Evidence for impaired skeletal muscle contraction-induced rapid vasodilation in aging humans

Rick E. Carlson,1 Brett S. Kirby,1 Wyatt F. Voyles,2 and Frank A. Dinenna1

1Department of Health and Exercise Science, Colorado State University, Fort Collins; and 2Heart Center of the Rockies, Poudre Valley Health System, Fort Collins, Colorado

Submitted 18 September 2007; accepted in final form 26 February 2008

Carlson RE, Kirby BS, Voyles WF, Dinenna FA. Evidence for impaired skeletal muscle contraction-induced rapid vasodilation in aging humans. Am J Physiol Heart Circ Physiol 294: H1963–H1970, 2008. First published February 29, 2008; doi:10.1152/ajpheart.01084.2007.—We tested the hypothesis that aging is associated with an impaired contraction-induced rapid vasodilation in healthy adults. We reasoned that employing single contractions of a small muscle mass would allow us to isolate the local rapid vasodilatory responses independent of systemic hemodynamic and sympathetic neural influences on forearm hemodynamics. We measured forearm blood flow (Doppler ultrasound) and arterial blood pressure (Finapres) on a beat-by-beat basis and calculated the changes in forearm vascular conductance (ΔFVC) in response to forearm contractions in 18 young (24 ± 1 yr) and 13 older (62 ± 2 yr) healthy subjects. Single, 1-s dynamic forearm contractions were performed with the experimental arm slightly above heart level at 5, 10, 20, and 40% of the subjects’ maximal voluntary contraction (MVC) in random order. In general, muscle contractions evoked a rapid increase in FVC that reached a peak within approximately four to five cardiac cycles postcontraction in both age groups. At 5% MVC, there were no significant age-related differences in contraction-induced forearm vasodilation. However, the peak vasodilatory responses were impaired ~40–45% in older adults at 10, 20, and 40% MVC, as were the total vasodilatory responses (area under curve ~40–50%; all P < 0.05). Additionally, the immediate vasodilation (first cardiac cycle postcontraction) for the 20% and 40% MVC trials was also impaired ~50% with age (P < 0.05). There were no significant age-group differences in MVC or forearm fat-free mass, and these variables were not correlated with local vasodilation within a given exercise intensity. Under the experimental conditions employed, the blunted responses with age reflect impaired local contraction-induced rapid vasodilation.

vascular control; exercise; blood flow

BLOOD FLOW AND OXYGEN DELIVERY increase to contracting muscle in proportion to exercise intensity, a complex response involving mechanical factors, metabolic and endothelium-dependent vasodilators, and the sympathetic nervous system (29). In aging humans, the majority of data indicate that muscle blood flow is reduced ~20–30% during large muscle, steady-state dynamic exercise (25, 26, 28), and this has been suggested to contribute to age-related declines in maximal oxygen consumption and physical functional capacity (16, 36). During this type of exercise, it is conceivable that the observed reduction in muscle blood flow could reflect age-associated impairments in central circulatory factors (i.e., cardiac output) and/or impairments in peripheral vascular control (25, 26).

In an effort to minimize the potential influence of age-related reductions in cardiac output on muscle blood flow during exercise, Donato et al. (12) and Lawrenson et al. (21), in separate studies, recently determined the effects of aging on muscle blood flow control during isolated knee extensor exercise. The primary finding from these investigations was that muscle blood flow was significantly reduced during steady-state exercise in older healthy adults, and this was associated with a reduction in vascular conductance (12, 21). Somewhat in contrast, muscle blood flow and vascular conductance during (12) and immediately after (17) steady-state dynamic handgrip exercise have been demonstrated to be preserved with age, although recent data from our laboratory during mild-intensity exercise challenge these findings (19). However, given the nature and designs of these previous experiments, it remains unclear whether any impairment in vascular control during exercise reflects impairments in local contraction-induced vasodilation or augmented sympathetic vasoconstriction with age (10).

