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Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise

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Abstract

Endurance exercise typically leads to beneficial cardiac adaptations manifested as increased cardiac mass, higher cardiac function and lower central hemodynamic load (blood pressure, aortic stiffness and wave reflections). However, studies in male marathoners suggest detrimental cardiac remodeling, such that larger cardiac mass is associated with reduced cardiac function and higher central hemodynamic load. There are well-established sex differences in cardiac adaptations to endurance exercise and central hemodynamics across the lifespan. Whether there are sex differences in cardiovascular adaptations in marathoners requires further scrutiny. We examined sex differences in 1) Left ventricle (LV) structure, 2) LV function 3) 24-hour central hemodynamic load and 4) ventricular-vascular coupling in marathon runners and recreationally active adults. LV structure and function were measured using 3-dimensional echocardiography (3DE). LV mass index (LVMI) was used as an index of LV structure. LV longitudinal (LS) circumferential (CS), area (AS), and radial strain (RS) were used as indices of LV function. An ambulatory oscillometric blood pressure (BP) cuff was used to measure 24-hour hemodynamic load after a non-exercise control day and following a 30-minute run/walk. 24-hour hemodynamic load was comprised of brachial and aortic BP, aortic stiffness measured as pulse-wave velocity (PWV) and pressure from wave reflections. Measures from central hemodynamics and 3DE were combined to derive the ratio of arterial elastance (Ea) to ventricular elastance (Elv) as a global measure of ventricular-vascular coupling. Our findings suggest that although female marathoners had larger LVMI they did not have LV dysfunction or increased central hemodynamic load and had better overall ventricular-vascular coupling. Furthermore, chronic marathon training and racing does not appear to be associated with LV dysfunction, or increased central hemodynamic load in otherwise healthy middle-aged men and women.
SEX DIFFERENCES IN CARDIOVASCULAR ADAPTATIONS TO CHRONIC Endurance Exercise

By

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Dissertation
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Key Concepts

**Endurance Exercise.** Aerobic exercise that includes activities such as, walking, jogging/running, cycling, swimming, dancing, tennis, basketball, soccer, racquetball. Endurance exercise constitutes activity that increases your breathing and heart rate for greater than 10 minutes at a time. The American College of Sports Medicine recommends 150 minutes of moderate aerobic exercise or 75 minutes of vigorous aerobic exercise a week.

**Recreationally-Active.** An individual is defined as recreationally active by the American College of Sports Medicine as performing exercise on less than or equal to 2 days a week for 80 minutes (total of 2 hours and 40 minutes a week). For the purpose of this study our participants fell into the recreationally active group if they completed <3 hours a week of exercise.

**Inactive.** An individual is defined as inactive if they are not doing enough physical activity, defined as not meeting the recommended daily amount of physical activity established by the American College of Sports Medicine (150 minutes of moderate aerobic exercise or 75 minutes of vigorous aerobic exercise a week).

**Sedentary.** An individual is defined as sedentary if they self-report or are objectively measured to spend a significant time during their day sitting and/or lying down.

**Marathon Race.**

A marathon running event is a 26.2 mile road race. Any distance beyond 26.2 miles is known as an ultra-marathon. Individuals between the ages of 35-50 years old, finish a marathon event on average between 4 hours and 22 minutes and 4 hours and 47 minutes. Competitive-age group individuals (35-50 yrs), for instance those who might qualify for the Boston Marathon, complete the marathon event between 3 hours and 40 minutes and 3 hours and 55 minutes for women, and between 3 hours and 10 minutes and 3 hours and 25 minutes for men. For this study, we
examined marathon runners between the ages of 35-50 yrs who on average completed a marathon in 3 hours and 45 minutes for men and 4 hours for women.

**Arterial Stiffness.**

Arterial stiffness is a term referring to the material properties of the blood vessels that carry blood away from the heart (i.e. arteries). Arteries are naturally elastic and stretch when the heart ejects blood into the vessel. With age and disease, the arteries lose elasticity (i.e. increase in stiffness) and affect how blood flow is delivered to tissues and organs and thus, transmitted throughout the body. This study examined large artery stiffness, particularly at the level of the aorta.

**Hemodynamics (aortic and brachial).**

Hemodynamics is an encompassing term used to describe the movement of both blood pressure and blood flow throughout the body. Central hemodynamics is referred to as aortic hemodynamics and peripheral hemodynamics might be referred to as brachial hemodynamics. In regards to hemodynamics, blood pressure and blood flow represent two separate forces. Blood pressure and blood flow travel at different speeds throughout the body and are altered by different factors. When the heart contracts, the pressure created is what propels the blood forward throughout the periphery of the body. However, contrary to intuition, blood pressure and blood flow do not travel in one direction; blood pressure and blood flow can move forward and backward (forward and backward wave reflections). In some settings, backward traveling blood pressure and blood flow can be detrimental to health. In the current study, we examine both resting and 24-hour aortic and brachial hemodynamics.
Left Ventricle.

The heart has four main chambers that allow the heart to properly relax and contract to receive and deliver blood flow from and to the body. The four chambers include: right ventricle, left ventricle, right atrium and left atrium. The left ventricle is the largest chamber and the most muscular part of the heart tissue. The left ventricle receives oxygenated blood from the lungs and then ejects the blood into the main artery off of the heart, the aorta, which transmits blood out to the body to be delivered to the working muscles, tissues and organs. High blood pressure, or atherosclerosis can increase the stress and pressure that the left ventricle must work against to eject blood. Thus, the health of the arteries throughout the body readily impact left ventricle function. This study will examine the size of the left ventricle and how well it is contracting and whether these indices are associated with the overall health of the systemic arteries.

Left Ventricle Systolic vs. Diastolic Function. The cardiac cycle is comprised of one-third time spent in systole and two-thirds time spent in diastole. Diastole is considered the filling or relaxing phase of the cardiac cycle, in which, the left ventricle fills with blood. Systole is considered the emptying or contracting phase of the cardiac cycle. Thus, diastolic dysfunction is defined as a condition in which the filling of the left ventricle is impaired, while systolic dysfunction may result from impaired ventricular contraction. For the purposes of this study, we focus on left ventricle systolic function and measure it via echocardiography and strain analysis.
Echocardiography.

Echocardiography also called an echo test, or heart ultrasound is a clinical test that takes “moving pictures” of the heart with sound waves. A trained sonographer uses ultrasound technology to capture the heart’s movements. Ultra-high frequency sound waves pick up the images of the heart with the help of clear ultrasound gel. Echocardiography does not use X-ray technology. Echocardiography can give lots of information regarding heart size and function. For the purposes of this study we will use 3-dimensional Echocardiography to quantify heart size and function of the left ventricle.

Left Ventricle Strain and Deformation.

Left ventricle strain is an index of left ventricle function and how well the heart muscle is moving with each heart contraction (beat). The ventricle wall motion is detected via displacement of the heart muscle, while wall deformation is detected via strain analysis. Displacement is the difference between the position of a given point of the ventricle wall during the cardiac cycle and the position of the wall at the onset of the cycle (L-L₀) (at QRS complex) [1]. Deformation is measured by strain, which evaluates the degree of deformation in a particular wall segment in relation to its initial dimension (E= L-L₀/L₀) [1]. L = the length of the muscle fiber at the end of contraction, L₀ = the initial length of the heart muscle fiber. Conventionally, lengthening/thickening or stretching is indicated by positive strain values while shortening/thinning is indicated by negative strain values. A higher strain value indicates optimal left ventricle function (strain, deformation) while a lower strain value indicates lower left ventricle function (strain, deformation). Measuring strain allows us to examine the multi-
directional nature of how the heart truly contracts (longitudinal, radial, circumferential directions). For the purpose of this study, we will measure LV function using LV longitudinal, area, radial and circumferential strain.

**Ventricular-vascular Coupling.**

The interaction between the left ventricle and the arterial system is typically described as ventricular-vascular coupling. Ventricular-vascular coupling is a measure of cardiovascular performance. The cardiovascular system is designed to provide adequate blood flow and pressure to the body’s tissues both at rest and during exercise. In order to determine the efficiency of the cardiovascular system, it is necessary to study the left ventricle (heart) properties (Elv) and also the arterial system which provides blood directly to the left ventricle (Ea). For the purpose of this study, we will measure ventricular-vascular coupling using the ratio of Ea:Elv.

**Physiological Adaptations.** Physiological adaptations are defined as healthy, normal adaptations. For the purpose of this study we are interested in physiological cardiovascular adaptations to endurance exercise of the left ventricle (structure and function) and of the vasculature (blood pressure and arterial stiffness). For this study, physiological cardiovascular adaptations will be defined as left ventricle size on average <95g/m² or >95g/m² in females, and <115 g/m² or >115 g/m² in males. If left ventricle relative wall thickness is 0.42 mm with a left ventricle size of <95g/m² and <115g/m² this will be defined as a physiological adaptation as well. Blood pressure values of <140/90 mmHg and arterial (aortic) stiffness values of <7.2 m/s will be considered physiological in the current study.

**Pathological Adaptations.** Pathological adaptations are defined as abnormal and unhealthy, typically due to disease. For the purpose of the current study, pathological cardiovascular adaptations will be defined as left ventricle size >95g/m² in females and >115g/m² in males.
combined with a left ventricle relative wall thickness of >0.42 mm. Blood pressure values of >140/90 mmHg and arterial (aortic) stiffness values of >7.2 m/s will be considered pathological in the current study.

**Non-Technical Summary**

**What is known?**

Over the past few decades there has been increased participation in endurance events, such as marathons. In particular, the number of female marathon participants has increased, such that there is almost the same number of female as male marathoners. The impact of aerobic exercise on risk for cardiovascular disease (CVD) is well-established as beneficial for the cardiovascular system. However, there is some debate as to whether excessive endurance exercise, such as completing multiple marathons, is detrimental to the cardiovascular system. Some studies in male marathoners note adverse cardiac structural remodeling (i.e. enlarged heart), ventricular contractile abnormalities [2, 3] coronary artery calcification and fibrosis [2, 3]. Additionally, studies report increased aortic stiffness and blood pressure in endurance trained men compared to controls. Despite, well-established sex differences in cardiovascular risk and physiology across the lifespan, no studies have examined the impact of chronic endurance exercise on the cardiovascular system in female marathoners. Thus, our study examined sex differences in cardiovascular structure, function and vascular hemodynamics in male and female marathon runners and recreationally active adults.

**What is new and noteworthy from our results?**

**Aim 1:** Surprisingly, when left ventricle mass was adjusted for differences in body size between male and females, female marathoners had a larger left ventricle compared to both their recreationally active female and male counterparts. We suggest in our sample, that female
marathoners have a larger left ventricle, that is not associated with increased blood pressure, aortic stiffness or cardiac dysfunction and is actually associated with increased cardiac efficiency (as measured by ventricular-vascular coupling).

**Aim 2:** Left ventricle function was similar between all groups, both men and women, and marathoners and controls. This is the first study to examine sex differences in left ventricle function in marathoners. Also, this is the first study to do so, utilizing three-dimensional echocardiography strain analysis. We found no sex or training differences in left ventricle function.

**Aim 3:** There were sex differences, but no training differences in 24-hour ambulatory hemodynamics following non-exercise control and post-exercise conditions. As expected women had lower resting 24-hour hemodynamics (arterial stiffness, and blood pressure) compared to men, irrespective of training status. Similarly, women had lower 24-hour hemodynamics following acute exercise. There were also no differences between resting and post-exercise 24-hour hemodynamics.

Lastly, we assessed overall ventricular-vascular coupling, a measure of the interaction between the left ventricle and the arterial system to determine cardiac performance and energetics, we found that female marathoners had better overall ventricular vascular coupling compared to both recreationally active controls and male counterparts. Adequate coupling between the heart and the arterial system is important as it results in optimal transfer of blood from the heart to the periphery without excessive changes in pressure [4]. Thus, our findings suggest that female marathoners have a larger heart, with preserved function, and lower central hemodynamic load, that might contribute to better observed ventricular-vascular coupling.

**Implications**
In our study, women irrespective of training status had lower blood pressure and aortic stiffness compared to men. Thus, sex differences in cardiovascular system are present in both the recreationally active and marathon runner population. This finding emphasizes the importance of examining sex differences in how endurance exercise affects the cardiovascular system. Previous studies that examine male marathoners with similar cardiac adaptations show that a larger ventricle is associated with reduced function, and higher hemodynamic load. The results of our study suggest that although female marathoners had a larger heart, they had preserved function, lower central hemodynamic load and optimal ventricular-vascular coupling. Thus, female sex may confer a level of cardio-protection from possible cardiac mal-adaptations with habitual endurance exercise training. Understanding the cardiovascular response to regular endurance exercise may also have important clinical implications for women as cardiovascular risk with age in women has been linked to greater risk of heart failure than men. Endurance exercise may offer an important therapeutic strategy to mitigate CVD risk in women.
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Chapter I: Introduction

Over the past three decades there has been an unprecedented number of athletes training for and racing at distances up to and exceeding the marathon. The number of marathon finishers has increased from 25,000 in 1976 to 550,636 in 2015 [5]. The percentage of female marathon finishers has reached an all-time high (43%) and is almost as high as the number of male marathon finishers [5]. Although exercise is generally viewed as beneficial for the heart [6], there are controversial reports of adverse cardiac structural remodeling, ventricular contractile abnormalities [2, 3] and fibrosis [2, 3] in long-distance runners. As such, new questions have surfaced concerning the effects of long-term endurance exercise on the cardiovascular system.

Endurance training results in myocardial structural adaptations such as increases in wall thickness [7-10] and increases in cardiac mass [11]. Historically these physiological adaptations are viewed as benign and considered a phenotypic expression of the “athlete’s heart” [12-14]. Recent studies have suggested that exercise-induced cardiac remodeling can progress to myocardial fibrosis in a subset of the athletic population. This is of concern as fibrosis is a pathological substrate for lethal arrhythmogenesis and sudden cardiac death [15]. Increases in cardiac mass are associated with myocardial dysfunction [16], which may play a role in the development of myocardial fibrosis [16]. Myocardial contractile dysfunction may precede the development of ventricular enlargement and subsequently myocardial fibrosis. Therefore, myocardial dysfunction may be a marker for myocardial damage and risk in endurance athletes [16].

Ventricular structural adaptations to endurance exercise are less pronounced in women compared to men [17-24]. Female athletes display smaller left ventricular (LV) mass and volumes compared to male athletes [21] even after adjusting for body size and lean body mass.
Whether there are sex differences in cardiac functional changes with endurance exercise is less explored as the majority of studies to date have examined men only [15, 27-29]. Women may have higher myocardial contractile function when compared to men of the same age [30]. It is possible that endurance-trained women may have better myocardial function than men, which may lead to a lesser degree of training-induced ventricular remodeling. The relationship between myocardial function and ventricular remodeling in female endurance athletes has yet to be examined.

Reasons for potential sex differences in myocardial function and ventricular remodeling with endurance training are unknown but may be related to differences in underlying central hemodynamics at rest and in response to exercise. Specifically, there are known sex differences in resting central hemodynamics (blood pressure, arterial stiffness and wave reflections) [31-33]. Studies show that men have higher arterial stiffness and blood pressure when compared to women while women have higher pressure from wave reflections than men [31, 34]. Increased blood pressure, arterial stiffness and pressure from wave reflections leads to increased afterload and is associated with increased LV mass [35]. Increased arterial stiffness and pressure from wave reflections have also been linked to reduced myocardial contractile function [36] and myocardial fibrosis [37].

Generally, regular endurance exercise training leads to reductions in blood pressure, arterial stiffness and wave reflections [38, 39]. Studies in men suggest that strenuous endurance exercise may lead to increased blood pressure and arterial stiffness with no change in wave reflections [40, 41]. Conversely, women experience reductions in blood pressure, arterial stiffness and wave reflections following strenuous endurance exercise [34, 42-48]. Differential acute hemodynamic responses to endurance exercise compounded over years of training may
give rise to *chronic* sex differences in central hemodynamic load. Sex differences in central hemodynamic load may lead to differences in LV afterload and ultimately explain differences in the magnitude of myocardial contractile function and myocardial remodeling.

