

Resistance exercise training improves age-related declines in leg vascular conductance and rejuvenates acute leg blood flow responses to feeding and exercise

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Phillips B, Williams J, Atherton P, Smith K, Hildebrandt W, Rankin D, Greenhaff P, Macdonald I, Rennie MJ. Resistance exercise training improves age-related declines in leg vascular conductance and rejuvenates acute leg blood flow responses to feeding and exercise. *J Appl Physiol* 112: 347–353, 2012. First published October 13, 2011; doi:10.1152/jappphysiol.01031.2011.—One manifestation of age-related declines in vascular function is reduced peripheral (limb) blood flow and vascular conductance at rest and in response to vasodilatory stimuli such as exercise and feeding. Since, even in older age, resistance exercise training (RET) represents an efficacious strategy for increasing muscle mass and function, we hypothesized that likewise RET would improve age-related declines in leg blood flow (LBF) and vascular conductance (LVC). We studied three mixed-sex age groups (young: 18–28 yr, $n = 14$; middle aged: 45–55 yr, $n = 20$; older: 65–75 yr, $n = 17$) before and after 20 wk of whole body RET in the postabsorptive state (BASAL) and after unilateral leg extensions (6×8 repetitions; 75% 1 repetition maximum) followed by intermittent mixed-nutrient liquid feeds (~ 6.5 $\text{kJ} \cdot \text{kg}^{-1} \cdot 30 \text{ min}^{-1}$), which allowed us to discern the acute effects of feeding (nonexercised leg; FED) and exercise plus feeding (exercised leg; FEDEX) on vascular function. We measured LBF using Doppler ultrasound and recorded mean arterial pressure (MAP) to calculate LVC. Our results reveal that although neither age nor RET influenced BASAL LBF, age-related declines in LBF responses to FED were eradicated by RET. Moreover, increases in LBF after FEDEX, which occurred only in young and middle-aged groups before RET ($+73 \pm 9\%$, and $+90 \pm 13\%$, $P < 0.001$, respectively), increased in all groups after RET (young $+78 \pm 10\%$, middle-aged $+96 \pm 15\%$, older $+80 \pm 19\%$, $P < 0.001$). Finally, RET robustly improved LVC under FASTED, FED, and FEDEX conditions in the older group. These data provide novel information that supports the premise that RET represents a valuable strategy to counter age-related impairments in LBF/LVC.

circulation; nutrition; muscle

HUMAN AGEING is associated with decreased arterial compliance, which leads to hypertension and coronary artery disease (10, 11, 20) such that cardiovascular disease-related morbidity and mortality increase markedly with age. Declines in peripheral (i.e., limb arterial) blood flow and increases in vascular resistance are one such characteristic manifestation of cardiovascular ageing. For example, Donato et al. (13) reported that older individuals exhibit 20–30% lower resting, postabsorptive limb blood flow and a $\sim 50\%$ decrease in leg vascular conductance

(LVC) compared with younger individuals. Such age-related changes are purported to contribute to the metabolic syndrome, a major precursor to atherosclerotic disease in humans that encompasses hyperinsulinemia, dyslipidemia, and hypertension (20).

Intriguingly, declines in peripheral blood flow with ageing are not restricted to postabsorptive periods but are also observed when subjects are challenged with vasodilatory stimuli, such as food intake (31) and exercise (13, 25). For example, characteristic increases in limb (forearm brachial) blood flow in the postprandial period are impaired in both older and diabetic adults (31), with age rather than diabetes being the principal determinant. Furthermore, compromised exercise hyperemia has also been demonstrated with elderly men displaying 20–30% lower LBF and LVC than younger men at various exercise workloads (13) of knee-extensor exercise or whole body bicycling (13, 25).

Significantly, both functional and metabolic consequences of declines in LBF responses to feeding and exercise have been suggested. First, decreases in LBF during/after exercise may explain decrements in functional performance and recovery [e.g., O_2 delivery, metabolite clearance, etc. (37)] in ageing skeletal muscles. Second, as LBF regulates delivery of insulin and amino acids for metabolism in skeletal muscles (8, 36) reduced LBF can contribute to declines in insulin sensitivity and muscle protein anabolic responses to both feeding and exercise (3, 5–7, 15, 37) with age. Thus it is likely that avenues for maintaining both resting postabsorptive LBF as well as “acute” responses in LBF to vasodilatory stimuli such as exercise and feeding represent an important avenue for preserving muscle health with ageing.

