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ORIGINAL ARTICLE

Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives

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Abstract Bilateral isometric handgrip (IHG) training lowers resting arterial blood pressure (BP) in medicated hypertensives. Numerous mechanisms have been suggested, but have yet to be investigated. One such mechanism is that of improved systemic endothelial-dependent vasodilation. The purpose of this investigation was twofold: (1) to determine if Bilateral IHG training had any beneficial effects on endothelial-dependent vasodilation, and (2) to see if improved systemic endothelial-dependent vasodilation was responsible for lowering BP. Sixteen participants performed four, 2 min IHG contractions at 30% of their maximal voluntary effort, using either a Bilateral ($n = 7$) or a Unilateral IHG protocol ($n = 9$), three times per week for 8 weeks. Brachial artery (BA) flow-mediated dilation (FMD, an index of endothelial-dependent vasodilation, measured in both arms) was assessed pre-and post-training. Following Bilateral IHG training, BA FMD improved in both arms (normalized to peak shear rate, 0.005 ± 0.001 to 0.02 ± 0.002 s^{-1}, $P < 0.01$). Following Unilateral IHG training, BA FMD improved in the trained arm only (normalized: 0.009 ± 0.002 to 0.02 ± 0.005 s^{-1}, $P < 0.01$). These findings suggest that although IHG training improves endothelial-dependent vasodilation, the improvements occur only locally in the trained limbs. This suggests that enhanced systemic endothelial-dependent vasodilation is not the mechanism responsible for the observed post-IHG training reductions in BP in medicated hypertensives.

Keywords Endothelium · Exercise · Hypertension · Blood flow

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Introduction

Hypertension is highly prevalent worldwide, and represents 4.5% of the global disease burden (WHO 2003). Hypertension is also associated with endothelial dysfunction, a condition characterized by the reduced formation and/or bioavailability of nitric oxide (NO, a potent vasodilator), causing a subsequent impairment of endothelial-dependent (NO-dependent) vasodilation (Egashira et al. 1995; Higashi et al. 1997; Panza et al. 1990). Potential causes of this phenomenon include: (1) reduced L-arginine concentrations (amino acid required for the synthesis of NO), (2) the down-regulation of the enzyme NO synthase (eNOS, also required for the synthesis of NO), (3) impaired eNOS activation, and (4) increased oxidative stress/reactive oxygen species-induced NO degradation (Faulx et al. 2003; Gielen and Hambrecht 2001; Green et al. 2004; Li and Forstermann 2000; Parnell et al. 2002). Additionally, the increased formation of endothelium-derived constricting factors, such as contractile prostaglandins, may also play a role (Stankevicius et al. 2003).

The benefits of aerobic exercise on the cardiovascular system are well documented. Evidence suggests that aerobic exercise training favorably alters resting arterial blood pressure (BP) (Pescatello et al. 2004) and endothelial function in persons with hypertension (Higashi et al. 1999a; Higashi et al. 1999b). In contrast,

there has been little investigation of the effects of isometric exercise on endothelial dysfunction.

It has been demonstrated that Bilateral isometric handgrip (IHG) training reduces BP in persons medicated for hypertension (Taylor et al. 2003), but the underlying mechanisms remain elusive. Blood pressure is elevated during acute bouts of IHG exercise in young, healthy persons with high-normal resting BP (Wiley et al. 1992) suggesting that increased exposure to systemic shear stress via the pressor response may enhance the release of endothelium-derived NO (Ray and Carrasco 2000; Taylor et al. 2003) and improve endothelial-dependent vasodilation. Improved systemic endothelial function may contribute to a reduction in systemic total peripheral resistance, thus lowering the resting BP. The purpose of this investigation was twofold: (1) to determine if Bilateral IHG training has beneficial effects on endothelial-dependent vasodilation in persons medicated for hypertension, and (2) to investigate the hypothesis, using a Unilateral IHG protocol, that improved systemic endothelial-dependent vasodilation may be responsible for reducing BP in the same population.