Conventionally, 2-dimensional echocardiography (2DE) has been used to characterize the “athlete’s heart” by assessing LV mass (LVM), dimensions and function in athletes [49]. Recent advances in 3D echocardiography (3DE) have allowed researchers to more accurately and expansively assess cardiac structure and contractile function. 3D speckle tracking echocardiography (3DSTE) assesses LV contractile function using strain analysis. Increased strain or a higher strain rate indicates optimal contractile function whereas decreased strain or a lower strain rate indicates contractile dysfunction [50]. Few cross-sectional studies in athletes have used strain analysis to characterize myocardial functional adaptations to exercise training found differences in cardiac function between strength and endurance-trained athletes [51-53]. Unlike the well-established literature surrounding cardiac enlargement with endurance training, disparities exist with regards to whether endurance-trained runners have higher cardiac function [3] or lower cardiac function [54] compared to sedentary individuals. Myocardial strain also may be transiently reduced immediately after endurance events (i.e. marathons, ultra-marathons), which suggests myocardial dysfunction or “cardiac fatigue” [2, 55, 56]. Previous studies that examined cardiac function in endurance-trained runners used 2DE not 3DE [3, 54]. We wish to use 3DE and 3DSTE to explore the impact of sex on cardiac structural and functional adaptations to habitual endurance exercise.

Despite increased female participation in competitive endurance events, *minimal* advances have been made to examine the cardiovascular adaptations to prolonged endurance exercise in women. Pre-menopausal women may never approach pathological thresholds of
ventricular remodeling and subsequently, may be cardio-protected with regards to possible adverse cardiac remodeling, cardiac dysfunction and risk for fibrosis. Understanding the ventricular-vascular responses to habitual endurance exercise training in lifelong male and female endurance athletes may give insight into sex differences in cardiac remodeling, function and future cardiovascular risk.

**Specific Aims**

**Aim 1:** To compare LV structure (i.e. LV mass) in marathoners and recreationally active women and men using 3DE imaging.

*Hypothesis 1:* Female marathoners will have lower LV mass (adjusted for body surface area and body composition) compared to male marathoners and higher LV mass compared to recreationally active women. Male marathoners will have higher LV mass compared to recreationally active men.

**Aim 2:** To examine LV function (i.e. strain analysis) in marathoners and recreationally active women and men using 3D STE.

*Hypothesis 2:* Female marathoners will have higher function (i.e. higher strain) compared to male marathoners and recreationally active women. Male marathoners will have lower function compared to recreationally active men.

**Aim 3:** To examine 24-hour central hemodynamic load (blood pressure, arterial stiffness, pressure from wave reflections) at rest and after acute exercise in marathoners and recreationally active women and men.

*Hypothesis 3a:* Female marathoners will have a lower 24-hour central hemodynamic load (blood pressure, arterial stiffness, pressure from wave reflections) at rest and following exercise
compared to male marathoners and recreationally active women. Male marathoners will have higher 24-hour central hemodynamic load compared to recreationally active men.

*Hypothesis 3b:* Higher 24-hour central hemodynamic load (blood pressure, arterial stiffness, pressure from wave reflections) will be associated with larger LV structure (LVM) and lower LV function (LV strain) in marathoners and recreationally active men and women.
Chapter II: Review of the Literature

I. The Effect of Physical Activity and Exercise on CVD Mortality and Morbidity

“All parts of the body, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are untuned and left idle they become liable to disease, defective in growth and age quickly” (Greek physician, Hippocrates, 460-375 B.C).

Over 2000 years ago, the Greek Physician Hippocrates dictated the importance of physical activity to overall health. Thousands of years later, in the 21st Century, evidence suggests that a sedentary lifestyle may be an adversary to optimal health [57]. An exemplar study in the field of physical activity epidemiology, performed by Morris et al. compared coronary heart disease (CHD) mortality rates of London double decker bus conductors who stood, walked, and climbed bus stairs for hours a day to the CHD mortality rates of London bus drivers who spent their day sitting [58]. This study found that the bus conductors had 50% lower CHD mortality rates compared to the bus drivers. The researchers attributed lower rates of CHD to increased daily physical activity performed by the bus conductors. The London bus conductor study had an immediate impact on physical activity epidemiology and emphasized the beneficial role of physical activity on several chronic diseases.

In accordance with Morris et al. several large epidemiological studies have determined that there is an inverse relationship between physical activity and cardiovascular events and mortality [59-62]. Highly active people have lower rates of cardiovascular disease (CVD) than inactive individuals [63-65]. The large body of evidence surrounding the association of physical activity and CVD led the federal government in 2008 to issue the first issue of physical activity guidelines for Americans [63]. The 2008 guidelines comprehensively reviewed several studies
and found that active men and women had an approximately 30-35% reduction in risk for developing CVD compared to inactive individuals. More importantly, the 2008 US federal physical activity guidelines drafted by The American College of Sports Medicine (ACSM) and American Heart Association (AHA) recommend that adults perform 150 min/week of moderate-intensity or 75 min/week of vigorous intensity physical activity [63, 66]. Since then, several epidemiological studies have determined that 15 minutes of exercise per day (~105 minutes) [67, 68] is the minimum dose of moderate intensity exercise that is associated with reduced CVD risk [61, 67]. Even individuals who perform the minimum level of physical activity have a reduced risk of CVD over a 15-year period compared to sedentary individuals [68, 69].

**Gender and Relationship of PA and CVD**

The inverse relationship between physical activity and risk of developing CVD is reported in both men and women [70]. It appears from several studies that more physical activity is associated with a reduced risk of CVD in both men and women, respectively [69, 71-79]. Interestingly, this relationship may be more pronounced in women than in men as the average relative risk reduction in active women was 40% [70] when compared to inactive women while the average risk reduction in men was 30% when compared to inactive men [70]. Even though the association may be stronger in women compared to men there are few studies that include gender comparisons because different studies use a variety of questionnaires to assess physical activity and categorize physical activity differently (intensity, duration, frequency, energy expenditure). Indeed, not only does sex impact the association between physical activity and CVD but also intensity, duration, frequency and energy expenditure of the physical activity performed may have a profound influence the association of physical activity and risk for CVD.

**Dose-Response Relationship between PA Energy Expenditure and Risk for CVD**
The inverse relationship between physical activity and CVD is well established however; the dose of physical activity is not well defined. The 2008 Guidelines of Physical Activity concluded that “greater amounts of activity appear to provide greater benefit but the shapes of any dose-response relations have not been well-defined” [63]. In order to explore this point two-hallmark studies will be discussed: The Harvard Alumni study and The Women’s Health Study. The Harvard Alumni Study, a large epidemiological study, determined the relationship between volume, intensity, and duration of physical activity and risk for CVD and mortality [61]. Approximately 7,000 male alumni were followed for 6 years to examine levels of daily physical activity. From this data, energy expenditure was calculated and men were placed into categories based on total energy expenditure per week (Figure 1). In men, the relationship between energy expenditure and levels of physical activity and risk for CVD was curvilinear where higher total physical activity was correlated with lower CVD risk but at approximately 3000 kcal/week and greater the risk reductions were of smaller and smaller magnitude (Figure 1)[61]. This suggests that there is a point at which higher volume of physical activity may not confer additional benefits [59].

A similar relationship between physical activity and risk for CVD has been established in women. The Women’s Health Study, a randomized trial of the effects of aspirin and vitamin E in the prevention of CVD and cancer in healthy women, assessed physical activity, energy expenditure and risk for CVD in...
approximately 27,000 women throughout 10 years [77]. Similar to the Harvard alumni study, women in this study were categorized based on their total weekly energy expenditure (Figure 2).

Contrastingly, the relationship between physical activity and CVD risk appears to be more linear in women. However, this relationship might be due to the lower weekly energy expenditure in women (200-1500 kcal/week) compared to men (1000-4000 Kcal/week) and the relationship in women (Figure 2) represents the beginning or lower end of the dose-response curve. It is evident from these studies that physical activity is associated with low mortality rates [70, 80]. However, it is currently unclear whether high/excessive volumes of physical activity are associated with additional risk reductions in CVD in both men and women [6, 70, 81]. Future studies need to examine the dose response of physical activity and risk for CVD in men and women matched for energy expenditure.

**Dose-Response Relationship between PA Intensity and Risk for CVD**

The dose response relationship between moderate and vigorous intensity physical activity and cardiovascular mortality appear to be different [67, 68, 82]. In contrast to the well-
established dose-response relationship of moderate intensity physical activity and CVD, there are discrepancies in the literature regarding the relationship between vigorous intensity activity and CVD. Some studies suggest a linear relationship between vigorous activity and risk for CVD, like moderate intensity physical activity [69, 75]. For instance, Lee et al. examined the association of vigorous and non-vigorous intensity physical activity with CVD mortality and found an inverse relationship between amount of vigorous physical activity and mortality but not between non-vigorous physical activity and mortality [83]. Similarly, Sesso et al. found that the total volume of physical activity and amount of vigorous intensity physical activity were significant predictors of reduced risk for CVD [75]. Thus, these studies suggest that vigorous activity is associated with the largest reductions in risk for CVD.

In contrast, other studies suggest that vigorous intensity activity yields a maximum risk reduction at lower exercise volumes than moderate intensity exercise [67, 68] suggesting that high volumes of vigorous exercise, above the ACSM/AHA recommendations (75 minutes), may not be reduce risk for CVD. In a prospective study, Wen et al. studied 416,175 Taiwanese adults for 13 years and found that individuals who performed 15 minutes of physical activity per day had significant reductions in risk for CVD and all-cause mortality compared to those who are inactive. After the 15 minutes per day of exercise, every additional 15 minutes of daily moderate intensity exercise was associated with greater reductions in risk for mortality (Black Line, Figure 3). However, this pattern only continued until 100 minutes per day of moderate intensity exercise, at which this study found no additional reductions in risk for CVD. More importantly, this study also found that there was no additional reductions in mortality risk in individuals who performed more than 50 minutes per day of vigorous activity (Red Line, Figure 3) [67].
Similarly, Mons et al. showed that individuals who expended over 14,700 kcals per week via vigorous activity had an increased risk for CVD [84]. This study found the highest hazard ratios for adverse cardiovascular outcomes in the least active patient group and the lowest in those who exercised moderately at 2-4 times per week. A higher rate of CV events was also found in daily exercisers compared to the moderate exercisers but not as high as that found in the least active group. These results suggest a reverse J-shaped curve describing the association of physical activity levels and CVD mortality [84]. Typically, high levels of moderate and vigorous intensity exercise are associated with larger reductions in CVD mortality however; there may be a threshold of physical activity in which there are no additional reductions in CVD mortality [67, 68, 82].
A recent retrospective study examined the dose response relationship between leisure
time physical activity and CVD mortality to determine whether there is an upper limit of
physical activity in which additional physical activity does not confer further reductions in CVD
risk. In a pooled analysis of 6 populations from the National Cancer Institute Cohort Consortium,
a total sample of 661,137 people and 116,686 deaths were studied [68]. Arem et al. found that
the individuals who performed just below the daily recommendations of physical activity had a
20% lower risk of CVD mortality, individuals who performed 1-2 times the recommended daily
dose of activity had a 31% reduction in risk, individuals who performed 2-3 times the
recommended daily amount of activity had a 37% reduction in risk and those who engaged in 3-
10 times the recommended daily amount of activity had 39% lower risk reduction, while people
who exercised >10 times the recommended amount only had a 31% lower CVD mortality risk which is the same amount as those individuals who performed just below the daily recommended dose (Figure 4). Thus, individuals who perform 10 times the recommended amount of physical activity had no additional reductions in risk. However, similar to the findings of Mons et al., because their risk was not significantly higher than those who performed less activity, the authors concluded that this level of activity does not lead to increased risk for cardiovascular mortality. These studies extend previous findings by Wen et al. that only examined the dose response relationship between physical activity and CVD mortality up to 40 MET-h/week or 5 times the recommended daily activity. Arem et al. found that beyond 40 MET-h/week there were no further reductions in mortality risk (Figure 4). Future studies need to examine the relationship between high volumes of moderate and vigorous physical activity and risk for CVD to confirm and extend these findings.

II. Endurance Exercise CVD Risk and Mortality

Long-distance/Endurance Running and Risk for CVD and Mortality

There are an unprecedented number of individuals training for and competing in strenuous endurance events such as marathon races [5]. Thus, an increasing number of individuals are exercising at volumes of physical activity that exceed the current physical activity guidelines. Running is an attractive form of aerobic exercise and has been regarded as a popular and practical form of high intensity vigorous aerobic exercise [85]. The effect of high volumes of strenuous aerobic exercise such as running on risk for CVD is currently debated. Some studies suggest that higher volumes of running are associated with lower risk of CVD and mortality [86-89]. While other studies suggest a U-shaped curve or reverse J-shaped curve between the amount of running and risk for CVD [85, 90-92]. The U-shaped relationship implies that sedentary or
inactive individuals and extremely/excessively runners have similar risk of CVD while the reverse J-shaped curve suggests that extreme endurance runners have significantly higher risk for CVD compared to those who exercise at moderate levels, respectively [84, 85, 89-92].

The National Runners’ Health Study examined the dose response relationship between CVD risk factors and vigorous exercise in 8,283 male recreational runners. As shown in Figure 5, the estimated 10-year CVD risk for events, determined by the Framingham study, decreased with more miles run per week, 9.3 (15k) miles to approximately 49-50 miles (80km) a week [87, 89]. However, there were no additional reductions in risk for CVD events in individuals who ran >50 miles (80km) a week.

![Figure 2.5: National Runner’s Study amount of distance run and 10-Year CVD risk in men, Modified from Williams et al. [85].](image)

Another study by the same research group, examined the dose response relationship between exercise energy expenditure (Metabolic Equivalents, MET-hours per day) and CVD related mortality in myocardial infarction survivors and observed a J-shaped relationship between risk for CV mortality and exercise energy expenditure [89]. As can been seen in Figure 2.5.
6, those who expended 3.6 to 5.4 MET hours per day (15-23 miles per week) had a 50% lower risk of CVD than those who exercised <1.07 MET h/d and those who exercised at 5.4-7.2 MET hours per day (23-30 miles per week) were at a 63% lower risk, and those individuals who exercised >7.2 MET-hours per day (>30 miles per week) had only a 12% lower risk. This study found higher energy expenditure from walking or running was associated with lower risk for CVD mortality until 7.2 MET-hours per day (>30 miles per week), which is equivalent to running 30 miles per week or briskly walking 46 miles/week [89, 93]. The results of this study suggest that the benefits of running or walking may not accrue indefinitely. In MI survivors, there was a significant increase in cardiovascular mortality in both walkers and runners who exercised more than 30 miles a week compared to those who exercised anywhere between 15-30 miles per week [89]. Increased cardiovascular mortality in the most active cohort is unclear and needs to be further examined, especially considering that this cohort also had lower CVD risk factors. However, this study was conducted in MI survivors so the results cannot be generalized to entire exercise population.

Figure 2.6: National Runner’s Study amount of energy expenditure from walking or running and CVD risk in men, Modified by Williams et al. [87].
Additionally, The Copenhagen City Heart Study, a prospective observational study of men and women joggers (1,100 joggers) and non-joggers (4,000), examined whether running was associated with all-cause mortality and cardiovascular mortality in healthy men and women [92]. In this study, running frequency, distance and speed were examined and the joggers were divided into 3 groups: low, moderate and strenuous/high intensity joggers (Figure 7). Researchers found that as expected, jogging was associated with lower mortality rates compared to non-jogging. The age adjusted increase in longevity for those who regularly jogged was 6.2 years for men and 5.6 years for women [92]
Interestingly this study also found that up to 2.5 hours (150 minutes) of moderate intensity jogging per week (5-6 miles per week for ≤ 3 times per week) was associated with the lowest mortality rates (Figure 7). However, strenuous jogging ≥4 times per week at ≥ 7 miles per hour appeared to increase risk for mortality. Thus, this study observed an unexpected U shaped curve/relationship with volume, frequency and intensity of jogging and mortality [91, 92]. As can be seen in Figure 7, this study found that the lowest CVD and all-cause mortality was among the low intensity joggers in relation to duration per week, frequency per week, and speed of

![Figure 2.7: The relationship of speed, frequency, distance, and time of running and relative risk in runners and non-runners, Modified from Schnohr et al. [89].](image-url)
jogging. Moderate intensity joggers had a significantly higher cardiovascular mortality rate compared with low intensity joggers but still lower than sedentary individuals. Conversely, strenuous intensity joggers (≥7 miles per hour) had a cardiovascular mortality rate that was not statistically different from that of non-joggers [91]. Thus, researchers suggest that strenuous/high intensity runners see no additional cardiovascular benefits compared to their sedentary counterparts.

