Isometric handgrip training does not improve flow-mediated dilation in subjects with normal blood pressure

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A B S T R A C T

Isometric HG (handgrip) training lowers resting arterial BP (blood pressure), yet the mechanisms are elusive. In the present study, we investigated improved systemic endothelial function as a mechanism of arterial BP modification following isometric HG training in normotensive individuals. This study employed a within-subject repeated measures design primarily to assess improvements in BA FMD (brachial artery flow-mediated dilation; an index of endothelium-dependent vasodilation), with the non-exercising limb acting as an internal control. Eleven subjects performed four 2-min unilateral isometric HG contractions at 30 % of maximal effort, three times per week for 8 weeks. Pre-, mid- and post-training resting ABP and BA FMD (exercised arm and non-exercised arm) were measured via automated brachial oscillometry and ultrasound respectively. BA FMD (normalized to the peak shear rate experienced in response to the reactive hyperaemic stimulus) remained unchanged [exercised arm, 0.029 ± 0.003 to 0.026 ± 0.003 to $0.029 \pm 0.004 \%/s^{-1}$ (pre- to mid- to post-training respectively); non-exercised arm, 0.023 ± 0.003 to 0.023 ± 0.003 to $0.024 \pm 0.003 \%/s^{-1}$ (pre- to mid- to post-training respectively); $P = 0.22$]. In conclusion, improved systemic endothelial function is unlikely to be responsible for lowering arterial BP in this population.

INTRODUCTION

Hypertension plays a prominent role in global all-cause and cardiovascular disease-related mortality [1]. Lifestyle modifications, including increased exercise, are recommended for the prevention and treatment of hypertension [1]. Dynamic aerobic training effectively lowers resting BP (blood pressure) in individuals without and with hypertension, probably due to training-related adaptations in the vascular system (e.g. improved endothelium-dependent vasodilation) [1].

A small body of evidence suggests that isometric exercise, including isometric HG (handgrip) training, reduces resting BP in individuals without and with hypertension [2–6]. The associated mechanisms have been proposed but not investigated, including improved endothelium-dependent vasodilation [2,4]. Increased exposure to systemic shear stress via the pressor response may improve endothelium-dependent function by augmenting the bioactivity and/or bioavailability of the potent vasodilator endothelium-derived nitric oxide [2,4,7], thus reducing total peripheral resistance and lowering resting

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Table 1 Baseline characteristics of the participants (n = 13)

Values are means $\pm$ S.D.

Characteristic	
Age (years)	27.5 $\pm$ 14.2
Sex (n)	
Men	10
Women	3
Height (cm)	176.0 $\pm$ 8.4
Weight (kg)	76.8 $\pm$ 11.2
Resting SBP (mmHg)	118.6 $\pm$ 7.4
Resting DBP (mmHg)	64.7 $\pm$ 6.8

BP. The aim of the present study was to investigate improved systemic endothelium-dependent vasodilation as a mechanism of BP modification following isometric HG training in subjects with normal BP.

MATERIALS AND METHODS

Participants

Thirteen participants with resting BP within the normal range (< 139/< 90 mmHg) were recruited from Hamilton, ON, Canada. Two participants (both men) were unable to complete the investigation; one due to extenuating family circumstances and the second to illness. Participants were regular exercisers ($\geqslant$ two exercise sessions per week), did not smoke, were free of overt disease (assessed via a medical history questionnaire) and were not taking medication. Exercise and nutritional habits were monitored and maintained throughout the investigation via tri-weekly personal communications with the exercise trainers in conjunction with exercise log-book tracking. Baseline participant characteristics are shown in Table 1.

The Research Ethics Board of Hamilton Health Sciences/McMaster University approved the investigation, procedures were followed in accordance with institutional guidelines and the Declaration of Helsinki of the World Medical Association, and participants provided informed written consent.

Study design

As the BP-lowering effects of isometric HG training have been established previously and reproduced in individuals with normal BP [3,4], the primary objective of this study was mechanistic and this was reflected in the study design. Specifically, a within-subject repeated measures design was used to assess improvements in BA FMD (brachial artery flow-mediated dilation; an index of endothelium-dependent vasodilation), with the non-exercising limb acting as an internal control. BP was not a primary outcome variable of the present study and

was evaluated using the same within-subject repeated measures design. Prior to baseline measurements, BP was measured in all participants, according to the protocol described below, to habituate them to the laboratory and testing environment and to minimize the potential for white coat hypertension [8].

