Reductions in ambulatory blood pressure in young normotensive men and women after isometric exercise training and its relationship with cardiovascular reactivity

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Abstract

There has been very little published work exploring the comparative effects of isometric exercise training in men and women. Most of the previously published work has involved men. The primary purpose of this proof-of-concept study was to test the hypotheses that in young, normotensive men and women, 10 weeks of isometric exercise training (isometric handgrip, IHG, 3 times per week) would: 1) elicit similar reductions in ambulatory blood pressure (BP), and 2) these reductions would be related to pre-training systolic BP reactivity to standard myocardial-mediated laboratory stress tasks (IHG task: a 2-minute sustained isometric contraction; Serial Subtraction task: a math task involving subtracting a 2 digit number from a series of numbers). There were no differences in the IHG training-induced reductions in 24-hour, daytime, and nighttime systolic ambulatory BP in men (n=13) and women (n=11, $p<0.05$); however these BP changes were not associated with systolic BP reactivity to either stress task (all $p>0.05$). Our data suggest that lower ambulatory BP can be achieved using IHG training, however its BP-lowering effectiveness cannot be predicted by systolic BP reactivity. Taken together, this work heralds a potentially novel approach to primary prevention of hypertension in both men and women and warrants further investigation.

Descriptors: Isometric handgrip training, ambulatory blood pressure, cardiovascular reactivity, primary prevention, hypertension

Introduction

As the population ages, expands, and globalizes, disease patterns are shifting and non-communicable diseases, like cardiovascular disease (CVD), are becoming more common (Smith et al., 2012). Presently, CVD is the leading cause of morbidity and mortality worldwide (WHO, 2013). Hypertension (HT), a condition characterized by sustained elevations in resting systolic (≥ 140 mmHg) or diastolic (≥ 90 mmHg) blood pressure (BP) is a major risk factor for CVD related events that has been steadily increasing in prevalence (WHO, 2013). Recognizing the importance of this causal relationship, the World Health Organization (WHO) has identified HT as a global health crisis and predicts an epidemic of HT in the near future. Accordingly, the WHO has made primary prevention of HT a focused component of its effort to reduce the global burden of CVD (WHO, 2013).

Despite such initiatives, primary prevention of HT is a challenging prospect that would, at present, require various measures ranging from lifestyle modification to pharmaceutical intervention (Julius et al., 2006). Isometric handgrip (IHG) training, a form of resistance exercise involving multiple timed sustained (static) contractions performed at a set percentage of maximum voluntary contraction (MVC) on a programmed handgrip dynamometer, may be useful for this purpose and was recently endorsed by the American Heart Association (AHA) as an alternative BP-lowering treatment (Brook et al., 2015; Brook et al., 2013). This recommendation was founded in the accumulating evidence of the efficacy of IHG training in reducing resting BP in men with some preliminary evidence of similar effects in women. This is the case for individuals with and without HT, including those medicated for HT and those who exercise regularly (Carlson et al., 2014; Millar et al., 2014; Badrov et al., 2013a; Badrov et al., 2013b; McGowan et al., 2006; McGowan et al., 2007a; McGowan et al., 2007b; Millar et al., 2007, Millar et al., 2008; Peters et al., 2006; Taylor et al., 2003; Wiley et al., 1992; Ray & Carrasco, 2000).

While the relationship between HT and CVD is clear, the consensus on which BP measurement is most meaningful, has been evolving. Ambulatory BP, a method that provides insight into 24-hour fluctuations in BP, has been found to be a better predictor of CVD risk than conventional, office-based resting BP measurements (Hansen et al., 2010; Pickering et al., 2006) and has emerged as the preferred approach for diagnosis and monitoring of therapeutic effectiveness (Niiranen et al., 2014; Piper et al., 2015). In the only published study to date on the effects of IHG training on ambulatory BP, Stiller-Moldovan and colleagues (2012) found that an IHG training protocol involving four, 2-minute bilateral IHG contractions at 30% MVC, 3 times per week for 8 weeks resulted in clinically relevant reductions in mean 24-hour (~3 mmHg; average of 24 hour fluctuations) and nighttime (~4 mmHg; measured from 10 p.m. – 6 a.m.) systolic BP in a population of well-controlled, medicated HT patients (mean ± SD, resting BP: 114 ± 13/61 ± 12 mmHg). However, there remains very little data relating to the comparative effects of isometric exercise training in men and women. Millar and colleagues (2008) observed that participants with higher pre-training resting BP values experienced greater reductions following training. Furthermore, little is known about the differences in training-induced BP reductions in women, compared to men. Indeed, it appears that post-menopausal normotensive women are more responsive to IHG training than age-matched normotensive men, as indicated by greater post-training reductions in resting BP (Millar et al., 2008). In contrast, preliminary data from Hanik and colleagues (2012) suggest IHG training is equally effective at reducing resting BP in young, normotensive men and women. The reason(s) for these discrepant responses is/are unclear and warrant further exploration to elucidate the differences between men and women.

Despite signals of efficacy, the BP response to IHG training is variable (Millar et al., 2007). Cardiovascular reactivity, or an individual's acute BP and heart rate (HR) response to a physical or mental stressor, has been shown to predict differences in post-IHG training response (Carrol et al., 2012). Work by Millar and colleagues (2009) demonstrated, using a retrospective design, that systolic BP reactivity to a myocardial-mediated serial subtraction task (SST; a math task involving subtracting a 2 digit number from a series of numbers) but not a vascular-mediated cold pressor task (CPT; a two minute hand immersion in a cold water bath) was predictive of reductions in resting systolic BP in older, normotensive individuals who trained 3 times per week for 8 weeks (4, 2 minute bilateral contractions at 30% MVC). Similarly, using a prospective design, Badrov and colleagues (2013a) demonstrated that systolic BP reactivity to both a SST and an IHG task (IHGT; a 2 minute isometric contraction at 30% MVC on a handgrip dynamometer), but not to a CPT, was predictive of responsiveness to IHG training in hypertensive participants such that individuals in the study who elicited the highest pre-training reactivity had the greatest reductions in systolic BP following 10 weeks of IHG training. However, the association between BP reactivity to psychophysiological stressors and IHG-training induced 24 hour ambulatory BP reductions and whether sex differences exist, has yet to be explored.

The current proof-of-concept study was designed to extend existing observations to normotensive individuals, in an effort to better understand the potential utility of IHG for primary prevention of HT in both sexes. More specifically, the current investigation aimed to: 1) compare the efficacy of IHG training in reducing ambulatory BP in young, normotensive individuals; 2) determine whether systolic BP reactivity to IHGT and SST could predict IHG training-induced reductions in ambulatory BP in both men and women. It was hypothesized that both men and women would experience similar reductions in ambulatory BP following 10 weeks of IHG training (Hanik et al., 2012). It was further hypothesized that systolic BP reactivity to an IHGT and SST, but not a CPT, would be predictive of IHG responsiveness, such that participants who responded to the SST and IHGT with the greatest increases in systolic BP would experience the greatest reductions in ambulatory BP following IHG training (Badrov et al, 2013a; Millar et al., 2009).

Method

Study Participants

Twenty-four young (24 ± 5), normotensive (110 ± 5/64 ± 7) men (n=13) and women (n=11) were recruited from Windsor, ON and the surrounding community and enrolled in the protocol. Exclusion criteria for the study included a prior diagnosis of HT or CVD and/or prescribed pharmacotherapies (e.g., beta-blockers) known to influence neurovascular function, and/or physical limitations impairing exercise performance.

Study Design

This investigation was cleared by the University of Windsor Research Ethics Board and all participants provided written informed consent. Upon establishing eligibility, participants underwent a familarization session to habituate themselves to the testing procedures. In effort to minimize potentional anxiety during the testing day, participants were able to practice all techniques and procedures. Following the familiarization session, all particpants underwent baseline testing on a separate day which involved presentation of the three stress tasks (IHGT, SST, CPT) to assess cardiovascular reactivity (systolic BP, diastolic BP, and HR response), and 24 hour ambulatory BP monitoring. Baseline testing was repeated following 10-weeks of IHG training (week 11), at least 48 hours following the last IHG training session. Please refer to Figure 1 for a schematic diagram of the study design.

Experimental Protocol

Both baseline and post-IHG training testing took place at the same time of day (within 2 hours), in a quiet, temperature-controlled room (range: 20-23°C), following a light meal, 24-hour abstinence from alcohol consumption and vigorous physical activity, and a 12-hour abstinence from caffeine (Badrov et al., 2013a). Participants voided their bladder prior to the testing session to avoid a potential rise in blood pressure due to bladder distention (Fagius & Karhuvaara, 1989).

Cardiovascular Reactivity

Participants performed the three cardiovascular stress reactivity tasks in random order. During each stress task, BP and HR were measured every minute via brachial artery oscillometry (Dinamap Carescape v100, Critikon, Tampa, FL, USA). Subsequent to each task, participants underwent a minimum stabilization period of 10 minutes to ensure a return of BP and HR to baseline prior to beginning the next task.

Serial Subtraction Task (SST): All participants viewed a computer monitor (Dell UltraSharp 24” monitor) displaying a 4-digit number and were asked to mentally subtract a 2-digit number (e.g., 13 at pre-testing, 17 at post-testing) from the number displayed and respond with their answers aloud prior to the appearance of the next number. Participants were shown 25 numbers in total where each number was displayed for 5 seconds, and participants responded within that time frame with his or her answer for each number. The number of correct and incorrect responses were recorded (Badrov et al., 2013a).

Isometric Handgrip Task (IHGT): Participants performed a single 2-minute sustained isometric contraction at 30% of their MVC with the non-dominant hand on a programmed handgrip dynamometer (CardioGrip, Westerville, OH, USA; Badrov et al., 2013a). MVC was determined prior to contraction via electronic linear load cells contained within the IHG device. The IHGT protocol was identical pre-and post-testing, and participants maintained a compliance score of 95% (% participants maintained 30% MVC).

Cold Pressor Task (CPT): Participants immersed their right hand (up to the wrist) in a temperature-controlled cold-water bath (4 ± 1°C) for 2 minutes (Badrov et al., 2013a) at both pre- and post-testing. The CPT was well tolerated as evidenced by all participants completing the task at both time points.

Ambulatory Blood Pressure: At the completion of the laboratory testing session, ambulatory BP was monitored for 24-hours (Stiller-Moldovan et al., 2012). Daytime (6 a.m. to 10 p.m.) BP and HR were recorded two times per hour, and nighttime (10 p.m. to 6 a.m.) BP and HR were recorded one time per hour. Values for the 24 hour period were averaged (mean 24-hour ambulatory BP) as well as during each time period (daytime and nighttime) (Stiller-Moldovan et al., 2012). Following the completion of baseline ambulatory BP monitoring, a detailed history of activities performed during this time was acquired. Participants were instructed to perform similar activities during post-testing data collection in order to standardize BP recordings. This was verified with the participants during detailed discussions following their 24-hour monitoring session.

IHG Training Protocol

All participants trained on-site 3 times per week for 10 weeks using the bilateral IHG exercise protocol (ZonaPLUS; Zona Health, Boise, ID, USA), which involved four, 2-minute isometric contractions, performed at 30% of MVC, separated by a 1-minute rest period, for a total of 12-minutes. All training sessions were supervised by an exercise trainer, and exercise log books were used to record date of completion, MVC scores, final compliance %, and any changes in diet, exercise or nutrition. Resting BP and HR were measured prior to the start of each training session following 10-minutes of seated rest (data not used for analysis).

Statistical Analysis

One-way ANOVAs were performed on all baseline ambulatory measures to examine initial differences between men and women. In order to assess the efficacy of IHG training in lowering BP in men and women, a two way repeated measures ANOVA was employed to ambulatory BP (mean 24-hour, daytime, and nighttime), and ambulatory HR. To determine cardiovascular reactivity (systolic BP, diastolic BP, and HR responses) to the IHGT, SST, and CPT, the difference between the peak stress task value and mean baseline resting value was calculated (Jennings et al., 1992). The relationship between cardiovascular reactivity and IHG training adaptations was assessed using Pearson correlation coefficients. Residualized change scores in systolic BP were used for the analysis as baseline BP and change in BP post-training have proven correlated effects (Llabre et al, 1991; Millar et al., 2007). This value was determined by regressing change in ambulatory systolic BP following the intervention on pre-intervention ambulatory systolic BP measures. The regression analysis was performed for all measures of ambulatory systolic BP.

All data were analyzed using IBM SPSS Statistics 21 software (SPSS Inc., Chicago, Illinois, USA) and statistical significance was set at $p \leq 0.05$. All data are presented as X ± SD unless otherwise stated.

Results

All 24 participants trained for 10 weeks and completed 30 IHG sessions. Compliance to the IHG protocol itself was 97%, and averaged 98% for men and 96% for women. Over that time, no changes in exercise, diet, or medication occurred in either sex. Importantly, no adverse events were reported in response to either the IHG testing or training interventions.

As shown in Table 1, men and women did not significantly differ in age, BMI, ambulatory diastolic BP, or ambulatory HR (all $p>0.05$) at baseline. Conversely, height, weight, and ambulatory systolic BP were significantly different between the two groups ($p<0.05$). Outcome variables were not influenced as the multilevel ANOVA employed accounted for these initial differences, and no interactions between men and women were observed ($p>0.05$).

Effects of IHG training on Ambulatory BP and HR

Similar magnitude, statistically significant ($p<0.001$) IHG training-induced reductions in all measures of systolic ambulatory BP were observed in both men and women (Figure 2 with no apparent interaction between sexes at any measurement point. Retrospective power analysis revealed an observed power of 0.98, 0.95, and 0.60 for measures of 24-hour mean, daytime, and nighttime ambulatory BP, respectively. In contrast, 24-hour mean, daytime, and nighttime diastolic ambulatory BP (Figure 3b) as well as 24-hour mean, daytime, and nighttime ambulatory HR (Table 2) remained unchanged in both men and women.

Cardiovascular Reactivity as a Predictor of IHG Training-induced Reductions in Ambulatory BP

Men had a significantly higher systolic BP reactivity to the IHGT and SST than women ($p<0.05$; Table 3), however task-induced cardiovascular reactivity was not associated with training-induced reductions in any measure of ambulatory BP or HR in both men and women for any task (all $p>0.05$).

Discussion

This study represents the first evaluation of the ambulatory BP-lowering effects of IHG training in young normotensive men and women. Importantly, and in accordance with our hypothesis, there were similar significant reductions in all measures of systolic ambulatory BP in both men and women. As ambulatory BP has greater prognostic value than resting BP (Pickering et al., 2006), our novel findings have important clinical implications, suggesting that IHG training may be an ideal tool to help attenuate BP rise over time in young, healthy individuals, and may be particularly helpful in those at high risk for future development of HT (e.g., heritable predisposition).

The present study provides compelling evidence to suggest that significant systolic BP reductions can be achieved following 10 weeks of IHG training, while supporting the exploratory prediction that ambulatory BP would be lowered equally in men and women. The reductions in daytime systolic ambulatory BP following IHG training were similar in magnitude to reductions following aerobic training interventions (3mmHg) in normotensive participants (Cornelissen & Smart, 2013; Cornelissen et al., 2011). However, our findings are distinguished from those observed with aerobic training in that reductions in 24-hour and nighttime systolic ambulatory BP were seen in addition to daytime measures following the IHG intervention. They also stand in contrast to similar studies with dynamic resistance training, where reductions in ambulatory BP have not been observed to date (Blumenthal et al., 1991; Van Hoof et al., 1996) suggesting unique mechanisms for BP lowering may be associated with IHG beyond exercise physiology itself.

Our observations are in line with previous work by Stiller-Moldovan and colleagues (2012), where clinically relevant reductions in mean 24-hour and nighttime ambulatory systolic BP were noted following 8 weeks of IHG training in well-controlled, medicated hypertensive participants as nightime ambulatory BP is a stronger predictor of CVD risk than daytime ambulatory BP, the finding of a sustained BP-lowering effect with IHG over a full 24-hour period that is independent of sex has important implications from a primary prevention standpoint (Hansen et al., 2010). Expanding the scope of this research to include non-hypertensive subjects with a heritable predisposition towards development of HT (Ference et al., 2014), along with a hypertensive populations with uncontrolled BP are logical extensions and would help define patient subgroups who would ultimately benefit from the potential BP-lowering effects of IHG.

Our findings also mesh with work by Stiller-Moldovan and colleagues (2012) in IHG training, as well as studies on dynamic resistance training (Blumenthal et al. 1991; Van Hoof et al, 1996), which found no change in measures of ambulatory diastolic BP and ambulatory HR following 10 weeks of intervention. However, it contrasts observations following aerobic training interventions where daytime diastolic BP reductions of ~3 mmHg were noted in normotensives (Cornelissen et al., 2013). These dissimilar findings could mean a greater stimulus targeting intervention length, frequency of training per week, duration of IHG stimulus, and/or force of contraction is required to produce reductions in diastolic ambulatory BP.

In addition to the effect on ambulatory BP, we also investigated cardiovascular reactivity responses, to ascertain their usefulness as potential predictive tools with respect to ambulatory BP-lowering effect of IHG training. While sex differences were noted in systolic BP responses to IHGT and SST, in contrast to the exploratory hypothesis, we found no correlation between BP and HR reactivity to any of the specific tasks and post-IHG training reductions in ambulatory BP. These data suggest that BP-lowering effects of IHG training may be independent of basal hemodynamic stress response; however, we did not collect information on chronic allostatic load or acute factors (e.g., traffic jam, inclement weather, receiving a poor test mark) that could have altered individual test dynamics (Karmarck et al., 2002).

These findings provide the first evidence that IHG therapy lowers ambulatory systolic BP in normotensive individuals, while providing evidence that this intervention is equally effective in young men and women, during both daytime and nighttime periods. Our results support the need for further study of IHG training as a time efficient means for targeted BP reduction in young, normotensive patients who may be at-risk for HT. Considering the tremendous prevalence of CVD worldwide, and the recent priority placed on HT by the WHO, IHG training represents a cornerstone strategy for future work aimed at primary prevention of HT worldwide.

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Table 1. Participant baseline characteristics

Characteristics	**Men (n=13)**	**Women (n=11)**
Age (years)	24 ± 4	25 ± 5
Height (cm)	179 ± 8	167 ± 9*
Weight (kg)	80 ± 14	63 ± 11*
BMI (kg/m^2)	25 ± 4	23 ± 4
Baseline Ambulatory measures		
24 hour systolic BP (mmHg)	131 ± 5	120 ± 4*
24 hour diastolic BP(mmHg)	72 ± 8	70 ± 5
24 hour ambulatory HR(beats/min)	67 ± 7	73 ± 9

BMI, body mass index; BP, blood pressure; HR, heart rate. Values are mean ± SD; *Significantly different from men ($p<0.05$).

Table 2. Effects of IHG training on ambulatory heart rate

Ambulatory HR (beats/minute)	**Men (n=13)**		**Women (n=11)**	
	pre	post	pre	post
Mean 24 hour	67 ± 8	67 ± 7	73 ± 9	72 ± 10
Daytime	69 ± 8	69 ± 7	76 ± 9	75 ± 9
Nighttime	63 ± 8	64 ± 9	69 ± 9	67 ± 12

BP, blood pressure; HR, Heart rate. Values are mean ± SD; RM ANOVA (all p>0.05)

Table 3. Baseline cardiovascular stress reactivity

	Δ Systolic BP (mmHg)	**Δ Diastolic BP (mmHg)**	**Δ HR (beats/minute)**
Men (n=13)			
IHGT	22 ± 8	11 ± 5	10 ± 5
SST	16 ± 5	11 ± 7	14 ± 5
CPT	24 ± 10	13 ± 7	10 ± 5
Women (n=11)			
IHGT	14 ± 3^{+}	9 ± 5	8 ± 5
SST	11 ± 6^{+}	8 ± 3	8± 4
CPT	20 ± 8	13± 5	10 ± 6

BP, blood pressure; HR, heart rate; IHGT, isometric handgrip task; SST, serial subtraction task; CPT, cold-pressor task. Values are mean ± SD; One-way ANOVA; $^{+}$Significantly different from men (p<0.05)

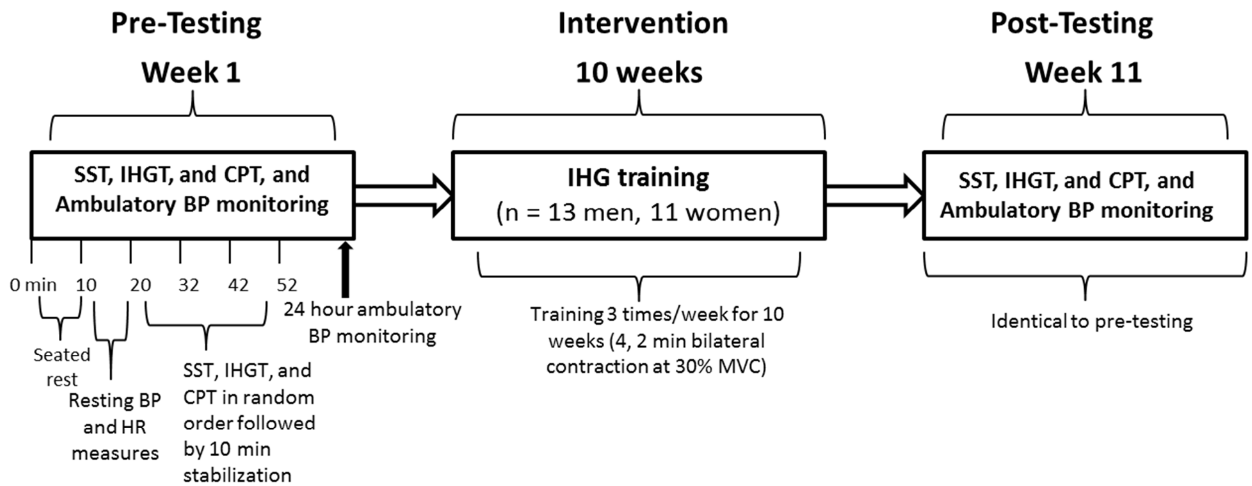

Figure 1. Schematic representation of study design**.** SST, serial subtraction task; IHGT, isometric handgrip task; CPT, cold pressor task; IHG, isometric handgrip; BP, blood pressure; HR, heart rate; MVC, maximum voluntary contraction

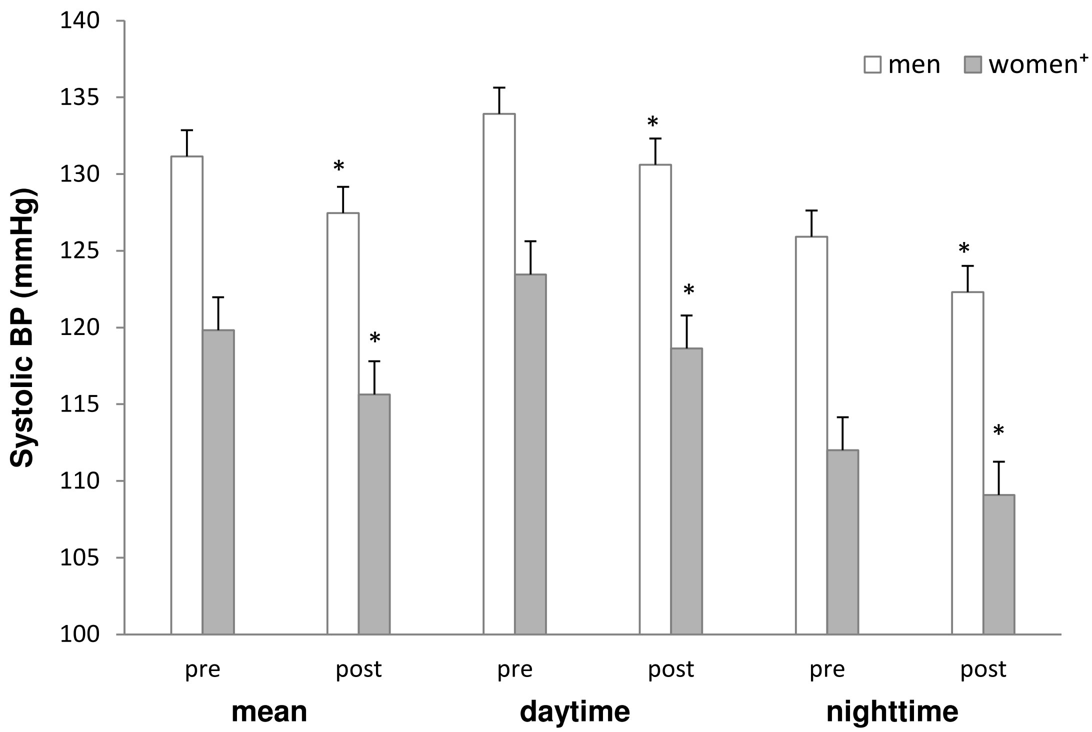

Figure 2. Effects of 10-weeks of IHG training on 24-hour mean, daytime, and nighttime systolic ambulatory BP in women (n=11) and men (n=13). Values are mean± SE; RM ANOVA; +Significantly different from men (p< 0.05). *Significantly different from pre (p<0.001).

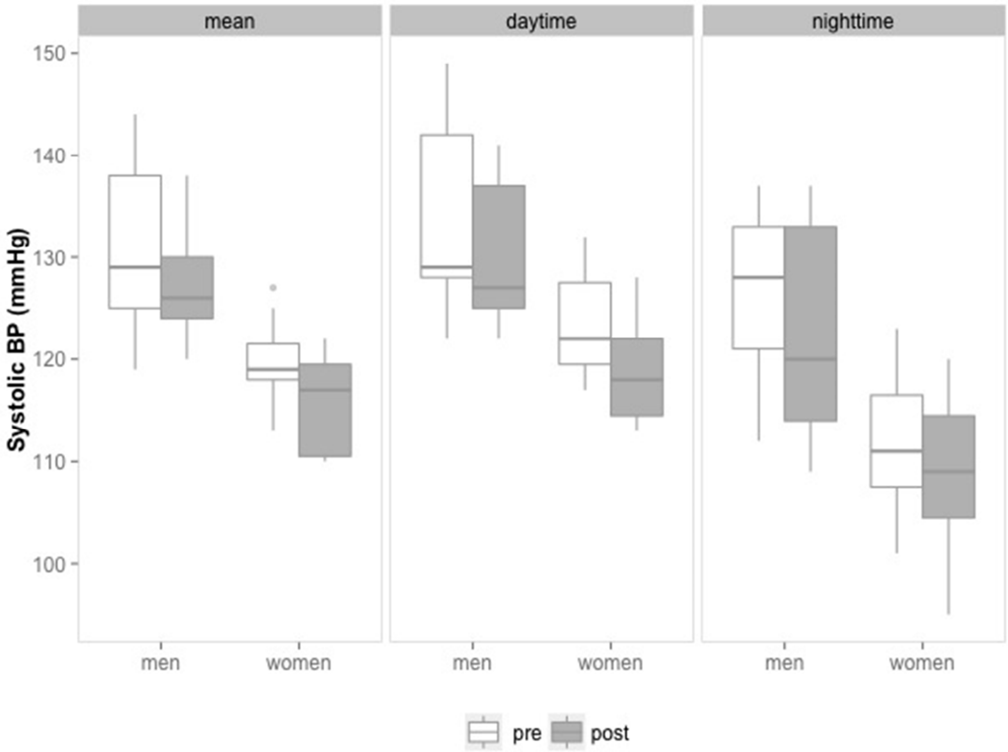

Figure 3a. Effects of 10 weeks of IHG training on mean, daytime, and nighttime systolic ambulatory BP in men (n=13) and women (n=11).

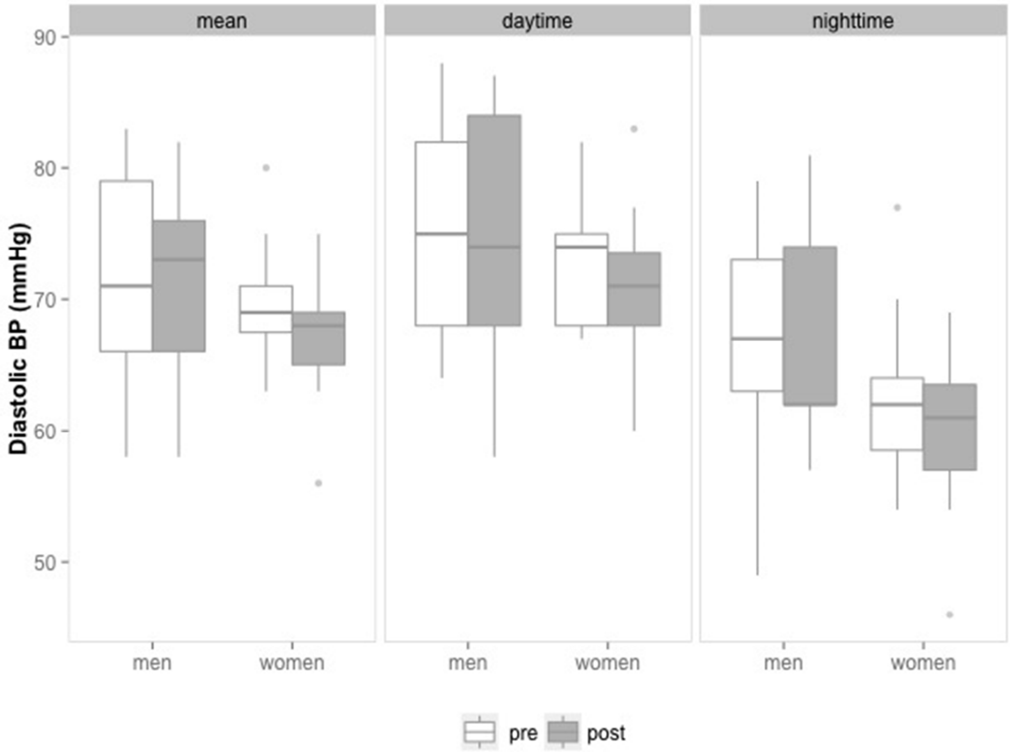

Figure 3b. Effects of 10 weeks of IHG training on mean, daytime, and nighttime diastolic ambulatory BP in men (n=13) and women (n=11).