Muscle strength is inversely correlated with all-cause mortality (21), and age-related declines in both muscle mass and strength are associated with comorbidities such as falls, fractures, and progressive disability (27, 28). Although it has been long known that resistance exercise training (RET) improves muscle mass and function, even in elderly subjects (33), RET has also shown novel efficacy such as modulating cardiovascular risk (9) and ameliorating age-related declines in postabsorptive LBF (1, 22, 34). Therefore, we hypothesized that RET could ameliorate age-related declines in LBF and LVC not only under postabsorptive conditions but also in responses to the vasodilatory stimuli of food intake and exercise. Specifically, adopting a unilateral (i.e., one-legged) acute exercise protocol enabled us to measure LBF and leg vascular conductance (LVC) both before and after 20 wk RET under three conditions: 1) BASAL: postabsorptive; 2) FED: in the nonex-

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exercised leg after feeding; and 3) FEDEX: in the exercised leg after feeding.

MATERIALS AND METHODS

Subject Characteristics

We recruited three groups consisting of young [Y: 24.9 ± 3.5 yr, 9 male, 5 female; body mass index (BMI) 23.5 ± 2.3 kg/m²], middle-aged [M: 49.5 ± 3.7 yr, 10 male, 10 female; BMI 26.7 ± 3.0 kg/m²], and older [O: 69.6 ± 3.2 yr, 10 male, 7 female; BMI 26.9 ± 1.9 kg/m²] individuals. All subjects were initially screened by means of a medical questionnaire, physical examination, and resting ECG with exclusions for overt muscle wasting (>2 SD below age norms) (4), metabolic, respiratory or cardiovascular disorders, or other signs and symptoms of ill-health. All subjects had normal blood chemistry, were normotensive (blood pressure $< 140/90$) and were not prescribed medication. All subjects performed activities of daily living and recreation but did not routinely participate in moderate- to high-intensity aerobic exercise and none had participated in RET in the last 2 yr. At least 1 wk before the first acute study the subjects' 1 repetition maximum (1-RM) for leg extension on their dominant leg was measured (ISO Leg Extension, Leisure Lines, Leicestershire, UK). All subjects gave their written, informed consent to participate after all procedures and risks were explained. This study was approved by The University of Nottingham Ethics Committee and complied with the Declaration of Helsinki.

Acute Studies (Before and After Training)

Subjects were instructed to refrain from exercise 72 h days prior to each study day and from alcohol and caffeine for 24 h. Subjects fasted from 2100 the night before (water ad libitum) and reported to the laboratory at 0800. Body composition was measured by dual-energy X-ray absorptiometry (DXA; Lunar Prodigy II, GE Medical Systems) before and after the 20 wk RET; leg composition was measured on the dominant leg as the area inferior to the lowest visible point of the coccyx.

BASAL measurement phase. After 70 min lying supine, measurements of LBF (femoral artery) were made intermittently from both legs for 40 min, with simultaneous measurements of blood pressure (BP) and heart rate (HR), designated as BASAL. A mean value from three measurements on each leg was used to obtain the basal value with no significant differences between the three measurements or between the legs. LBF was measured using the Doppler ultrasound technique (Toshiba Nemio-17). All measurements were taken with the subject supine, with no visual or aural stimuli. A single 5-MHz frequency probe was used to measure mean blood velocity (MBV) and arterial lumen diameter in the common femoral arteries of both legs. Measurements were made 2–3 cm proximal to the bifurcation of the femoral artery to minimize the effect of turbulence; the insonation angle was $<60^\circ$. Arterial lumen diameter (mm) was measured by

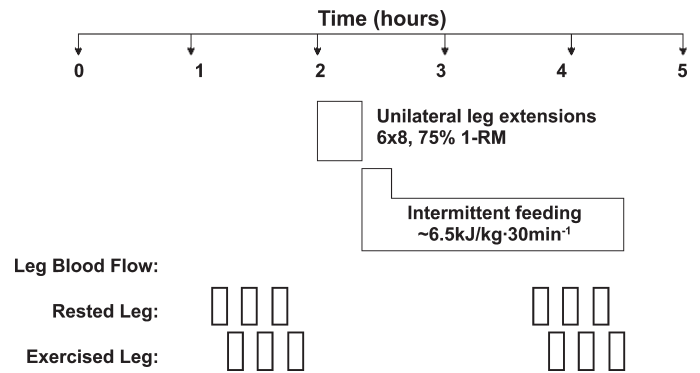


Fig. 1. Acute study protocol. 1-RM, one repetition maximum.