Arterial diameter and vascular reactivity measurements were obtained from both arms using identical testing procedures at all time points (pre-, mid- and post-training). Mid-training testing took place during week 5 of the training intervention, and post-testing was conducted the week following the last isometric HG training session.

All assessments of BP and vascular reactivity were conducted in a quiet dark temperature-controlled room (range of 4 °C) following a 4-h fast, 12-h abstinence from caffeine and 24-h abstinence from vigorous exercise. To control for the influence of menstruation, pre-menopausal female participants were tested during their menstrual phase (if not on oral contraceptives) or low hormone phase (if on triphasic oral contraception) at all time points [9–11]. All of the tests were conducted within 2 h of the initial pre-testing time of day.

Exercise training protocol

Participants completed four sets of 2-min isometric HG contractions using a programmed HG dynamometer (CardioGrip; Zona Health) three times per week for 8 weeks. Isometric contractions were performed at 30 % maximal voluntary contraction (determined at the onset of each exercise session via electronic linear load cells contained within each isometric HG device), using the non-dominant hand, and each contraction was separated by a 4-min rest interval. All isometric HG training sessions took place under the direct supervision of an exercise trainer at the Exercise Metabolism and Research Group Laboratory at McMaster University, Hamilton, ON, Canada.

Resting BP measurements

Resting supine BP was measured in the right brachial artery with the right arm in the anatomical position at heart level, using automated brachial oscillometry (CBM-7000; Colin Medical Instruments). The BP cuff was placed approx. 2.5 cm proximal to the antecubital fossa. Three resting BP measurements were obtained by the same trained investigator following 12, 14 and 16 min of rest, and then averaged.

Resting and reactive hyperaemic brachial artery diameters and blood velocity measurements

A high-resolution ultrasound (System FiVe; GE Vingmed Ultrasound) and linear-array probe (10 MHz) system was used to acquire resting brachial artery diameters. Images were measured approx. 3–5 cm proximal to the

antecubital fossa, while participants were supine with the arm extended and immobilized. For each vessel, three images of the brachial artery were obtained in the brightness mode. All images were ECG-gated and captured one complete heart cycle (sampling frequency, 10 frames/s and approx. 100 brachial artery measurements/frame). Images were digitally stored for off-line analyses. Heart rate was monitored continuously from two sets of three electrodes positioned on the chest (Cardiomatic MSC 7123; Medical Systems Corp.) to generate ECG-gated ultrasound images and to determine blood velocity. All blood velocity measurements were collected at a pulse wave frequency of 4.0 MHz, a velocity range gate of 500 cm/s and a sample volume that captured the entire blood vessel.

Blood velocity in the brachial artery was assessed from a 10-s pulse-wave Doppler signal obtained from the entire brachial artery. The raw audio signal output corresponding to the blood velocity signal was input into a spectral analyser (Neurovision 500M TCD; Multigon Industries). Fast-Fourier transformation was used to determine mean blood velocity. The corresponding mean blood velocity analogue signals were sampled at a frequency of 200 Hz, and converted into digital signals using a data acquisition board (ML 795; AD Instruments) and stored on a computer for later off-line beat-to-beat analysis.

BA FMD was assessed by inducing reactive hyperaemia using a forearm occlusion cuff (SC12D; Hokanson), according to published guidelines [11]. This stimulus allowed for subsequent measurement of: (i) reactive hyperaemic blood velocity for calculation of peak BA FMD blood flow, and (ii) BA FMD [11]. The pneumatic cuff was inflated to 200 mmHg for 5 min (E20 Rapid Cuff Inflator, AG 101 Cuff Inflator Air Source; Hokanson) [11]. At cuff release, pulse-wave Doppler was used for 15 s to assess peak BA FMD blood velocity [11]. Continuous digital images of ECG-gated brachial artery diameter were collected between 53 and 70 s following cuff release (16.7 s video clip), ensuring acquisition of peak brachial artery diameter ([11,12], and C. L. McGowan, M. Rakobowchuk, N. McCartney and M. J. MacDonald, unpublished work).

