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ACUTE VASCULAR RESPONSES TO ISOMETRIC HANDGRIP (IHG) EXERCISE AND THE EFFECTS OF TRAINING IN PERSONS MEDICATED FOR HYPERTENSION

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ABSTRACT

Previous work from our laboratory demonstrated that isometric handgrip (IHG) training improved local, endothelial-dependent vasodilation in medicated hypertensives (23, 24). We investigated whether changes in the capacity of smooth muscle to dilate (regardless of endothelial factors) influenced this training-induced change, and examined the acute vascular responses to a single bout of IHG.

Seventeen subjects performed 4, 2-min unilateral IHG contractions at 30% of maximal voluntary effort, 3X/week for 8 weeks. Pre- and post-training, brachial artery flow mediated dilation (FMD, an index of endothelial-dependent vasodilation) and nitroglycerin - mediated maximal vasodilation (an index of endothelial-independent vasodilation) were measured in the exercised arm using ultrasound prior to and immediately following acute IHG exercise.

IHG training resulted in improved resting brachial FMD ($p < 0.01$) and no change in nitroglycerin-mediated maximal vasodilation. Pre- and post-training, brachial artery FMD decreased following an acute bout of IHG exercise (normalized to peak shear rate, pre-, before-IHG exercise: 0.01 + 0.002, after-IHG exercise: 0.008 + 0.002 $\%/s^{-1}$; post-, before-IHG exercise: 0.020 + 0.003, after-IHG exercise: 0.010 + 0.003 $\%/s^{-1}$; $p < 0.01$).

Post-training, resting brachial artery FMD improved yet nitroglycerin-mediated maximal vasodilation was unchanged in persons medicated for hypertension. This suggests that the training-induced improvements in resting brachial artery FMD were not due to underlying changes in the forearm vasculature. Acute IHG exercise attenuated brachial artery FMD, and although this impairment may be interpreted as hazardous to medicated

hypertensives with already dysfunctional endothelium, the effects appear transient as repeated exposure to the IHG stimulus improved resting endothelial-dependent vasodilation.

KEY WORDS

Acute Exercise, Isometric Training, FMD, Hypertension, Blood Flow

Word Count: 250

INTRODUCTION

Hypertension is associated with endothelial dysfunction, a condition characterized by reduced endothelial-dependent, nitric oxide-mediated vasodilation (7, 11, 26). Evidence suggests that aerobic exercise training favorably alters endothelial function in persons with hypertension (12, 13). It has been proposed that a shear stress-related mechanism is responsible for the training-induced improvements in endothelial function, primarily via the intermittent and repetitive augmentations in pulsatile flow along the endothelium (21), and the resulting increase in nitric oxide synthesis (9).

The acute effects of aerobic exercise on endothelial function are under-investigated, yet evidence suggests that brachial artery flow-mediated dilation (FMD; an index of endothelial-dependent vasodilation) is either unaffected (30) or improved (10) in persons with endothelial dysfunction, while it is attenuated following a maximum intensity aerobic exercise bout (30). Brachial artery FMD is dependent upon the release of nitric oxide, which diffuses out of the endothelium and into the vascular smooth muscle cells in response to increased blood flow, where it ultimately causes vasodilation (4). In humans, nitric oxide formation is elevated following a single session of aerobic exercise (17), and may play a role in post-exercise increases in endothelial-dependent vasodilation (9). Alternatively, impairment in endothelial-dependent vasodilation at higher intensities of exercise may result from increases in oxidative stress (2, 30), as reactive oxygen species superoxide radicals react vigorously with nitric oxide to form oxidant peroxinitrite, which reduces the bioavailability of nitric oxide (18, 19, 30). The effects of aerobic training on acute exercise-induced changes in endothelial-dependent vascular function are unknown.

Handgrip training (rhythmic and isometric) improves local, endothelial-dependent vasodilation in persons with endothelial dysfunction, including those medicated for hypertension (15, 23, 24). Several mechanisms may be responsible for this improvement, including shear stress-mediated improvements in the bioactivity and/or bioavailability of nitric oxide, improved antioxidant activity, underlying changes in vascular structure and/or enhanced endothelial-independent dilation (6, 9). With respect to the latter, rhythmic handgrip training does not improve endothelial-independent vasodilation (an indicator of smooth muscle function) in persons with endothelial dysfunction (15), yet the influence of isometric handgrip (IHG) training on the smooth muscle vasculature is unknown.

