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## The effects of aging and activity on muscle blood flow

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### Abstract

**Background:** Our purpose was to determine if aging had an influence on muscle blood flow independent of habitual physical activity levels.

**Methods:** Blood flow was measured in the femoral artery by Doppler ultrasound after cuff occlusion of 10 minutes. Active and inactive older subjects ( $73 \pm 7$  years) were compared to active and inactive young subjects ( $26 \pm 6$  years).

**Results:** Peak blood flow capacity when normalized to lean muscle mass was related to activity level ( $p < 0.001$ ), but not to age. Specifically, the young active group had higher peak blood flows than the young inactive ( $p = 0.031$ ) or older inactive ( $p = 0.005$ ) groups. Resting blood flow and conductance were not significantly different between groups. Mean arterial pressure was significantly higher in the older compared to young group ( $p = 0.002$ ). Conductance was related to both activity ( $p = 0.002$ ) and age ( $p = 0.003$ ). A prolonged time for blood flow to recover was found in the older compared to the young group ( $p = 0.038$ ) independent of activity status.

**Conclusions:** The prolonged recovery time in the older subjects may suggest a reduced vascular reactivity associated with increased cardiovascular disease risk. Peak blood flow capacity is maintained in older subjects by physical activity. In summary, maximal flow capacity and prolonged recovery of blood flow are influenced by different mechanisms in young and older active and inactive subjects.

### Background

Aging has been associated with decreased function and exercise performance [1,2]. Decreased exercise performance has been related to decreased oxidative capacity [3,4] and decreased muscle mass [4]. Vascular alterations in structure and function due to aging could also contribute to decreased exercise performance through impaired blood flow [5]. Decreased capillary density [6] and a thickening of vascular walls [7] are present with aging.

Vascular function is altered with aging and may influence muscle blood flow and exercise performance. Altered vascular function in older individuals is evidenced as impaired endothelial function [8–10], an altered ratio of endothelin receptors [11], and/or altered reactivity of the smooth muscle to sympathetic activity [7,12]. Reduced endothelial function is related to impaired formation and decreased activation of nitric oxide [13,14] and is particularly prominent in older subjects with evidence of cardiovascular disease [15], diabetes [16], or obesity [17].

Interestingly, aging does not appear to effect endothelium independent vasodilation [10,14].

These structural and functional alterations in the vascular system may explain age associated reductions in muscle blood flow. Decreased leg blood flow and vascular conductance are present in elderly compared to young subjects during whole body exercise [18] and in response to reactive hyperemia [13]. Decreased basal limb blood flow was related to increased vasoconstriction in the elderly compared to younger individuals [19]. However, not all studies have shown age related changes in blood flow. Resting blood flow and post exercise hyperemia was similar in elderly compared to younger subjects [20]. Blood flow responses to single limb exercise have also been preserved in older individuals [21,22]. Discrepancies in aging effects on muscle blood flow may be due to the use of active [18] or inactive subjects [13]. In addition, it is not clear whether the age related changes in blood flow were a result of reduced cardiac output during whole body exercise or reduced local vascular capacity. These inconsistent findings of reduced blood flow in older subjects suggest that other age-associated factors are involved.

Physical activity status influences vascular function and may explain alterations in muscle blood flow. Exercise training increases cardiac output during exercise and increases skeletal muscle blood flow in response to reactive hyperemia [23]. Arterial diameters [19,24], capillary density [5,25], vascular reactivity [26,27], and endothelial function [9,28] are improved with training and reduced with inactivity.

The purpose of this study was to determine if aging had an influence on muscle blood flow independent of habitual physical activity levels. Specifically, we examined single leg blood flow in response to reactive hyperemia with active and inactive older subjects in comparison to active and inactive young subjects. We tested the hypothesis that aging would result in reductions in limb blood flow independent of physical activity.

