Published in final edited form as:

Metabolism. 2012 December ; 61(12): 1739–1746. doi:10.1016/j.metabol.2012.07.014.

Exercise training improves hemodynamic recovery to isometric exercise in obese men with type 2 diabetes but not in obese women

Jill A. Kanaley^{1,2}, Styliani Gouloupoulou², Ruth Franklin³, Tracy Baynard⁶, Robert L Carhart Jr⁴, Ruth S Weinstock^{4,5}, and Bo Fernhall⁶

¹Department of Nutrition and Exercise Physiology, University of Missouri, Columbia, MO

²Department of Exercise Science, Syracuse University, Syracuse, NY

³Department of Kinesiology, University of Illinois, Urbana, IL

⁴Department of Medicine, SUNY Upstate Medical University, Syracuse, NY, USA

⁵Department of Veterans Affairs Medical Center, SUNY Upstate Medical University, Syracuse, NY

⁶Department of Kinesiology & Nutrition, University of Illinois at Chicago, Chicago, IL

Abstract

Objectives—Women with type 2 diabetes (T2D) show greater rates of mortality due to ischemic heart disease than men with T2D. We aimed to examine cardiovascular and autonomic function responses to isometric handgrip (IHG) exercise between men and women with T2D, before and after an exercise training program.

Materials/Methods—Hemodynamic responses were measured in 22 men and women with T2D during and following a 3-minute IHG test, and before and after 16 wks of aerobic exercise training.

Results—Women had a smaller decrease in mean arterial pressure (MAP) and systolic blood pressure (BP) during recovery from IHG ($\Delta\text{MAP}_{\text{REC}}$) than men pre- and post-training ($P<0.05$). Men showed a greater reduction in diastolic BP during recovery from IHG ($P<0.05$), and exercise training improved this response in men but not in women (men, pre-training: -13.9 ± 1.8 , post-training: -20.5 ± 5.3 mmHg vs. women, pre-training: -10.7 ± 1.7 , post-training: -4.1 ± 4.9 mmHg; $P<0.05$). Men had a greater reduction in sympathetic modulation of vasomotor tone ($P<0.05$), as estimated by blood pressure variability, following IHG. This response was accentuated after training, while this training effect was not seen in women. Post-training $\Delta\text{MAP}_{\text{REC}}$ was correlated with recovery of low frequency component of the BP spectrum ($\Delta\text{LF}_{\text{SBP}_{\text{REC}}}$, $r=0.52$, $P<0.05$).

Conclusions—Differences in BP recovery immediately following IHG may be attributed to gender differences in cardiovascular autonomic modulation. An improvement in these responses

© 2012 Elsevier Inc. All rights reserved.

Correspondence: Jill Kanaley, PhD 217 Gwynn Hall Columbia, MO 65211 kanaleyj@missouri.edu Phone: 573-882-2519 .

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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

occurs following aerobic exercise training in obese men, but not in obese women with T2D which reflects a better adaptive autonomic response to exercise training.

Keywords

exercise; mean arterial pressure; blood pressure variability

Introduction

Poor glycemic control and insulin resistance are associated with autonomic neuropathies, hemodynamic irregularities and increased peripheral sympathetic nervous system activity. Static exercise, or isometric hand grip exercise (IHG), is a clinically useful tool as it invokes increases in heart rate (HR), blood pressure (BP) and muscle sympathetic nerve activity (MSNA) via central command and the exercise pressor reflex. Obese individuals have reduced sympathetic activity during IHG compared to lean persons, and obese individuals with type 2 diabetes (T2D) show a smaller rise in diastolic BP (DBP) during IHG compared to those without diabetes, suggesting that obesity and diabetes are associated with reduced hemodynamic and autonomic responses to IHG.

Many studies report sexual dimorphism in autonomic nervous system function, as well as in the metabolic and cardiovascular responses to prolonged submaximal exercise in healthy, non-obese individuals. Christou et al. have shown that premenopausal women have lower tonic sympathoadrenal activity-related autonomic nervous system support of BP and less effective baroreflex buffering of BP than men of similar age. In healthy individuals, data regarding gender differences in the cardiovascular and autonomic response to IHG have been conflicting. One study found differences in adrenergic patterns between men and women in response to isometric exercise, and another study demonstrated attenuated increases in BP and MSNA in women compared to men. On the other hand, Jones et al. reported that gender did not influence sympathetic neural reactivity to IHG.

Gender differences in morbidity and mortality in individuals with T2D have been observed and there are greater rates of mortality due to ischemic heart disease in women than in men with T2D. It is also well established that autonomic dysfunction is associated with early mortality from cardiovascular disease, thus differences in autonomic function between men and women with T2D are potentially important. It has been suggested that gender differences in autonomic neural damage in diabetic patients is an important factor possibly explaining the higher cardiovascular risk in women. However autonomic function differences among populations are not always present at rest, but become evident following a stressor, such as upright tilt or acute exercise, including IHG.

Aerobic exercise training is often prescribed as a lifestyle modification to patients with T2D because of its hypoglycemic effects and its influences on sympathetic overactivity and insulin resistance. Prior work from our laboratory has shown that exercise training improved HR variability (index of cardiac autonomic modulation) and increased the high frequency (HF) component of HR spectrum (HF_{RRI}, index of cardiac parasympathetic modulation) to upright tilt in obese subjects without T2D, but not in those with T2D. Conversely, we have reported that exercise training can reverse the blunted autonomic response to glucose intake in patients with T2D. Taken together, these studies suggest that obese individuals with T2D gain different benefits from exercise training depending on the stress stimuli and raise the question of whether exercise training influences the hemodynamic and autonomic responses to IHG in this population. Yet no study to date has examined gender differences in response to training for both cardiovascular and autonomic function in this population.