video calipers for each measurement and defined as the maximum distance between the media-adventitia interface of the near wall and the lumen-intima interface of the far wall of the vessel. LBF (l/min) was calculated as $\{MBV \text{ (cm/s)} \times \pi \times [\text{femoral artery radius (mm)}]^2\} / 1,000 \times 60$. Using the Doppler ultrasound technique to measure basal LBF we found a coefficient of variation of 9% for three independent measures under each condition assessed, suggesting that we could reliably detect changes of $\sim 18\%$ of the basal value. When data were normalized for lean leg mass the results were identical to the nonnormalized data presented.

FED/FEDEX measurement phases. At 120 min the subjects performed 6×8 repetitions of full-cycle unilateral leg extensions at 75% 1-RM on a free-standing machine (ISO Leg Extension, Leisure Lines). Immediately after exercise the subjects received, over 2 h, an oral-feed (Fortisip, Nutricia Clinical Care, Wiltshire, UK) which supplied energy at 4.25 times basal metabolic rate (BMR), as calculated by standard equations (17). The feed had a composition similar to that of a normal mixed-meal (16% protein, 49% carbohydrate, and 35% fat) and was given as a priming bolus (3 doses immediately after exercise), with four further doses every 30 min thereafter. Doses were between 61 and 96 ml, based on subject body weight to provide 6.5 kJ·kg body wt⁻¹·30 min⁻¹. BP, HR, and LBF were measured at 100, 120, and 140 min postexercise. LBF measurements were made from both legs alternately (providing data for the effects of FED and FEDEX) with the mean value of these three measurements used to provide LBF values for responses to feeding and to exercise plus feeding. Blood flows were stable throughout the measurement period, i.e., at 100, 120, and 140 min after exercise. This protocol was repeated at least 3 days, but less than 7 days after the subjects last training bout at the end of the supervised 20 wk whole body RET regime (Fig. 1). This allowed us to study the effects of RET rather than any remaining acute effects of a single exercise session.

Table 1. Physiological measurements before and after resistance exercise training

	Young		Middle Aged		Old	
	Pre-RET	Post-RET	Pre-RET	Post-RET	Pre-RET	Post-RET
Lean body mass, g	49,209 \pm 2682	51,260 \pm 3037*	49,777 \pm 2342	50,498 \pm 2266*	49,235 \pm 2866	49,690 \pm 2814
Lean leg mass, g	8,718 \pm 450	9,093 \pm 444*	8,503 \pm 444	8,633 \pm 445	8,247 \pm 547	8,536 \pm 572
Fat mass, g	18,358 \pm 2226	17,586 \pm 2509	22,394 \pm 1187	21,322 \pm 1282*	22,786 \pm 1451	22,158 \pm 1395*
Strength, N	5,729 \pm 405	7,609 \pm 377*	4,921 \pm 387	6,535 \pm 460*	4,082 \pm 202	5,630 \pm 374*
Homeostasis model assessment	1.12 \pm 0.08	1.14 \pm 0.08	1.14 \pm 0.17	0.88 \pm 0.11*	1.63 \pm 0.25	1.13 \pm 0.10*
Basal mean arterial pressure, mmHg	105 \pm 2	106 \pm 2	114 \pm 2	105 \pm 2*	120 \pm 2	111 \pm 2*
Basal systolic pressure, mmHg	112 \pm 3	125 \pm 3	132 \pm 3	122 \pm 3*	140 \pm 3	131 \pm 3*
Basal diastolic pressure, mmHg	72 \pm 2	71 \pm 3	82 \pm 2	73 \pm 2*	82 \pm 2	75 \pm 2*
Resting heart rate, beats/min	67 \pm 2	59 \pm 2*	64 \pm 1	57 \pm 2*	67 \pm 3	65 \pm 2

Values are means \pm SE. RET, resistance exercise training. * $P < 0.05$ vs. before training in the same age group.