## Methods

### Subjects

Thirty-five subjects participated in the study between the ages of 20 and 81 years. Subjects were divided into four groups, Young Active (YA) (mean = 27 years, n = 10), Young Inactive (YI) (mean = 21 years, n = 9), Older Active (OA) (mean = 70 years, n = 8), and Older Inactive (OI) (mean = 77 years, n = 8). Subjects were classified as active if they reported participating in 40 minutes of moderate intensity exercise at least three times a week for the previous six months. The subjects classified as inactive reported no regular physical exercise. All subjects reported no history of disease or other confounding factors. The physical

characteristics of the subjects are shown in Table 1. The study was conducted with the approval of the Institutional Review Board at the University of Georgia.

### Protocol

Subjects rested in a supine position for 10–15 minutes prior to testing. Resting blood pressure was obtained. Ischemia was induced in the lower limb by inflation of a blood pressure cuff 100 mmHg above systolic blood pressure measured in the arm. Blood flow was measured at rest and in response to 10 minutes of cuff ischemia. Cuff placement was distal to the Doppler probe and was placed directly above the knee. Cuff inflation and deflation was rapid (1–2 seconds) using a rapid inflation device (D.E. Hokanson, Inc). Blood pressure was measured continuously to measure changes during the test as a result of cuff ischemia (Finapres, Ohmeda).

### Blood Flow

Blood flow was measured continuously in the common femoral artery using quantitative Doppler ultrasound (General Electric LogiQ 400 CL) with a frequency of 6 MHz. Pulsed Doppler ultrasound was recorded using an insonation angle of 45°–60°. The velocity gate was set to include the entire arterial diameter. Doppler waveforms were analyzed to determine the time average maximum velocity by General Electric's advanced vascular program software. B-mode images were measured during diastole to determine vessel diameter. Peak systolic blood flow was calculated as the product of the vessel cross sectional area and time average maximal velocity. Blood flow response to 10 minutes of cuff ischemia was an index of peak blood flow response [27]. Conductance was calculated by dividing the maximal blood flow by the mean arterial pressure (MAP). Half time to recovery was determined as the time where blood flow dropped to one half the magnitudes between maximum flow and resting flow values.

### Near Infrared Spectroscopy (NIRS)

Muscle oxygen delivery was determined by the half time of recovery of oxygen saturation after cuff ischemia[29]. Oxygen saturation was measured using a continuous light source, dual wavelength NIRS device (Runman CW2000, NIM, Inc., Philadelphia). The probe contained two small tungsten filament lamps, 6 cm apart which emit white light, and two photo detectors with filters for 760 and 850 nm light located between the lights. Brief flashes of light migrated through the tissue and were collected by the detectors at wavelengths set by two optical filters. Oxyhemoglobin has a greater absorbance at 850 nm compared to 760 nm, with deoxyhemoglobin absorbing more at 760 than 850 nm. The difference between the signal at 760 and 850 nm was used as the index of relative oxygen saturation.

**Table 1: Subject Characteristics – Means (SD)**

	Differences by Group				Age Effects	
	Young Active	Young Inactive	Older Active	Older Inactive	Young	Older
Age (yrs)	27.3 (6.0)	21.3 (1.0)	69.6 (6.5)	76.8 (4.6)	25.6 (5.8)*	73.2 (6.5)
Gender (Male: Female)	7:3	4:5	5:3	4:4	11:8	9:7
Height (m)	1.75 (0.08)	1.77 (0.14)	1.75 (0.09)	1.71 (0.12)	1.76 (0.10)	1.73 (0.11)
Weight (kg)	67.8 (10.8)	76.6 (18.6)	79.6 (9.3)	80.5 (17.4)	70.8 (13.8)	80.1 (13.5)
BP Systolic/Diastolic (mmHg)	124/68	120/68	138/78	140/76	122/68*	139/77
Mean Arterial Pressure	90 (10)	84 (9)#	98 (9)	103 (18)	89 (10)*	101 (14)
Heart Rate (BPM)	54 (8)&	68 (16)	71 (8)	73 (15)	60 (14)	72 (11)
Lean Leg Vol. (cm <sup>3</sup> )	1670 (372)	1710 (446)	1366 (245)	1518 (308)	1690* (390)	1442 (280)
Diameter (cm)	0.68 (0.09)	0.57 (0.09)	0.63 (0.10)	0.62 (0.13)	0.63 (0.09)	0.63 (0.11)

Notes: # MAP significantly different from older inactive ( $p = 0.015$ ). &Heart rate significantly different than the older active ( $p = 0.037$ ) and older inactive ( $p = 0.020$ ). \* Young and older groups significantly different at  $p < 0.05$ .

