Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension

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McGowan, Cheri L., Andrew S. Levy, Philip J. Millar, Juan C. Guzman, Carlos A. Morillo, Neil McCartney, and Maureen J. MacDonald. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. Am J Physiol Heart Circ Physiol 291: H1797–H1802, 2006.—Previous work from our laboratory demonstrated that isometric handgrip (IHG) training improved local, endothelium-dependent vasodilation in medicated hypertensives [McGowan CL (PhD Thesis), 2006; McGowan et al. Physiologist 47: 285, 2004]. We investigated whether changes in the capacity of smooth muscle to dilate (regardless of endothelial factors) influenced this training-induced change, and we examined the acute vascular responses to a single bout of IHG. Seventeen subjects performed four 2-min unilateral IHG contractions at 30% of maximal voluntary effort, three times a week for 8 wk. Pre- and posttraining, brachial artery flow-mediated dilation (FMD, an index of endothelium-dependent vasodilation) and nitroglycerin-mediated maximal vasodilation (an index of endothelium-independent vasodilation) were measured in the exercised arm by using ultrasound before and immediately after acute IHG exercise. IHG training resulted in improved resting brachial FMD (P < 0.01) and no change in nitroglycerin-mediated maximal vasodilation. Pre- and posttraining, 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). Posttraining, 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 the resting brachial artery FMD were 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 endothelium-dependent vasodilation.

Acute exercise; isometric training; flow-mediated dilation; blood flow

HYPERTENSION is associated with endothelial dysfunction, a condition characterized by reduced endothelium-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 underinvestigated, yet evidence suggests that brachial artery flow-mediated dilation (FMD; an index of endothelium-dependent vasodilation) is either unaffected (30) or improved (10) in persons with endothelial dysfunction, whereas it is attenuated following a maximum intensity aerobic exercise bout (30). Brachial artery FMD is dependent on 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 postexercise increases in endothelium-dependent vasodilation (9). Alternatively, impairment in endothelium-dependent vasodilation at higher intensities of exercise may result from increases in oxidative stress (2, 30) because reactive oxygen species superoxide radicals react vigorously with nitric oxide to form oxidant peroxynitrite, which reduces the bioavailability of nitric oxide (18, 19, 30). The effects of aerobic training on acute exercise-induced changes in endothelium-dependent vascular function are unknown.

Handgrip training (rhythmic and isometric) improves local, endothelium-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 endothelium-independent dilation (6, 9). With respect to the latter, rhythmic handgrip training does not improve endothelium-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 endothelium-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, and indirect-acting antioxidants) (1, 18, 34). It is possible that impairment in endothelium-dependent vasodilation may result from this increase in oxidative stress.

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The effects of IHG training on the acute endothelium-dependent dilation response following a bout of IHG exercise are currently unknown.

The purpose of the current study was twofold: 1) to investigate improved endothelium-independent dilation as a contributor to training-induced change in endothelium-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. On the basis of the literature, it was hypothesized that: 1) changes in the capacity of the smooth muscle to dilate (endothelium-independent vasodilation) would not be responsible for improved post-IHG training endothelium-dependent vasodilation in subjects medicated for hypertension, and 2) endothelium-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 midinvesigation 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 biweekly personal communications with the exercise trainers in conjunction with exercise log-book tracking. All participants were regular exercisers (≥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, endothelium-dependent vasodilation in persons medicated for hypertension (24). The same training protocol was used in the current investigation. Specifically, participants completed four sets of 2-min unilateral IHG contractions using a programmed handgrip dynamometer (Cardiogrip, SEL, Zona Health, Boise, ID), three times per week for 8 wk. Isometric contractions were performed at 30% of maximal effort, using the nondominant arm, and each contraction was separated by a 4-min rest interval.

Study design. This investigation employed a within-subject repeated measure design. Endothelium-dependent and -independent vasodilation were assessed pre- and posttraining.

Testing protocol. Endothelium-dependent vasodilation was assessed via brachial artery FMD using Doppler ultrasound before and immediately after an acute bout of IHG exercise executed by the nondominant arm. Endothelium-independent vasodilation was then assessed in the same arm after the administration of sublingual nitroglycerin 10 min following the last FMD test (see Fig. 1).