Thus, we hypothesized that women with T2D would demonstrate an attenuated cardiovascular response during and immediately following IHG than men, and that a 16 wk aerobic exercise program would improve the hemodynamic responses (e.g. mean arterial pressure (MAP) and HR) to IHG in both men and women with T2D. Further, it was hypothesized that exercise training would augment both restoration of cardiac vagal modulation (e.g. greater increase in HF_{RRI} during recovery from IHG following training) and recovery of sympathetic vasomotor modulation following IHG (e.g. greater reduction in low frequency component of SBP spectrum, (LF_{SBP}), during recovery from IHG following training).

Methods

Experimental design

These data are part of a larger project that has been reported in detail previously. On the subject's first laboratory visit, an exercise stress test was conducted to determine cardiovascular fitness and to screen for heart disease. On the second visit (a minimum of one wk later), subjects arrived at the lab at 0700 h following a 12-h overnight fast. Subjects rested quietly, and then the IHG test was conducted. Following this study day, all subjects were exercise-trained for 16 wks and all testing was repeated at the end of the exercise program.

Subjects

Twenty-six obese individuals, who had been previously diagnosed with T2D by their physician (average time of diagnosis: 4 years prior to inclusion in the study), were recruited. Twenty-two subjects (men, n=10; women, n=12) completed all testing (attrition rate: 15%). To be included in the study subjects had to be in the age range of 40-60 y, have a BMI between 30-45 kg/m², a fasting glucose ≥ 126 mg/dL, and 2 h oral glucose tolerance test (OGTT) glucose ≥ 200 mg/dL. The exclusion criteria have been previously reported. Briefly, all subjects were physically inactive, did not have overt peripheral neuropathy (no pain or tingling in the feet), were nonsmokers, had no signs or history of overt heart disease, were not taking β -blockers, did not have orthopedic limitations and none were taking insulin or Byetta. We excluded subjects that were taking medications known to alter heart rate, treated for cancer or diagnosed with chronic conditions (e.g. lupus, etc). Some of the women were post-menopausal (n=3) and all of these women were on hormone replacement therapy (n=3). Pre-menopausal women were studied within the first 10 days of their menstrual cycle. All subjects were on some medications, but the medication and the dosage was held constant throughout the study (Table 1). No subject had a change in medication while enrolled. Written informed consent, approved by the Institutional Review Boards at Syracuse University and SUNY Upstate Medical University, was obtained from all subjects. We received funding for this project from the National Institute of Health.

Anthropometric testing

Height and weight were obtained (Healthometer, Sunbeam Products Inc, Boca Raton, FL). and body mass index was calculated. Percent body fat was measured using the Bod Pod (Life Measurements Inc., Concord, CA) according to the manufacturer's guidelines. Residual volume was determined using the breathing technique prescribed by the manufacturer. All subjects wore a bathing suit and swim cap while being tested in the Bod Pod.

Oral glucose tolerance test

An OGTT was conducted prior to and after the exercise training program as previously reported. At 0700 h following an overnight fast, a catheter was placed in a forearm vein prior to any testing. Baseline blood samples were taken. Upon completion of the IHG testing, subjects consumed 75 g dextrose drink (NERL Diagnostics, East Providence, RI, USA) and a 5 ml blood sample was drawn every 30 min for 4 h. The line was kept patent with saline during this time period. Glucose and insulin values reported here are based on these measurements.

Exercise Training

Pre- and post-intervention, all subjects had an exercise stress test performed on the treadmill, which was evaluated by a cardiologist. A continuous treadmill protocol was used to determine the peak oxygen consumption (VO_2 peak, aerobic capacity) (22). Subjects started walking at 2.5 mph and every 2 min treadmill speed was increased by 0.5 mph. Once a speed of 3.5 mph was attained the grade was increased by 2% every 2 min until exhaustion. Indirect calorimetry (Cosmed Quark K4b², Rome, Italy) was used to measure oxygen consumption. VO_2 peak was selected as the highest O_2 consumption attained according to procedures previously described. During this test subjects wore a 10 lead EKG which was monitored and evaluated by the cardiologist. The VO_2 peak was utilized to determine the initial training load and the effectiveness of the exercise program.

The exercise training program had a duration of 16 weeks and the training regime required subjects to walk for 30 min/day, 4 days/wk at 65% of their respective VO_2 peak. At week 8, exercise duration was increased to 45 min/day. This was a supervised home-based program where the subjects trained in a one-on-one supervised setting one day/wk and then trained the other 3 days/wk on their own. Subject had the choice of walking outdoors or on a treadmill and were allowed to split their training into shorter durations if that fit their schedule better, but were encouraged to maintain intensity. Weekly training with the subjects reinforced the workload prescribed. All subjects were familiarized with monitoring their exercise intensity using HR and ratings of perceived exertion and were required to complete exercise logs, which were discussed in weekly meetings (22). Subjects included in this analysis attended 90% of the training sessions (compliance rate), and were consistently within the prescribed HR and RPE range. Subjects were asked to maintain their dietary habits.

