

Isometric exercise training lowers resting blood pressure and improves local brachial artery flow-mediated dilation equally in men and women

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Abstract

Introduction Isometric resistance training has repeatedly shown to be an effective exercise modality in lowering resting blood pressure (BP), yet associated mechanisms and sex differences in the response to training remain unclear. Exploration into potential sex differences in the response to isometric resistance training is necessary, as it may allow for more optimal and sex-based exercise prescription, thereby maximizing the efficacy of the training intervention.

Purpose Therefore, we investigated, in normotensives, whether sex differences exist in the response to isometric handgrip (IHG) training.

Methods Resting BP and endothelium-dependent vasodilation (brachial artery flow-mediated dilation; FMD) were assessed in 11 women (23 ± 4 years) and 9 men (21 ± 2 years) prior to and following 8 weeks of IHG training (four, 2-min unilateral contractions at 30 % of maximal voluntary contraction; 3 days per week).

Results Main effects of time were observed (all $P < 0.05$), whereby IHG training reduced systolic BP ($\Delta 8 \pm 6$ mmHg), diastolic BP ($\Delta 2 \pm 3$ mmHg), mean

arterial pressure ($\Delta 4 \pm 3$ mmHg), and pulse pressure ($\Delta 5 \pm 7$ mmHg), accompanied by increases in absolute ($\Delta 0.09 \pm 0.15$ mm) and relative ($\Delta 2.4 \pm 4.1$ %) brachial artery FMD; however, no significant sex differences were observed in the magnitude of post-training change in any variable assessed (all $P > 0.05$).

Conclusion IHG training effectively lowers resting BP and improves endothelium-dependent vasodilation in men and women, without significant sex differences in the magnitude of response.

Keywords Isometric exercise training · Resting blood pressure · Endothelium-dependent vasodilation · Flow-mediated dilation · Sex differences · Hypertension

Abbreviations

AMS	Artery measurement system
BP	Blood pressure
DICOM	Digital imaging and communications in medicine
FMD	Flow mediated dilation
HR	Heart rate
IHG	Isometric handgrip
MVC	Maximal voluntary contraction
ROI	Region of interest
SD	Standard deviation

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Introduction

Exercise training represents a widely recommended component in the treatment and prevention of high blood pressure (BP) (Pescatello et al. 2004). Indeed, aerobic exercise training has consistently proven to effectively reduce resting and ambulatory BP (Pescatello et al. 2004). More

recently, a large and emerging body of evidence supports isometric resistance training as an effective exercise modality to lower resting BP in both normotensive and hypertensive populations (Wiley et al. 1992; Ray and Carrasco 2000; Howden et al. 2002; Taylor et al. 2003; Peters et al. 2006; McGowan et al. 2007a, b; Millar et al. 2008; Devereux et al. 2010; Wiles et al. 2010; Baross et al. 2012; Millar et al. 2013; Badrov et al. 2013a, b; Gill et al. 2015). Two recent meta-analyses suggest that isometric resistance training may be capable of eliciting greater BP reductions than traditional aerobic and resistance exercise training (Cornelissen and Smart 2013; Carlson et al. 2014). Based on this accumulating evidence, the American Heart Association suggests that isometric resistance training, and in particular, isometric handgrip (IHG) training, may be used as a potential alternative strategy to lower resting BP (Class IIB, Level of Evidence C; Brook et al. 2013).

An important and overlooked consideration is whether sex differences exist in the magnitude of BP attenuation that occurs following isometric resistance training. While differences between men and women in several aspects of BP control are well established (Hart et al. 2012), limited data exists pertaining to the effect of sex on the hypotensive response to exercise training. In the aerobic and resistance training literature, some evidence suggests that BP decreases similarly in men and women (Ishikawa et al. 1999; Kelley et al. 2001; Cornelissen and Smart 2013), while other data shows that women may respond with greater reductions (Hagberg et al. 2000; Collier et al. 2011; Morita and Okita 2013). In the isometric resistance training literature, early exploratory evidence suggests that older normotensive women may be more responsive to the IHG stimulus than older men (Millar et al. 2008), while a recent systematic review and meta-analysis observed a non-significant trend towards larger reductions in men (Inder et al. 2016). Furthermore, the associated mechanisms responsible for the hypotensive response remain elusive and are likely to differ across populations, including sex (Millar et al. 2014).