Methods and technique

Participants

Participants, who were medicated for hypertension, were recruited from Hamilton, Ontario, Canada, and were randomized to a Bilateral IHG training group or to a Unilateral IHG training group upon written informed consent. Eighteen individuals were recruited to participate; yet two participants in the Bilateral IHG training group did not complete the study due to extenuating circumstances. Participants were not stratified according to their BP or endothelial function status. Individuals were excluded if they had diabetes, congestive heart failure, took hormone supplements and/or regular nitrate medications, and/or were current smokers. Vasoactive medications (including cholesterol medications), external exercise sessions and nutritional habits were monitored and controlled 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 participant characteristics are described in Table 1. The Research Ethics Board of Hamilton Health Sciences/McMaster University approved the investigation and the procedures were followed in accordance with institutional guidelines.

Study design

Prior to baseline measurements, BP was measured in all participants according to the protocol described below, to habituate them to the testing environment and to minimize the potential for white coat hypertension (Pickering 2002). All participants underwent identical measurement procedures before and after the intervention to determine resting BP, brachial artery diameter and vascular reactivity. Diameter and vascular reactivity measurements were obtained first from the left arm, then from the right arm. Fasting lipid levels were measured due to the effects of cholesterol-lowering on endothelial function (Koh 2000; Tsiara et al. 2003). All assessments of BP and vascular reactivity were conducted in a quiet, dark, temperature-controlled room (20–23°C) following a 4 h fast whereby the last meal was standardized across all testing time points, a 12 h abstinence from caffeine, and a 24 h abstinence from vigorous exercise. All post-testing took place the week following the last IHG training session, was conducted within 2 h of initial pre-testing time of day, and the time of medication ingestion was standardized. Blood sampling occurred on a separate day 12 h post-prandial (Corretti et al. 2002).

Exercise training protocol

Participants randomized to the Bilateral IHG training group performed four sets of 2 min IHG contractions on a programmed handgrip dynamometer (IBX H-101, MD Systems Inc., Westerville, OH, USA) at 30% of their maximal voluntary contraction (MVC, determined at the onset of each exercise session via electronic linear load cells contained within each IHG device) using alternate hands. Each contraction was separated by a 1 min rest period, thus there were 4 min of rest between contractions performed by the same arm. Participants randomized to the Unilateral IHG training group completed four sets of 2 min IHG contractions with their non-dominant hand using a programmed handgrip dynamometer (IBX H-101, MD Systems Inc., Westerville, OH, USA). Contractions were performed at 30% MVC and each contraction was separated by a 4 min rest period.

All participants trained three times per week for 8 weeks, where two IHG training sessions per week took place under the direct supervision of an exercise trainer at the Centre for Health Promotion and Rehabilitation at McMaster University in Hamilton, Ontario, Canada, and the third session took place at home. Participants were provided with detailed instructions to ensure proper at-home training, and

Table 1 Baseline characteristics

Characteristic	Bilateral IHG group ($n = 7$)	Unilateral IHG group ($n = 9$)
Age (years)	61.7 ± 4.2	66.1 ± 6.3
Sex		
Men	5	7
Women	2	2
Height (cm)	176.2 ± 5.2	169.6 ± 9.5
Weight (kg)	85.9 ± 5.8	80.0 ± 7.6
Established coronary artery disease (#)	4	2
Resting systolic arterial blood pressure (kPa, mmHg)	17.8 ± 0.7 (133.9 ± 5.0)	18.9 ± 0.5 (141.6 ± 3.8)
Resting diastolic arterial blood pressure (kPa, mmHg)	9.8 ± 0.4 (73.2 ± 3.2)	10.6 ± 0.5 (79.6 ± 3.8)
Medication classification(#)[a]		
ACE inhibitor	1	3
ACE inhibitor + beta blocker	2	0
ACE inhibitor + beta blocker + diuretic	0	2
ACE inhibitor + diuretic	0	1
ACE inhibitor + calcium channel blocker	0	2
Calcium channel blocker	0	1
Calcium channel blocker + diuretic	1	0
Diuretic + angiotensin II antagonist	1	0
ACE inhibitor + beta blocker + calcium channel blocker	1	0
Calcium channel blocker + beta blocker + diuretic	1	0
Plasma lipids (mmol l^{-1})		
Total cholesterol	4.6 ± 0.6	4.5 ± 0.3
High-density lipoprotein cholesterol	1.1 ± 0.06	1.3 ± 0.1
Low-density lipoprotein cholesterol	2.6 ± 0.4	2.5 ± 0.3