### Leg volume

Leg volume measurements were determined by Doppler ultrasound measurements of fat thickness and by circumference measurements of the lower leg. Subcutaneous fat was determined by B-mode images of the thickness between skin and muscle fascia. Measurements were attained every three centimeters over the Medial Gastrocnemius and over the Anterior Tibialis muscles. Based on the circumference and fat measurements total leg, fat, and lean area volume, were calculated.

### Analysis

An analysis of variance (ANOVA) (SPSS version 10.0) was conducted to test for aging and activity effects as well as to test for differences by group. Data was analyzed to verify normality and to test for any outliers. Analyses were conducted at a significance level of 0.05.

## Results

### Baseline data

Subjects in the older groups had higher resting systolic blood pressure ( $p = 0.003$ ), diastolic blood pressure ( $p = 0.012$ ), MAP ( $p = 0.002$ ), and heart rate ( $p = 0.013$ ) compared to the young groups (Table 1). There were no differences in blood pressure or heart rate with physical activity level. Lean leg volume was 15% lower in the older subjects compared to the younger subjects ( $p = 0.049$ ), despite a lack of difference in height, or body weight. When comparing the four groups separately, MAP was higher in the older inactive compared to young inactive group ( $p = 0.015$ ). The older inactive group had a higher systolic blood pressure compared to the young inactive group that approached significance ( $p = 0.084$ ). Resting heart rate was lower in the young active group compared to both of the older groups ( $F(3,32) = 4.561$ ,  $p = 0.010$ ,  $H^2 = 0.243$ ). Resting femoral artery diameter as well as resting normal-

ized blood flow and resting conductance were not different on aging or activity effects or on differences between groups (Table 2).

### Cuff ischemia

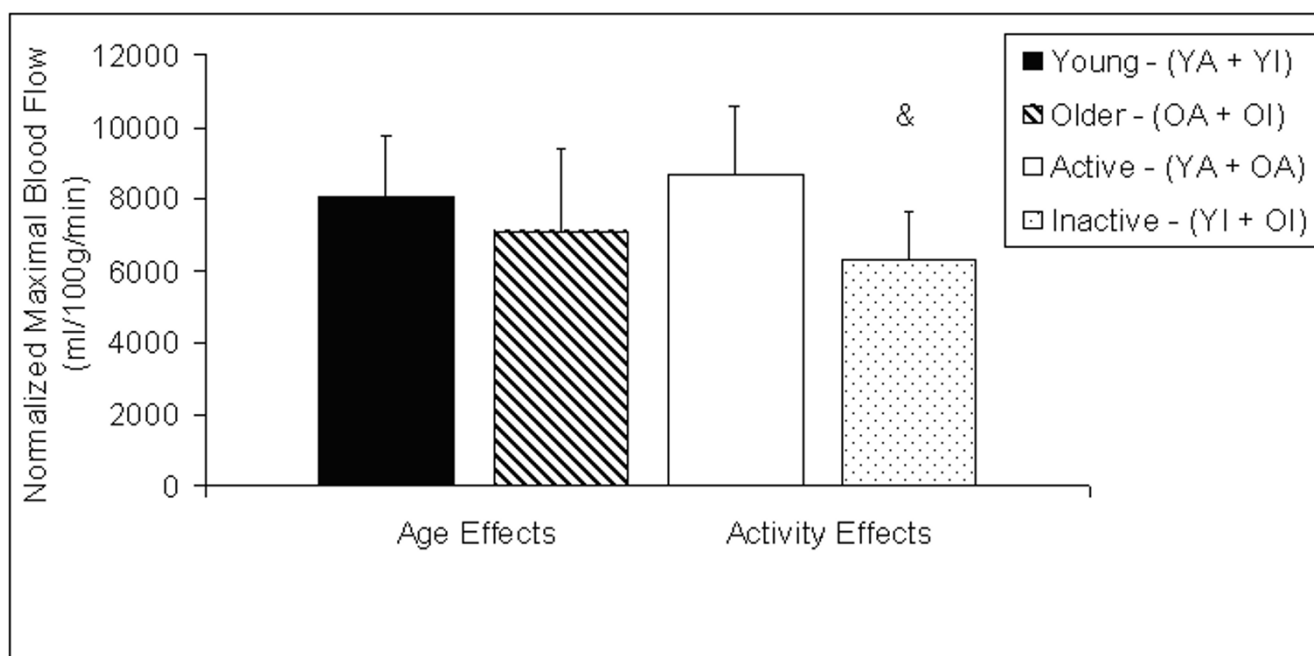
The cuff occlusion protocol was not associated with any changes in heart rate or blood pressure. There was a greater time averaged maximal blood flow in the younger groups ( $2180 \pm 590$  ml/min vs.  $1700 \pm 570$  ml/min, for young versus older, respectively;  $F(1,35) = 5.986$ ,  $p = 0.020$ ,  $H^2 = 0.154$ ) and active groups ( $2220 \pm 640$  ml/min versus  $1680 \pm 470$  ml/min, for active versus inactive, respectively;  $F(1,35) = 8.015$ ,  $p = 0.008$ ,  $H^2 = 0.195$ ). The maximal blood flow was different between groups ( $F(3,35) = 5.764$ ,  $p = 0.003$ ,  $H^2 = 0.358$ ) with the young active group having higher blood flow than the young inactive group ( $p = 0.047$ ) and the old inactive group ( $p = 0.002$ ) (Table 2).

