Brachial artery modifications to blood flow-restricted handgrip training and detraining

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Hunt JE, Walton LA, Ferguson RA. Brachial artery modifications to blood flow-restricted handgrip training and detraining. J Appl Physiol 112: 956–961, 2012. First published December 15, 2011; doi:10.1152/japplphysiol.00905.2011.—Low load resistance training with blood flow restriction (BFR) can increase muscle size and strength, but the implications on the conduit artery are uncertain. We examined the effects of low-load dynamic handgrip training with and without BFR, and detraining, on measures of brachial artery function and structure. Nine male participants (26 ± 4 yr, 178 ± 3 cm, 78 ± 10 kg) completed 4 wk (3 days/wk) of dynamic handgrip training at 40% 1 repetition maximum (1RM). In a counterbalanced manner, one forearm trained under BFR (occlusion cuff at 80 mmHg) and the other under nonrestricted (CON) conditions. Brachial artery function [flow-mediated dilation (FMD)] and structure (diameter) were assessed using Doppler ultrasound. Measurements were made before training (pretraining), after training (posttraining), and after 2-wk no training (detraining). Brachial artery diameter at rest, in response to 5-min ischemia (peak diameter), and ischemic exercise (maximal diameter) increased by 3.0%, 2.4%, and 3.1%, respectively, after BFR training but not after CON. FMD did not change at any time point in either arm. Vascular measures in the BFR arm returned to baseline after 2 wk detraining with no change after CON. The data demonstrate that dynamic low-load handgrip training with BFR induced transient adaptations to conduit artery structure but not function.

brachial artery; remodeling; ischemic exercise; forearm

LOW-LOAD RESISTANCE TRAINING with blood flow restriction (BFR) has been shown to elicit similar hypertrophic and strength gains as traditional high-load resistance training (25). The alteration in normal blood flow, on which this modality is based, exposes the vasculature to distorted hemodynamic (42), redox (13, 19), and chemical/metabolic signals (34, 40, 42), which could all have adaptive effects on the vasculature. However, relatively little is known regarding the effect of BFR training on the peripheral vasculature.

Conduit-artery modifications have been shown to occur in response to localized short-term resistance exercise training (3, 45, 47). A transient increase in flow-mediated dilation (FMD) is often evident before structural remodeling of the conduit artery (46, 47). Although primarily a measure of conduit endothelial function, the FMD response is largely influenced by the magnitude of the reactive hyperemic shear stimulus, governed by the extent of ischemic microvascular dilation (24). Since low-load resistance exercise training with BFR can increase reactive hyperemic blood flow (reflecting resistance vessel dilatory capacity) (30) and microvascular filtration capacity (reflecting capillarity) (15), an enhanced FMD response would be expected. Intriguingly, both acute (35) and chronic (14) BFR exercise have been shown to decrease conduit artery FMD. It is assumed that this reduced FMD is a product of diminished endothelial function; however, alterations to conduit artery geometry could also explain findings. Larger arteries display a smaller dilatory response to functional stimulation (37, 44), raising the possibility that structural enlargement of the conduit artery could account for decreased FMD. Maximal dilation after ischemic exercise is an accepted (27) and frequently used (46, 47) method to examine conduit structure. This technique could be used, alongside FMD measures, to verify whether the alterations in artery function occur as a result of structural changes following BFR training.

Changes to conduit-artery structure and function after removal of the BFR training stimulus have not been investigated. Several experimental models demonstrate that inactivity (e.g., deconditioning or limb unloading) provides a strong stimulus for rapid structural remodeling of the conduit arteries and changes to reactive hyperemic flow (8, 33). Therefore, a detraining effect will identify the vascular response to changes within the local milieu caused by the removal of contraction and BFR-induced shear, transmural, and metabolic stress.

The aim of the present investigation was to examine the effects of low-load dynamic handgrip training with and without BFR, and detraining, on measures of brachial artery function and structure.