Resting and reactive hyperaemic brachial artery images were obtained from the same portion of the brachial artery using anatomic land-marking. To ensure accurate anatomic land-marking and comparisons over time, brachial artery images from the pre-testing session were displayed for the ultrasonographer at each subsequent testing session.

All blood velocity measurements were analysed using Chart 5 for Windows (AD Instruments), after correcting for the angle of insonation (all $\leqslant 68°$). Resting blood velocity was quantified by: (i) determining beat-to-beat mean blood velocity using the area under each blood velocity curve during a heart cycle; and (ii) averaging

beat-to-beat mean blood velocity measurements over the 10-s sample. Peak BA FMD blood velocity was defined as the largest single-beat mean blood velocity following release of the occlusion cuff, but excluding the first beat. Resting and peak BA FMD blood flows were calculated as the product of their respective mean blood velocity and resting brachial artery cross-sectional area.

Off-line measurements of brachial artery diameters were made by the same ultrasonographer, using custom-designed automated edge-detection software to minimize observer bias (Artery Measurement System II version 1.133; Chalmers). All brachial artery diameters were measured from leading edge to leading edge. Mean resting brachial artery diameters were determined by: (i) measuring frame-by-frame mean brachial artery diameter throughout one heart cycle in the three separately acquired brachial artery images; (ii) averaging frame-by-frame mean brachial artery diameters in each of the three images to determine average mean brachial artery diameter; and (iii) averaging mean brachial artery diameters from all three images. Post-reactive hyperaemia brachial artery diameters were analysed at end-diastole [11,13], and were determined by: (i) measuring mean brachial artery diameter in each end-diastolic frame from 53–70 s post cuff-release (approx. 10–12 frames); (ii) averaging the end-diastolic brachial artery diameters; and (iii) expressing normalized BA FMD (normalized to the peak shear rate experienced in response to the reactive hyperaemic stimulus) using the following equations [11]:

$$\text{Normalized BA FMD} = \text{relative BA FMD/peak shear rate} \tag{1}$$

where relative BA FMD is:

$$\begin{aligned}\text{Relative BA FMD} = [&(\text{end-diastolic BA FMD diameter} \\ &- \text{end-diastolic resting diameter})/ \\ &\text{end-diastolic resting diameter}] \\ &\times 100\,\% \end{aligned} \tag{2}$$

and peak shear rate is:

$$\begin{aligned}\text{Peak shear rate} = (&4 \times \text{peak BA FMD mean blood} \\ &\text{velocity})/\text{resting brachial artery diameter}\end{aligned} \tag{3}$$

Statistical analysis

BP data were analysed using ANOVA (main effect for time). All pre-testing vascular reactivity data were analysed using one-way ANOVA to determine if baseline differences existed between the two arms. Vascular reactivity data were subsequently analysed using two-way ANOVA (arm × time) with repeated measures. Tukey's post-hoc procedures were used to evaluate specific differences between means, where applicable. All data were analysed using STATISTICA (version 6.0), and an α level of $\leqslant 0.05$ was considered statistically significant. Results are means $\pm$ S.D., unless otherwise specified.

Table 2   Resting vascular characteristics following isometric HG training ($n = 11$)

Values are means $\pm$ S.D. No main effects for time were observed, as determined by ANOVA.

Variable	Pre-training	Mid-training	Post-training
Resting mean blood flow (ml/min)			
Exercised arm	24.9 $\pm$ 9.3	25.2 $\pm$ 6.6	24.3 $\pm$ 12.6
Non-exercised arm	26.3 $\pm$ 9.2	27.4 $\pm$ 9.6	23.1 $\pm$ 8.3
Resting shear rate (s^{-1})			
Exercised arm	28.3 $\pm$ 8.6	29.0 $\pm$ 6.0	26.7 $\pm$ 8.0
Non-exercised arm	28.5 $\pm$ 12.3	28.4 $\pm$ 9.0	25.8 $\pm$ 13.2
Resting brachial artery diameter (cm)			
Exercised arm	0.42 $\pm$ 0.03	0.42 $\pm$ 0.03	0.42 $\pm$ 0.03
Non-exercised arm	0.43 $\pm$ 0.07	0.44 $\pm$ 0.07	0.43 $\pm$ 0.07

Table 3   Vascular reactivity characteristics following isometric HG training ($n = 11$)

Values are means $\pm$ S.D. *Significantly different from pre-training ($P = 0.008$). All other P values $\geqslant 0.05$.

