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## Cardiorespiratory Fitness, Body Fatness Effect on Submaximal Systolic Blood Pressure and Cardiovascular Prognosis among Young Adults

Vivek Kumar Prasad  
*University of South Carolina*

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Cardiorespiratory fitness, body fatness effect on submaximal systolic blood pressure and cardiovascular prognosis among young adults

By

Vivek Kumar Prasad

Bachelor of Medicine Bachelor of Surgery  
Sikkim Manipal University, 2009

Master of Public Health  
University of South Carolina, 2012

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Submitted in Partial Fulfillment of the Requirements

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Accepted by:

Steven N. Blair, Major Professor

Clemens Drenowatz, Committee Member

Gregory A. Hand, Committee Member

Carl J. Lavie, Committee Member

Xuemei Sui, Committee Member

Lacy Ford, Senior Vice Provost and Dean of Graduate Studies

## DEDICATION

To my parents, Dr. Vasudha Rani and Dr. Kamal K. Prasad and my wife, Dr. Swati Kumari  
for their enormous support, love and care

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I am extremely fortunate to work, study and complete my Ph.D in the guidance of Dr. Blair. I never thought that, I will end up doing my Ph.D under the supervision of one of the most outstanding figures in the field of Exercise Science. Thank you very much Dr. Clemens for your guidance and expertise throughout my dissertation preparation, and letting me knock on your door anytime without an appointment. I am sure that, you will be a very well-known personality in the field of Exercise Science in near future. A sincere thank you to Dr. Hand for providing me professional opportunities since I joined University of South Carolina.

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## ABSTRACT

Cardiovascular (CV) diseases (CVDs) are known to be the leading cause of death globally, as CVDs account for the highest rate of mortality compared to any other causes. The mortality from CVDs, is projected to increase to nearly 23.3 million by 2030. Mortality number due to CVD in the United States is 600,000 per year, thus representing nearly 1 in every 4 deaths. Exercise blood pressure (BP) is an important marker of CV events that are associated with incident CV morbidity and mortality among individuals with or without any CVD at present. Elevated exercise BP among individuals with normal resting BP is a marker of incidence of hypertension and other CV events later in life. Cardiorespiratory fitness (CRF), body mass index (BMI) and body fatness are known predictors for CVD risk factors, morbidity, and mortality. It is important to examine how CRF, BMI and body fatness effect submaximal systolic blood pressure (SSBP). We therefore examined the independent and combined associations of CRF, BMI and body fatness with SSBP in young healthy adults.

This dissertation is comprised of three studies that were designed to 1) analyze the relation and trend of SSBP with CRF among young healthy men; 2) analyze the relation and trend of SSBP with body fatness among young healthy men; and 3) examine the association and trend displayed by SSBP with different levels of CRF and body fatness among young healthy women. Data used in these studies were drawn from the Energy

Balance Study, an observational study done in Columbia, SC involving young healthy adults (N=430). We calculated body fat percentage (BF%) and fat mass index using total body fat (BF) measured by dual X-ray absorptiometry (DXA); BMI was calculated using the average of two height and two weight measurements. Graded exercise tests (GXT) using a Modified Bruce protocol on a motorized treadmill were used to measure CRF and SSBP was measured at each stage of GXT.

Study 1 found that a quadratic trend was evident between SSBP and CRF in a model adjusted for age, race, BF%, resting systolic blood pressure (SBP), alcohol intake and smoking, with the largest reduction in SSBP observed between men in Quintile (Q) 1 and 2. This is followed by a plateau at Q 3, and increase in the higher quintiles although still lower than Q 1.

Study 2 found that there was no significant change in SSBP with increase in weight and fatness from normal to overweight range but a significant rise with further increase in obese range at minutes 6, 8, and 10 ( $P < 0.05$  in most or borderline associations in few) after adjusting for age, race, resting SBP, alcohol intake, smoking, and CRF.

Study 3 found that CRF appeared to be independently associated with SSBP at the lower exercise intensities whereas, BMI at the higher intensities. BF% was not independently associated with SSBP at any intensity of exercise.

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## LIST OF ABBREVIATIONS

BP.....	Blood pressure
BF.....	Body fat
BMI.....	Body mass index
CV.....	Cardiovascular
CVD.....	Cardiovascular disease
CRF.....	Cardiorespiratory fitness
CHD.....	Coronary heart disease
DXA.....	Dual X-ray absorptiometry
EDV.....	Endothelium dependent vasodilation
ECG.....	Electrocardiography
GXT.....	Graded exercise test
HTN.....	Hypertension
IR.....	Insulin resistant
LVH.....	Left ventricular hypertrophy
NO.....	Nitric oxide
Q.....	Quintile

SSBP.....Submaximal systolic blood pressure

SBP.....Systolic blood pressure

VO<sub>2</sub>.....Oxygen consumption

## CHAPTER 1

### OVERALL INTRODUCTION

Individual's blood pressure (BP) varies throughout the day, depending upon cardiovascular (CV) reactivity to behavioral and environmental challenges, such as dynamic cold water immersion, mental arithmetic tasks, and both dynamic and isometric exercises. Increase in BP during exercise depends on many factors including health conditions (E.g. cardiovascular diseases, diabetes, dyslipidemia, and ventricular hypertrophy), lifestyle (E.g. physical inactivity, unhealthy diet, alcohol, and tobacco), age, sex, race, genetics and family history. Increased arterial stiffness, impaired endothelial dependent vasodilation and endothelial dysfunction are associated with submaximal systolic BP (SSBP) response. Endothelial dysfunction may contribute to exaggerated SSBP responses during day to day activities, resulting in repetitive rise in the workload of the heart and vessels resulting in higher CV events risk.

Most CVDs can be prevented by controlling risk factors such as physical inactivity, smoking, unhealthy diet and obesity, high BP, hyperglycemia and hyperlipidemia. Exaggerated SSBP response among normotensive individuals during physical exertion and day to day activity is associated with increased risk for CV events. Furthermore, it might be a predisposing factor for CV events later in life. Early prediction of individuals at

increased risk for CV events is warranted so that appropriate interventions could be applied. This dissertation consists three studies that have been developed to better understand 1) the relation of SSBP with cardiorespiratory fitness (CRF) among young healthy men, 2) the relation between body fatness (BF), and SSBP among young healthy men, and 3) the association of SSBP with CRF and BF among young healthy women.

#### Statement of the problem

Cardiovascular diseases (CVDs) are the number one cause of death globally: killing more people yearly than from any other cause. CVDs caused approximately 17.3 million deaths in 2008, representing as high as 30% of all global deaths, the majority of which occurred due to coronary heart disease (CHD) and stroke. The number of deaths from CVDs, mainly from heart disease and stroke, is projected to remain at the peak and reach 23.3 million by 2030. It is important to prevent incident CVDs by determining the risk in advance. One way of doing that is by investigating how risk factors affects SSBP, a predictor of future CV events.

#### SCOPE OF THE STUDY

The overall goal of these studies are to 1) understand the relation of CRF, and fatness with SSBP, 2) identify trends of SSBP across levels of CRF and fatness, and 3) demonstrate relative and combined effects of CRF and fatness on SSBP

## SPECIFIC AIMS AND RESEARCH QUESTIONS

### Paper 1

Evaluating the association of cardiorespiratory fitness with submaximal systolic blood pressure among young healthy men.

Aims:

- A. Association between CRF, and SSBP in young healthy men.
- B. Association between CRF, and SSBP after adjusting for covariates.
- C. Analyzing the trend displayed by SSBP with different levels of fitness.

### Paper 2

Evaluating the association between body fatness and submaximal blood pressure among young healthy men.

Aims:

- A. Association between fat mass index and SSBP.
- B. Association between body mass index and SSBP.
- C. Predicting the trend displayed by SSBP with different levels of body fatness.

### Paper 3

Evaluating the association of cardiorespiratory fitness and body fatness with submaximal systolic blood pressure among young healthy women.

Aims:

- A. Evaluating association of CRF and body fatness with SSBP in an unadjusted model.
- B. Evaluating association between CRF and SSBP in fatness adjusted model.
- C. Evaluating association between body fatness and SSBP in CRF adjusted model.



## CHAPTER 2

### LITERATURE REVIEW

#### **Prevalence of cardiovascular disease and hypertension**

Cardiovascular (CV) diseases (CVDs) are the leading cause of mortality globally with the largest number of people dying annually from CVDs than from any other cause.(World Health Organization. 2011) Around 17.3 million people died from CVDs in 2008, representing as high as 30% of all global deaths.(World Health Organization. 2011) Of these deaths, the highest was estimated to be due to coronary heart disease (CHD) with 7.3 million followed by stroke with 6.2 million deaths.(World Health Organization. 2011) The number of killings due to CVDs, will rise to reach 23.3. million by 2030.(World Health Organization. 2011)(Mathers and Loncar 2006)

Approximately 600,000 people die of CVDs in the United States annually—that is 25% of all deaths.(Murphy, Xu, and Kochanek 2013) CHD is the most common type of CVD, causing nearly 380,000 deaths yearly.(Murphy, Xu, and Kochanek 2013) Every year about 720,000 individuals in United States have a heart attack.(Go et al. 2014)

Globally, mortality due to high BP is projected to be 7.5 million, approximately 12.8% of the total deaths.(2014) This includes approximately 51% of deaths due to strokes and 45% of deaths due to CHD.(World Health Organization. 2008) High BP is a major risk factor for

CHD and hemorrhagic as well as ischemic stroke. In addition to CHDs and stroke, complications of high BP include peripheral artery disease, heart failure, visual impairment, retinal hemorrhage and renal impairment.(2014) Most CVDs can be prevented and managed by addressing risk factors such as sedentary lifestyle, unhealthy diet, obesity, and smoking.(World Health Organization. 2011)

The high prevalence and incidence of hypertension (HTN) globally is the major contributor of the present leading cause of death, CVD. During the past century, HTN has advanced from a minor cause of mortality and morbidity to one of the major global health concerns.(Levenson, Skerrett, and Gaziano 2002) HTN is critical not only because of its high incidence and prevalence but also because it is a known modifiable risk factor for CVD.(Poulter 2003) In a national representative sample 30% of adult Americans during 2005--2008 had HTN and another NHANES analysis has shown that this statistic remained unchanged over the past decade.(Yoon, Ostchega, and Louis 2010)

A meta-analysis including 61 observational studies and 1 million individuals displayed a strong and direct relation of BP and mortality caused by vascular diseases, and each increment of 20 mm Hg systolic BP or 10 mmHg diastolic BP was associated with more than a two-fold increase in stroke deaths, and with a two-fold increase in mortality from ischemic heart disease and other vascular causes of death among individuals aged 40--69 years.(Lewington et al. 2002)

### **Cardiorespiratory fitness, exercise dose and health benefits (a J-curve trend)**

CRF a major predictor of CV and overall health.(Swift et al. 2013, Blair et al. 1989, Kokkinos and Myers 2010) Approximately 2.5 decades ago Blair et al.(Blair et al. 1989) found that there is was a significant decrease in all-cause mortality among individuals with high CRF compared to those with low CRF. Since then, there has been constant corroboration showing that even a slight increase in CRF and exercise dose provide a substantial CV and health benefits(Kokkinos and Myers 2010, Lee et al. 2014) Studies have shown that the maximum reduction in mortality rate is between CRF quintile 1 and 2 or between the lowest fit and the next lowest fit groups followed by further decline in mortality with increase in CRF from fair to good where it plateaus.(Blair et al. 1989, Kokkinos and Myers 2010) Health benefits from CRF plateaus at 9-10 metabolic equivalents with no further benefits from further increases in CRF.(Blair et al. 1989, Kokkinos and Myers 2010, O'Keefe, Franklin, and Lavie 2014) Therefore, even a slight increase in CRF provides a substantial benefit with CRF. This level of CRF could be achieved by most sedentary individuals with even a brisk walk of 30 minutes on most days.(Pate et al. 1995) Like any other medicine, exercise if overdosed might have side effects or loss of benefits to some extent especially in terms of CV health.(O'Keefe, Franklin, and Lavie 2014, O'Keefe, Schnohr, and Lavie 2013, Lavie, O'Keefe, and Sallis 2015) Marathon running is getting embedded in the United States culture and the number of people running marathons has increased substantially over the last 4 decades(O'Keefe et al. 2012) however the superior levels of their CRF does not translate to better CV prognosis and could possibly be associated with a sudden cardiac arrest.(Kim et al. 2012) Several studies have reported a

J-curve relationship between health benefits and exercise dosing indicating that moderate levels of exercise dose provides the maximum benefits in terms of CV and overall health.(O'Keefe and Lavie 2013, Lee et al. 2014, O'Keefe, Schnohr, and Lavie 2013, La Gerche and Prior 2007, Vuori, Lavie, and Blair 2013, Lollgen, Bockenhoff, and Knapp 2009) A study of cardiac patients indicated that individuals with moderate dose of exercise were at lowest risk of CVD mortality compared to those with the lowest and highest dose of exercise. (Mora et al. 2003)

### **Prognostic significance of Exercise blood pressure**

Exaggerated or high exercise BP is an important predictor of CV events that are associated with CV morbidity,(Miyai et al. 2000, Nakashima et al. 2004, Sharabi et al. 2001, Singh et al. 1999, Miyai et al. 2002, Laukkanen et al. 2004, Laukkanen et al. 2006, Kurl et al. 2001) mortality(Allison, Cordeiro, et al. 1999, Filipovsky, Ducimetiere, and Safar 1992) in individuals with or without any signs and symptoms of CVD. Data have shown that individuals identified with elevated exercise BP may account for 40% of individuals at high risk of CV events.(Laukkanen et al. 2006) Hypertensive patients have a reduced exercise capacity, which is attributed to functional and structural changes in CV system and this could be traced back to adolescence.(Lim et al. 1996)

