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The Relation between the Blood Pressure Response to Exercise during Training and Detraining Periods

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The Relation between the Blood Pressure Response to Exercise
during Training and Detraining Periods

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Master of Science Thesis

The Relation between the Blood Pressure Response to Exercise
during Training and Detraining Periods

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List of Abbreviations

Hypertension	HTN
Blood Pressure	BP
Systolic Blood Pressure	SBP
Diastolic Blood Pressure	DBP
Cardiovascular Disease	CVD
Metabolic Syndrome	MetS
Aerobic Vigorous Group	ATvig
Resistance Training Group	RT
Aerobic & Resistance Group	AT/RT
American College of Sports Medicine	ACSM
Maximal Oxygen Consumption	VO _{2max}
7 th Report of the Joint National Committee	JNC7
Repetition Max	RM
Body Mass Index	BMI
Waist Circumference	WC

Chapter 1 - Introduction

Background and Significance

Hypertension (HTN) [systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg] is a major public health concern. Over one billion adults worldwide have HTN and approximately 7.1 million deaths per year are attributed to HTN (1). In the United States (US) approximately 74.5 million (25%) adults have HTN and an additional 86 million (28%) have preHTN (SBP 120-139 mmHg and/or DBP 80-89 mmHg) (1). Higher resting blood pressure (BP) increases the risk of developing HTN and cardiovascular disease (CVD). Over a four year period, 19% of individuals with preHTN will develop HTN (2). By 2020, 1.56 billion adults worldwide will have HTN (3).

Resting BP is a major CVD risk factor. Beginning at a BP of 115/75 mmHg, an increase in SBP of 20 mmHg or DBP of 10 mmHg doubles the risk of developing CVD (4). Additionally, HTN is a contributor to the metabolic syndrome (MetS) (5). The Adult Treatment Panel III (ATP III) defines the MetS as having three or more of the following CVD risk factors simultaneously: fasting triglycerides ≥ 150 mg/dL, BP $\geq 130/85$ mmHg, fasting glucose ≥ 100 mg/dL, BP $\geq 130/85$ mmHg, waist circumference for men ≥ 102 cm and women ≥ 88 cm, and fasting high density lipoprotein < 40 mg/dL for men and < 50 mg/dL for women (6). Individuals with the MetS have increased prevalence of HTN (49%) when compared to individuals who do not have the MetS (40%) (7) and experience a two-fold increase in CVD risk (8). Furthermore, 71.6% of all individuals with HTN will develop the MetS (9).

The role of lifestyle modifications, such as engaging in exercise, is critical for the prevention, treatment and control of HTN. Aerobic exercise lowers resting BP 5 to 7 mmHg, while resistance exercise (used as a supplement to aerobic exercise) reduces BP 2 to 3 mmHg among those individuals with HTN (10). The American College of Sports Medicine [(ACSM) (10)] therefore recommends individuals with HTN to engage in moderate intensity, aerobic exercise on most days of the wk for 30-60 min·d⁻¹ supplemented by resistance exercise 2-3 d·wk⁻¹.

Although exercise is recommended as an initial lifestyle therapy to lower BP, over 80% of the US adult population does not meet the recommended amount of daily physical activity (3). Individuals with HTN are less physically active than individuals without HTN (11). Physical inactivity is a major public health concern that increases the risk of mortality by 20-30% when compared to those individuals who meet the physical activity requirements per week (3). Physical inactivity may also contribute to HTN, higher rates of type 2 diabetes mellitus, dyslipidemia, and the risk of developing CVD which can further increase morbidity and/or mortality. In 2010, physical inactivity contributed to 9% of all-cause mortality in the US adult population (12).

Aerobic exercise is reported to lower resting BP among those with HTN. However, the BP response to exercise is quite variable (13). Indeed, 25% of those with HTN do not lower their BP following aerobic exercise training (14). One explanation for this variability is the law of initial values such that individuals with the highest resting baseline BP experience the greatest reductions (15). Further, Bouchard et al. (13) examined 481 healthy, young sedentary (17-29 yr) men and women with normal to preHTN BP during submaximal cycle exercise training. Bouchard and colleagues found,

the mean SBP response to exercise decreased an average of 8.2 mmHg however; the standard deviation ± 11.8 mmHg exceeded the mean SBP change across the total sample. In conclusion, there is considerable intra- and inter- variability in the BP response to exercise training.

The antihypertensive effects of aerobic exercise training occur rapidly within three sessions, persist with continued training, and diminish to pre-training levels within 2 wk after training has ceased (16,17). Meredith et al. (16) found healthy individuals with normal BP reduced SBP and DBP 5 mmHg after one month of cycling at 60-70% maximal oxygen consumption (VO_{2max}) for 40 min, three times per wk. However, the magnitude of the BP reduction was maximized within the first three sessions. After the cessation of exercise training, BP regressed back to resting values within 2 wk. Murray et al. (17) observed similar results with healthy, young men who performed 30 min (60% VO_{2peak}) bouts of aerobic exercise on a cycle ergometer, three to four times per wk. Within the first four exercise training sessions BP reductions were seen, SBP decreased 11 mmHg and DBP 9 mmHg. After one wk of exercise cessation, BP regressed back to resting levels (SBP increased 5 mmHg and DBP 3 mmHg). These studies show that within one wk of the onset or cessation of aerobic exercise training there is a rapid BP reduction and disappearance respectively in response to exercise training.

Statement of the Problem

Exercise is recommended as a non-pharmacological therapy for the prevention, treatment and control of HTN. Despite the consensus that endurance exercise lowers BP 5-7 mmHg among those with HTN, 25% of these individuals do not reduce their BP following endurance exercise for reasons that are unclear (14). Shortly after exercise

training has ceased, within one wk, BP increases during detraining and returns to pre-exercise training values (16,17). However, the relation between the BP response during exercise training and a detraining period has yet to be examined in the same group of people. Clinically, it is important for physicians and exercise specialists to identify which individuals respond and do not respond to exercise training as an antihypertensive therapy. Additionally, to examine and identify baseline predictors of individuals at risk with adverse response to exercise training, further offering an alternative approach to modifying and executing a more effective exercise prescription as an antihypertensive therapy.

Therefore, the purpose of this study was to examine the BP response after 6 months of exercise training followed by a 2 wk detraining period among middle-aged, sedentary adults with preHTN and mild to moderate dyslipidemia from the clinical trial, Studies of a Targeted Risk Reduction through Defined Exercise (STRRIDE-AT/RT) (1R01HL57354; 2003-2008; NCT00275145) (18).

Specific Aims

The primary aim of this sub-study is to investigate the BP response before and after 6 months of exercise training and 2 wk of detraining among subjects from STRRIDE-AT/RT with preHTN and mild to moderate dyslipidemia. Secondly, this sub-study intended to explore clinical characteristics that may modulate the BP response to exercise training and detraining. We hypothesize middle-aged adults with preHTN and mild to moderate dyslipidemia will decrease their BP with 6 months of exercise training. Furthermore, we hypothesize that the same group of individuals will increase their BP with exercise detraining.

Chapter 2 - Review of Literature

Introduction

In the United States one in three adults have HTN (1). HTN, SBP \geq 140 and/or DBP \geq 90 mmHg and/or taking antihypertensive medication, is a significant public health problem that continues to grow in prevalence. Over a four-year period, 19% of individuals with preHTN developed HTN (2). Resting BP is a major independent risk factor for CVD. Beginning at a BP of 115/75 mmHg, an increase in SBP of 20 mmHg or 10 mmHg in DBP doubles the risk of developing CVD (4). Therefore, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends exercise as lifestyle therapy to prevent, treat, and control HTN (19).

Although exercise is recommended as the initial lifestyle therapy to lower BP, over 80% of the United States adult population does not meet the recommended daily physical activity requirements (3). Further, individuals who are less physically active and less fit than those who meet the physical activity recommendations have a 30-50% greater risk for having HTN (1). Therefore, it is important for individuals to engage in the recommended amount of physical activity/day to lower BP and prevent the progression of preHTN to HTN.

The Antihypertensive Effects of Aerobic Exercise

The JNC 7 recommends exercise as a lifestyle therapy for the prevention, treatment and control of HTN. Those with HTN who engage in aerobic exercise exhibit a BP reduction of 5 to 7 mmHg (10). Further, the ACSM recommends moderate intensity aerobic exercise performed on most days of the week for 30-60 min·d⁻¹ to lower BP. Fagard (20) meta-analyzed the influence of exercise characteristics and the BP response

to dynamic aerobic or endurance exercise in healthy individuals with normal BP and individuals with HTN. The results from the meta analysis concluded aerobic training 3 d·wk⁻¹ for 40 min·d⁻¹ at 65% VO_{2max} reduces BP on average 3/2 mmHg in individuals with optimal BP, however greater reductions were seen among individuals with HTN; 7 mmHg SBP and 6 mmHg DBP (20). Therefore, training 3-5 d·wk⁻¹ for 30-60 min·d⁻¹ at 40-50% VO_{2max} exhibits an effective mode of exercise to reduce BP and supports the ACSM guidelines for exercise. Mughal et al. (21) looked at the changes in BP with aerobic exercise over a 12 wk period in 27 men (39 yr) with HTN (143/91 mmHg). Subjects engaged in an exercise training protocol walking at 50% VO_{2max} for 30 min·d⁻¹, 3-5 d·wk⁻¹. The results showed BP reductions of 5.7 mmHg SBP and 1.4 mmHg DBP. Although these reductions are slightly less than ACSM, these findings indicate that walking, a low cost activity can still reduce BP in individuals with HTN.

