawson EA, DHJT. Why isn't flow-mediated dilation enhanced in athletes? *Medicine and science in sports and exercise*. 2013; 45(1):75–82. [PubMed: 22843111]
14. Green DJ, Swart A, Exterkate A, Naylor LH, Black MA, Cable NT, Thijssen DH. Impact of age, sex and exercise on brachial and popliteal artery remodelling in humans. *Atherosclerosis*. 2010; 210(2):525–30. [PubMed: 20197189]
15. Groot HJ, Trinity JD, Layec G, Rossman MJ, Ives SJ, Morgan DE, Bledsoe A, Richardson RS. The role of nitric oxide in passive leg movement-induced vasodilatation with age: insight from alterations in femoral perfusion pressure. *The Journal of physiology*. 2015; 593(17):3917–28. [PubMed: 26108562]
16. Groot HJ, Trinity JD, Layec G, Rossman MJ, Ives SJ, Richardson RS. Perfusion pressure and movement-induced hyperemia: evidence of limited vascular function and vasodilatory reserve with age. *American journal of physiology Heart and circulatory physiology*. 2013; 304(4):H610–19. [PubMed: 23262136]
17. Hambrecht R, Adams V, Erbs S, Linke A, Krankel N, Shu Y, Baither Y, Gielen S, Thiele H, Gummert JF, Mohr FW, Schuler G. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation*. 2003; 107(25):3152–58. [PubMed: 12810615]
18. Johnson BD, Wallace JP. A comparison of postexercise shear rate patterns following different intensities and durations of running in healthy men. *Clin Physiol Funct Imaging*. 2012; 32(3):234–40. [PubMed: 22487159]
19. Kawashima S. Malfunction of vascular control in lifestyle-related diseases: endothelial nitric oxide (NO) synthase/NO system in atherosclerosis. *J Pharmacol Sci*. 2004; 96(4):411–419. [PubMed: 15613778]
20. Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. *Arteriosclerosis*. 1985; 5(3):293–302. [PubMed: 3994585]
21. La Favor JD, Kraus RM, Carrithers JA, Roseno SL, Gavin TP, Hickner RC. Sex differences with aging in nutritive skeletal muscle blood flow: impact of exercise training, nitric oxide, and alpha-adrenergic-mediated mechanisms. *American journal of physiology Heart and circulatory physiology*. 2014; 307:H524–532. [PubMed: 24951753]
22. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a “set up” for vascular disease. *Circulation*. 2003; 107(1):139–46. [PubMed: 12515756]
23. Lawrenson L, Poole JG, Kim J, Brown C, Patel P, Richardson RS. Vascular and metabolic response to isolated small muscle mass exercise: effect of age. *Am J Physiol Heart Circ Physiol*. 2003; 285(3):H1023–31. [PubMed: 12738622]
24. Lloyd-Jones DM, Bloch KD. The vascular biology of nitric oxide and its role in atherogenesis. *Annual review of medicine*. 1996; 47:365–75.
25. McDaniel J, Hayman MA, Ives S, Fjeldstad AS, Trinity JD, Wray DW, Richardson RS. Attenuated exercise induced hyperaemia with age: mechanistic insight from passive limb movement. *J Physiol*. 2010; 588(22):4507–4517. [PubMed: 20876201]
26. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacological reviews*. 1991; 43(2):109–42. [PubMed: 1852778]
27. Mortensen SP, Askew CD, Walker M, Nyberg M, Hellsten Y. The hyperaemic response to passive leg movement is dependent on nitric oxide: a new tool to evaluate endothelial nitric oxide function. *The Journal of physiology*. 2012; 590(17):4391–4400. [PubMed: 22733658]