METHODS

Participants

Nine healthy males (age 26 ± 4 yr, height 178.1 ± 3.2 cm, body mass 78.1 ± 9.5 kg, resting systolic blood pressure 127 ± 6 mmHg, resting diastolic blood pressure 70 ± 7 mmHg) volunteered to take part in the investigation. All participants were habitually physically active but none were partaking in resistance exercise training. The participants were fully informed of the purposes, risks, and discomforts associated with the experiment before providing written, informed consent. This study conformed to current local guidelines and the Declaration of Helsinki and was approved by Loughborough University Ethics Advisory Committee.

Experimental Design

Participants completed 4 wk (3 sessions/wk) of unilateral dynamic handgrip training at 40% 1 repetition maximum (1RM) to volitional fatigue under restricted and nonrestricted blood flow conditions. This was followed by 2 wk of no training (detraining). Measures of brachial artery function (FMD), structure (maximum diameter), and handgrip strength (1RM) were made on both arms, before training (pretraining), after training (posttraining), and after detraining. Posttraining measures took place 2 days after the last exercise session.

Familiarization

Participants were familiarized to testing procedures and training devices during two preliminary visits, 1 wk prior to experimental
measures. During the first visit, brachial artery properties were assessed in the right arm in accordance with the experimental protocol (described below). This established optimal brachial artery image location and familiarized the participant with the occlusion procedures. During the second preliminary visit, participants were familiarized with the handgrip exercise device, 1RM was determined, and a BFR handgrip training protocol experienced.

Experimental Protocol

Participants maintained a habitual pattern of physical activity and dietary habits during the study period. Brachial artery measures (pre-, post-, and detraining) were conducted in both arms at the same time in the morning (± 1 h), following a 10-h overnight fast, and in a quiet temperature-controlled room (24 ± 1°C). Participants abstained from vitamin supplementation for 72 h and from exercise, alcohol and tobacco for 12 h prior to vascular tests. Upon arrival participants lay supine for 20 min prior to basal assessment. Brachial artery properties were assessed using Doppler ultrasound. The right arm was always imaged first with a 15-min period allowed between each assessment. Following vascular assessments forearm anthropometry and strength measurements were then made.

Brachial Artery Assessments

Doppler ultrasound imaging was performed by the same sonographer using a Toshiba Powervision 6000 with a multifrequency linear array transducer (7–11 MHz). Participants lay supine with imaged arm extended and immobilized at an angle ∼80° from the torso. A 90° B-mode image of the brachial artery at 3-cm depth was obtained >3 cm proximal of the olecranon process. In duplex mode the sample volume was centralized within the artery and the ultrasound beam aligned with direction of flow (insolation angle ≤60°). Once a satisfactory image was made, the probe was held in a constant position for the duration of the test. Ultrasound settings were standardized for each individual and kept constant for repeated measures. A vascular ECG gating module (Medical Imaging Applications) triggered acquisition of the ultrasound images on the R-wave pulse of an ECG signal. Sequential end-diastolic images were stored from on-line image digitization.

FMD. Resting brachial diameter and blood flow were recorded for 20 cardiac cycles following a 20-min rest period. For the ischemic FMD stimulus a pneumatic cuff (E20 Rapid cuff inflator and AG101 Cuff Inflator Air Source, Hokanson, WA) was placed immediately distal to the olecranon process and inflated to 200 mmHg. Occlusion was maintained for 5 min before rapid cuff deflation. Recording of real-time duplex imaging was resumed 10 s before deflation and continued for ~3 min postdeflation, capturing the transient changes in flow and diameter over a total of 200 cardiac cycles.

Dilatory capacity (DC). Brachial diameter and flow were remeasured and a return to baseline values ensured before commencing the DC protocol. For the ischemic DC stimulus, the pneumatic cuff was positioned on the upper arm proximal to the ultrasound probe. The cuff was inflated to 200 mmHg with occlusion maintained for 5 min. During the middle 3 min, rhythmic ischemic handgrip exercise was performed using a 10-kg weight at 20 contractions/min. Real-time duplex imaging was performed as described for FMD.