RET

The fully supervised RET program was designed to achieve skeletal muscle hypertrophy and improvements in strength, based on previously published recommendations for exercise intensity and duration (29). Subjects trained three times per week, with each session lasting ~60 min. During 4 wk of induction training (to ensure adoption and adherence to correct technique), intensity was increased from 40% to 60% 1-RM. For the remaining 16 wk of training intensity was set at 70% 1-RM, with multiple sets of 12 repetitions and 2 min rest between sets. The same number of repetitions (16 sets of 12 repetitions) were performed each session over a total of 8 exercises; seated chest press, latissimus-pull down, seated lever row, leg extension, leg curl, leg press, back extension, and abdominal curl. One-RM assessments were made every 4 wk to ensure that the intensity of training was constant, i.e., 70% 1-RM, to account for strength improvements. Subjects were excluded from the study for noncompliance, defined as nonattendance for >6 consecutive sessions, less than 75% attendance, or failure to complete the set exercise regime on >15% attendance. Muscle strength was determined every 4 wk by the 1-RM assessments performed on six of the eight machines used during the training. Whole body strength was determined by the sum of force produced by three lower body exercises: leg extension, leg curl, and leg press; and three upper body exercises: latissimus-pull down, lever seated row, and seated chest press with newtons calculated as weight lifted \times 9.807 based on a standard gravitational field.

MAP, HR, and LVC

Heart rate, and systolic and diastolic blood pressures were measured using an OMRON (OMRON Healthcare) automated blood pressure monitor and were recorded as the mean of three measurements. Mean arterial blood pressure (MAP), calculated as $(2/3 \text{ diastolic blood pressure}) + (1/3 \text{ systolic blood pressure})$ was measured to calculate leg vascular conductance (LVC) as $LVC (\text{l}\cdot\text{min}^{-1}\cdot 100 \text{ mmHg}^{-1}) = LBF (\text{l}\cdot\text{min}^{-1})/\text{MAP} \times 100$.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism Version 5.00 (La Jolla, CA). All data are reported as means \pm SE with significance set at $P < 0.05$. Repeated-measures ANOVA and Bonferroni post hoc analysis were used to compare pre- and posttraining strength and blood flow values. Pearson's correlation was used to explore relationships between age and blood flow responses to feeding and to exercise plus feeding.

RESULTS

Body Composition

Before training there were no significant differences in whole body or dominant whole leg lean mass between the young, middle-aged, and older groups as assessed by DXA (Table 1). This remained true after RET. Nevertheless, there were significant increases in whole body lean mass after the RET regime in the young and middle-aged subjects (young, $+5.0 \pm 1.1\%$, $P < 0.001$; middle-aged, $+1.7 \pm 0.8\%$, $P < 0.05$) and increases in whole leg lean mass in the young subjects ($+4.3 \pm 1.4\%$, $P < 0.01$).

Measures of Muscle Strength

All three age groups showed significant increases in muscle strength after RET. Before training, the muscle strength (the sum of the 6 previously mentioned exercises) of the young ($5,729 \pm 405$ N) was higher than that of the middle-aged ($4,921 \pm 387$ N), both of which were higher than that of the

older individuals ($4,082 \pm 202$ N, $P < 0.01$) (Table 1). All three groups showed similar strength gains, with the young increasing from $5,729 \pm 405$ to $7,609 \pm 377$ N (+36%), middle-aged from $4,921 \pm 387$ to $6,535 \pm 460$ N (+35%), and old from $4,082 \pm 282$ to $5,630 \pm 374$ N (+39%). The 39% strength increase in the older group took their mean strength to a value similar to that in the young before training ($5,630$ vs. $5,729$ N).

Measures of LBF

Using the Doppler ultrasound technique to measure basal LBF we found a coefficient of variation of 9% for three independent measures under each condition assessed, suggesting that we could reliably detect changes of ~18% of the basal

