Acute ascorbic acid ingestion increases skeletal muscle blood flow and oxygen consumption via local vasodilation during graded handgrip exercise in older adults

Jennifer C. Richards, Anne R. Crecelius, Dennis G. Larson, and Frank A. Dinenno

1Human Cardiovascular Physiology Laboratory, Department of Health and Exercise Science, Colorado State University, Fort Collins, Colorado; and 2Medical Center of the Rockies Foundation, University of Colorado Health System, Loveland, Colorado

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Richards JC, Crecelius AR, Larson DG, Dinenno FA. Acute ascorbic acid ingestion increases skeletal muscle blood flow and oxygen consumption via local vasodilation during graded handgrip exercise in older adults. Am J Physiol Heart Circ Physiol 309: H360–H368, 2015. First published May 15, 2015; doi:10.1152/ajpheart.00209.2015.—Human aging is typically associated with reduced skeletal muscle perfusion in response to single muscle contractions (10, 11, 13, 31) as well as during continuous exercise (28, 31–33, 40, 41, 46) although the mechanism(s) underlying this age-associated impairment may differ depending on the stimuli (31). With respect to “steady-state” exercise, the reduction in muscle blood flow observed with age has been attributed, in part, to impaired endothelial-mediated vasodilation (51, 52) and, more specifically, reduced NO bioavailability (50). Recent work also indicates that greater endothelin-mediated vasoconstriction with age may also limit blood flow to active muscle in older adults (3). Furthermore, older adults have a decreased ability to blunt sympathetically mediated vasoconstriction during exercise (20, 29, 39, 60), which could potentially exacerbate any age-related impairment in muscle perfusion as exercise intensity and/or the amount of muscle mass engaged increases.

Our laboratory previously demonstrated that intra-arterial ascorbic acid (AA) significantly improves endothelium-dependent vasodilation and skeletal muscle perfusion during exercise in older adults (31). We further demonstrated that this ability of AA to improve muscle blood flow during exercise in older adults is abolished by NO synthesize inhibition (16). Although these experiments were designed to understand the potential roles of endothelial dysfunction, oxidative stress, and reduced NO bioavailability in the impaired muscle blood flow during exercise with advancing age, intra-arterial (and iv) AA infusions yield supraphysiological circulating concentrations. Thus, it is presently unknown whether an acute oral dose of vitamin C; aging; sympathetic vasoconstriction

NEW & NOTEWORTHY

Our findings indicate that muscle blood flow and oxygen consumption are increased during exercise 2 h after ingestion of ascorbic acid in older adults, and this is due to local vasodilation. This may represent a strategy to improve skeletal muscle perfusion and exercise tolerance in older healthy and diseased humans.

DURING EXERCISE, AN INCREASE IN metabolic demand drives an increase in blood flow to working muscle as a means to adequately deliver oxygen and nutrients to the active skeletal muscle (1, 6, 7, 37). The net blood flow response to a given exercise intensity is determined by mechanical factors associated with skeletal muscle contraction, locally released metabolic and endothelium-derived substances, substances within the blood, and the sympathetic nervous system (49). A number of local and endothelial-derived factors have been implicated in governing increases in blood flow, including but not limited to nitric oxide (NO), prostaglandins, K⁺, adenosine, adenosine triphosphate, and lactate (14). However, to date, no single factor is considered entirely responsible for augmenting muscle blood flow; rather, there appears to be redundancy such that blood flow is maintained following the elimination of one dilator (14, 27). Furthermore, as exercise intensity increases, unidentified local factors are capable of blunting sympathetically mediated vasoconstriction (functional sympatholysis), a phenomenon believed to ensure adequate blood flow and oxygen delivery to exercising muscles as the sympathetic nervous system is activated (8, 44, 53, 55, 57).

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AA is capable of improving muscle blood flow and oxygen delivery in otherwise healthy older adults during exercise and, if so, whether this results in greater oxygen utilization by the working tissue. Additionally, whether oral AA enhances the ability to blunt sympathetically mediated vasoconstriction during exercise is also unknown. Although NO is an important vasodilator, experimental evidence in humans indicates that it may not be involved in functional sympatholysis (18, 48), and therefore augmenting NO bioavailability via AA may improve local blood flow control but may not improve sympatholysis in older adults.