The prevalence of HTN increases with age with higher DBP values until the age of 55 at which values slowly decline, while SBP values continue to increase with age (22). Therefore it is important and beneficial to engage in exercise training for the prevention, treatment, and management of HTN. As previously discussed the literature indicates aerobic exercise is an effective non-pharmacological treatment to prevent, manage and treat HTN. BP reductions occur over a short period of time within 1-2 wk of the onset of aerobic exercise training and persist with continued exercise (16,17). Further, BP reductions are exhibited in individuals with normal BP and in individuals with HTN regardless of their pre exercise (resting) BP status. However, the antihypertensive effects of aerobic exercise training appear to be more pronounced among individuals with preHTN or HTN.

Variability to BP Response to Exercise Training

Although aerobic exercise has shown to be an effective antihypertensive strategy, the magnitude and duration of these BP reductions vary widely across studies. Bouchard and Rankinen (13) noted high levels of heterogeneity in the BP response to different exercise programs and modalities (aerobic, resistance, and combined aerobic and resistance exercise) among individuals with HTN. SBP was taken during an acute bout of exercise, cycling at 50 Watts. These researchers from the HERITAGE family study (13) reported that 723 sedentary men and women aged 17-29 yr had a BP average overall reduction of 8.2 ± 11.8 mmHg. However, individuals with higher resting mean SBP reduced overall BP 13.4 ± 12.2 mmHg and individuals with lower resting mean SBP resulted in a lesser BP reduction of 3 ± 8.8 mmHg. In addition, the standard deviation of the overall reduction exceeded the average mean change (8.2 ± 11.8 mmHg), which demonstrated the wide variability in the BP response to exercise training from individual to individual. The study concluded that there is evidence that there is considerable heterogeneity in the response of physiological indicators of risk factors to regular physical activity and pretraining levels of SBP which has an impact on determining the response to exercise training (23).

The Antihypertensive Effects of Resistance Exercise

As a supplement to aerobic exercise, the ACSM (2004) recommends individuals with HTN perform resistance exercise $2-3 \text{ d} \cdot \text{wk}^{-1}$ of at least one set of 8-12 repetitions [60-80% of 1 repetition maximum (RM)] (24). There is a large body of evidence to support the antihypertensive effects of aerobic exercise on resting BP. However, resistance training has been deemed safe for individuals with HTN (25) with average

reductions of 3 mmHg post training when performed in accordance with the current ACSM recommendations (24). These reductions exhibited with resistance training are less than those with aerobic training therefore resistance training is recommended as a supplement to aerobic training.

Resistance training has positive health effects by increasing strength and by decreasing resting BP. Sallinen et al. (26) examined 43 men (58 yr) with HTN (130.1/82.4 mmHg) but otherwise healthy over 42 wk. Individuals were randomized to a strength training group (n=20) or a control group (n=19). Individuals in the strength group performed 14 exercise on standard exercise machines completing 3-6 sets of pyramid repetitions (10-15, 8-10, 5-8) at 40-80% 1 RM (intensity progressed), 3 d·wk⁻¹. At the end of the 21 wk SBP and DBP were reduced 4 mmHg with no further reductions seen in SBP after 42 wk however DBP did statistically reduce when compared to the control group. The findings of the present study are consistent with previous literature and demonstrate that strength training can be helpful for individuals with preHTN to reduce BP safely and effectively.

Cornelissen et al. (27) examined the frequency, intensity, time, and type (FITT) principle in a Meta analysis. The authors concluded that training performed on weight machines 3 d·wk⁻¹ for 16 weeks, 3 sets of 8 exercises of 76% 1 RM exhibited an overall decrease in BP in individuals with preHTN (3.9 in SBP and 3.6 mmHg in DBP). Further concluding, an established resistance training regimen could be used as a non-pharmacological aid to prevent, treat, and control high BP.

In summary, as the previous literature shows resistance training if done in accordance to ACSM guidelines is safe and can help reduce BP in individuals with

preHTN and HTN. Therefore, resistance training as a supplement to aerobic training can be used as a non-pharmacological aid to prevent, treat, and control high BP.

The Antihypertensive Effects of Concurrent Aerobic and Resistance Exercise

There is limited literature examining the BP lowering effects of concurrent aerobic and resistance training regimen. Keese et al. (28) examined middle-aged men (20-30 yr) with optimal BP (111/73 mmHg) performing four acute experimental visits. The protocol consisted of one control session of seated rest and three acute exercise sessions of different modalities; aerobic exercise at 65% VO_{2peak} on a cycle ergometer for 60 min, resistance training of 3 sets of 8 exercises performed at 80% of 1 RM, and aerobic plus resistance training session with similar protocol of the aerobic and resistance sessions. Aerobic exercise, acute training, alone reduced SBP 6.3 ± 1.3 mmHg and DBP 1.8 ± 1.0 mmHg, while resistance training reduced BP $4.1 \pm 3.0 / 1.8 \pm 1.1$ mmHg, respectively.

Shaw et al. (29) examined 37 sedentary adult males (25 yr) that performed aerobic or concurrent aerobic and resistance training for 16 weeks, $3 \text{ d} \cdot \text{wk}^{-1}$ for $60 \text{ min} \cdot \text{d}^{-1}$. Subjects were divided into one of three groups; control group, aerobic (60% HRmax), or an aerobic (60% of maximum heart rate) and resistance-training group combined (8 exercises of 2 sets of 15 repetitions at 60% 1 RM). Both aerobic and concurrent exercise showed effective and favorable improvements in SBP. However, BP reductions with the aerobic group exhibited smaller reductions of 3.9 ± 3.8 mmHg while the concurrent group elicited BP reductions of 9.8 ± 1.4 mmHg. The results demonstrate that concurrent training can help reduce BP the same as aerobic training alone taking note that concurrent training only did half of the aerobic training as the aerobic training only group.

Similarly, Wallace et al. (30) examined 16 sedentary men (41 yr) with hyperinsulemia in addition to two other components of the MetS that performed endurance or a concurrent endurance and resistance training group for 14 wk. Subjects randomized into endurance group (60-70% heart rate reserve) engaged in walking on the treadmill or the cycle ergometer for 30 min·d⁻¹, the concurrent group followed the same protocol as the aerobic group but added resistance training (8 exercises of 4 sets of 8-12 sets at 75% 1 RM). After the exercise program concluded, SBP reductions were greater in the concurrent group (14.6±5.5 mmHg) than the endurance training group (8.3±6.8 mmHg) indicating adding resistance training to endurance training produce greater SBP reductions.

In summary aerobic and resistance exercise combined has shown to lower BP similar to aerobic or resistance training in individuals with preHTN. Additionally, concurrent training can be as effective in an antihypertensive therapy than aerobic or resistance exercise done in isolation.

The Blood Pressure Response to Detraining

The effects of detraining on BP have not been extensively researched. Meredith et al. (16) examined the effects of detraining following four weeks of exercise training of 3 d·wk⁻¹ at 60-70% VO_{2max} for 40 min·d⁻¹ on a bicycle ergometer. Ten sedentary men (5) and women (5), with normal BP and otherwise healthy adults (age 21 yr), decreased resting BP by 8/5 mmHg following one month of exercise training. Reductions in BP were seen within the first three visits or one week of the onset of exercise training and were fully established by the fourth training visit with no further reductions in BP over

the next month. After the cessation of exercise, BP returned to baseline values within 2 weeks signifying that BP reductions occur and disappear rapidly.

Murray et al. (17) examined the effects of aerobic exercise training, cycle ergometer 30 min·d⁻¹ at 60% VO_{2peak} among 17 young (22 yr) men with preHTN. After one week, or four sessions, from the onset of exercise, SBP was lowered by 10±1 mmHg and DBP by 8±7 mmHg with no further reductions occurring after the second week. Following the cessation of exercise, resting SBP not only returned back to pretraining values within one week but also increased 5 mmHg above pretraining values. DBP values remained lower than pretraining values for the first week. By the end of the second week of detraining, DBP values not only returned back to pretraining but also increased 3 mmHg above pretraining values.