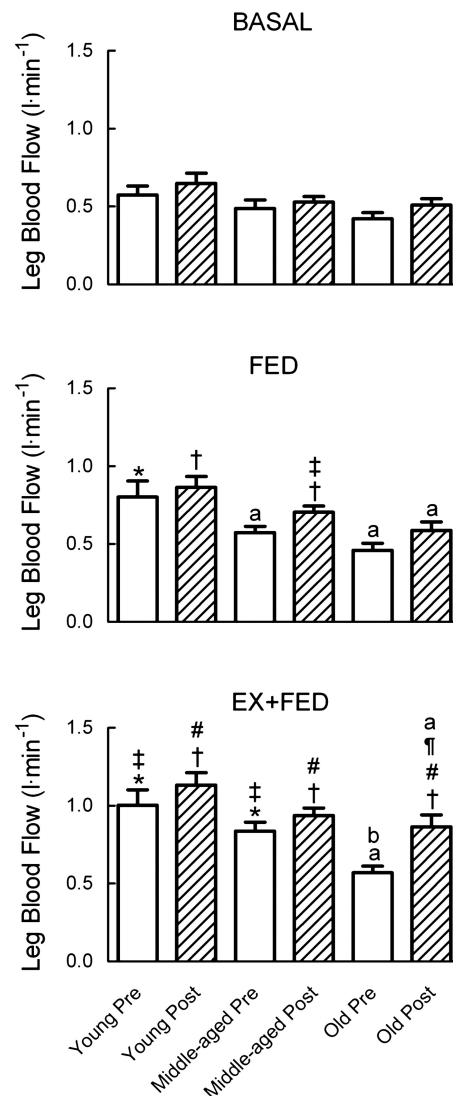


Fig. 2. Effect of resistance exercise training on femoral artery blood flow in postabsorptive conditions (BASAL), after feeding (FED), or after exercise plus feeding (EX + FED) in young, middle-aged, and older subjects. Values are means \pm SE for 14 young, 20 middle-aged, and 17 old subjects. * $P < 0.05$ vs. basal pretraining; † $P < 0.05$ vs. basal posttraining; ‡ $P < 0.05$ vs. feeding pretraining; § $P < 0.05$ vs. feeding pretraining; # $P < 0.05$ vs. feeding posttraining; ¶ $P < 0.05$ vs. exercise plus feeding pretraining; ^a $P < 0.05$ vs. young in the same condition; ^b $P < 0.05$ vs. middle-aged in the same condition, all via ANOVA with Bonferroni postanalysis.

value. When data were normalized for lean leg mass the results were identical to the nonnormalized data presented.

LBF under BASAL, FED, and FEDEX conditions before and after RET. Before and after RET there were no differences in BASAL LBF between the age groups (Fig. 2). Before RET, only the young group demonstrated increased FED LBF ($P < 0.01$) and only the young and middle-aged groups demonstrated increased FEDEX LBF ($P < 0.001$). After RET, both the young and middle-aged groups increased FED LBF ($P < 0.01$) and all groups increased LBF in response to FEDEX (Y: $+78.4 \pm 10.3\%$, $P < 0.001$; M: $+95.7 \pm 14.6\%$, $P < 0.001$; O: $+79.8 \pm 19.0\%$, $P < 0.001$), displaying LBF values significantly higher after FEDEX than after FED alone ($P < 0.001$) (Fig. 2). Adopting (AGE \times LBF) correlation analyses we found that before RET, both FED (Fig. 3A) and FEDEX LBF responses were blunted with increasing age (Fig. 3B), but these age-related decreases were no longer apparent after RET (Fig. 3, C and D).

Measures of LVC

Relationships between BASAL LVC and age. BASAL LVC was significantly greater in the young than in the old before RET (0.56 ± 0.06 vs. 0.36 ± 0.03 l·min⁻¹·100 mmHg⁻¹, $P < 0.01$). After RET, BASAL LVC in the older group was significantly increased (0.36 ± 0.03 vs. 0.47 ± 0.04 l·min⁻¹·100 mmHg⁻¹, $P < 0.001$), and there was a trend for it to also increase in the middle-aged group (0.43 ± 0.05 vs. 0.50 ± 0.04 l·min⁻¹·100 mmHg⁻¹, $P = 0.095$). After RET there were no significant differences in BASAL LVC between the age groups (Y: 0.63 ± 0.06 ; M: 0.50 ± 0.04 ; O: 0.47 ± 0.04 l·min⁻¹·100 mmHg⁻¹) (Fig. 4).

LVC under BASAL, FED, and FEDEX conditions before and after RET. BASAL LVC was significantly greater in the middle-aged and older groups after RET (M: 0.53 ± 0.04 vs.