To date, the influence of sex on the response to IHG training has yet to be directly nor prospectively investigated. Examination of potential sex differences in the response to IHG training is required as it may allow for more optimized and sex-based exercise prescription, thereby maximizing the efficacy of the training intervention. Therefore, we explored potential sex differences in the BP lowering effects of, and peripheral vascular adaptations (endothelium-dependent vasodilation) to, IHG training in young normotensives. We hypothesized that women would experience greater post-IHG training BP reductions in comparison to men (Millar et al. 2008), concomitant with greater improvements in endothelium-dependent vasodilation.

Methods

Participants

Twenty normotensive (<140/<90 mmHg) women ($n = 11$) and men ($n = 9$) participated in the current investigation. Women were aged 23 ± 4 years and were 165 ± 5 cm in height and 58 ± 6 kg in weight (Body mass index = 21 ± 2 kg m⁻²). Men were aged 21 ± 2 years and were 179 ± 8 cm in height and 77 ± 12 kg in weight (Body mass index = 24 ± 2 kg m⁻²). All participants were recreationally active (\geq two exercise sessions per week), non-smoking, and free of any overt disease (established via a standardized health questionnaire). Women were tested during the early follicular phase of their menstrual cycle (if not on oral contraceptives) or low hormone phase (if on oral contraception) at all time points. No changes in diet, exercise, or medication use occurred during the study period.

The investigation was cleared by the University of Windsor Research Ethics Board and all procedures were performed in accordance with the Declaration of Helsinki. All participants provided informed written consent and were familiarized to all testing protocols prior to study participation.

Experimental design

This study utilized a prospective cohort design. Participants completed a laboratory testing session to assess resting BP and heart rate (HR), and endothelium-dependent vasodilation. This laboratory testing session was repeated following 8 weeks of IHG training.

Isometric handgrip training

Participants trained 3 days per week for 8 weeks. IHG exercise was performed using a programmed handgrip dynamometer (IBX H-101, MD Systems, Inc., Westerville, Ohio, USA). Each exercise session consisted of four, 2-min unilateral contractions at 30 % of maximal voluntary contraction (MVC; determined at the start of each exercise session via electronic linear load cells contained within each handgrip device). All exercise was performed using the non-dominant hand and each contraction was separated by a 4-min rest period.

Experimental measures

All testing was conducted in a quiet, darkened, and temperature-controlled laboratory (20–24 °C) following at least a 4-h fast, a 12-h abstinence from caffeine and other

stimulants, and a 24-h abstinence from exercise and alcohol. Participants voided their bladder prior to testing commencement. All repeat testing (i.e., following 8 weeks of IHG training) was conducted within 2 h of the initial baseline testing time of day.

Resting blood pressure

Resting BP was measured in the seated position in the brachial artery of the dominant arm using automated brachial oscillometry (Dinamap CareScope v100, Critikon, Tampa, FL, USA). Four BP and HR measurements, each separated by 2 min, were obtained following 10 min of seated rest. The latter three measures were averaged and used in the final analysis.