In summary, the BP adaptations to exercise appear and disappear rapidly. BP reductions are seen within one week of the onset of exercise and persist with continued exercise training, however, BP returns to pretraining values after the cessation of exercise within one week. However 25% of the population does not lower BP with exercise for reasons that are unclear. In addition it is imperative to continue to exercise, even in individuals who do not respond to exercise training, to maintain the many health benefits associated with regular exercise including lowering BP or preventing preHTN developing into HTN.

The Metabolic Syndrome

Background

The ATP III defines the MetS as having three or more of the following: fasting triglycerides ≥150 mg/dL, BP ≥130/85 mmHg, fasting glucose ≥100 mg/dL, waist

circumference for men ≥ 102 cm and ≥ 88 cm for women, and fasting high density lipoprotein < 40 mg/dL for men and < 50 mg/dL for women (ATP III) (6). Although the cause of the MetS remains unclear, many consider the most prominent underlying contributors to be abdominal obesity and insulin resistance (40). However, some consider HTN to be the most important contributor to the MetS because of the increased risk for obesity and insulin resistance associated with HTN (31,32). For individuals with HTN, 65-75% of are obese and 50% are insulin resistant (33,34). Furthermore, 85% of the individuals with the MetS have HTN (32).

Metabolic Syndrome and Blood Pressure

Ishizaka et al. (36) analyzed cross-sectional data of 8144 apparently healthy men and women (19-88 yr) from a general health screening. Of this sample, 19% of the men and 7% of the women were diagnosed with the MetS based on the criterion from ATP III. Among the five metabolic risk factors, HTN was the most observed in individuals with the MetS; 85% of men and 87% of women having HTN. The authors concluded that BP control is important in reducing the risk for the MetS among healthy individuals.

The prevalence of the MetS doubles in individuals with preHTN when compared to individuals with normal BP (37,38). Onat et al. (37) prospectively examined 1501 men and 1533 women of middle age (mean age= 48 yr) with normal BP (n=978), preHTN (n=996), and HTN (n=1060) to predict the concurrent development of HTN and the MetS. At baseline 39.9% of men and 40.7% of women were identified as having the MetS and an additional 454 individuals developed MetS after 6.6 yr follow up. Further, 317 individuals with normal BP at baseline developed preHTN (5% incidence /yr), 333 individuals with preHTN developed HTN (4.5% incidence/yr), and 133 individuals with

normal BP developed HTN (1.9% incidence/yr). The authors concluded that having preHTN doubled the risk for developing the MetS compared to having optimal BP. Furthermore, Kanauchi et al. (38) examined the relationship between resting BP levels and the prevalence of the MetS among apparently healthy men and women with optimal BP, preHTN or HTN. As resting BP increased, the number of MetS components increased, 9.9% for normal BP, 19.2% for preHTN, and 35.5% for HTN. They concluded as baseline BP increase so does the number of components of the MetS suggesting HTN may be an etiologic agent of the MetS (39).

There is a link between high baseline BP and the increase risk for HTN with HTN being one of the major components that can contribute to the MetS (40). Aerobic training has shown to be an efficient mode of exercise to reduce BP while simultaneously improving and addressing other components associated with the MetS (41). HTN can be a contributor in the MetS through the pathway of obesity and insulin resistance with a hyperactivity of the sympathetic nervous system (Figure 1) (51,52,56).

Hypertension: An etiologic agent of the Metabolic Syndrome

Mechanisms

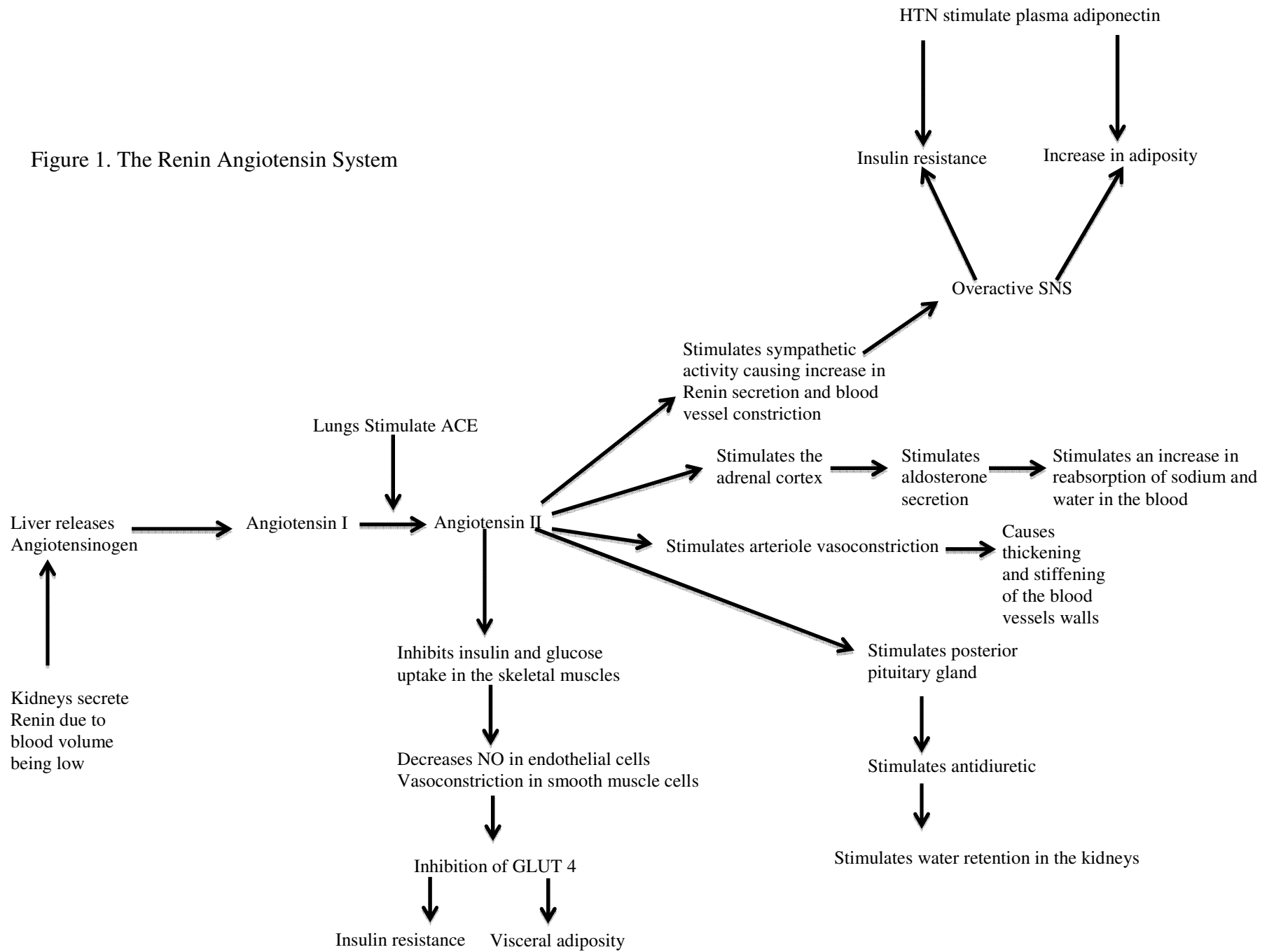
HTN affects 40% of individuals with the MetS (50). Additionally, individuals with HTN have an increased risk of obesity and/or insulin resistance. Approximately 65-75% of individuals with HTN are obese, while 50% of individuals with HTN are insulin resistant (32,33). The kidneys, a vital organ in BP regulation, help with maintenance and regulation of sodium and fluid homeostasis (33). Disturbance of regular kidney function may result in development of HTN with further complications that are associated with the

MetS (i.e., visceral adiposity and/or insulin resistance). Therefore, HTN may be an important contributor in the etiologic agent of the MetS.

Renin Angiotensin System and Blood Pressure

The renin angiotensin system (RAS) is an important regulator of blood volume and systemic vascular resistance. Further, the RAS is an important mechanism in BP control and may partially explain how HTN can be a contributor in the MetS. The RAS pathway is involved with sodium and water retention that increases blood volume and inhibits the release of renin in the blood. Renin then acts on angiotensinogen, secreted from the liver, to form angiotensin I. Angiotensin converting enzyme converts angiotensin I into angiotensin II, a vasopressor. Angiotensin II has physiological effects on the kidney as well as the adrenal cortex, vascular smooth muscle, and the brain (51). Stimulation of angiotensin II may lead to short term functional changes including an increase in sympathetic activity, tubular reabsorption causing water retention, the release of aldosterone which acts on the kidneys to increase sodium and fluid retention, secretion of antidiuretic hormone from the pituitary gland leading to an increase in kidney fluid retention, and last, constriction of the arteriole vessels (50). These short-term adaptations lead to an increase in blood volume, vasoconstriction of the blood vessels, and an increase in BP (Figure 1) (51,52,56).