### **Mechanism explaining exaggerated blood pressure**

Exaggerated SSBP could be due to endothelial dysfunction characterized as reduced vasodilation and pro-inflammatory conditions in the vasculature.(Endemann and Schiffrin 2004) Endothelial dysfunction is due to a decreases in production and bioactivity of

vasodilator (NO) and an increase in the vasoconstrictor endothelin, which potentially lead to arterial stiffness and reduced vasodilation(Lerman and Burnett 1992) followed by reduced ability to buffer the increase in systolic blood pressure during exercise.(Stewart et al. 2004, Olson et al. 2012) Endothelial dysfunction is associated with HTN, peripheral arterial disease, CHD, congestive cardiac failure, peripheral artery disease, and diabetes mellitus.(Endemann and Schiffrin 2004, Olson et al. 2012)

A clinical trial demonstrated the extent to which NO synthase contribute to BP control by a complete autonomic block and found a 30 mm Hg rise above the baseline levels which support the notion that decrease in production and bioavailability of NO could lead to HTN(Gamboa et al. 2007) via an impaired EDV.(Luscher et al. 1989) Exercise induces the production of NO which contributes to up regulation of endothelial progenitor cells that helps in improved endothelial function and cardiovascular homeostasis.(Yang et al. 2007)

Some studies have suggested a relation between metabolic disorders, insulin resistance (IR) and blood cholesterol lead to an increase in BP during exercise.(Sironi et al. 2004, Brett, Ritter, and Chowienczyk 2000) Insulin in healthy individuals triggers the production of NO synthase and endothelin with a predominating vasodilation effect of NO synthase. However, the effect and production of endothelin prevail over NO synthase among those with IR.(Sarafidis and Bakris 2007)

There are various mechanisms connecting, obesity, IR, NO production and exercise BP that explains elevated BP during exercise.(Webb et al. 2010, Seifalian et al. 2010) Previous studies have shown that arterial stiffness is associated with IR.(Webb et al. 2010, Seifalian

et al. 2010) One of the major characteristics among individuals with IR and obesity is a decrease in NO production and bioavailability.(Seifalian et al. 2010) Obesity is related to metabolic syndrome including high blood glucose, chronic inflammation, hypertension which could be attributed to deregulated production of adipokines.(Hutley and Prins 2005)

Age, gender(Najjar, Scuteri, and Lakatta 2005, Daida et al. 1996) and genetic predispositions are the other factors effecting endothelial dysfunction.(Colombo et al. 2003) Previous studies show that aging leads to a series of structural and functional alteration of large vasculatures, including wall stiffness and thickness, diameter, endothelial dysfunction.(Najjar, Scuteri, and Lakatta 2005, Daida et al. 1996) Exercise BP is higher among men than women.(Daida et al. 1996)

Acute exercise causes an increase in blood flow to the heart and skeletal vessels blood flow followed by an increase in vascular endothelial NO production and EDV.(Tzemos, Lim, and MacDonald 2002, Niebauer and Cooke 1996)

Previous studies have shown that, NO is involved in the pathophysiology of clinical outcomes like atherosclerosis, CVD, HTN and hyperglycemia in obesity.(Datta et al. 2004, Sobrevia and Mann 1997, Williams et al. 2002) There is a growing premise that obesity-related oxidative stress and non-esterified fatty acid decreases the production and bioavailability of NO resulting in abnormal endothelium dependent vasodilation.(Higashi et al. 2001, Huang et al. 2001, Kerr et al. 2011) Studies have shown a positive relation of CRF and exercise training with NO formation and its bioactivity which may help to explain

the beneficial effects of CRF on CV prognosis.(Jungersten et al. 1997, Green et al. 2004) A clinical study has indicated that regular exercise training among patients of chronic heart failure improves both vascular endothelial NO formation and bioavailability followed by agonist-mediated endothelium-dependent vasodilation. Improved endothelium function also results in a significant increase in CRF.(Hambrecht et al. 1998) Factors that might contribute to CVD in obesity are multifactorial including pathophysiological and structural changes. Pathophysiological changes are metabolic dysregulation with increased prevalence of IR, HTN, and dyslipidemia whereas, structural changes are characterized by LVH, chamber dilatation, abnormal ventricular dysfunction.(Poirier et al. 2011)

### **Cardiorespiratory fitness effects on cardiovascular diseases and exercise blood pressure**

Low levels of CRF are associated with high risk of CVD and HTN.(Blair et al. 1989, Blair et al. 1995, Stevens et al. 2004, Myers et al. 2002, Gulati et al. 2003, Mora et al. 2003, Blair et al. 1984) Moreover, Kokkinos et al(Kokkinos et al. 2002) observed in a large population of 1411 normotensive and hypertensive women that there was an association between low CRF and higher submaximal SBP (SSBP) response during submaximal exercise, in resting SBP, heart rate, BMI, age, and time to exhaustion in an adjusted model. Low fitness is a known major precursor of mortality. The protective effect of CRF is consistent irrespective of smoking history, cholesterol levels or BP, in unhealthy and healthy individuals. Moderate CRF seems to protect against the influence of these predictors of mortality.(Blair et al. 1996) Studies have shown that the risk of having metabolic

syndrome increases in those with lower levels of CRF.(Farrell, Cheng, and Blair 2004, Church et al. 2002)

Higher BMI and CRF are associated with lower exercise SBP in middle-aged healthy men.(Mundal et al. 1997) A recent study showed that a decrease in exercise SBP was independently associated with decreased fatness, and increased CRF among older adults.(Barone et al. 2009) Aerobic training and regular vigorous exercise significantly reduces submaximal BP.(Cox et al. 1996, Van Hoof et al. 1989) Both clinical and experimental studies have linked improved CRF and improved vascular endothelial function to increase NO production and its bioactivity.(Arvola et al. 1999, Hambrecht et al. 2003) To the best of our knowledge there is no study that examines the association between CRF and SSBP among young healthy individuals.

### **Obesity effects on cardiovascular diseases and exercise blood pressure:**

Obesity is a global epidemic.(World Health Organization. 2000) In the United States, nearly 70% of adults are categorized in the overweight or obese range.(Flegal et al. 2002, Lavie and Milani 2003, Manson and Bassuk 2003) Moreover, the distribution of BMI has skewed towards morbid obesity.(Poirier et al. 2006, Klein et al. 2004, Flegal et al. 2002, Lavie and Milani 2003, Manson and Bassuk 2003, Lavie, Milani, and Ventura 2009)

Obesity is associated with higher CV mortality.(Allison, Fontaine, et al. 1999, Lee et al. 2001, Troiano et al. 1996, Albert et al. 2003, Stevens et al. 2002, Klein et al. 2004) Moreover, CV mortality is related to BMI with a two to three times higher risk for mortality among obese with BMI  $\geq 35$  kg/m<sup>2</sup> compared to those with normal BMI.(Calle et



al. 1999) Results displayed by different studies are inconsistent, with one study suggesting that high BMI is associated lower exercise SBP after 7 years among middle aged healthy men(Mundal et al. 1997) whereas, a randomized control exercise training study done among sedentary individuals with pre hypertension and mild hypertension showed that, a decrease in waist circumference is associated with lower exercise SBP.(Barone et al. 2009)

## CHAPTER 3

### GENERAL METHODOLOGY

#### **Enrollment process and inclusion criteria**

The three studies in this dissertation used baseline data collected in the Energy Balance Study (EBS), a prospective observational study following healthy young men and women for 36 months.(Hand et al. 2013) All participants were recruited between June 2011 and July 2012, and were from Columbia, South Carolina and nearby areas. Individuals interested in participation were instructed to complete an online screener on the study website (<http://energybalance.sc.edu/>). Participants were invited to attend an orientation program to determine if they met study inclusion/exclusion criteria. Inclusion criteria consisted a BMI range of  $\geq 20$  and  $\leq 35$  kg/m<sup>2</sup> and age  $\geq 21$  and  $\leq 35$  years. Exclusion criteria included; currently diagnosed or on treatment for any chronic health conditions, resting BP exceeding 150 mmHg systolic and/or 90mmHg diastolic, an ambulatory blood glucose level of greater than 145 mg/dl. Further, those who were undergoing treatment or have planned bariatric or liposuction surgery to lose weight, started or quit smoking in the previous 6 months were excluded. Individuals with a history of or receiving treatment for anxiety, depression, phobia or panic attacks were excluded.

## **Study design**

The Energy Balance Study consisted of a series of measurements and assessments during three laboratory visits. Laboratory visit #1 consisted of participants completing a comprehensive personal medical history, and an extensive set of psychometric, demographic, and physical activity recall questionnaires. Finally, this visit included dietary assessment training to orient them for telephone administered 24-hour dietary recalls. Laboratory visit #2 included determination of cardiorespiratory fitness (CRF) via a graded exercise test (GXT) using a modified Bruce protocol with 12-lead electrocardiogram (ECG) while monitoring exercise BP at each stage of GXT. Additionally, this visit included measurements of resting BP, weight, height, waist and hip circumference, body composition via dual-energy X-ray absorptiometry (DXA).

Laboratory visit #3 included measurements of height, weight, waist and hip circumferences, collection of blood sample, and resting metabolism test. Finally, armbands with the instructions and manual on how to use, were provided for 10 days energy expenditure assessment. Three random telephone administered 24-hour dietary recalls began at the conclusion of Laboratory visit #3.

All study protocols were approved by the University of South Carolina Institutional Review Board, and informed consent was obtained from each participant prior to data collection.

## **Anthropometry**

Anthropomorphic measurements and collection of blood samples were performed with the participant dressed in basic medical scrubs and in bare feet. BMI ( $\text{kg}/\text{m}^2$ ) was calculated from the average of two height and weight readings using a traditional stadiometer and electronic scale and recorded to the nearest 0.1 centimeter and 0.1kg, respectively. Body composition was scanned with no metal on the participant's body, using a Lunar fan-beam dual X-ray absorptiometry (DXA) (GE Healthcare model 8743, Waukesha, WI). Total fat and lean tissue mass, as well as torso, upper limb and lower limb tissue composition were determined. Fat mass index ( $\text{kg}/\text{m}^2$ ) was calculated from the average of two height measurements and total fat mass. Body fat percentage was calculated by using total fat mass and average of two body weight measurement. Participants were instructed to stand straight with their hands parallel to the floor to determine waist circumference at the point midway between the costal margin and iliac crest, in the mid-axillary line approximately 2 inches above the umbilicus. Hip circumference was recorded at the widest point around the greater trochanter. Circumferences in the data set were the average of two measurements and third one taken if the difference in first two was more than 0.4cm.

Exercise testing procedure: CRF was assessed by a trained exercise physiologist. Eligible participants were prepared for the GXT including a standard 12-lead Electrocardiogram (ECG). A BP cuff of a manual sphygmomanometer was placed on left arm of the individual followed by an examination of the pre-exercise BP, real-time resting ECG, and heart rate.

On approval for participation in terms of BP and ECG, the exercise physiologist administered the GXT using a Modified Bruce protocol on a motorized treadmill (Full Vision, Inc., Newton, KS). The modified Bruce GXT starts at a speed of 1.7 mph and 0% grade for first 2 min then progresses to 1.7 mph and 5% grade for next 2 min. The speed and grade at stage 1, 2, 3, 4 and 5 were 1.7 mph, 0%; 1.7 mph, 5%; 2.5 mph, 10%; 3.4 mph, 12%; 4.2 mph, 16% respectively. After 4 min the protocol is synonymous to that of the Bruce Protocol. All participants were instructed to exercise to volitional fatigue and indicate when to stop the treadmill. The test was followed by continued walking at a slow pace and 0% grade until BP and HR returned to near baseline levels. Criteria for a maximal test included 2 of the following variables: a heart rate plateau or  $VO_2$  plateau with increasing workload, a respiratory quotient (RQ)  $\geq 1.15$ , and a rate of perceived exertion (RPE)  $\geq 17$  using the Borg scale of perceived exertion. Respiratory gas exchange was determined at each stage of GXT. Oxygen consumption at the maximal effort is defined as peak  $VO_2$ . BP was recorded at each stage of the protocol by a trained staff member. The participant was instructed to rest their left arm on the shoulder of the staff member at each stage of the GXT during BP measurement. They were also instructed to keep their palm facing up to avoid gripping of the staff's shoulder and getting an external support during the test.

Smoking history was documented by providing the individuals a personal medical history questionnaire and alcohol intake was calculated from the multiple 24-hr dietary recall interviews. Resting SBP was calculated from an average of two measurements. Two measures of sitting SBP were recorded using the manual sphygmomanometer by trained

technicians and third measurement was taken if the difference in SBP was more than 10 mm Hg.

## STUDY 1 METHODOLOGY

Purpose: This study will address Aim#1 which is to analyze the association between CRF and SSBP in a cohort of young healthy men.

### Research questions

Research question 1.1: What is the association between SSBP and CRF in an unadjusted model?

Research question 1.2: What is the association between SSBP and CRF in an adjusted model including age, race, BF%, resting SBP, alcohol intake and smoking?

Research question 1.3: What is the trend displayed by SSBP with a broad spectrum of CRF?

Study Design: This study has a cross sectional design

### Study population

This analysis will include young healthy men who participated in EBS and completed the baseline laboratory visits (n=204).

## Study measurements

For this study, CRF and SSBP were recorded during GXT using a modified Bruce protocol, BF% was calculated using total fat mass measured by DXA full body scan, alcohol intake was assessed via telephone administered multiple dietary recalls and smoking history via personal medical history.

## Statistical Analysis

Participants were categorized in quintiles (Qs) of CRF with Q 1 representing the group of men with lowest CRF, whereas Q 5 represented those with the highest CRF. Multivariate analyses was done including potential covariates, age, race, BF%, resting SBP, alcohol intake and smoking to determine the association between SSBP with CRF at minutes 4, 6 and 10 of the GXT. All computation were done using SPSS version 22 with  $P < 0.05$  for statistical significance.