Like aerobic exercise, there has been little investigation into the effects of acute isometric exercise on endothelial-dependent vascular function in persons with endothelial dysfunction, such as persons with hypertension. In young, healthy individuals, oxidative stress increased following an acute bout of IHG exercise performed at 50% of maximal voluntary effort, potentially via an increase in reactive oxygen species production (1), the concentrations of which may have ultimately surpassed the antioxidant capacity of the system (i.e., antioxidant enzymes, antioxidants, indirect-acting antioxidants)(1, 18, 34). It is possible that impairment in endothelial-dependent vasodilation may result from this increase in oxidative stress. The effects of IHG training on the acute endothelial-dependent dilation response following a bout of IHG exercise are currently unknown.

The purpose of the current study was to two-fold: 1) to investigate improved endothelial-independent dilation as a contributor to training-induced change in endothelial-dependent vasodilation, and 2) to examine the acute vascular responses to a single bout of

IHG in the exercised arm of persons medicated for hypertension. Based on the literature, it was hypothesized that: 1) changes in the capacity of the smooth muscle to dilate (endothelial-independent vasodilation) would not be responsible for improved post-IHG training endothelial-dependent vasodilation in persons medicated for hypertension, and 2) endothelial-dependent vasodilation would be attenuated immediately following a bout of IHG exercise.

MATERIALS AND METHODS

Participants

Twenty participants, all of whom were medicated for hypertension, were recruited from Hamilton, Ontario, Canada. Three participants were unable to complete the study, as one voluntarily withdrew, and two had mid-investigation medication changes. Participants were excluded if they had diabetes, congestive heart failure, took hormone supplements or regular nitrate medications and/or were current smokers. Vasoactive medications, external exercise sessions and nutritional changes were monitored throughout the investigation via bi-weekly personal communications with the exercise trainers in conjunction with exercise log-book tracking. All participants were regular exercisers ($\geq$ 2 exercise sessions per week). Baseline characteristics of the participants are described in Table 1. The Research Ethics Board of Hamilton Health Sciences/McMaster University approved the investigation, all procedures were followed in accordance with institutional guidelines, and all participants provided written, informed consent.

Exercise training protocol

Recent work from our laboratory demonstrated that unilateral IHG training improved local, endothelial-dependent vasodilation in persons medicated for hypertension (24). The

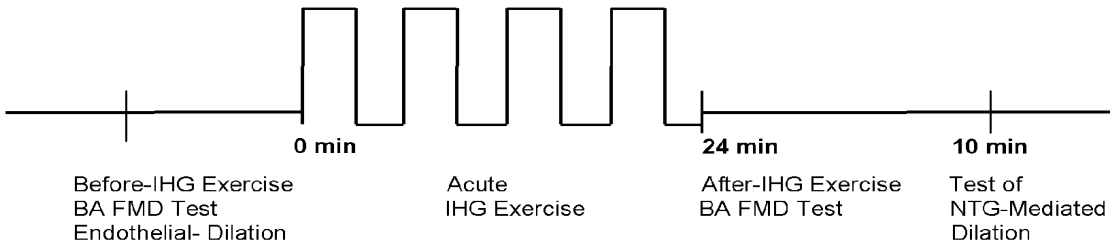
same training protocol was used in the current investigation. Specifically, participants completed 4 sets of 2-minute unilateral IHG contractions using a programmed handgrip dynamometer (Cardiogrip, IBX H-101, MD Systems, Westerville, OH, USA), 3 times per week for 8-weeks. Isometric contractions were performed at 30% of maximal effort, using the non-dominant arm and each contraction was separated by a 4-minute rest interval.

Study design

This investigation employed a within-subject repeated measure design. Endothelial-dependent and independent vasodilation were assessed pre- and post-training.