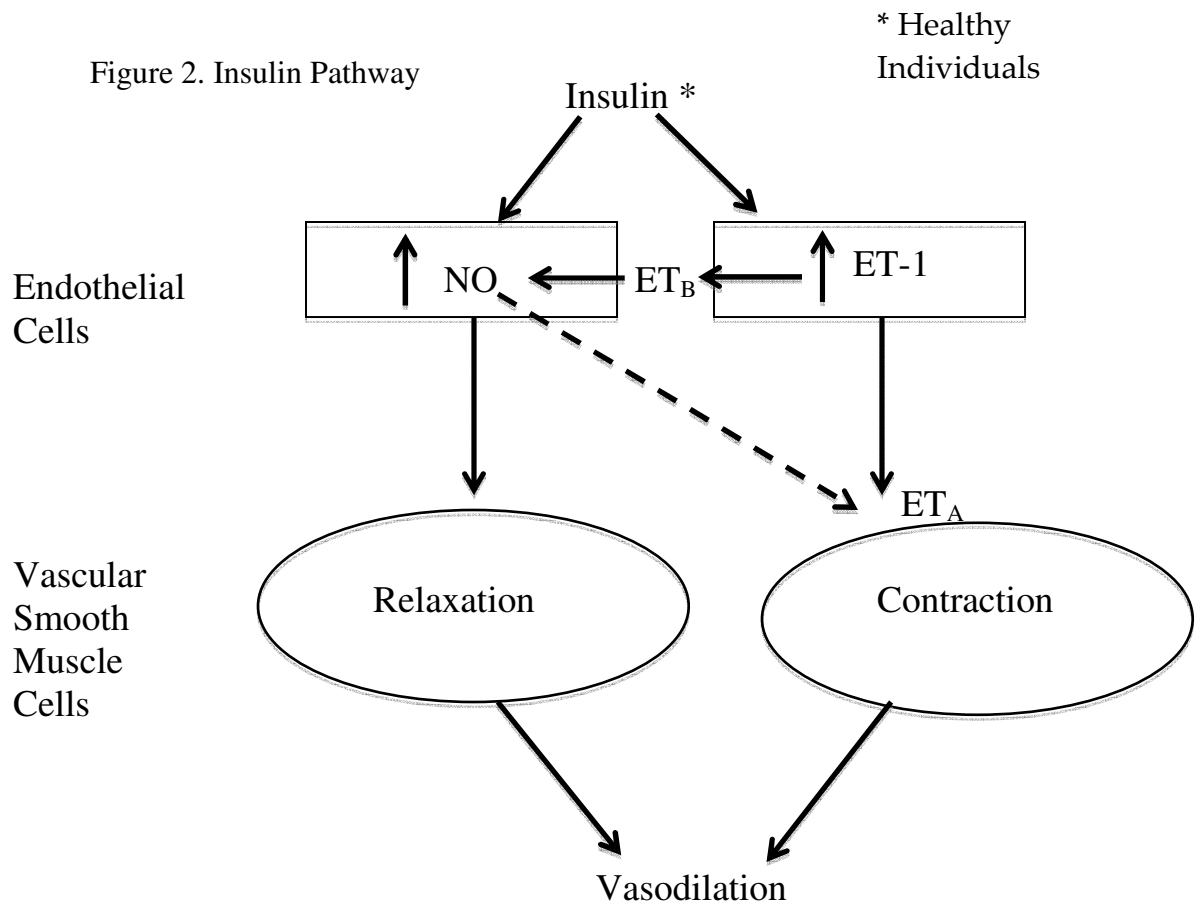
Figure 1. The Renin Angiotensin System



Insulin and Blood Pressure

Insulin is an important hormone in glucose and lipid metabolism and in the maintenance of endothelial function. In a healthy individual insulin (≥ 5 -20 pmol/L) signals to insulin receptor substrate-1 which increases activation of phosphatidylinositol-3 kinase (PI-3K) leading to phosphorylation and activation of pyruvate dehydrogenase kinase isozyme 1 (PDK-1), which then phosphorylates the activation of protein kinase B (Akt/PKB). Akt phosphorylates nitric oxide synthase-3 (NOS3) resulting in increased activity of NOS3 and production of nitric oxide (NO), a vasodilator that improves endothelial function and positively influences BP. Additionally in healthy individuals insulin stimulates production of endothelin-1 (ET-1) and NO from endothelial cells. ET-1 binds to a receptor located in smooth muscle tissue of blood vessels, endothelial type A, which leads to constriction of the vascular smooth muscle cells. Further, ET-1 binds to endothelial type B receptor, found on endothelial cells that release NO which inhibits ET-1 action on vascular smooth muscles cells resulting in vasodilation. However, in individuals with elevated level of insulin, an increase in insulin blocks the endothelial type B receptor inhibiting NO from being released causing vasoconstriction of the blood vessels (Figure 2) (57).

Figure 2. Insulin Pathway



Additionally, angiotensin II can also inhibit the vasodilator effects of insulin on blood vessels causing a decrease of NO in the endothelial cells. Inhibiting insulin signaling on the PI-3K pathway results in vasoconstriction in the smooth muscle cells. Subsequently causing vasoconstriction of the arterioles resulting in an increase in BP (HTN). Angiotensin II also inhibits glucose uptake into skeletal and fat muscles by blocking GLUT-4 translocation, a transporter of glucose primarily found in adipose tissue and skeletal muscles (52,53). The effect of angiotensin II inhibiting insulin and glucose uptake leads to insulin resistance and/or visceral adiposity (52,50). Therefore, inhibiting insulin on the insulin signaling PI-3K pathway may lead to impaired vascular function (i.e., endothelial dysfunction).

As previously stated, the activation of the RAS including Angiotensin II stimulates and increases sympathetic nervous activity resulting in various short term functional changes and subsequently contributing to an increase in BP (HTN). Further, impairment of the PI-3K signaling in the endothelium may cause an imbalance with NO production and ET-1 secretion (vasoconstriction) further leading to a decrease in blood flow and an increase in BP (58). Additionally, HTN causes vasoconstriction and structural changes of the blood vessels reducing the ability of arteries to vasodilate.

Together these factors contribute to an increased risk of insulin resistance and visceral adiposity thus being a possible explanation for HTN being an etiologic agent in the MetS.

Last, adiponectin is a hormone secreted by adipocytes that regulates metabolism of lipids, glucose and vascular function (54). Further adiponectin demonstrates protection properties on blood vessels and anti-inflammatory properties in the endothelium by altering NO levels (55). In healthy individuals, adiponectin demonstrates similar characteristics to insulin by promoting glucose uptake and stimulation of NO production in the endothelium (56,54). Like insulin, adiponectin is dependent on the activation of the PI-3K pathway and PDK-1 that directly stimulates phosphorylation of Akt.

Phosphorylation of Akt then activates endothelial nitric oxide synthase resulting in increase production of NO. In healthy individuals plasma adiponectin remains high, however, low levels are negatively associated with visceral adiposity, insulin resistance, and endothelial dysfunction (51) and can further lead to an increase in BP (54). HTN can lead to inhibition of adiponectin along with removal of glucose in skeletal and muscle cells that may result in insulin resistance and/or an increase in adiposity (51). In conclusion, adiponectin and insulin demonstrate similar vascular functions and increase

the development of insulin resistance and/or adiposity. Additionally the PI-3K signaling pathway is necessary for production of NO in the endothelium and may be a possible mechanism to HTN being the etiologic agent of the MetS.

Regardless if it is an etiologic agent or an associated factor of the MetS, exercise is recommended to prevent, treat and control BP as well as improve other components of the MetS ultimately reducing the risk of acquiring CVD and Type 2 diabetes mellitus (42,43). Bateman et al. (41) examined 234 sedentary and overweight men and women (18-70 yr) with mild to moderate dyslipidemia in the STRRIDE study. Individuals were randomized into one of three exercise groups; aerobic (65-80% VO_{2peak}), resistance training (3 d·wk⁻¹, 3 sets of 8-12 reps), or concurrent (same exercise protocol for aerobic and resistance training). A continuous score using the five MetS variables based on the ATP III criteria were used to formulate the MetS z-score allowing to show improvements in components of the MetS. After 6 months of training, the participants in the resistance training group did not improve the parameters of the MetS or the MetS z-score (0.13 ± 1.76), whereas aerobic exercise training showed improvements in the MetS z-score (-0.76 ± 2.20) and an even more significant improvement noted in the concurrent exercise group (-1.10 ± 1.70), however aerobic training improved the MetS more than the resistance training did. Thus aerobic training has shown to be an efficient mode of exercise to reduce BP while simultaneously improving other components associated with the MetS. However, reasons for the differences among the exercise groups was not clear, although, Bateman et al. (41) speculated that the improvements in the MetS z-score from the concurrent group were attributed to exercising longer, almost twice as much as those in the aerobic or resistance group alone.

Katzmarzyk et al. (44) examined 621 apparently healthy sedentary men and women (17-65 yr) from the HERITAGE study. At baseline 105 (16.9%) of the 621 individuals had the MetS. After 20 wk of aerobic exercise training performed three times/wk at 55-75% VO_{2max} on a cycle ergometer, 32 (30.5%) participants became free of the MetS. These results showed the effects of exercise training reduce and prevent future development of the MetS.