## STUDY 2 METHODOLOGY

Purpose: This study will address Aim#2 which is to analyze the association of SSBP with FMI and BMI in a cohort of young healthy men.

## Research questions

Research question 1.1: What is the association between SSBP and FMI in a model adjusted for age, race, resting SBP, alcohol intake, smoking, and CRF?

Research question 1.2: What is the association between SSBP and BMI in a model adjusted for age, race, resting SBP, alcohol intake, smoking, and CRF?

Research question 1.3: What is the trend of SSBP with BMI and FMI in an adjusted model?

Study Design: This study will employ a cross sectional design.

Study population

This analysis will include young healthy men who participated in EBS and completed the baseline laboratory visits. (n=212)

Study measurements

For this study FMI was calculated using total body fatness measured using DXA, BMI was calculated using average of two measures of weight and height, SSBP was recorded during GXT, alcohol intake was recorded via telephone administered multiple dietary recalls, smoking history via personal medical history was used, and CRF was assessed using a GXT.

Statistical Analysis

Participants were categorized in quintiles (Qs) of FMI and BMI with Q 1 representing the group of men with lowest FMI and BMI, whereas Q 5 represented those with the highest FMI and BMI. Multivariate analyses was done including potential covariates, age, race, resting SBP, alcohol intake, smoking, and CRF to determine the association of SSBP with FMI and BMI at minute 4, 6 and 10 of GXT. All computations were done using SPSS version 22 with  $P < 0.05$  for statistical significance.



## STUDY 3 METHODOLOGY

Purpose: This study will address Aim#3 which is to analyze the association of CRF and BF with SSBP in a cohort of young healthy women

### Research questions

Research question 1.1: What is the association of SSBP with BF% and BMI in unadjusted and adjusted models?

Research question 1.2: What is the association between SSBP and CRF in an unadjusted and adjusted model?

Research question 1.3: What happens to the associations when they are further adjusted for each other?

Study Design: This study will employ a cross sectional design

### Study population

This analysis will include young healthy women who participated in EBS and completed the baseline laboratory visits. (n=212)

### Study measurements

For this study FMI was calculated using total body fat assessed by DXA full body scan, BMI was calculated using an average of two height and weight measurements, CRF assessed by GXT using a modified Bruce protocol, SSBP recorded during GXT, alcohol intake via

telephone administered multiple dietary recalls, and smoking history via personal medical history were.

#### Statistical Analysis

Participants were categorized in quartiles (Qs) of BF%, BMI, and CRF with Q 1 representing the group of men with lowest BF%, BMI, and CRF whereas Q 5 represented those with the highest BF%, BMI, and CRF. Multivariate analyses were done including potential covariates, age, race, resting SBP, alcohol intake and smoking to determine the association between SSBP with BF%, BMI, and CRF at stages 1 through 4 of GXT. All computations were done using SPSS version 22 with  $P < 0.05$  for statistical significance.

## CHAPTER 4

### MANUSCRIPT 1: ASSOCIATION BETWEEN CARDIORESPIRATORY FITNESS AND SUBMAXIMAL SYSTOLIC BLOOD PRESSURE IN YOUNG HEALTHY MEN: A REVERSED J- CURVE PATTERN RELATIONSHIP

Vivek K. Prasad, Clemens Drenowatz, Gregory A. Hand, Carl J. Lavie, Xuemei Sui, Madison Demello, Steven N. Blair. Submitted to *Journal of Hypertension*, 2/17/2015.

## Abstract

**Objectives:** The purpose of this study was to evaluate association between submaximal systolic blood pressure (SSBP) and cardiorespiratory fitness (CRF) among young healthy men. Further, we investigated the trend displayed by SSBP across different levels of CRF.

**Methods:** Graded Exercise Test (GXT) using a Modified Bruce protocol was performed on 204 normotensive (resting BP < 140/90 mm Hg) men; SSBP was recorded at each stage of the protocol. Quintiles of CRF were established on the basis of peak oxygen consumption ( $VO_2$ ) with the 1st quintile (Q) being the lowest fit group and 5th Q the most fit.

**Results:** The mean  $VO_2$  peak in Q 1 through 5 were 32.3, 39.1, 43.4, 48.1 and 55.5 ml/kg/min, respectively, with a quadratic trend being evident between SSBP and CRF. In a model adjusted for age, race, body fat percentage, resting systolic blood pressure, alcohol intake and smoking, the largest reduction in SSBP was observed between men in Q 1 and 2, with 7.6 mmHg ( $p=0.05$ ), 9.4 mmHg ( $p=0.02$ ), and 9.5 mmHg ( $p=0.04$ ) lower SSBP at minutes 6, 8 and 10 of GXT, respectively. SSBP plateaus at Q 3, followed by an increase in the higher Qs.

**Conclusion:** There was a reversed J-curve pattern relationship between SSBP and CRF. Improving CRF from poor to fair or good should progressively decrease SSBP and cardiovascular disease risks. Further, the benefits from improvements in the CRF on SSBP plateau at a point, beyond which there are no additional benefits or potentially some loss of the benefits.

Keywords: submaximal systolic blood pressure, cardiorespiratory fitness, cardiovascular diseases, hypertension.

## Introduction

Cardiovascular (CV) diseases (CVDs) are the leading cause of death globally, as more people die annually from CVDs than from any other causes.(World Health Organization. 2011) CVD deaths are projected to increase to nearly 23.3 million annually by 2030.(World Health Organization. 2011)(Mathers and Loncar 2006) About 600,000 people die of CVD in the United States every year, thus representing nearly 1 in every 4 deaths.(Murphy, Xu, and Kochanek 2013) Exercise blood pressure (BP) is an important marker of CVD events, such as incident hypertension (HTN),(Miyai et al. 2000, Nakashima et al. 2004, Sharabi et al. 2001, Singh et al. 1999, Miyai et al. 2002) myocardial infarction,(Laukkanen et al. 2006, Laukkanen et al. 2004) stroke,(Kurl et al. 2001) and CVD mortality(Allison, Cordeiro, et al. 1999, Filipovsky, Ducimetiere, and Safar 1992) among individuals with or without high resting BP or overt CVD signs at present. A study has reported that among middle aged men without a history of coronary heart disease (CHD), an exaggerated exercise BP response may account for 4.31 times higher risk for myocardial infarction.(Laukkanen et al. 2006) Systolic BP (SBP) during submaximal exercise at and after 6 minutes of exercise has been investigated extensively, and generally higher submaximal SBP (SSBP) is an excellent predictor of left ventricular hypertrophy (LVH),(Gottdiener et al. 1990, Papademetriou et al. 1989, Polonia et al. 1992) which is a major predictor of CVD mortality.(Lavie et al. 2014) Exaggerated SBP during exercise among 426 normotensive

individuals was associated with higher atherosclerotic markers, which signifies that despite no apparent symptoms or signs of CVD, an end organ damage is occurring and this could potentially later lead to an increased risk of CVD events.(Idoue et al. 2015)

Low levels of cardiorespiratory fitness (CRF) are associated with higher risk of CVD and HTN (Blair et al. 1989, Blair et al. 1995, Stevens et al. 2004, Myers et al. 2002, Gulati et al. 2003, Mora et al. 2003, Blair et al. 1984). It is also known that the risk of having metabolic syndrome is higher in those with lower levels of CRF (Blair et al. 1996, Farrell, Cheng, and Blair 2004). Almost 2 decades ago, researchers reported that CRF was associated with lower SSBP after 7 years among middle-aged healthy men (Mundal et al. 1997). Moreover, Kokkinos et al (Kokkinos et al. 2002) observed in a population of 1411 normotensive and hypertensive women that there was an association between low CRF and higher SSBP response after 6 minutes of exercise. A recent study reported that lower SSBP was independently associated with higher CRF among older adults with untreated pre-hypertension or mild hypertension (Barone et al. 2009). A previous study presented evidence suggesting that aerobic exercise training in African Americans with severe systemic HTN attenuates an exaggerated BP during exercise (Kokkinos et al. 1997). Other research shows that both aerobic training and regular vigorous exercise significantly reduces SSBP (Cox et al. 1996, Van Hoof et al. 1989). Clinical and experimental studies have linked the effect of CRF on all-cause mortality to improved vascular endothelial function (Hambrecht et al. 1998, Arvola et al. 1999, Hambrecht et al. 2003).

To the best of our knowledge, there is no study demonstrating the relation and trend between SSBP and CRF among young healthy men. Therefore, the purpose of this study is to examine the association between SSBP and CRF after 6 minutes of exercise during graded exercise test (GXT) in young healthy men. Further we assessed the trend displayed by SSBP across a broad spectrum of CRF.

## Methods

Participants and enrollment process: The participants in this investigation were drawn from the Energy Balance Study, a prospective observational study.(Hand et al. 2013) A sample of 204 normotensive (resting BP < 140/90 mm Hg) men aged 21-35 years with a body mass index (BMI) between 20 and 35 kg/m<sup>2</sup> was included in the analysis. Exclusion criteria included use of medications to lose weight, started or stopped smoking in the previous 6 months, or planned weight loss surgery. Further, men were excluded for resting BP exceeding 150 mmHg systolic and/or 90mmHg diastolic, an ambulatory blood glucose level of greater than 145 mg/dl, or those currently diagnosed with/or taking medications for a major chronic health condition. Men with a history of anxiety, depression, or panic were excluded, as were those taking selective serotonin inhibitors for any reason. Informed consent was obtained from every men prior to data collection.

Anthropometry: All anthropometric measurements were performed with the participant wearing surgical scrubs and in bare feet; BMI (kg/m<sup>2</sup>) was calculated from the average of two height and weight measurements. Body fat (BF) was measured using a dual X-ray absorptiometry (DXA) scanner and used to calculate BF%.

Exercise testing procedure: A trained exercise physiologist prepared participants for the GXT, including a standard 12-lead electrocardiography (ECG) and BP measurement. BP cuff of a manual auscultatory sphygmomanometer was placed on left arm of the individual followed by an examination of the pre-exercise BP, resting ECG, and heart rate (HR). Once the participant is cleared for participation in terms of pre-exercise BP ( $\leq 150/80$  mmHg) and ECG, the GXT is administered using a Modified Bruce protocol on a motorized treadmill. The first three stages (6 minutes) of the modified Bruce GXT are for warming up at a slow speed of 1.7 mph at 0%, 5%, and 10% grade respectively. After 6 minutes of GXT, the speed and grade both increase every 2 minutes. Speed and grade at minutes 6, 8, and 10 are 1.7 mph, 10%; 2.5 mph, 12%; 3.4 mph, 14% respectively. All subjects exercised to volitional fatigue and criteria for a maximal test included two of the following variables: a respiratory quotient  $\geq 1.15$ , rate of perceived exertion  $\geq 17$  using the Borg scale of perceived exertion, achieved age predicted max HR, and oxygen consumption ( $VO_2$ ) or HR plateaued with increasing workload. A maximal test criterion was achieved by a majority of the men (89.1%). CRF was defined as the  $VO_2$  peak during the GXT. SSBP was recorded after 90 seconds in each stage of the protocol by trained staff member. The subject was instructed to rest their left arm on the shoulder of the staff at each stage of GXT to examine the SSBP. They were also instructed to keep their palm facing up to avoid gripping of the staff's shoulder and getting an external support as it was examined while the subject was walking/running on the treadmill.

Smoking history was recorded by providing the individuals a medical history questionnaire and alcohol intake was calculated from multiple, telephone administered,



24-hr dietary recall interviews. Resting systolic BP (SBP) was calculated from an average of two measurements recorded using a manual auscultatory sphygmomanometer by trained technicians. A third measurement was taken if the difference in SBP was more than 10 mm Hg for the first two measurements. All study protocols were approved by the University of South Carolina Institutional Review Board.

Statistical analysis: Quintiles (Qs) of CRF were established with Q 1 representing the group of men with lowest CRF, whereas Q 5 represented those with the highest CRF. One way ANOVA was used to determine the means across all the Q of CRF. Chi-square was used to calculate the number of men who were white and who ever smoked. Multivariate analyses including potential covariates (age, race, BF%, resting SBP, alcohol intake and smoking) were performed to determine the association between SSBP at various exercise stages and Q of CRF. Analyses were done using SPSS version 22 with  $P < 0.05$  for statistical significance.

## Results

Table 1 shows the descriptive statistics for men in various Q of CRF; Mean  $VO_2$  peak  $\pm$  SD in Q 1 through 5 were  $32.3 \pm 3.5$ ,  $39.1 \pm 1.8$ ,  $43.4 \pm 1.0$ ,  $48.1 \pm 1.5$ ,  $55.5 \pm 3.0$ , respectively. Categorizing the mean  $VO_2$  peak according to the American College of Sports Medicine, Guidelines for Exercise Testing and Prescription (Thompson et al. 2013) displayed a broad spectrum of CRF which appeared to skew towards the higher end of CRF; Q 1 was more likely to represent poor CRF, Q 2 fair CRF, Q 3 good CRF, Q 4 excellent CRF and Q 5 superior CRF levels. However, there was no quintile that represented a very poor CRF level. Age,

resting SSBP, alcohol intake and smoking history did not differ significantly across the Q of CRF, but there were significant differences in CRF, weight, BF%, BMI and race ( $p < 0.01$ ).