Endothelium-dependent vasodilation

Endothelium-dependent vasodilation was assessed using brachial artery flow-mediated dilation (FMD; Celermajer et al. 1992), in accordance with published guidelines (Harris et al. 2010; Thijssen et al. 2011). Participants rested in the seated position with their non-dominant arm extended at heart level and fitted with a pneumatic cuff (Hokanson SC12D, D.E. Hokanson, Inc., Bellevue, Washington, USA) 2–4 cm distal to the antecubital fossa. A 13-MHz linear array probe attached to a high-resolution Doppler ultrasound machine (Vivid *i*, GE Healthcare, Pittsburgh, PA, USA) was used to image the brachial artery approximately 3–5 cm proximal to the antecubital fossa. Simultaneous B-mode images and continuous Doppler were obtained for the determination of brachial artery diameter and blood velocity, respectively. All recordings were obtained using an insonation angle of 60° and a sample volume spanning the entire width of the brachial artery, but kept clear of the vessel walls. HR was continuously obtained from two sets of three electrodes on the chest to generate ECG-gated ultrasound images and blood velocity samples. Following 20 min of seated rest, baseline resting measures assessing brachial artery diameter and blood velocity were acquired for 1-min. Upon completion of baseline resting measures, the pneumatic cuff was inflated via a rapid cuff inflator (Hokanson E20 Cuff Inflator, D.E. Hokanson, Inc., Bellevue, Washington, USA) to a pressure above systolic BP (~200 mmHg) for 5 min, which provided the ischemic stimulus responsible for reactive hyperemia and subsequent FMD. Measures of brachial artery diameter and blood velocity were acquired 30 s prior to cuff deflation and continued for 5 min post-deflation.

Resting and reactive hyperemic brachial artery images were saved at end-diastole in Digital Imaging and Communications in Medicine (DICOM) format for off-line analysis. Individual end-diastolic frames were stacked and saved in a new digital DICOM file using DICOM editing software

(Sante DICOM Editor, Version 3.0.12; Santesoft LTD, Athens, Greece). Brachial artery diameters were analyzed by the same trained investigator using semi-automated edge detection software (Artery Measurement System (AMS) v2, Image and Data Analysis, Gothenburg, Sweden). Briefly, a region of interest (ROI) was chosen to include both the near and far wall of the brachial artery. Brachial artery diameter was determined from leading edge to leading edge throughout the subsequent frames of the DICOM file. The AMS software performs approximately 100 diameter measures within the selected ROI to determine a mean brachial artery diameter for each frame of the DICOM file. If necessary, the investigator could manually correct the chosen borders. Mean blood velocity was analyzed from the continuous Doppler mode spectra. All brachial artery diameter and mean blood velocity measures were analyzed using 3-s average time-bins.

From the synchronized brachial artery diameter and blood velocity data, blood flow (product of blood vessel cross-sectional area and mean blood velocity) and shear rate (eight times mean blood velocity divided by blood vessel diameter) were calculated. Brachial artery FMD is reported as the absolute (mm) and relative (%) diameter change from baseline.

Statistical analysis

All data were analyzed using two-way analyses of variance with repeated measures to test for the effects of sex (men vs. women) and time (pre- vs. post-). Shapiro-Wilk tests were used to assess for normality of all variables, with non-normally distributed data undergoing logarithmic transformation. When required, Tukey's post hoc procedures were used to evaluate specific differences between means. Estimates of effect size are provided as Cohen's *d* values ($d = 0.2$, small effect; $d = 0.5$, medium effect; $d = 0.8$, large effect; Cohen 1992). All statistical analyses were performed using SigmaPlot 12.0 (Systat Software, San Jose, CA, USA) and the significance level was set at $P < 0.05$. Data are presented as mean \pm SD.

Results

All participants adhered to the exercise prescription, completing all 24 exercise sessions over the 8-week training period. As expected, at baseline, women had significantly lower height, weight, body mass index, systolic BP, and pulse pressure in comparison to men (all $P < 0.05$). Furthermore, at baseline, women had lower resting and peak brachial blood flow and a smaller brachial artery diameter (all $P < 0.05$). There were no significant differences between men and women in any other baseline characteristic. IHG training had no effect on MVC strength in either