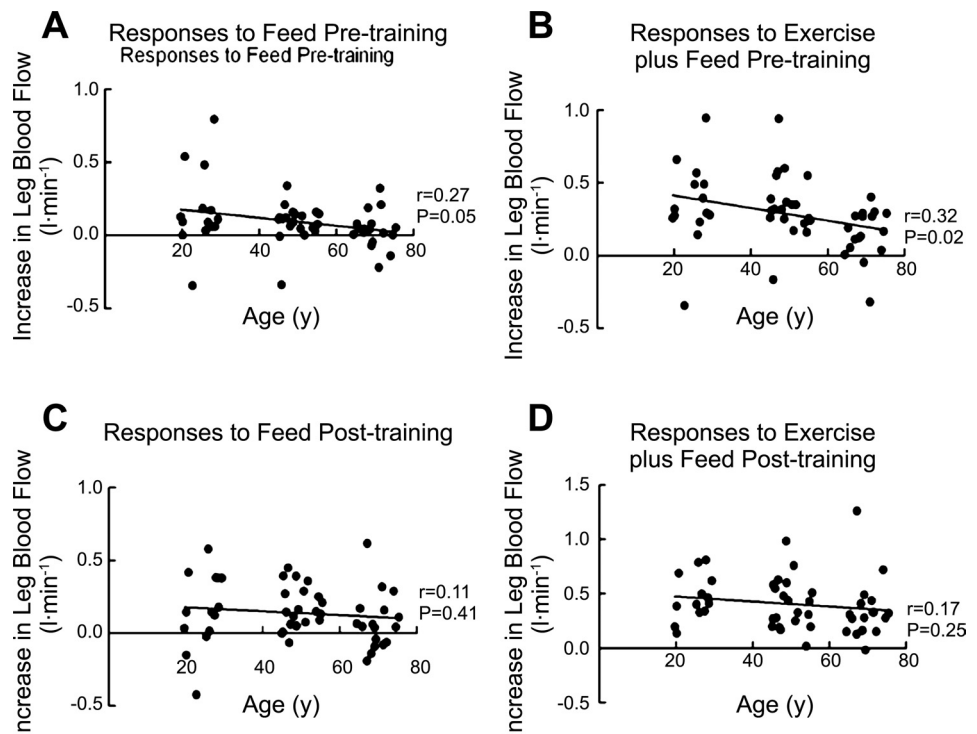
0.67 ± 0.04 ; O: 0.41 ± 0.05 vs. 0.55 ± 0.06 l·min⁻¹·100 mmHg⁻¹, both $P < 0.05$). Before RET only in the young was there an increase in FED LVC (0.56 ± 0.06 vs. 0.78 ± 0.10 l·min⁻¹·100 mmHg⁻¹, $P < 0.01$), whereas after RET the young (0.63 ± 0.06 vs. 0.86 ± 0.08 l·min⁻¹·100 mmHg⁻¹, $P < 0.001$) and the middle-aged groups (0.50 ± 0.04 vs. 0.67 ± 0.04 l·min⁻¹·100 mmHg⁻¹, $P < 0.01$) increased. All three age groups increased LVC with FEDEX both before RET (Y: 0.56 ± 0.06 vs. 0.98 ± 0.09 , $P < 0.001$; M: 0.43 ± 0.05 vs. 0.77 ± 0.05 , $P < 0.001$; O: 0.36 ± 0.03 vs. 0.50 ± 0.04 l·min⁻¹·100 mmHg⁻¹, $P < 0.05$) and after RET (Y: 0.63 ± 0.06 vs. 1.12 ± 0.09 ; M: 0.50 ± 0.04 vs. 0.89 ± 0.05 ; O: 0.47 ± 0.04 vs. 0.81 ± 0.08 l·min⁻¹·100 mmHg⁻¹, all $P < 0.001$). The increase in the old was significantly greater after RET (49 ± 11 vs. $80 \pm 19\%$, $P < 0.01$) such that FEDEX LVC in the old after RET was not different from that of the young before RET, effectively restoring LVC responses in the old to those typical of younger subjects (Fig. 4).

DISCUSSION

In summary we report that age-related declines in FED and FEDEX (but not BASAL) LBF are ameliorated by RET, which is concomitant with a restoration of LVC. We are the first to report that age-related dysregulation in LBF under FED and FEDEX conditions (along with associated diminutions in LVC) may be ameliorated by RET. Although we were unable to seek a mechanism for our findings in this large cohort, it is evident that RET may in some cases reverse age-related declines in leg LBF/LVC, which are indicative of pathological changes in vessel structure and/or vascular tone.

Our findings in terms of BASAL LBF are consistent with previous reports of age-related declines in untrained older humans (11) that are unrelated to muscle mass (lean mass was similar between our older and younger groups). Thus other

Fig. 3. Effect of resistance exercise training on the relationship between increases in femoral artery blood flow after feeding, or exercise-plus-feeding, and age. Analysis by Pearson's correlation. There is a significant decrease in response to feeding with age pretraining ($r = 0.27$; $P = 0.05$) (A). There is also a significant decrease in response to exercise-plus-feeding with age pretraining ($r = 0.32$; $P = 0.02$) (B). There is no significant decrease in the response to feeding with age posttraining ($r = 0.11$; $P = 0.41$) (C). There is no significant decrease in the response to exercise-plus-feeding with age posttraining ($r = 0.17$; $P = 0.25$) (D).