A significant quadratic trend was displayed by SSBP across Q of CRF at minutes 6, 8 and 10 of the GXT (P value for quadratic trend  $\leq 0.02$ ) (Table 2). Compared with men in CRF Q 1, those in Q 2 and 3 had significantly lower SSBP, whereas there was no significant difference among those in CRF Q 4 and 5 (however these values were lower than Q 1). The quadratic trend remained significant across all the time points after adjustment of potential confounders including resting SBP, body fat percentage, age, race, smoking and alcohol intake. In an adjusted model (Table 3), the largest difference in SSBP was observed between men in Q 1 and 2, those achieving a  $VO_2$  peak of  $39.1 \pm 1.8$  ml/kg/min versus those achieving  $32.3 \pm 3.5$  ml/kg/min, with 7.6 mmHg ( $p=0.05$ ), 9.4 mmHg ( $p=0.02$ ), and 9.5 mmHg ( $p=0.04$ ) lower SSBP at minutes 6, 8 and 10, respectively. SSBP plateaus at Q 3, among those achieving a  $VO_2$  peak of  $43.4 \pm 1.0$  ml/kg/min, followed by an increase in the higher Q, with  $VO_2$  peaks of  $48.1 \pm 1.5$  ml/kg/min and  $55.5 \pm 3.0$  ml/kg/min. Figure 1 displays a quadratic trend between SSBP and CRF adjusted for the covariates at minute 6, 8 and 10 of the GXT, showing a decrease in SSBP, followed by plateauing and then, finally, an increase.

## Discussion

These results demonstrate a reverse J-curve pattern relationship between SSBP and CRF. Increases in CRF from low to fair or good were associated with a significantly lower SSBP at minutes 6, 8 and 10 of GXT. A substantial decrease in SSBP was detected with slight

increase in CRF from men with poor CRF to fair CRF (e.g. Q 1 to 2). However, SSBP plateaued with further increase in CRF among men with good CRF (Q 3). Moreover, a potential increase in SSBP among men with excellent and superior CRF (Q 4 and 5) indicated a reversed J-curve pattern. Metabolic demands after six minutes of exercise on GXT are similar to the demand of most routine day to day activities; it is likely that the cardiac workload during such activities is relatively low in men with fair and good CRF.

Previous studies have provided evidence that improving CRF from poor to fair to good is one of the cornerstones of therapeutic behavioral changes for better CVD prognosis and overall survival (Swift et al. 2013, Blair et al. 1989, Blair et al. 1995, Prasad et al. 2014). Among middle-aged men and women, the health benefits due to improvements in the CRF plateau at the  $VO_2$  of 35.0 and 31.5 respectively, with no further survival benefit compiling from higher CRF levels.(Blair et al. 1989, Kokkinos and Myers 2010) Studies have shown that the maximum difference in mortality is between CRF Q1 and 2 or lowest CRF and the next lowest CRF categories (Blair et al. 1989, Kokkinos and Myers 2010) with a further decline accruing from increase in CRF followed by a plateau.(Blair et al. 1989, Kokkinos and Myers 2010, O'Keefe, Franklin, and Lavie 2014) Moreover, recent studies have also shown that there could be a loss of CV health benefits, to some extent, with extreme levels of CRF and exercise producing a J-curve pattern between CRF and CV prognosis.(O'Keefe, Franklin, and Lavie 2014, O'Keefe, Schnohr, and Lavie 2013, Lavie, O'Keefe, and Sallis 2015, O'Keefe and Lavie 2013) Data has shown that despite the extraordinary CRF, CV abnormalities in marathon runners are reported each year.(Kim et al. 2012) Our data includes men with a broad CRF distribution consisting of extreme

higher levels which could be the potential factor that is resulting in a J curve pattern association.

Although our study design does not allow us to determine the specific mechanisms responsible, the findings generate some speculation. Exercise or physical conditioning helps in reducing the work of the heart during submaximal workloads, leading to lower HR at a given cardiac output,(Saltin 1986) which could be partially explained by the mechanism of the Frank Starling law (increased left ventricular ejection resulted from improved diastolic function),(Jensen-Urstad et al. 1998) and by reduced afterload due to lower total peripheral resistance.(Saltin 1986) Increased CRF is associated with lower arterial stiffness among healthy adults.(Vaitkevicius et al. 1993) Studies have suggested a positive relation of CRF and exercise with vasodilator Nitric oxide (NO) formation and its bioactivity among healthy individuals. (Jungersten et al. 1997, Green et al. 2004) Moreover, another study among individuals with chronic heart failure has reported that exercise training improves both vascular endothelial NO formation and agonist-mediated endothelial dependent vasodilation (EDV) of the skeletal muscle vasculature that could lead to correction of endothelial dysfunction.(Hambrecht et al. 1998)Exaggerated SSBP could be attributed to endothelial dysfunction defined as reduced EDV and pro-inflammatory condition in the vasculature.(Endemann and Schiffrin 2004) Primary cause for endothelial dysfunction is decrease in production and bioactivity of NO and increase in vasoconstrictor endothelin which potentially leads to arterial stiffness and reduced EDV(Lerman and Burnett 1992) followed by reduced ability to buffer the increase in SBP during exercise.(Stewart et al. 2004)

At the other end of CRF spectrum, cardiac overuse could potentially be the cause for increasingly common consequence of overdosing of exercise,(O'Keefe et al. 2012, O'Keefe and Lavie 2013) which may be associated with adverse outcomes, including accelerated coronary calcification, early aging of the heart, LVH, and cardiac muscle fibrosis.(O'Keefe, Schnohr, and Lavie 2013, Maron 2007) Extreme exercise may also amplify oxidant stress and transiently stiffen blood vessels.(Trivax et al. 2010, Michaelides et al. 2011) LVH may lead to an increase in SSBP during submaximal workload due to a higher force of systolic contraction, while arterial stiffening which weakens the ability of the arteries to buffer the rise in SSBP generated by left ventricular ejection.(Stewart et al. 2004)

To the best of our knowledge, this is the first study demonstrating the association between SSBP and CRF among healthy men aged 21-35 years. Our data represent men with a broad range of CRF, which is useful in examining the trend at both the ends of CRF spectrum; however, it should be noted that the overall CRF trend was skewed towards higher CRF levels with no quintile having very poor CRF. Furthermore our data consist of SSBP at various time points of GXT, with similar trends evident at various stages after 6 minutes. Lastly, both resting SBP and SSBP were measured using a manual and not the automated sphygmomanometer by trained staff members.(Landgraf, Wishner, and Kloner 2010)

Several study limitations should be emphasized. A majority of the participants enrolled in the study were non-Hispanic whites and with moderate to high socioeconomic status. Additionally, a large % of this population was from the university campus, including

students and staff, so future research must determine if these results are generalizable to other populations. A small % of data (5.4%) was lost due to missing SSBP and a covariate, alcohol intake history. Failure in measurement of SSBP during the GXT, was mainly due to staff being unable to hear the korotkoff sound during BP measurement; however, the characteristics of men who were lost in the analysis were similar to those present in the analysis. Finally, as with any other cross-sectional study, causality between the dependent variable (SSBP) and independent variable (CRF) cannot be established.

In conclusion, there was a reverse J-curve pattern relationship between SSBP and CRF, suggesting that men with poor CRF had the highest SSBP, whereas the lowest SSBP was noted in men with fair and/or good CRF. It is comforting to know that fair to good levels of CRF, which is easily obtainable in most with poor CRF by simply obtaining modest amounts of PA, are associated with lower SSBP, which could translate into favorable CV prognosis.

Table 4.1. Means  $\pm$  SD of descriptive variables across the quintiles of cardiorespiratory fitness

	Quintile 1 (N=40)	Quintile 2 (N=42)	Quintile 3 (N=40)	Quintile 4 (N=41)	Quintile 5 (N=41)	*P value
Age (years)	28.7 $\pm$ 3.7	27.3 $\pm$ 3.8	27.6 $\pm$ 3.7	27.6 $\pm$ 4.1	26.3 $\pm$ 3.7	0.11
VO2 peak	32.3 $\pm$ 3.5	39.1 $\pm$ 1.8	43.4 $\pm$ 1.0	48.1 $\pm$ 1.5	55.5 $\pm$ 3.0	<0.01
Weight (kg)	90.2 $\pm$ 15.8	83.0 $\pm$ 12.7	79.5 $\pm$ 11.9	79.9 $\pm$ 8.8	75.0 $\pm$ 6.7	<0.01
Body fat %	30.6 $\pm$ 5.6	24.4 $\pm$ 7.1	21.9 $\pm$ 5.4	20.2 $\pm$ 5.5	16.5 $\pm$ 4.8	<0.01
BMI (kg/m <sup>2</sup> )	28.5 $\pm$ 3.8	25.9 $\pm$ 3.3	24.5 $\pm$ 2.8	25.4 $\pm$ 2.1	23.5 $\pm$ 2.0	<0.01
Resting SBP (mmHg)	128.0 $\pm$ 10.3	126.6 $\pm$ 11.6	123.8 $\pm$ 12.1	129.0 $\pm$ 10.0	126.6 $\pm$ 11.8	0.29
Alcohol (g/day)	9.1 $\pm$ 29.5	8.4 $\pm$ 14.3	13.9 $\pm$ 23.6	17.8 $\pm$ 21.0	15.6 $\pm$ 25.9	0.29
Race (whites) %	52.5	59.5	62.5	75.6	87.8	<0.01
Ever smoked (N)	30.0	23.8	30.0	36.6	21.9	0.89

Abbreviations: VO2; oxygen consumption, BMI; body mass index, SBP; systolic blood pressure  
\*P value for linear trend

Table 4.2. Means of submaximal systolic blood pressure across various quintiles of cardiorespiratory fitness  
(Crude model)

	Quintile 1 (N=36)	Quintile 2 (N=41)	Quintile 3 (N=39)	Quintile 4 (N=39)	Quintile 5 (N=40)	P value*
Minute 6	158.6 (153.0-164.2)	148.6 (143.4-153.9)	147.3 (141.9-152.7)	153.3 (147.9-158.7)	153.0 (147.7-158.3)	0.01
Minute 8	170.7 (165.0-176.3)	158.7 (153.4-164)	157.9 (152.5-163.3)	164.5 (159.0-169.9)	163.4 (158.0-168.7)	<0.01
Minute 10	183.7 (177.1-190.2)	171.7 (165.5-177.8)	165.5 (159.2-171.8)	178.0 (171.7-184.3)	176.1 (169.9-182.3)	<0.01

\*P value is for quadratic trend



Table 4.3. Means of submaximal systolic blood pressure across various quintiles of cardiorespiratory fitness (adjusted model)

	Quintile 1 (N=35)	Quintile 2 (N=41)	Quintile 3 (N=39)	Quintile 4 (N=38)	Quintile 5 (N=40)	*P value
Minute 6	156.0 (149.8-162.2)	148.4 (143.4-153.3)	149.2 (144.2-154.2)	152.9 (147.7-158.1)	154.5 (148.9-160.1)	0.03
Minute 8	167.9 (161.6-174.3)	158.5 (153.4-163.5)	159.5 (154.3-164.7)	164.1 (158.8-169.4)	165.3 (159.6-171.0)	0.01
Minute 10	180.6 (173.2-188.0)	171.1 (165.1-177.0)	167.4 (161.3-173.4)	177.6 (171.4-183.9)	178.5 (171.7-185.2)	<0.01

\*P value for quadratic trend

Adjusted for age, race, body fat percentage, systolic blood pressure, alcohol intake and smoking history

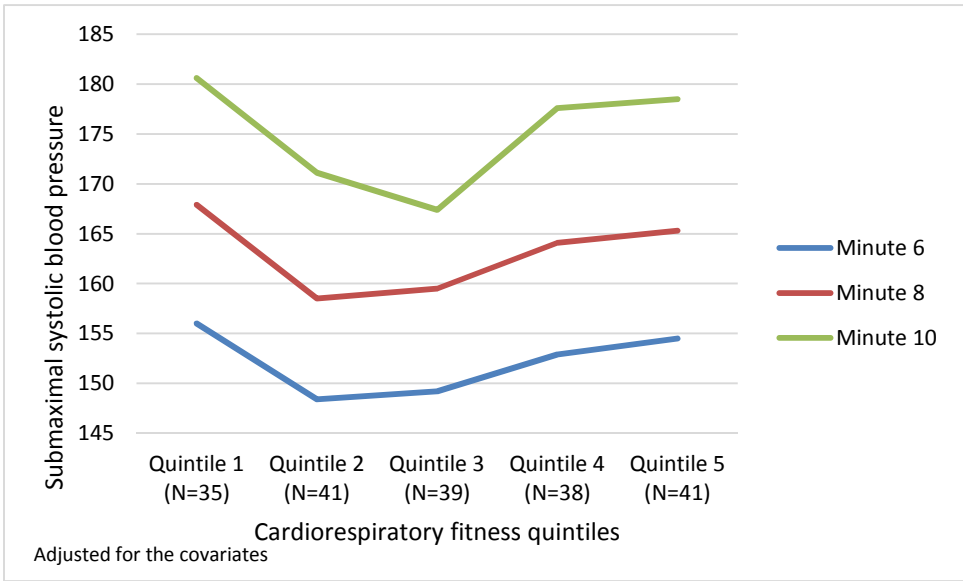


Figure 4.1. Trend displayed between submaximal systolic blood pressure and cardiorespiratory fitness

## CHAPTER 5

### MANUSCRIPT 2: ASSOCIATION OF FAT MASS INDEX AND BODY MASS INDEX WITH SUBMAXIMAL SYSTOLIC BLOOD PRESSURE AMONG YOUNG ADULT MEN

Vivek K. Prasad, Clemens Drenowatz, Gregory A. Hand, Carl J. Lavie, Xuemei Sui, Madison Demello, Steven N. Blair. To be submitted to *American Journal of Cardiology*.

## Abstract

**Objectives:** We examined the association of body fat (BF) with submaximal systolic blood pressure (SSBP) in young adult men.

**Methods:** A sample of 212 young adult and generally healthy men with a body mass index (BMI) between 20 and 35 kg/m<sup>2</sup> were included in the analysis. BF was measured using dual X-ray absorptiometry and fat mass index (FMI kg/m<sup>2</sup>) and BMI (kg/m<sup>2</sup>) were calculated using height and weight (total fat mass and total weight, respectively) measurements. Cardiorespiratory fitness was measured using a graded exercise test with SSBP being measured during each stage. Quintiles (Qs) of FMI and BMI were created with Qs 1 lowest and Qs 5 highest FMI and BMI. Qs 1-4 appeared to represent normal to overweight range and Qs 5 represented obese range.