Variable	Pre-training	Mid-training	Post-training
Peak shear rate (s^{-1})			
Exercised arm	322.8 $\pm$ 66.0	342.5 $\pm$ 40.1	279.8 $\pm$ 32.8
Non-exercised arm	322.9 $\pm$ 111.7	305.4 $\pm$ 79.6	297.8 $\pm$ 95.9
Relative BA FMD (%)			
Exercised arm	8.9 $\pm$ 2.7	8.6 $\pm$ 3.0	7.9 $\pm$ 3.0*
Non-exercised arm	6.9 $\pm$ 2.7	6.8 $\pm$ 2.3	6.5 $\pm$ 2.3*
Normalized BA FMD (%/s^{-1})			
Exercised arm	0.03 $\pm$ 0.01	0.03 $\pm$ 0.01	0.03 $\pm$ 0.01
Non-exercised arm	0.02 $\pm$ 0.01	0.02 $\pm$ 0.1	0.02 $\pm$ 0.01

RESULTS

Effects of isometric HG training on vascular reactivity

One-way ANOVA revealed that resting brachial artery diameter, resting mean blood flow, resting shear rate, peak BA FMD blood flow and peak shear rate in the exercised and non-exercised arm were not significantly different from each other at baseline ($P = 0.50$, 0.72, 0.95, 0.64 and 0.99 respectively).

Resting mean blood flow and peak BA FMD blood flow

Main effects for time were not observed in resting mean blood flow ($P = 0.52$), resting shear rate ($P = 0.58$) or peak shear rate ($P = 0.09$) (Tables 2 and 3) following two-way ANOVA with repeated measures. A main effect for time was, however, observed with peak BA FMD blood flow ($P = 0.04$); however, there was no interaction effect ($P = 0.34$). Specifically, peak BA FMD blood flow was significantly higher at mid-training than it was at post-training in both arms [exercised arm, 283.0 $\pm$ 23.8 to 303.7 $\pm$ 27.0 to 246.0 $\pm$ 19.9 ml/min (pre- to mid- to post-training respectively); non-exercised arm, 296.2 $\pm$ 13.8 to 294.0 $\pm$ 21.9 to 278.7 $\pm$ 22.1 ml/min (pre- to mid- to post-training respectively)].

BA FMD

Following isometric HG training, two-way ANOVA with repeated measures revealed that resting brachial artery diameters in both arms were unchanged from pre-training values (no main effect for time: $P = 0.38$; Table 2). A main effect for time was observed in relative BA FMD ($P = 0.008$), whereby it decreased with training in both arms and was significantly lower at post-training (Table 3). No interaction effect was observed ($P = 0.31$). When relative BA FMD was normalized to the peak post-

FMD blood flow stimulus, however, no changes were observed over time ($P = 0.22$; Table 3).

Effects of isometric HG training on resting BP

Following isometric HG training, one-way ANOVA of SBP (systolic BP) revealed a main effect for time where SBP decreased linearly from baseline through mid-training, reaching significance at post-training [118.1 $\pm$ 2.4 to 114.3 $\pm$ 1.3 to 113.2 $\pm$ 1.3 mmHg (pre- to mid- to post-training respectively); $P = 0.04$]. In contrast, DBP (diastolic blood pressure) remained unchanged from baseline at all time points [64.2 $\pm$ 2.2 to 62.3 $\pm$ 1.4 to 64.1 $\pm$ 1.2 mmHg (pre- to mid- to post-training respectively), $P = 0.47$].

DISCUSSION

To our knowledge, this is the first study to demonstrate that brachial artery endothelium-dependent vasodilation is not improved following isometric HG training. As endothelium-dependent vasodilation remained unchanged in both the exercised and non-exercised vascular beds, our findings suggest that improved systemic endothelium-dependent vasodilation may not be a mechanism responsible for the decrease in BP following isometric HG training in subjects with normal BP. These findings are in accordance with our previous work involving individuals taking medication for hypertension [14,15]. Unlike the normotensive population in the present study, however, isometric HG training did give benefit to the endothelium by improving local endothelium-dependent vasodilation in the exercised limb.