Isometric Handgrip Test

Measurement of IHG was conducted at ~0800 h in all subjects before and after the training period. Following familiarization with the IHG protocol, handgrip maximal voluntary contraction (MVC) was measured three times. Briefly, maximal isometric force of the dominant hand was measured three times 1-2 min apart using a calibrated handgrip dynamometer (Biopac Systems Inc., Santa Barbara, CA) with the subjects being in the seated position with their elbow flexed at 90°. Subjects were told to squeeze the dynamometer as hard as possible and to hold this for 3-5 sec. The highest value was used as the subject's MVC. After determination of MVC, subjects performed a sustained isometric contraction at 30% MVC for 3 min, and visual feedback was provided to ensure the subjects were at the appropriate intensity. Electrocardiographic R-R intervals were continuously recorded via a modified CM5 lead interfaced with a digital acquisition system (Biopac) and arterial pressure was measured with beat-by-beat finger plethysmography (Portapres, TNO Biomedical Instrumentation, Amsterdam, The Netherlands) during 3 min of quiet rest, 3 min of isometric exercise at 30% MVC and 3 min of recovery from IHG. Systolic blood pressure (SBP), DBP, mean arterial pressure (MAP), HR, cardiac output (CO) and total peripheral resistance (TPR) were derived from the arterial pressure waveform obtained from the

Portapress. During this test, subjects were instructed to breathe at a regular pace, closely watched for breathholding and to avoid the Valsalva maneuver.

Data Analyses

Heart Rate Variability—After visual filtering and automatic editing of the ECG signal according to procedures described by Huikuri et al., HR variability data were analyzed in 2 min epochs (Heart Signal software, Oulu, Finland). The high frequency power of the HR variability spectrum (HF_{RRI}) was used as an index of cardiovagal modulation and was expressed in normalized units (nu, normalized to total power of the HR spectrum), while the low frequency (LF_{RRI})/ HF_{RRI} ratio was used as an indirect measure of cardiac sympathovagal dominance.

Blood Pressure Variability & Baroreflex Sensitivity—Systolic BP variability was calculated from the systolic arterial pressure waveform collected by the Portapres (WinCPRS, Absolute Aliens Oy, Turku, Finland). The spectrum of the non-equidistant waveform of the systolic BP time series was calculated using fast Fourier transformation in the frequency domain and spectral power at low frequency ranges (LF_{SBP} : 0.05-0.15 Hz) was used as an index of sympathetic modulation of vasomotor tone.

Baroreflex sensitivity (BRS) was determined from the coupling between fluctuations in R-R intervals and SBP using the sequence technique as previously described (WinCPRS, Absolute Aliens Oy, Turku, Finland). Briefly, the slope of the regression line between SBP and R-R intervals that changed in the same direction for 3 or more consecutive beats for at least 4 msec was used to calculate BRS ($\text{ms}\cdot\text{mm Hg}^{-1}$).

Blood analyses—The YSI 2300 Stat (Yellow Springs Instruments, Inc., Yellow Springs, OH) was employed to determine blood glucose concentrations. Blood samples for insulin concentrations were assayed in duplicate with kits from Diagnostic Products Corp (Los Angeles, CA). Hemoglobin A1C (HbA1c) was determined with kits from Diabetes Technologies Inc. (Thomasville, GA). Insulin sensitivity was calculated using the quantitative insulin sensitivity check index (QUICKI) equation and insulin resistance using the homeostatic model assessment for insulin resistance (HOMA-IR).

Hemodynamic data—Hemodynamic data are reported as absolute responses and as change (Δ) (e.g., MAP change during recovery from IHG, $\Delta\text{MAP}_{\text{REC}}$ = average of last 2 min of recovery values – the average of the last 2 minutes of the IHG contraction). The last 2 min of recordings for task and recovery were used to coincide with the data used for the HR and BP variability analyses. This time frame was selected to obtain a stationary signal for the HR and BP variability analyses.

Statistical Analysis—A 2×2 analysis of variance with repeated measures was used to determine differences in descriptive characteristics pre- and post-training between groups. The indexes of BP and HR variability were not normally distributed and thus, statistics on these measures were performed after logarithmic transformation ($\ln$). All data are expressed as mean $\pm$ SE. The data were analyzed using a 3-way analysis of variance (ANOVA) with repeated measures ($2(\text{male, female}) \times 2(\text{IHG, recovery}) \times 2(\text{pre-, post-training})$). In addition, Pearson correlations were performed. If significant interactions were detected, post hoc analysis with a Bonferroni correction was performed. The significance level of all statistical analyses was set at $\alpha=0.05$. A power analysis was conducted prior to initiating the study based on preliminary data and indicated that a sample size of 10 subjects per group will be sufficient to give better than 80% power to detect at least a 1.3 standard deviation difference between genders when the alpha is set at a 0.05 level in a two sided analysis.

Results

At the beginning of the study, men weighed more, greater fat free mass (FFM) and a lower percent body fat compared to the women ($P<0.05$, Table 2) but there were no group differences in age, fasting glucose levels, fasting insulin levels, HbA1c, insulin resistance (HOMA) or insulin sensitivity (QUICKI equation). Exercise training did not affect any of the above variables ($P>0.05$). Men had higher pre-training VO_2 peak (ml/kg/min) and exercise training increased VO_2 peak ($P<0.01$) similarly in both groups (Table 2), indicating an exercise training effect. The men had a greater fat free mass (FFM) than women pre training as would be expected ($P<0.01$) but neither men nor women showed a significant change in their FFM or fat mass with the exercise training. IHG strength was greater in the men than in the women ($P<0.01$) and was not affected by training (men, pre-training: 57.8 ± 3.1 kg, post-training: 56.7 ± 2.4 kg; women, pre-training: 38.8 ± 2.7 kg, post-training: 37.7 ± 2.3 kg).

Table 3 shows the hemodynamic variables for the men and women before and after exercise training. Resting SBP, DBP, and MAP were significantly higher in men than in women both pre- and post-training ($P<0.05$) but there were no differences in resting HR. There was no effect of training on resting BP or HR. Resting BRS was significantly lower in men compared to women (7.4 ± 0.9 vs. 10.5 ± 0.6 ms/mmHg, $P<0.05$, Table 3), and there was no training effect on BRS.