Ultrasound data analysis. Brachial artery diameter and flow velocity were analyzed with a custom-designed edge detection and wall tracking software (Vascular Research Tools 5, Medical Imaging Applications, LLC, Coralville, IA). Media-to-media diastolic diameter was measured within a specified region of interest on B-mode images. The Doppler flow velocity spectrum was traced and time average mean velocity (TAMV) (cm/s) computed. Synchronized diastolic diameter and velocity data, sampled at 20 Hz, enabled calculation of blood flow and shear rate. Resting diastolic diameter (mm) was averaged over 20 cardiac cycles. The dilatory response to FMD and DC protocols was determined from smoothed data (moving average across 3 cardiac cycles) and peak and maximal diameter defined, respectively, FMD and DC are presented as the absolute (mm) and relative (%) change in poststimulus diameter. (maximum poststimulus diameter − baseline diameter)/baseline diameter. Time to peak diameter (s) was calculated from the point of cuff deflation to the maximum postdeflation diameter. Blood flow (ml/min) was calculated as (TAMV × πr²) × 60, where r is the radius of the brachial artery lumen. Resting blood flow was averaged over 20 cardiac cycles. Peak blood flow was recorded as the highest value (across a single cardiac cycle) following cuff deflation. Shear rate was derived from Poiseuille’s law and calculated accordingly as (4 × TAMV)/diameter. The accumulated shear stimulus contributing to the FMD response was defined as the area under the shear rate curve (SRAUW) calculated for data up to the point of peak dilation for each individual. Given the uncertainty regarding an appropriate strategy for normalization of the FMD response, FMD% and SRAUW were presented independently. The day-to-day reproducibility of brachial artery measurements was: diameter (0.5%), blood flow (8.7%), FMD% (6.5%), and DC% (3.1%), respectively.

Forearm Strength and Anthropometry

One repetition maximum (1RM) was determined on a custom-made handgrip dynamometer. Participants flexed their fingers, which lifted and lowered weights (kg) hanging over a pulley. To isolate the finger flexors and extensors as the sole producers of force, participants lay supine with arm extended 90° at the shoulder and forearm in supination. A successful lift was acknowledged when the participant completed the repetition with a full range of movement (6–8 cm) at the maximum weight possible. The 1RM was achieved within five attempts. Maximum forearm circumference was measured in supination at one-sixth of the distance between the olecranon process and ulnar styloid. Forearm volume was determined using water displacement; the arm was submerged to a proximal marker (olecranon process) and water discarded before immersion to a distal marker (ulnar styloid) and the volume of water displaced measured.

Exercise Training

Participants completed a supervised 4-wk forearm exercise training program (3 sessions/wk). Each training session involved three sets of unilateral dynamic handgrip exercise at 40% 1RM, at a frequency of 20 contractions per minute (duty cycle of 2-s contraction/1-s relaxation) performed to volitional fatigue, each separated by 1 min rest. Participants exercised first with BFR before completing a work (repetition)-matched protocol in the contralateral arm without blood flow restriction (CON). BFR was applied in a counterbalanced manner to the dominant or nondominant arm. Partial BFR was induced by inflation of a 13-cm pneumatic cuff on the upper arm to 80 mmHg. Pressure was maintained for the duration of the three sets, including the 1-min intervening rest periods, and amounted to 510 ± 164 s under BFR.

Statistics

A Shapiro-Wilk test was used to confirm normal distribution and a Mauchley test of sphericity to verify homogeneity of variance. Initially, a two-way (2 × 3) ANOVA with repeated measures was conducted to analyze the within-subject effect of exercise condition (BFR, CON) and time (pretrain, postrain, detrain). This was followed by one-way repeated-measures ANOVA to confirm change over time in each arm separately. Bonferroni post hoc t-tests were then used to locate significance. All data are presented means ± SD. Significance was accepted at P < 0.05.

RESULTS

All participants successfully completed the 12 training sessions with 100% compliance. Heart rate (HR) and blood
pressure during dynamic handgrip exercise was similar between conditions and throughout training. Exercise to volitional fatigue in the BFR arm (which was matched by the CON arm) progressively increased over the training period (451 ± 99 s, 477 ± 112 s, 522 ± 173 s, and 586 ± 220 s for weeks 1–4, respectively). All baseline (pretraining) variables were similar between the BFR and CON arms.