Values are means ± SD unless otherwise stated

[a] Medications had been stable for at least 2 months

were also instructed to record their exercise, nutritional and medication data in their exercise log books.

Fasting lipid measurements

Prior to and following the intervention period, fasting total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were measured in all participants using previously described methods (Nazir et al. 1999). For each participant, blood samples were collected in two separate blood collection tubes: (1) heparin coated and (2) additive free. Blood collected in the additive free tubes was allowed to clot at room temperature for 30 min. To separate serum or plasma, tubes were centrifuged at 4,500 rpm for 5 min at 277 K (4°C). All serum and plasma samples were analyzed in duplicate, in the Clinical Chemistry Laboratory at McMaster University.

Resting BP measurements

Resting supine BP was measured in the right brachial artery using automated brachial oscillometry (CBM-7000, Colin Medical Instruments, San Antonio, USA) following 10 min of supine rest. As seated and supine BP measurements are similar in elder individuals, supine BP was measured to better control body position and promote relaxation (Pickering 2002). Participants rested with the right arm in the anatomical position, at heart level. The BP cuff (adult size 25–35 cm arm circumference) was placed approximately 2.5 cm proximal to the antecubital fossa (PAHI 2003). Three BP measures were obtained by the same trained investigator 12, 14 and 16 min after the start of the resting period, and then averaged.

Resting and reactive hyperemic brachial artery diameters and blood velocity acquisition

High-resolution ultrasound (System FiVe, GE Vingmed Ultrasound, Horten, Norway) was used for acquiring resting brachial artery diameter and blood velocity, using a previously described protocol (Rakobowchuk et al. 2005). Heart rate was continuously monitored from two sets of three electrodes positioned on the chest (Cardiomatic MSC 7123, Medical Systems Corp, Miami, FL, USA) to generate ECG-gated ultrasound images and blood velocity samples.

Following resting measures, brachial artery vascular reactivity and flow-mediated dilation (FMD, an index of endothelial-dependent vasodilation) were assessed using Doppler ultrasound, by inducing reactive

hyperemia using a forearm occlusion cuff (SC12D, Hokanson, Bellvue, WA, USA), as described earlier (Rakobowchuk et al. 2005) and according to published guidelines (Corretti et al. 2002). In brief, a forearm cuff was inflated to 27 kPa (200 mmHg), or at least 7 kPa (50 mmHg) above systolic BP for 5 min.

Measurement protocol

All blood velocity measures were collected at a pulse wave frequency of 4.0 MHz, a velocity range gate of 500 cm s^{-1}, and a sample volume that captured the entire blood vessel. Measurements were analyzed using Chart 5 for Windows (Powerlab ML 795, AD Instruments, Colorado Springs, CO, USA), after correcting for angle of insonation (all $\leq 68°$). Resting and post-reactive hyperemia blood velocity samples were used to calculate resting and peak reactive hyperemic blood flow, where 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). Resting and peak reactive hyperemic blood flows were calculated as the product of their respective MBV and resting BA cross-sectional area.