28. Newcomer SC, Leuenberger UA, Hogeman CS, Proctor DN. Heterogeneous vasodilator responses of human limbs: influence of age and habitual endurance training. *Am J Physiol Heart Circ Physiol.* 2005; 289(1):H308–15. [PubMed: 15778285]
29. Nishiyama SK, Wray DW, Richardson RS. Aging affects vascular structure and function in a limb-specific manner. *J Appl Physiol.* 2008; 105(5):1661–70. [PubMed: 18719234]
30. Nyberg M, Blackwell JR, Damsgaard R, Jones AM, Hellsten Y, Mortensen SP. Lifelong physical activity prevents an age-related reduction in arterial and skeletal muscle nitric oxide bioavailability in humans. *The Journal of physiology.* 2012; 590(21):5361–70. [PubMed: 22890714]
31. Padilla J, Simmons GH, Fadel PJ, Laughlin MH, Joyner MJ, Casey DP. Impact of aging on conduit artery retrograde and oscillatory shear at rest and during exercise: role of nitric oxide. *Hypertension.* 2011; 57(3):484–489. [PubMed: 21263118]
32. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM. A collection of Physical Activity Questionnaires for health-related research. *Medicine and science in sports and exercise.* 1997; 29(6):S1–205. [PubMed: 9243481]
33. Perrotta I, Brunelli E, Sciangula A, Zuccala V, Donato G, Tripepi S, Martinelli GL, Cassese M. Inducible and endothelial nitric oxide synthase expression in human atherogenesis: an immunohistochemical and ultrastructural study. *Cardiovasc Pathol.* 2009; 18(6):361–368. [PubMed: 18835789]
34. Pierce GL, Donato AJ, LaRocca TJ, Eskurza I, Silver AE, Seals DR. Habitually exercising older men do not demonstrate age-associated vascular endothelial oxidative stress. *Aging Cell.* 2011; 10(6):1032–37. [PubMed: 21943306]
35. Pierce GL, Eskurza I, Walker AE, Fay TN, Seals DR. Sex-specific effects of habitual aerobic exercise on brachial artery flow-mediated dilation in middle-aged and older adults. *Clinical science.* 2011; 120(1):13–23. [PubMed: 20642454]
36. Pyke K, Green DJ, Weisbrod C, Best M, Dembo L, O'Driscoll G, Tschakovsky M. Nitric oxide is not obligatory for radial artery flow-mediated dilation following release of 5 or 10 min distal occlusion. *American journal of physiology Heart and circulatory physiology.* 2010; 298(1):H119–26. [PubMed: 19880668]
37. Schmidt MD, Cleland VJ, Shaw K, Dwyer T, Venn AJ. Cardiometabolic risk in younger and older adults across an index of ambulatory activity. *Am J Prev Med.* 2009; 37(4):278–84. [PubMed: 19765498]
38. Seals DR, Desouza CA, Donato AJ, Tanaka H. Habitual exercise and arterial aging. *J Appl Physiol.* 2008; 105(4):1323–1332. [PubMed: 18583377]
39. Shechter M, Marai I, Marai S, Sherer Y, Sela BA, Feinberg MS, Rubinstein A, Shoenfeld Y. The association of endothelial dysfunction and cardiovascular events in healthy subjects and patients with cardiovascular disease. *Isr Med Assoc J.* 2007; 9(4):271–276. [PubMed: 17491220]
40. Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, Takahashi A, Katsuki T, Namiki A, Hirohata A, Matsumura T, Yamazaki S, Yokoi H, Tanaka S, Otsuji S, Yoshimachi F, Honye J, Harwood D, Reitman M, Coskun AU, Papafakis MI, Feldman CL. Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics: The PREDICTION Study. *Circulation.* 2012; 126(2):172–81. [PubMed: 22723305]
41. Sun D, Huang A, Recchia FA, Cui Y, Messina EJ, Koller A, Kaley G. Nitric oxide-mediated arteriolar dilation after endothelial deformation. *Am J Physiol Heart Circ Physiol.* 2001; 280(2):H714–721. [PubMed: 11158970]
42. Taddei S, Galetta F, Viridis A, Ghiadoni L, Salvetti G, Franzoni F, Giusti C, Salvetti A. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation.* 2000; 101(25):2896–2901. [PubMed: 10869260]
43. Taddei S, Viridis A, Ghiadoni L, Salvetti G, Bernini G, Magagna A, Salvetti A. Age-related reduction of NO availability and oxidative stress in humans. *Hypertension.* 2001; 38(2):274–79. [PubMed: 11509489]
44. Taylor CA, Hughes TJ, Zarins CK. Effect of exercise on hemodynamic conditions in the abdominal aorta. *J Vasc Surg.* 1999; 29(6):1077–89. [PubMed: 10359942]