Mean arterial pressure increased in response to IHG (MAP_{IHG}) and there were no gender differences in these responses pre- and post-training ($P<0.001$, Table 3, Figure 1a). There were no training effects on MAP responses to IHG. These results did not change after adjusting for gender differences in resting MAP values. Women had a smaller reduction in MAP following IHG ($\Delta\text{MAP}_{\text{REC}}$) than men (Figure 1b) and this difference was evident pre- and post-training ($P<0.05$, gender by training interaction). Adjusting the data for gender differences in body weight, BMI, MVC, resting VO_2 or resting BP values did not alter these findings.

SBP and DBP increased in response to IHG similarly in men and women and exercise training did not affect these responses. Conversely, men showed a greater reduction in SBP and DBP (greater ΔSBP and ΔDBP from IHG values) during recovery from IHG ($P<0.05$, Table 3) and exercise training improved recovery DBP (e.g. greater reduction in DBP following IHG) in men but not in women (men, pre-training: -13.9 ± 1.8 mmHg, post-training: -20.5 ± 5.3 mmHg vs. women, pre-training: -10.7 ± 1.7 mmHg, post-training: -4.1 ± 4.9 mmHg; gender by training interaction, $P<0.05$).

Total peripheral resistance (TPR) increased during IHG and decreased following the task (rest: 0.63 ± 0.31 mmHg.s/mL vs. IHG: 0.66 ± 0.029 mmHg.s/mL vs. recovery: 0.60 ± 0.023 mmHg.s/mL; task effect, $P<0.0001$) similarly in men and women, and exercise training did not alter these responses. IHG induced an increase in CO, which was greater in men compared to women (men, rest: 8.7 ± 0.5 , IHG 10.1 ± 0.6 L/min vs. women, rest: 8.3 ± 0.5 , IHG 8.8 ± 0.5 L/min, task by gender interaction, $P<0.05$). Further, men exhibited a larger decrease in CO during recovery from IHG ($\Delta\text{CO}_{\text{REC}}$, men: 0.42 ± 0.07 L/min vs. women: 0.16 ± 0.07 L/min, $P<0.05$). CO responses to IHG and recovery from IHG did not change following exercise training in either men or women.

There were no gender differences in HR increase in response to IHG (HR_{IHG}) and decrease following IHG (HR_{REC}) and exercise training had no impact on these variables. BRS was reduced during IHG and was restored to resting values during recovery from IHG (task effect, $P<0.001$) similarly in men and women, pre- and post-training.

There were no gender differences in $\ln\text{LF}_{\text{SBP}}$ during rest and in response to IHG (Figure 2a); however, $\ln\text{LF}_{\text{SBP}}$ following IHG ($\Delta\ln\text{LF}_{\text{SBP}}^{\text{Prec}}$) increased in women while it decreased in men ($P<0.05$). There were significant main effects of training ($P<0.01$) and gender ($P<0.05$) on the $\Delta\ln\text{LF}_{\text{SBP}}^{\text{Prec}}$, but the improvement in $\Delta\ln\text{LF}_{\text{SBP}}^{\text{Prec}}$ was greater in men compared to women, as reflected by a more negative response ($P<0.05$ training by gender interaction, Figure 2b). These data indicate that aerobic exercise training improved recovery of sympathetic vasomotor tone following IHG in men but not in women with T2D.

HF_{RRI} decreased in response to IHG ($P<0.05$) and there was no effect of training or gender on this response (Table 3). Training augmented HF_{RRI} recovery from IHG ($\Delta\text{HF}_{\text{REC}}$: pre-training: $0.023\pm0.033 \text{ msec}^2$, post-training: $0.071\pm0.038 \text{ msec}^2$, main effect, $P<0.01$) similarly in both groups, suggesting that aerobic exercise training improves restoration of cardiac vagal modulation following IHG in both men and women with T2D. $\text{LF}_{\text{RRI}}/\text{HF}_{\text{RRI}}$, an index of sympathovagal dominance, showed an increase during IHG and a decrease during recovery similarly in both groups, pre- and post-training ($\text{LF}_{\text{RRI}}/\text{HF}_{\text{RRI}}^{\text{(REC)}}$, men: pre-training, 0.146 ± 0.260 ; post-training, 0.416 ± 0.289 vs. women: pre-training, 0.022 ± 0.240 , post-training, -0.378 ± 0.196 , task and training main effects, $P<0.05$).

Post-training $\Delta\text{MAP}_{\text{REC}}$ was correlated with $\Delta\text{LF}_{\text{SBP}}^{\text{Prec}}$ ($r=0.519$, $p=.033$) and MVC ($r=-0.482$, $p<0.05$). These correlations were not gender dependent.

Discussion

The main finding of this study is that despite similar responses to an IHG task, obese men and women with T2D have different hemodynamic and autonomic recovery responses immediately following IHG and that exercise training improves these responses only in men. These gender differences in the recovery responses cannot be attributed to differences in resting BP values, body weight, FFM, BMI, aerobic capacity or diabetic status.