Resting and post-FMD brachial artery images were obtained from the same portion of the brachial artery using anatomic landmarking. To ensure accurate anatomic landmarking and comparisons over time, images from the pre-testing session were displayed to the ultrasonographer at the post-testing session. Off-line measurements of brachial artery diameters were made by the same ultrasonographer, using custom-designed, automated edge-detection software, to minimize observer bias and in accordance with published procedures (Artery Measurement System (AMS) II version 1.133, Chalmers, Sweden) (Rakobowchuk et al. 2005). The intra-observer reproducibility of brachial artery FMD assessed by this ultrasonographer in persons medicated for hypertension is: 3.0% (coefficient of variation), 5.3% (method error), and 0.98 (correlation coefficient). Diameters were expressed as a percent increase of the baseline value of the diameter (Corretti et al. 2002), then were normalized to the peak shear rate experienced in response to the FMD stimulus using previously described methods (Rakobowchuk et al. 2005).

Statistical analysis

Lipid series and BP data were analyzed using one-way analysis of variance (time) with repeated measures. Vascular reactivity data were analyzed using one-way analysis of variance (time) with repeated measures (Bilateral IHG group) and two-way (arm × time) analysis of variance with repeated measures (Unilateral IHG group). Tukey post hoc procedures were used to evaluate specific differences between means, wherever applicable. All data were analyzed using STATISTICA (version 6.0), and an alpha level of ≤ 0.05 was considered statistically significant. Data were presented as means ± standard error, unless otherwise specified.

Results

Effects of IHG training on fasting lipid series

Vasoactive and cholesterol medications remained constant throughout the investigation in all participants. Total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol values remained unchanged from baseline following Bilateral IHG training and Unilateral IHG training (all $P > 0.05$).

Effects of IHG training on resting BP

Systolic BP was significantly reduced following 8 weeks of Bilateral IHG training (pre-: 17.8 ± 0.7 kPa [133.9 ± 5.0 mmHg] to post-: 15.8 ± 0.5 kPa [118.5 ± 4.0 mmHg]), and Unilateral IHG training (pre-: 18.9 ± 0.5 kPa [141.6 ± 3.8 mmHg] to post-: 17.6 ± 0.6 kPa [132.4 ± 4.4 mmHg] all $P \leq 0.05$). Diastolic BP remained unchanged from baseline after both interventions (Bilateral IHG training, pre-: 9.8 ± 0.4 kPa [73.2 ± 3.2 mmHg] to post-: 9.0 ± 0.4 kPa [67.2 ± 3.4 mmHg]; Unilateral IHG training, pre-: 10.6 ± 0.5 kPa [79.6 ± 3.8 mmHg] to post-: 10.1 ± 0.4 kPa [76.0 ± 3.1 mmHg] all $P \geq 0.05$).

Effects of IHG training on vascular reactivity

Endothelial-dependent vasodilation

Significant improvements in relative (1.5 ± 0.3 to 4.4 ± 0.6%, $P < 0.01$) and normalized FMD (Fig. 1) were noted following Bilateral IHG training. Following Unilateral IHG training, improvements in relative (exercised-: 2.4 ± 0.4 to 6.6 ± 1.2 %) and normalized FMD (Fig. 2) were only noted in the trained arm (non-trained arm: 2.3 ± 0.5 to 2.5 ± 0.5% and Fig. 2, respectively). Resting brachial artery diameters remained unchanged following Bilateral IHG training, yet decreased following Unilateral IHG training (Tables 2, 3).