To date, studies comparing muscle blood flow and vascular control during exercise in young and older adults have only assessed limb hemodynamics once steady-state exercise has been achieved, and thus no information is available related to the immediate dynamic vasodilator response to muscle contractions. In this context, at the onset of exercise in healthy humans and experimental animals, muscle blood flow increases immediately upon the release of a contraction and peaks within approximately four to six cardiac cycles (18, 24, 34). The magnitude of this hyperemic response is graded with the level of contraction intensity (18, 34) and is independent of sympathetic neural influences (3, 6). Importantly, during certain types of exercise (e.g., isolated handgrip exercise), this can also occur independent of significant alterations in heart rate and arterial blood pressure and therefore reflects a local response within the vascular bed of the contracting muscle (6, 18, 24, 34). Previous studies had attributed this rapid hyperemic response to a muscle pump effect (i.e., widening of the arteriovenous pressure gradient) (20, 32); however, more recent evidence indicates that vascular smooth muscle cell hyperpolarization (and thus vasodilation) is obligatory to observe this response (14, 22). Although the exact mechanisms underlying the entire dynamic response have yet to be determined, it appears that mechanical influences on vascular tone (5, 18) and K+ released from contracting myocytes (1) play a role in contraction-induced rapid vasodilation. It is currently unknown whether aging influences contraction-induced rapid vasodilation in humans.

In the present study, we tested the hypothesis that aging is associated with an impaired rapid vasodilator response to brief exercise.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
muscle contractions in healthy adults. Brief contractions of the forearm were employed to test this hypothesis, since any age-related increase in sympathetic nervous system activity to the upper limb (forearm) does not result in a greater basal vasoconstrictor tone compared with young adults (8, 15). Furthermore, brief contractions with a small muscle mass do not significantly impact systemic hemodynamics (18, 34) nor evoke reflex increases in sympathetic outflow (31). Thus we contend this model permits the study of local vasodilation in the absence of systemic hemodynamic and sympathetic neural influences on contraction-induced hyperemia.

METHODS

Subjects. A total of 18 young (9 men, 9 women; age = 23 ± 1 yr) and 13 older (7 men, 6 women; age = 62 ± 1 yr) healthy adults participated in the present study (see Table 1). All were nonsmokers, nonobese, normotensive, not taking any medications, and were sedentary to moderately active. Older subjects were further evaluated for clinical evidence of cardiopulmonary disease with a physical examination and resting and maximal exercise electrocardiograms. To control for possible hormone influences on the primary outcome variables, young female participants were studied during the early follicular phase (days 1–4 after the onset of menstruation) of their menstrual cycle or during the placebo phase of oral contraceptives. Older women were not taking any form of hormone replacement therapy. Studies were performed in a temperature-controlled environment (20–22°C) after a minimum of a 4-h fast. The subjects abstained from caffeine and exercise the day of the study, and all studies were performed with the subjects in the supine position. This research was approved by the Human Research Committee of Colorado State University, and all subjects gave their written informed consent to participate.

Body composition and forearm fat-free mass. Body composition was determined by dual-energy X-ray absorptiometry (DEXA; DXP-IQ, Lunar Radiation). Forearm fat-free mass (FFM) was calculated via regional analysis of the experimental forearm (from the proximal to distal radioulnar joint) from whole body DEXA scans with Lunar software version 4.7e. Body mass index (BMI) was calculated as body weight (kg) divided by height (meters) squared.

Arterial blood pressure and heart rate. Resting arterial blood pressure was measured noninvasively over the brachial artery of the control arm after 30 min of supine rest before any experimental trials (Cardiocap/5;Datex-Ohmeda, Louisville, CO). Beat-by-beat arterial blood pressure was then measured at the heart level by finger photoplethysmography (Finapres; Ohmeda) on the middle finger of the control hand during all experimental trials. Heart rate was determined using a three-lead electrocardiogram (Cardiocap/5; Datex-Ohmeda).