**Brachial Artery Measures**

Resting diameter, blood flow, and shear rate. Resting diameter increased posttraining and decreased after detraining in the BFR but not the CON arm (condition × time interaction; P = 0.019, Fig. 1). In the BFR arm resting diameter increased by 3.0% following training (Bonferroni t-test, P = 0.019, Fig. 1). In the CON arm, resting diameter increased by 3.1% following training (Bonferroni t-test, P = 0.02) and returned to near baseline values after detraining. In the CON arm, maximal diameter changed over time but post hoc analysis failed to locate significance (Table 1). There was a significant time effect for DC (2-way ANOVA; P = 0.05), but no changes in each arm independently (Table 1) were observed.

**Forearm Strength and Anthropometry**

The 1RM increased posttraining in both arms (2-way ANOVA, P < 0.001, Table 2). There were no changes in forearm volume or circumference after training (Table 2).

**DISCUSSION**

This study has demonstrated that 4 wk of dynamic low-load handgrip training with BFR increased brachial artery diameter at rest, in response to ischemia (peak diameter) and ischemic exercise (maximal diameter), compared with no changes with low-load training alone. Due to the similar increases in resting stimulated diameters, flow-mediated dilation (FMD%) and maximal dilatory capacity (DC%) remained unchanged. These adaptations were transient as all measures returned to pretraining values after 2 wk detraining.

There was a 3% increase in resting diameter of the brachial artery, which may reflect functional influences on vascular tone.

**Table 1.** Brachial artery characteristics measured pretraining (week 0), posttraining (week 4), and detraining (week 6) in blood flow-restricted (BFR) and nonrestricted (CON) arms

<table>
<thead>
<tr>
<th></th>
<th>BFR Arm</th>
<th>CON Arm</th>
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<tr>
<td></td>
<td>Pretraining</td>
<td>Posttraining</td>
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<tr>
<td><strong>Resting</strong></td>
<td></td>
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<tr>
<td>Diameter, mm</td>
<td>4.31 ± 0.28</td>
<td>4.44 ± 0.37</td>
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<tr>
<td>BF, ml/min</td>
<td>160 ± 67</td>
<td>172 ± 76</td>
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<tr>
<td>SR, s⁻¹</td>
<td>167 ± 51</td>
<td>169 ± 55</td>
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**Response to 5-min ischemia**

<table>
<thead>
<tr>
<th></th>
<th>Peak diameter, mm</th>
<th>Peak BF, ml/min</th>
<th>FMD, %</th>
<th>SR&lt;sub&gt;AUC&lt;/sub&gt;</th>
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<tbody>
<tr>
<td></td>
<td>4.59 ± 0.32</td>
<td>897 ± 286</td>
<td>6.5 ± 2.7</td>
<td>24,707 ± 9,881</td>
</tr>
<tr>
<td></td>
<td>4.70 ± 0.39*</td>
<td>1,061 ± 247†</td>
<td>5.7 ± 2.0</td>
<td>24,509 ± 6,543</td>
</tr>
<tr>
<td></td>
<td>4.63 ± 0.31</td>
<td>999 ± 250</td>
<td>6.7 ± 2.4</td>
<td>23,453 ± 5,621</td>
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<tr>
<td></td>
<td>4.68 ± 0.44</td>
<td>900 ± 204</td>
<td>6.9 ± 1.6</td>
<td>21,673 ± 6,239</td>
</tr>
<tr>
<td></td>
<td>4.69 ± 0.43</td>
<td>910 ± 244</td>
<td>6.6 ± 2.6</td>
<td>23,727 ± 5,178</td>
</tr>
<tr>
<td></td>
<td>4.68 ± 0.42</td>
<td>994 ± 339</td>
<td>6.3 ± 2.5</td>
<td>19,782 ± 8,801</td>
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**Response to 5-min ischemic exercise**