Healthy, non-obese women show smaller cardiovascular responses to IHG compared to men; however, our findings demonstrate that there are no differences in hemodynamic responses to IHG between obese men and women with T2D. Previous investigators postulated that the muscle metaboreflex contribution to sympathetic outflow during exercise might be reduced in healthy women compared to men. Further, earlier studies have shown that women are more fatigue resistant to isometric exercise than men, which has been attributed to differences in the metaboreflex response or differences in the sensitivity of the type III/IV afferents to this stimulus. Differences in the amount of the muscle mass activated and maximal strength have also been linked to gender differences in hemodynamic responses to isometric exercise tasks. In the present study, obese women with T2D had a 33% lower absolute strength than obese men with T2D while exercising at the same relative intensity. The greater strength produced by the men could result in higher intramuscular pressures, greater compression of the active tissue vasculature and a higher imbalance between blood supply and demand. In contrast to the anticipated outcome, in our study, women with T2D showed similar responses to IHG as men, suggesting that diabetes may have altered their hemodynamic response to this stressor (e.g. similar and not lower BP responses to IHG compared to men); however, this speculation warrants further investigation.

Exercise training improved restoration of cardiovagal autonomic modulation following IHG in both men and women, but improved recovery of sympathetic vasomotor tone after IHG in men also. The gender-specific autonomic adaptations to aerobic exercise training cannot be attributed to gender differences in strength, since partial correlation suggested no gender differences in the relationship between MAP and MVC, and muscle strength did not

improve in any group with training. No differences were observed between the men and women in their fasting glucose, insulin or insulin sensitivity values; therefore, gender differences in vascular sympathetic modulation cannot be attributed to differences in diabetic status. Based on a significant association between the $\Delta\text{LF}_{\text{SBP}}$ recovery and the $\Delta\text{MAP}_{\text{REC}}$, we suggest that a greater BP recovery after an isometric task seen in men with T2D is attributed to greater recovery of sympathetic vasomotor tone in this population, reflecting an improvement in autonomic adaptations to modulatory input or simply a faster recovery of sympathetic tone per se. The women with T2D showed a small change in BP variability responses during recovery from IHG following exercise training, and consequently, they did not experience any improvement in BP recovery responses. LF_{SBP} recovery accounted for ~25% of total variance in MAP responses after IHG, indicating that additional factors (e.g. endocrine, medications, absolute forearm muscle mass, etc.) are responsible for gender differences in MAP recovery from IHG and response to exercise training. It is noteworthy that the improvements in the hemodynamic profile of men with T2D in this study occurred in the absence of any changes in body composition and glycemic control, suggesting that a walking program of moderate-intensity may not improve body composition and diabetic status in medicated men with T2D but it improves autonomic and hemodynamic responses following physiological stressors.

The gender differences observed in BP responses during the recovery period following IHG may be partially attributed to differences in CO; the men showed a 0.5 L/min decline in CO while women had a 0.2 L/min decline following IHG. This decrease in CO following resistance exercise has been reported on numerous occasions. Previous studies have shown greater decrements in CO post-exercise training, and the degree of change appears to be dependent on the initial state of hypertension. In our study, there were no differences in resting BP but most of the men were treated with anti-hypertensive medications. Thus, gender differences in recovery CO may have contributed to gender differences in BP recovery following IHG.

There are limitations with this study. First, the sample size is relatively small; however we were still able to detect significant gender differences and this indicates that gender differences need to be further examined with regards to exercise training in individuals with T2D. Further, we did not compare the stress-induced hemodynamic changes to a non-exercising group of obese individuals with T2D, but most of these measures are relatively stable over time in the absence of outside stresses. Also, we did not measure sympathetic neural activity directly and have speculated on these differences between men and women based on indirect assessments of HR and BP variability. Additionally, we selected an exercise training stimulus, which was not specific to the task (handgrip) being tested. Nevertheless, the mode of exercise selected was to maximize the relevance of our exercise training program for the population tested since this type of training is typically recommended to patients with T2D. Although we did noted gender-differences in this study, we do acknowledge there are many factors beyond just biological sex differences that may contribute to the differences we observed.

In conclusion, studies have suggested gender differences in the morbidity and mortality of diabetic patients, and potentially gender differences in autonomic neural damage in patients with T2D may explain this phenomenon. Our data suggest that men and women with T2D have a differential response to aerobic exercise training, with men showing better adaptability of the autonomic nervous system and hemodynamic improvements, and with women exhibiting a blunted response to this training stimulus. Interestingly, cardiovascular improvements in men with T2D occur in the absence of any change in body weight, body composition and glycemic control and are accompanied by improvements in sympathetic modulation of vasomotor tone. These data may have important clinical implications because

they suggest that women have poorer responses to the typical lifestyle treatments and this may confound their risk profile and contribute to the gender disparity in CVD mortality trends. Finally, our findings suggest that gender differences should be considered when hemodynamic responses to IHG are studied.

Acknowledgments

We thank Rose Kingsbury, RN, NP for her dedication to the study and placing all of the catheters. This project was supported by National Institute of Health (NIH) Grant R21DK063179.

Jill A. Kanalley – study design, data collection, data analysis, interpretation and manuscript preparation

Styliani Gouloupoulou - data collection, data analysis, interpretation and manuscript preparation Ruth Franklin - data collection, data analysis, and manuscript preparation

Tracy Baynard - data collection, data analysis, and manuscript preparation

Robert L Carhart, Jr - data collection and manuscript preparation

Ruth S Weinstock - data analysis, interpretation and manuscript preparation

Bo Fernhall – study design, data analysis, interpretation and manuscript preparation