Effects of isometric HG training on vascular reactivity

In the present study, normalized BA FMD in both the trained and untrained arm remained unchanged from

baseline at all of the time points. We place emphasis on our normalized BA FMD measures, because peak post-BA FMD blood flow was altered throughout the course of the investigation. Normalizing relative measures of BA FMD to peak shear rate eliminates the impact of stimulus variability on BA FMD response [16]. The fact that relative BA FMD decreased with training in both arms provides evidence of the impact of stimulus variability on BA FMD response.

This finding is contrary to the speculation in the literature that the heart rate and BP increases during a bout of isometric HG exercise would be of a magnitude great enough to increase systemic pulsatile blood flow and improve systemic vasodilation with repetitive exposure over a short training period [2,4]. It is in accordance, however, with the weight of evidence that suggests that stimulus-induced endothelium-dependent vasodilation is not improved in healthy individuals following exercise training, particularly in response to forearm training [7].

BA FMD has become a popular non-invasive method to measure shear-stress-induced endothelium-dependent vasodilation following a period of ischaemic forearm occlusion [11,17]. We induced the ischaemic stimulus downstream of the brachial artery to minimize the direct effects of ischaemia on that vessel. Following cuff release, forearm blood flow was augmented by dilating distal vascular beds, thus inducing a shear stress stimulus through the brachial artery [11]. It is purported that the shear stress stimulus provokes the release of endothelium-derived nitric oxide, a potent vasodilator. The resulting vasodilation can be quantified as an index of endothelium-dependent vascular function [11]. Recent evidence from our laboratory suggests that, in individuals taking medication for hypertension, shear rates increase 3–4-fold over pre-exercise values during isometric HG contractions performed at 30 % of maximal voluntary contraction and held for 2 min, and remain elevated 4–5-fold for at least 1 min following release of the isometric HG contraction [17a]. Shear rates observed throughout the isometric HG protocol, however, are comparatively lower that those observed following 5 min of cuff-induced occlusion in healthy and hypertensive populations [14,15].

The increase in peak BA FMD blood flow observed at mid-training may be indicative of functional changes influencing the resistance vessel vasculature. Isometric HG exercise causes repetitive increases in forearm flow and sympathetic nerve traffic [18]. Isometric HG training may have therefore improved basal nitric oxide-related endothelial function in the resistance vessels of the forearm. This is supported by the findings of Kingwell et al. [19], who observed improvements in basal production of nitric oxide in healthy participants following 4 weeks of endurance training. Post-training reductions in peak BA FMD blood flow may result from attenuation in metabolite production in response to the same ischaemic stimulus, indicating that a better balance might

exist between aerobic and anaerobic metabolism [20]. Alternatively, the reduction in peak BA FMD blood flow may suggest a heightened vasoactive sensitivity to the BA FMD-induced blood flow stimulus. In accordance with this notion, we felt it important to normalize our relative BA FMD to the peak shear rate experienced in response to the reactive hyperaemic stimulus to account for the variability in the stimulus pre- to post-training. This observation was made in both the trained and the non-trained arm, suggesting the occurrence of neurally driven cross-education or cross-transfer strength adaptations that influence vascular flow [21,22].

Effects of isometric HG training on BP

In the present study, reductions in resting SBP were noted after 8 weeks of unilateral isometric HG training. Although the effect of isometric HG training on BP was not the primary focus of the present study, our findings support the weight of evidence that suggests that isometric HG training reduces resting BP in normotensive individuals. For example, Wiley et al. [3] observed reductions in SBP and DBP of 9.5 and 9.0 mmHg respectively, following isometric HG training, and Ray and Carrasco [4] observed reductions in resting mean BP and DBP of 4 and 5 mmHg respectively. Our findings must be interpreted with caution, however, as we did not include a non-isometric HG-trained control group.

Exercise training is an integral component of hypertension management [1]. Numerous rigorously conducted meta-analyses of randomized controlled trials investigating the effects of aerobic training on resting BP have been performed in individuals without and with hypertension. In subjects with resting BP within the normal range, post-training reductions of 2.6 and 1.8 mmHg in SBP and DBP respectively, have been reported [1]. In contrast, resistance training has not consistently lowered resting BP in normotensive individuals, and at present is currently recommended as a supplement to aerobic exercise for hypertension management [1]. The effects of exercise on the magnitude of BP reduction appear to be minimally influenced, if at all, by the frequency, mode, duration and/or intensity of exercise [1].