In support of the previous controversial findings, a recent study examined 55,000 adults between 18-100 years of age and followed them for 15 years. Analyses revealed that runners had a 30-45% lower overall risk of all-cause mortality, cardiovascular mortality and a higher life expectancy by 3 years compared to non-runners, even after controlling for age and gender. Additionally, running 50-120 min, ≤ 3 times per week at a modest pace of 6-7 miles per hour conferred the highest reductions in cardiovascular risk. However, similar to The Copenhagen City Heart Study, higher doses of running (≥4 times per week) were associated with 33-50% higher risk for cardiovascular mortality compared to that seen with moderate doses of running [85].

In summary, there are limited studies examining the effects of high volumes of frequent vigorous aerobic exercise on risk for CVD in highly competitive endurance trained individuals. High volumes of strenuous endurance exercise may accelerate risk for CVD. The benefits of regular physical activity are well-established but long-term training for and competing in strenuous endurance events may predispose or accelerate cardiovascular issues that may not be seen at more moderate intensity physical activity [28, 29, 94, 95]. The literature appears to conclude that highest reductions in cardiovascular mortality rates is at ≤ 30 miles per week, < 4 times per week, at 5-6 miles per hour of running or ≤ 46 miles of walking. Typically, avid
marathon runners report weekly exercise in excess of 30 miles/week, 6-15 hours per week, >100 METS per week, 6-7 days per week [96]. The number of people participating in marathons and multiple marathons a year is increasing yet there is scarce epidemiological data advising these populations on health benefits or the potential consequences of habitual strenuous exercise on cardiovascular health. A growing body of literature suggests that too much exercise may be detrimental for CVD risk. Moreover, the attenuation and potential reversal of the beneficial effects of exercise on CVD risk may be related to the underlying physiological cardiovascular responses to repeated exposure to vigorous endurance exercise.

III. Cardiovascular Adaptations to Endurance Exercise: The “Athlete’s Heart”

Exercise and LV Remodeling

Endurance athletes engage in prolonged daily exercise thereby eliciting repeated increases in heart rate, blood pressure, stroke volume and cardiac output that consequently lead to increases cardiac mass and dimensions [97]. Endurance training places increased hemodynamic demand on the heart, that when repeated chronically throughout life acts as a physiological stimulus for cardiac adaptations [98]. The frequent increased blood flow generated by endurance training places a volume load on the ventricles which contributes to significant cardiac remodeling [82]. There are established upper limits of normal cardiac remodeling associated with “athlete’s heart” that are necessary to distinguish physiological from pathological adaptations. The magnitude of cardiac structural changes detected in athletes is large and if detected in the general population would indicate clinical cardiac abnormalities.

Previous studies utilizing echocardiography have clearly established a link between training and LV enlargement (9, 22). Conventionally, 2DE M-mode echocardiography was used to determine LV hypertrophy and dilation (23). Numerous cross sectional studies have examined
LV remodeling in endurance and strength trained athletes [99-106]. Overwhelmingly these studies found that LVM is significantly higher in athletes compared to controls [99-106]. Moreover, the data show that the highest degree of LV hypertrophy occurs in athletes with the largest body size and in those athletes participating in endurance sports. Hence, more recent studies control for body surface area, body fat percentage and/or lean body mass.

Endurance and resistance exercise are associated with distinctly different LV structural adaptations. Cardiac adaptations to endurance exercise training and strength training are largely defined based on volume and pressure overload, respectively. Morganroth et al. first used echocardiography to image and define the athlete’s heart and stated that cardiac remodeling is specific to each training modality [99]. According to the “Morganroth Hypothesis” typically, endurance athletes engaging in continuous dynamic exercise (i.e. running), experience prolonged elevations in cardiac output (increases from 6 L/min to 40 L/min during intense exercise) [107], presenting the heart with a volume load. This stimulates eccentric cardiac hypertrophy, manifesting as an increase in LV internal dimension and mass with minor changes in LV wall thickness [8, 99]. Contrastingly, strength athletes (i.e. weight lifters) engaging in predominately static or isometric exercise, experience increases in blood pressure as high as approximately 320/250 mmHg [108, 109], presenting the heart with a pressure load. This stimulates concentric LV hypertrophy, whereby LV wall thickness and mass increase, with little to no change in LV wall dimensions [12]. Athletes that incorporate both dynamic and static components (i.e. rowers and cyclists) exhibit a significant increase in LV wall thickness and even larger increase in LV internal dimensions. These athletes experience extreme pressure and volume loads on the myocardium.
Additional aspects of myocardial remodeling in athletes include right ventricular chamber enlargement [110], atrial dilation [10] and mild aortic remodeling. Remodeling, specifically enlargement of the athlete’s LV, is beneficial in providing the ability for the heart to pump more blood with greater contractile force. However, a larger myocardium requires more oxygen consumption and energy and thus has greater metabolic requirements compared to a smaller myocardium. If increases in myocardial oxygen demand are not met, myocardial ischemia occurs and fibrosis can develop. Thus, LV hypertrophy is associated with myocardial fibrosis or scarring, which is a pathological substrate for arrhythmias and increased risk for SCD. Indeed, LV hypertrophy in endurance athletes may be of pathological concern. Recent studies have examined LV function in athletes at rest using cross-sectional designs [111]. Conventionally, ejection fraction has been used to measure LV function and this has been determined to be relatively normal in athletes except for a few studies [111]. Recent advances in functional cardiac imaging including LV strain measured by STE has also suggested that endurance training may lead to beneficial changes in LV function [112, 113] or in some cases diminished LV function at rest, that cannot be detected using LV ejection fraction. This paradox in the literature regarding LV function in athletes needs to be explored further.

The athlete’s heart provokes controversial discussions with respect to its cardiovascular health implications and predispositions to disease. Traditionally, LV remodeling and hypertrophy in endurance athletes have been primarily attributed to volume overload placed on the heart chambers. Cardiac functional parameters may give better insight into LV structural adaptations and future risk for pathological adaptations in endurance-trained athletes. Additionally, evidence suggests increased chronic hemodynamic (arterial) load (i.e. blood pressure, arterial stiffness and
wave reflections) may help to partially explain LV remodeling in response to long-term endurance training.

**Imaging of the Endurance Athlete’s Heart**

Echocardiographic and MRI studies demonstrate that athletes have larger hearts [7, 12]. Recent developments in imaging technology enable researchers to assess in depth myocardial morphology and function. Conventional echocardiography techniques to measure structure and function include, M-mode, Tissue Doppler imaging (TDI) and 2-dimensional echocardiography (2DE), however these techniques have limitations (Table 1). Recent developments in 3-dimensional echocardiography (3DE) have helped provide more detailed morphological and functional myocardial measurements. [114]. 3DE offers more comprehensive details of LV remodeling as it can distinguish differences in length, shape of LV chamber, geometry, function and synchronicity of contraction between different populations, including athletes [49, 114]. 3DE evaluation of cardiac chamber volumes and mass avoids geometric assumptions made by 2DE acquisition and has the capability to assess regional LV wall motion and strain. As a novel imaging technique, 3DE is able to detect cardiac structure and function in a similar way to cardiac magnetic resonance imaging (CMRI). 3DE is as accurate as cardiac magnetic resonance imaging (considered the gold standard for assessing cardiac structure/function) for quantifying myocardial structure and function. 3DE has ideal image spatial resolution and quality that is not influenced by body size allowing for precise cardiac chamber size, mass and function measurements. Moreover, when 3DE is compared to CMRI in the assessment of ventricular morphology optimal intra-observer and inter-observer reliability is observed compared with other standard imaging techniques [49, 114, 115]. Therefore, 3DE is a reliable, accurate, novel
imaging technique that may provide novel insight into pathological versus physiological cardiac structural and functional adaptations in athletes.

IV. LV Wall (Function) Mechanics and Strain Analysis

LV wall function measured by Myocardial Strain

Conventional cardiac imaging techniques only provide one-dimensional (linear motion) and two-dimensional (horizontal and vertical components) quantifications of cardiac structure and function. Thus, these conventional techniques merely assume the actual geometric dimensions of the myocardium. Physiologically, myocardial contraction occurs in three planes of motion as seen in Figure 8: longitudinal (base to apex) shortening, radial (endo- to epicardial) thickening and circumferential shortening (Figure 10). In simpler terms, an object may undergo motion and/or deformation. The motion of an object is determined by both 1) the distance it travels (displacement) and 2) by the time it takes for that object to arrive at its destination (velocity). However, not all objects that move undergo deformation or change shape. For instance, a stiff object that does not stretched readily may move but not change shape and thus, this moving object does not undergo deformation (as long as every part of the object moves at the same velocity). Thus this object has purely linear or translational velocity but the shape of the object remains the same. On the contrary, if different parts of the object have different velocities the object has to change shape, as different components of that object are being stretched to move at different times during its movement. This is exemplified in Figure 8, as the box is being deformed and stretched and compressed in different directions causing it to change shape. As compression/shortening occurs in one direction stretching or expansion in other directions balances this deformation. Thus, deformation is analogous to differential motion and local (regional) deformation is a proxy for global (total) deformation. The concepts of deformation and
motion can be applied to the heart, which has a stationary apex but mobile base. As the apex is stationary, the base moves toward the apex in systole (when the heart is contracting) and away from the apex in diastole. Thus, deformation of the heart is between zero (at the apex) and is at its maximum at the base. During the cardiac cycle as the heart contracts (is stretched) and relaxes the cardiac myofibers undergo motion, displacement and deformation. The magnitude of regional myocardial contraction is dependent on the local arrangement of myofibers within the myocardial wall at an angle of inclination with respect to the longitudinal axis of the ventricle [1].

Figure 2.8: Three planes of myocardial contractile motion and deformation: longitudinal, radial, circumferential, modified from Shiota et al. [114]

The segmental/regional function and the global function are of equal importance. Both regional and global functional components can be obtained from wall motion and deformation measurements. Wall motion is detected via displacement of the myofibers while wall
deformation is detected via strain analysis which is calculated as the initial length of the myofiber subtracted from the length of the myofiber at the end of contraction or relaxation divided by the initial length of the myofiber. Figure 11 represents the calculation of displacement and deformation of a single myofiber. As can be seen in Figure 11, Displacement is the difference between the position of a given point of the myocardial wall during the cardiac cycle and the position of the wall at the onset of the cycle (L-L0) (at QRS complex) [1]. Also represented in Figure 9, Deformation is the percentage of wall displacement during a point in the cardiac cycle from the onset of the cardiac cycle (E= L-L0/L0). Deformation is measured by strain, which evaluates the degree of deformation in a particular wall segment in relation to its initial dimension (E= L-L0/L0) [1]. Systole would be met with longitudinal shortening, circumferential shortening and radial thickening. Conventionally, lengthening/thickening or stretching is indicated by positive strain values while shortening/thinning is indicated by negative strain values. A higher strain value indicates optimal myocardial contractile function/deformation while a lower strain value indicates lower myocardial contractile function.
Advances in the field of echocardiography have allowed for an estimation of strain using speckle tracking technology (STE). STE is a novel method that estimates tissue velocities from grey scale imaging with high reproducibility of results and no angle dependence. STE is a pattern recognition software that tracks the speckle pattern throughout the cardiac cycle. These speckles are known as kernels that are placed on the myocardial wall during the analysis to track wall motion and calculate deformation. The kernel allows for identification of a specific area on the wall and then tracks it by identifying the kernel in the next frame. STE is a technique that is based on analysis of many of these speckles or kernels throughout the cardiac cycle. Changes in the speckle patterns can be assessed to determine the motion and deformation of the myocardial wall. Speckle tracking algorithms are used to track local tissue wall patterns of patches, which
contain numerous speckles. The displacement of a single patch between two consecutive frames during the cardiac cycle corresponds to myocardial motion.

Older methods used to assess wall strain include Tissue Doppler Imaging (TDI) and 2DE [1]. Comparisons of the three methods of measuring myocardial function via strain are provided in Table 1. TDI generates detailed information regarding tissue velocities at any location in one dimension. TDI is a relatively easy method and can also estimate wall deformation and mechanics. However, TDI is limited to one dimension, is angle dependent and the wall mechanic measurements are noisy[1]. TDI velocities may also be heavily influenced by global heart translational movement and by blood flow. These issues cannot be fixed but may be reduced by having the patient hold their breath for several heart beats. 2DE strain is an approach for quantification of strain, strain rate, tissue velocity and displacement. However, this approach has limitations, principally due to the use of geometric assumptions, high inter-observer variability, probe positioning issues [1, 50]. 2DE is the most used technique however; the use of 3DE STE represents a further advancement in the field of STE that can overcome conventional limitations of the 2D STE irregular tracking.

Novel technology includes 3D strain analysis, which is ideal for evaluating the deformation of the 3D LV cavity. 3D strain properties include measurements in the longitudinal, circumferential, and radial planes of motion. 3D STE Strain analysis has the ability to link the cardiac contractile mechanics with the underlying cardiac structure and fiber arrangement. This improves the physiological understanding of the myocardial contraction. Future studies are necessary that utilize the capabilities of 3D STE to establish normative values and improve the accuracy of myocardial strain values.
Table 2.1: Strengths and Limitations of Echocardiography Techniques to Measure Myocardial Strain

<table>
<thead>
<tr>
<th>Imaging Modality for Myocardial Function</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Dimensional Echocardiography (2DE)</td>
<td>Measures tissue velocities</td>
<td>TDI is only 1-dimensional</td>
</tr>
<tr>
<td>Tissue Doppler Imaging (TDI)</td>
<td>Tracks wall motion, calculates strain</td>
<td>Angle dependent</td>
</tr>
<tr>
<td></td>
<td>High temporal resolution</td>
<td>Strain analysis is noisy and erroneous</td>
</tr>
<tr>
<td></td>
<td>Software is readily accessible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reproducible</td>
<td></td>
</tr>
<tr>
<td>2-Dimensional Echocardiography (2DE)</td>
<td>Measures tissue velocities and strain</td>
<td>Suboptimal tracking of endo-cardial border</td>
</tr>
<tr>
<td>Speckle Tracking</td>
<td>Measures wall motion/strain in multiple planes</td>
<td>Speckles may not always be tracked well in 2D due to 3D nature of myocardium</td>
</tr>
<tr>
<td></td>
<td>Validated measure of deformation/strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angle independent</td>
<td></td>
</tr>
<tr>
<td>3-Dimensional Echocardiography (3DE)</td>
<td>Track wall motion irrespective of direction, multi-planar</td>
<td>Analysis dependent on image quality</td>
</tr>
<tr>
<td>Speckle Tracking</td>
<td>Reduced examination time</td>
<td>Needs further validation and testing</td>
</tr>
<tr>
<td></td>
<td>Multiple segments analyzed simultaneously</td>
<td>No accepted Normative values</td>
</tr>
</tbody>
</table>

Myocardial Strain Norms and Relationship to Disease States

Conventionally, myocardial function is measured by ejection fraction (i.e. the amount of blood pumped out of the heart); however, strain values may provide additional insight into LV
systolic function. Longitudinal strain is associated with LV ejection fraction [116] and has proven useful in differentiating between different clinical and athletic populations [111, 117]. Strain is additionally sensitive enough to characterize differences between athletes, athletes with LVH and patients with HCM [118, 119].

Abnormalities in myocardial strain have been seen in early development of chronic diseases. Impaired longitudinal strain has been implicated in diabetes patients [120, 121], coronary artery disease [122], valvular disease [123], heart failure [124], and cardiomyopathies [125]. Studies have also determined that longitudinal strain is a predictor of LV remodeling and adverse events such as congestive heart failure and death [126]. Thus, impaired myocardial strain may be a marker for pathological adaptations.

STE allows for novel comprehensive assessment of myocardial function across physiologic and pathologic states beyond traditional echocardiographic techniques. Strain parameters are influenced by age, gender, race, ethnicity, anthropometrics, heart rate, blood pressure, LV size and wall thickness. However, due to the novelty of STE, few studies have established how these variables might influence myocardial strain. However, normative values of deformation indices have been published from 2D TDI in healthy individuals [127-129]. Kuznetsova et al. determined LV strain and strain rates in the general population (18-89 years old). Their study is the first comprehensive study to determine that longitudinal strain was similar in 480 men and women. Normative values of longitudinal strain were -22% (strain rate, 1.31 s⁻¹) and radial strain of -59.2% (strain rate, 3.40s⁻¹). The mean range is 15-25% and 50-70% for longitudinal and radial strain respectively [127]. Low longitudinal strain was reported to be 18.4% and low radial strain 44.3% with cut off values as normal is above 18.5% and 44.5%. Marwick et al. examined longitudinal strain in 242 individuals with an average age of 51 years
(44% men, 56% women) and found the average strain value to be -18.6% [129]. However, this study did not examine differences in strain values with age or sex.