Abbreviations

(T2D)	type 2 diabetes
(IHG)	isometric handgrip
(MAP)	mean arterial pressure
(SBP)	systolic blood pressure
(Δ)	change
(ΔLFSBPrec)	recovery from IHG ($\Delta\text{MAP}_{\text{REC}}$) low frequency component of the BP spectrum
(HR)	heart rate
(DBP)	diastolic blood pressure
(MSNA)	muscle sympathetic nerve activity
(HF)	high frequency
(HF_{RRI}, index of cardiac parasympathetic modulation)	component of HR spectrum
(OGTT)	oral glucose tolerance test
(VO₂ peak, aerobic capacity)	peak oxygen consumption
(MVC)	maximal voluntary contraction
(CO)	cardiac output
(HF_{RRI}) normalized units (nu)	HR variability spectrum
(LF_{RRI})	low frequency
(HbA1c)	Hemoglobin A1C
(QUICKI)	quantitative insulin sensitivity check index
(HOMA-IR)	homeostatic model assessment for insulin resistance

(ln)	logarithmic transformation
(TPR)	Total peripheral resistance
(HR _{IHG})	HR response to IHG
(HR _{REC})	HR response following IHG

References

1. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, et al. Sympathetic activation in obese normotensive subjects. *Hypertension*. 1995; 25(4 Pt 1):560–3. Epub 1995/04/01. [PubMed: 7721398]
2. Grassi G, Seravalle G, Colombo M, Bolla G, Cattaneo BM, Cavagnini F, et al. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation*. 1998; 97(20):2037–42. [PubMed: 9610534]
3. Vaz M, Jennings G, Turner A, Cox H, Lambert G, Esler M. Regional sympathetic nervous activity and oxygen consumption in obese normotensive human subjects. *Circulation*. 1997; 96(10):3423–9. Epub 1997/12/13. [PubMed: 9396437]
4. Jarvis SS, VanGundy TB, Galbreath MM, Shibata S, Okazaki K, Reelick MF, et al. Sex differences in the modulation of vasomotor sympathetic outflow during static handgrip exercise in healthy young humans. *Am J Physiol Regul Integr Comp Physiol*. 2011; 301(1):R193–200. Epub 2011/04/22. [PubMed: 21508291]
5. Dipla K, Zafeiridis A, Koidou I, Geladas N, Vrabas IS. Altered hemodynamic regulation and reflex control during exercise and recovery in obese boys. *Am J Physiol Heart Circ Physiol*. 2010; 299(6):H2090–6. Epub 2010/10/19. [PubMed: 20952664]
6. Ettinger SM, Silber DH, Collins BG, Gray KS, Sutliff G, Whisler SK, et al. Influences of gender on sympathetic nerve responses to static exercise. *J Appl Physiol*. 1996; 80(1):245–51. Epub 1996/01/01. [PubMed: 8847310]
7. Valensi P, Ngoc PTB, Idriss S, Paries J, Cazes P, Lormeau B, et al. Haemodynamic response to an isometric exercise test in obese patients: influence of autonomic dysfunction. *Int J Obes Relat Metab Disord*. 1999; 23:543–9. [PubMed: 10375059]
8. Ewing DJ, Irving JB, Kerr F, Wildsmith JA, Clarke BF. Cardiovascular responses to sustained handgrip in normal subjects and in patients with diabetes mellitus: a test of autonomic function. *Clin Sci Mol Med*. 1974; 46(3):295–306. Epub 1974/03/01. [PubMed: 4818212]
9. Davis SN, Galassetti P, Wasserman DH, Tate D. Effects of gender on neuroendocrine and metabolic counterregulatory responses to exercise in normal man. *J Clin Endocrinol Metab*. 2000; 85(1):224–30. Epub 2000/01/14. [PubMed: 10634391]
10. Nolan RP, Barry-Bianchi SM, Mechettiuc AE, Chen MH. Sex-based differences in the association between duration of type 2 diabetes and heart rate variability. *Diab Vasc Dis Res*. 2009; 6(4):276–82. Epub 2010/04/07. [PubMed: 20368222]
11. Christou DD, Jones PP, Jordan J, Diedrich A, Robertson D, Seals DR. Women have lower tonic autonomic support of arterial blood pressure and less effective baroreflex buffering than men. *Circulation*. 2005; 111(4):494–8. Epub 2005/02/03. [PubMed: 15687139]
12. Sanchez J, Pequignot JM, Peyrin L, Monod H. Sex differences in the sympatho-adrenal response to isometric exercise. *Eur J Appl Physiol Occup Physiol*. 1980; 45(2-3):147–54. Epub 1980/01/01. [PubMed: 7193125]
13. Jones PP, Spraul M, Matt KS, Seals DR, Skinner JS, Ravussin E. Gender does not influence sympathetic neural reactivity to stress in healthy humans. *Am J Physiol*. 1996; 270(1 Pt 2):H350–7. Epub 1996/01/01. [PubMed: 8769771]
14. Kawamura Y. Assessment of autonomic nerve activity: approach to gender differences in cardiovascular events in patients with diabetes. *Circulation journal : official journal of the Japanese Circulation Society*. 2011; 75(6):1320–1. Epub 2011/04/12. [PubMed: 21478629]

15. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care*. 2003; 26(6):1895–901. [PubMed: 12766130]
16. Fernhall B, Figueroa A, Collier S, Baynard T, Giannopoulou I, Gouloupoulou S. Blunted heart rate response to upright tilt in people with Down syndrome. *Arch Phys Med Rehabil*. 2005; 86(4):813–8. Epub 2005/04/14. [PubMed: 15827937]
17. Figueroa A, Baynard T, Fernhall B, Carhart R, Kanaley JA. Impaired postexercise cardiovascular autonomic modulation in middle-aged women with type 2 diabetes. *Eur J Cardiovasc Prev Rehabil*. 2007; 14(2):237–43. Epub 2007/04/21. [PubMed: 17446802]
18. Figueroa A, Collier SR, Baynard T, Giannopoulou I, Gouloupoulou S, Fernhall B. Impaired vagal modulation of heart rate in individuals with Down syndrome. *Clin Auton Res*. 2005; 15(1):45–50. Epub 2005/03/16. [PubMed: 15768202]
19. Heffernan KS, Sosnoff JJ, Ofori E, Jae SY, Baynard T, Collier SR, et al. Complexity of force output during static exercise in individuals with Down syndrome. *J Appl Physiol*. 2009; 106(4):1227–33. Epub 2009/01/24. [PubMed: 19164775]
20. Gouloupoulou S, Baynard T, Franklin RM, Fernhall B, Carhart R Jr. Weinstock R, et al. Exercise training improves cardiovascular autonomic modulation in response to glucose ingestion in obese adults with and without type 2 diabetes mellitus. *Metabolism*. 2010; 59(6):901–10. Epub 2009/12/18. [PubMed: 20015524]
21. Kanaley JA, Shadid S, Sheehan MT, Guo Z, Jensen MD. Relationship between plasma free fatty acid, intramyocellular triglycerides and long-chain acylcarnitines in resting humans. *J Physiol*. 2009; 587(Pt 24):5939–50. Epub 2009/10/28. [PubMed: 19858228]
22. Loimaala A, Huikuri K, Kööbi T, Rinne M, Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. *Diabetes*. 2003; 52:1837–42. [PubMed: 12829654]
23. Kanaley JA, Gouloupoulou S, Franklin RM, Baynard T, Holmstrup ME, Carhart R Jr. et al. Plasticity of heart rate signalling and complexity with exercise training in obese individuals with and without type 2 diabetes. *Int J Obes (Lond)*. 2009; 33(10):1198–206. Epub 2009/08/05. [PubMed: 19652657]
24. McArdle, WD.; Katch, FI.; Katch, VL. *Exercise Physiology: Energy, Nutrition, and Human Performance*. 4th ed. Williams & Wilkins; Philadelphia: 2001.
25. Franklin RM, Baynard T, Weinstock RS, Gouloupoulou S, Carhart R Jr. Ploutz-Snyder R, et al. Autonomic responses to physiological stressors in women with type 2 diabetes. *Clin Auton Res*. 2008; 18(2):66–73. Epub 2008/04/10. [PubMed: 18398634]
26. Huikuri HV, Valkama JO, Airaksinen KE, Seppanen T, Kessler KM, Takkunen JT, et al. Frequency domain measures of heart rate variability before the onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. *Circulation*. 1993; 87(4):1220–8. [PubMed: 8462148]
27. Huikuri HV, Linnaluoto MK, Seppanen T, Airaksinen KE, Kessler KM, Takkunen JT, et al. Circadian rhythm of heart rate variability in survivors of cardiac arrest. *Am J Cardiol*. 1992; 70(6):610–5. [PubMed: 1510009]
28. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J*. 1996; 17(3):354–81. [PubMed: 8737210]
29. Akselrod S, Gordon D, Madved J, Snidman N, Shannon D, Cohen R. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol*. 1985; 249:H867–75. [PubMed: 4051021]
30. Kanaley JA, Baynard T, Franklin RM, Weinstock RS, Gouloupoulou S, Carhart R Jr. et al. The effects of a glucose load and sympathetic challenge on autonomic function in obese 20 women with and without type 2 diabetes mellitus. *Metabolism*. 2007; 56(6):778–85. Epub 2007/05/22. [PubMed: 17512310]
31. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000; 85(7):2402–10. Epub 2000/07/21. [PubMed: 10902785]

32. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care*. 2001; 24(3):539–48. Epub 2001/04/06. [PubMed: 11289482]
33. Clark BC, Collier SR, Manini TM, Ploutz-Snyder LL. Sex differences in muscle fatigability and activation patterns of the human quadriceps femoris. *Eur J Appl Physiol*. 2005; 94(1-2):196–206. Epub 2005/03/26. [PubMed: 15791418]
34. Coote JH, Hilton SM, Perez-Gonzalez JF. The reflex nature of the pressor response to muscular exercise. *J Physiol*. 1971; 215(3):789–804. Epub 1971/07/01. [PubMed: 5090995]
35. McCloskey DI, Mitchell JH. Reflex cardiovascular and respiratory responses originating in exercising muscle. *J Physiol*. 1972; 224(1):173–86. Epub 1972/07/01. [PubMed: 5039977]
36. Hicks AL, Kent-Braun J, Ditor DS. Sex differences in human skeletal muscle fatigue. *Exerc Sport Sci Rev*. 2001; 29(3):109–12. Epub 2001/07/28. [PubMed: 11474957]
37. Kagaya A, Homma S. Brachial arterial blood flow during static handgrip exercise of short duration at varying intensities studied by a Doppler ultrasound method. *Acta Physiol Scand*. 1997; 160(3):257–65. Epub 1997/07/01. [PubMed: 9246389]
38. Momen A, Handly B, Kunselman A, Leuenberger UA, Sinoway LI. Influence of sex and active muscle mass on renal vascular responses during static exercise. *Am J Physiol Heart Circ Physiol*. 2006; 291(1):H121–6. Epub 2006/02/08. [PubMed: 16461376]
39. MacDonald JR. Potential causes, mechanisms, and implications of post exercise hypotension. *J Hum Hypertens*. 2002; 16(4):225–36. Epub 2002/04/23. [PubMed: 11967715]
40. Chrysant SG. Current evidence on the hemodynamic and blood pressure effects of isometric exercise in normotensive and hypertensive persons. *J Clin Hypertens (Greenwich)*. 2010; 12(9):721–6. Epub 2010/10/05. [PubMed: 20883233]
41. Gouni-Berthold I, Berthold HK, Mantzoros CS, Bohm M, Krone W. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. *Diabetes Care*. 2008; 31(7):1389–91. Epub 2008/04/01. [PubMed: 18375411]

Figure 1. A. Mean arterial pressure (MAP) at rest, during isometric handgrip exercise and recovery both before and after 16 weeks of aerobic training (n=10 men, n=12 women). B. The absolute change in MAP from handgrip to recovery ($\Delta\text{MAP}_{\text{REC}}$). (*P<0.05 gender difference; †P<0.05 gender by training interaction), mean $\pm$ SE.