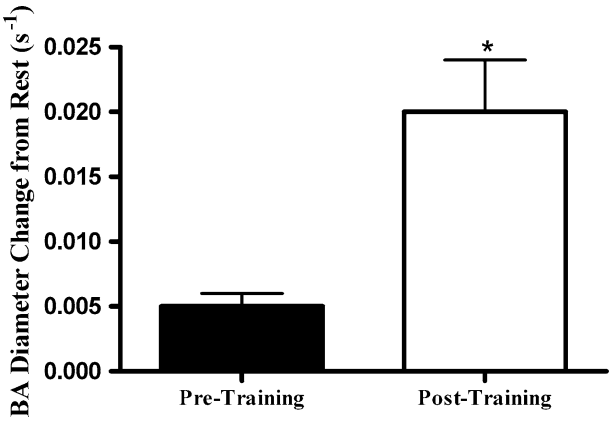

Fig. 1 Post-occlusion brachial artery diameter change from rest normalized to peak shear rate following Bilateral IHG training. * Significantly different from pre-training ($P < 0.01$)

Resting and reactive hyperemic blood flow

Resting blood flow, peak reactive hyperemic blood flow, peak shear rate, resting diameter and FMD (relative and normalized to peak shear rate) in the left and right brachial arteries were not significantly different from each other at baseline, in either the Bilateral IHG or Unilateral IHG training groups (all $P \geq 0.05$). To determine the general effects of IHG training on endothelial-dependent vasodilation and its associated hemodynamic parameters, left and right brachial artery data were collapsed for subsequent analysis in the Bilateral IHG training group. Following Bilateral IHG training, a main effect for time was observed in peak reactive hyperemic blood flow and peak shear rate (Table 2), where both variables were significantly lower following IHG training than at baseline. Similar observations were made following Unilateral IHG training, whereby a main effect for time was observed in peak reactive hyperemic blood flow (Table 3), although peak shear rate remained unchanged. Neither resting blood flow nor resting shear rate differed from pre-training following either Bilateral or Unilateral IHG training (Tables 2, 3).

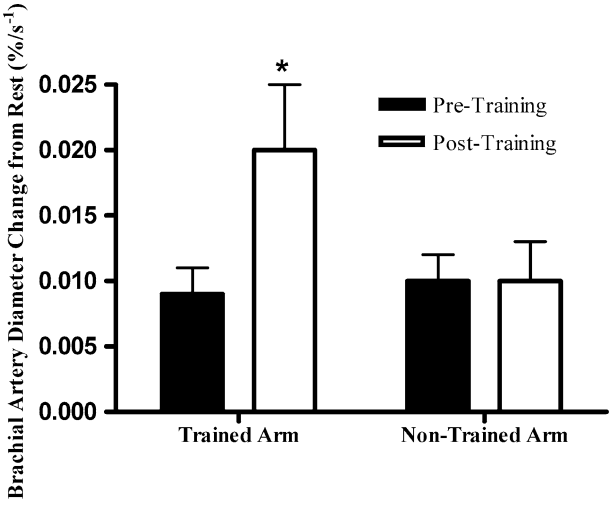

Fig. 2 Post-occlusion brachial artery diameter change from rest normalized to peak shear rate following Unilateral IHG training. * significantly different from pre-training ($P < 0.01$)

Table 2 Vascular characteristics following Bilateral IHG training

Variable	Bilateral IHG group ($n = 7$)	
	Pre-training	Post-training
Resting blood flow (ml min^{-1})	43.3 ± 5.8	44.9 ± 8.6
Resting shear rate (s^{-1})	38.4 ± 3.3	38.9 ± 4.3
Peak reactive hyperemic blood flow (ml min^{-1})	353.0 ± 38.1	263.3 ± 28.7*
Peak shear rate (s^{-1})	314.2 ± 20.1	249.5 ± 21.2*
Resting brachial artery diameter (cm)	0.44 ± 0.02	0.44 ± 0.02

Values are means ± standard error unless otherwise stated

* Significantly different from pre-training (main effect for time, $P < 0.01$)

Discussion

IHG training reduces BP in persons medicated for hypertension, yet mechanisms responsible for the reductions remain elusive. Improved systemic endothelial-dependent vasodilation was thought to contribute to a reduction in post-training total peripheral resistance, thus lowering BP. To our knowledge, this is the first study to demonstrate that 8 weeks of IHG training produce profound improvements in endothelial-dependent vasodilation in persons medicated for hypertension, and that these improvements only occur in the trained limb. Taken together, this suggests that improved systemic endothelial-dependent vasodilation is likely not the mechanism responsible for improved post-IHG training BP reductions in persons medicated for hypertension.