Dalen et al. also performed a study that examined longitudinal strain to determine the global and segmental strain/strain rates according to sex and age in individuals with no known CVD [30]. This study included 1266 people (673 females, 623 males) of Norwegian descent in the HUNT (Norwegian Helseundersokelsen I Nord-trondelag) study using 2DE. Similar to Kuznetsova et al. with increased age strain is significantly reduced and strain values were significantly higher in women across all age groups [127]. The normative average values Dalen et al reported for global strain were -17.4% (strain rate, 1.05s-1) and -15.9% (strain rate -1.01 s-1) in women and men respectively [30]. Thus, both gender and age were significant predictors of strain. Due to the novelty of 3DE there are no established normative values for 3DE and it is well-established that strain methodology is not interchangeable[1].

**Myocardial Strain in Athletes**

Cross sectional studies using both 2DE and 3DE have compared myocardial function, assessed by regional strain measurements, in various exercise-trained individuals [51-53]. Monte et al. compared myocardial performance using 3D STE in male strength trained, endurance trained (cyclists, swimmers) and sedentary individuals. They found that the strength-trained group had a significantly reduced longitudinal, circumferential, and radial strain. Even though both the endurance trained and strength trained athletes had similar increases in LVM, the reduction in LV function in strength-trained athletes was suggested to be due to reports of increased aortic stiffness and blood pressure in the strength athlete population [51]. In contrast, Poulsen et al. examined longitudinal strain using 2D STE in male non-competitive endurance-trained, strength-trained and sedentary controls and found that the average strain was
significantly higher in strength athletes compared to both endurance athletes and controls [52]. Similarly, Demirelli et al. used 2D echocardiography to examine LV strain rates in retired male wrestlers (strength trained), marathoners and healthy controls and determined that after 10 years of cessation of organized exercise training, wrestlers had higher overall strain rate compared to both marathoners and controls [53]. The disagreement in these studies might be reflective of samples that include mixed athletic populations, varying years of training experience, which might influence values of strain.

**Myocardial Strain in Runners**

In addition, cross-sectional studies have examined myocardial function in endurance trained individuals, specifically, marathon runners and there is some debate as to whether runners have higher or lower overall LV strain [3, 54, 130]. Szauder et al. compared 2DE LV strain in male ultra-marathon and marathon runners, body builders and controls. This study found similar morphological/structural changes (i.e. LV mass) in runners and body builders however, they observed that runners had the lowest global longitudinal strain which was inversely associated with increased LV-EDV, LV mass and BSA [3]. In contrast, Schattke et al. used 2DE to examine resting LV strain rate in amateur male and female marathon runners and compared these values to normative control values established in the literature by Dalen et al. [3, 30]. This study observed higher strain rates in the marathoners compared to the reported strain rates in the general population. Thus, it was concluded that runners have higher myocardial performance compared to un-trained individuals.

These studies do not provide convincing data that endurance-trained runners have better or worse LV function when compared to their counterparts. Not only is there a lack of studies that examine LV function in endurance-trained athletes but also there are key methodological
differences in the current studies discussed. For instance, studies include mixed gender and inconsistent definitions of training status. The study performed by Schattke et al. examined amateur marathoners (20-30 miles/week) who may not be exposed to similar magnitude of long term strenuous high intensity exercise as more experienced competitive marathoners such as observed in the study by Szauder et al. (individuals who had trained for 5 or more years at 40-50 miles/week). Additionally, longitudinal studies might be necessary to discern exercise-induced functional adaptations to the myocardium.

**Myocardial Strain in Response to Acute Exercise**

Recent acute longitudinal studies have examined LV function following acute prolonged endurance exercise. Acute exercise studies have examined the effect of endurance exercise on measures of strain and strain rate by measuring LV function before and after marathons or ultramarathon races with some studies suggesting no change in LV function while others indicate a reduction LV function [2, 54-56]. Some data note temporary reductions in LV strain values in the longitudinal, radial and circumferential axis following prolonged exercise >180 minutes [2, 131, 132]. Although transient, acute reductions in myocardial strain may compound over years of repeated exposure to high intensity endurance exercise and may thereby negatively impact LV function among life-long endurance athletes. However, there is currently no data that examines the effects of years of endurance training/competitions (i.e. marathon racing >3 hours) on LV strain. Reductions in acute LV strain could predispose these well-trained individuals for the development of fibrosis and arrhythmias and ultimately, sudden cardiac death.

Both Table 2.2 and Table 2.3 summarize the studies that examine LV strain in athletes, and endurance athletes along with studies that have previously examined the impact of life-long endurance exercise on cardiovascular risk and adaptations. This area of research has a lot of
disagreement and it is important to highlight reasons for these discrepancies which might be related to lack of consistency with regards to age group studied, mixed gender samples, inconsistent definitions of training status, varying years of experience of the athletes in the studies. Ultimately, there are a lack of studies that have examined the impact of lifelong endurance exercise on risk for cardiovascular disease. Table 2.2 and Table 2.3 highlight some of these differences.

Table 2.2: Summary of Studies

<table>
<thead>
<tr>
<th>Summary Table Myocardial Strain in Athletes</th>
<th>Author, Year</th>
<th>Population</th>
<th>Measures</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross Sectional Studies</td>
<td>HCM Patients, soccer players, controls</td>
<td>2DE STE Radial, Longitudinal, Circumferential Strain, LVEDV</td>
<td>Global strain in athletes &gt; Global strain in HCM patients</td>
<td></td>
</tr>
<tr>
<td>Richard, 2007</td>
<td>Strength-trained, endurance-trained, controls</td>
<td>2DE STE longitudinal strain</td>
<td>Global strain in strength-trained athletes &gt; Global strain in endurance-trained athletes</td>
<td></td>
</tr>
<tr>
<td>Poulsem, 2007</td>
<td>HCM patients, handball athletes, controls</td>
<td>2DE STE Longitudinal Strain</td>
<td>Longitudinal strain in athletes &gt; Longitudinal Strain HCM patients</td>
<td></td>
</tr>
<tr>
<td>Butz, 2010</td>
<td>Amateur Male, Female marathon runners and normative values</td>
<td>2DE Longitudinal strain</td>
<td>Longitudinal strain in runners &gt; normative values</td>
<td></td>
</tr>
<tr>
<td>Schattke, 2014</td>
<td>Strength-trained, endurance-trained, controls</td>
<td>3DE STE longitudinal, radial, circumferential strain</td>
<td>Global strain in strength-trained athletes &lt; Global strain in endurance-trained athletes</td>
<td></td>
</tr>
<tr>
<td>Monte, 2015</td>
<td>Wrestlers, Marathoners, controls</td>
<td>2DE STE longitudinal strain</td>
<td>Longitudinal strain in wrestlers &gt; marathoners, controls</td>
<td></td>
</tr>
<tr>
<td>Dimirielli, 2015</td>
<td>Male ultra-marathon, marathon runners, body builders and controls</td>
<td>2DE Longitudinal Strain</td>
<td>Longitudinal strain in ultra-marathons/marathon runners &lt; body builders and controls</td>
<td></td>
</tr>
<tr>
<td>Szander, 2015</td>
<td>Acute Exercise Studies</td>
<td>2DE global strain, M-Mode, TDI</td>
<td>reduced RV function immediately post-marathon</td>
<td></td>
</tr>
<tr>
<td>Whyte, 2005</td>
<td>Male and Female Runners young (22-59 yrs) vs. old (60-72 yrs) male runners</td>
<td>TDI to measure Strain</td>
<td>No reductions in LV strain but reductions in RV strain post-marathon</td>
<td></td>
</tr>
<tr>
<td>Knebel, 2009</td>
<td>Healthy Males</td>
<td>2DE Global Strain</td>
<td>Reduced LV strain following 3 hours of cycling</td>
<td></td>
</tr>
<tr>
<td>Vitiello, 2013</td>
<td>Male cyclists</td>
<td>2DE Longitudinal strain pre- and post-60 minutes of High intensity cycle</td>
<td>Reduced LV strain following 6 minutes of high intensity cycling</td>
<td></td>
</tr>
<tr>
<td>Stewart, 2015</td>
<td>3DE, 3-dimensional echocardiography; 2DE, 2-dimensional echocardiography; LV, Left ventricle; RV, Right ventricle.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.3: Summary of studies examining impact of lifelong endurance exercise on risk for cardiovascular disease and cardiovascular adaptations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range (years)</th>
<th>Population</th>
<th>Gender</th>
<th>Main Outcome</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnohr, 2015</td>
<td>20-93</td>
<td>1,098 joggers, 3950 non-joggers</td>
<td>Mixed</td>
<td>CVD risk, All-Cause Mortality</td>
<td>Moderate-light running reduced risk, no jogging and strenuous jogging highest risk</td>
</tr>
<tr>
<td>Mohlenkamp, 2008</td>
<td>50-72</td>
<td>108 lifetime marathoners</td>
<td>Males</td>
<td>Coronary Artery Calcification Scores</td>
<td>Increased coronary artery Calcification scores in marathoners</td>
</tr>
<tr>
<td>Breuckmann, 2009</td>
<td>50-72</td>
<td>102 lifetime marathoners</td>
<td>Males</td>
<td>Myocardial Fibrosis</td>
<td>High rate/prevalence of fibrosis in marathoners</td>
</tr>
<tr>
<td>Nassenstein, 2009</td>
<td>50-72</td>
<td>105 lifetime marathoners</td>
<td>Males</td>
<td>Cardiac mass and volumes, coronary artery calcification scores, Age and BP predict cardiac adaptations</td>
<td>Coronary artery calcification scores in marathoners related to number of cardiac risk factors and not # of marathons completed</td>
</tr>
<tr>
<td>Roberts, 2017</td>
<td>42-82</td>
<td>50 marathoners</td>
<td>Males</td>
<td>Coronary Artery Calcification Scores, Cardiac risk factors</td>
<td>Lower prevalence of coronary artery calcification scores in women than men; coronary artery calcification scores associated with older age, risk factors and # of marathons completed</td>
</tr>
<tr>
<td>Roberts, 2017</td>
<td>42-82</td>
<td>26 marathoners</td>
<td>Females</td>
<td>Coronary Artery Calcification Scores, Cardiac risk factors</td>
<td>Exercise induced blood pressure associated with increased prevalence of fibrosis; higher prevalence of fibrosis in male triathletes vs. female</td>
</tr>
<tr>
<td>Tahir, 2018</td>
<td>Mean age 43</td>
<td>46 triathletes</td>
<td>Mixed</td>
<td>Myocardial Fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

V. Central Hemodynamics: Arterial Stiffness, Wave Reflections

Although the exact mechanism behind the documented reductions in LV strain among endurance athletes is unknown central hemodynamics may provide insight into reasons for reductions in LV strain with endurance exercise.

Arterial Stiffness

Arterial stiffness refers to the material structural properties of the arterial wall and ultimately, influences the functional properties of the arterial wall as it affects blood pressure, blood flow and arterial diameter with each cardiac cycle [133]. Arterial stiffness can be measured in both peripheral muscular arteries and large/central elastic arteries. The elasticity of
the arteries depends on the properties of the arterial wall including elastin, collagen and smooth muscle. The peripheral muscular arteries (i.e. brachial) modulate vascular conductance (i.e. blood flow as it related to mean pressure) and have more smooth muscle content and collagen while the central elastic arteries contain more elastin [134, 135]. Large elastic arteries such as the aorta and the carotid arteries, modulate blood pressure and peripheral blood flow. These arteries passively transfer oxygenated blood from the heart to the peripheral arteries and tissues and actively buffer or dampen the hemodynamic impact of LV stroke volume that occurs with each heart contraction [136]. As can be seen in Figure 2.10, in a healthy elastic artery, as blood is ejected from the LV, the artery expands and contracts in response to blood flow and the blood travels slowly down the arterial tree.

**Figure 2.10: Healthy, Elastic Artery**

During LV contraction, the large arteries act to dampen the pulsatile output of the LV changing the flow from rhythmic to continuous [133]. Interestingly, during systole, some of the blood pumped out of the LV is also stored in the large arteries and thus, the aorta acts as a reservoir. In a healthy vessel during systole, only a percentage of the stroke volume from the LV is ejected to the periphery while the rest is stored in the aorta. This stored potential energy helps to push the blood to the periphery. The continuous flow of blood from the aorta occurs due to the healthy elastic properties of the large arteries. Therefore, the arteries respond to the hemodynamic impact of the
LV stroke volume by expanding and storing the blood and recoiling during diastole, propelling the remaining blood forward, providing energy to drive the continuous blood flow throughout the arterial tree to the peripheral organs and tissues.

With age and in the absence of disease, the large arteries stiffen \([34, 137]\). Hypertension, inflammation, metabolic alterations and other diseases can change the structure and function of the arteries by degrading the elastin content and promoting collagen content resulting in the acceleration of increased arterial stiffness \([135]\). Increased arterial stiffness predicts adverse CV events independent of traditional risk factors, thus consideration of arterial stiffness may be useful in identifying individuals at intermediate risk for CVD \([136, 138, 139]\). In stiffer arteries the stroke volume that is stored during systole decreases, the energy stored in diastole decreases, and consequently, diastolic pressure decreases and more stroke volume is ejected to the periphery \([140]\). Increased arterial stiffness leads to increases in systolic blood pressure, decreases in diastolic blood pressure and ultimately, increases in pulse pressure. Increases in arterial stiffness reduce the buffering capacity of the large arteries and are more likely to transfer this pulsatile flow downstream causing damage to the vessels in other organs \([141]\). As can be seen in Figure 2.11, in a stiffer artery that is less elastic, as blood is ejected from the LV, the artery does not expand and contract readily to blood flow and blood travels much faster down the arterial tree.

**Figure 2.11: Stiff, Inelastic Artery**
Wave Reflections

The relationship between LV and arterial stiffness is also influenced by wave reflections. As blood is ejected from the LV a blood pressure waveform is generated and is comprised of a forward and backward travelling wave [142]. Blood pressure is modulated by the elastic properties of the aorta/large arteries. When the blood pressure wave is generated by the LV a forward wave travels down the arterial tree. When this forward wave encounters various reflections sites, such as bifurcations or branches in the smaller arteries/vessels, areas of systemic vascular resistance or impedance (resistance to flow) the wave is reflected back towards the heart. This reflected wave is superimposed on the forward pressure wave and creates the blood pressure waveform that impacts cardiovascular function. The magnitude and speed of the reflected wave is dependent on the distance to the bifurcations, aortic stiffness and vasomotor function [143]. The timing and magnitude of these waves may ultimately impact cardiac function. Thus, wave reflections characterize the interaction between the heart and arterial load.

In healthy arteries, the forward pressure wave arrives towards the end of systole and then the superimposition of the backward and forward waves occurs during diastole. Thus, under optimal conditions the forward wave largely establishes systolic blood pressure, while the backward wave maintains or increases diastolic blood pressure [134]. In a healthy elastic artery, there is optimal continuous flow and no unnecessary increases in LV afterload or load at against which the ventricular contracts to eject blood. In stiffer arteries, the forward and backward waves travel faster along the arterial tree. Thus, increased arterial stiffness causes the backward wave to arrive in early systole, augmenting systolic pressure [134, 135]. This augmented pressure from wave reflections increases systolic pressure and subsequently, increases afterload. Additionally, there is less pressure arriving in diastole so there is a reduction in both diastolic pressure and the
pressure gradient driving coronary perfusion. Increased arterial stiffness may lead to increases in systolic blood pressure and decreases in diastolic blood pressure through increases in wave reflections. These alterations to the arterial load, increases LV afterload and myocardial work, leading to reductions in coronary perfusion, ultimately influencing the magnitude of LV function and structural remodeling.

**Arterial Stiffness, Wave Reflections and LV Structure and Function**

Adequate coupling between the left ventricle and the arterial system results in optimal transfer of blood from the LV to the periphery (optimal efficiency) without excessive changes in pressure [4]. Thus, increased arterial stiffness may negatively affect cardiac function through this relationship. Increases in arterial stiffness with age are coupled with an increase in ventricular stiffness most likely as a means to maintain the ventricular-vascular coupling. Although acutely this coupling may indicate enhanced contractility, chronically this adaptation can reflect structural adaptations in the myocardium which ultimately, reduce contractility [36]. Increased arterial stiffness and pressure due to wave reflections can increase LV systolic load, which may lead to ventricular remodeling and cardiac dysfunction.