Accordingly, the purpose of this study was twofold: 1) to determine whether acute ingestion of AA improves forearm blood flow (FBF) and oxygen consumption (VO₂) via increases in vascular conductance during mild and moderate-intensity rhythmic forearm exercise (Protocol 1), and 2) to determine whether acute ingestion of AA improves the ability to blunt a sympathetically mediated vasoconstrictor stimulus during exercise (sympatholysis) in healthy older adults (Protocol 2). We hypothesized that acute oral AA ingestion would improve exercising FBF and that elevated FBF would be associated with greater VO₂. Furthermore, we hypothesized that oral AA ingestion would not influence the ability to blunt sympathetically mediated vasoconstriction during handgrip exercise in older adults.

METHODS

Subjects

With Institutional Review Board approval and following written informed consent, a total of 8 older healthy male subjects participated in Protocol 1, and 10 older healthy adults (6 males and 4 females) participated in Protocol 2. We chose to include women in Protocol 2 in an effort to study a more heterogeneous participant population. All participants were sedentary to moderately active, nonsmokers, nonobese, normotensive, and not taking any medications, including over the counter supplements. Female participants were postmenopausal (2+ yr) and not taking hormone supplements. All participants were evaluated for clinical evidence of cardiopulmonary disease with a physical examination and resting and maximal exercise electrocardiograms. Studies were performed after a 12-h fast with the subjects in the supine position. The experimental arm of the subject was slightly elevated above heart level to minimize any potential influence of the muscle pump on forearm hemodynamics (54). All studies were performed according to the Declaration of Helsinki.

Venous Catheterization, Blood Gas Measurements, and VO₂: Protocol 1

In Protocol 1, an 18-gauge catheter (3.8 cm) was inserted in retrograde fashion in an antecubital vein of the experimental arm for deep venous blood samples. Saline was continuously infused through the catheter at a rate of ~3 ml/min for the duration of the study to keep it patent (15). Venous blood samples were immediately analyzed with a clinical blood gas analyzer (Siemens Rapid Point 405 Automatic Blood Gas System, Los Angeles, CA) for partial pressures of venous oxygen and carbon dioxide, venous oxygen content, pH, and oxygen saturation. Forearm VO₂ was calculated as: FBF × (arterial – venous O₂ content). Arterial oxygen content was assumed to be 20 ml/dl (25, 47), similar to values reported by our laboratory ~5,000 feet above sea level (15). Importantly, several studies have shown that arterial oxygen content does not change during mild to moderate forearm (handgrip) exercise in humans (12, 15).

Heart Rate and Mean Arterial Pressure: Protocols 1 and 2

Heart rate (HR) was monitored with a three-lead electrocardiogram. Mean arterial pressure (MAP) was measured by placing a finger pressure cuff around the middle phalanx of the middle finger on the nonexperimental arm (Finomter; Finapres Medical Systems, Amsterdam, The Netherlands). Resting arterial blood pressure was measured over the brachial artery following 30 min of supine rest, and just before each exercise trial (CardioCap 5; Datex Òhmeda, Louisville, CO), and resting Finometer MAP was corrected for differences between the two readings (30).

FBF and Vascular Conductance: Protocols 1 and 2

A 12-MHz linear-array ultrasound probe (Vivid 7; General Electric, Milwaukee, WI) was used to determine brachial artery mean blood velocity and brachial artery diameter. Foam tape was used to mark the outline of the probe for consistent placement and measurement over the course of the experiments. For blood velocity measurements, the probe insonation angle was maintained at <60 degrees, and the frequency used was 5 MHz. The Doppler shift frequency spectrum was analyzed via a Multigon 500M TCD (Multigon Industries, Mt. Vernon, NY) spectral analyzer from which mean velocity was determined as a weighted mean of the spectrum of Doppler shift frequencies. Brachial artery diameter measurements were made in duplex mode at end diastole at rest and between contractions (in triplicate) during steady-state conditions. FBF was calculated as: FBF = mean blood velocity × π (brachial artery diameter/2)² × 60, where the FBF is in milliliters per minute, the mean blood velocity is in centimeters per second, the brachial diameter is in centimeters, and 60 was used to convert from milliliters per second to milliliters per minute. A fan was directed toward the experimental arm to minimize the potential contribution of skin blood flow to forearm hemodynamics. As an index of vascular tone, forearm vascular conductance (FVC) was calculated as: (FBF/MAP) × 100 and expressed as (ml/min/100 mmHg) (16, 45).