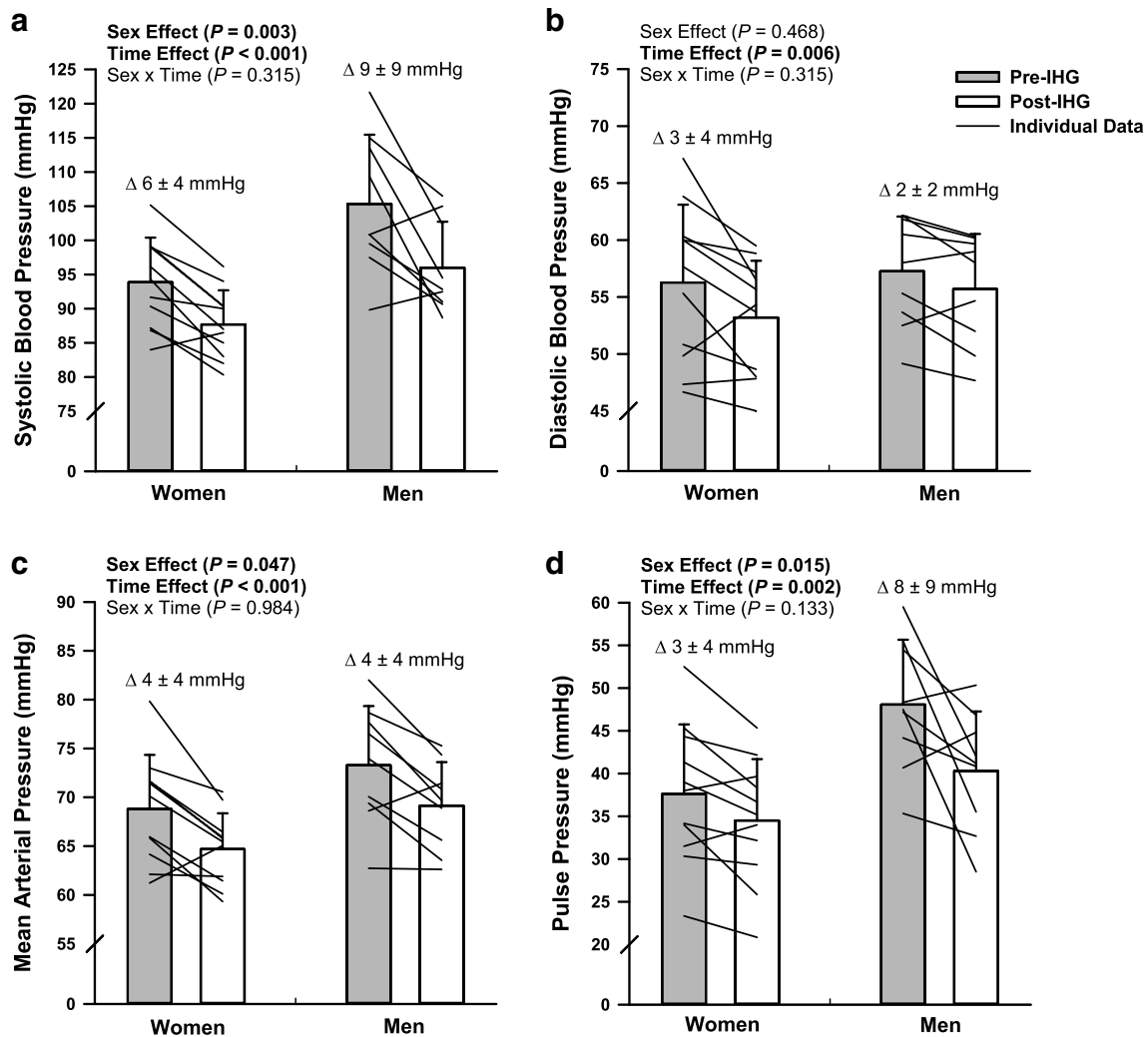


Fig. 1 Effects of 8-weeks of isometric handgrip (IHG) training on **a** systolic blood pressure, **b** diastolic blood pressure, **c** mean arterial pressure, and **d** pulse pressure in men and women. Values are mean \pm SD

women (22.1 ± 4.3 to 23.3 ± 6.3 kg; $P > 0.05$, $d = 0.22$) or men (37.5 ± 8.0 to 40.9 ± 10.8 kg; $P > 0.05$, $d = 0.36$).