**Results:** There was no significant difference in SSBP across FMI Qs 1 to 4 but SSBP was significantly higher in Quintile (Q) 5 at minutes 6, 8, and 10 (P<0.05) after adjusting for age, race, resting Systolic BP (SBP), alcohol intake, smoking, and CRF. There were no significant differences in SSBP across BMI in Qs 1 to 4 but a significantly higher SSBP in Q 5 when compared to Qs 1, 2, 3, and 4 at minutes 6, 8, and 10 (P<0.02 for each and P=0.07 between Q4 and Q5 at minute 10 ).

**Conclusion:** There seems to be a cut point for an increase in SSBP that exist between overweight and obese weight range.

## Introduction

Standardized graded exercise testing (GXT) protocols in controlled circumstances are now generally available to assess individual's cardiovascular (CV) and overall health. Submaximal systolic blood pressure (SSBP) during the GXT is an important marker to foresee CV events including hypertension (HTN),(Miyai et al. 2002) stroke,(Kurl et al. 2001) acute myocardial infarction,(Laukkanen et al. 2006) and CV morbidity and mortality(Allison, Cordeiro, et al. 1999, Filipovsky, Ducimetiere, and Safar 1992) among individuals with and without any signs of CV disease (CVD). In addition, individuals characterized by exaggerated exercise blood pressure (BP), may account for 4.3 times higher risk of myocardial infarction.(Laukkanen et al. 2006)

It has been reported that, higher SSBP among normotensive individuals and in the general overall population is a predictor of left ventricular (LV) hypertrophy (LVH) conferring an increased risk of CV and all-cause mortality.(Gottdiener et al. 1990, Polonia et al. 1992, Cuspidi et al. 2015, Lavie et al. 2014) It has also been shown that exaggerated SSBP among healthy individuals has a high predictive value for new resting HTN with an odds ratio of 2.41.(Allison, Cordeiro, et al. 1999) Furthermore, exercise BP response among patients with HTN is important in terms of future HTN and CV prognosis, with an increased peripheral resistance, impaired LV diastolic function, and LVH among those having an exaggerated exercise BP response.(Lim et al. 1996)

Body fatness (BF) is a known predictor of CVD risk factors,(Christou et al. 2005) morbidity, and mortality.(Berrington de Gonzalez et al. 2010, Lavie, Milani, and Ventura 2009)

Studies investigating relations between SSBP and BF have reported inconsistent results, with one study suggesting that high body mass index (BMI) is associated with lower SSBP after 7 years among middle-aged healthy men (Mundal et al. 1997) but another study reported that a decrease in BF is associated with lower SSBP among older adults. (Barone et al. 2009) To the best of our knowledge, there is no study examining the association between SSBP and BF among young healthy men. It is important to further understand the relationship between SSBP and BF, and how the association is exhibited among young healthy men.

## Methods

Participants and enrollment process: The study recruited 212 men aged 21-35 years with a BMI between 20-35 kg/m<sup>2</sup>. Participants were excluded if they had 1) a change in smoking status in the previous 6 months; 2) used medications to lose weight; 3) planned a weight loss surgery; 4) resting BP exceeding 150 mmHg systolic and/or 90mmHg diastolic; 5) an ambulatory blood glucose level of greater than 145 mg/dl; 6) been diagnosed with/or taking medications for a major chronic health condition; or 7) a history of anxiety, depression, or panic attack or taking selective serotonin inhibitors for any reason. (Hand et al. 2013)

Anthropometry: Anthropometric measurements were performed with the men wearing basic medical scrubs and in bare feet. BF was measured using a dual X-ray absorptiometry (DXA) scanner and used to calculate fat mass index (FMI kg/m<sup>2</sup>). FMI and BMI (kg/m<sup>2</sup>)

were calculated from height and weight (total BF and total weight respectively) measurements.

Exercise testing procedure: SSBP and cardiorespiratory fitness (CRF) defined as peak oxygen consumption ( $VO_2$ ) were measured using a GXT administered by a trained exercise physiologist. The subject was instructed to rest their left arm on the shoulder of the staff member before and during each stage of GXT. They were also instructed to avoid gripping of the shoulder of staff member and getting an external support while walking or running during the GXT. After the examination of pre-exercise BP, GXT was administered using a modified Bruce protocol, which starts at a grade of 0% at 1.7 mph for initial 2 min and progresses to 5% grade at the same speed for next 2 min. After 4 minutes of GXT the protocol is similar to that of the Bruce protocol. The speed and grade at time points 6, 8, and 10 minute of GXT were 1.7 mph, 10%; 2.5 mph, 12%; 3.4 mph, 14% respectively. All men exercised to volitional fatigue and indicated when to stop. The test followed continued walking at 1.7 mph and 0% grade until their BP returned to near baseline level and  $HR \leq 120$ . SSBP was recorded at the second minute of each stage of the GXT by a trained staff member.

Ambulatory systolic BP (SBP) was measured twice in the seated position by a well-trained technician using a manual mercury sphygmomanometer. The average of two readings was used for the representative examination value. A third measurement was taken if the difference in resting SBP was greater than 10 mm Hg. In addition, alcohol consumption was calculated using multiple, telephone administered, 24-hr dietary recall

interviews and smoking history was self-reported via a personal medical history questionnaire.

Statistical analysis: Quintiles (Qs) of FMI and BMI were established with quintile (Q) 1 representing the groups of men with the lowest FMI and BMI whereas Q 5 represented those with the highest FMI and BMI. One way ANOVA was used to determine the descriptive means across all the Qs of FMI and BMI. Chi-square was used to determine differences in the number of Caucasian men and number of individuals who ever smoked. Multivariate analysis including potential covariates was done to determine the association between SSBP at minutes 6, 8 and 10 of GXT and Qs of FMI and BMI. This was examined via multivariate analysis of variance, adjusting for age, race, resting SBP, alcohol intake, smoking history, and CRF. All analyses were done using SPSS (version 22) with  $P < 0.05$  for statistical significance.

## Results

Table 1 shows the descriptive characteristics of men across the Qs of FMI and BMI. FMI Q 1-3 represent normal BMI range, Q 4 overweight and Q 5 obese. Resting SBP, alcohol intake and smoking history did not differ significantly across the Qs of FMI, but there were significant differences in age, race, BMI, and  $VO_2$  peak ( $P \leq 0.02$ ). BMI Q 1 and 2 represent normal BMI range, Q 3 and 4 overweight and Q 5 obese. There were no significant differences in race, resting SBP, alcohol intake and smoking history, whereas age, FMI, and  $VO_2$  peak differed significantly across the Qs of BMI ( $P \leq 0.03$ ). Categorizing the mean  $VO_2$  peak according to the American College of Sports Medicine, Guidelines for Exercise



testing and Prescription, ninth edition (Philadelphia: Lippincott Williams & Wilkins, 2013)(Thompson et al. 2013) showed that CRF levels in FMI and BMI Qs 1-4 are considered excellent to fair, whereas Q 5 represents poor CRF level.

There was no significant difference in SSBP across FMI Qs 1-4 but SSBP was significantly higher in FMI Q 5 at minutes 6, 8, and 10 after adjusting for age, race, resting SBP, alcohol intake, smoking and CRF (P<0.05 or borderline associations with P= 0.05, 0.1, 0.07 between Qs 1 and 5 at 6, 8, and 10 minutes respectively) (Table 2). It appears that there was no or a borderline significant difference between FMI Qs 1 and 5 which means, with further decrease in FMI in Q 5 there is slight increase in SSBP. Table 3 shows that there was no significant difference in SSBP across Qs 1-4 but a significantly higher SSBP in Q 5 when compared to Qs 1-4 at minutes 6, 8, and 10 (P<0.02 for each and P=0.07 for association between Qs 4 and 5 at minute 10). The differences in SSBP evident between the mean of Qs 1-4 and Q 5 were 13.67mmHg, 13.42mmHg and 13.02mmHg at minutes 6, 8 and 10 respectively. There was no significant increase in SSBP with increase in BF across normal weight Qs and overweight Qs whereas a substantial increase in obese Q which signifies a threshold at a point between overweight and obese. Figure 1 and 2 display SSBP across Qs of FMI and BMI respectively in which the threshold is evident between Qs 4 and 5.

## Discussion

These results show that there is no significant difference in SSBP across normal weight and overweight young healthy men but there was a substantially higher value in obese

participants. This signifies that in young men, FMI and BMI appear to have an adverse effect on SSBP only in the obese range and not at the overweight category, which could possibly be due to preserved CRF levels in overweight participants. Compared with men in the obese range, those in the overweight range had significantly lower SSBP whereas, there was no additional decrease in SSBP with further reduction in BF among normal weight men. There appears to be a threshold for an increase in SSBP with obesity whereas on the other end, normal weight range does not have a lower SSBP compared with overweight range, resulting a plateau.

A study done among 1.4 million white adults in an age range of 19-84 has shown that, there is a J curve pattern between BMI and all-cause mortality with lowest death in the BMI range of 20.0-24.9 kg/m<sup>2</sup>.(Berrington de Gonzalez et al. 2010) Additionally, previous studies, which did not assess details of body composition and BF, have consistently reported that improvements in CRF beyond 9-10 metabolic equivalents among middle aged men and women does not provide further survival benefits.(Blair et al. 1989, Kokkinos and Myers 2010) Epidemiological studies in healthy populations have reported a plateau for exercise and long-term outcomes indicating moderate exercise markedly reduces the risk of CVD and all-cause mortality.(O'Keefe, Schnohr, and Lavie 2013, O'Keefe, Franklin, and Lavie 2014) In our study there is a significant drop in SSBP from obese BF level to overweight BF level with no further significant changes in SSBP accruing at lower BF levels. Like the above mentioned studies, men in our cohort in the normal to overweight range (moderate range) have lower SSBP. In addition we can also speculate that lowering the body weight to overweight range would be sufficient to have lower SSBP

and better CV prognosis. An individual is not required to have low fatness, considering dropping from an obese fatness level to overweight level would already provide substantial benefits in terms of SSBP and CV prognosis. Moreover, there is potentially some loss of benefits among men in the lowest or leanest FMI Q with best results in the moderate levels.

In the past few years, there has been a paradigm shift from the belief that adipose tissue is merely an inert compartment of energy to an endocrine organ that involves a number of vital systemic phenomena.(Scherer 2006) Adipose tissue is known to be highly enriched in adipocytes including adiponectin which have a CV protective role by exhibiting anti-inflammatory, antiatherogenic and anti-hyperglycemic properties.(Nigro et al. 2014, Scherer 2006) This could explain our results in which normal to overweight BF range did not have any significant difference in SSBP. Obese fatness range might cause dysregulation of adipokines which could lead to CV complications (Diaz-Meleán et al. 2013, Kriketos et al. 2004) and this explains the significant rise in SSBP among obese individuals.

Fatness-related changes to the structure and function of the vasculature include increased arterial stiffness, intima media thickening, LVH, LV and right ventricular diastolic and systolic dysfunction, and vascular endothelial dysfunction, all of which are known to predict future CVDs.(Ferreira et al. 2004, Grassi et al. 2010, Woo et al. 2004, Alpert et al. 2014) Endothelial dysfunction advocates apoptosis(Paterick and Fletcher 2001) and reduced levels of vasodilator, nitric oxide (NO)(Lerman and Burnett 1992) leading to

arterial stiffness (Mackey et al. 2002) that partially impairs the ability of the circulatory system to buffer the rise in SBP generated by LV contraction.(Olson et al. 2012) Studies have consistently shown that NO production and bioavailability could partly explain the pathophysiology between obesity and its clinical outcomes including CVD, and HTN.(Datta et al. 2004, Williams et al. 2002) There is a notion that obesity-related oxidative stress and non-esterified fatty acid attenuates the bioactivity of NO resulting in restricted endothelium dependent vasodilation.(Higashi et al. 2001, Huang et al. 2001, Kerr et al. 2011)

To the best of our knowledge, this is the first analysis examining the association of BF on SSBP in healthy men aged 21-35. Our data consist of SSBP at various intensities of GXT and similar trends were displayed at all the intensities. This study consists of a cross-sectional analysis using objectively measured BF and SSBP. Despite the strengths of our study, there were also several limitations. A majority of the men participated in the study were well-educated, non-Hispanic whites from middle to upper socioeconomic strata, and a large percentage of population was from the university campus area, including students, faculty and staff. A small amount of data (9%) was excluded from the current analysis due to missing SSBP or covariates. The missing SSBP data were due to failure in measurement of SSBP during the GXT when the staff member was unable to hear the korotkoff sounds accurately during BP measurement. Nevertheless the characteristics of men who were excluded from the study were identical to those present in the study. Lastly, as this is a cross-sectional study, causality between the independent variables of

BF and dependent variable (SSBP) cannot be established and a prospective study is recommended in future.

In summary, this cross-sectional study of young healthy men signifies that there was no significant difference in SSBP with increase BF across normal to overweight range with a threshold occurring at the obese level resulting in a substantial increase. Achieving the weight range between normal to overweight may be sufficient enough to have lower SSBP and better CV prognosis. There is need for future work examining the role of BF changes on SSBP.