Handgrip Exercise: Protocols 1 and 2

Maximum voluntary contraction (MVC) was determined for each subject as the average of at least three maximal squeezes of a handgrip dynamometer (Stoelting, Chicago, IL) that were within 3% of each other. Subjects lifted a weight corresponding to their %MVC over a 4- to 5-cm distance using a pulley. Both audio and visual cues were used to ensure correct timing of contraction (1 s) and relaxation (2 s) (18, 19).

Sympathetic Nervous System Activation via Lower-Body Negative Pressure: Protocol 2

To elicit sympathetically mediated vasoconstriction during rest and exercise, subjects were supine and the lower extremities were sealed in an airtight chamber at the level of the iliac crest (30). Lower-body negative pressure (LBNP) was administered at ~40 mmHg for 2 min to unload baroreceptors and reflexly increase muscle sympathetic nervous activity (17). Previous studies in our laboratory indicate that, when separated by 15 min of rest, the forearm vasoconstrictor response to LBNP under resting conditions is repeatable over time (30).

Plasma Measures: Protocol 1

In study 1, plasma samples were collected to determine AA (High Performance Liquid Chromatography; ARUP Laboratories, Salt Lake City, UT) and oxidized low-density lipoprotein (LDL) (ELISA; University of Colorado Hospital CTRC Core Laboratory, Aurora, CO) concentrations before and 2 h following ingestion of 2 g of AA.

Experimental Protocols

In Protocol 1, each exercise trial consisted of 2 min of resting baseline followed by continuous incremental handgrip exercise, 4 min
Eight older healthy males [age: 65 ± 3 yr; body mass index (BMI): 28.6 ± 1.4 kg/m²] participated in the AA trial in protocol 1, whereas 10 older healthy adults (6 males and 4 females; age: 63 ± 2 yr; BMI 25.1 ± 1.6 kg/m²) participated in protocol 2. All participants in both protocols had normal cholesterol (total, high-density lipoprotein, and LDL) levels, and there were no significant differences with respect to body fat (31 ± 3 vs. 29 ± 1% body fat in protocols 1 and 2, respectively), forearm volume (1,148 ± 53 vs. 971 ± 53 ml), or handgrip MVC (44 ± 3 vs. 40 ± 1 kg).

**Protocol 1: Influence of Acute AA Ingestion on FBF and V̇O₂ during Graded Handgrip Exercise in Older Adults**

**Hemodynamics.** There were no significant differences in resting forearm (FBF and FVC) or systemic hemodynamics (MAP and HR) between the trials performed before and following AA (Table 1). Compared with control conditions (trial 1), there were no significant differences in any hemodynamic variable at the lowest workload (5% MVC) following AA consumption. Oral AA consumption (trial 2) significantly increased FBF at 15% MVC (248 ± 16 vs. 198 ± 13 ml/min; P < 0.05) and 25% MVC (403 ± 33 vs. 342 ± 24 ml/min; P < 0.05) (Fig. 1A). FVC was also significantly greater at both 15% (245 ± 19 vs. 199 ± 16 ml·min⁻¹·mmHg⁻¹; P < 0.05) and 25% (387 ± 38 vs. 325 ± 27 ml·min⁻¹·mmHg⁻¹; P < 0.05) MVC following AA (Table 1). In addition, V̇O₂ was significantly greater following AA during both 15% (34 ± 3 vs. 26 ± 2 ml/min; P < 0.05) and 25% (50 ± 6 vs. 43 ± 4 ml/min; P < 0.05) MVC exercise (Fig. 1B). Although FBF, FVC, and V̇O₂ increased following AA at 15 and 25% exercise, AA had no effect on HR or MAP (Table 1). Within the time control visit, there were no significant differences in any variable between trial 1 (control) and trial 2 (placebo) at rest or during exercise (Table 1).

**Deep venous blood gases.** There were no significant differences in any blood gas variables between trial 1 (control) or trial 2 (AA or placebo) at rest or during exercise (Table 2).