Effects of IHG training on resting blood pressure

Analysis of resting BP revealed no sex differences in the magnitude of change following IHG training (all sex \times time interactions, $P > 0.05$). However, significant main effects of time were observed, whereby IHG training significantly lowered resting systolic BP ($P < 0.001$; Women: $\Delta 6 \pm 4$ mmHg, $d = 1.08$; Men: $\Delta 9 \pm 9$ mmHg, $d = 1.11$), diastolic BP ($P < 0.01$; Women: $\Delta 3 \pm 4$ mmHg, $d = 0.52$; Men: $\Delta 2 \pm 2$ mmHg, $d = 0.32$), mean arterial pressure ($P < 0.001$; Women: $\Delta 4 \pm 4$ mmHg, $d = 0.90$; Men: $\Delta 4 \pm 4$ mmHg, $d = 0.79$), and pulse pressure ($P < 0.01$; Women: $\Delta 3 \pm 4$ mmHg, $d = 0.41$; Men: $\Delta 8 \pm 9$ mmHg, $d = 1.07$) (Fig. 1).

Effects of IHG training on endothelium-dependent vasodilation

Analysis of brachial artery FMD revealed no significant sex \times time interactions for absolute or relative brachial artery FMD (all $P > 0.05$). However, significant main effects of time were observed, whereby IHG training significantly improved absolute ($P < 0.05$; Women: $\Delta 0.09 \pm 0.11$ mm, $d = 0.72$; Men: $\Delta 0.08 \pm 0.20$ mm, $d = 0.57$) and relative ($P < 0.05$; Women: $\Delta 2.8 \pm 3.7$ %, $d = 0.68$; Men: $\Delta 1.9 \pm 4.7$ %, $d = 0.59$) brachial artery FMD (Fig. 2). Resting vascular and vascular reactivity characteristics are presented in Table 1. No sex differences or changes were observed in resting brachial artery diameter, resting blood flow, or resting and peak shear rate following IHG training (all $P > 0.05$). However, a main effect of time was observed for peak reactive hyperemic blood

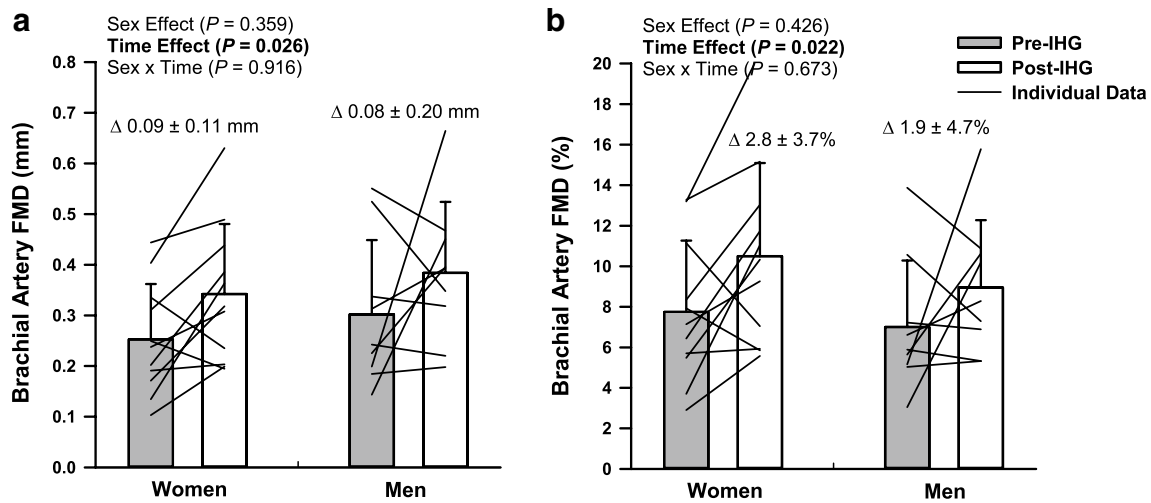


Fig. 2 Effects of 8-weeks of isometric handgrip (IHG) training on **a** absolute (mm) and **b** relative (%) brachial artery flow-mediated dilation (FMD) in men and women. Values are mean \pm SD