Table 5.1. Descriptive characteristics across the quartiles of fat mass index and body mass index

	Quintile 1 (N=42)	Quintile 2 (N=43)	Quintile 3 (N=42)	Quintile 3 (N=43)	Quintile 5 (N=42)	P value
<b>FMI quintiles</b>						
Age, mean (SD), y	26.1 (4.0)	26.9 (3.8)	26.9 (3.6)	29.0 (3.9)	28.6 (3.3)	0.001
Race: whites, No. (%)	30 (71.4)	30 (69.8)	27 (64.3)	26 (60.5)	31 (73.8)	0.44
SBP, mean (SD), mmHg	128.0 (12.2)	125.9 (11.0)	124.6 (10.9)	126.3 (10.4)	128.8 (11.3)	0.44
FMI, mean (SD)	2.9 (0.6)	4.3 (0.4)	5.4 (0.3)	7.0 (0.5)	9.9 (1.4)	<0.001
BMI, mean (SD)	23.5 (2.6)	23.8 (1.9)	24.7 (2.1)	26.1 (2.3)	30.6 (2.2)	<0.001
Alcohol intake, mean (SD) g/d	14.7 (26.4)	16.1 (20.9)	14.1 (20.1)	9.4 (16.3)	11.1 (30.1)	0.66
Vo2 peak mean (SD), ml/kg/min	50.5 (7.7)	48.1 (6.3)	44.3 (5.5)	40.8 (6.7)	35.7 (5.4)	<0.001
Ever smoked, No. (%)	10 (23.8)	10 (23.2)	16 (38.1)	10 (23.2)	14 (33.3)	0.4
<b>BMI quintiles</b>	(N=42)	(N=42)	(N=40)	(N=45)	(N=43)	
Age, mean (SD), y	25.5 (3.2)	27.0 (3.5)	27.9 (4.1)	28.2 (4.3)	28.8 (3.3)	<0.001
Race: whites, No. (%)	26 (61.9)	32 (76.3)	24 (60)	28 (62.2)	34 (79.1)	0.20
SBP, mean (SD), mmHg	123.4 (12.6)	124.7 (10.4)	126.5 (10.5)	127.2 (10.3)	131.5 (10.6)	0.009
FMI, mean (SD)	3.8 (1.0)	4.6 (1.5)	5.6 (1.4)	6.1 (1.7)	9.2 (2.5)	<0.001
BMI, mean (SD)	21.4 (1.0)	23.5 (0.5)	24.9 (0.6)	26.6 (0.8)	30.7 (1.8)	<0.001
Alcohol intake, mean (SD) g/d	11.2 (19.4)	15.7 (26.0)	13.1 (19.9)	11.2 (17.8)	14.3 (30.8)	0.34
Vo2 peak mean (SD), ml/kg/min	47.2 (8.0)	46.8 (8.0)	45.0 (7.6)	43.6 (7.5)	36.9 (5.7)	<0.001
Ever smoked, No. (%)	9 (21.4)	15 (35.7)	9 (29.0)	14 (31.1)	13 (30.2)	0.54

Abbreviations: SBP, systolic blood pressure; FMI, fat mass index; BMI, body mass index.  
P value for linear trend across the quartiles.

Table 5.2. Means of submaximal systolic blood pressure across various quintiles of fat mass index

	Quintile 1 (N=38)	Quintile 2 (N=39)	Quintile 3 (N=37)	Quintile 4 (N=42)	Quintile 5 (N=37)	*P value
Minute 6	151.6 (146.0-157.1)	150.0 (144.8-155.2)	152.3 (147.2-157.5)	147.1 (142.1-152.0)	160.2 (154.4-166.1)	0.02
Minute 8	163.3 (157.5-169.1)	159.4 (154.0-164.7)	162.4 (157.1-167.7)	159.5 (154.3-164.7)	170.6 (164.6-176.7)	0.02
Minute 10	175.1 (168.3-181.9)	169.5 (163.2-175.8)	175.3 (169.0-181.5)	170.3 (164.3-176.4)	185.1 (177.9-192.2)	0.01

\*P value for quadratic trend  
Adjusted for age, race, systolic blood pressure, alcohol intake, cardiorespiratory fitness, and smoking history

Table 5.3. Means of submaximal systolic blood pressure across various quintiles of body mass index

	Quintile 1 (N=35)	Quintile 2 (N=40)	Quintile 3 (N=40)	Quintile 4 (N=39)	Quintile 5 (N=39)	*P value
Minute 6	148.8 (143.3-154.3)	149.5 (144.5-154.4)	148.3 (143.5-153.2)	150.7 (145.7-155.6)	163.0 (157.3-168.6)	0.006
Minute 8	159.5 (153.8-165.3)	159.5 (154.4-164.7)	159.5 (154.4-164.5)	162.2 (157.1-167.3)	173.6 (167.7-179.5)	0.012
Minute 10	172.6 (165.7-179.4)	168.9 (162.8-175.0)	170.9 (164.9-176.9)	176.7 (170.6-182.8)	185.3 (178.3-192.3)	0.02

\*P value for quadratic trend

Adjusted for age, race, systolic blood pressure, alcohol intake, cardiorespiratory fitness, and smoking history



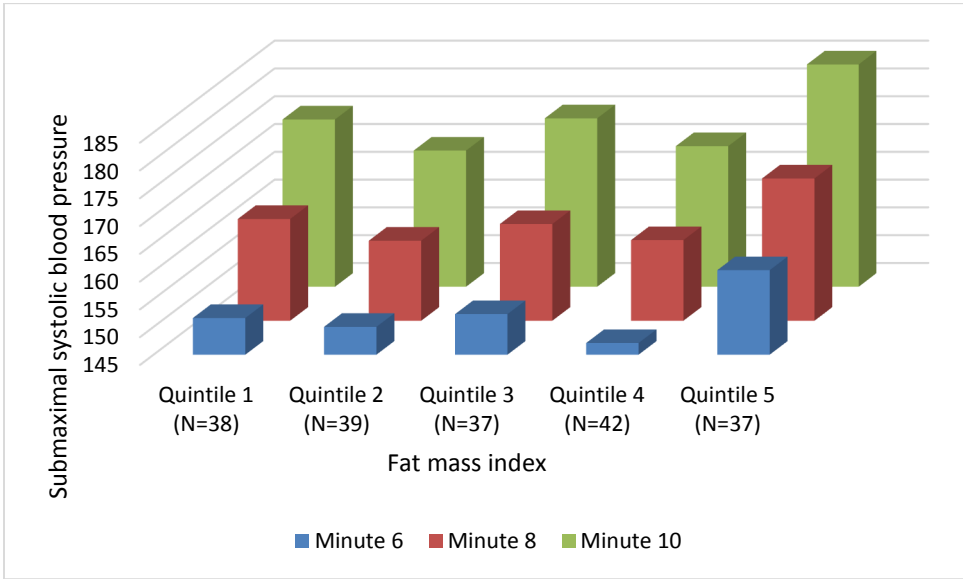


Figure 5.1. Submaximal systolic blood pressure across fat mass index quintiles

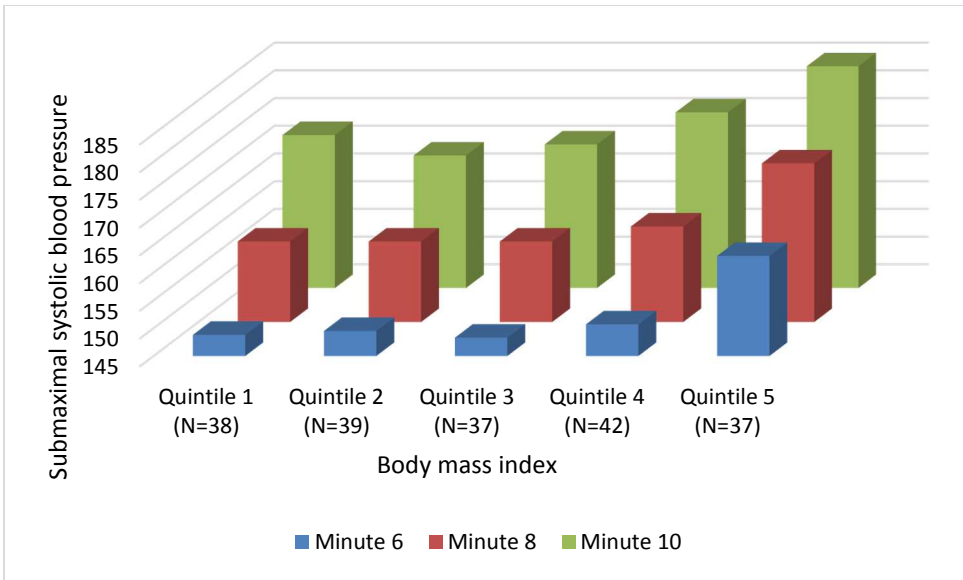


Figure 5.2. Submaximal systolic blood pressure across body mass index quintiles

## CHAPTER 6

### MANUSCRIPT 3: CARDIORESPIRATORY FITNESS, BODY FATNESS AND SUBMAXIMAL SYSTOLIC BLOOD PRESSURE AMONG YOUNG ADULT WOMEN

Vivek K. Prasad, Clemens Drenowatz, Gregory A. Hand, Carl J. Lavie, Xuemei Sui, Madison Demello, Steven N. Blair. Submitted to *Journal of Women's Health*, 04/04/2015.

## Abstract

**Objectives:** We examined the independent and combined associations of body fatness and cardiorespiratory fitness (CRF) with submaximal systolic blood pressure (SSBP) in young adult women.

**Methods:** Analyses included a sample of 211 normotensive women with a body mass index (BMI) between 20 and 35 kg/m<sup>2</sup>; body fat percentage (BF%) was calculated using total BF measured from dual X-ray absorptiometry (DXA), CRF was measured by a graded exercise test (GXT), and SSBP was measured at each stage.

**Results:** There was a direct association of SSBP with BF% and BMI whereas, an inverse association between SSBP and CRF when adjusted for covariates. There was no significant association between SSBP and BF% across the stages 1-3 with a nearly significant association at stage 4 when further adjusted for CRF whereas, no association at any of the stages when adjusted for BMI. A borderline significant association between SSBP and BMI was found at stage 1 with significant associations at stages 2-4 when additionally adjusted for CRF, whereas the association disappeared at stages 1-2 when adjusted for BF%. The inverse associations between SSBP and CRF were no longer significant at stages 3-4 when further adjusted for BF% with borderline association at stages 1-2. The associations remained significant at the stages 1-2 but not at stages 3-4 after adjusting for BMI.

Conclusion: CRF appeared to be a major determinant of SSBP at the lower exercise intensities, whereas, BMI was major determinant at the higher intensities. BF % was not independently associated with SSBP.

Keywords: Cardiovascular diseases, cardiorespiratory fitness, body fatness, submaximal systolic blood pressure, graded exercise test

## Introduction

Cardiovascular disease (CVD) is the number one cause of death globally (World Health Organization, 2011), therefore it is important to identify CVD risk early in life so that an appropriate intervention could be applied. An approach commonly used to predict the risk is by monitoring exercise blood pressure (BP) during a number of standard graded exercise test (GXT) protocols because it is an important marker of cardiovascular (CV) morbidity (Miyai et al. 2000, Nakashima et al. 2004, Sharabi et al. 2001, Singh et al. 1999, Miyai et al. 2002, Laukkanen et al. 2006, Laukkanen et al. 2004, Kurl et al. 2001) and mortality (Allison, Cordeiro, et al. 1999, Filipovsky, Ducimetiere, and Safar 1992) in individuals with and without apparent signs of CVD. There has been a consistent corroboration by a number of studies that, elevated exercise BP is a marker of incidence of hypertension (HTN) later in life among normotensive individuals. (Nakashima et al. 2004, Sharabi et al. 2001, Singh et al. 1999, Miyai et al. 2002) Additionally, both rate and extent of elevation of submaximal systolic BP (SSBP) during GXT was a predictor for myocardial infarction (MI). (Laukkanen et al. 2006) It has been reported that individuals

with elevated SSBP had 2.3 fold increased risk of developing any strokes and 2.3 fold increased risk of developing ischemic stroke.(Kurl et al. 2001)

A study reported that among normotensive individuals exaggerated SSBP has been shown to be a predictor of left ventricular (LV) hypertrophy (LVH) by a probability of 0.64(Gottdiener et al. 1990) which is associated with an cardiac end organ damage. Another study suggested that SSBP at low levels of exercise intensity corresponding to usual daily activities may be an important marker of LVH among hypertensive individuals.(Papademetriou et al. 1989) Moreover, an exaggerated exercise BP response has a prognostic value for CV damage and mortality which may be attributed to impaired left ventricular diastolic function, increased peripheral resistance and LVH.(Lim et al. 1996) Studies have demonstrated that CRF and aerobic exercise training have protective roles on SSBP.(Kokkinos et al. 1997, Kokkinos et al. 2002) Another study investigating relations between SSBP and body fat (BF) have reported that a decrease in BF is associated with lower SSBP among older adults.(Barone et al. 2009)

CRF and BF are associated with CV risk factors,(Carnethon et al. 2003, Christou et al. 2005, Diaz et al. 2006, Myers et al. 2015) morbidity, and mortality.(Berrington de Gonzalez et al. 2010, Kodama et al. 2009, Lavie, Milani, and Ventura 2009, Wessel et al. 2004) Considering the different levels CRF and obesity in the population, it is critical to understand the independent and combined effect of CRF and fatness on CV and overall health.(Christou et al. 2005, Diaz et al. 2006, Wessel et al. 2004, Hu et al. 2004, Lee, Blair, and Jackson 1999) Some analysis suggests that CRF can negate the detrimental effect of

obesity on health;(Lee, Blair, and Jackson 1999, Sui et al. 2007) whereas others report that higher categories of CRF attenuates, but unable to eliminate the adverse association of fatness with CV prognosis.(Hu et al. 2004, Stevens et al. 2002, Lee et al. 2012) To the best of our knowledge, there is no study that assesses the relative and combined effects of fitness and fatness on SSBP. We, therefore, examined the independent and combined associations of CRF and body composition with SSBP in young adult women.

## Methods

Participants and enrollment process: The sample for this analysis was taken from the Energy Balance Study, a 3- year prospective observational study(Hand et al. 2013) and included 211 normotensive (resting BP < 140/90 mm Hg) women aged 21-35 years with a BMI between 20 and 35 kg/m<sup>2</sup>. Exclusion criteria included currently diagnosed with/or taking medications for a major chronic health condition, resting BP exceeding 140 mmHg systolic and/or 90mmHg diastolic BP, a fasting blood glucose level of greater than 145 mg/dl, stopped or started smoking in the previous 6 months, use of medications to lose weight or planned weight loss surgery. Further, women were excluded with a history of depression, anxiety, and panic, or taking selective serotonin inhibitors for any reason. Finally women who became pregnant or had planned birth in the previous 12 months and those who had begun or changed their birth control regimen in the previous 3 months were also excluded.