45. Thijssen DH, Dawson EA, Tinken TM, Cable NT, Green DJ. Retrograde flow and shear rate acutely impair endothelial function in humans. *Hypertension*. 2009; 53(6):986–992. [PubMed: 19380611]
46. Trinity JD, Groot HJ, Layec G, Rossman MJ, Ives SJ, Morgan DE, Gmelch BS, Bledsoe A, Richardson RS. Passive leg movement and nitric oxide-mediated vascular function: the impact of age. *American journal of physiology Heart and circulatory physiology*. 2015; 308(6):H672–79. [PubMed: 25576629]
48. Trinity JD, Groot HJ, Layec G, Rossman MJ, Ives SJ, Runnels S, Gmelch B, Bledsoe A, Richardson RS. Nitric oxide and passive limb movement: a new approach to assess vascular function. *The Journal of physiology*. 2012; 590(6):1413–25. [PubMed: 22310310]
49. Tschakovsky ME, Pyke KE. Counterpoint: Flow-mediated dilation does not reflect nitric oxide-mediated endothelial function. *J Appl Physiol* (1985). 2005; 99(3):1235–1237. discussion 1237–1238. [PubMed: 16103525]
50. Tudor-Locke C, Bassett DR Jr. How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Med*. 2004; 34(1):1–8. [PubMed: 14715035]
51. VanderLaan PA, Reardon CA, Getz GS. Site specificity of atherosclerosis: site-selective responses to atherosclerotic modulators. *Arteriosclerosis, thrombosis, and vascular biology*. 2004; 24(1):12–22.
52. Welk GJ, Blair SN, Wood K, Jones S, Thompson RW. A comparative evaluation of three accelerometry-based physical activity monitors. *Med Sci Sports Exerc*. 2000; 32(9):S489–97. [PubMed: 10993419]
53. Wray DW, Nishiyama SK, Donato AJ, Richardson RS. Human vascular aging: limb-specific lessons. *Exerc Sport Sci Rev*. 2010; 38(4):177–85. [PubMed: 20871234]
54. Wray DW, Uberoi A, Lawrenson L, Richardson RS. Evidence of preserved endothelial function and vascular plasticity with age. *Am J Physiol Heart Circ Physiol*. 2006; 290(3):H1271–77. [PubMed: 16272199]
55. Wray DW, Witman MA, Ives SJ, McDaniel J, Trinity JD, Conklin JD, Supiano MA, Richardson RS. Does brachial artery flow-mediated vasodilation provide a bioassay for NO? *Hypertension*. 2013; 62(2):345–51. [PubMed: 23774225]
56. Young CN, Deo SH, Padilla J, Laughlin MH, Fadel PJ. Pro-atherogenic shear rate patterns in the femoral artery of healthy older adults. *Atherosclerosis*. 2010; 211(2):390–392. [PubMed: 20394928]

Figure 1. Physical Activity and Fitness Levels

Average steps taken per day (*A*); Total daily physical activity (*B*, activity counts/min); both steps per day and total daily physical activity were assessed as the average from at least 7 days of accelerometry; Absolute (*C*, l/min) and relative (*D*, ml/kg/min) volume of oxygen consumed at peak exercise during a graded cycling test to volitional exhaustion. Young sedentary $n = 12$, old sedentary $n = 12$, old active $n = 10$, old endurance trained $n = 10$. # $p < 0.05$, significantly different from the young; \$ $p < 0.05$, significantly different from the old sedentary; † $p < 0.05$, significantly different from the old active. Values are mean $\pm$ SEM.

Figure 2. Passive Leg Movement (PLM)-Induced Changes in Leg Vascular Conductance in the Supine and Upright-Seated Posture with Age and Across Physical Activity and Fitness Levels Second-by-second tracing of the change in leg vascular conductance (ml/min/mmHg) throughout 1 min of PLM in the supine (*A*) and upright-seated (*B*) postures; peak change in LVC from baseline (LVC_{peak} , ml/min/mmHg) in the supine (*C*) and upright-seated (*D*) postures. Young sedentary $n = 12$, old sedentary $n = 12$, old active $n = 10$, old endurance trained $n = 10$. * $p < 0.05$, significantly different from the supine posture. # $p < 0.05$, significantly different from the young; § $p < 0.05$, significantly different from the old sedentary. Values are mean $\pm$ SEM.

Figure 3. Passive Leg Movement (PLM)-Induced Vasodilatory Reserve Capacity with Age and Across Physical Activity and Fitness Levels

The difference in the PLM-induced peak change in leg vascular conductance (LVC_{peak} , ml/min/mmHg) between the supine and upright-seated posture (vasodilatory reserve capacity). Young sedentary $n = 12$, old sedentary $n = 12$, old active $n = 10$, old endurance trained $n = 10$. # $p < 0.05$, significantly different from the young; § $p < 0.05$, significantly different from the old sedentary. Values are mean $\pm$ SEM.

Figure 4. Passive Leg Movement (PLM)-Induced Rapid Vasodilation in the Supine and Upright-Seated Posture with Age and Across Physical Activity and Fitness Levels

The rate of increase in the leg vascular conductance (LVC, ml/min/mmHg) over time was determined for the first 9 s of PLM in the supine (*A*) and upright-seated (*B*) postures; *C*, the difference in the slope between the supine and upright-seated posture (rapid vasodilatory reserve capacity, ml/min/mmHg/s). Young sedentary $n = 12$, old sedentary $n = 12$, old active $n = 10$, old endurance trained $n = 10$. * $p < 0.05$, significantly different from the supine posture. # $p < 0.05$, significantly different from the young; § $p < 0.05$, significantly different from the old sedentary. Values are mean $\pm$ SEM.