LV remodeling may result in a dilated ventricle leading to an increase in myocardial oxygen demand [144] and consequently a reduction in diastolic coronary perfusion as systolic pressure increases and diastolic pressure decreases [36]. Increased arterial stiffness can lead to LV diastolic dysfunction, which increases cardiac filling pressure (preload) and limits coronary perfusion [145, 146]. LV remodeling and increases in LV mass can occur due to wall thickening in response to pressure overload or from chamber dilation due to volume overload. Therefore, ventricular enlargement may be due to increased arterial stiffness, which increases both myocardial oxygen demand and pressure load from the peripheral arteries (i.e. vascular
afterload). Lastly, increased arterial stiffness may also influence myocardial function [35]. In hypertensive individuals, increased arterial stiffness contributes to altered LV function manifested as a reduction in LV strain (150). Increased arterial stiffness coupled with increases in wave reflections may potentiate the development of LV dysfunction and ultimately LV hypertrophy.

**VI. Arterial Stiffness, Wave Reflections, and Endurance Exercise**

Generally, endurance exercise reduces arterial stiffness and pressure from wave reflections [147-152]. Endurance athletes generally exhibit lower arterial stiffness and wave reflections compared to their sedentary or recreationally active counterparts [153, 154]. However, some studies suggest that strenuous long-term endurance exercise training and acute endurance exercise may increase arterial stiffness and wave reflections [41, 148, 153] [40].

Recent cross-sectional studies have observed higher arterial stiffness in marathon [40], and ultra-marathon [41] runners, suggesting that repetitive high intensity exercise may lead to increased arterial stiffness [95, 155-157]. Vlachopoulos et al. examined 49 endurance trained men and found that marathoners had increased arterial stiffness and blood pressure but similar wave reflections when compared to sedentary controls [40]. More importantly, in this study exercise volume was a predictor of increased arterial stiffness in marathon runners who trained for over 11 years. In another study, Burr et al. studied 18 veteran ultra-marathon runners and found that the ultra-runners had increased arterial stiffness compared to age-matched untrained controls [41]. These studies suggest that high volumes of strenuous endurance exercise may lead to increased arterial stiffness in relatively healthy adults.

In contrast, additional cross-sectional studies note no differences in arterial stiffness [148] or lower stiffness [158] in marathon runners compared to controls. Nualnim et al. showed a
lower arterial stiffness in runners and swimmers compared to sedentary controls [148]. Similarly, Radtke et al. examined arterial stiffness in 51 non-elite middle-aged male marathons, ultramarathon runners and controls and found that there were no differences between the three groups. Thus, they concluded that strenuous endurance exercise did not have a negative impact on indices of arterial stiffness; however, their recreationally active controls performed the same volume of exercise per week as the marathon runners and had previously run marathons. Thus, the recreationally active group may not have been a true control group, which leaves the conclusions of this study questionable. Furthermore, the studies that found lower arterial stiffness in endurance athletes did not examine veteran athletes who have years of training/racing experience.

In addition to cross-sectional studies, acute exercise studies in men demonstrate that following acute strenuous prolonged exercise (i.e. marathon race, ultra-race) runners have increased arterial stiffness with no change in wave reflections [40, 41, 159]. For instance, Burr et al. suggest that arterial stiffness is transiently increased following an ultra-marathon race while Muller et al. showed that arterial stiffness is increased during an acute bout of strenuous aerobic exercise [41, 159]. These studies undermine the question of whether these acute increases in arterial stiffness due to strenuous endurance exercise sessions may lead to chronic increased arterial stiffness. This hypothesis might be more readily examined in individuals who engage in repeated bouts of strenuous endurance exercise over years of training.

Traditionally, regular aerobic exercise induces repetitive bouts of augmented blood flow that may modulate decreases in arterial stiffness that is observed with most exercise training [160]. Contrastingly, prolonged habitual vigorous exercise such as marathon running may increase arterial stiffness over time by increasing inflammation [161], increasing catecholamines,
producing excessive oxidative stress and vasoconstrictor substances [162]. Additionally, increased arterial stiffness resulting from high intensity endurance training may be due to reductions in vasodilator capacity [162-165]. Based on these mechanisms and in accordance with conclusions made by several epidemiological studies on physical activity levels and risk for CVD, habitual strenuous exercise such as marathon running may result in a U-shaped curve with arterial stiffness; no exercise leads to high arterial stiffness while some exercise is associated with the low arterial stiffness and high/excessive amounts of endurance exercise is associated with high arterial stiffness and comparable levels to those who do not exercise.

Future studies are warranted to examine whether excessive endurance exercise may lead to increased arterial stiffness and wave reflections in endurance-trained athletes. The current disparities in studies investigating arterial stiffness in endurance athletes may be due to the study of only male athletes, inclusion of athletes from different training modalities/histories, and a lack of consistent control group (active vs. sedentary). Future studies should follow these considerations to help determine the effect of lifelong endurance exercise on central hemodynamics.

**VII. Sex Differences in LV Structure, LV Function and Central Hemodynamics**

*Origins of sex differences in cardiovascular physiology*

There are notable sex differences in risk for CVD throughout the lifespan. Sex differences in risk for CVD primarily stem from the influence of menstrual cycle hormones on female cardiovascular physiology. Increased age in women is accompanied by reductions in estrogen concentrations. Indeed, after menopause the risk for CVD is greater in women than in men. The role of estrogen in cardiac physiology remains to be examined, as it is known that cardiac myocytes have functional estrogen receptors such that estrogen may attenuate cardiac
hypertrophy [17]. Estrogen has been implicated in the slowed progression of heart failure and may also be protective in the development of LVH. Additionally, estrogen receptors are located on the vascular wall and estrogen is a potent vasodilator. Arterial stiffness is modulated by estrogen concentrations, as low estrogen levels in post-menopausal women are associated with increases in arterial stiffness [166]. Thus, the disparity in risk for CVD between men and women may be partially explained by consequential sex differences in cardiac and arterial function and structure.

*Sex differences in LV Structural Adaptations to Endurance Exercise*

There are profound sex differences in ventricular adaptations to endurance exercise. Ventricular adaptations to endurance exercise are less pronounced in women compared to men [17-24]. Cross sectional studies reveal that female athletes display smaller LV mass and volumes compared to male athletes [21] even after adjusting for body size and lean body mass [22, 25, 26]. Pelliccia et al. reported 2DE characteristics of 600 Olympic female athletes by sport to determine the normal structural LV adaptations in female athletes. Additionally, this study compared the 600 female athletes to 738 elite male athletes of similar age, ethnicity, intensity of training and competition, and level of achievement. LVM was significantly higher in male athletes compared to female athletes. Interestingly, LVM was still 31% lower in female athletes (80 g/m²) compared to male athletes (105 g/m²) indexed for body surface area [19]. George et al. examined 10 university female endurance athletes and found that mean LVM expressed to fat free mass to be significantly lower than male athletes [18]. However, Morales et al. found no significant sex differences in LVM in training-matched distance runners when expressed for FFM or BSA [24] while Rowland et al. found that when training volume, body size and
composition are considered male endurance athletes have greater cardiac dimensions and mass compared to their female counterparts [22].

Additional cross sectional studies compared LVM in male and female cross-country skiers and distance runners and found a 25% greater relative LVM in trained males compared to trained females but found no difference between untrained males and females [18]. In long distance runners, Mumford et al. observed not only a 34% greater relative LVM in trained males compared to trained females but also reported 20% greater LVM in untrained males compared to untrained females [20]. Similarly, Smith et al. examined sex differences in LVM in highly trained athletes and normally active individuals LVM in trained males was higher compared to trained female athletes and reported a similar magnitude of difference between LVM in untrained males and females. These studies suggest that there are physiological sex differences in untrained individuals and sex differences in training adaptations.

Longitudinal studies suggest that sex differences may not be solely due to inherent biological differences but also due to difference in the response to endurance exercise training [17, 20, 167]. These studies report significant sex differences in LV adaptations to endurance training [17]. Recently, Arbab-Zadeh et al. demonstrated that sedentary individuals who underwent 1 year of intensive endurance training had increases in cardiac mass to levels similar to that observed in elite endurance athletes [168]. In a second study, researchers examined whether males or females experienced similar cardiovascular adaptations to 1 year of endurance training when matched for volume and intensity. Twelve previously sedentary males and females underwent an intensive endurance-training program for 1 year. Both females and males experienced significant increases in LVM but males had a greater increase in LVM compared to females. The results of the study indicated that males had a more pronounced LV hypertrophy
adaptation throughout the 1-year program while females reached the maximal LVM after 3 months of training. This data indicates clear sex differences in the cardiac response to endurance training even when males and females were subjected to the same training stimulus and volume [17]. Contrastingly, previous studies have observed no significant differences in the cardiovascular response in males and females to 90 days of intense endurance training [169], which is a much shorter training duration than 1 year. Sex differences may only be apparent in response to long-term training. Future studies need to examine sex differences in response life-long endurance-training men and women. However, before a longitudinal study is completed cross sectional studies are necessary to determine possible reasons for the sex differences in LV adaptations. Sex differences in structural cardiac adaptations to endurance training may be related to sex differences in LV function.

**Sex Differences in LV Function in Response to Endurance Exercise**

There is limited data regarding sex differences in LV function/strain in endurance athletes. Nonetheless there are a few studies that examine LV function in response to acute endurance exercise. A study by Scott et al. found sex differences in LV function in amateur triathletes following a half-ironman triathlon race performed at 80% of their maximum heart rate. This study examined 9 males triathletes and 8 female triathletes who had 2 years of training experience. The main findings of this study suggest that LV function decreased to a greater extent in males compared to females following prolonged exercise [170]. Similarly, Cote et al. performed an additional study that examined ventricular strain in endurance-trained and normally active males (11 males) and females (9 females) following high-intensity bout of cycling exercise of approximately 45 minutes of exercise. This study found that men had significantly reduced strain following a bout of high intensity cycling compared to females [171].
MacGavock et al. examined LV function at rest and in response to prolonged strenuous exercise in female triathletes. Participants performed a 40km cycling time trial followed by a 10km run at approximately 90% of their maximum heart rate. Contrary to the hypothesis that prolonged exercise would elicit a reduction in LV function, this study found an enhanced LV function following 2 hours of strenuous exercise in female triathletes [172]. These studies suggest there might be sex differences in cardiac function in response to acute strenuous endurance exercise.

In contrast, Cote et al. found that women and men had similar exercise induced LV dysfunction following an ultra-marathon race. This study used 2DE to examine 34 athletes (21 males, 13 females) with an average of 14 lifetime ultra-marathons each over an average of a 5-year period had their LV function and structure measured before and after an ultra-endurance race [173]. Sex differences in acute LV dysfunction following prolonged endurance exercise may become chronic sex differences LV function as endurance athletes engage in daily exercise sessions and compete in multiple endurance events. There are limited studies that examine sex differences in LV function in endurance-trained athletes and the current studies available use different methodologies (TDI, 2DE, vs. 3DE) making it difficult to compare results. Future studies need to examine sex differences in LV function and how it relates to LV structure to determine whether sex differences in LV function might explain sex differences in LV structure. The underlying mechanisms and reasons for sex differences in LV structural adaptations to endurance exercise are unknown, however numerous factors may be at play.

**Possible Mechanisms for Sex differences in LV Structural Adaptations to Endurance Exercise**

Current potential mechanisms that might help to explain sex differences in LV adaptations with endurance exercise might be differences in sympathetic nervous system function [170, 171] and androgenous hormones. Women have a greater parasympathetic
predominance both at rest and in response to exercise while men have a greater sympathetic activation [170, 171]. Increased sympathetic activation is associated with increased myocardial contractility, subsequently leading to higher SV and cardiac output and thus, larger LVM. Increased sympathetic activity in males may explain sex differences in LV adaptations with exercise. Studies suggest that the relationship between muscle sympathetic nerve activity (MSNA) and wave reflections is dependent on sex [174] [175]. Increased MSNA is associated with increased wave reflections in men, however increased MSNA is associated with a decrease in wave reflections in women [174, 175]. Thus, the sympathetic beta-adrenergic receptor activity in women may be unregulated or more sensitive than that in men [174, 175]. In addition, the role of estrogen in cardiac physiology remains to be examined, as it is known that cardiac myocytes have functional estrogen receptors such that estrogen may modulate cardiac hypertrophy. High estrogen concentrations may also be associated with slower progression of heart failure. High estrogen concentrations in pre-menopausal women may give insight into why females may have attenuated cardiac structural hypertrophy compared to males in response to endurance training. More importantly, considering the influence of estrogen on the vasculature, sex differences in arterial stiffness and wave reflections may also provide a novel insight into differential LV remodeling in endurance athletes.

**Sex differences in Central Hemodynamics at Rest**

Numerous studies have noted sex differences in resting arterial stiffness and wave reflections [31-33]. Men are reported to have higher arterial stiffness when compared to premenopausal women until the age of 60 years when women enter menopause and subsequently, have higher arterial stiffness compared to men [45]. Interestingly, the association between arterial stiffness, wave reflections and LV mass is greater in women than in men [146].
Women have a larger reflected wave magnitude than men, which may be due to a smaller stature and shorter height of women. Such biological characteristics are associated with a reduced distance between the heart and the peripheral reflecting sites [34] and greater taper of the arteries between the aorta and the periphery [46]. However, one study examined prepubescent children and showed that girls had significantly higher augmentation index even when compared to boys of the same age and height [176]. Thus, body height may not account for all sex differences in wave reflections [176]. Given that women have greater wave reflections compared to men and there are known differences in arterial stiffness, sex differences in central hemodynamic load may influence LV afterload, function and structural remodeling [47, 48, 176].

**Sex differences in central hemodynamics in response to acute exercise**

In addition to sex differences in central hemodynamics at rest there are also sex differences in central hemodynamics in response to acute exercise. Studies in men suggest that strenuous high intensity exercise may lead to increased arterial stiffness with no change in wave reflections [40, 41]. Conversely, women experience reductions in large artery stiffness and wave reflections following acute high intensity/high volume exercise [34, 42-48]. Few studies have examined sex differences in central hemodynamic load in response to prolonged exercise. Nieman et al. examined arterial stiffness in 16 runners (8 males, 8 females) before and after a 2-hour intense run on a treadmill. This study noted a significant decrease in arterial stiffness, blood pressure and augmentation index following the prolonged run in females but noted no change in arterial stiffness and augmentation index and a significant increase in blood pressure following the 2-hour run in males. Thus this study concluded that there seems to be a sex difference in the recovery pattern of central hemodynamics following prolonged exercise [43]. However, this study had a small sample size and did not measure cardiac mass or function to determine whether
the relationship between central hemodynamics, LV mass and function in endurance-trained individuals explains the sex difference in LV adaptation to endurance exercise.

Cote et al. found similar exercise induced cardiac fatigue in men and women following an ultra-marathon but interestingly found that individuals with lower baseline arterial stiffness had less cardiac fatigue following the ultra-marathon race. This novel finding suggests there is a relationship between arterial stiffness and altered ventricular function. The relationship between ventricular function and arterial function is well recognized and a central determinant of cardiovascular performance and function [177]. This novel finding suggests there may be a relationship between arterial stiffness and altered ventricular function.

Additionally, differences in resting and exercise blood pressure might explain sex differences in LV mass in endurance athletes. Women are reported to have lower resting blood pressure and peak exercise blood pressure compared to men [42, 178, 179]. There is a well-established relationship between LVM, LVH and resting and exercise brachial blood pressure. Studies suggest that even in the absence of hypertension exaggerated blood pressure during exercise is related to an increased prevalence of LVH [180-182]. Thus, a greater blood pressure during exercise could be a reflection of similar blood pressure responses throughout the day to various physical and emotional stimuli [183].

The differential central hemodynamics at rest, during and in response to acute strenuous endurance exercise likely suggests day-to-day variation in central hemodynamic load that may differ by sex. The day-to-day variation may subsequently lead to different cumulative central hemodynamic load, which may likely influence LV structural adaptations. This is important because endurance athletes train daily for years and complete numerous endurance races thus, are repeatedly exposed to this underlying central hemodynamic load. Thus, sex differences in 24-
hour (daily) cumulative hemodynamic load may explain sex differences in LV adaptations to endurance training.

**Sex Differences in Central Hemodynamic Load/Central Hemodynamic load in athletes**

Central hemodynamic load is defined as the cumulative effects of arterial load overtime: arterial stiffness, blood pressure and wave reflections. Central hemodynamic load may mediate LV remodeling and subsequently explain magnitude of LV function and structural remodeling in endurance athletes. Considering the hemodynamic principles and the diurnal variability in blood pressure [184, 185] and hemodynamics examination of 24-hour central hemodynamic load may provide a mechanism for LV adaptation.