Testing Protocol

Endothelial-dependent vasodilation was assessed via brachial artery FMD using Doppler ultrasound prior to and immediately following an acute bout of IHG exercise executed by the non-dominant arm. Endothelial-independent vasodilation was then assessed in the same arm after the administration of sublingual nitroglycerin 10-minutes following the last FMD test:



Schematic Diagram of Testing Protocol

* Note: brachial artery is represented by BA, and nitroglycerin by NTG

We do acknowledge that the second assessment of FMD was imposed while contraction-induced reactive hyperemia was still present. We performed the second test of endothelial-dependent vasodilation 4 minutes following the last IHG contraction because that

time point represented the true end-point of the IHG exercise protocol used in the current and previous training intervention studies conducted by our laboratory. This timing was used to obtain a true representation of the impact of IHG exercise on endothelial-dependent vasodilation immediately following an IHG exercise bout, a bout which includes the last 4-minute rest period.

The same investigator performed all measurements using a high-resolution ultrasound and linear array probe (10 MHz) system (System FiVe, GE Vingmed Ultrasound, Horten, Norway). Post-testing was conducted the week following the last IHG training session. Prior to baseline measurements, participants were habituated to the laboratory and testing environment. All assessments of endothelial-dependent and independent vascular function were conducted in a quiet, dark, temperature-controlled room (range of 2°C) following a 4-hour fast, 12-hour abstinence from caffeine, and 24-hour abstinence from vigorous exercise. All tests were conducted within 2 hours of initial pre-testing time of day.

Assessment of Endothelial-Dependent and Independent Vasodilation

All data was acquired while participants were seated behind a table with the forearm resting immediately in front on the tabletop, at a 90° angle from the upper arm. Heart rate and arterial blood pressure were continuously monitored using electrocardiography (Cardiomatic MSC 7123, Medical Systems Corp, USA), and radial artery applanation tonometry (CBM-7000, Colin Medical Instruments, San Antonio, TX, USA), respectively. Resting brachial artery images were measured approximately 3 – 5 cm proximal to the antecubital fossa in the exercised arm. Resting blood velocity measures were obtained from the entire brachial artery in pulse wave -mode. Brachial artery FMD was assessed according to previously established guidelines (27). After a resting period of at least 10 minutes

following the after-IHG exercise FMD Test, participants were given a 0.4 mg dose of sublingual nitroglycerin spray (5). One ECG-gated brightness-mode image of 1 complete heart cycle was recorded at the following post-nitroglycerin administration time points to ensure the capture of peak brachial artery dilation: 2 minutes, 2.5 minutes, 3 minutes, 3.10 minutes, 3.20 minutes, 3.30 minutes, 3.40 minutes, 3.50 minutes, 4 minutes, 4.30 minutes, and 5 minutes (5).

Measurement Protocol

Off-line measurements of brachial diameters were made by the same ultrasonographer, using custom-designed, automated edge-detection software to minimize observer bias (Artery Measurement System (AMS) II version 1.133, Chalmers, Sweden). All diameters were expressed as a percent increase of the baseline value of the diameter, then normalized to the peak shear rate experienced in response to the FMD stimulus using previously described methods (27).

Pre- and post-FMD blood velocity samples were used to calculate resting and peak reactive hyperemic blood flow, where pre-FMD velocity samples were 10s in length, and peak reactive hyperemic blood velocity was defined as the largest single-beat mean blood velocity following release of the occlusion cuff (excluding the first beat). All blood velocity measurements were analyzed as previously described (27). Measures of heart rate, mean arterial blood pressure ((2 • diastolic blood pressure) + systolic blood pressure)/3), vascular conductance (mean blood flow/mean arterial pressure) and vascular resistance (mean arterial pressure/mean blood flow) were calculated during the pre-FMD and peak reactive hyperemic blood flow phases. In accordance with the views of Monahan and colleagues(25), both vascular conductance and vascular resistance variables were calculated and reported due to

the debate over which variable more accurately represents changes in vascular tone. For calculation of endothelial-independent vasodilation, BA diameters were measured at ED in each of the 11 post-nitroglycerin brachial artery images, and then averaged (5, 32). Endothelial-independent dilation was expressed as a percent increase of the baseline value of the diameter.