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 endothelium-dependent vasodilation 4 min after 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 endothelium-dependent vasodilation immediately after an IHG exercise bout, a bout that includes the last 4-min 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). Posttesting was conducted the week following the last IHG training session. Before baseline measurements, participants were habituated to the laboratory and testing environment. All assessments of endothelium-dependent and -independent vascular function were conducted in a quiet, dark, temperature-controlled room (range of 2°C) after a 4-h fast, 12-h abstinence from caffeine, and 24-h abstinence from vigorous exercise. All tests were conducted within 2 h of initial pretesting time of day.

Assessment of endothelium-dependent and -independent vasodilation. All data were 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 by using electrocardiography (Cardiomatic MSC 7123, Medical Systems) and radial artery applanation tonometry (CBM-7000, Colin Medical Instruments, San Antonio, TX), respectively. Resting brachial artery images were measured ~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 min 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 one complete
heart cycle was recorded at the following postnitroglycerin administration time points to ensure the capture of peak brachial artery dilation: 2, 2.5, 3, 3.10, 3.20, 3.30, 3.40, 3.50, 4, 4.30, and 5 min (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 II version 1.133, Chalmers, Sweden). All diameters were expressed as a percent increase of the baseline value of the diameter and 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 10 s 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). Measurements of heart rate, mean arterial blood pressure \((2 \times \text{diastolic blood pressure}) + (\text{systolic blood pressure})/3\), 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 endothelium-independent vasodilation, brachial artery diameters were measured at end diastole in each of the 11 postnitroglycerin brachial artery images and then averaged (5, 32). Endothelium-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 endothelium-independent dilation data using one-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 by using two-way analysis of variance with repeated measures (FMD test \(\times\) 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 \(\leq 0.05\) was considered statistically significant. Descriptive data are presented as means \(\pm \text{SE}\), unless otherwise specified.

### RESULTS

Effects of IHG training on resting endothelium-dependent and -independent vasodilation, and other cardiovascular and vascular reactivity responses. FMD measures obtained before the acute IHG bout were compared pre- and posttraining to examine any training-induced alterations in resting endothelium-dependent vasodilation. Relative FMD increased from baseline and was significantly higher at posttraining (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%/s\(^{-1}\), post-: 0.02 \(\pm\) 0.003%/s\(^{-1}\), Fig. 2). Endothelium-independent vasodilation was unchanged with IHG training (pre-: 9.0 \(\pm\) 0.7\% to post-: 8.8 \(\pm\) 0.8\%; \(P > 0.05\)), as were all other cardiovascular and vasoreactivity parameters (Table 2).

Effects of an acute bout of IHG exercise on endothelium-dependent vasodilation, cardiovascular and vascular reactivity, and the influence of training. Relative endothelium-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 \(\pm\) 0.002%/s\(^{-1}\), after IHG exercise: 0.008 \(\pm\) 0.002%/s\(^{-1}\); post-, before IHG exercise: 0.02 \(\pm\) 0.003%/s\(^{-1}\), after IHG exercise: 0.01 \(\pm\) 0.003%/s\(^{-1}\), Fig. 3). After 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 after a bout of IHG exercise. All other cardiovascular and vascular reactivity responses were unchanged. Eight weeks of IHG training did not alter the endothelium-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 endothelium-dependent vasodilation.
in the brachial artery of the exercised limb. Because endothelium-independent vasodilation did not change with 8 wk 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 endothelium-dependent vasodilation in persons medicated for hypertension. This latter observation is particularly remarkable, because IHG performed at 30% maximal voluntary contraction is such a small stimulus, yet it is sufficient to acutely impair brachial artery FMD and improve resting endothelium-dependent vasodilation after repetitive exposure to the stimulus over an 8-wk period.