In summary, HTN is the most important contributor to the MetS and is present in up to 85% of individuals with the MetS (32). As an initial lifestyle modification, endurance exercise is an efficacious treatment for mild to moderate HTN additionally reducing the risk of developing or reducing the components of the MetS.

Chapter 3 - Methods

STRRIDE Overview

This is a sub-study of the Studies of a Targeted Risk Reduction Intervention through Defined Exercise or STRRIDE-AT/RT (1R01HL57354; 2003-2008; NCT00275145) (18). The two primary purposes of STRRIDE were to: 1) investigate the effects of different types and intensities of exercise training regimens on established CVD risk factors; and 2) to study the peripheral biologic mechanisms through which exercise training altered these CVD risk factors. In addition, researchers also obtained pre- and post anthropometric measurements, cardiometabolic biomarkers, and BP following 6 months of exercise training and after a 2 wk detraining (18).

Sub-Study Overview

Subjects

Volunteers were STRRIDE-AT/RT participants recruited through the local newspaper, the Internet and word of mouth in Durham, Greenville and other surrounding communities in North Carolina. Subjects included men and women 18-70 yr who were exercising ≤ 2 d/wk or had a peak oxygen uptake (VO_{2peak}) of ≤ 35 mL \cdot kg $^{-1}\cdot$ min $^{-1}$. Study inclusion criteria were: (a) body mass index (BMI) 25-35 kg \cdot m $^{-2}$; (b) resting SBP <160 mmHg and/or DBP <90 mmHg; and (c) fasting low density lipoprotein (LDL) 130-190 mg \cdot dL $^{-1}$; or fasting high density lipoprotein-cholesterol (HDL) for men ≤ 40 mg \cdot dL $^{-1}$ and women ≤ 45 mg \cdot dL $^{-1}$. Subjects had no known metabolic, muscular, or coronary heart disease(s) and were not taking any antilipidemic or antihypertensive medications. Additionally, they were willing to be randomized to one of three exercise groups. Prior to

participating in the study, individuals were screened by telephone and signed a written informed consent approved by the IRB of the participating institutions.

Procedures

Study Design Overview. Figure 1.

This STRRIDE-AT/RT sub-study was conducted to investigate the BP response before and after 6 months of exercise training followed by 2 wk of detraining among middle aged, sedentary adults with preHTN and mild-to-moderate dyslipidemia. The institutional review boards of Duke University Medical Center and East Carolina University approved the experimental design of STRRIDE-AT/RT, which has been described in detail elsewhere (18). Only the methods used in this sub-study are described in detail below.

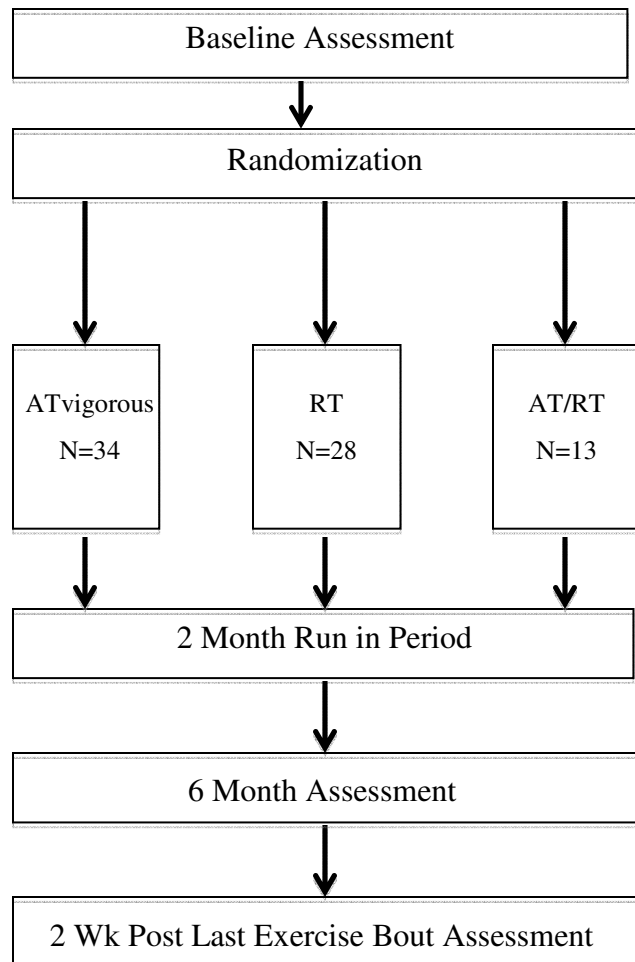


Figure 1. Overview of STRRIDE study. AT_{vigorous} = Aerobic training vigorous intensity (65-80% $VO_{2\text{peak}}$); RT = Resistance training (70-85% of one repetition maximum); AT/RT = Aerobic training and resistance training combined.

Subjects attended a baseline assessment prior to the start of the 6 month exercise training intervention where they completed a health screening questionnaire and a series of health fitness and anthropometric measurements including resting BP (mmHg), height (cm), weight (kg), and waist circumference (WC). Height and weight were used to calculate BMI ($\text{kg}\cdot\text{m}^2$). Fasting plasma samples were obtained to determine HDL-cholesterol, triglycerides, and glucose. A cardiopulmonary exercise test (CPET) with a 12-lead electrocardiogram was used to determine $VO_{2\text{peak}}$ ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and the exercise intensity of the aerobic exercise training program. Pre exercise measurements were performed at the completion of the 10 wk run in period, and again following the 6 month exercise training intervention and 2 wk detraining period.

Following baseline assessments, subjects were randomized into one of three exercise groups: aerobic vigorous intensity (AT_{vigorous}) (n=34), resistance training (RT) (n=28), or aerobic exercise and resistance training combined (AT/RT) (n=13). Subject randomization was performed using a standard computer based block design. Last, subjects had to have obtained BP measurements pre 6 months exercise training, post 6 months exercise training, and after 2 wk detraining period.

Exercise Training Intervention

Aerobic Training Vigorous [AT_{vigorous} (n=34)] group performed a CPET after the run in period to ensure the appropriate exercise training intensity was maintained as cardiorespiratory fitness increased. Subjects exercised 3 $\text{d}\cdot\text{wk}^{-1}$ at 65-80% $VO_{2\text{peak}}$ on

average $130 \pm 22.7 \text{ min} \cdot \text{wk}^{-1}$ expending the caloric equivalent to walking or jogging 20 miles per wk. To ensure attainment of the proper aerobic training intensity, subjects wore a heart rate monitor (Polar Electro, Inc., Woodbury, NY) at each session that was uploaded weekly. Subjects were instructed to use the treadmill as the primary mode of training, however the bicycle ergometer, elliptical, and stair climber were other modality choices

Resistance Training [RT (n=28)] group also began with a run in period, and then one set for the first 2 wk followed by two sets during wk three and four until they reached the intended three sets during wk five. Subjects trained at 70-85% of their one repetition maximum 3 d·wk⁻¹.

Subjects used Cybex weight machines (Cybex International Inc; Medway, MA) to perform three sets of 8-12 repetitions of eight exercises (four upper and four lower) targeting major muscle groups. The Duke RT group used only Cybex machines while East Carolina University used Cybex weight machines to perform lower body exercises, abdominal crunch exercises were incorporated and at wk 14 transitioned to free weights for upper body exercises. Subjects able to perform three sets of 12 repetitions in two consecutive sessions increased resistance in five pound increments.

Aerobic + Resistance Training [AT&RT (n=13)] group performed the identical training program of the aerobic and resistance training groups in combination.

Exercise Supervision

To ensure safety and adherence both sites closely monitored all training sessions. East Carolina University provided direct supervision while Duke had direct supervision and/or FitLinxx Strength Training Partner™ (FitLinxx; Norwalk, CT). FitLinxx Strength

Training Partner™ is a computer system designed to electronically track workouts and automatically send training results to the FitLinxx server.

Anthropometric Assessments

Height was measured to the nearest quarter cm and weight to the nearest 0.1 kg on a digital scale (Scale 5005; Scale Tronix Inc, Wheaton, IL) to determine BMI ($\text{kg}\cdot\text{m}^2$).

WC measurements were taken around the abdominal waist at the iliac crest. Each measurement was taken twice to the nearest 0.1 cm and averaged.

Blood Pressure

A trained research nurse measured BP by auscultation on the non-dominant arm following standard procedures (WelchAllyn; Skaneateles Falls, NY)(Pickering et al., 2005). Subjects sat quietly in the laboratory for 60 min with feet flat on the floor in the relaxed position. Two BP measurements were obtained 20-30 min apart and then averaged by a nurse trained in standard procedures (45). Mean arterial pressure (MAP) was determined by: $\text{DBP} + 0.33 * (\text{SBP} - \text{DBP})$.