Statistical analysis

The effects of IHG exercise on resting endothelial function were determined by analyzing the before-IHG exercise FMD and endothelial-independent dilation data using 1-way (Time) analysis of variance with repeated measures. To examine the acute cardiovascular and vascular reactivity responses to IHG exercise and ascertain any training effects, before-IHG exercise and after-IHG exercise FMD data were analyzed using 2-way analysis of variance with repeated measures (FMD Test X Training). Tukey *post hoc* procedures were used to evaluate specific differences between means, where applicable. All data were analyzed using STATISTICA (version 6.0), and an alpha level of ≤ 0.05 was considered statistically significant. Descriptive data are presented as means $\pm$ standard error, unless otherwise specified.

RESULTS

Effects of IHG training on resting endothelial dependent and independent vasodilation, and other cardiovascular and vascular reactivity responses

FMD measures obtained prior to the acute IHG bout were compared pre- and post-training to examine any training-induced alterations in resting endothelial dependent vasodilation. Relative FMD increased from baseline and was significantly higher at post-training (pre-: 3.1 $\pm$ 0.4, post-: 5.0 $\pm$ 0.7 %, $p = 0.002$), and improvements were still observed when relative FMD was normalized to the peak reactive hyperemic stimulus (pre-: 0.01 $\pm$

0.002, post-: 0.02 ± 0.003 %/s^{-1}, Figure 1). Endothelial-independent vasodilation was unchanged with IHG training (pre-: 9.0 + 0.7 to post-: 8.8 + 0.8 %; p>0.05), as were all other cardiovascular and vasoreactivity parameters (Table 2).

Effects of an acute bout of IHG exercise on endothelial-dependent vasodilation, cardiovascular and vascular reactivity, and the influence of training

Relative endothelial-dependent vasodilation decreased significantly after a single session of IHG exercise, and this was unchanged with training (Table 3). These findings were upheld when relative FMD was normalized to the peak reactive hyperemic stimulus (pre-, before-IHG exercise: 0.01 ± 0.002, after-IHG exercise: 0.008 ± 0.002 %/s^{-1}; post-, before-IHG exercise: 0.02 ± 0.003, after-IHG exercise: 0.01 + 0.003 %/s^{-1}, Figure 2). Following acute IHG exercise, significant increases were observed in pre-FMD heart rate, mean blood flow, shear rate and vascular conductance, yet vascular resistance declined. Peak reactive hyperemic blood flow, peak shear rate and post-FMD vascular conductance were also elevated following a bout of IHG exercise. All other cardiovascular and vascular reactivity responses were unchanged. Eight weeks of IHG training did not alter the endothelial-dependent vasodilatory, cardiovascular and/or vascular reactivity responses to a bout of IHG exercise (All data presented in Table 3).

DISCUSSION

In the current investigation, and as previously observed, IHG training improved resting endothelial-dependent vasodilation in the brachial artery of the exercised limb. As endothelial-independent vasodilation did not change with 8-weeks of IHG training, inherent changes in the capacity of the vascular smooth muscle to dilate (regardless of the influence of endothelial factors) were ruled out as the mechanism responsible for these training-induced improvements in brachial artery FMD. To our knowledge, this is the first study to

demonstrate that a single bout of IHG exercise acutely reduces brachial artery endothelial-dependent vasodilation in persons medicated for hypertension. This latter observation is particularly remarkable, as IHG performed at 30% MVC is such a small stimulus, yet it is sufficient to acutely impair brachial artery FMD and improve resting endothelial-dependent vasodilation after repetitive exposure to the stimulus over an 8-week period.