Effects of IHG training on vascular reactivity

Brachial artery FMD has become a popular non-invasive method to measure shear stress induced endothelial-dependent vasodilation following a period of ischemic forearm occlusion (Corretti et al. 2002; Faulx et al. 2003). In the present study, the ischemic stimulus was induced downstream from the brachial artery to

Table 3 Vascular reactivity following Unilateral IHG training

Variable	Trained arm ($n = 9$)		Untrained arm ($n = 9$)	
	Pre-training	Post-training	Pre-training	Post-training
Resting blood flow (ml min^{-1})	31.0 ± 4.7	26.5 ± 3.8	34.5 ± 4.3	30.8 ± 5.1
Resting shear rate (s^{-1})	44.5 ± 10.9	42.8 ± 11.5	36.0 ± 6.0	40.6 ± 7.8
Peak reactive hyperemic blood flow (ml min^{-1})	260.9 ± 31.5	215.2 ± 24.0*	292.0 ± 28.5	256.0 ± 26.1*
Peak shear rate (s^{-1})	335.7 ± 56.6	308.3 ± 50.8	295.0 ± 25.6	279.4 ± 36.1
Resting brachial artery diameter (cm)	0.42 ± 0.03	0.40 ± 0.02*	0.44 ± 0.02	0.44 ± 0.02*

Values are means ± standard error unless otherwise stated

* Significantly different from pre-training (main effect for time, $P < 0.05$)

minimize the direct effects of ischemia on that vessel. Following cuff release, the forearm blood flow was augmented by dilating distal vascular beds, thus inducing a shear stress stimulus through the brachial artery (Corretti et al. 2002). Although the precise mechanism(s) associated with post-occlusion vasodilation are not completely understood, it is purported that the shear stress stimulus provokes the release of endothelium-derived NO, a potent vasodilator. The resulting vasodilation can be quantified as an index of endothelial-dependent vascular function (Corretti et al. 2002). In the current investigation, relative measures of FMD were normalized to peak shear rate to eliminate the impact of stimulus variability on FMD response (Pyke et al. 2004). This was particularly important as peak reactive hyperemic blood flow was decreased following both Bilateral and Unilateral IHG training despite improvements in normalized FMD. The observation of reduced peak reactive hyperemic blood flow following the unilateral protocol suggests the occurrence of neurally-driven, cross-education or cross transfer strength adaptations that influence vascular flow (Farthing and Chilibeck 2003; Yasuda and Miyamura 1983).

In either training situation, higher peak reactive hyperemic blood flow responses at baseline may have resulted from an increased accumulation of metabolites (e.g., lactic acid) in response to the ischemic challenge. Following 8 weeks of IHG training, a better balance may exist between aerobic and anaerobic metabolism, contributing to a reduction in metabolite production in response to the same ischemic stimulus (Sinoway et al. 1996), thereby resulting in less demand for blood flow to the forearm tissues following cuff release. Moreover, it is possible that following training, less compressive force was exerted by the occlusion cuff on the vessels despite being inflated to the same absolute pressure, allowing for greater perfusion and oxygen supply during occlusion, and resulting in a reduced flow stimulus (Hunter et al. 2006). Alternatively, the reductions in post-training peak reactive hyperemic blood flow may be attributed to changes in vascular smooth muscle function or to underlying changes in vascular structure. We do not have data to support or refute the first contention, yet we consider the latter unlikely, as recent observations from our laboratory suggest that IHG training does not alter BA compliance or endothelial-independent vasodilation in persons medicated for hypertension (McGowan 2006; Visocchi et al. 2004).