Forearm blood flow and vascular conductance. A 4-MHz pulsed Doppler probe (model 500V; Multigun Industries, Mt. Vernon, NY) was used to measure brachial artery mean blood velocity (MBV) with the probe securely fixed to the skin over the brachial artery as previously described (9, 18). The probe isonation angle relative to the skin was 45 degrees. We conducted pilot studies in our laboratory in which we continuously recorded brachial artery diameter in four young healthy subjects (2 men, 2 women) pre- and post-single muscle contractions at intensities used in the present study. Brachial artery diameter was measured off-line (in triplicate) at baseline and at 5, 10, 20, and 30 s postcontraction for all experimental contraction intensities. During this type of exercise, the brachial artery is not mechanically compressed; thus, any change in brachial diameter would be the result of increasing blood velocity (and shear stress) along the vessel wall. Given that I) our pilot data indicated no change in brachial diameter (all P < 0.05) in response to contractions in young adults and 2) aging is associated with a reduction in shear stress-induced vasodilation (4), brachial diameter was measured in triplicate at the end of the study and averaged for calculation of forearm blood flow (FBF). To do so, a linear 7.0-MHz echo Doppler ultrasound probe (Sonos 4500; Hewlett-Packard, Andover, MA) was placed over the skin where the velocity probe was secured to measure brachial arterial diameter. FBF was calculated as:

\[
\text{FBF} = \frac{\text{MBV} \times \pi \times \text{brachial artery diameter}^2}{60} \times 60, \]

where the FBF is in milliliters per minute, the MBV is in centimeters per second, the brachial diameter is in centimeters, and 60 is used to convert from milliliters per second to milliliters per minute.

Forearm vascular conductance (FVC) was calculated as (FBF/MAP) × 100, and expressed as milliliters per minute per 100 millimeters mercury, where MAP is mean arterial pressure.

Forearm position. The subject lay supine with the experimental (nondominant) arm abducted 90° and slightly elevated above heart level upon a tilt-adjustable table. All measurements and procedures were performed in this manner to decrease forearm venous volume and minimize the influence of the muscle pump on forearm hemodynamics (13, 33–35). Additionally, a fan was directed toward the experimental arm to minimize the contribution of skin blood flow to forearm hemodynamics.

Dynamic handgrip exercise. Maximum voluntary contraction (MVC) for each subject was determined for the experimental arm as the average of three maximal squeezes of a handgrip dynamometer (Stoelting, Chicago, IL) that were within 3% of each other. For the experimental trials, brief dynamic forearm contractions were performed with the experimental arm at 5, 10, 20, and 40% of the subject’s MVC using a handgrip pulley system attached to weights corresponding to each workload. The weight was lifted 4–5 cm over the pulley for a single, 1-s dynamic forearm muscle contraction. Subjects were instructed to contract and relax on verbal command issued from laboratory personnel in sequence with an audio and visual metronome. Each contraction was visually observed by laboratory personnel to ensure the proper timing of contraction, and only trials in which contractions were performed correctly were analyzed. Two minutes of relaxation were given between each contraction to allow continuous measures of forearm hemodynamics postcontraction, as well as ample time for hemodynamics to return to baseline values (18, 34). Single, 1-s forearm muscle contractions were chosen to 1) limit the contribution of systemic hemodynamics to forearm vasodilator responses and 2) eliminate reflex activation of the sympathetic nervous system and thus isolate the local effects of muscle contractions on forearm vascular tone. Subjects were instructed to remain relaxed before and during all contractions to minimize potential anticipatory hemodynamic responses to exercise (i.e., central command). Workload intensity was randomized and counterbalanced across subjects to eliminate any order effect, and trials were performed in triplicate to calculate an average response for each subject.