Anthropometry: BMI was calculated from the average of two height and weight measurements. Body composition was measured using a dual X-ray absorptiometry (DXA) scanner and used to calculate body fat percentage (BF%).

Exercise testing procedure: CRF was measured by a GXT using a modified Bruce protocol that was administered by a trained exercise physiologist. Pre-exercise BP was measured with the BP cuff of a manual sphygmomanometer on left arm of the individual. The modified Bruce GXT begins on a treadmill at a speed of 1.7 mph and 0% grade for first 2 min and advances to 1.7 mph at 5% grade for next 2 min. The speed and grade at stages 1 through 4 were 1.7 mph, 0%; 1.7 mph, 5%; 1.7 mph, 10%; 2.5 mph, 12%, respectively. Participants were instructed to exercise to volitional fatigue and let the exercise physiologist know when to stop the test. GXT was followed by gradual decrease in speed and grade, continued by slow walking at 0% grade until heart rate (HR) returned to  $\leq 120$  and BP near pre- exercise levels.  $VO_2$  peak is defined as the oxygen consumption during maximum workload. The criteria for an achieved  $VO_2$  peak were two of the following; 1. Plateau of  $VO_2$  or HR with increase in workload, 2. Achieved age predicted maximum HR. 3. A respiratory quotient of  $\geq 1.15$ , 4. Rate of perceived exertion  $\geq 17$  on Borg scale of perceived exertion. The participant was instructed to place their left arm on the shoulder of the staff member at each stage of GXT followed by BP measurement at 90 seconds in each stage of the protocol.

Participants were instructed to complete a personal medical history questionnaire including smoking history, and alcohol intake was obtained from multiple, telephone



administered, 24-hr dietary recall interviews. Resting SBP was calculated from an average of two measurements. Two measures of sitting SBP were recorded using a manual sphygmomanometer by trained technicians and a third measurement was done if the difference in SBP was more than 10 mm Hg for the first two measurements.

Statistical analysis: Quartiles (Qs) of BF%, BMI, and CRF were established with Q 1 representing the groups of women with the lowest BF%, BMI, and CRF, respectively, whereas Q 4 representing those with the highest BF%, BMI, and CRF, respectively. One way ANOVA was used to determine the descriptive means across all the Qs of BF% and BMI. Chi-square analyses were used to evaluate the number of women who were white and those who ever smoked. Multivariate analyses including potential covariates were performed to determine the association between SSBP at various exercise stages and BF%, BMI and CRF. Two different models were created based on Qs of BF%, BMI and CRF, adjusting for different potential covariates in each model. Model 1 consisted of BF%, BMI and CRF Q adjusted for resting BP, BF%, age, smoking, and alcohol intake, whereas model 2 further adjusted for CRF, BMI or BF% depending on the independent variable. All computations were performed using SPSS (version 22) with  $P < 0.05$  for statistical significance.

## Results

Table 1 shows the descriptive statistics of women across the Qs of BF% and BMI. There were no significant differences in age, alcohol intake, and smoking history across Qs of BF% and BMI. SBP, weight, and  $VO_2$  peak were significantly different across Qs of both

BF% and BMI. Race was significantly different across Qs of BMI, but was not across Qs of BF%. Classification and cut points from the American College of Sports Medicine, Guidelines for Exercise testing and Prescription (Thompson et al. 2013) seems to display a narrow range of distribution for BF% and CRF in this data set.

SSBP had significant direct linear associations with BF% and BMI, and an inverse association with CRF in age, race, resting SBP, alcohol intake and smoking adjusted model (Model 1: Table 2). Associations between SSBP and BF% were not significant across stages 1-4 when further adjusted for CRF (Model2: Table 3) although the association was nearly significant for stage 4. The association was eliminated at all the stages when adjusted for BMI. Table 4 shows that the associations between SSBP and BMI Qs were nearly significant for stage 1 and were significant in stages 2-4 when further adjusted for CRF, whereas the association was eliminated in stages 1 and 2 when adjusted for BF%.

Table 5 includes data for associations between CRF and SSBP adjusted for BMI and BF%. There were significant inverse trends across Qs of CRF in stages 1 and 2 but not in stages 3 and 4 for the model which included BMI. SSBP and CRF were nearly significant in stages 1 and 2, whereas there was no association in stages 3 and 4 in the model that included BF%. This shows that CRF is independently associated with SSBP in the initial stages of the GXT, but once an individual is in the later stages, BF% or BMI inclusion in the models eliminated the association between CRF and SSBP.

## Discussion

The Results show that in age, race, resting SBP, alcohol intake and smoking adjusted analysis, BF% and BMI have direct significant associations with SSBP at stages 1-4 of the GXT; whereas, VO<sub>2</sub> peak has an inverse significant relation with SSBP. In model 1, women with higher BF% and BMI and lower CRF have significantly high SSBP compared to those with lower BF% and BMI and higher CRF. After adjusting for each other in model 2, BF% seems to have no association with SSBP, whereas BMI was independently associated with SSBP at the higher intensity exercise and CRF at the lower intensity exercise.

The association between BMI and SSBP could be due to high overall weight and not the body composition, as there is no association between SSBP and BF% in BMI- adjusted model 2. High CRF helps to lower SSBP at lower intensity exercise, but once an individual is at the higher intensity, high BMI would potentially cause an increase in SSBP when compared with lower BMI. It is well known that overweight and obesity are associated with CVD risk factors, morbidity and mortality in adults.(Melanson et al. 2001) We have consistently shown that CRF seems to reduce the harmful effects independent of body fatness on health in adults.(Barlow et al. 1995, Lee, Blair, and Jackson 1999, Sui et al. 2007) The current study had similar results, in that CRF appeared to be the major independent determinant of SSBP in lower intensity exercise. However, BMI seems to be the major independent determinant of SSBP in higher intensity exercise.

Endothelial dysfunction, which is described by increased arterial stiffening(Mackey et al. 2002) or reduced bioavailability of the vasodilator nitric oxide (NO),(Lerman and Burnett

1992) could result in an impairment in arterial vasodilation and decreased capacity to buffer an increase in SBP during LV contraction.(Hadi, Carr, and Al Suwaidi 2005, Stewart et al. 2004) Arterial stiffness early in life have been shown to be the causal pathway between low CRF and stiffness related CV morbidity, including LVH, heart failure, and stroke.(Boreham et al. 2004) Study has shown that individuals with high CRF have lower arterial stiffness.(Vaitkevicius et al. 1993) Additionally, acute bouts of exercise helps in decreasing both central and peripheral vascular stiffness.(Heffernan et al. 2007) A randomized control trial including patients of type 2 diabetes, hypertension and high cholesterol found that there is a significant decrease in arterial stiffness followed by 3 months of vigorous aerobic training.(Madden et al. 2009) Data has also shown that CRF and exercise results in improved vascular NO formation and its bioavailability among healthy individuals and as well as those with CVD.(Jungersten et al. 1997, Green et al. 2004) A study done among individuals with congestive cardiac failure reported that exercise training and increase in CRF had an important role in improvement of both basal endothelial NO formation and endothelial dependent followed by a sequel of corrected endothelial dysfunction.(Hambrecht et al. 1998)

Exercise training is known to reduce the exertion on the heart during submaximal exercise which is attributed to a lower HR at a given cardiac workload and lower peripheral vascular resistance.(Saltin 1986) Additionally, there is an enhanced LV performance as a consequence of rise in end diastolic volume followed by a sequel of enhanced LV ejection which could be partially explained by the law of Frank Starling.(Jensen-Urstad et al. 1998) Exercise results in improved systolic function which is

attributed to higher ejection fraction and this lead to an overall improved cardiac performance.(Jensen-Urstad et al. 1998) These mechanisms could potentially explain lower SSBP among women with high CRF in the lower intensity exercises in this data.

This is the first study demonstrating the association of fatness and CRF on SSBP in young adult women aged 20-35. One significant strength of the current study is the objectively measured BF using DXA, CRF and SSBP. However, there are limitations in this study. Participants enrolled in the study predominantly consisted of well- educated, non-Hispanic whites from middle to upper class which limit the generalizability of the results. A large percentage of the participants was from the university campus, including students and staff. However, the homogeneity of our study potentially reduces the likelihood of confounding by these variables. It is unclear whether results in this study could be extended to men. Further, this study did not have a broad spread for BF%, and CRF which could potentially limit the significant values in the results. Finally, as with any other cross-sectional study, causality between the independent variables of fatness and CRF and the dependent variable (SSBP) cannot be confirmed.

In summary, this cross-sectional study of young healthy women showed that CRF (inversely) whereas BF% and BMI (directly) were associated with SSBP. When adjusting for each other, BF % had no association, and BMI was a major determinant at higher intensity exercise, whereas CRF was the major determinant at lower intensity exercise. Clinicians should consider the importance of recommending physical activity and regular exercise training to either improve CRF or lower BMI, which could reduce SSBP and CV

health risks.(Vuori, Lavie, and Blair 2013) Further, there is need for future work examining the role of weight loss and gain in CRF on SSBP.

Table 6.1. Descriptive characteristics across the quartiles of body fat percentage and body mass index

<b>BF% quartiles</b>	Quartile 1 (N=52)	Quartile 2 (N=53)	Quartile 3 (N=55)	Quartile 4 (N=51)	P value
Age, mean (SD), y	27.5 (3.6)	27.5 (3.3)	27.6 (3.7)	28.6 (4.0)	0.34
Race: whites, No. (%)	41 (78.8)	38 (71.7)	31 (56.4)	27 (52.9)	0.08
SBP, mean (SD), mmHg	116.2 (9.7)	116.8 (9.9)	122.1 (11.7)	121.7 (12.8)	0.007
Weight, mean (SD), kg	61.4 (8.5)	63.6 (8.2)	72.1 (12.4)	80.9 (11.1)	<0.001
BF%, mean (SD)	25.2 (3.2)	31.6 (1.6)	36.8 (1.4)	42.2 (2.6)	<0.001
BMI, mean (SD)	22.0 (2.1)	23.6 (2.7)	26.5 (3.4)	30.2 (3.3)	<0.001
Alcohol intake, mean (SD) g/d	6.9 (11.8)	6.5 (11.2)	9.6 (2.1)	5.9 (11.7)	0.45
Vo2 peak mean (SD), ml/kg/min	40.4 (7.2)	34.1 (6.3)	31.0 (5.6)	26.0 (4.2)	<0.001
Ever smoked, No. (%)	11 (21.1)	12 (22.6)	11 (20.0)	11 (21.6)	1

<b>BMI quartiles</b>	Quartile 1 (N=54)	Quartile 2 (N=51)	Quartile 3 (N=54)	Quartile 4 (N=52)	P value
Age, mean (SD), y	27.6 (3.2)	27.8 (3.9)	28.0 (3.5)	27.8 (4.1)	0.94
Race: whites, No. (%)	39 (72.2)	39 (76.5)	34 (63.0)	25 (48.1)	0.001
SBP, mean (SD), mmHg	114.9 (9.2)	118.6 (11.2)	118.3 (10.7)	125.3 (11.9)	<0.001
Weight, mean (SD), kg	57.2 (4.6)	62.8 (5.4)	72.3 (7.2)	85.8 (8.8)	<0.001
BF%, mean (SD)	28.4 (5.1)	30.9 (5.2)	35.5 (4.5)	40.9 (3.8)	<0.001
BMI, mean (SD)	20.6 (0.9)	23.1 (0.7)	26.3 (1.4)	31.4 (1.9)	<0.001
Alcohol intake, mean (SD) g/d	8.6 (14.3)	7.9 (12.6)	6.5 (13.2)	5.9 (10.7)	0.67
Vo2 peak mean (SD), ml/kg/min	36.7 (7.2)	35.9 (7.9)	31.7 (7.3)	27.6 (5.3)	<0.001
Ever smoked, No. (%)	15 (27.8)	11 (21.6)	10 (18.5)	9 (17.3)	0.5

Abbreviations: BF%, body fat percentage; SBP, systolic blood pressure; BMI, body mass index.

P value for linear trend across the quartiles.

Table 6.2. Mean (95% CIs) submaximal systolic blood pressure across the quartiles of body fat percentage, body mass index and cardiorespiratory fitness (Model 1)

	Quartile1	Quartile2	Quartile3	Quartile4	P
<b>BFP</b>	(N=51)	(N=53)	(N=53)	(N=49)	value
Stage 1	122.3 (119.1 - 125.4)	123.3 (120.2 - 126.3)	126.5 (123.5 - 129.6)	126.3 (123.1- 129.5)	0.04
Stage 2	125.9 (122.5 - 129.3)	130.5 (127.2 - 133.8)	133.8 (130.5 - 137.1)	134.7 (131.2 - 138.1)	<0.001
Stage 3	134.4 (130.2 - 138.7)	137.7 (133.7 - 141.8)	141.2 (136.1 - 144.3)	143.1 (138.9 - 147.4)	0.004
Stage 4	143.9 (139.0 - 148.7)	147.7 (143.0 - 152.4)	150.3 (145.5 - 155.0)	157.0 (152.1 - 161.9)	<0.001
<b>BMI</b>	Quartile1 (N=54)	Quartile2 (N=50)	Quartile3 (N=51)	Quartile4 (N=51)	
Stage 1	122.0 (119.0 - 125.0)	122.7 (119.6 - 125.8)	126.0 (123.0 - 129.1)	127.8 (124.6 - 131.0)	0.005
Stage 2	126.4 (123.1 - 129.7)	129.4 (126.0 - 132.7)	133.4 (130.1 - 136.7)	135.9 (132.4 - 139.3)	<0.001
Stage 3	133.4 (129.3 - 137.4)	135.2 (131.1 - 139.2)	143.0 (139.0 - 147.0)	144.1 (139.9 - 148.2)	<0.001
Stage 4	142.3 (137.7 - 146.8)	144.4 (139.8 - 149.0)	152.1 (147.6 - 156.7)	160.1 (155.4 - 164.9)	<0.001
<b>CRF</b>	Quartile1 (N=49)	Quartile2 (N=52)	Quartile3 (N=52)	Quartile4 (N=51)	
Stage 1	129.3 (126.1 - 132.5)	126.1 (123.1 - 129.1)	120.6 (117.6 - 123.6)	122.7 (119.7 - 125.8)	0.001
Stage 2	136.4 (132.9 - 139.9)	134.2 (131.0 - 137.5)	127.6 (124.3 - 130.9)	126.9 (123.5 - 130.2)	<0.001
Stage 3	143.4 (139.1 - 147.8)	142.4 (138.3 - 146.5)	134.8 (130.7 - 138.9)	135.1 (130.9 - 139.2)	0.001
Stage 4	156.1 (151.0 - 161.2)	153.1 (148.3 - 157.8)	145.2 (140.4 - 150.0)	144.8 (140.0 - 149.7)	<0.001

Abbreviations: BF%, body fat percentage; SBP, systolic blood pressure; BMI, body mass index.