<table>
<thead>
<tr>
<th></th>
<th>Max diameter, mm</th>
<th>DC, %</th>
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<tbody>
<tr>
<td></td>
<td>4.82 ± 0.29</td>
<td>12.0 ± 3.7</td>
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<tr>
<td></td>
<td>4.97 ± 0.30*</td>
<td>12.6 ± 3.3</td>
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<tr>
<td></td>
<td>4.84 ± 0.30</td>
<td>12.0 ± 3.3</td>
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<td></td>
<td>4.87 ± 0.39</td>
<td>12.1 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>4.93 ± 0.36</td>
<td>12.8 ± 3.3</td>
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<td></td>
<td>4.87 ± 0.39</td>
<td>11.1 ± 3.2</td>
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Values are means ± SD. BF indicates blood flow; SR, shear rate; FMD, flow-mediated dilation; SR<sub>AUC</sub>, shear rate area under the curve; DC, dilatory capacity. Significant difference from pretraining: *P < 0.05, †P < 0.005 (Bonferroni t-test).
as well as an increase in artery size (27). Changes in basal vascular tone are likely to be locally mediated (6) by myogenic mechanisms and endothelial factors [such as nitric oxide (NO) and endothelin-1 bioavailability], which act on underlying vascular smooth muscle (22). The enhanced expression of vascular endothelial growth factor (VEGF) that has been observed following BFR exercise (42) may modulate NO bioavailability (32, 38), therefore reducing vascular tone. Alternatively, the increase in resting diameter may be explained by artery remodeling. Indeed, the concurrent increase in maximal diameter (evoked by ischemic exercise) suggests structural enlargement in the brachial artery of the BFR arm (27) likely mediated by exposure to excessive shear, transmural, and metabolic stress during exercise (1, 20).

Recent studies investigating conduit-artery adaptations to exercise training have used a form of BFR (45, 47) specifically designed to manipulate exercise-induced shear rate (SR). This was achieved by inflating a distal (forearm) cuff at a low pressure (60 mmHg). The attenuation of brachial artery SR in this manner during endurance-type (30 min) handgrip training actually prevented functional change (FMD) and structural enlargement (DC) (47) but not wall remodeling (45). In contrast, the aim of the present study was to assess brachial artery adaptation to “traditional” BFR resistance exercise. Subsequently, we positioned the cuff proximal to the exercising muscle (on the upper arm) and inflated to a higher pressure to occlude venous flow before commencing a low-load resistance exercise bout. Indeed, our training load was even lower (<10 min at 40% 1RM, 3 days/wk) compared with those commonly employed to mediate vascular adaptation in healthy populations [20–30 min at 40–75% maximal voluntary contraction, 3–5 days/wk (3, 5, 45, 47)]. This may explain why artery function and structure in the uncuffed “control” arm remained unchanged in contrast to the aforementioned studies. Enlargement of the brachial artery in the BFR arm, despite the low training load (which was matched between arms), demonstrates the capacity for the BFR stimulus to augment the training response. Our discrepant findings could be explained by alternative mechanisms of adaptation as a result of differences in the methodology highlighted previously.

Structural remodeling may have occurred by mechanisms independent of shear stress. Forearm exercise with proximal BFR (cuff placed on the upper arm) exposes the assessed brachial region to ischemic and/or metabolic factors (43). An enhanced contribution of NO to conduit-artery vasodilation occurs under these conditions (hypoperfusion) compared with exercise under normal inflow (10, 12), augmenting the stimulus for structural adaptation. The enhanced release of metabolites (e.g., adenosine), endothelial progenitor cells, and VEGF with ischemic exercise (11, 36, 42) may also stimulate vascular growth, although the exact contribution to conduit arteriogenesis is at present unknown (31).