Data acquisition and analysis. Data were collected and stored on a computer at 250 Hz and analyzed off-line with signal-processing software (WinDaq, DATAQ Instruments, Akron, OH). Baseline FBF and MAP represent an average of the last 60 s of the resting time period before any muscle contractions. For each contraction trial, the last 10 s before contraction were used as the baseline from which to quantify the hyperemic responses (18, 34). Hyperemic values were calculated starting with the first unimpeded brachial velocity waveform postcontraction and for each cardiac cycle thereafter for 30 cycles. The reported values reflect the average of three trials for all subjects. Figure 1 illustrates representative arterial pressure and blood velocity waveforms for a 40% MVC trial in a young and older adult. The hyperemic responses for each contraction intensity were calculated as the percent increase in FBF post-forearm muscle contraction as follows:

\[
\left(\frac{\text{FBF postcontraction} - \text{FBF precontraction}}{\text{FBF precontraction}}\right) \times 100.
\]
We also quantified the vasodilator response as percent increases in FVC, and this was calculated in a similar fashion. Finally, the total contraction-induced hyperemic and vasodilator responses were calculated as the sum of FBF and FVC, respectively, above baseline for each contraction intensity (area under dynamic response curve). Although we found no significant heart rate responses in either group at each exercise intensity, R-R interval was calculated to determine whether there were any rapid alterations in cardiac interval. The baseline R-R interval represents the average interval of 10 cardiac cycles before contraction, and the postcontraction data represent the 15 cycles after contraction in both young and older adults.

**Statistics.** All values are reported as means ± SE. Specific hypothesis testing was performed using repeated-measures ANOVA. In the case of a significant F value, the Newman-Keul’s method for multiple comparisons was used to determine where differences occurred. Univariate correlational analyses were performed to determine the relations between specific variables and peak contraction-induced vasodilation. Statistical significance was set a priori at P < 0.05.

**RESULTS**

**Subject characteristics.** The mean age difference between the young and older adults was ~40 yr. There were no significant age-group differences in BMI, whole body FFM, forearm FFM, or baseline hemodynamics (Table 1). Furthermore, MVC was not significantly different between young and older adults (P = 0.47). However, body fat percentage was greater in older compared with young adults (28 ± 2 vs. 20 ± 1%, respectively; P < 0.05). For all contraction intensities, there were no significant changes in MAP or heart rate postcontraction in either young or older adults (data not shown). R-R interval was not significantly altered in either the young and older adults for contraction intensities of 5, 10, and 20% MVC. At 40% MVC, there was a significant reduction in R-R interval in young adults for beat 1 postcontraction, whereas this was significant only for beat 2 postcontraction in older adults (Table 2; only first 15 cycles shown). All other intervals were not significantly different than baseline in both age groups.

**Mild intensity forearm contractions.** Dynamic blood flow and vascular conductance responses following forearm muscle contractions at 5% MVC are shown in Fig. 2, A and B. At 5% MVC, both young and older adults had a peak dilatory response at four cardiac cycles postcontraction. The immediate

---

Table 1. Subject characteristics and baseline forearm hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>9/9</td>
<td>7/6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>23 ± 1</td>
<td>62 ± 1*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173 ± 2</td>
<td>167 ± 3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69 ± 4</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0 ± 1.1</td>
<td>25.0 ± 1.5</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>20 ± 2</td>
<td>28 ± 2*</td>
</tr>
<tr>
<td>Whole-body FFM, kg</td>
<td>51 ± 3</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>Forearm FFM, g</td>
<td>733 ± 49</td>
<td>693 ± 61</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>122 ± 3</td>
<td>128 ± 3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74 ± 1</td>
<td>81 ± 2*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>90 ± 2</td>
<td>96 ± 3</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>49 ± 2</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>55 ± 2</td>
<td>55 ± 2</td>
</tr>
<tr>
<td>FBF, ml/min</td>
<td>26 ± 3</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>FBF/100 g FFM, ml·100 g⁻¹·min⁻¹</td>
<td>3.0 ± 0.2</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>FVC, ml·min⁻¹·100 mmHg⁻¹</td>
<td>30 ± 3</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>MVC, kg</td>
<td>39 ± 2</td>
<td>36 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. BMI, body mass index; FFM, fat-free mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; FBF, forearm blood flow; FVC, forearm vascular conductance; MVC, maximal voluntary contraction. *P < 0.05 vs. young adults.