Table 1 Resting vascular and vascular reactivity characteristics pre- and post-IHG training

	Pre-IHG	Post-IHG
Resting BA diameter (mm)		
Women	3.32 \pm 0.33	3.31 \pm 0.26
Men	4.30 \pm 0.47	4.30 \pm 0.39
Resting blood flow (mL min ⁻¹)		
Women	40.1 \pm 19.5	41.3 \pm 25.0
Men	81.5 \pm 49.9	98.7 \pm 83.2
Resting shear rate (s ⁻¹)		
Women	184.9 \pm 72.3	201.7 \pm 131.0
Men	170.5 \pm 98.4	194.8 \pm 139.8
Peak blood flow (mL min ⁻¹)		
Women	245.9 \pm 43.4	309.0 \pm 48.6
Men	482.9 \pm 161.6	546.8 \pm 179.9
Peak shear rate (s ⁻¹)		
Women	1269.5 \pm 252.2	1431.2 \pm 299.2
Men	1038.3 \pm 336.4	1008.13 \pm 152.3
Shear rate AUC (AU)		
Women	37330.4 \pm 13982.1	39888.9 \pm 14306.0
Men	30337.5 \pm 16141.4	26058.6 \pm 7517.7
Time to peak dilation (s)		
Women	54.6 \pm 22.5	48.5 \pm 7.6
Men	57.7 \pm 15.3	57.2 \pm 16.4

Values are mean \pm SD. No significant sex \times time interactions were found for any variable assessed (all $P > 0.05$). Effects of sex were found for resting BA diameter, resting blood flow, and peak blood flow (all $P < 0.05$). An effect of time was found for peak blood flow ($P < 0.05$)

IHG isometric handgrip, *BA* brachial artery, *AUC* area under the curve, *AU* arbitrary units

flow, which increased following IHG training ($P < 0.05$; Women: $\Delta 63.1 \pm 66.5$ mL min⁻¹, $d = 1.37$; Men: $\Delta 64.0 \pm 185.2$ mL min⁻¹, $d = 0.38$); however, no difference between sexes in the magnitude of improvement existed ($P > 0.05$).

Discussion

To date, the majority of IHG training research has sampled combined populations of men and women without direct investigation into potential sex differences. To our knowledge, this is the first study to directly and prospectively assess differences between men and women in the effects of IHG training on resting BP and endothelium-dependent vasodilation, a potential mechanism involved in the BP change. Our results suggest that IHG training effectively lowers resting BP in both men and women, without sex differences in the magnitude of attenuation. Furthermore, exploration into potential mechanisms responsible revealed improvements in endothelium-dependent vasodilation, without significant differences between men and women.

Effects of IHG training on resting blood pressure

We found no differences between men and women in the magnitude of resting BP reduction following IHG training in our young, normotensive population. However, significant effects of IHG training were observed, whereby all indices of resting BP were lowered significantly following the IHG intervention. Our results demonstrate the strength

of the IHG training effect, as 85 % of participants in the present study experienced clinically relevant reductions in BP (i.e., ≥ 2 mmHg; Pescatello et al. 2004), despite already normal baseline BP. Our findings add to an impressive body of literature attesting to the substantial hypotensive benefits of IHG training in populations with and without high BP (Wiley et al. 1992; Ray and Carrasco 2000; Taylor et al. 2003; Peters et al. 2006; McGowan et al. 2007a, b; Millar et al. 2008, 2013; Badrov et al. 2013a, b). In contrast to previously reported trends in the literature (Millar et al. 2008; Inder et al. 2016), we show for the first time, using a prospective cohort design, that young men and women respond to IHG training with similar reductions in resting BP. Essential to the implementation of IHG training as a therapeutic intervention in the management of BP is specificity in exercise prescription to sex, age, and pathology. Moving forward, large-scale randomized controlled trials should be employed to further investigate sex differences in the BP response to IHG training in various age and patient groups to fully maximize the benefit of this treatment modality.