Studies have examined the association of increased blood pressure and incidence of hypertension and end target organ damage [186-189]. Although the traditional oscillatory blood pressure that is taken in clinical practice has been utilized for decades, this measurement only provides a single point measurement that is typically taken under conditions that influence blood pressure. A single clinical measurement of brachial systolic blood pressure and diastolic blood pressure alone provides only indirect information about the adequacy of tissue and organ perfusion. In order to overcome the limitations of office visit blood pressure, techniques to obtain automated blood pressure over a 24-hour period have been developed. In fact, underlying blood pressure in hypertensive individuals cannot be confirmed without an out of clinic blood pressure measurement such as a 24-hour ambulatory blood pressure [190]. Measurement of chronic hemodynamic load can thus, be achieved via 24-hour ambulatory monitoring device.

Only one known study has examined 24-hour blood pressure in male and female athletes to directly explore the sex differences in LV mass with exercise training [42]. Zemva et al. examined 24-hour brachial blood pressure in male and female dancers to determine whether
there are sex differences in 24-hour blood pressure that may give insight into apparent sex differences in LV mass with exercise training. This study chose to assess dancers in their study since dance partners presumably are exposed to the same training stimulus. This study found significant differences in LVM, resting and 24-hour blood pressure between male and female dancers [42]. Female dancers had a lower LVM, which was related to a lower peak exercise blood pressure, resting blood pressure and 24 hour blood pressure compared to male dancers. Thus, lower LVM in female dancers could be partially explained by lower 24-hour systolic blood pressure. However, this study did not examine endurance athletes and only reported measures of 24-hour brachial blood pressure and did not examine resting or 24-hour central blood pressure, arterial stiffness or wave reflections, which may provide more insight into sex differences in LV mass.

It is well established that systolic blood pressure and pulse pressure are higher in the peripheral arteries compared to the central arteries. This “amplification” of pressure is largely due to the progressive decrease in arterial diameter and increase in arterial stiffness down the arterial tree [134, 135]. Thus, central pressures are more important than brachial/peripheral pressures in determining risk for CVD [135]. After all, it is central systolic pressure that the heart ejects against (afterload) and it is central pulse pressure that expands the arteries. Central systolic blood pressure and pulse pressure are highly associated with LVH, hypertension and end target organ damage in multiple populations [191, 192]. Indeed, studies show that central pressures are better predictors of cardiovascular outcomes than peripheral/brachial pressures [193]. For these reasons measurements of central pressures are advantageous.

Therefore, to further our understanding of the central hemodynamics of the circulation, efforts over the last several decades have sought to noninvasively assess central blood pressure.
Analysis of the arterial waveform allows researchers to dissect out the relative contributions of LV ejection and wave reflection, and to discern the longitudinal effects of these interactions on the myocardium. Thus, the development of non-invasive 24-h central hemodynamic load provides insight into the structure and function of the LV weber [194]. Sex differences in resting central hemodynamics, and the hemodynamic response to acute exercise may lead to chronic hemodynamic differences that may lead to differential LV afterload and ultimately modulate LV function and structural remodeling in endurance athletes.

**VIII. Proposed Study**

The purpose of the proposed study is to examine sex differences in 1) LV structure, 2) LV function, and 3) 24-central hemodynamic load in endurance athletes and recreationally active controls.

It is hypothesized that endurance-trained women will have lower LV mass (adjusted for body surface area and body composition) compared to endurance-trained men and higher LV mass compared to recreationally active women. Endurance-trained men will have higher LV mass compared to recreationally active men. Further we hypothesize that endurance-trained women will have higher function (i.e. higher strain) compared to endurance-trained men and recreationally active women. Endurance-trained men will have similar LV function compared to recreationally active men. Lastly, we believe that endurance-trained women will have a lower 24-hour central hemodynamic load (blood pressure, arterial stiffness, and pressure from wave reflections) at rest and following exercise compared to endurance-trained men and recreationally active women and endurance-trained men will have a similar 24-hour central hemodynamic load to recreationally active (Figure 10).
Figure 2.12: Theoretical Framework

Significance

CVD is the leading cause of morbidity and mortality in women in the United States [195]. With increasing age, risk for CVD in women exceeds that in men [196]. It is expected that by 2020 approximately 20% of the population of the United States will be 65 years or older [197]. In order to improve cardiovascular health, it is essential that implement strategies of *early prevention in midlife, targeting at risk populations, such as women, is critical*. As women age, they experience greater increases in artery stiffness and wave reflections which contributes to reduced LV function and LV mass and ultimately increased incidence of heart failure.
Aerobic exercise is a well-established and effective lifestyle strategy to attenuate risk for CVD in women [198-200]. Over the past 30 years there has been a steady increase in the number of women racing competitive endurance events such as marathons. However, there is little research examining the effects of this chronic strenuous endurance exercise training on cardiovascular health in women. Recent research in men suggests the potential for adverse ventricular remodeling and myocardial fibrosis, which may lead to cardiac arrhythmias and sudden cardiac death [27-29]. However, there is evidence to suggest that women may actually be cardio-protected from this type of strenuous exercise. Pre-menopausal women are reported to have attenuated ventricular remodeling in response to strenuous endurance training even when women are subjected to the same training duration and stimulus as men [17]. Thus, pre-menopausal women may never approach pathological thresholds of ventricular remodeling. As such, there may be a level of cardio-protection afforded by female sex with regards to potentially adverse LV functional and structural adaptations to endurance exercise, but this has yet to be explored.

Despite increased female participation in competitive endurance events, minimal advances have been made beyond these findings to examine the cardiovascular adaptations to prolonged endurance exercise in women. Future studies are necessary to discern the hypothesis that excessive endurance exercise may lead to fibrosis and premature death. The public impact of this hypothesis that high intensity-high volume exercise might promote pathologic adaptations is substantial for both athletes and patients with CVD [89]. This is even more relevant considering the recent evidence that was presented suggesting that small amounts of exercise may be more than ideal in preventing the development of CVD [85]. Our understanding of exercise-induced LV remodeling has advanced tremendously in the past decade due to developments in
technology and cardiac imaging. However, our understanding of how extreme exercise modalities, such as marathon running, positively or negatively affect risk for CVD is still unclear.

**Innovation**

This study will examine whether sex differences in central hemodynamic load are related to sex-specific ventricular functional and structural adaptations in endurance athletes. More importantly, the results of the current study will provide information on cardiac adaptations in not only endurance-trained men but also endurance-trained women.

First, the proposed study is novel in how we propose to measure LV structure and function. Sex differences in LV morphology may be confounded by scalar variables such as body size. Smaller body size is associated with smaller LVM while larger body size is associated with larger LVM and volume. As such, cardiac metrics are often expressed relative to body surface area (BSA). Typically, heart size measures (LV mass) adjust for BSA indirectly using 2D BSA. Currently, most clinicians use an equation to indirectly measure BSA, which was adopted in 1916 (Dubois and Dubois, 1916). However, these conventional 2D BSA methods often underestimate BSA, as they cannot depict the 3D nature of the body. The 3D body scanner is a novel method that is able to examine body contour and definition resulting in more accurate BSA measurements compared to 2D methodology. 3D BSA is able to measure cross-sectional area and slice area in addition to surface area. Also, 3D BSA measurements allows for rotation of the 3D image so the entire anatomic surface area can be fully captured. In the proposed study, we will directly measure BSA using a novel 3D body scanner and adjust our LVM measures for 3D BSA.
We will also measure LV function using 3D STE, which is novel technology to assess both regional and global LV strain in endurance athletes. As previously outlined in Table 1 in Chapter 2, there are many limitations to assessing LV function using conventional TDI and 2DE techniques that are overcome by using 3DE. Similar to the benefits of using 3DE to measure LV structure, using 3DE to measure LV function allows for a more sensitive, comprehensive picture of myocardial function. 3DE STE can simultaneously provide strain values in three planes of motion, which may mitigate the effect of beat-to-beat variation in LV contraction on strain values. Only a few studies have utilized the capabilities of the 3DE STE to examine cardiac structure and function in athletes and no study has directly examined both LV function and structure in both male and female endurance-trained athletes.

In our study, we will recruit a healthy recreationally active control group rather than an sedentary control group. Studies that utilize a sedentary control group are assuming that sedentary individuals are healthy controls. The U.S Centers of Disease Control (CDC) have identified that physical inactivity or sedentary behavior may be an “actual” cause of chronic disease [201]. Recreationally active individuals are much healthier than sedentary individuals. A sedentary lifestyle is not a healthy lifestyle and is extensively associated with Alzheimer’s Disease, Cancer, atherosclerosis, obesity, osteoporosis, Type 2 Diabetes, and sarcopenia [202]. Moreover, as it pertains to the proposed study, sedentary behavior is associated with increased arterial stiffness, augmentation index, intima media wall thickness (IMT), and thus, subclinical atherosclerosis [203, 204]. Therefore, if a sedentary group is used as a control group in exercise-related studies it may perpetuate misinterpretation of results such that sedentary group is healthy when in reality this group is more than likely not a healthy population. It is for these reasons that
we propose to recruit recreationally active adults rather than sedentary adults for our control group.

Additionally, we will use a validated oscillometric 24h ambulatory device to monitor central hemodynamic load in endurance trained women and men. This device assesses not only 24-hour peripheral/brachial blood pressure but also central blood pressure, together with estimations of pressure from wave reflections and aortic stiffness. Only study has examined chronic hemodynamic load in endurance trained men and women and of those studies, brachial blood pressure was used as the measure of hemodynamic load [42]. However, as previously discussed brachial pressure is noted to be a poor surrogate for cardiovascular disease risk and central hemodynamic load experienced by the LV. Central blood pressure is more predictive of LV mass, cardiac events and prognosis [205, 206]. Additionally, consequences of increased arterial stiffness and wave reflections on CV mortality are well established [207]. This approach will allow us to directly determine whether day-to-day hemodynamic load is associated with the sex-specific adaptations in ventricular function and remodeling in endurance-trained athletes.
Chapter III: Preliminary and Feasibility Data

**Preliminary and Feasibility Data.** The student principal investigator has extensive experience with the vascular measures and research methodology required in the proposed study and has personally collected all feasibility/preliminary data presented below. The PI has been involved in research in the Human Performance Laboratory throughout her MS/PhD and is familiar with physiological measures described in the methodology and preliminary data section. The PI has collected data on over 400 participants (9-89 years old) in the Human Performance Laboratory in the past 7 years.

**Preliminary research of Principal Investigator**

Primarily my research has focused on the influence of sex on vascular adaptations to endurance and resistance exercise and how differential responses to exercise may explain sex differences in risk for cardiovascular disease. The previous work of the PI is discussed below as it relates to the current proposal.

**Sex differences in responses to exercise and other physiological stimuli**

Recently in two separate studies, the student PI examined how chronic high intensity endurance exercise in women might influence risk for atherosclerosis in amenorrheic (i.e. hypoestrogenic) women [208] and how being physically fit and centrally obese might modulate risk for cardiovascular disease in women [209]. We found that endurance trained women (n=28) who engaged in chronic strenuous endurance exercise had lower arterial stiffness (PWV, p<0.05) and wave reflections (AIx, p<0.05) compared to their sedentary counterparts (n=15) [208] (Table 1). These findings indicated that amenorrheic women have reduced vascular function but no structural abnormalities. Thus, they may not have increased risk for CVD. Measures of LV afterload and coronary perfusion were also measured. LV wasted pressure effort (LVWPE) is a
measure of LV afterload due to wave reflections and is associated with LV remodeling and hypertrophy [210]. Diastolic pressure time integral (DPTI) is an estimate of oxygen supply while systolic pressure time integral (SPTI) is a measure of LV work or oxygen demand [210]. The ratio of oxygen supply/demand is the sub-endocardial viability ratio (SEVR) [210]. We found that endurance-trained women had lower LV afterload (p<0.05) as indicated by a lower SPTI and LVWPE and greater coronary/myocardial perfusion as indicated by a higher SEVR and DPTI than the sedentary controls (p<0.05). Thus, the endurance-trained women displayed no mismatch between oxygen demand and supply suggesting the potential for attenuated ventricular remodeling (Table 1). *These results differ from previous studies in men* that suggest endurance-trained men may have higher or similar level of arterial stiffness and wave reflections, and substantial LV remodeling compared to sedentary counterparts [40].

**Table 3.1: Sex differences in cardiac mechanics**

<table>
<thead>
<tr>
<th></th>
<th>Endurance-trained (n=28)</th>
<th>Sedentary (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>21 ± 3</td>
<td>23 ± 4</td>
<td>0.26</td>
</tr>
<tr>
<td>Augmentation Index (Heart rate, 75 %)</td>
<td>3.7 ± 10.6</td>
<td>6.6 ± 10.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Pulse Wave Velocity (m/s)</td>
<td>4.81 ± 0.71</td>
<td>5.40 ± 0.80</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic pressure time integral (SPTI, aU)</td>
<td>1679 ± 374</td>
<td>2051 ± 259</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic pressure time integral (DPTI, aU)</td>
<td>3341 ± 340</td>
<td>3091 ± 211</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Sub-endocardial Viability Ratio (SEVR, aU)</td>
<td>210 ± 56</td>
<td>153 ± 26</td>
<td>0.02</td>
</tr>
<tr>
<td>LV Wasted Pressure Effort (WPE, aU)</td>
<td>582 ± 1062</td>
<td>1054 ± 1122</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

*Significantly different from Endurance-trained women, p<0.05

Additionally, the student PI performed an independent study to examine whether the menstrual cycle influences the vascular response to resistance exercise. This study found that the response to resistance exercise did not differ between menstrual cycle phases and thus estrogen may not modulate vascular responses to resistance exercise in women. In this study, we used the proposed ambulatory brachial oscillometric device (Mobil-o-graph) and applanation tonometry
(gold standard) to measure central hemodynamics both during a rest period and immediately following moderate intensity resistance exercise in 18 young healthy women (28±7 years). Moreover, the results of this study allowed us to compare the PWV values estimated from the Mobil-o-graph to the gold standard measure of PWV using applanation tonometry. Using Bland-Altman analysis, arterial stiffness (pulse wave velocity, PWV) values using the mobil-o-graph device were in good agreement with the gold standard measure of PWV using applanation tonometry at rest (Fig.1) and immediately following intense exercise (Figure. 1 and Figure 2) [211].

Figure 3.1: Mobil-o-graph PWV vs. SphygmoCor PWV at rest
Figure 3.2: Mobil-o-graph PWV vs. SphygmoCor PWV post-exercise

Sex differences in Cerebrovascular, Cognitive function and Exercise in Older Adults

Our laboratory also has a unique interest in how systemic vascular function and exercise may influence cerebrovascular function and thus cognitive function. We have the capabilities to examine brain blood flow as we show in a study that examined the acute effects of resistance exercise on cerebral blood flow. We found that even though resistance exercise increases cerebral artery stiffness it does not negatively impact cerebral blood flow [212]. Recently, our laboratory has developed a technique to examine neuro-vascular coupling, which allows us to
determine the matching of vascular supply to neuronal demand during a mental stress or cognitive engagement task. Increases in arterial stiffness may negatively impact neuro-vascular coupling and thus impair cognitive function and performance. This becomes an especially interesting model to apply to populations that may have increased arterial stiffness due to aging or varying disease states. Our lab has examined this model in older adults.

Sex differences may exist in neurovascular coupling and stimuli such a mental stress may give us insight into these physiological differences. Mental stress is known to increase blood pressure and arterial stiffness. In response to perturbations of mental stress, women have blunted increases in blood pressure compared to men. These differences are noted in brachial blood pressure and primarily premenopausal women. Thus, our lab examined whether these sex differences exist in postmenopausal women and older adults. We found that mental stress did not elicit differential cardiovascular responses in postmenopausal women and men. This finding is similar to observed sex differences in cardiovascular parameters with endurance exercise. In response to mental stress and endurance exercise training, premenopausal women appear to have a smaller magnitude of increase in blood pressure, arterial stiffness and cardiac remodeling compared to endurance-trained men (Table 2, 4).