Effects of IHG training on resting endothelial dependent and independent vasodilation

Brachial artery FMD has become a popular non-invasive method to measure shear stress induced dilation following a 5-minute period of ischemic forearm occlusion and is quantified as an index of endothelial-dependent vasodilation (5). Although our IHG protocol had 4, 2-minute periods of static-contraction induced occlusion that likely elicited post-contraction increases in brachial artery endothelial-dependent vasodilation, the lack of change in pre-FMD brachial artery diameter following an acute bout of IHG exercise (Table 3) demonstrates that the vasodilatory response was diminished by the end of the IHG protocol. Our observations of improved resting cuff-induced brachial artery FMD following IHG training in persons medicated for hypertension support previous findings from our laboratory in the same population (24). The impairment of endothelial-dependent vasodilation following acute IHG exercise may be interpreted as hazardous to these individuals who already have dysfunctional endothelium. On the contrary, the acute effects appeared transient, and repeated exposure to the IHG stimulus improved resting endothelial-dependent vasodilation. Importantly, in all investigations relative FMD measurements were elevated to values close to or within the normal range of 4.5% to 15% FMD (8, 16, 33).

Endothelial-independent vasodilation did not change with training in the current investigation, suggesting that our post-training measures of endothelial-dependent vasodilation were not influenced by changes in the underlying forearm vasculature (5).

Effects of an acute bout of IHG exercise on endothelial-dependent vasodilation and the influence of training

In the present study, reductions in brachial artery FMD following an acute bout of IHG exercise were noted. This observation supports the findings of Silvestro and colleagues who showed a 2.3-fold reduction in persons with endothelial dysfunction (intermittent claudication) following a single session of maximal treadmill exercise (30). Silvestro and colleagues (30) reasoned that the exercised-induced ischemic conditions were responsible for the observed changes. The formation of reactive oxygen species (superoxide free radicals) increases during ischemia, affecting the antioxidant/superoxide balance whereby free radical formation exceeds the antioxidant capacity of the system, and oxidative stress increases (1, 29). Reactive oxygen species react vigorously with nitric oxide and form the powerful oxidant peroxynitrite (19). Thus, Silvestro and colleagues (30) further deduced that the observed reductions in endothelial-dependent vasodilation were the result of the inactivation/reduced bioavailability of nitric oxide (30). In relation to the present study, as participants performed the acute bout of IHG, metabolites likely accumulated, increasing the production of reactive oxygen species (3, 28) and decreasing the bioavailability of nitric oxide. These occurrences may well be responsible for our observed reductions in post-IHG exercise endothelial-dependent vasodilation. Increased temperature in the exercising muscles, inflammation induced by muscle-fibre damage, and/or repetitive ischemia-reperfusion may have also augmented superoxide formation throughout the IHG protocol (1, 14), however we have no data to support or refute these contentions.

In the current study, reductions in brachial artery FMD following acute IHG exercise were unaltered following 8-weeks of IHG training. This suggests that the local antioxidant capacity of the system was still surpassed during the post-training IHG bout (29), contributing to augmented reactive oxygen species accumulation and reduced bioavailability of nitric oxide.

Effects of an acute bout of IHG exercise on other cardiovascular and vascular reactivity characteristics and the influence of training

Increases in pre-FMD mean blood flow and shear rate were noted following an acute bout of IHG exercise in the current investigation. The post-IHG exercise FMD test was administered immediately following the last rest interval of the IHG protocol, and 4 minutes following the last IHG contraction. Although heart rate was significantly increased following the acute IHG bout, the small rise in heart rate (~ 2 bpm) and the four minute rest period may not have sufficiently washed out the vasodilatory metabolites that accumulated throughout the course of the IHG protocol or during the last contraction itself. The rise in pre-FMD vascular conductance (> 1.4 fold) and the concomitant decline in pre-FMD vascular resistance (> 1.3 fold) following acute IHG (Table 3) indicate that greater metabolic stimuli and increased resistance vessel dilation may explain the augmented pre-FMD mean blood flow and shear rate responses following an acute bout of IHG exercise. These parameters were unaltered with training, suggesting that the time course of metabolic clearance and resistance vessel response were unaffected with repeated exposure to the IHG stimulus.