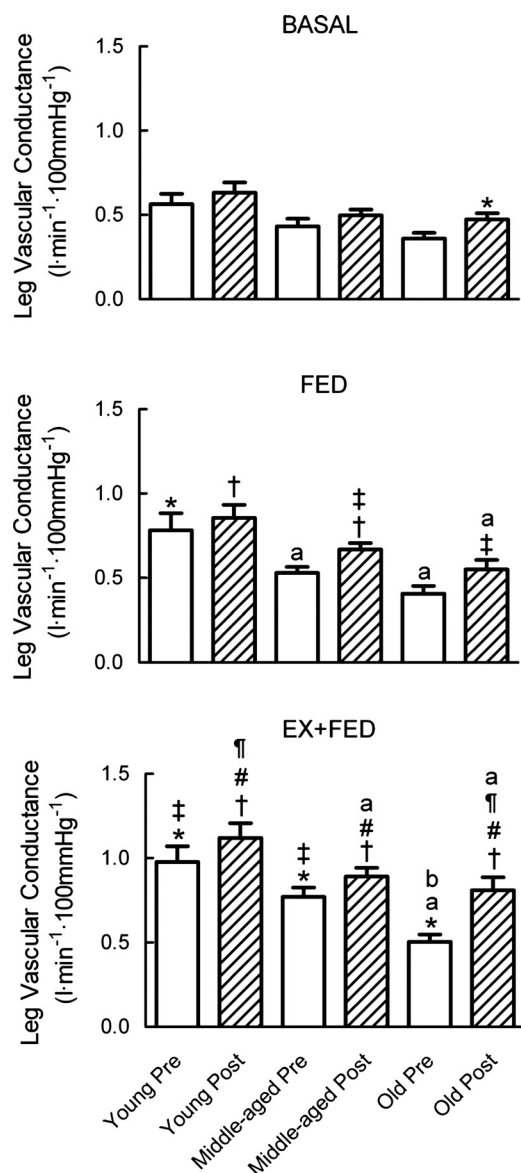


Fig. 4. Effect of resistance exercise training on limb vascular conductance in postabsorptive conditions (BASAL), after feeding (FED), or after exercise plus feeding (EX+FED) in young, middle-aged, and older subjects. Values are means \pm SE for 14 young, 20 middle-aged, and 17 old subjects. * $P < 0.05$ vs. basal pretraining; † $P < 0.05$ vs. basal posttraining; ‡ $P < 0.05$ vs. feeding pretraining; ‡‡ $P < 0.05$ vs. feeding posttraining; # $P < 0.05$ vs. feeding pretraining; ¶ $P < 0.05$ vs. exercise-plus-feeding pretraining; ^a $P < 0.05$ vs. young in the same condition; ^b $P < 0.05$ vs. middle-aged in the same condition, all via ANOVA with Bonferroni post analysis.

mechanisms such as chronic vasoconstriction due to increased α -adrenergic tone and/or a lower O_2 demand (12, 37) are more likely candidates than lower muscle mass (i.e., sarcopenia) per se. Although RET is expected to cause muscle hypertrophy, somewhat surprisingly [given the common view of such vascular adaptations being specific to endurance training (35)], it has also been shown to increase BASAL LBF (1, 34). For example, Tanimoto and colleagues reported that 13 wk of high (85–90% 1-RM)- or low-intensity (50–60% 1-RM) RET was equally effective in increasing BASAL LBF (34), and it is well established from cross-sectional studies that LBF in RET individuals is better preserved with ageing (22). It would

therefore have been expected that age-related declines in BASAL LBF may be ameliorated by RET. Nonetheless, our data do not support this as we found no increase in BASAL LBF after RET in any age group; moreover when all our data were expressed relative to age and/or lean leg mass, declines in postabsorptive LBF with advancing age were still evident even after RET. This is reflected by the fact that increases in LVC in older subjects after RET were principally due to decreases in MAP (rather than increases in LBF), which we speculate may have been due to an amelioration of increased sympathetic nerve activity directed to muscle vascular beds that has been reported in ageing (24). Finally, as no groups demonstrated increased BASAL LBF after RET despite displaying hypertrophy, this further supports the prior notion of dissociation between muscle mass and LBF per se (11).