Table 3.2: Sex differences in Hemodynamics in Older Adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males (n=51)</th>
<th>Females (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 6</td>
<td>67 ± 6</td>
<td>0.80</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>128 ± 14</td>
<td>124 ± 11</td>
<td>0.05*</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>80 ± 6</td>
<td>77 ± 6</td>
<td>0.89</td>
</tr>
<tr>
<td>Pulse Wave Velocity (m/s)</td>
<td>9.4 ± 2.5</td>
<td>9.9 ± 2.5</td>
<td>0.52</td>
</tr>
<tr>
<td>Augmentation Index (%)</td>
<td>34 ±14</td>
<td>30.6 ± 9</td>
<td>0.024*</td>
</tr>
</tbody>
</table>

*indicates significant difference at p<0.05

Sex Differences in Cardiovascular Parameters in Children ages 9-12 years old
The P.I. has also collected data on over 150 children ages 9-12 years old as a part of a larger grant examining the effect of lead exposure on cardiovascular and psychological parameters in young children. In examination of the current data even at a young age there are significant sex differences in cardiovascular parameters. Boys have a significantly higher pulse wave velocity, aortic systolic blood pressure, pulse pressure and LVM index compared to girls (Table 3). Previous studies have attributed these differences to a taller stature and bigger body surface area in boys than in girls, however, even when adjusting for body surface area in children (LVM-index) we observe significantly higher LVM in boys compared to women.

Table 3.4: Sex differences in Children Ages 9-12 years old

<table>
<thead>
<tr>
<th>Variable</th>
<th>Boys (n=82)</th>
<th>Girls (n=57)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Wave Velocity (m/s)</td>
<td>4.7 ± 0.1</td>
<td>4.4 ± 0.1</td>
<td>0.03*</td>
</tr>
<tr>
<td>Aortic Systolic Blood Pressure (mmHg)</td>
<td>96 ± 1</td>
<td>98 ± 1.0</td>
<td>0.03*</td>
</tr>
<tr>
<td>Aortic Diastolic Blood Pressure (mmHg)</td>
<td>69 ± 1</td>
<td>69 ± 1.0</td>
<td>0.67</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>20 ± 1</td>
<td>20 ± 1.0</td>
<td>0.29</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.4 ± 0.0</td>
<td>0.4 ± 0.0</td>
<td>0.92</td>
</tr>
<tr>
<td>Pulse Pressure (mmHg)</td>
<td>27 ± 1.0</td>
<td>30 ± 1.0</td>
<td>0.04*</td>
</tr>
<tr>
<td>Augmentation Index (%)</td>
<td>6.8 ± 1</td>
<td>5.9 ± 1</td>
<td>0.66</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>93 ± 3</td>
<td>85 ± 3</td>
<td>0.06</td>
</tr>
<tr>
<td>LVM-Index (g/kg)</td>
<td>70 ± 1</td>
<td>63 ± 2</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*indicates significant difference at p<0.05

Sex differences in aortic stiffness following acute resistance exercise

There are established sex differences in vascular structure and function and neurovascular blood pressure (BP) regulation at rest and in response to various stressors. Below is a summary of a recently published study by the P.I. that is a secondary analysis of two previously published studies that both used the same methods and study design. Briefly, 27 young healthy adults...
between the ages of 18-35 participated in these studies ($n = 13$ female). The purpose of this study is to examine sex differences in aortic stiffness and central BP in response to acute RE. We hypothesized that women would have an attenuated increase in aortic stiffness and central BP in response to acute RE. Significant group-by-time interactions were detected for heart rate, brachial and central pressures, and aPWV (table 2, $p<0.05$). Compared to men, women had an attenuated hemodynamic response (lessened increases in HR and BP) to acute RE. There are sex differences in changes in aortic stiffness following acute RE that appear to be pressure mediated. Women have an attenuated increase in aortic stiffness following acute RE relating to attenuated central hemodynamic reactivity. Underlying sex differences in muscular strength may affect the pressor response to the exercise bout, mediating functional changes in aortic stiffness.

Figure 3.5: Sex differences in Hemodynamic Response to RE
Table 3.5: Sex differences in Hemodynamic Response to RE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males (n=14)</th>
<th>Females (n=13)</th>
<th>Time Effect</th>
<th>Group Effect</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brachial SBP (mmHg)</strong></td>
<td></td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline</td>
<td>120±10*^</td>
<td>111±9</td>
<td>0.00</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>P10</td>
<td>145±19*^</td>
<td>115±11</td>
<td>0.66</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>P20</td>
<td>132±11*^</td>
<td>114±11</td>
<td>0.17</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Brachial DBP (mmHg)</strong></td>
<td></td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td>Baseline</td>
<td>68±6</td>
<td>68±7</td>
<td>0.17</td>
<td>0.32</td>
<td>0.06</td>
</tr>
<tr>
<td>P10</td>
<td>74±7*^</td>
<td>63±8</td>
<td>0.22</td>
<td>0.13</td>
<td>0.24</td>
</tr>
<tr>
<td>P20</td>
<td>66±5</td>
<td>64±8</td>
<td>0.00</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Brachial PP (mmHg)</strong></td>
<td></td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline</td>
<td>52±6*^</td>
<td>45±9</td>
<td>0.00</td>
<td>0.15</td>
<td>0.53</td>
</tr>
<tr>
<td>P10</td>
<td>72±17*^</td>
<td>52±10*</td>
<td>0.31</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>P20</td>
<td>67±9*^</td>
<td>50±11*</td>
<td>0.22</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Mean Arterial Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92±7</td>
<td>88±7</td>
<td>0.12</td>
<td>0.81</td>
<td>0.05</td>
</tr>
<tr>
<td>P10</td>
<td>106±11*^</td>
<td>87±8</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>P20</td>
<td>96±7</td>
<td>87±9</td>
<td>0.31</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Central SBP (mmHg)</strong></td>
<td></td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline</td>
<td>109±11</td>
<td>107±11</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>P10</td>
<td>140±21*^</td>
<td>110±11*</td>
<td>0.31</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>P20</td>
<td>127±12*^</td>
<td>108±11</td>
<td>0.22</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Central DBP (mmHg)</strong></td>
<td></td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline</td>
<td>69±6</td>
<td>69±6</td>
<td>0.57</td>
<td>0.00</td>
<td>0.12</td>
</tr>
<tr>
<td>P10</td>
<td>75±8*^</td>
<td>64±8*</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>P20</td>
<td>68±6</td>
<td>64±11*</td>
<td>0.37</td>
<td>0.00</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Central PP (mmHg)</strong></td>
<td></td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline</td>
<td>40±9^</td>
<td>35±7</td>
<td>0.27</td>
<td>0.15</td>
<td>0.53</td>
</tr>
<tr>
<td>P10</td>
<td>65±19*^</td>
<td>46±11*</td>
<td>0.59</td>
<td>0.15</td>
<td>0.53</td>
</tr>
<tr>
<td>P20</td>
<td>59±11*^</td>
<td>43±12*</td>
<td>0.00</td>
<td>0.00</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*significantly different from baseline  
^significantly different than females  
P10, 10 minutes following resistance exercise protocol  
P20, 20 minutes following resistance exercise protocol  
*italicized p value, Adjusted for 5RM strength
Pilot data for the Proposed Study

In a recent feasibility study, 4 young, normotensive participants (2F, 2M, 25±1yrs) wore the Mobil-o-graph device for 24h (Figure. 3) to ensure that the device meets acceptable acquisition guidelines for ambulatory blood pressure monitoring [213]. In this small pilot study, we were able to measure over 70% of planned hemodynamic measures and obtained approximately 56 measures during daytime hours and approximately 16 during nighttime hours (guidelines, >20 daytime, >7 nighttime) [141]. Based on our feasibility and pilot data, we are confident that the cuff-based method will reliably assess central hemodynamic load for 24h at rest and post-exercise as proposed for our current study design. Taken together, our results highlight our ability to accurately assess central hemodynamic load over a 24-hour time period and further suggest that women may display some level of cardio-protection in response to strenuous endurance exercise training.

Figure 3.3 24-hour Hemodynamics in Men and Women

![Figure 3: 24h PWV and AIx75 in males/females](image)
Chapter IV: Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise

Abstract

Endurance exercise typically leads to beneficial cardiac adaptations manifested as increased cardiac mass, higher cardiac function and lower central hemodynamic load (blood pressure, aortic stiffness and wave reflections). However, studies in male marathoners suggest detrimental cardiac remodeling such that larger cardiac mass is associated with reduced cardiac function and higher central hemodynamic load. There are well-established sex differences in cardiac adaptations to endurance exercise and central hemodynamics across the lifespan. Whether there are sex differences in cardiovascular adaptations in marathoners requires further scrutiny.

PURPOSE: To examine sex differences in 1) Left ventricle (LV) structure, 2) LV function 3) 24-hour central hemodynamic load and 4) ventricular-vascular coupling in marathon runners and recreationally active adults. METHODS: 52 marathon runners (n=28 female 41±5 yrs) and 49 recreationally active controls (n=25 female 42±5 yrs) participated in the current study. LV structure and function were measured using 3-dimensional echocardiography (3DE). LV mass index (LVMI) was used as an index of LV structure. LV longitudinal (LS), circumferential (CS), area (AS), and radial strain (RS) were used as indices of LV function. An ambulatory oscillometric blood pressure (BP) cuff was used to measure 24-hour hemodynamic load after a non-exercise control day and following a 30-minute run/walk. 24-hour hemodynamic load was comprised of brachial and aortic BP, aortic stiffness measured as pulse-wave velocity (PWV) and pressure from wave reflections measured Pb. Measures from central hemodynamics and 3DE were combined to derive the ratio of arterial elastance (Ea) to ventricular elastance (Elv) as a global measure of ventricular-vascular coupling. A 2x2 ANOVA was used to detect mean
differences in LVMI, LV strain indices, 24-hour hemodynamic load and Ea:Elv. A 2x2 repeated measures ANOVA was performed to compare mean differences in resting and post-exercise 24-hour hemodynamic load. **RESULTS:** Female marathoners had larger mean LVMI compared to both recreationally active and male counterparts (Sex effect, p=0.00; Training effect, p=0.04). There were no sex or training effects detected in LS, CS, AS, and RS (p>0.05). Females independent of training status had lower mean 24-hour hemodynamic load compared to males (Sex effect, p=0.00; Training effect, p=0.03). This was manifested as lower mean 24-hour resting and post-exercise mean aortic systolic blood pressure (aSBP, p=0.00), mean arterial pressure (MAP, p=0.00), mean aortic diastolic blood pressure (aDBP, p=0.00), and mean resting PWV (p=0.05) in females. Female marathoners had lower mean Ea/Elv than both recreationally active females and male counterparts (Sex effect, p=0.05; Training effect, p=0.05). **CONCLUSIONS:** This study suggests that although female marathoners had larger LVMI they did not have LV dysfunction or increased central hemodynamic load and had better overall ventricular-vascular coupling compared to both recreationally active and male counterparts. Furthermore, chronic marathon training and racing does not appear to reduce LV function, or increase central hemodynamic load in otherwise healthy middle-aged men and women, suggesting that running multiple marathons is not detrimental to cardiovascular health.
**Abbreviations**

AIx, augmentation index
(a) SBP, (aortic) systolic blood pressure
(a) DBP, (aortic) diastolic blood pressure
BP, blood pressure
BMI, body mass Index
BSA, body surface area
Ea, arterial elastance
EDV, end-diastolic volume
ESV, end-systolic volume
EF, ejection fraction
Elv, ventricular elastance
FFM, fat free mass
FS, fractional shortening
GAS, global area strain
GCS, global circumferential strain
GLS, global longitudinal strain
GRS, Global radial strain
IVS, interventricular septum
LVDd, left ventricle diameter during diastole
LVDs, left ventricle diameter during systole
LVM, left ventricle mass
LVMI, left ventricle mass index
LV, left ventricle
MAP, Mean arterial pressure
Pb, backward wave pressure
Pf, Forward wave pressure
PWV, pulse wave velocity
Q, cardiac output
RWT, relative wall thickness
SV, stroke volume
Introduction

Endurance exercise training results in myocardial structural adaptations such as increases in wall thickness [7-10] and mass [11]. Historically these physiological adaptations were viewed as benign and considered a phenotypic expression of the “athlete’s heart” [12-14]. Although exercise is generally considered beneficial for the heart [6], there are controversial reports of increased cardiovascular mortality in life-long endurance athletes [89, 214]. Increases in ventricular mass with habitual endurance exercise training have been shown to be dependent on blood pressure, suggesting that myocardial enlargement may not only be a response to exercise, but an indicator of early subclinical cardiac target organ damage [215]. Indeed, select studies have reported reduced ventricular function [216, 217], adverse cardiac structural remodeling (e.g. increased ventricular stiffness and myocardial fibrosis [2, 3, 218, 219], and increased coronary artery calcification [220] occurring in male long-distance runners.

Aberrant ventricular remodeling and reduced myocardial function in endurance-trained individuals may be influenced by underlying central hemodynamic load. Increased arterial stiffness and pressure from wave reflections results in altered ventricular-vascular coupling, increasing cardiac work and reducing cardiac efficiency, contributing to reduced myocardial contractile function [221], myocardial fibrosis [37], coronary calcification [222] and increased left ventricular (LV) mass [35]. Generally, regular endurance exercise training leads to reductions in arterial stiffness and pressure from wave reflections [38, 39]. However, studies suggest that strenuous endurance exercise may lead to increased arterial stiffness with possible increases in pressure from wave reflections [40, 41].

To date, literature noting adverse ventricular and vascular structural and functional adaptations in response to endurance training is largely, if not exclusively, in male marathoners [15, 27-29].
LV structural adaptations to endurance training are less pronounced in female athletes suggesting possible sex differences in response to the stimulus of exercise [17-24]. Studies suggest that females athletes display smaller LV mass and volumes compared to male athletes [21] even after adjusting for body size, lean body mass and training load [22, 25, 26]. Moreover, women experience reductions in arterial stiffness and wave reflections following strenuous endurance exercise [34, 42-48]. However, these studies are not performed in female marathoners, specifically. Differential acute hemodynamic responses to endurance exercise over years of training may give rise to chronic sex differences in central hemodynamic load. Thus, female sex may confer a level of cardio-protection from possible cardiac mal-adaptations with habitual endurance exercise training. Whether there are sex differences in ventricular-vascular changes with habitual endurance exercise requires further scrutiny.

The percentage of female marathon finishers in the United States has reached an all-time high (44%, 223, 344) and now rivals the number of male marathon finishers (56%, 284, 256) [223]. Understanding sex differences in ventricular-vascular coupling may give insight into the nature of cardiac remodeling (i.e. physiological or pathophysiological) and future cardiovascular risk in both male and female marathon runners. Understanding the ventricular-vascular response to regular endurance exercise may also have important clinical implications for women as ventricular-vascular uncoupling in women has been linked to their greater risk of heart failure with preserved ejection fraction [44, 48]. Recoupling with exercise may offer an important therapeutic strategy to mitigate CVD risk [224].

The purpose of the current study was to examine sex differences in ventricular-vascular coupling in marathon runners and recreationally active adults. Ventricular structure and function was assessed in detail as LV mass and LV strain using three-dimensional (3D)
echocardiography. Arterial stiffness and pressure from wave reflections were taken as proxies of central hemodynamic load and assessed using novel ambulatory (24-hour) recordings both under resting conditions and following acute exercise (as it may be argued that habitually endurance trained adults ambulate in a mostly post-exercise state). Finally, select measures from central hemodynamics and 3D echocardiography were combined and used to derive the ratio of arterial elastance to ventricular elastance as a global measure of ventricular-vascular coupling. We hypothesized that compared to male marathoners, female marathoners would have more optimal ventricular-vascular coupling, smaller LV mass, higher LV function and lower 24-hour central hemodynamic load both at rest and following acute exercise.

Methodology

Participants.

50 marathon runners (25 men, 25 women) and 50 recreationally active adults (25 men, 25 women), 35-50 years of age were recruited for this study. Marathon runners were included in the study if they self-reported completing at least 5 full marathons over the course of the past 3 years, were currently running 5-7 days a week, completing >25 miles/week at approximately 6 min per mile to 10 min/mile, and performing ≤1-2 strength training sessions per week. This criterion is similar to previous studies that examined lifelong male marathoners and found fibrosis [27]. Participants were included in the recreationally active group if they were performing aerobic exercise <3 hours per week (jogging, running <10 miles per week), performing ≤1-2 strength sessions per week, and had not engaged in any half- or full marathons in the past 20 years.