Table 1

Subject Characteristics

	Young	Old Sedentary	Old Active	Old Trained
n	12	12	10	10
Age (y)	23 ± 1	73 ± 2 [#]	71 ± 2 [#]	72 ± 1 [#]
Height (cm)	176 ± 2	176 ± 1	180 ± 2	177 ± 1
Weight (kg)	75 ± 3	82 ± 4	77 ± 3	71 ± 1 [§]
BMI (kg/m ²)	24.2 ± 0.9	26.4 ± 1.1	24.0 ± 0.6	22.6 ± 0.4 [§]
Thigh Volume (dl)	70 ± 3	65 ± 3	66 ± 3	67 ± 2
CFA Diameter (cm)	0.90 ± 0.02	1.01 ± 0.05 [#]	1.10 ± 0.06 [#]	1.15 ± 0.04 [#]
Glucose (mg/dl)	72 ± 3	73 ± 3	81 ± 3	90 ± 4 ^{#§}
Cholesterol (mg/dl)	163 ± 12	182 ± 8	178 ± 8	197 ± 11
Triglycerides (mg/dl)	114 ± 29	93 ± 11	73 ± 6	56 ± 2 ^{§†}
HDL (mg/dl)	45 ± 3	50 ± 3	54 ± 4 [#]	86 ± 5 ^{#§†}
LDL (mg/dl)	101 ± 9	117 ± 7	113 ± 7	111 ± 6
Haemoglobin (g/dl)	15.8 ± 0.3	15.3 ± 0.2	15.0 ± 0.4	14.7 ± 0.3 [#]
Maximum Work Rate (W)	235 ± 11	175 ± 14 [#]	230 ± 16 [§]	275 ± 19 [§]

BMI, body mass index; CFA diameter, common femoral artery diameter; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

[#] $p < 0.05$, significantly different from the young;

[§] $p < 0.05$, significantly different from the old sedentary;

[†] $p < 0.05$, significantly different from the old active. Values are mean ± SEM.

Central and Peripheral Hemodynamics During Rest and Passive Leg Movement (PLM) in the Supine and Upright-Seated Posture with Age and Across Physical Activity and Fitness Levels

Table 2

	Rest					
	Young		Old Sedentary		Old Active	
	Supine	Upright	Supine	Upright	Supine	Upright
MAP (mmHg)	86 ± 1	86 ± 2	92 ± 3	92 ± 4	97 ± 6	96 ± 3
CO (l/min)	5.6 ± 0.3	5.6 ± 0.2	5.1 ± 0.5	4.9 ± 0.4	5.0 ± 0.8	4.3 ± 0.4
SV (ml/beat)	99 ± 5	95 ± 5	94 ± 10	91 ± 9	98 ± 18	84 ± 8
HR (beat/min)	57 ± 3	59 ± 2	56 ± 3	58 ± 3	51 ± 3	53 ± 3
LBF (ml/min)	367 ± 33	359 ± 47	230 ± 19#	245 ± 21#	339 ± 53	320 ± 43
LVC (ml/min/mmHg)	4.3 ± 0.4	4.3 ± 0.7	2.6 ± 0.2#	2.7 ± 0.3#	3.4 ± 0.4	3.4 ± 0.5

	Passive Leg Movement (peak)					
	Young		Old Sedentary		Old Active	
	Supine	Upright	Supine	Upright	Supine	Upright
MAPpeak (mmHg)	-6 ± 2	-5 ± 1	-6 ± 2	-6 ± 2	-11 ± 2	-7 ± 1
COpeak (l/min)	1.4 ± 0.2	1.1 ± 0.2	1.3 ± 0.3	1.2 ± 0.3	0.8 ± 0.2	0.6 ± 0.1
SVpeak (ml/beat)	13 ± 2	11 ± 1	9 ± 2	12 ± 2	8 ± 3	7 ± 2
HRpeak (beat/min)	11 ± 2	7 ± 2	16 ± 5	12 ± 5	7 ± 1	8 ± 3
LBFpeak (ml/min)	577 ± 58	950 ± 87*	446 ± 49	431 ± 51#	489 ± 56	678 ± 72#§*
LVCpeak (ml/min/mmHg)	6.9 ± 0.7	11.8 ± 1.3*	4.9 ± 0.5#	4.6 ± 0.5#	5.9 ± 1.0	7.3 ± 0.8#§*

MAP, mean arterial pressure; CO, cardiac output; SV, stroke volume; HR, heart rate; LBF, leg blood flow; LVC, leg vascular conductance; peak, peak change from baseline. Young sedentary n = 12, old sedentary n = 12, old active n = 10, old endurance trained n = 10.

* $p < 0.05$, significantly different from the supine posture.

$p < 0.05$, significantly different from the young;

§ $p < 0.05$, significantly different from the old sedentary. Values are mean ± SEM.