When maximal blood flow was normalized to estimated lean muscle mass there was a higher blood flow in the active compared to inactive groups ( $F(1,33) = 15.690$ ,  $p < 0.001$ ,  $H^2 = 0.356$ ) (Figure 1) with no significant age effects. Maximal blood flow when normalized to lean muscle mass was different between the four groups ( $F(3,33) = 5.784$ ,  $p = 0.003$ ,  $H^2 = 0.374$ ) with the young active group having greater blood flow than the young inactive ( $p = 0.031$ ) and the old inactive groups ( $p = 0.005$ ) (Table 2). Conductance of normalized maximal blood flow was greater in the young ( $F(1,33) = 10.513$ ,  $p = 0.003$ ,  $H^2 = 0.253$ ) and the active ( $F(1,33) = 11.011$ ,  $p = 0.002$ ,  $H^2 = 0.262$ ) groups (Figure 2). Conductance of normalized maximal blood flow was higher in the young active compared to old inactive group ( $p < 0.001$ ) (Table 2).

**Table 2: Flow data and half time to recovery data for groups – Means (SD)**

	Young Active	Young Inactive	Older Active	Older Inactive
Normalized Resting Blood Flow (ml/100 g/min)	850 (500)	540 (370)	530 (160)	880 (500)
Resting Conductance (ml/100 g/min/mmHg)	9.4 (5.2)	6.6 (4.8)	5.4 (1.6)	8.6 (4.7)
Normalized Maximal Blood Flow (ml/100 g/min)	9102 (824)*	6630 (1748)	8110 (2756)	6080 (1204)
Maximal Conductance (ml/100 g/min/mmHg)	103 (16)#	83 (23)	82 (23)	59 (9)
Half Time to Recovery of Blood Flow (seconds)	55 (12)	51 (20)	60 (9)	75 (31)
Half Time to Recovery of NIRS (seconds)	24 (17)	20 (8)	25 (21)	37 (21)

Notes: \* Significantly different than young inactive ( $p = 0.031$ ) and older inactive ( $p = 0.005$ ). # Significantly different than the older inactive ( $p < 0.001$ ).