There is little published information concerning acute responses in LBF to FED. Fugmann et al. (14) showed a long lasting (>2 h) increase in peripheral blood flow in response to feeding using venous capacitance plethysmography, as did Hernandez et al. (18), to the magnitude of 16–25%, although the method used in the latter study (indocyanine green dye dilution) is inherently more variable than either plethysmographic or Doppler techniques. Coupling the use of Doppler and contrast enhanced ultrasound (CEUS), Vincent et al. (37) reported a 33% increase in brachial artery blood flow, (similar to the 40% increase in FED LBF we observed in the young before RET) and a 50% increase in forearm muscle microvascular blood volume 60 min after a mixed meal [2,008 kJ, 68% carbohydrate, 16% fat, and 17% protein (37)]. In line with these findings, we found that LBF increased in response to FED in our younger subjects. Moreover, this increase was not apparent in our middle-aged or older subjects and further age \times LBF correlation analyses confirmed age-related declines in LBF responses to FED, a relationship also found by others (31). Collectively these data signify a physiological increase in FED LBF that is diminished with age. Intriguingly, RET improved these diminutions such that FED LBF responses increased significantly in the middle-aged and older groups (when compared with their pretraining values) and the negative relationship between increasing age and FED LBF responses was ameliorated, presumably via enhancement of FED LVC. Thus, although we were unable to uncover specific mechanisms at this time, these data highlight that RET can reverse declines in FED LBF responses in ageing. Furthermore, we speculate that as the vast majority of LBF goes to skeletal muscles, improved LBF and LVC after RET may positively impact age-related declines in glucose disposal (14, 20) and amino acid deposition; clearly this conjecture warrants further investigation.

Exercise hyperemia is evident in active muscles both during and for sustained periods afterward and is important for performance and ensuing recovery and remodeling alike (30). Importantly, such hyperemic responses also seem to be diminished in ageing (13, 25), which may contribute to reduced performance and maladaptation to exercise training in older age (16). In the present study we elected to measure LBF during the recovery period from exercise, which reflects the “remodeling” period [e.g., where muscle protein turnover is heightened (19)]. We also chose to study the combined effects of exercise and feeding (rather than exercise hyperemia per se) to maximize practical ramifications of the work. For instance, practicably most people would (or be recommended to) com-

bine resistance exercise with feeding to maximize muscle anabolic responses (23). It is therefore of significance that RET abolished blunted LBF responses to FEDEX seen before RET in both the middle-aged and older subjects. In young healthy men RET reportedly increased peak limb vasodilatory capacity (26), which raises the possibility that decreased arteriolar tone could contribute to the increased capacity for higher LBF after RET. Thus decreased α -adrenergic tone [known to be elevated in older individuals (12, 32)] and perhaps improved redistribution of LBF to working muscles (i.e., improved functional sympatholysis) are attractive possibilities to contribute to improvements in LBF and corresponding normalization of LVC in response to FEDEX.

In conclusion, RET rejuvenates age-related declines in LVC and LBF under FED and FEDEX conditions, which symbolizes improved peripheral LBF and LVC and suggests that vascular adaptation represents a key facet in the metabolic benefits of RET. Although we have studied “healthy” subjects, it is speculated that improved LBF and LVC with RET may also benefit those with cardiovascular or metabolic conditions (2).

Study Limitations

We acknowledge there are limitations to our elected study design. First our measures under FED and FEDEX conditions precluded inclusion of an exercise-only condition. Second, although the unilateral exercise model provides a good model to investigate how whole body RET has modulated peripheral blood flow as tissue perfusion is closely matched with demand, we accept that it is possible that our results may not have arisen from isolated lower-limb RET (i.e., which may not have affected MAP) and that performing acute whole body rather than unilateral leg exercise prior to measurements could have influenced our “acute” findings. Third, the large subject number and diverse age groups negated the option to include a time control group (both for practicable and cost reasons). Finally, it should be noted that some of our positive results in LVC (i.e., increases in BASAL LVC) were based on proportionally greater reductions in MAP, rather than increases in LBF, although this was not the case in other conditions (i.e., LVC under FEDEX conditions in older individuals).

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

B.P., J.W., P.J.A., W.H., and D.R. performed experiments; B.P., P.J.A., and K.S. analyzed data; B.P., J.W., P.J.A., and K.S. interpreted results of experiments; B.P. prepared figures; B.P. and M.R. drafted manuscript; B.P., J.W., P.J.A., K.S., P.L.G., I.A.M., and M.R. designed studies and edited and revised.

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