Although the mechanisms underlying post-training reductions in BP following all magnitudes and methods of training remain speculative, they are probably caused by adaptations in the vascular system that reduce total peripheral resistance, as chronic exercise appears to minimally (if at all) influence cardiac output [1]. Modifications in neural (e.g. reductions in basal sympathetic nervous system activity), hormonal (e.g. reductions in circulating noradrenaline), structural (e.g. increased lumen diameter) and, in some cases, functional (e.g. desensitized noradrenaline receptors, reduced endothelin-1 levels, increased nitric oxide bioavailability and release/improved endothelium-dependent vasodilation) factors may contribute to training-induced BP

modification [1]. Specifically, the mechanisms responsible for post-isometric HG training BP reductions in individuals with normal BP may include alterations in central arterial compliance and/or baroreceptor function, autonomic function and/or cardiac output [2,23–26].

Taken together, our present findings do not support the hypothesis that BP reductions following isometric HG training in individuals with normal BP were the result of improved systemic endothelial function and subsequent endothelium-dependent improvements in total peripheral resistance. The results of this investigation are notable and contribute to the scientific literature, yet we acknowledge the fact that we did not include a non-exercising control group. The study was primarily designed to investigate endothelium-dependent vasodilation as a mechanism of BP reduction following isometric HG training and we used the non-exercising limb as an internal control. We feel, however, that the results of the BP portion of our investigation remain valid and applicable for a number of reasons: (i) participants underwent familiarization procedures to reduce the apprehension-induced variability of the baseline measurements; (ii) the same trained investigator collected and analysed the BP at all time points; and (iii) our sample size had enough statistical power to detect intervention-induced differences if they were present. Furthermore, training-induced improvements in resting BP have been established and reproduced in randomized controlled trials conducted previously [2,3].

In the present study, we normalized our FMD data to the peak shear occurring in the brachial artery immediately following cuff release. It is important to note that Pyke et al. [27] have suggested recently that normalizing for shear by calculating the area under the shear rate curve up to the point of maximal diameter change post-cuff deflation may be a more appropriate way to represent the data. At the time of our data collection, however, this was not known. Furthermore, our ultrasound technology permitted either brightness-mode image acquisition or pulsed-wave mode Doppler acquisition, but not both simultaneously, and it did not allow for concurrent acquisition of diameter and velocity measurements. As such, we used resting brachial artery diameter to calculate peak shear rate, rather than the diameter when peak shear rate actually occurred. Taken together, we acknowledge that, although our normalization protocol was the most appropriate method to use at the time, a more suitable method may now be available [27].

Conclusions

The vascular and BP responses to isometric HG training suggest that improved systemic endothelial function is unlikely to be the mechanism responsible for BP reductions following isometric HG training in subjects with normal BP. The mechanisms of BP reduction following isometric HG training remain elusive.