---

Fig. 1. Representative arterial blood pressure and blood velocity waveforms pre- and postcontraction at 40% maximal voluntary contraction (MVC) in a young (top) and older (bottom) adult.
vasodilation at 5% MVC, whereas there were significant age-related impairments at 10% MVC. *P < 0.05 vs. baseline of 40% maximal voluntary contraction trial.

Cardiac Cycle 5% Young 5% Older 10% Young 10% Older 20% Young 20% Older 40% Young 40% Older
Baseline 1.12 ± 0.04 1.11 ± 0.04 1.14 ± 0.04 1.11 ± 0.04 1.14 ± 0.04 1.10 ± 0.04 1.13 ± 0.05 1.12 ± 0.04
1 1.10 ± 0.04 1.04 ± 0.03 1.03 ± 0.05 1.05 ± 0.04 1.07 ± 0.06 1.05 ± 0.05 1.00 ± 0.05* 1.01 ± 0.04
2 1.06 ± 0.04 1.03 ± 0.03 1.04 ± 0.05 1.04 ± 0.03 1.04 ± 0.04 1.02 ± 0.03 1.03 ± 0.05 1.00 ± 0.03*
3 1.09 ± 0.05 1.05 ± 0.03 1.06 ± 0.05 1.06 ± 0.03 1.08 ± 0.05 1.03 ± 0.04 1.05 ± 0.04 1.03 ± 0.03
4 1.10 ± 0.04 1.05 ± 0.03 1.07 ± 0.05 1.06 ± 0.04 1.09 ± 0.04 1.04 ± 0.03 1.05 ± 0.04 1.04 ± 0.03
5 1.10 ± 0.04 1.06 ± 0.03 1.09 ± 0.04 1.06 ± 0.04 1.09 ± 0.04 1.06 ± 0.04 1.07 ± 0.04 1.05 ± 0.03
6 1.08 ± 0.04 1.05 ± 0.03 1.09 ± 0.04 1.06 ± 0.04 1.09 ± 0.04 1.06 ± 0.03 1.07 ± 0.04 1.05 ± 0.03
7 1.07 ± 0.04 1.05 ± 0.04 1.08 ± 0.04 1.06 ± 0.04 1.09 ± 0.04 1.06 ± 0.04 1.06 ± 0.04 1.05 ± 0.03
8 1.08 ± 0.05 1.05 ± 0.04 1.09 ± 0.04 1.06 ± 0.04 1.09 ± 0.04 1.05 ± 0.04 1.06 ± 0.04 1.05 ± 0.03
9 1.08 ± 0.04 1.04 ± 0.04 1.08 ± 0.04 1.07 ± 0.04 1.08 ± 0.03 1.04 ± 0.04 1.05 ± 0.04 1.04 ± 0.03
10 1.07 ± 0.04 1.05 ± 0.04 1.09 ± 0.04 1.06 ± 0.04 1.08 ± 0.04 1.04 ± 0.04 1.07 ± 0.04 1.05 ± 0.03
11 1.07 ± 0.04 1.05 ± 0.04 1.11 ± 0.05 1.07 ± 0.04 1.08 ± 0.04 1.05 ± 0.04 1.10 ± 0.04 1.05 ± 0.04
12 1.08 ± 0.04 1.05 ± 0.04 1.07 ± 0.04 1.07 ± 0.04 1.09 ± 0.04 1.05 ± 0.04 1.09 ± 0.04 1.05 ± 0.04
13 1.11 ± 0.05 1.06 ± 0.04 1.07 ± 0.04 1.07 ± 0.04 1.09 ± 0.04 1.05 ± 0.04 1.09 ± 0.04 1.04 ± 0.04
14 1.10 ± 0.04 1.06 ± 0.04 1.11 ± 0.05 1.01 ± 0.04 1.06 ± 0.04 1.05 ± 0.04 1.09 ± 0.04 1.05 ± 0.04
15 1.09 ± 0.04 1.07 ± 0.04 1.10 ± 0.04 1.06 ± 0.04 1.10 ± 0.04 1.06 ± 0.04 1.09 ± 0.04 1.06 ± 0.03

Values are mean R-R interval (s) ± SE for each corresponding cardiac cycle postcontraction. Baseline values are mean R-R intervals over 10 cardiac cycles before each contraction. *P < 0.05 vs. baseline of 40% maximal voluntary contraction trial.

Table 2. R-R interval response to increasing contraction intensities

(first cardiac cycle postcontraction; ΔFVC = 25 ± 4 vs. 32 ± 6%) and peak vasodilatory responses were not significantly different between age groups (77 ± 11 vs. 73 ± 13%, young and older adults, respectively; Figs. 2 and 3). Similarly, the total hyperemic and vasodilatory responses were not significantly different between young and older adults (Fig. 4).

Dynamic blood flow and vascular conductance responses following forearm muscle contractions at 10% MVC are shown by 10.220.33.6 on October 15, 2017 http://ajpheart.physiology.org/ Downloaded from http://ajpheart.physiology.org/ by 10.220.33.6 on October 15, 2017
in Fig. 2, C and D. Both young and older adults reached a peak dilatory response at four cardiac cycles. Although there was no statistically significant difference in the immediate response postcontraction ($\Delta FVC = 69 \pm 10$ vs. $46 \pm 12\%$; $P = 0.15$), there was a significant impairment in the peak response in older adults ($161 \pm 20$ vs. $99 \pm 17\%$, young and older, respectively; Figs. 2 and 3; $P < 0.05$). Furthermore, the total hyperemic and vasodilatory responses were also significantly impaired in the older subjects (Fig. 4).

Moderate intensity forearm contractions. The dynamic blood flow and vascular conductance responses following forearm muscle contractions at 20% MVC are shown in Fig. 5, A and B. Similar to mild intensities, peak responses occurred at four cardiac cycles postcontraction in both young and older adults. However, in contrast to the mild intensities, the immediate postcontraction response was significantly impaired in the older adults ($\Delta FVC = 124 \pm 18$ vs. $63 \pm 12\%$, young vs. older, respectively; Figs. 3 and 5), as were the peak responses ($299 \pm 41$ vs. $167 \pm 26\%$; Figs. 3 and 5; both $P < 0.05$). Additionally, both the total hyperemic and vasodilatory responses were significantly impaired in the older group (Fig. 4).

The dynamic blood flow and vascular conductance responses following forearm muscle contractions at 40% MVC are shown in Fig. 5, C and D. For this workload, both groups reached a peak dilatory response at five cardiac cycles postcontraction. Similar to the responses following 20% MVC, older individuals demonstrated an impaired immediate ($\Delta FVC = 210 \pm 25$ vs. $101 \pm 25\%$) and peak ($423 \pm 39$ vs. $249 \pm 34\%$ young vs. older, respectively, Figs. 3 and 5, both $P < 0.05$) response compared with the young adults. Furthermore, both the total hyperemic and vasodilatory responses were significantly impaired in the older group (Fig. 4).

Physiological correlates. Although there were no significant age-related reductions in MVC, statistical correlations were employed to evaluate the relation between absolute workload and the peak vasodilatory responses for all exercise intensities. Pooled across workloads, there was a significant relation between absolute workload and peak vasodilator responses ($r = 0.66$; $P < 0.05$). However, within a given relative contraction intensity, there were no significant relations between the absolute workload and forearm vasodilator responses ($r = 0.19 – 0.26$; all not significant). Additionally, there were no significant correlations between peak vasodilation at 40% MVC and forearm FFM ($r = 0.15$), body fat percentage ($r = -0.13$), and BMI ($r = 0.02$).

DISCUSSION

In the present study, we employed single, brief muscle contractions of a small muscle mass to test the hypothesis that aging is associated with an impaired local contraction-induced vasodilation in humans. The primary new findings are as follows. First, the rapid vasodilatory and total hyperemic responses to low-level (5% MVC) single forearm contractions
are preserved with age in healthy humans. Second, the peak and total hyperemic and vasodilatory responses to mild contractions (10% MVC) are significantly blunted in older adults. Third, for moderate contraction intensities at 20 and 40% MVC, the immediate, peak, and total hyperemic and vasodilatory responses are significantly impaired with age. Finally, these age-associated impairments cannot be explained by age-related declines in forearm FFM or absolute workload intensity, since both were not different in the two age groups and were weakly correlated with local vasodilation within a given exercise intensity. Taken together, our findings are the first to demonstrate impaired local contraction-induced rapid vasodilation in aging humans.

Effects of aging on contraction-induced rapid vasodilation in humans. To date, studies designed to determine the effect of aging on muscle blood flow and vascular control during exercise in humans have focused on steady-state hyperemic responses using a variety of exercise modalities and workloads. Depending on the muscle mass engaged during exercise (large vs. small), the exercise intensities employed (mild, moderate, or heavy), and the limb chosen for study (upper vs. lower), blood flow to contracting muscle can be influenced by the complex interaction between systemic hemodynamics, local vasodilator mechanisms (e.g., mechanical influences, endothelium-dependent dilation, and metabolic vasodilator signals), and the sympathetic nervous system (29). To the best of our knowledge, no studies have determined the effects of single contractions on the local dynamic vascular responses in aging humans. Therefore, the present study was designed to specifically isolate the effects of skeletal muscle contractions on the local rapid vasodilator responses in aging humans independent of systemic hemodynamic and sympathetic neural influences.

Our findings from the present study in young healthy adults are in agreement with recent studies regarding the time-to-peak vasodilation (~4–6 cardiac cycles postcontraction) as well as the magnitude of vasodilation observed (18, 34). With respect to aging, the general findings from the present study indicate that the rapid vasodilator responses evoked by muscle contractions >5% MVC were significantly impaired in older healthy compared with young adults. At 10% MVC, we found that the peak and total hyperemic and vasodilator responses to brief muscle contractions were significantly impaired with age. Furthermore, we found that aging was associated with a blunted immediate, peak, and total contraction-induced hyperemic and vasodilator response to moderate contraction intensities (20 and 40% MVC). We are unaware of any studies that have measured the dynamic hyperemic responses to single muscle contractions in aging humans, and, as such, these are the first data demonstrating impaired local contraction-induced rapid vasodilation in older healthy adults.

Impaired contraction-induced rapid vasodilation with age: potential mechanisms. The basic mechanisms underlying contraction-induced rapid vasodilation are not completely understood, but it appears that multiple mechanisms are involved. Emerging evidence indicates that “mechanical” factors, most likely due to increases in intramuscular pressure and subsequent resistance vessel deformation, can evoke rapid vasodilation in isolated vessels (5) as well as in the human forearm (18) and therefore contribute to exercise hyperemia (i.e., a “myogenic-like” response) (23). Furthermore, recent data indicate that K+ released from the contracting myocytes evokes vascular smooth muscle cell hyperpolarization and contributes to the peak vasodilator response (1). The prolonged and sustained vasodilation that occurs in response to muscle contractions is intensity dependent (i.e., greater total vasodilation with greater levels of muscle activation), but the mechanisms underlying this dynamic response are unknown. It seems plausible to speculate that endothelium-dependent vasodilation is involved in this response, and, if several redundant vasodilators such as nitric oxide and prostaglandins contribute to this response, age-related reductions in these putative endothelium-dependent dilators may contribute to the blunted total response of a single contraction (30). Finally, impairments in acetylcholine-mediated conducted vasodilation (2) and age-related increases in resistance vessel stiffness (21) could play a role. Whether any and/or all of these potential mechanisms involved in contraction-induced rapid vasodilation explain this impairment with age remains to be determined.