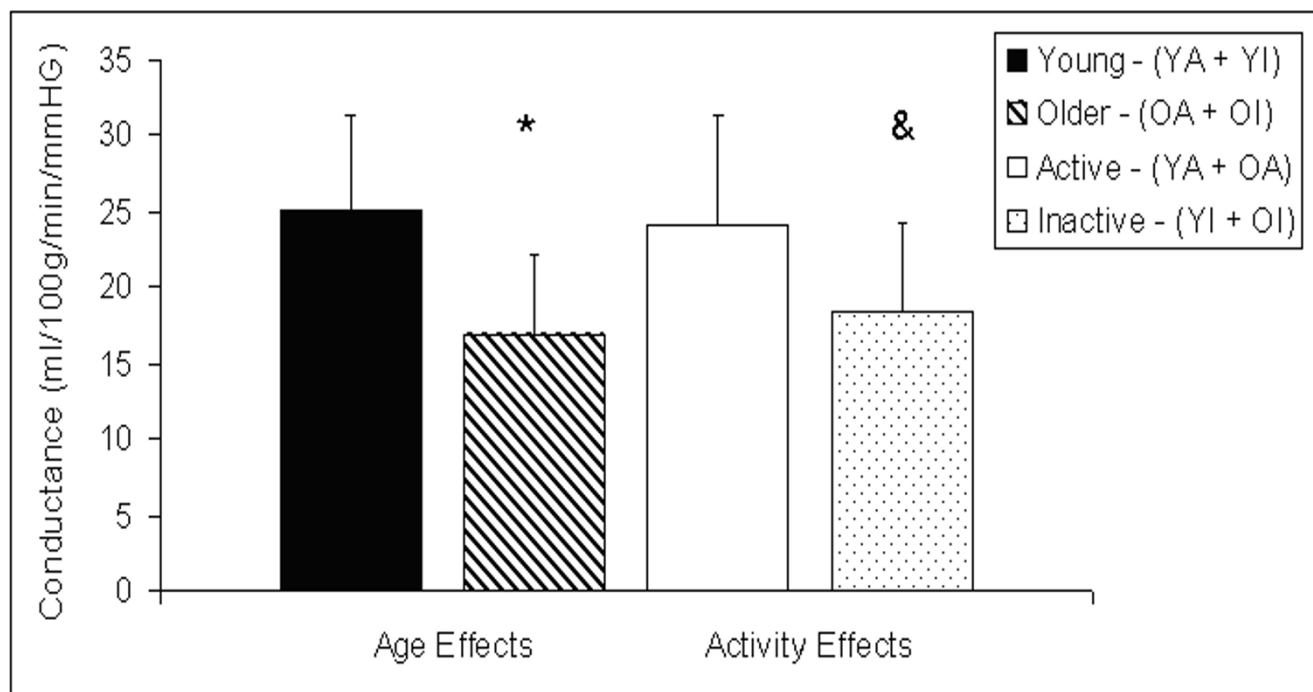
**Figure 1**

Normalized maximal blood flow for aging effects on left and activity effects on right (Means  $\pm$  SD). Young is the sum of young active (YA) and young inactive (YI). Older is sum of older active (OA) and older inactive (OI). Active is sum of young active (YA) and older active (OA). Inactive is sum of young inactive (YI) and older inactive (OI). & Active and inactive groups are significantly different at  $p < 0.001$ .

Maximal blood flow had a slower return to resting values (half time to recovery) in the older groups compared to the younger groups ( $F(1,35) = 4.684$ ,  $p = 0.038$ ,  $H^2 = 0.124$ ) (Figure 3). The half time to recovery of blood flow was not different between the active and inactive groups. Half time to recovery approached significance between the four groups ( $F(3,35) = 2.406$ ,  $p = 0.086$ ,  $H^2 = 0.189$ ) (Table 2). The half time of recovery of oxygen saturation measured with NIRS was not different between groups, although the older inactive group appeared to have slower recovery values (Table 2).

**Discussion**

The purpose of this study was to determine if aging or activity had an effect on peripheral blood flow. The primary finding of this study was that peak blood flow capacity was related to activity level while there was no age effect independent of activity level. Our results are consistent with others which have reported no age-related changes in maximal flow capacity after exercise [20–22]. A strength of this study was that maximal blood flow capacity was normalized to estimated lean muscle mass, to correct for age-related decreases in muscle mass [2].