REFERENCES

1   Pescatello, L., Franklin, B., Fagard, R., Farquhar, W., Kelley, G. A. and Ray, C. A. (2004) Exercise and hypertension. Med. Sci. Sports Exercise **36**, 533–553
2   Taylor, A. C., McCartney, N., Kamath, M. V. and Wiley, R. (2003) Isometric training lowers resting blood pressure and modulates autonomic control. Med. Sci. Sports Exercise **35**, 251–256
3   Wiley, R. L., Dunn, C. L., Cox, R. H., Hueppchen, N. A. and Scott, M. S. (1992) Isometric exercise training lowers resting blood pressure. Med. Sci. Sports Exercise **24**, 749–754
4   Ray, C. and Carrasco, D. (2000) Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. Am. J. Physiol. Heart Circ. Physiol. **279**, H245–H249
5   Kiveloff, B. and Huber, O. (1971) Brief maximal isometric exercise in hypertension. J. Am. Geriatr. Soc. **19**, 1006–1012
6   Buck, C. and Donner, A. P. (1985) Isometric occupational exercise and the incidence of hypertension. J. Occup. Med. **27**, 370–372
7   Green, D., Maiorana, A., O'Driscoll, G. and Taylor, R. (2004) Effect of exercise training on endothelium-derived nitric oxide function in humans. J. Physiol. **561**, 1–25
8   Pickering, T. G. (2002) Principles and techniques of blood pressure measurement. Cardiol. Clin. **20**, 207–223
9   Meendering, J. R., Torgrimson, B. N., Houghton, B. L., Halliwill, J. R. and Minson, C. T. (2005) Effects of menstrual cycle and oral contraceptive use on calf venous compliance. Am. J. Physiol. Heart Circ. Physiol. **288**, H103–H110
10 Hashimoto, M., Akishita, M., Eto, M. et al. (1995) Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. Circulation **92**, 3431–3435
11 Corretti, M., Anderson, T., Benjamin, E. et al. (2002) Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. A report of the international brachial artery reactivity task force. J. Am. Coll. Cardiol. **39**, 257–265
12 Betik, A., Luckham, U. and Hughson, R. (2004) Flow-mediated dilation in human brachial artery after different circulatory occlusion conditions. Am. J. Physiol. Heart Circ. Physiol. **286**, H442–H448
13 Walsh, J., Bilsborough, W., Maiorana, A. et al. (2003) Exercise training improves conduit vessel function in patients with coronary artery disease. J. Appl. Physiol. **95**, 20–25
14 McGowan, C. L., Visocchi, A., Faulkner, M. et al. (2006) Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. Eur. J. Appl. Physiol. **98**, 355–362
15 McGowan, C. L., Levy, A. S., Millar, P. J. et al. (2006) Acute vascular responses to isometric handgrip (IHG) exercise and the effects of training in persons medicated for hypertension. Am. J. Physiol. Heart Circ. Physiol. **291**, H1797–H1802

16 Pyke, K. E., Dwyer, E. M. and Tschakovsky, M. E. (2004) Impact of controlling shear rate on flow-mediated dilation responses in the brachial artery of humans. J. Appl. Physiol. **97**, 499–508

17 Faulx, M., Wright, A. and Hoit, B. (2003) Detection of endothelial dysfunction with brachial artery ultrasound scanning. Am. Heart J. **145**, 943–951

17a McGowan, C. L. (2006) Isometric Handgrip Training and Arterial Blood Pressure: Effects and Mechanisms. Ph. D. Thesis, McMaster University, Hamilton, ON, Canada

18 Batman, B. A., Hardy, J. C., Leuenberger, U., Smith, M. B., Yang, Q. X. and Sinoway, L. (1994) Sympathetic nerve activity during prolonged rhythmic forearm exercise. J. Appl. Physiol. **76**, 1077–1081

19 Kingwell, B., Sherrard, B., Jennings, G. and Dart, A. (1997) Four weeks of cycle training increases basal production of nitric oxide from the forearm. Am. J. Physiol. **272**, H1070–H1077

20 Mostoufi-Moab, S., Widmaier, E., Cornett, J. A., Gray, K. and Sinoway, L. (1998) Forearm training reduces the exercise pressor reflex during ischemic rhythmic handgrip. J. Appl. Physiol. **84**, 277–283

21 Farthing, J. P. and Chilibeck, P. D. (2003) The effect of eccentric training at different velocities on cross-education. Eur. J. Appl. Physiol. **89**, 570–577

22 Yasuda, Y. and Miyamura, M. (1983) Cross transfer effects of muscular training on blood flow in the ipsilateral and contralateral forearms. Eur. J. Appl. Physiol. Occup. Physiol. **51**, 321–329

23 Sinoway, L., Shenberger, J., Leaman, G. et al. (1996) Forearm training attenuates sympathetic responses to prolonged rhythmic forearm exercise. J. Appl. Physiol. **81**, 1778–1784

24 Ray, C. and Hume, K. (1998) Sympathetic neural adaptations to exercise training in humans: insights from microneurography. Med. Sci. Sports Exercise **30**, 387–391

25 Kingwell, B., Cameron, J., Gillies, K., Jennings, G. and Dart, A. (1995) Arterial compliance may influence baroreflex function in athletes and hypertensives. Am. J. Physiol. **268**, H411–H418

26 Parnell, M. M., Holst, D. P. and Kaye, D. M. (2002) Exercise training increases arterial compliance in patients with congestive heart failure. Clin. Sci. **102**, 1–7

27 Pyke, K. E., Gill, R., Hartnett, J., Krzak, D. and Tschakovsky, M. E. (2006) The magnitude of FMD is determined by the area under the curve of the reactive hyperemia. Med. Sci. Sports Exercise **38**, S59