Fasting Blood Determinations

Lipids and Lipoproteins

HDL cholesterol and triglycerides were analyzed from fasting plasma using nuclear magnetic resonance (LipoScience; Raliegh, NC).

Glucose

Subjects fasted 12 hr only consuming water during this time. Fasting plasma samples were used to determine glucose by nuclear magnetic resonance (LipoScience; Raliegh, NC).

Metabolic Syndrome Classification

The MetS was defined as having three or more of the following: triglycerides ≥ 150 mg/dL, BP $\geq 130/85$ mmHg, fasting glucose ≥ 100 mg/dL, WC for men ≥ 102 cm and women ≥ 88 cm, and/or high fasting density lipoprotein < 40 mg/dL for men and women < 50 mg/dL (JAMA, 2001). Last, the MetS components were used to calculate the MetS z-score.

Metabolic Syndrome z-score

The MetS z-score was a continuous standardized calculation of the five MetS components: HDL-cholesterol, triglycerides (TG), fasting blood glucose (FBG), WC, and MAP. The MetS z-score enabled the five MetS components with different scales to be compared. Individual subject data, current ATP III criteria, and standard deviations from the entire STRRIDE AT/RT cohort at baseline were used to calculate the MetS z-score. The MetS z-score equations used separate standard deviations for men and women, specifically for HDL-cholesterol and WC.

The equations used to calculate the MetS z-score were as follows: {z-Score = [(40-HDL)/6.2] + [(TG-150)/66.2] + [(FBG-100)/10.4] + [(WC-102)/9.3] + [(MAP-100)/8.7]} for men and {z-Score = [(50-HDL)/11.8] + [(TG-150)/66.2] + [(FBG-100)/10.4] + [(WC-88)/9.2] + [(MAP-100)/8.7]} for women (Bateman et al., 2011).

Cardiopulmonary Graded Exercise Test

The CPET was completed for individuals in the aerobic group after the run in period and after completion of 6 months of exercise training. The test was performed on a treadmill with a 12-lead electrocardiograph and expired gas analysis using a TrueMax 2400 Metabolic Cart (ParvoMEDics; Sandy, UT). The test protocol included two min

stages with the workload increasing by one metabolic equivalent per stage. VO_{2peak} ($mg \cdot kg^{-1} \cdot min^{-1}$) was determined by averaging the two consecutive highest 15 second readings. A respiratory exchange ratio ≥ 1.10 was the criteria used to terminate the test.

Muscle Strength Evaluation

Total amount of weight lifted in kilograms during a single session during wk 5 was used to calculate muscle strength for baseline measurements. At wk 32 the same measurements were used for end of the training measurements. Total amount weight lifted was determined by accumulation of weight, number of repetitions multiplied by number of sets.

Statistical Analysis

Descriptive statistics (mean \pm SD) were calculated for all sub-study variables. Repeated measures analysis of covariance (ANCOVA) was used to test the change in BP before versus after training and over 2 wk of detraining (i.e., after training versus after 2 wk of detraining) and within and between training groups (AT_{vigorous}, RT, and AT/RT). Gender was used as a fixed factor and baseline BMI, MetS z-score, and VO_{2peak} were used as covariates. Chi-Square was used to test the frequencies of individuals who decreased (i.e., responders) or increased (i.e., non-responders) BP before versus after exercise training and after training versus after detraining. The median, zero, was used as the cut point to determine responder (changes less than zero) and non responder (changes greater than or equal to zero). A linear and multivariable regression was performed to explore subject characteristics and the BP response to detraining as predictors of the BP response to exercise training. In addition, the variance inflation factor (VIF) less than 3

was used to determine there was no collinearity among the various independent variables used in the multivariable regression models.

Last, to examine the inter and intra variability in the response to CVD risk factors to exercise training, a chi-square was used to test the frequencies of those individuals who decreased (i.e., responders) and increased (i.e., non-responders) the sum of the response of the individual components of the cardiometabolic profile before versus after exercise training. The sum of the cardiometabolic profile was determined by assigning 1 as a favorable change and -1 as an unfavorable change for the following components: BMI, WC, fasting glucose, triglycerides, VO_{2peak} , and BP (mmHg). The median, zero, was used as the cut point to determine favorable (changes less than zero) and unfavorable changes (changes greater than or equal to zero). Statistical Package for Social Science (SPSS) version 19.0 for Macintosh (IBM, Armonk, NY) with $p < 0.005$ was used as the level of statistical significance.

Chapter 4 - Results

Descriptive Characteristics

Subject Characteristics

The sub-study population consisted of 75 sedentary, middle aged, overweight men and women with mild to moderate dyslipidemia and PreHTN (Table 1). Exercise SBP responders had a higher BMI ($p=0.025$) and resting BP ($p=0.003$) and lower glucose levels ($p=0.031$) and VO_{2peak} ($p=0.051$) than exercise non-responders. Exercise DBP responders had a higher resting BP compared to DBP non-responders ($p=0.025$). All other characteristics were not different between exercise SBP and DBP responders and non-responders ($p>0.05$).

Blood Pressure Response to Exercise Training and Detraining among the Total

Sample and by Modality

The change in SBP/DBP of $0.4\pm 10.6/-0.8\pm 7.0$ mmHg pre to post 6 months of exercise training was not different among the total sample ($p>0.05$). In addition, the change in SBP/DBP pre to post 6 months of exercise training was not different by modality, i.e., $1.9\pm 10.8/0.1\pm 6.0$ mmHg for AT_{vigorous} ($n=34$), $2.5\pm 8.3/-0.8\pm 5.5$ mmHg for RT ($n=28$), and $-4.0\pm 10.1/-2.4\pm 9.1$ mmHg for AT/RT ($n=13$) ($p>0.05$).

The change in SBP/DBP of $0.3\pm 11.7/0.9\pm 8.7$ mmHg after 2 wk of detraining was not different among the total sample ($p>0.05$). In addition, the change in SBP/DBP following 2 wk of detraining was not different by modality, i.e., $-1.4\pm 11.0/-2.3\pm 8.2$ mmHg for AT_{vigorous} ($n=34$), $-0.6\pm 10.2/1.4\pm 7.8$ mmHg for RT ($n=28$), and $3.1\pm 11.3/3.9\pm 8.3$ mmHg for AT/RT ($n=13$) ($p>0.05$).

The change in VO_{2peak} $mL \cdot kg^{-1} \cdot min^{-1}$ pre to post 6 months of exercise training was not different among the total sample ($p > 0.05$). In addition, the change in VO_{2peak} pre to post 6 months of exercise training was not different by modality, i.e., $1.9 \pm 10.8 / 0.1 \pm 6.1$ $mL \cdot kg^{-1} \cdot min^{-1}$ for $AT_{vigorous}$ ($n=34$), 2.5 ± 8.2 $mL \cdot kg^{-1} \cdot min^{-1}$ for RT ($n=28$), and $-4.2 \pm 9.8 / -2.5 \pm 9.5$ $mL \cdot kg^{-1} \cdot min^{-1}$ for AT/RT ($n=13$) ($P > 0.05$).

Blood Pressure Response to Exercise Training and Detraining among Responders and Non-Responders

Exercise training responders decreased SBP 10.0 ± 6.7 ($n=19$) and DBP 9.1 ± 4.9 ($n=25$); whereas exercise training non-responders increased SBP 9.6 ± 7.6 ($n=28$) and DBP 6.2 ± 5.3 ($n=26$) pre to post 6 months of exercise training ($p < 0.001$). Furthermore, the SBP ($p < 0.001$) /DBP ($p < 0.001$) change pre to post 6 months of exercise training was different between responders and non-responders ($p < 0.001$). In addition, exercise detraining responders decreased SBP 9.1 ± 5.4 ($n=28$) and DBP 7.4 ± 5.0 ($n=26$); whereas exercise detraining non-responders increased SBP 12.4 ± 8.4 ($n=19$) and DBP 7.0 ± 8.4 ($n=25$) at the conclusion of exercise training followed by 2 wk of detraining ($p < 0.001$). Additionally, the SBP/DBP change at the conclusion of exercise training followed by 2 wk of detraining was different between responders and non-responders ($p < 0.001$).

Of the 29 people that decreased SBP with training (i.e., responders), 65.5% increased SBP with detraining; however, 34.5% decreased SBP with detraining. In addition, of the 46 people that increased SBP with training (i.e., non-responders), 48.6% increased SBP with detraining, while 73.7% decreased SBP with detraining ($p=0.034$). Similar trends were found with DBP. Of the 34 people that decreased DBP with training (i.e., responders), 80.6% increased DBP with detraining; whereas 19.4% decreased DBP with

detraining. Of the 44 people that increased DBP with training (i.e., non-responders), 41.9% increased DBP with detraining; while 81.3% decreased DBP with detraining ($p=0.001$).