Our findings of local improvements in FMD following Unilateral IHG training are consistent with those of Hornig et al. (1996), who showed improved endothelial function in the trained arm of persons with congestive heart failure following rhythmic handgrip training. In contrast to the suggestion that the pressor response induced during IHG exercise elicits systemic increases in shear stress (Ray and Carrasco 2000; Taylor et al. 2003), the localized improvement in endothelial-dependent vasodilation suggests that shear stress increases were restricted to the vascular bed of the exercising arm. Other mechanisms may have been responsible however for improving local endothelial-dependent vasodilation, including enhanced endothelial-independent vasodilation and underlying changes in vascular structure. Again, although we do not have data from the current investigation to support or refute these suggestions, we consider this unlikely as observations from our laboratory suggest that IHG training does not alter BA compliance (Visocchi et al. 2004) or endothelial-independent vasodilation (McGowan 2006) in persons medicated for hypertension.

Unlike the Bilateral IHG protocol, Unilateral IHG training elicited a reduction in resting brachial artery diameter in both the trained and untrained arms. Although the reductions were statistically significant, the changes in brachial artery diameter were small and primarily affected the trained arm, and one might expect to see similar changes following Bilateral IHG training where both limbs are exercised. The observed reductions in resting brachial artery diameter following

Unilateral IHG training, although statistically meaningful, do fall near or within the range in normal day-to-day variability of resting BA diameter (Shoemaker et al. 1996).

Although we interpret our findings to suggest that improved systemic endothelial-dependent vasodilation is not responsible for reducing systolic BP following IHG training in persons medicated for hypertension, it is important to note that FMD assesses the response of the NO-vasodilator system to maximal increases in shear stress. In the current investigations, it is possible that an increase in the resting capacity of the NO-dilator system to produce, release and/or utilize NO may have contributed to the post-training reductions in systolic BP. These improvements would not have been captured by the FMD measurement technique. Likewise, it is possible that the reactive hyperemic stimulus may have contributed to the release of other vasodilatory substances, including prostacyclin and ischemic metabolites (Eskurza et al. 2001). If these factors were altered in either arm following training, NO-mediated improvements in FMD may have been obscured, thus influencing our assessment of endothelial function. Other possible contributing mechanisms include alterations in central arterial compliance and/or baroreceptor function, autonomic function and cardiac output.

The results of this investigation are noteworthy, but we do acknowledge some limitations. First, participants of the current investigation were medicated for hypertension, and some anti-hypertensive medications are known to influence endothelial function (ACE inhibitors, calcium channel blockers) (Lind et al. 2000; Spieker et al. 2000). To account for this, all medications (including lipid-lowering, endothelial function-enhancing medications) were strictly monitored throughout each investigation and all measurement techniques were performed at a standardized time from medication ingestion. However, it should be noted that this might be considered as the strength of the current investigation, as it is representative of persons living with hypertension in the general population. Second, the authors acknowledge that brachial artery FMD measures the dilatory response of the artery to a maximal stimulus. Future studies should aim to include measures of assymetric dimethylarginine (an inhibitor of the enzyme nitric oxide synthase, eNOS), endothelin-1, renin, central efferent sympathetic outflow, and/or the dilatory response to N^G-mono-methyl-L-arginine (L-NMMA, an eNOS inhibitor). Despite these potential confounders, this small-scale investigation was a notable attempt to conduct a mechanistic study in a cohort of medicated hypertensives representative of the larger clinical population. At present, the impact in a large population intervention is unknown. Investigation of the long-term effects of IHG training and/or adherence to the treatment regiment are of great importance.

Conclusions

Hypertension is a major health threat worldwide. IHG training lowers resting BP in persons medicated for hypertension, yet the mechanisms remain elusive. Research is needed to determine the mechanisms for BP changes in order to optimize and generalize the application of this form of exercise. IHG training could be an important addition to the pharmacologic management of hypertension, and may potentially reduce stroke, coronary artery disease and mortality.

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