Effects of IHG training on endothelium-dependent vasodilation

While the BP lowering effects of IHG training are well established, the mechanistic pathway(s) mediating this response have yet to be fully elucidated. A reduction in total peripheral resistance through an improvement in endothelium-dependent vasodilation has been proposed as a potential contributor to the observed reductions in resting BP following IHG training (Millar et al. 2014). Whether the effect of IHG training on brachial artery FMD differs between men and women is unknown. In the current study, reductions in resting BP were concomitant with improvements in both absolute and relative brachial artery FMD; however, there were no differences between sexes in the magnitude of change.

Previously, we observed no change in brachial artery FMD following an identical 8-week IHG training intervention in a group of young normotensives (McGowan et al. 2007a). A potential explanation for the discrepancy in results may be the larger sample size ($N = 20$ vs. $N = 13$) studied in the current study, increasing power to detect a change in brachial artery FMD. Similarly, studies to date in healthy subjects on the effect of localized exercise training (i.e., handgrip training) on endothelial function have yielded somewhat inconsistent results. For example, rhythmic handgrip exercise in healthy men improved brachial artery FMD at weeks 2, 4, and 6 of training (Tinken et al. 2010), whereas 4 weeks of rhythmic handgrip training, also in men, had no effect (Hunt et al. 2012). Furthermore, several studies have shown enhanced endothelium-dependent vasodilation following handgrip training interventions in

young individuals (Allen et al. 2003; Credeur et al. 2010), yet other studies have observed no such change (Green et al. 1994; Franke et al. 1998). Differences in handgrip training protocols and intervention lengths make direct comparison to the current study difficult, as these studies typically employed rhythmic handgrip training protocols for a period of 4 weeks, in comparison to the 8-week interventions used commonly with isometric resistance exercise. However, our current findings are consistent with previous reports in hypertensive subjects (McGowan et al. 2006, 2007b), in which conduit artery endothelial function was improved significantly following 8 weeks of IHG training. The improvement in brachial artery FMD following IHG training may be due to shear-stress mediated increases in nitric oxide bioavailability and/or improved oxidative stress (Green et al. 2004), the latter of which has been shown to occur following IHG training (Peters et al. 2006). Yet, it cannot be ruled out that improvements were due to altered vascular structure and/or changes in endothelium-independent vasodilation, both of which were not measured in the current study. However, the fact that IHG training has no effect on brachial artery compliance (Visocchi et al. 2004), and has previously improved brachial artery FMD without changes in nitroglycerin-mediated vasodilator capacity (McGowan et al. 2006), makes this conjecture unlikely.

Also noteworthy, and in accordance with previous work in normotensives (McGowan et al. 2007a), is our finding of increased peak reactive hyperemic blood flow following the IHG training intervention, which may be indicative of functional and/or structural changes in the resistance vessel vasculature (Naylor et al. 2005). This supports our recent work (Badrov et al. 2013a), in which resistance vessel endothelial function (assessed using venous strain-gauge plethysmography) was improved in young normotensives following 8 weeks of IHG training. However, in this study (Badrov et al. 2013a), BP was reduced after 4 weeks of training without accompanying change in resistance vessel function, suggesting that multiple pathways may interact to mediate the effect of IHG training. Taken together, our current results suggest that improvements in conduit and resistance vessel endothelial function may play a role in the observed BP reductions following IHG training in both men and women, although other mechanisms are likely involved (Millar et al. 2014). Nonetheless, brachial artery FMD has proven to be an independent predictor of future cardiovascular disease in healthy adults (Yeboah et al. 2009), and therefore, improvements with IHG training yield great benefit independent of the potential contribution to the BP lowering effects of the exercise.

In conclusion, we demonstrate that an 8-week IHG training intervention reduces resting BP in men and women with normal BP, without sex differences in the magnitude

of reduction. Furthermore, reductions in resting BP occurred simultaneously to improvements in conduit and resistance vessel endothelium-dependent vasodilation in both men and women, suggesting that improvements in vascular endothelial function may contribute to the post-training BP response.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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