Higher peak reactive hyperemic blood flow and shear rate responses following acute IHG exercise may be attributed to an increased additive accumulation of metabolites in response to forearm cuff occlusion. Cuff occlusion introduced another ischemic challenge, and because post-FMD heart rate remained unchanged, the responses were likely due to

increased metabolite accumulation over and above the after-IHG exercise pre-FMD values. The metabolite-driven augmentation of both peak reactive hyperemic blood flow and shear rate is supported by the concomitant rise in vascular conductance (~ 1.1 fold increase; Table 3). As post-FMD mean arterial pressure remained unchanged following the IHG bout, the lack of decline in post-FMD vascular resistance (Table 3) indicates that the rise in peak hyperemic blood flow was not of a magnitude large enough to significantly reduce vascular resistance. All parameters were unaltered with 8-weeks of IHG training, suggesting that the additive metabolite response to the IHG and cuff occlusion ischemic stimuli was unchanged by the repetitive exposure to IHG exercise.

The results of this investigation are noteworthy, but we do acknowledge some limitations. First, we did not include a non-exercising control group, however we feel that the results of the training portion of our investigation remain valid and applicable for numerous reasons: 1) participants underwent familiarization procedures to reduce the apprehension-induced variability of the baseline measures, 2) the same trained investigator collected and analyzed the vascular measurements at both pre- and post-training time points, and 3) our sample size had enough statistical power to detect intervention-induced differences, if they were present. Furthermore, training-induced improvements in resting endothelial-dependent vasodilation have been established and reproduced in previously-conducted randomized, controlled trials using a non-exercising control group, and a within-study design where the non-exercising arm served as an internal control (15, 22, 24). Second, all participants were medicated for hypertension, and some anti-hypertensive medications are known to positively influence endothelial function (i.e., angiotensin converting enzyme inhibitors and calcium channel blockers) (20, 31). Although this was not controlled for in the present study, all

medications (including lipid-lowering, endothelial function-enhancing medications) were strictly monitored throughout the investigation. In addition, all measurement sessions were conducted at a standardized time from medication ingestion.

CONCLUSIONS

Endothelial-dependent vasodilation was attenuated in the exercised arm of persons medicated for hypertension following an acute bout of IHG exercise, possibly via reactive oxygen species superoxide-mediated reductions in nitric oxide bioavailability, and this was unaltered with IHG training. In accordance with previously conducted investigations, post-training improvements in resting endothelial-dependent vasodilation were observed. Endothelial-independent dilation was unchanged with IHG training, suggesting that the post-training improvements in endothelial-dependent vasodilation were not attributed to underlying changes in the forearm vasculature. In summary, IHG training, using a simple hand-held, non-time consuming device that requires minimal effort to perform, improves local, dysfunctional endothelium in persons medicated for hypertension to values within the normal range. This improvement in local endothelial-dependent vasodilation occurs despite transient post-IHG reductions, an occurrence that also happens post-training. These observations may have important implications for future isometric-related interventions aimed at improving endothelial dysfunction in persons medicated for hypertension, a population which includes a large number of North Americans.

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FIGURE LEGENDS

Figure 1. Post-occlusion brachial artery diameter change from rest normalized to peak shear rate following IHG training

* Significantly different from pre-IHG exercise brachial artery FMD test ($p = 0.009$)

Figure 2. Post-occlusion brachial artery diameter change from rest normalized to peak shear rate prior to and following an acute bout of IHG exercise

* Significantly different from pre-IHG exercise brachial artery FMD test ($p < 0.01$)

FIGURES

Figure 1.

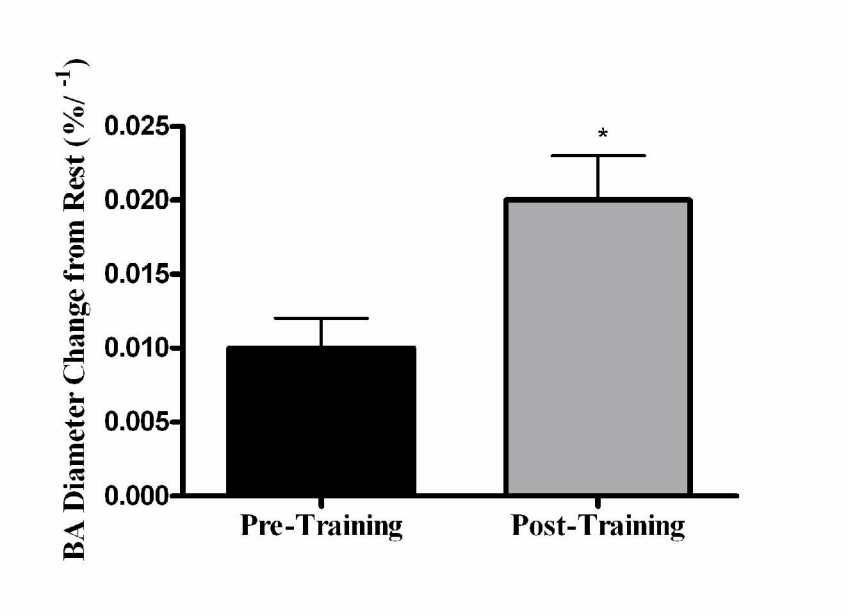
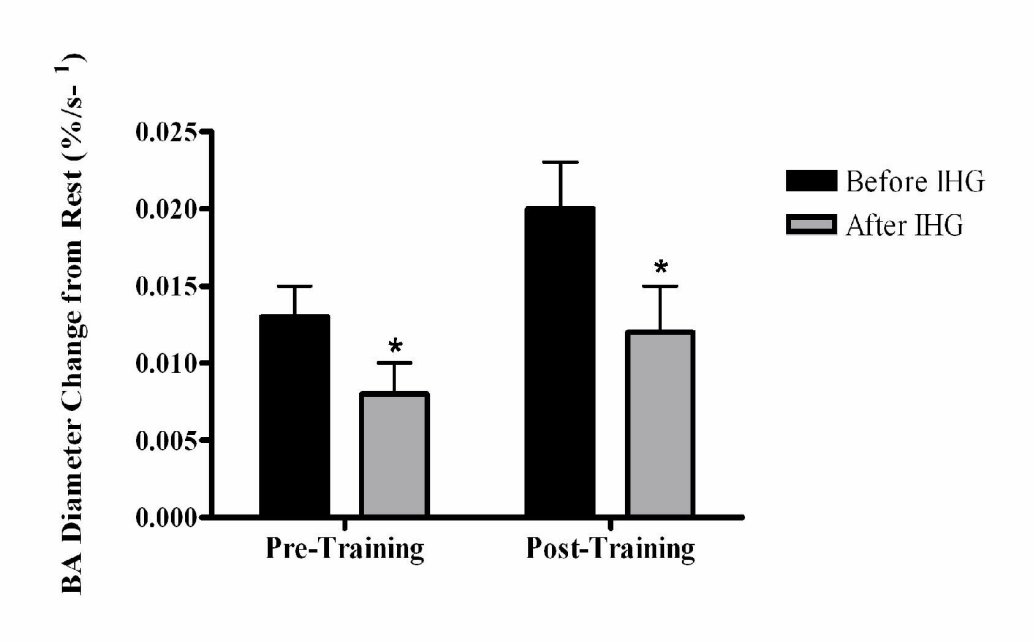


Figure 2



TABLES

Table 1. Participant baseline characteristics (n=20)

Characteristic	
Age (yrs, SD)	66.9 ± 5.8
Height (cm, SD)	176.9 ± 13.1
Weight (kg, SD)	83.1 ± 17.8
Established CAD (#)	9
Medication Classification (#)	
Ace Inhibitor	6
Beta Blocker	1
Calcium Channel Blocker	1
Diuretic	4
Ace Inhibitor + Beta Blocker	3
Ace Inhibitor + Calcium Channel Blocker	1
Ace Inhibitor + Diuretic	2
Ace Inhibitor + Beta Blocker + Calcium Channel Blocker	1
Ace Inhibitor + Beta Blocker + Diuretic	1
Time on Medication (yrs, SD)	7.7 ± 7.3
Resting SBP (mmHg)	126.9 ± 2.4
Resting DBP (mmHg)	72.2 ± 2.0

Values are means ± standard error.