Our results could directly relate to the impact of the overlying cuff. External compression resulting in an increase in extravascular pressure causes a reduction in diameter and transmural pressure of the underlying brachial artery (7). The decrease in diameter may elevate wall shear stress while the increase in artery distensibility [with reduced transmural pressure (51)] combined with exercise-induced pressure changes may enhance cyclic stretch. These mechanical forces stimulate
the endothelial cells to release NO (20) and could initiate vessel remodeling. However, we are unable to confirm the mechanical forces acting on the vessel underlying the cuff without intravascular ultrasound. Another possibility is that regional increases in blood flow immediately following BFR exercise could explain brachial artery remodeling. Enhanced hyperemia is observed after BFR, compared with non-BFR exercise (29), stimulating greater FMD of the upstream conduit vessel (2). Repeated exposure to this reperfusion may increase shear stress on the arterial walls under the cuff, stimulating structural remodeling of the conduit artery.

Increases in baseline diameter can impact on the magnitude of FMD and DC change. Indeed, the magnitude of endothelium-dependent (FMD) and glycercyl trinitrate-independent (GTN) vasodilation is inversely correlated with baseline artery size, which reflects the reduction in shear rate stimulus and wall-to-lumen ratio associated with artery enlargement (37, 44). The structural adaptation in the BFR arm may have obviated the need for ongoing functional adaptations (46). Previous studies have demonstrated that functional changes in the conduit artery occur rapidly but are short lived as the artery enlarges to mitigate the stresses placed upon it. Indeed, brachial artery FMD increases after just 1 wk of handgrip training (3) before peaking and decreasing after a further 2 wk (47). It is reasonable to speculate that BFR exercise induced an increase in NO bioavailability which led to structural enlargement before normalization of circumferential wall and shear stress returned NO-dependent function to baseline levels. As a result we did not demonstrate a change in the shear rate stimulus or FMD response post-BFR training. This is in contrast with Credeur et al. (14), who observed a reduced FMD after BFR training despite higher shear rate AUC, suggesting a blunted vasodilatory response to a greater shear stimulus. The reduced FMD observed by Credeur et al. (14) may, however, be a result of increased levels of oxidative stress, which is implicated in endothelium dysfunction through decreased NO bioavailability (16, 18). This is likely to have originated from the heavy training load (60% maximal voluntary contraction) and prolonged blood flow restriction (20 min), which is greater than typical BFR resistance exercise protocols (<10 min at 20–40% 1RM). Short-duration (<10 min) exercise protocols under partial vascular occlusion, such as that used in the present study, result in only modest production of reactive oxygen species (ROS) (17, 43), which in fact may be involved in the vascular remodeling process, since it is now becoming accepted that repeated exposure to moderate levels of exercise-induced ROS can confer beneficial adaptive signaling responses (41, 48).

Uniquely, the return of both resting and maximal brachial artery diameters to pretraining values was observed 2 wk after the cessation of BFR training. Similar changes in diameter were observed in the femoral artery in response to unilateral leg endurance training and detraining (26). Inward remodeling of the conduit arteries induced by deconditioning (unloading) is attributed to the removal of pulsatile stretch and shear stress on the arterial wall that would normally occur during muscle contractions (4). Our observation of the transient modification in brachial diameter, therefore, confirms the sensitivity of the vasculature to the BFR training stimulus.

The increases in strength were the same (12%) following handgrip exercise training with and without BFR. This is surprising since BFR has consistently been shown to enhance gains in strength with low-load exercise training (15, 30, 39). Our results are similar to Burgomaster et al. (9), who did not observe any differences in strength between the BFR and control arm after biceps training at 50% 1RM. Similar gains in strength between the BFR and CON arm indicate a cross-transfer effect (23, 28) and a reduced effect of BFR on the stimulus for increases in strength when exercising at moderate to high intensities (>40–50% 1RM) (21, 43, 49, 50).

In conclusion, the present study has demonstrated that 4 wk of dynamic low-load handgrip training with BFR resulted in brachial artery structural modifications as indicated by increases in resting and maximal diameters. The rapid return of vascular measures following the cessation of BFR exercise demonstrates the sensitivity of the BFR stimulus. To confirm the mechanisms responsible for the peripheral vascular adaptations, future studies require infusion protocols to directly examine smooth muscle and endothelial health in response to BFR exercise training.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES