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Reductions in ambulatory blood pressure in young normotensive men and women after isometric resistance 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 resistance training (IRT) on BP in men and women. Most of the previously published work has involved men, and used resting BP as the primary outcome variable. Early evidence suggests IRT is particularly effective in older women, and has positive influence on ambulatory BP, a better predictor of disease risk. With the World Health Organization now placing global emphasis on the primary prevention of hypertension, the main goal of this proof-of-concept study was to 1) examine if sex differences exist in the ambulatory BP-lowering effects of IRT in young, normotensive men and women, and 2) determine if these reductions can be predicted by simple laboratory stress tasks (a 2-minute sustained isometric contraction and a math task involving subtracting a 2 digit number from a series of numbers). There were no differences in the IRT-induced reductions in 24-hour (men: Δ4 mmHg, women: Δ4mmHg), daytime (men: Δ3 mmHg, women: Δ4 mmHg), or nighttime (men: Δ4 mmHg, women: Δ3 mmHg) ambulatory BP in men (n=13) and women (n=11, $p<0.05$); and these 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, to a similar magnitude in young healthy women as well as men, with IRT; however, the 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 in a larger clinical outcome trial.

Key Descriptors

Sex differences; ambulatory blood pressure; cardiovascular reactivity; isometric exercise; hypertension

1.0 Introduction

As the population ages, expands, and globalizes, disease patterns are shifting and non-communicable diseases, like cardiovascular disease (CVD), are becoming more common [1]. Presently, CVD is the leading cause of morbidity and mortality worldwide [2]. Hypertension (HT), a condition characterized by sustained elevations in resting systolic (≥ 140 mmHg) and/or diastolic (≥ 90 mmHg) blood pressure (BP) is a major risk factor for CVD related events that has been steadily increasing in prevalence [2]. 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 [2].

Despite such initiatives, primary prevention of HT is a challenging prospect that requires various measures ranging from lifestyle modification to pharmaceutical intervention(s) [3]. Isometric resistance training (IRT) involves multiple timed sustained (static) contractions performed at a set percentage of maximum voluntary contraction (MVC) on a programmed handgrip dynamometer was recently recommended by the American Heart Association (AHA) as an alternative BP-lowering treatment [4, 5]. This recommendation was founded in the accumulating evidence of the efficacy of IRT in reducing resting BP in individuals with and without HT, including those medicated for HT and those who exercise regularly [6-19]. Early evidence also suggests that IRT may be particularly effective in older women versus age-matched men [19], and has a positive influence on ambulatory BP [20]; a comprehensive measure of BP that provides insight into 24 hour BP fluctuations. Ambulatory BP is a better predictor of CVD risk than conventional office-based resting BP measurements [21, 22] and has emerged as the preferred approach for diagnosis and monitoring of therapeutic effectiveness [23, 24]. However, these have been largely under-investigated and have not been explored in young cohorts.

Cardiovascular reactivity, an individual's acute BP and heart rate (HR) response to a physical or mental stressor, has been used to probe these discrepant post-IRT responses [25]. Work by Millar and colleagues [14] 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 [9] 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 IRT 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 IRT. The association between BP reactivity to psychophysiological stressors and IRT-induced ambulatory BP reductions as well as whether sex differences exist has yet to be explored.

With the WHO now placing global emphasis on the primary prevention of HT, this proof-of-concept study was designed to extend these observations to young, healthy individuals. Aside from primary prevention efforts, most studies examining the effects of IRT have been designed to detect changes in BP following training and have not specifically addressed sex differences in responsiveness to the training stimulus. It has been previously demonstrated that IRT is particularly effective in post-menopausal women [19] and, thus, investigating if sex plays a role in IRT responsiveness in younger individuals is a natural extension to these findings. More specifically, the current investigation aimed: to 1) examine if sex differences exist in the ambulatory BP-lowering effects of IRT in young, normotensive men and women, and 2) determine if these reductions can be predicted by simple laboratory handgrip and math tasks (IHGT, SST). It was hypothesized that both men and women would experience similar reductions in ambulatory BP following 10 weeks of IRT [26]. It was further hypothesized that systolic BP reactivity to an IHGT and SST, but not a CPT, would be predictive of training 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 IRT [9, 14].

2.0 Method

2.1 Study Participants

Eligible participants were between 18-40 years of age, had normal resting BP (<140/90 mmHg), and physical activity levels and diet were monitored to ensure consistency throughout the intervention. Exclusion criteria for the study included a prior diagnosis of HT or CVD and/or prescribed pharmacotherapies (e.g., beta-blockers) known to influence cardiovascular function, and/or physical limitations impairing exercise performance. Of the 41 individuals screened, 35 were deemed eligible, and 24 young (25 ± 5 years), normotensive (resting office measure: 110 ± 5/64 ± 7 mmHg) men (n=13) and women (n=11) participated in the protocol.

2.2 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 order 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 IRT (week 11), at least 48 hours following the last training session. Please refer to Figure 1 for a schematic diagram of the study design.

2.3 Experimental Protocol

All participants were tested within 3 hours of each other (10 a.m.-1 p.m.), and baseline and post-IRT testing for each participant was performed at the same time of day (within 2 hours). All testing took place 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 [9]. Participants voided their bladder prior to the testing session to avoid a potential rise in blood pressure due to bladder distention [27].

2.4 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.

2.4.1 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 [9].

2.4.2 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) [9]. MVC was determined prior to contraction via electronic linear load cells contained within the handgrip dynamometer. The IHGT protocol was identical pre-and post-testing, and participants maintained a compliance score of 95% (% participants maintained 30% MVC).

2.4.3 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 [9] at both pre- and post-testing. The CPT was well tolerated as evidenced by all participants completing the task at both time points.

2.5 Ambulatory Blood Pressure: Once participants returned to baseline resting BP, following the completion of the last cardiovascular stress reactivity task (see section 2.4), ambulatory BP was monitored for 24-hours [24]. 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) [20]. Following the completion of baseline ambulatory

BP monitoring, a detailed history was documented of activities performed during this time. 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.

2.6 IRT Protocol

All participants trained on-site 3 times per week for 10 weeks using the bilateral IRT protocol (ZonaPLUS; Zona Health, Boise, ID, USA), which involved four, 2-minute isometric handgrip contractions, performed using alternating hands 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, protocol compliance % for each IRT bout (e.g., % of time 30% MVC was maintained over the duration of the bout), 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).

3.0 Statistical Analysis

One-way ANOVAs were performed on all baseline ambulatory measures to examine initial differences between men and women. The data set was tested for normality using the Shapiro-Wilk test and in order to assess the efficacy of IRT 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 [28]. The relationship between cardiovascular reactivity and IRT 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 [29, 19]. 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.

4.0 Results

All 24 participants trained for 10 weeks and completed 30 IRT sessions. Overall compliance to the IRT protocol was 97%, and averaged 98% for men and 96% for women. Over that time, activity and diet journal entries indicated that no changes in exercise, diet, or medication occurred in either sex. Importantly, no adverse events were reported in response to either the testing sessions or training intervention. BP and HR prior to and following training were normally distributed in both sexes. Shown in Table 1 and Table 2, men and women did not significantly differ in age, body mass index (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 ($p>0.05$).

4.1 Effects of IRT on Ambulatory BP and HR

Similar significant training-induced reductions in mean 24-hour (p<0.001, η_p^2 =0.51), daytime (p<0.001, η_p^2 =0.54), and nighttime (p<0.05, η_p^2 =0.30) systolic ambulatory BP were observed in both men and women (Table 2) with no interaction between sexes for mean systolic ambulatory BP over 24-hour (p=0.77), during daytime (p=0.36), or at nighttime (p=0.81). Figure 2 depicts the variation in measures of systolic and ambulatory diastolic BP between men and women. 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 2b) as well as 24-hour mean, daytime, and nighttime ambulatory HR remained unchanged in both men and women (Table 2). Despite no significant differences found between young men and women in the ANOVA analysis, it does appear that the range of mean and daytime systolic BP decreased more for men than women (Figure 2a).

4.2 The Relationships between Cardiovascular Reactivity Tests and 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).

5.0 Discussion

This study represents the first evaluation of the ambulatory BP-lowering effects of IRT 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 [22], our novel findings have important clinical implications, suggesting that IRT 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 are achieved with 10 weeks of IRT, and supports the idea that ambulatory BP would be lowered equally in men and women. While we interpret our findings to suggest IRT lowered systolic ambulatory BP, we understand that the reductions observed may reflect a regression to the mean. However, in a previous investigation from our lab assessing IRT-induced changes in ambulatory BP in medicated-hypertensives, clinically significant reductions were observed in comparison to the control group [20]. This suggests that the reduction in ambulatory BP observed in young men and women may be attributed to IRT.

Our observed reductions in daytime systolic ambulatory BP following IRT were similar in magnitude to reductions following aerobic training interventions (3mmHg) in normotensive participants [30, 31]. 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 IRT intervention. They also stand in contrast to similar studies with dynamic resistance training, where reductions in ambulatory BP have not been observed to date [32, 33]. Taken together, this could suggest a uniquely powerful BP-lowering training stimulus associated with this type of isometric resistance training, probably linked to local metabolite accumulation [34]. Our observations are in line with previous IRT work by Stiller-Moldovan and colleagues [20] who studied well-controlled medicated hypertensives, and showed clinically relevant reductions in mean 24-hour and nighttime ambulatory systolic BP following IRT. As nighttime ambulatory BP is a stronger predictor of CVD risk than daytime ambulatory BP, the finding of a sustained BP-lowering effect with IRT over a 24-hour period that is independent of sex may have important implications from a primary prevention standpoint [21]. Expanding the scope of this research to include non-hypertensive subjects with a heritable predisposition towards development of HT [35], along with 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 IRT.

The equal systolic ambulatory BP reductions observed in young men and women differ from previous work examining normotensive post-menopausal women and age-matched men. Specifically, an 8 week isometric resistance intervention by Millar and colleagues [13] revealed that normotensive post-menopausal women experience greater reductions in resting systolic BP than age-matched men following training. Although not stated in the study, the greater reduction in systolic BP observed in post-menopausal women may have been due to a higher pre-training systolic BP than men. Previously, it has been shown that individuals with higher pre-training resting BP values experience greater reductions following IRT [19]. Evidence suggests that post-menopausal women have higher BP values than pre-menopausal women, suggesting ovarian hormones may play a role in modulation of BP [36]. Work by Hart and colleagues [37] point to post-menopausal women having altered neuro-humoral BP control compared to young women and may explain why risk of HT development is higher in young men and post-menopausal women. The potentially protective β-adrenergic effect in young women, which is thought to blunt the vasoconstrictor effect of sympathetic nervous system activity, appears to be lost after menopause and may contribute to increases in BP [37]. It is possible that IRT may counteract the B-adrenergic effect in women and thus may be a more potent stimulus in post-menopausal women. Exploring the effects of IRT in post-menopausal women is an area that warrants further investigation and may represent an efficacious method for HT prevention in this high risk population.

The smaller range in mean and daytime systolic BP values for men post-IRT suggest an overall shift in systolic BP values for the group, potentially indicating a greater effect in men than women. This suggestion of effect requires further examination through additional research with larger sample sizes.

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 IRT. While sex differences were noted in systolic BP responses to the 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-IRT reductions in ambulatory BP. These data suggest that BP-lowering effects of IRT 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 [38]. Moreover, it is important to note that previous work examining cardiovascular reactivity and its association with IRT-induced reductions in resting BP were addressed in normotensive and hypertensive, older individuals [14, 9]. The predictive correlations found in these older populations may be due to higher pre-training sympathetic tone, as related to higher resting BP, than in young, normotensive counterparts [39].

Our findings provide the first evidence that IRT may lower ambulatory systolic BP in normotensive individuals, and that this intervention has potential benefit in both young men and women. Our results support the need for further study of IRT as a time-efficient means for targeted BP reduction in young, normotensive people who may be at-risk of HT, especially in women of all ages. Considering the prevalence of CVD worldwide, and the recent priority placed on prevention of HT by the WHO [2], IRT could represent a cornerstone strategy for future work aimed at primary prevention of HT worldwide.

6.0 Limitations

The current proof-of-concept study was exploratory and thus, was not designed to elucidate the mechanisms behind the observed reductions in ambulatory systolic BP following IRT. Despite there being a small sample size and the absence of a true control group, the study was sufficiently powered to detect statistical significance and had a moderate effect size to indicate practical significance. Moreover, this study provides the first head to head comparison between men and women with respect to the effects of IRT training on ambulatory BP, setting the foundation for future randomized control trials.

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Figure Captions

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 2a. Effects of 10 weeks of IRT on mean, daytime, and nighttime systolic ambulatory BP in men (n=13) and women (n=11). Boxplot representation of the variation in systolic ambulatory BP.

Figure 2b. Effects of 10 weeks of IRT on mean, daytime, and nighttime diastolic ambulatory BP in men (n=13) and women (n=11). Boxplot representation of the variation in diastolic ambulatory BP.

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 ± 10⁺
BMI (kg/m^2)	25 ± 4	23 ± 3

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

Table 2

Table 2. Effects of IRT on ambulatory measures

	Men (n=13)		**Women (n=11)**		
	pre	post	pre	post	*p*-value
Systolic BP (mmHg)					
mean 24 hour	131 ± 7	127 ± 5	120 ± 3	116 ± 4	<0.001
daytime	134 ± 8	131 ± 7	123 ± 5	119 ± 4	<0.001
nighttime	126 ± 8	122 ± 10	112 ± 6	109 ± 7	0.03
Diastolic BP (mmHg)					
mean 24 hour	72 ± 8	72 ± 7	69 ± 4	67 ± 5	0.20
daytime	75 ± 8	75 ± 8	73 ± 5	71 ± 6	0.20
nighttime	66 ± 9	66 ± 8	62 ± 6	60 ± 6	0.44
HR (beats/minute)					
mean 24 hour	67 ± 8	67 ± 7	73 ± 9	72 ± 10	0.68
daytime	69 ± 8	69 ± 7	76 ± 9	75 ± 9	0.65
nighttime	63 ± 8	64 ± 9	69 ± 9	67 ± 12	0.75

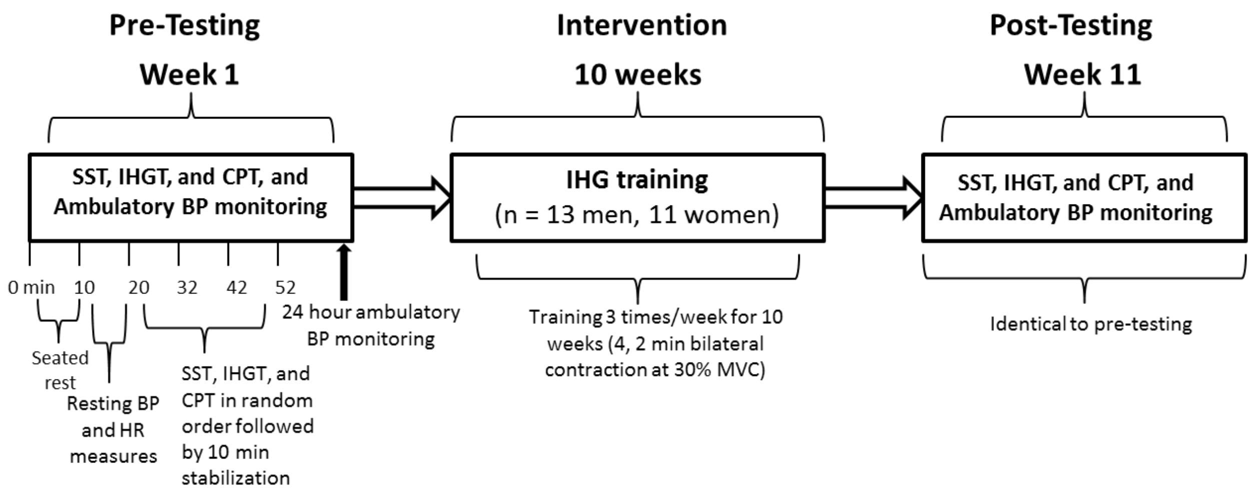
BP, blood pressure; HR, heart rate. Values are mean ± SD; RM ANOVA. No interaction effects (sex * time) were observed for any ambulatory measure (p>0.05).

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



Pre-Testing
Week 1
Intervention
10 weeks
Post-Testing
Week 11
SST, IHGT, and CPT, and Ambulatory BP monitoring
IHG training
(n = 13 men, 11 women)
SST, IHGT, and CPT, and Ambulatory BP monitoring
0 min
10
20
32
42
52
24 hour ambulatory BP monitoring
Seated rest
Resting BP and HR measures
SST, IHGT, and CPT in random order followed by 10 min stabilization
Training 3 times/week for 10 weeks (4, 2 min bilateral contraction at 30% MVC)
Identical to pre-testing

Figure 2a

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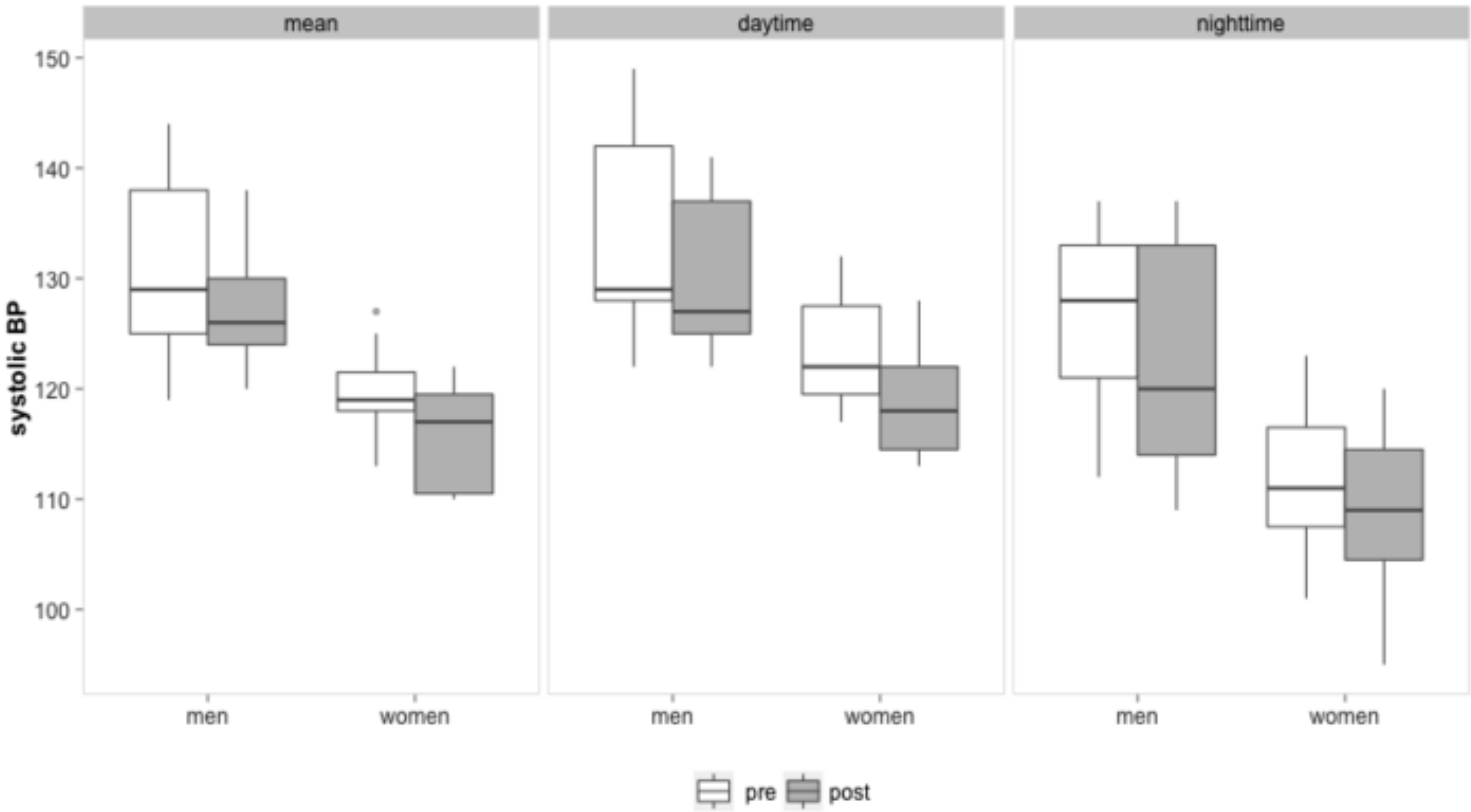

Figure 2b

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