**Plasma measures.** Following oral ingestion of 2 g of AA, plasma concentrations of AA at 2 h were significantly greater than control (73 ± 7 vs. 38 ± 5 µmol/l; P < 0.001) (Fig. 2A). Oxidized LDL did not change following consumption of AA (76 ± 8 vs. 73 ± 5 µ/l) (Fig. 2B).

**Protocol 2: Influence of Acute AA Ingestion on Sympathetically Mediated Vasoconstriction during 15% MVC Handgrip Exercise in Older Adults**

**Hemodynamics.** There were no significant differences in resting forearm or systemic hemodynamics between the control and AA trial (Table 1). The degree of vasoconstriction that occurred in response to LBNP at rest in trial 1 (control) and trial 2 (AA) was not different (ΔFVC = -16 ± 2 vs. -16 ± 2%; Fig. 3). During handgrip exercise at 15% MVC, FBF was significantly greater following AA ingestion (212 ± 20 vs. 185 ± 15 ml/min; P < 0.05) (Table 1). However, the degree of vasoconstriction to LBNP during exercise was not significantly different before or after AA ingestion (ΔFVC = -12 ± 2 vs. -11 ± 4%) (Fig. 3). Furthermore, within each condition (control and AA), the vasoconstrictor responses to LBNP during 15% handgrip exercise were not significantly different from that observed at rest.

**DISCUSSION**

The primary findings of the present study are as follows. First, an acute oral dose of AA significantly improves FBF and V̇O₂ during moderate-intensity (15 and 25% MVC) handgrip exercise in older healthy adults (protocol 1). Second, this improvement in skeletal muscle perfusion was not due to elevations in HR or MAP (i.e., perfusion pressure); rather this was due to elevations in FVC (protocols 1 and 2). Third, despite the ability of AA to improve local blood flow and vascular conductance during exercise, it did not enhance the ability of older individuals to blunt a sympathetically mediated vasoconstrictor stimulus in resting or contracting skeletal muscle (protocol 2). Collectively, these findings indicate that acute oral AA can augment exercising muscle blood flow and V̇O₂ (~20%) in older humans, and this is due to improvements in local vasodilator signaling.

**AA and Skeletal Muscle Blood Flow during Exercise in Older Adults**

Our laboratory and others have demonstrated impaired skeletal muscle blood flow in response to both single and sustained muscle contractions in aging humans (10, 13, 28, 31, 41, 46, 53 vs. 29...
### Table 1. Hemodynamics during protocol 1 (graded handgrip exercise) and protocol 2 (exercise + LBNP) at rest and during exercise

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rest</th>
<th>5% MVC</th>
<th>15% MVC</th>
<th>25% MVC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, beats/min</td>
<td>MAP, mmHg</td>
<td>FBF, ml/min</td>
<td>FVC, ml · min⁻¹ · mmHg⁻¹</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 8)</td>
<td>57 ± 2</td>
<td>93.9 ± 2.8</td>
<td>35.8 ± 5.1</td>
<td>38 ± 5.2</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 8)</td>
<td>57 ± 2</td>
<td>95.3 ± 2.9</td>
<td>30.2 ± 3.5</td>
<td>31 ± 3.5</td>
</tr>
<tr>
<td>Placebo control</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(n = 4)</td>
<td>60 ± 2</td>
<td>90.6 ± 3.5</td>
<td>33.3 ± 7.3</td>
<td>37 ± 7.4</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 4)</td>
<td>54 ± 3</td>
<td>96.6 ± 1.1</td>
<td>28.4 ± 5.0</td>
<td>29 ± 5.6</td>
</tr>
</tbody>
</table>