Predictors of Blood Pressure with Exercise Training

Table 2 displays the multivariate regression predictors of the BP response pre to post 6 months of exercise training. Factors accounting for 44.8% of the variance in SBP were pretraining SBP, the SBP response to detraining, and the change in the MetS z-score pre to post 6 months of exercise training ($p<0.001$). Factors accounting for 60.1% of the variance in the DBP to exercise training were the pretraining DBP, the DBP response to detraining, and the change in the MetS score pre to post 6 months of exercise training ($p<0.001$).

Comparison of the Blood Pressure and Cardiometabolic Profile Response to Exercise Training

There were no differences exhibited in the BP response pre to post 6 months of exercise training and the sum of individual components response of the cardiometabolic profile and the MetS z-score to exercise training for the total sample ($p>0.05$). Exercise SBP and DBP responders improved the MetS z-score pre to post 6 months of exercise training ($p<0.001$), and this response did not improve for SBP and DBP non-responders ($p<0.001$). All other components of the cardiometabolic profile were not different between exercise SBP and DBP responders and non-responders pre to post 6 months of training ($p>0.05$).

Among the 29 people that decreased SBP with exercise training (i.e., responders), 30.0% increased the sum of the individual components of the cardiometabolic profile

with exercise training indicating an unfavorable response, while 48.6% were found to decrease the sum of the individual components of the cardiometabolic profile indicating a favorable response pre to post 6 months of exercise training. In addition, of the 46 people that increased SBP with exercise training (i.e., non-responders), 60.9% increased the sum of the individual components of the cardiometabolic profile, while 39.1% decreased the sum of the individual components of the cardiometabolic profile pre to post 6 months of exercise training ($p=0.079$).

Similar trends were found with DBP. Among the 31 that decreased DBP with exercise training (i.e., responders), 31.0% increased the sum of the individual components of the cardiometabolic profile with exercise training (i.e., non-responders), while 54.5% decreased the sum of the individual components of the cardiometabolic profile pre to post 6 months of exercise training. Of the 44 that increased DBP with exercise training, 65.9% increased the sum of the individual components of the cardiometabolic profile with exercise training (i.e., non-responders), while 34.1% were found to decrease the sum of the individual components of the cardiometabolic profile pre to post 6 months of exercise training ($p=0.034$).

Table 1. Pretraining Subject Characteristics (Mean±SD) of the Total Sample and by Those Who Decreased Blood Pressure After Exercise Training (Responders) and Those Who Did Not (Non-Responders)

Variable	Total Sample (n=75)	SBP		DBP	
		Responder (n=29)	Non responder (n=46)	Responder (n=31)	Non responder (n=44)
Age (yr)	50.2±10.6	52.6±12.0	48.7±9.5	50.2±11.0	50.3±10.4
SBP (mmHg)	120.0±13.7	125.8±14.3**	116.3±12.0	121.7±15.9	118.7±11.9
DBP (mmHg)	79.1±9.2	80.7±9.7	78.1±8.8	81.9±9.7*	77.1±8.4
BMI (kg/m ²)	30.5±3.2	31.5±2.7*	29.8±3.3	30.3±2.9	30.6±3.3
WC (cm)	97.0±9.8	97.3±9.8	96.7±9.9	97.5±10.0	96.5±9.7
CHOL (mg·dL ⁻¹)	226.2±31.6	228.7±36.8	224.6±28.2	228.6±31.4	224.5±31.9
HDL (mg·dL ⁻¹)	52.1±15.0	55.2±14.6	50.2±15.1	51.8±16.6	52.4±13.9
LDL (mg·dL ⁻¹)	144.2±25.1	143.4±30.5	144.8±21.3	143.9±26.	144.4±24.6
TG (mg·dL ⁻¹)	153.3±85.7	150.0±68.6	155.4±95.5	171.8±101.2	140.3±71.2
Glucose (mg·dL ⁻¹)	92.4±11.5	88.8±13.9*	94.7±9.1	89.9±14.3	94.3±8.8
Insulin (mg·dL ⁻¹)	8.9±4.5	9.2±5.7	8.7±3.6	8.5±4.6	9.3±4.5
VO _{2peak} (mL·kg ⁻¹ ·min ⁻¹)	28.1±6.5	26.3±5.6*	29.3±6.8	29.8±6.9	27.0±6.0

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BMI, Body Mass Index; WC, Waist Circumference; CHOL, Cholesterol; HDL, High Density Lipoprotein; LDL, Low-Density Lipoprotein; VO_{2peak}, Peak Oxygen Uptake; Metabolic Syndrome Score; {z-Score = [(40-HDL)/6.2] + [(TG-150)/66.2] + [(FBG-100)/10.4] + [(WC-102)/9.3] + [(MAP-100)/8.7]} for men and {z-Score = [(50-HDL)/11.8] + [(TG-150)/66.2] + [(FBG-100)/10.4] + [(WC-88)/9.2] + [(MAP-100)/8.7]} for women; Responder vs Non Responder *p<.05, ** p<.001

Table 2. Multivariable Regression Predictors of the Blood Pressure Change Pre to Post 6 Months of Exercise Training among STRRIDE Participants (n=75)

Exercise Training						
Blood Pressure Change	Predictors	β	t	Partial r	r ²	p
Systolic Blood Pressure	Change Detraining Systolic Blood Pressure	-.461	-5.149	-.521		<.001
	Pretraining Systolic Blood Pressure	-.379	-4.171	-.444		<.001
	Metabolic Syndrome Z-Score	.235	2.536	.288		.013
Model Summary				.686	.448	<.001
Diastolic Blood Pressure	Change Detraining Diastolic Blood Pressure	-.448	-5.595	-.553		<.001
	Pretraining Diastolic Blood Pressure	-.339	-4.245	-.450		<.001
	Metabolic Syndrome Z-Score	.371	4.405	.463		<.001
Model Summary				.786	.601	<.001

Table 3. The Change (Mean±SD) in the Individual Components of the Cardiometabolic Profile and the Metabolic Syndrome Z Score of the Total Sample and by Those Who Decreased (Responder) and Increased (Non Responder) BP Pre to Post 6 Months of Exercise Training.

Cardiometabolic Profile Component	Total Sample (n=75)	SBP		DBP	
		Responder (n=29)	Non Responder (n=46)	Responder (n=31)	Non Responder (n=44)
BMI (kg/m ²)	-0.6±3.1	-0.1±0.8	-1.0±3.9	-0.5±1.1	-0.7±4.0
WC (cm)	-1.1±3.5	-0.3±2.7	-1.6±3.8	-2.0±3.9	-0.4±3.1
TG (mg·dL ⁻¹)	-18.1±54.4	-25.1±53.5	-13.7±61.5	-32.2±61.0	-8.2±55.1
GLU (mg·dL ⁻¹)	0.4±9.1	0.02±8.5	0.7±9.6	0.01±9.1	0.7±9.2
Metabolic Syndrome Score	-0.5±2.0	-1.4±1.6** §	0.06±2.1	-1.6±2.1**§	0.3±1.6

**p<0.001 Responder vs Non Responder, §p<0.001 pre to post exercise training

STRRIDE, Studies of a Targeted Risk Reduction Intervention through Defined Exercise
 BMI, Body Mass Index; WC, Waist Circumference; TG, Triglycerides ; GLU, Glucose;
 SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; Metabolic Syndrome
 Score; {z-Score = [(40-HDL)/6.2] + [(TG-150)/66.2] + [(FBG-100)/10.4] + [(WC-
 102)/9.3] + [(MAP-100)/8.7]} for men and {z-Score = [(50-HDL)/11.8] + [(TG-
 150)/66.2] + [(FBG-100)/10.4] + [(WC-88)/9.2] + [(MAP-100)/8.7]} for women

Chapter 5 - Discussion

The purpose of this STRRIDE-AT/RT sub-study was to examine the BP response after 6 months of exercise training followed by a 2 wk detraining period among middle aged, sedentary men and women with preHTN and mild to moderate dyslipidemia. The major findings of this STRRIDE-AT/RT sub-study were there was no difference in BP before versus after exercise training and following 2 wk detraining among the total sample, regardless of modality. However, the change in BP after 6 months of exercise training was significantly and negatively correlated with the change in SBP ($r = -0.474$) and DBP ($r = -0.540$) after 2 wk detraining. Approximately one third of STRRIDE-AT/RT participants decreased BP with exercise training *and* increased BP with detraining. However, contrary to our hypothesis, over one third of STRRIDE-AT/RT participants increased BP with exercise training *and* decreased BP with detraining.

Additionally the major predictors of the SBP/DBP response to training were the BP response to detraining ($r = -0.521/-0.553$), pretraining BP ($r = -0.444/-0.450$), and number of MetS components ($r = 0.288/0.463$), which overall accounted for 44.8%/60.1% of the variability in the SBP/DBP response to exercise training, respectively. It is of interest to note that although the number of components of the MetS accounted for 8%/21% of the SBP and DBP response to exercise training, there was variability in the response of the various components of the cardiometabolic profile to exercise training. Approximately one third of the participants that decreased BP experienced an unfavorable change in the overall cardiometabolic profile following exercise training; whereas another one third of the participants that increased BP experienced a favorable change in the overall cardiometabolic profile following exercise training.