**Figure 2**

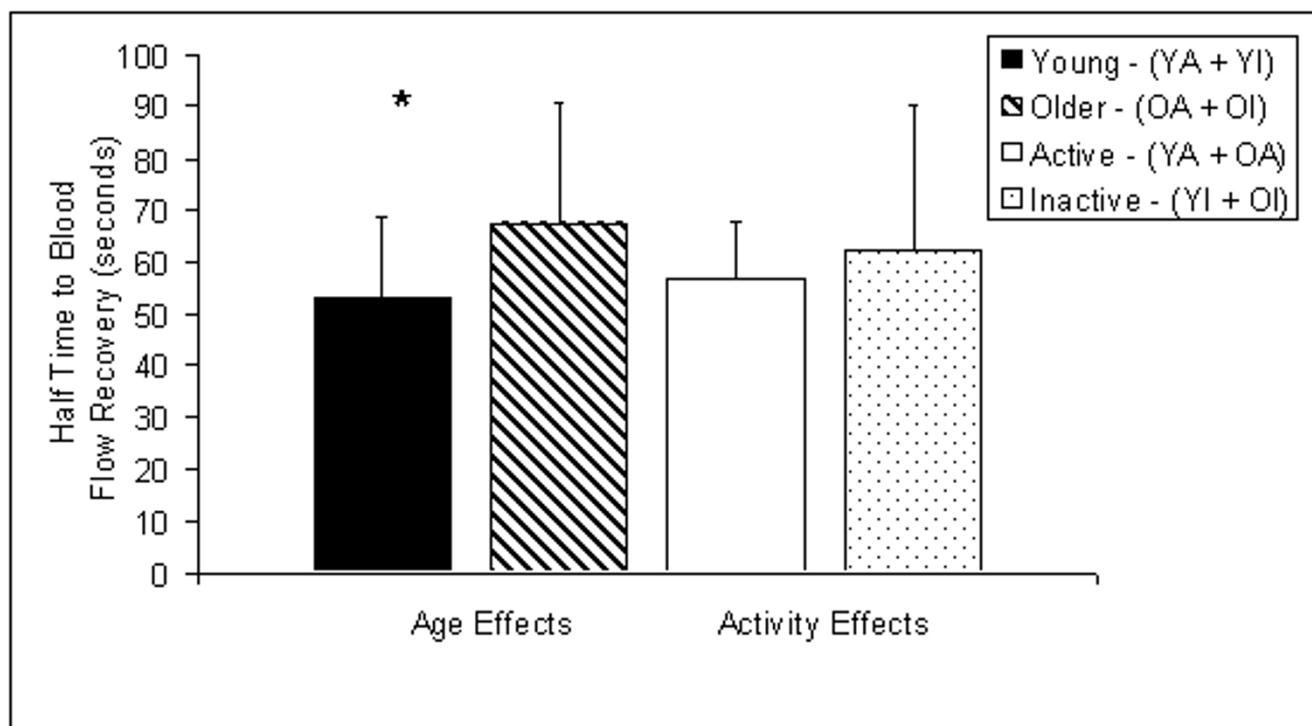
Conductance of normalized maximal blood flow for aging effects on left and activity effects on right (Means  $\pm$  SD). Young is the sum of young active (YA) and young inactive (YI). Older is sum of older active (OA) and older inactive (OI). Active is sum of young active (YA) and older active (OA). Inactive is sum of young inactive (YI) and older inactive (OI). \* Young and older groups are significantly different at  $p = 0.003$ . & Active and inactive groups are significantly different at  $p = 0.002$ .

We did not find age related changes in resting blood flow or resting diameter. In contrast, other studies have found age-related changes in resting blood flow which have been attributed to increases in sympathetic tone [19,30]. Aging has been associated with reduced blood flow and vascular conductance during whole body exercise [18]. The reduction in blood flow and conductance have been related to alterations in cardiac output and blood volume due to aging [23]. Several of our resting blood flow variables approached significance ( $p$  values below 0.10) indicating that our results may have been significant with a larger sample size. However, the significance of age related changes in resting blood flow are unclear other than serving as a marker for altered sympathetic tone; especially if maximal blood flow capacity is not changed with age.