Table 2. Cardiovascular and vascular reactivity characteristics following IHG training (n = 17)

Variable	Pre-training	Post-training
Pre-FMD Brachial Artery Diameter (cm)		
	0.43 + 0.01	0.43 + 0.01
Pre-FMD Heart Rate (bpm)		
	55.8 + 2.7	54.7 + 1.7
Pre-FMD Mean Arterial Pressure (mmHg)		
	95.9 + 2.5	91.9 + 3.4
Pre-FMD Mean Blood Flow (ml/min)		
	23.0 + 2.1	22.9 + 2.0
Pre-FMD Shear Rate ($s^{-1)}$	25.2 + 2.3	24.6 + 1.6
Pre-FMD Conductance (ml/mmHg/min)		
	0.2 + 0.03	0.2 + 0.02
Pre-FMD Resistance (mmHg/ml/min)		
	4.6 + 0.3	4.4 + 0.4
Post-FMD Heart Rate (bpm)		
	58.1 + 2.7	55.8 + 2.1
Post-FMD Mean Arterial Pressure (mmHg)		
	96.6 + 2.6	91.2 + 4.0
Peak Reactive Hyperemic Blood Flow (ml/min)		
	238.9 + 14.3	248.2 + 21.1
Peak Shear Rate (s^{-1})	256.3 + 12.5	269.1 + 19.8
Post-FMD Conductance (ml/mmHg/min)		
	2.5 + 0.1	2.8 + 0.2
Post-FMD Resistance (mmHg/ml/min)		
	0.4 + 0.03	0.4 + 0.03

Values are means $\pm$ standard error.

Table 3. Cardiovascular and vascular reactivity characteristics prior to and following a bout of IHG exercise (n=17)

Variable	Pre-training		Post-training	
	Before IHG	After IHG	Before IHG	After IHG
Pre-FMD Brachial Artery Diameter (cm)				
	0.43 + 0.01	0.43 + 0.01	0.43 + 0.01	0.43 + 0.01
Pre-FMD Heart Rate (bpm)				
	55.8 + 2.7	57.5 + 2.6*	54.7 + 1.7	56.1 + 2.3*
Pre-FMD Mean Arterial Pressure (mmHg)				
	95.9 + 2.5	97.3 + 2.3	91.9 + 3.4	93.8 + 3.3
Pre-FMD Mean Blood Flow (ml/min)				
	23.0 + 2.2	41.4 + 7.3*	22.9 + 2.0	33.3 + 3.8*
Pre-FMD Shear Rate ($s^{-1)}$				
	25.2 + 2.3	41.9 + 5.2*	24.6 + 1.6	34.1 + 2.3*
Pre-FMD Conductance (ml/mmHg/min)				
	0.2 + 0.03	0.4 + 0.08*	0.2 + 0.02	0.3 + 0.04*
Pre-FMD Resistance (mmHg/ml/min)				
	4.6 + 0.3	3.3 + 0.4*	4.4 + 0.4	3.4 + 0.4*
Post-FMD Heart Rate (bpm)				
	58.1 + 2.7	59.0 + 2.9	55.8 + 2.1	57.3 + 2.2
Post-FMD Mean Arterial Pressure (mmHg)				
	96.6 + 2.6	96.5 + 2.7	91.2 + 4.0	94.1 + 3.2
Peak Reactive Hyperemic Blood Flow (ml/min)				
	238.9 + 14.3	276.9 + 23.1*	248.2 + 21.1	293.5 + 24.6*
Peak Shear Rate (s^{-1})				
	256.3 $\pm$ 12.5	286.9 $\pm$ 21.0*	269.1 $\pm$ 19.8	307.6 $\pm$ 15.9*

Post-FMD Conductance (ml/mmHg/min)			
2.5 + 0.1	2.8 + 1.1*	2.8 + 0.2	3.1 + 0.2*
Post-FMD Resistance (mmHg/ml/min)			
0.4 + 0.03	0.4 +0.05	0.4 + 0.03	0.35 + 0.03
Relative Brachial Artery FMD (%)			
3.1 + 0.4	2.1 + 0.4*	5.0 +0.7	3.3 + 0.6*

Values are means + standard error; * Significantly different from Before-IHG exercise Brachial Artery FMD test (main effect for time, $p < 0.05$).