**Protocol 1: Graded Handgrip Exercise**

**Protocol 2: 15% MVC + LBNP**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rest</th>
<th>LBNP</th>
<th>15% MVC</th>
<th>15% MVC + LBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, beats/min</td>
<td>MAP, mmHg</td>
<td>FBF, ml/min</td>
<td>FVC, ml · min⁻¹ · mmHg⁻¹</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 9)</td>
<td>60 ± 3</td>
<td>97.5 ± 3.0</td>
<td>26.7 ± 2.3</td>
<td>27.3 ± 2.0</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 9)</td>
<td>57 ± 3</td>
<td>101.3 ± 4.2</td>
<td>26.7 ± 2.0</td>
<td>26.5 ± 1.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects; MVC, maximal voluntary contraction; HR, heart rate; MAP, mean arterial blood pressure; FBF, forearm blood flow; FVC, forearm vascular conductance; LBNP, lower-body negative pressure. *P < 0.05 vs. control in respective study.
Previous studies have demonstrated that acute intra-arterial infusion of AA improves muscle blood flow during mild steady-state handgrip exercise in older healthy adults, and this was associated with improved endothelial function as assessed via local vasodilator response to acetylcholine (31). In a follow-up study, we found that the improvement in exercising muscle blood flow in older adults during intra-arterial AA infusion was abolished by NO synthase inhibition, indicating that the improvement in blood flow was via elevated NO-mediated vasodilation (16). Given that these studies used supraphysiological local doses of AA, it was not clear whether similar improvements in skeletal muscle hemodynamics would be observed in response to a physiological oral dose of AA.

In protocol 1 of the present study, we directly determined whether ingestion of 2 g of AA improved muscle blood flow during exercise in older adults. Our data indicate that, although AA did not improve FBF at rest (16, 31) or during mild intensity exercise, it did significantly improve blood flow during moderate- to high-intensity handgrip exercise. This improvement was not due to changes in systemic hemodynamics, but was due to elevations in local vasodilator signaling as reflected by parallel increases in FVC. In addition to a signifi-
significant improvement in blood flow during 15 and 25% MVC exercise, we also observed a significant increase in forearm VO$_2$ at these exercise intensities. The increase in oxygen utilization of the tissue following AA suggests that blood flow impairments in older individuals may be limiting oxygen utilization by contracting skeletal muscle.

**AA and Sympathetic Vasoconstriction during Exercise in Older Adults**

In young healthy humans, sympathetic vasoconstrictor responses are blunted in contracting muscle in a graded fashion with exercise intensity, a phenomenon believed to ensure optimal tissue blood flow and oxygen delivery during exercise (8, 44, 49). This is particularly important during larger muscle mass and high-intensity exercise, since sympathetic vasoconstrictor activity is increased to restrain peripheral vasodilation and thus maintain arterial blood pressure (49). The ability of contracting muscle to blunt sympathetically mediated vasoconstriction has been termed “functional sympatholysis” (44), and, compared with young, older adults demonstrate impaired functional sympatholysis with age independent of AA ingestion. Taken together, acute oral AA appears to improve muscle blood flow via local vasodilation in older adults without influencing the ability to blunt sympathetic vasoconstriction during acute sympathoexcitation.

**Potential Mechanisms**

One mechanism by which AA may have improved skeletal muscle perfusion during exercise is via increased NO bioavailability. AA is an antioxidant that could indirectly increase NO signaling by reducing superoxide (26, 36), a primary source of oxidative stress in the vasculature that inactivates NO and is
elevated with age (43, 56). This mechanism is consistent with what we have demonstrated experimentally in prior studies whereby local intra-arterial infusion of AA led to significant improvements in skeletal muscle blood flow during exercise (31) that were abolished via NO synthase inhibition (16). In the present study, a significant increase in plasma AA concentration was observed 2 h following consumption, yet there was no change in oxidized LDL concentrations (a surrogate marker of oxidative stress). The lack of a decrease in oxidized LDL following AA is in agreement with other studies (4), and, although it may be unlikely that 2 h was sufficient to observe an influence of AA on oxidized LDL, this does not preclude the ability of AA to act as an antioxidant and improve NO bioavailability (16, 31).

Experimental Considerations

In the present study, we used forearm (handgrip) exercise to examine the effect of oral AA ingestion on skeletal muscle blood flow in older adults. This type of exercise engages a small muscle mass, and therefore the increase in skeletal muscle perfusion during exercise is not limited centrally by cardiac output. Additionally, activation of this small muscle mass during mild-moderate handgrip exercise may limit any reflex-mediated activation of the sympathetic nervous system. In this context, our laboratory recently reported that acute blockade of sympathetic α-adrenergic vasoconstriction did not impact the change in skeletal muscle blood flow and vascular conductance from rest to graded handgrip exercise of similar intensities in young or older adults, indicating that the age-related impairment in skeletal muscle perfusion in this model of exercise is not due to greater sympathetic vasoconstriction with age but rather due to impaired local vasodilator signaling (46).

Our findings associated with improvements in exercising muscle blood flow during handgrip exercise may not be extrapolated to the vasculature within larger muscle masses such as the lower limbs. At rest, unlike the upper limbs, the lower limbs of older adults exhibit a greater degree of basal sympathetic vasoconstrictor tone (21, 22), and it is unknown whether there is further sympathetically mediated restraint of skeletal muscle blood flow during lower limb exercise in older adults. Given that AA did not improve sympatholysis in the forearm model, it is unknown whether AA would lead to improvements in exercising blood flow in the leg of older adults if there is a greater role for sympathetically mediated vasoconstrictor tone both at rest and during exercise. This awaits further study.

In the second protocol we determined whether acute ingestion of AA would improve the ability to blunt a sympathetically mediated vasoconstrictor stimulus by applying LBNP for 2 min at the end of exercise. Despite a significantly greater blood flow during muscle contractions following AA ingestion, there was no difference in the degree of vasoconstriction observed during exercise, indicating that AA does not improve functional sympatholysis in older adults. Given that previous studies have reported that intravenous infusion of AA does not alter sympathetic outflow as assessed by microneurography (muscle sympathetic nerve activity) in both young and older adults (5), we do not believe that acute ingestion of AA influenced sympathetic nervous system activity in our subjects. Although it remains uncertain whether AA influenced the transduction of sympathetic nerve activity to vasoconstrictor responses, the finding that resting hemodynamics were unaffected by AA with presumably similar levels of sympathetic outflow would argue against this.

Perspectives and Conclusions

In the present study, we observed a significant increase in exercising FBF and VO₂ during acute ingestion of AA. The improvement in exercising blood flow in the present study is similar to that previously observed following intra-arterial infusion of AA (~20%), and thus indicates improved skeletal muscle perfusion during exercise 2 h after acute ingestion of AA that was facilitated by greater local vasodilation. These findings are of potential clinical significance in that improving muscle blood flow to active muscle may improve exercise tolerance in older healthy and diseased populations characterized by reduced muscle perfusion (e.g., heart failure, peripheral arterial disease). Whether chronic supplementation with oral AA continues to elicit improvements in muscle blood flow 2 h after the last ingestion remains to be determined.

Recently, there has been growing interest in understanding how antioxidant supplementation in conjunction with an aerobic exercise training program may impact cardiovascular adaptations in humans. In the present study, we acutely administered a dose of AA and observed a significant increase in exercising muscle blood flow 2 h after ingestion when blood concentrations were anticipated to be at their peak. However, a recent study reported that, compared with placebo, 8 wk of daily resveratrol (believed to increase endogenous antioxidant activity) supplementation resulted in smaller increases in exercise capacity (i.e., VO₂max) at the end of the training program in older adults (24). These findings suggest that there was no added benefit of including resveratrol to an exercise training program and that it may actually limit some positive adaptations. However, it is unknown if the same results would be observed with chronic ingestion of AA in older populations participating in an exercise training program, particularly if the exercise training bout was performed within a similar time frame as the peak increases in circulating AA. It is feasible that repeatedly ingesting AA 2 h before the start of an exercise program could lead to greater gains in aerobic performance or peripheral vascular function. If blood flow and oxygen delivery were maximized following AA ingestion, then perhaps aerobic capacity would increase to a greater extent compared with a placebo condition. This warrants further study.

In conclusion, acute ingestion of AA significantly increased skeletal muscle blood flow and VO₂ during moderate-intensity handgrip exercise in healthy older adults. Furthermore, despite greater exercise hyperemia associated with AA ingestion, this did not impact the ability to modulate sympathetic vasoconstriction in contracting muscle. It is unknown whether the enhanced vasodilation observed in the forearm would translate to improvements in skeletal muscle blood flow during leg or whole body exercise, since these likely engage the sympathetic nervous system, whereas the forearm model does not. Finally, additional studies are warranted to determine whether repeated ingestion of an oral dose of AA 2 h before exercise would impact any cardiovascular or skeletal muscle adaptations to regular exercise training particularly in clinical populations.
such as heart failure patients where augmented oxygen delivery to the skeletal muscle during exercise may improve exercise tolerance.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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