Adjusted for age, race, resting systolic blood pressure, alcohol intake and smoking

P value for linear trend across the quartiles.



Table 6.3. Mean Submaximal systolic blood pressure (95% CIs) across quartiles of body fat percentage (model 2)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
<b>Adjusted for model 1 plus CRF</b>					
Stage 1	124.9 (121.1-128.7)	123.6 (120.6-126.6)	125.7 (122.6-128.8)	124.2 (120.5-127.9)	1
Stage 2	128.9 (124.8-133.0)	130.8 (127.6-134.1)	132.8 (129.4-136.1)	132.3 (128.3-136.3)	0.26
Stage 3	136.9 (131.8-142.0)	138.1 (134.0-142.1)	139.4 (135.2-143.6)	141.1 (136.1-146.1)	0.29
Stage 4	146.1 (140.3-152.0)	148.0 (143.3-152.7)	149.6 (144.7-154.5)	155.3 (149.5-161.1)	0.06
<b>Adjusted for model 1 plus BMI</b>					
Stage 1	124.1 (120.5-127.8)	124.3 (121.1-127.5)	126.0 (122.9-129.1)	123.9 (119.9-127.9)	0.91
Stage 2	128.3 (124.3-132.2)	131.8 (128.3-135.2)	133.1 (129.8-136.5)	133.1 (129.8-136.5)	0.31
Stage 3	138.3 (133.5-143.1)	139.8 (135.6-144.1)	139.1 (135.1-143.2)	138.1 (132.8-143.4)	0.93
Stage 4	150.1 (144.6-155.5)	151.1 (146.4-155.9)	148.6 (144.0-153.2)	148.9 (143.0-154.9)	0.7

Abbreviations: BFP, body fat percentage; BMI, body mass index.  
P value for linear trend across the quartiles.

Table 6.4. Mean Submaximal systolic blood pressure(95% CIs) across quartiles of body mass index (model 2)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
<b>Adjusted for model 1 plus CRF</b>					
Stage 1	123.0 (119.8-126.2)	122.9 (119.8-129.0)	126.1 (123.0-129.1)	126.5 (123.1-129.9)	0.09
Stage 2	128.0 (124.5-131.4)	129.7 (126.3-133.0)	133.3 (130.0-136.6)	133.9 (130.3-137.6)	0.014
Stage 3	134.4 (130.2-138.6)	135.4 (131.2-139.5)	143.0 (138.9-147.0)	142.8 (138.3-147.3)	0.003
Stage 4	143.1 (138.3-147.9)	144.5 (139.8-149.3)	152.1 (147.5-156.8)	159.1 (154.0-164.2)	<0.001
<b>Adjusted for model 1 plus BF%</b>					
Stage 1	123.0 (119.4-126.6)	123.2 (119.9-126.4)	125.8 (122.7-128.9)	126.6 (122.7-130.5)	0.2
Stage 2	128.5 (124.6-132.4)	130.3 (126.9-133.8)	132.8 (129.5-136.2)	133.3 (129.1-137.5)	0.12
Stage 3	134.3 (129.6-139.0)	135.6 (131.4-139.9)	142.7 (138.7-146.8)	142.9 (137.7-148.0)	0.01
Stage 4	143.3 (137.9-148.6)	144.8 (140.0-149.6)	151.8 (147.2-156.5)	158.9 (153.1-164.7)	<0.001

Abbreviations: BFP, body fat percentage; BMI, body mass index.

P value for linear trend across the quartiles.

Table 6.5. Mean Submaximal systolic blood pressure(95% CIs) across quartiles of cardiorespiratory fitness (model 2)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
<b>Adjusted for model 1 plus BMI</b>					
Stage 1	128.4 (124.9-131.9)	125.8 (122.8-128.8)	121.0 (117.9-124.1)	123.4 (120.2-126.7)	0.02
Stage 2	134.5 (130.7-138.3)	133.7 (130.4-139.9)	128.5 (125.1-131.8)	128.3 (124.8-131.8)	
Stage 3	140.6 (135.9-145.3)	141.5 (137.5-145.5)	136.1 (132.0-140.3)	137.3 (133.0-141.6)	
Stage 4	151.0 (145.7-156.4)	151.4 (146.9-156.0)	147.6 (142.9-152.3)	148.8 (143.9-153.7)	
<b>Adjusted for model 1 plus BF%</b>					
Stage 1	128.1 (124.4-131.9)	125.6 (122.6-128.7)	120.9 (117.8-123.9)	124.0 (120.3-127.8)	0.09
Stage 2	134.1 (130.1-138.1)	133.3 (130.0-136.7)	128.1 (124.8-131.4)	129.4 (125.4-133.4)	
Stage 3	141.1 (136.1-146.1)	141.5 (137.3-145.6)	135.3 (131.2-139.4)	137.7 (132.7-142.7)	
Stage 4	151.9 (146.1-157.8)	151.4 (146.5-156.2)	146.1 (141.3-150.8)	149.6 (143.7-155.4)	

Abbreviations: BFP, body fat percentage; BMI, body mass index.

P value for linear trend across the quartiles.

## CHAPTER 7

### OVERALL DISCUSSION

Our studies analyzed different associations between CRF, body fatness and SSBP among young healthy adults drawn from the Energy Balance Study, a prospective observational study done in Columbia, South Carolina. We tried to determine the major determinants of SSBP, a predictor of CV prognosis. Following are the major findings of the dissertation

- 1) A reverse J-curve pattern relationship was found between SSBP and CRF among men. Increase in CRF from low to fair or good was associated with a significantly lower SSBP however, there was a slight rise in SSBP among men with excellent and superior CRF levels.
- 2) Among young healthy men there was no significant difference in SSBP with increases in BF across normal to the overweight range, with a threshold occurring at the obese level resulting in a substantial increase. The men in the overweight range had significantly lower SSBP when compared to those in the obese range followed by a plateau or no further decrease in SSBP in normal weight men. Moreover, it appears that there was a potential loss of significance with a further decreases in fatness among men with the lowest FMI.
- 3) BMI was a major determinant at higher intensity exercise whereas, CRF was a major determinant at lower intensity exercise among young healthy women. BF% was not associated independently with SSBP.

It appears that both CRF and BF plays important roles in determining the SSBP. Additionally, moderate levels of these two variables seem to provide the largest benefit in terms of SSBP and potentially CV prognosis in men. The difference in results among men and women could potentially be due to differences in the distribution of the main variables including CRF and fatness among men and women. The distribution in CRF and fatness for men had a wide spread whereas, it was narrow for women.

Previous studies have provided evidence that moderate levels of CRF, and exercise provide most benefits in terms of overall health. Improving CRF from poor to fair to good is associated with substantial improvement in CV health and overall health.(Swift et al. 2013, Blair et al. 1989, Blair et al. 1995, Prasad et al. 2014) Additionally, a the number of studies done among middle-aged men and women, have reported health benefits in terms of CV prognosis and overall health with increases in the CRF plateau at about 9-10 metabolic equivalents(Blair et al. 1989, Kokkinos and Myers 2010) producing a broad spectrum of CRF that has maximum health benefits. However, on the other end of the CRF spectrum, despite extremely high CRF among marathon runners, adverse CV prognosis are reported each year.(Kim et al. 2012) Epidemiological studies have also shown reverse J-curve relationship for exercise dose and health outcomes, indicating that moderate exercise dose, as compared with inactivity, substantially reduces the risk of CV morbidity and mortality.(Lee et al. 2014, O'Keefe and Lavie 2013, O'Keefe, Schnohr, and Lavie 2013) Approximately 50% of Americans fail to obtain the recommended dose of physical activity (PA). (Centers for Disease and Prevention 2013) Moreover, at the upper

end 5% of the distribution are doing too much exercise, potentially losing some benefits.  
(O'Keefe, Franklin, and Lavie 2014, Williams and Thompson 2014)

In recent years, there has been a shift from the paradigm that adipose tissue is merely an inert chamber of energy but is a vital endocrine organ that involves multiple systemic phenomena.(Scherer 2006) Body fat is known to be highly enriched in adipocytes, predominantly adiponectin that have a CV protective role by exhibiting anti-inflammatory, antiatherogenic and anti-hyperglycemic properties.(Nigro et al. 2014, Scherer 2006) However, very high fatness levels with low CRF would cause dysregulation of adipokines which may potentially lead to CV complications.(Diaz-Meleán et al. 2013, Kriketos et al. 2004, Kim, Seo, and Kim 2014) This mechanism could potentially explain the results of our data that, maximum benefits persisted in the moderate levels of fatness.

Various potential mechanisms are present that explain benefits of exercise and CRF. Exercise training helps in reducing workloads on the heart during exercise, leading to lower HR,(Saltin 1986) which could be partially explained by the mechanism of Frank-Starling law (increased left ventricular ejection resulted from an increase in the end-diastolic volume),(Jensen-Urstad et al. 1998) and secondly by reduced afterload due to lower total peripheral resistance.(Saltin 1986) Lower SSBP during GXT could be attributed to improved cardiovascular performance and homeostasis after exercise training.(Keul et al. 1996) On the other end, exaggerated SSBP could be due to endothelial dysfunction defined as reduced vasodilation and pro-inflammatory condition in the vasculature.(Endemann and Schiffrin 2004) Endothelial dysfunction is characterized by

decreases in the production and bioactivity of NO, a vasodilator, and an increase in the vasoconstrictor endothelin, which potentially leads to arterial stiffness and reduced vasodilation(Lerman and Burnett 1992) followed by a reduced ability to buffer the increase in systolic blood pressure during exercise.(Stewart et al. 2004) Endothelial dysfunction has been associated with chronic diseases including HTN, peripheral arterial disease, CHD, congestive cardiac failure, peripheral artery disease, and diabetes mellitus.(Endemann and Schiffrin 2004)

Studies have suggested that there is a positive relation of CRF and exercise with NO formation and its bioavailability, which may help to explain the beneficial effects of CRF on SSBP and CV prognosis.(Jungersten et al. 1997, Green et al. 2004) Data have also shown that aerobic exercise decreases both central and peripheral arterial stiffness.(Heffernan et al. 2007, Madden et al. 2009, Vaitkevicius et al. 1993) Exercise training among patients with chronic heart failure improves both endothelial NO formation and agonist-mediated EDV of the skeletal muscle vasculature, which could lead to improved endothelial function(Hambrecht et al. 1998) and result in lower SSBP and better CV prognosis.

At the other end of the CRF or exercise spectrum, cardiac overuse injury may result from overdosing of exercise,(O'Keefe et al. 2012, O'Keefe and Lavie 2013) which could be associated with adverse CV outcomes, including LVH, myocardial fibrosis, accelerated coronary calcification, and premature aging of the heart.(O'Keefe, Schnohr, and Lavie 2013, Maron 2007) Moreover, overdosing of exercise may amplify oxidant stress in the

CV system and transiently stiffen blood vessel.(Trivax et al. 2010, Michaelides et al. 2011)  
LVH may potentially lead to an increase in SSBP due to a higher force of systolic contraction.(Stewart et al. 2004)

To the best of our knowledge, the research done in this dissertation is novel and provides critical public health messages in terms of SSBP and CV prognosis. SSBP has higher prognostic value for future CVD as compared to resting SBP.(Nakashima et al. 2004, Sharabi et al. 2001, Singh et al. 1999, Miyai et al. 2002, Kurl et al. 2001, Allison, Cordeiro, et al. 1999) We have objectively measured CRF, SSBP and body composition. Some limitations, however, need to be considered when interpreting the findings of these studies. A majority of the participants enrolled in the study were non-Hispanic whites in moderate to high socioeconomic status with a broad spread of CRF among men whereas, there was a more narrow spread among women. Additionally, a considerable number of our population was from the university campus area, including students and staff, so future research must determine if these findings are generalizable to other populations. We were not able to accommodate both men and women in a single paper because of a considerable difference in the data, results and overall messages among men and women. We had a broad distribution of CRF among men whereas the CRF spectrum for women was narrow. Finally, like any other cross-sectional study, causality between the dependent variable (SSBP) and independent variables (CRF), BMI and body fatness cannot be established.



Overall conclusions from our data are that among men moderate levels of CRF and body fatness had favorable results for SSBP whereas, among women high CRF and low fatness were associated with the lowest SSBP. Our data potentially provide evidence that moderation is best in terms of CRF and fatness. Even a modest increase in CRF provides substantial CV benefits and this could be critical element in public health. CRF should also be assessed during a regular clinician visit with the BMI.

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