We found that our active subjects had greater maximal blood flow capacity ( $\approx 30\%$ ) than our inactive subjects regardless of age. Consistent with our results Martin et al. [31] reported a greater vasodilatory capacity in trained than untrained subjects independent of age. Inactivity has been associated with impaired efficiency of peripheral oxygen extraction [32] and reduced blood flow after cuff ischemia [33]. Conversely, exercise training results in greater maximal flow capacity [31,34]. Regular aerobic ex-

ercise also prevents the age-associated loss in endothelium dependent vasodilation maintaining maximal flow capacity [9]. Our findings support previous research that maximal flow capacity is maintained by aerobic exercise and is independent of age.

Because blood flow is dependent on perfusion pressure, blood flow data is often presented as conductance (flow divided by mean arterial pressure). This is important in aging studies as age is associated with increases in blood pressure [19,30]. We found that maximal conductance was reduced in our older subjects, consistent with a higher mean arterial pressure in these subjects. We also found higher maximal conductance in the young active group compared to the older inactive subjects, again explained by differences in mean arterial pressure. Another study has reported aging to be associated with reduced conductance [18]. However, it is unclear how important differences in maximal conductance between groups is when there is no difference in maximal blood flow. The lack of difference in blood flow suggests that oxygen delivery is not compromised despite the reduced conductance. It is possible that the vascular system in the older subjects has compensated for the higher mean arterial pressures.



**Figure 3**

Half time to recovery of blood flow in seconds for aging effects on left and activity effects on right (Means  $\pm$  SD). Young is the sum of young active (YA) and young inactive (YI). Older is sum of older active (OA) and older inactive (OI). Active is sum of young active (YA) and older active (OA). Inactive is sum of young inactive (YI) and older inactive (OI). \* Young and older groups are significantly different at  $p = 0.038$ .

Consistent with the lack of age differences in maximal blood flow, we found no age differences in oxygen delivery as measured by NIRS. Oxygen delivery after exercise has been found to be similar between healthy active older and younger subjects [35]. It was expected, however, that oxygen delivery would be different between the active and inactive individuals. The older inactive did appear to have prolonged oxygen delivery but the young inactive did not. This suggests that oxygen delivery may be more sensitive to the interaction of age and inactivity. Future studies are needed to clarify the influence of age and activity level on oxygen delivery.

An interesting finding in this study was that the half time to recovery of blood flow was prolonged ( $\approx 28\%$ ) in the older compared to young subjects, independent of activity status. This is one of the first studies to our knowledge that has investigated blood flow recovery kinetics in these populations. Slow recovery of blood flow has been used as an index of reduced vascular reactivity in coronary arteries [36]. The hyperemic response to ischemia is dependent on the presence and response to metabolic factors and vasoactive substances such as nitric oxide and adenosine [37]. The prolonged recovery of blood flow in our study

could be due to either a greater buildup of metabolic factors/vasoactive substances and/or a diminished ability to remove them in the older subjects. This study, however, was not designed to determine the mechanism for the increased time for blood flow to recover. A prolonged half time to recovery has been associated with a decreased nitric oxide and prostanoid production [8] and a loss of endothelium dependent vasodilation [9]. Reduced vascular reactivity is associated with many diseases that are associated with aging [15–17]. We did not find activity effects on half time to recovery. This finding contrasts other previously published studies which have shown decreased vascular reactivity in individuals who are required to be on bed rest [26,38] and in individuals with spinal cord injuries [27]. It is possible that the differences in activity levels between our groups in this study were not large enough to produce the same effects that are seen with bed rest and spinal cord injury.

In summary, we found that maximal blood flow capacity was significantly related to activity level but was not related to age. Blood flow calculated as conductance was related to aging and activity, consistent with the reduced blood flow in the inactive subjects and the higher blood pres-

tures in the older subjects. In addition, the older subjects had evidence of reduced vascular reactivity, as measured by prolonged half time to recovery, independent of activity status. The prolonged half time to recovery in the older subjects is likely related to a reduced vascular reactivity associated with increased cardiovascular disease risk. Thus, maximal flow capacity and the half time to recovery of blood flow are influenced by different mechanisms in young and older active and inactive subjects.

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