Figure 2. The effect of IHG exercise on low frequency power of systolic blood pressure spectrum ($\ln LF_{SBP}$) before and after 16 weeks of aerobic training. B. The absolute change in $\ln LF_{SBP}$ from handgrip and recovery. ($\dagger P < 0.05$ training by gender interaction; $** P < 0.01$ main effect of training, $\ddagger P < 0.05$ main effect of gender), mean $\pm$ SE.

Table 1

Subject medications

	Women (n=12)	Men (n=10)
<i>Glucose lowering drugs</i>		
Metformin	10	9
Sulfonylurea	0	1
TZD	2	5
<i>Lipid lowering drugs</i>		
Statin	4	4
Fibrate	1	1
<i>Antihypertensives</i>		
HCTZ	0	1
ACE-I	4	4
Valsartan	0	3
Hormone replacement therapy	3	0
Antidepressants	5	1
No medications	0	1

ACE-I, angiotensin converting enzyme inhibitors; HCTZ, hydrochlorothiazide; TZD, thiazolidinediones

Table 2

Subject characteristics and resting metabolic variables pre- and post-training in obese individuals with type 2 diabetes.

	Women (n=12)		Men (n=10)	
	Pre	Post	Pre	Post
Age (y)	48.1±1.04		49.9±1.6	
Weight (kg) *	93.6±6.0	91.9±5.9	128.0±6.2	128.1±6.1
Body mass index (kg/m ²)	36.0±1.6	35.4±1.6	39.1±1.7	39.2±1.7
Percent body fat *	45.6±2.1	45.7±2.2	37.9±2.2	37.4±2.3
Fat Free Mass (kg) *	50.3±2.0	49.2±2.0	73.8±2.2	74.7±2.2
Fat mass (kg)	43.3±5.2	42.6±5.3	52.6±5.7	52.1±5.8
VO ₂ peak (ml/kg/min) * [†]	21.1±1.2	23.2±1.1	23.7±1.4	24.2±1.3
Fasting glucose (mmol/L)	7.2±0.5	7.2±0.6	7.2±0.5	6.7±0.6
Fasting insulin (pmol/L)	76.0±21.1	109.6±22.0	132.7±21.9	109.3±23.1
Hemoglobin A1c (%)	6.9±0.4	7.2±0.4	7.6±0.3	7.1±0.5
HOMA *	3.2±0.6	3.4±0.8	5.4±1.1	5.5±1.35
QUICKI	0.38±0.01	0.37±0.02	0.35±0.1	0.37±0.02

insulin sensitivity check index.

* P<0.05 sex differences,

[†] P<0.05 training effect, mean ± SE;

HOMA - homeostatic model assessment, VO₂ – oxygen consumption, QUICKI - Quantitative

Table 3

Hemodynamic and heart rate variability data in response to the isometric handgrip task and during recovery, pre- and post-training in obese men and women with type 2 diabetes.

	Women (n=12)						Men (n=10)					
	Pre			Post			Pre			Post		
	Rest	IHG	Recovery	Rest	IHG	Recovery	Rest	IHG	Recovery	Rest	IHG	Recovery
SBP (mmHg) ^{*P§}	120±4	144±4 [‡]	129±4 [‡]	114±39	139±5 [‡]	129±5.2 [‡]	134.3±4	170±5 [‡]	149±5 [‡]	132±4	163±7 [‡]	128±6 [‡]
DBP (mmHg) ^{*P}	60±3	75±3 [‡]	63±3 [‡]	56±3	68±4 [‡]	65±3 [‡]	67±3	83±3 [‡]	69±3 [‡]	68±3	81±4 [‡]	60±4 [‡]
Heart rate (b/min)	70±3	76±4	71±3	71±2	76±3	73±2	70±3	79±4	70±3	71±3	78±4	70±4
BRS (ms/mmHg) ^{*P}	11.6±1.0	8.8±0.6	10.4±0.7	11.7±0.8	9.2±0.6	11.2±0.7	7.7±1.4	6.2±0.8	8.1±1.0	7.8±1.1	7.0±0.9	8.0±1.0
HF _{RRI} (nu)	.41±.05	.33±.05	.33±.04	.33±.05	.26±.05	.32±.05	.40±.06	.38±.05	.34±.05	.40±.05	.30±.06	.37±.06
lnLF _{RRI} /HF _{RRI}	.40±.23	.83±.24	.85±.23	.84±.23	1.19±.28	.85±.24	.45±.25	.58±.27	.73±.25	.42±.26	1.06±.30	.65±.26

^{*P} <0.05 sex differences, mean ± SE;

[‡] P<0.01 vs rest;

[‡] P<0.01 vs IHG;

[§] P<0.05 sex by task interaction

SBP- systolic blood pressure, DBP- diastolic blood pressure, MAP- mean arterial pressure, HF_{RRI} (nu) - high frequency power using the R-R interval (normalized units), lnLF_{RRI}/HF_{RRI} - low frequency R-R interval/HF_{RRI}, BRS- baroreceptor sensitivity