The results of this sub-study provide novel findings demonstrating middle aged, sedentary, men and women with preHTN may not respond to the antihypertensive effects of exercise but rather respond to the antihypertensive effects of detraining. Furthermore, the BP response to exercise training does not necessarily align with the response of the other components of the cardiometabolic profile to exercise training. Reasons are unclear as to why some individuals experience an adverse BP response to exercise training, however, our findings are consistent with the reports of others that approximately 25% of people do not lower their BP as a result of exercise training (46,15), and the mean BP response is often exceeded by the SD of the response (13). Most recently, Bouchard et al. (23) consolidated the findings from six of the largest exercise training studies conducted to date that include STRRIDE and found 12.2% of the STRRIDE-AT/RT sub-study participants experienced an adverse SBP response to exercise training. In addition, these authors found the BP response to exercise training was not only variable among individuals, but the response of the various components of the cardiometabolic profile is quite variable both within an individual and among individuals (23). For someone who experiences an adverse BP response to exercise training, may not experience an adverse response of other components of the cardiometabolic profile to exercise training.

Our findings and those of Bouchard (13,23) suggest that eventually health care professionals may identify which individuals respond and do not respond to exercise training as antihypertensive therapy by obtaining a baseline cardiometabolic profile. Further, clinicians may be able to use baseline predictors (i.e., BP, MetS z-score) to identify individuals at risk for an adverse response to exercise and provide an alternative treatment approach for their high BP.

Blood Pressure Response to Exercise Training and Detraining

As hypothesized the SBP ($r = -0.474$) and DBP ($r = -0.540$) response to training and detraining was negatively correlated ($p < 0.01$). This finding supports our hypothesis and is consistent with the existent literature. Meredith et al. (16) found individuals with optimal BP exercising $3-4 \text{ d}\cdot\text{wk}^{-1}$ on a bicycle ergometer at $60-70\% \text{ VO}_{2\text{max}}$ exhibited BP reductions of 8 mmHg for SBP and 5 mmHg for DBP after one month of the onset of exercise training. However, after 2 wk of stopping exercise training, BP returned to baseline values. Similarly, Murray et al. (17) reported men with optimal BP exercising $30 \text{ min}\cdot\text{d}^{-1}$ at $60\% \text{ VO}_{2\text{peak}}$ for one month decreased SBP 10 mmHg and DBP 8 mmHg . Within 1 wk after the cessation of exercise SBP increased 5 mmHg and DBP 3 mmHg and regressed to baseline values. The findings of Meredith et al. (16) and Murray et al. (17) further support the notion that exercise training needs to continue for the antihypertensive benefits of exercise to persist, and these benefits rapidly diminish with the cessation of exercise training.

However, what was unexpected is that we found $65.5\%/73.7\%$ (SBP/DBP respectively) of STRRIDE participants responded to the antihypertensive effects of exercise training where as $80.6\%/81.3\%$ (SBP/DBP respectively) responded to the antihypertensive effects of detraining. Although it is generally thought that BP decreases with exercise training and returns to baseline values with detraining, there is growing evidence of documenting the considerably variability that exists of the response of health related phenotypes to exercise (13,46). Although reasons for this variability remain unclear, identifying clinical characteristics accounting for this variability provides important insight that should be investigated further.

Predictors of Blood Pressure Response to Exercise Training

Reasons for the unexpected findings of BP increasing with exercise training and decreasing with detraining in this sub-study may reside within the predictors of the BP response to training that we found. The major predictors of the BP response to exercise training were the BP response to detraining, pretraining BP and the MetS z-score, which overall accounted for 44.8% and 60.1% of the variance in the SBP/DBP response to exercise training.

These findings are in agreement with previous studies showing baseline BP and the presence of the MetS is associated with the BP response to exercise training. Erdogan et al. (47) examined individual progression of preHTN to HTN among 98 men and women (30-65 yr) with the MetS and preHTN. The aim of the study was to examine the risk of individuals developing HTN while investigating possible predictors of the change in BP status over a 3 yr period. At enrollment 51 (52%) individuals were classified as having the MetS (the presence of three or more risk factors), however, during the 3 yr follow up 29 (30%) individuals developed HTN and 69 (70%) remained preHTN. Individuals who developed HTN over the 3 yr follow up exhibited lower levels of HDL-C, displayed higher baseline SBP and the presence of the MetS was significantly higher at the 3 yr follow up, when compared to individuals who maintained preHTN status. These results indicate the progression of preHTN to HTN significantly and positively correlated with baseline SBP ($p=0.002$) and the presence of the MetS ($p=0.009$). Furthermore, these findings lend support that baseline BP and the presence of the MetS clinically important predictive validity regarding the progression of preHTN to HTN among middle age individuals.

In addition to baseline BP, the presence of the MetS may also be a predictor for the BP response to exercise training. Ferriera et al. (48) performed a 6 yr longitudinal study using data from apparently healthy adults in an ongoing observational study. They examined the change in the MetS status and carotid remodeling (structural and functional adaptations) and stiffening. At baseline individuals with persistent MetS exhibited significantly higher interadventitial diameter lumen diameter, circumferential wall tension and wall stress, and Young's elastic modulus when compared to those who never developed MetS.

Over the follow up period, individuals with persistent MetS exhibited arterial enlargement due to greater increases in intima media thickness while the same group of individuals displayed increases in interadventitial diameter, lumen diameter, circumferential wall tension and wall stress, and Young's elastic modulus as a result of an increase in BP. Over the follow up period individuals with persistent MetS exhibited significantly greater increases in intima media thickness and cross sectional area of intima media thickness, interadventitial diameter, lumen diameter, and circumferential wall tension and wall stress resulting in structural and functional adaptations (i.e., increase BP). Individuals with the MetS displayed increases in intima, the innermost layer of the arterial wall made up of endothelial cells, resulting in a thicker intima causing the lumen diameter to decrease. Further the reductions in the lumen diameter resulted in vasoconstriction of the arteries and a reduction in blood flow.

The authors concluded that individuals with persistent MetS exhibit loss of elasticity as a result of increased interadventitial diameter, lumen diameter, and Young's elastic modulus a the media layer further explaining arterial enlargement. Furthermore,

increases in interadventitial diameter and lumen diameter were related to changes in SBP and DBP. However, changes in SBP were more strongly linked to the changes in interadventitial diameter and lumen diameter than changes in DBP.

Limitations and Strengths

Limitations of this STRRIDE-AT/RT sub-study were the main outcome did not intend to examine the BP response to training and detraining. The data used in this sub-study were collected at two test sites: East Carolina University and Duke Center for living. However, to ensure consistent data collection was obtained, a standardized protocol was adhered to. The concurrent group required double the amount of time commitment which resulted in lower adherence. Last, misclassification may have resulted from BP measurement error (23). A strength of STRRIDE-AT/RT was that it was a randomized control trail. To ensure proper technique and intensity, participants were supervised at each session, and, as previously stated, a computer program on the Cybex machines and a heart rate monitors were used to confirm adherence to the prescribed intensity.

Conclusion/Future Directions

In this sub-study, we observed no difference in the BP response to exercise training and detraining among the total sample, regardless of modality. However, the change in BP after 6 months of exercise training was significantly and negatively correlated with the change in BP after 2 wk detraining. Of the 29 people that decreased SBP with training (i.e., responders), 65.5% increased SBP with detraining as expected. In addition, of the 46 people that increased SBP with training (i.e., non responder), 73.7% decreased SBP with detraining. Similar trends were found with DBP. Of the 31 people

that decreased DBP with training, 80.6% increased DBP with detraining, while of the 44 people that increased DBP with training 81.3% decreased DBP with detraining.

Surprisingly, a third of the men and women did not respond to the antihypertensive effects of exercise but rather responded to the antihypertensive effects of detraining.

Further the BP response to detraining, resting BP and MetS accounted for 44.8% of SBP and 60.1% of DBP variability in the BP response to exercise training. Our findings support the work of the HERRITAGE study suggesting considerable there is intra-and inter-variability of the response of health related phenotypes such as BP to exercise training. Additionally, the work of Erdogan et al. (47) suggests that the presence of the MetS is an important predictor of the progression of preHTN to HTN. Currently there have been no studies that have investigated the BP response to exercise training and detraining in the same group of individuals. Further research is needed to elucidate why some individuals decrease their BP with exercise training while others increase their BP with exercise training.

Clinical Significance

It is of importance for clinicians to identify those baseline characteristics (i.e., BP) that predict the response of cardiometabolic risk factors to exercise among individuals at a greater risk for adverse response to exercise training to help reduce and prevent incidences of cardiovascular risks.

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