Impaired rapid vasodilation with age: implications for repeated contractions? Although we were able to demonstrate significant impairments in contraction-induced rapid vasodilation with age, it is presently unclear how this relates to muscle blood flow control during rhythmic and repeated contractions. For example, if muscle blood flow during mild steady-state exercise is preserved with age (12, 17, 27), our data could have...
implications for blood flow kinetics from rest to exercise. In this context, the dynamics of the blood flow response could be impaired with age but ultimately achieve the same steady-state levels, similar to what has been documented for pulmonary oxygen uptake kinetics (7). Alternatively, if muscle blood flow during steady-state exercise is reduced with age (19, 25, 26, 28), this impairment in the immediate rapid vasodilation upon release of a contraction could explain, in part, the net reduction in muscle blood flow in exercising older adults.

Experimental considerations. One potential limitation of this study is the inability to extrapolate our findings to muscle contractions of the lower limb. However, as mentioned previously, the primary goal of this study was to isolate the local effects of muscle contraction on vascular tone. The forearm muscle was chosen because this is a relatively small muscle mass that is not under greater tonic sympathetic vasoconstriction compared with young adults (8, 15). As such, future studies will be needed to determine whether contraction-induced rapid vasodilation is impaired in the leg circulation with advancing age. However, given that the leg circulation is under greater tonic sympathetic vasoconstriction in older compared with young adults (11), efforts will be required to determine whether contraction-induced rapid dilation is impaired in the lower limb with age independent of augmented basal sympathetic tone (i.e., sympathetic restraint). Finally, future studies will also be required to understand how this local impairment in contraction-induced vasodilation contributes to the net reduction in muscle blood flow during large muscle mass dynamic exercise in older adults.

Although each contraction was visually observed and only contractions that were performed correctly were analyzed, we realize that, without an objective measure of contraction duration and muscle activation (e.g., electromyogram), the stimulus for vasodilation may vary slightly between subjects. Thus, although we have no reason to believe that there were significant age-group differences in the stimulus and most likely does not explain the impaired contraction-induced rapid vasodilation with age, one must keep this in mind when interpreting the data from the present study.

Finally, we understand that any differences in forearm muscle mass and/or muscle strength between age groups could potentially lead to blunted vasodilatory responses in the older subjects. However, there were no significant age-group differences in forearm FFM or MVC in our study population. Furthermore, there were very weak and nonsignificant relations between forearm FFM and absolute workload and peak contraction-induced vasodilation within a given exercise intensity. Therefore, we believe our findings are independent of these potentially modulating variables and, as such, reflect age-related impairments in contraction-induced rapid vasodilation.
associated impairments in the local vascular responses to brief muscle contractions.

Conclusions

In conclusion, the findings from the present study indicate that human aging is associated with a blunted contraction-induced rapid vasodilation in the forearm circulation of healthy adults. Given that we employed single, brief contractions of a small muscle mass to minimize systemic hemodynamic and sympathetic neural influences on contraction-induced hyperventilation, we contend this age-related impairment reflects a local vascular dysfunction within contracting muscle of older adults. Future investigations will be required to determine the mechanisms underlying this age-related impairment.

ACKNOWLEDGMENTS

We thank Rachel Markwald for technical assistance throughout this study. We also thank the subjects who volunteered for this study.

GRANTS

This research was supported by National Institutes of Health Grants AG-022337, AG-027150, and HL-087952 (to F. A. Dinenno).

REFERENCES