Effects of IHG training on resting endothelium-dependent and -independent vasodilation. Brachial artery FMD has become a popular noninvasive method to measure shear stress-induced dilation after a 5-min period of ischemic forearm occlusion and is quantified as an index of endothelium-dependent vasodilation (5). Although our IHG protocol had four, 2-min periods of static contraction-induced occlusion that likely elicited postcontraction increases in brachial artery endothelium-dependent vasodilation, the lack of change in pre-FMD brachial artery diameter after 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 after IHG training in persons medicated for hypertension support previous findings from our laboratory in the same population (24). The impairment of endothelium-dependent vasodilation after 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 endothelium-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).

Endothelium-independent vasodilation did not change with training in the current investigation, suggesting that our posttraining measures of endothelium-dependent vasodilation were not influenced by changes in the underlying forearm vascular (5).

Effects of an acute bout of IHG exercise on endothelium-dependent vasodilation and the influence of training. In the present study, reductions in brachial artery FMD after an acute bout of IHG exercise were noted. This observation supports the findings of Silvestro and colleagues (30) who showed a 2.3-fold reduction in persons with endothelial dysfunction (intermittent claudication) following a single session of maximal treadmill exercise. Silvestro and colleagues (30) reasoned that the exercise-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 endothelium-

Table 3. Cardiovascular and vascular reactivity characteristics before and after a bout of IHG exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-FMD</th>
<th>Post-FMD</th>
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<tbody>
<tr>
<td></td>
<td>Before IHG</td>
<td>After IHG</td>
</tr>
<tr>
<td>Brachial artery diameter, cm</td>
<td>0.43±0.01</td>
<td>0.43±0.01</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>55.8±2.7</td>
<td>57.5±2.6*</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>95.9±2.5</td>
<td>97.3±2.3</td>
</tr>
<tr>
<td>Mean blood flow, ml/min</td>
<td>23.0±2.2</td>
<td>41.4±7.3*</td>
</tr>
<tr>
<td>Shear rate, s⁻¹</td>
<td>25.2±2.3</td>
<td>41.9±5.2*</td>
</tr>
<tr>
<td>Conductance, ml/mmHg⁻¹·min⁻¹</td>
<td>0.2±0.03</td>
<td>0.4±0.08*</td>
</tr>
<tr>
<td>Resistance, mmHg·ml⁻¹·min⁻¹</td>
<td>4.6±0.3</td>
<td>3.3±0.4*</td>
</tr>
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Values are means ± SE; n = 17 subjects. *Significantly different from before-IHG exercise brachial artery FMD test (main effect for time, P < 0.05).

Fig. 3. Postocclusion BA diameter change from rest normalized to peak shear rate before and after an acute bout of IHG exercise. *Significantly different from pre-IHG exercise BA FMD test (P < 0.01).
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, endothelium-dependent vasodilation. Increased temperature in the exercising muscles, inflammation induced by muscle-fiber 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 after 8 wk of IHG training. This suggests that the local antioxidant capacity of the system was still surpassed during the posttraining 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 after an acute bout of IHG exercise in the current investigation. The post-IHG exercise FMD test was administered immediately after the last rest interval of the IHG protocol and 4 min after the last IHG contraction. Although heart rate was significantly increased following the acute IHG bout, the small rise in heart rate (~2 beats/min) and the 4-min rest period may not have sufficiently washed out the vasodilatory metabolites that accumulated throughout 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). Because 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 wk 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 nonexercising 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 posttraining 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 endothelium-dependent vasodilation have been established and reproduced in previously conducted randomized, controlled trials using a nonexercising control group and a within-study design where the nonexercising 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.

In conclusion, endothelium-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, posttraining improvements in resting endothelium-dependent vasodilation were observed. Endothelium-independent dilation was unchanged with IHG training, suggesting that the posttraining improvements in endothelium-dependent vasodilation were not attributed to underlying changes in the forearm vasculature. In summary, IHG training, using a simple handheld, 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 endothelium-dependent vasodilation occurs despite transient post-IHG reductions, an occurrence that also happens posttraining. These observations may have important implications for future isometric-related interventions aimed at improving endothelial dysfunction in persons medicated for hypertension, a population that includes a large number of North Americans.

GRANTS
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REFERENCES