Exclusion criteria for all participants included diabetes mellitus, diagnosed cardiovascular disease, hypertension, hypercholesterolemia, current smoker, and obesity defined as BMI
>35kg/m². Only premenopausal, regularly menstruating women who were not taking any form of hormonal contraception were included in the current study. This study was approved by the Syracuse University Institutional Review Board and conformed to the standards outlined in the Declaration of Helsinki. All participants provided written informed consent prior to study initiation.

**Study Design.**

Participants were tested on four separate visits: 1) Health screening and resting vascular structure/function measurements followed by 24-hour ambulatory central hemodynamic measurement; 2) Peak aerobic fitness test, 3) Acute exercise followed by 24-hour ambulatory central hemodynamic measurement, and 4) 3-D Echocardiography. Visits 1-3 took place at the Human Performance Laboratory at Syracuse University and Visit 4 was completed at SUNY Upstate Medical University. Visits 1-3 were scheduled within 7 days to avoid sub-acute influences of training and changes in menstrual cycle. Visit 4 was scheduled at maximum within 1-2 weeks of Visit 1. Female participants’ visits 1-3 were scheduled during the early follicular phase of the menstrual cycle (Days 1-7) to avoid influence of menstrual hormones on the vasculature.

**Health Screening.**

Participants arrived to the Human Performance Laboratory following a 12-hour fast and abstinence from caffeine, alcohol and exercise (>24rs prior). Participants completed a health history, marathon history, menstrual questionnaire and the international physical activity questionnaire (IPAQ) [225] to confirm health status, exercise history, menstrual history and current physical activity levels. Metabolic equivalents (METs) were calculated from the IPAQ as the sum of the total METs from moderate, vigorous, and walking activity from a 7-day period:
Total METs = (3.3 x minutes walking x days/week) + (4.0 x minutes moderate activity x days/week) + (8.0 x minutes vigorous activity x days/week). A 12-lead electrocardiogram was performed on all participants to ensure participants did not have pre-existing cardiac conditions or potentially dangerous arrhythmias. Height was measured with a stadiometer and weight with an electronic scale to determine Body Mass Index (BMI) and Body surface area (BSA). Waist circumference was measured with a tape measure at the level of the umbilicus at the end of a normal exhalation. Body fat percentage was assessed using air displacement plethysmography (BodPod; COSMED, Concord, CA). Fat free mass (FFM) was calculated as: Body weight – Fat Mass (as determined by body fat percentage x body weight).

BSA was directly measured using a 3D body scanner (Vitus Smart LC3 scanner, Human Solutions). A CCD-Camera with integrated image processing hardware was combined with a laser pointing towards the participant to generate an avatar. An avatar was then created using the body scan measurements and a triangular mesh surface reconstruction was then used to calculate BSA measures.

Serum Lipoproteins (Total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG)) and fasting plasma glucose (GLU) levels were measured via finger stick (Cholestech LDX, Alere Medical). The proportion by volume of red blood cells (i.e. hematocrit) (StatSpin, Inc, Norwood, Mass) and hemoglobin (The Hemocue Hemoglobin System, Hb201+; Angelholm, Sweden) were also assessed from a finger stick.

**Accelerometry.**

Physical activity levels were monitored with accelerometry worn on the right hip (ActiGraph GTX3+ Model 7164, ActiGraph, LLC Pensecola, FL) during 24 hours for 7 consecutive days. At visit 1 participants were given the accelerometer. Participants were
instructed to remove the monitor when bathing or coming in contact with water. Data was considered non-wear time if interval of at least 60 minutes of zero activity intensity counts in accelerometer channel. Additionally, for participants’ data to be included in the study, participants needed to have 10 hours of data for 4 days. Sleep time was identified using similar algorithm created to calculate sleep [226, 227] and this algorithm was recently validated in a young adult sample [228]. Activity counts, non-wear time and moderate to vigorous intensity physical activity (MVPA) were processed using the low frequency extension [229]. Step counts were calculated using the default extension [230]. Time spent in MVPA, moderate and vigorous physical activity were defined as moderate intensity when greater than 2020 counts per minute were detected, and vigorous when greater than 5999 counts per minute were detected [231].

**Aerobic Capacity.**

Peak aerobic capacity (VO₂ Peak) was determined using indirect calorimetry (TrueOne 2400 Metabolic Measurement System, ParvoMedics, Sandy, Utah) at Visit 2. A graded exercise test on a treadmill was performed using the Jack Daniel’s Protocol [232]. Heart rate was measured continuously and ratings of perceived exertion (RPE) were assessed every two minutes, using a Polar Heart Rate Monitor and Borg RPE scale, respectively. A VO₂ peak test was considered valid if 2 or the following criteria was achieved: 1) an R-value of 1.10 or higher; 2) an RPE score of greater than 17; or 3) maximal heart rate achieved was greater than 85% age-predicted maximum 4) plateau in HR and/or oxygen consumption with increasing intensity.

**Lifetime Training Hrs.**

Lifetime training hrs was calculated from a self-reported number of hours/week of exercise and number of years performing the respective exercise on the exercise history questionnaire as: the average endurance hrs/week + the average strength hrs/week x 52 x number
of years. This number ensured that our participants are in fact regular exercisers. Previous studies that examine lifelong endurance athletes report an average of $4,670 \pm 4402$ lifetime hrs of exercise [233].

3D Echocardiography: LV Structure.

3D echocardiography (3DE) was used to determine LV mass, volumes and function using Speckle-tracking Technology (STE) [234]. The 3DE ultrasound measurements comprise a dynamic multi-slice acquisition technology with the ability to simultaneously acquire images up to 12 slices of the myocardium in tri-plane measurements (frame rates $>25$ frames/s). For 3DE the LV volumes and mass and strain indices were obtained by acquiring an apical 4-chamber view of the myocardium. When necessary, the 3DE data acquisition was obtained in an end-expiratory breath-hold lasting 6-8 seconds (depending on heart rate) and recorded at the LV apex with a mean volume rate of greater than or equal to 30 volume/second and a six-beat acquisition to ensure optimal temporal and spatial resolution. Data sets were stored digitally in raw data format and exported to a separate workstation (EchoPac, PC 110.1.1, GE Healthcare) equipped with commercially available software (4D Auto LVQ software, GE Healthcare) for off line analysis of LVM and 3D STE parameters. A mesh-based surface-tracking model along with automated tracing of the endocardial and epicardial border allowed for measurement of LVM, end-diastolic, end-systolic volumes and stroke volume (EDV, ESV, SV).

LV Function: 3DE STE.

Global and regional strain values were calculated based on speckle tracking technology (STE). A strain bull’s eye plot was accompanied by time–strain curves. Global longitudinal strain (GLS), global circumferential strain (GCS) and global radial strain (GRS) were calculated as weighted averages of the regional values from the 17-myocardial segments. Global area strain
(GAS) was calculated as the percentage variation in the surface area defined by the longitudinal and circumferential strain vectors. The LV was divided into 3 regions including base, mid-LV and apex. The regional LS, CS, AS, RS was calculated as the average LS, CS, AS, and RS of the segments in the region respectively. Increased strain or a higher strain value indicates optimal contractile function whereas decreased strain or a lower strain percent indicates contractile dysfunction [50, 234]. All data acquisition was performed by a professionally trained echo-cardiologist who was blinded to the study group identification. Inter-class correlation coefficients for LV strain analyses were: \( r = 0.86, r = 0.87, r = 0.86, r = 0.88 \) for longitudinal, circumferential, area, and radial, respectively.

**Resting Aortic Stiffness.**

Aortic stiffness was assessed using carotid-femoral pulse wave velocity (PWV) during Visit 1. Blood pressure waveforms from the carotid and the femoral artery were captured with applanation tonometry (AtCor Medical, Sydney, Australia) over a 10s period along with simultaneous ECG for R-wave gating. The waveforms were measured between the: 1) right common carotid artery (CCA) and right femoral artery. The distances between measurement sites were measured in a straight line with a tape measure to the nearest millimeter. For measures of carotid-femoral PWV, distance from the sternal notch to the carotid pulse site was subtracted from the carotid-femoral path length to account for the bi-directional nature of pressure propagation. PWV was calculated using the difference in the distances between sites (\( \Delta \) distance) and the measured time delay (\( \Delta \) time) between proximal and distal waveforms.

**Resting Aortic Blood Pressure and Wave Reflections.**

Resting systolic (SBP) and diastolic blood pressure (DBP) were measured via an automatic device on the participant’s left arm (BP786N, Omron Healthcare Inc., Lakeforest, IL)
during Visit 1. Pressures were taken in duplicate and averaged. If values differed more than 5 mmHg a third measure was taken and the average of the two closest measures was used for analyses. Aortic pressures were obtained via applanation tonometry. Aortic waveforms (estimated from radial waves using a validated generalized transfer function) were averaged to a single waveform for determination of aortic systolic blood pressure. Aortic pressure waveforms were calibrated to brachial mean pressure (MP) and DBP. MP and pulse pressure (PP) were calculated as 1/3 SBP + 2/3 DP and SBP – DBP, respectively. From this radial artery pressure waveform, a reconstructed central aortic pressure waveform was generated using a generalized validated transfer function to determine central BP and LV end systolic pressure (ESP).

Augmentation Index (AIx) was used as a measure of global wave reflection magnitude. AIx was calculated as the difference between the early (P1) and late systolic (P2) peaks of the pressure waveforms to the total PP expressed as a percentage: (P2-P1)/(PP x 100) and standardized to a heart rate of 75 beats per minute (AIx75). Wave separation analysis was derived from the radial PWA data acquisition. In particular, aortic wave reflections, forward wave pressure (Pf) and backward wave pressure (Pb), were obtained from the analysis of each radial blood pressure waveform. Reflection magnitude was calculated as the ratio between Pb and Pf and taken as a measure of the magnitude of reflected wave pressure.

**Ambulatory 24h Central Hemodynamic Load.**

24-hr ambulatory central hemodynamic parameters were assessed using an oscillometric brachial cuff-based validated device (Welch Allyn 7100 ABPM, I.E.M., Stolberg, Germany) [194]. This device uses the ARCSolver method to estimate aortic pressures based on brachial pressure waves recorded with a brachial cuff [193]. From the aortic pressure wave aortic stiffness (PWV) and indices of wave reflections (Pf, Pb, RM and AIx) can be derived.
Participants were fit with a cuff on their non-dominant arm, based on the circumference of their left arm ensuring that the cuff bladder covered 80-100% of arm circumference and the bladder was placed over the brachial artery. The cuff was placed on the non-dominant arm with the tubing passing upwards around the participant’s neck to be connected to the monitor on the waist. These measurements were performed twice, for a 24-hour period (non-exercise condition, post-Visit 1) following a 24-hour period of no exercise and following a 24-hour period (post-exercise post-Visit 3) after a standardized 30-minute moderate intensity running session (exercise condition, 60-70% HR max, post-Visit 3) in the laboratory.

The definition of daytime and nighttime intervals was determined by using typical sleep time reported by participants prior to receiving the device. The device was formatted to take a measurement every 20-min during waking hours and every 30-min during night hours. After the data were obtained and transferred to a computer-based hypertension management software (HMS), the data were edited and excessive noise and artifacts were deleted. The automated recording of pressures waves via cuff based oscillometry were calibrated non-invasively by brachial MAP/DBP values. This is currently the most reliable approach that provides more accurate estimations of aortic SBP values. These calibrated values are closest to the actual invasively measured aortic pressure values (C2-methodology). The European Society of Hypertension Guidelines state that there must be 70% of expected measurements every 30 minutes throughout the 24-h period (14-20 measurements during daytime and 7 measurements during nighttime) [141]. At the very minimum there needs to be 2 valid daytime measurements per hour and 1 valid nighttime measurement per hour. If a participant’s trial did not meet these guidelines set forth by the European Society of Hypertension than the 24-h measurement was repeated.
**Ventricular-Vascular Coupling**

Arterial elastance (Ea) was calculated as ESP/SV determined by applanation tonometry and 3D echocardiography, respectively. Ventricular elastance was calculated as ESP/ESV determined by applanation tonometry and 3D echocardiography, respectively. Global Ventricular vascular coupling was determined as the ratio of Ea to Elv.

**Statistical Analyses.**

Apriori power calculations (2-tailed test, independent groups) using an effect size of 1.64, power of 0.80, and alpha level of 0.05 indicate that sixteen participants per group would be necessary to detect sex differences and training differences across LVM, LV strain and 24-hour central hemodynamics. We powered our study based primarily on previous studies that examined sex and training differences in LVM and 24-hour BP. No study has used 3DE STE to examine LV strain in male and female endurance trained athletes and compared them to recreationally active counterparts.

All data are presented as mean ± standard deviation and statistical significance was established a priori as p<0.05. Normality of distribution for variables was assessed qualitatively using histograms and Q-Q plots and quantitatively using Shapiro-Wilk test. Non-normally distributed variables were transformed and re-assessed for normality. We assessed descriptive characteristics, vascular and 2D and 3D cardiac parameters across sex and training status using a 2x2 (2 sex groups x 2 training statuses) ANOVA. Main effects of sex, training status and sex x training interactions were further explored with Scheffe’s corrected post-hoc tests. In order to compare resting 24-hour ambulatory hemodynamics to post-exercise 24-hour ambulatory hemodynamics we used a 2x2x2 (2 sex groups x 2 training statuses x 2 time points) repeated measures ANOVA. Main effects of sex, training status, time, sex x training x time interactions
were further explored with Scheffe’s corrected post-hoc tests. 2x2 ANCOVA’s were performed for aortic PWV, 3D LVMI, and 24-hour aSBP while co-varying for variables that were significantly different between men and women and also known to affect LV structure and function. Additionally, we explored vascular correlates (PWV, RM, AIx, aSBP, Ea, Elv, Ea:Elv) of LV structure and function in men and women using Pearson’s Bivariate correlations.

Results

**Participant Characteristics.**

52 marathon runners (28 women 41±5 yrs; 24 men, 42±5 yrs) and 49 healthy recreationally active controls (25 women 42±5 yrs; 24 men, 42±4 yrs) completed this study. Participant characteristics are shown in Table 1. All participants self-reported being Caucasian\(^1\) as their primary ethnicity. Participants were well-matched across groups for mean age and within groups (i.e. sex) for body mass index (BMI), body surface area (BSA) and waist circumference (Table 1; \(p>0.05\)). Across all groups, females had significantly lower mean body fat percentage, BMI, waist circumference, and BSA compared to males (Table 1; \(p<0.05\)). Both female and male marathoners had significantly lower mean body fat percentage compared to same sex controls (Table 1; \(p<0.05\)). There were no sex by training interactions in participant characteristics (\(p>0.05\)).

\(^1\) Caucasian defined as “white” or of “European Descent”. Historically the use of Caucasian identifier was referred to as superior and non-Caucasian as inferior. Thus, the preference instead of using Caucasian is to identify as “white or of European Descent”.

**Blood Lipids and Red Blood Cell Profile.**

There was a significant sex effect and training effect in blood lipids (Table 1; \(p<0.05\)). Female marathoners and female controls had higher mean HDL, lower LDL, nHDL, TC/HDL and blood
glucose compared to male counterparts (Table 1; p<0.05). Female marathoners had significantly lower mean blood glucose compared to the female controls while male marathoners had similar mean glucose compared to male controls (Sex by Training interaction, p<0.05). There were no significant training effects in mean hematocrit and hemoglobin (p>0.05). Hematocrit was similar across all groups (p>0.05). Hemoglobin was significantly lower in the females compared to males, independent of training status (p<0.05).

Marathon History.

Male and female marathoners reported completing a similar mean number of marathons in the last year, last 3, and last 5 years. Female marathoners reported a significantly higher number of marathons in the last 20 years. All marathoners reported a similar average finishing time, miles per week and average running pace (Table 2; p>0.05).

Aerobic Fitness and Physical Activity Levels.

There was a significant sex effect in VO$_2$ max and VO$_2$ max$_{FFM}$ where females had lower mean VO$_2$ max compared to males (Table 2; p<0.05). Also, female marathoners and male marathoners had higher mean VO$_2$ max and VO$_2$ max$_{FFM}$ compared to the female and male controls (Table 2; p<0.05). Thus, as expected there was a significant training effect in VO$_2$ Max results and the marathoners were categorized into a significantly higher VO$_2$ max percentile for their age (Table 2; p<0.05). However, the significant training effect in VO$_2$ max$_{FFM}$ was only present in females, as male marathoners had similar VO$_2$ max$_{FFM}$ compared to male controls. There was no sex by training interaction in VO$_2$ max or VO$_2$ max$_{FFM}$ (p>0.05), suggesting that the overall effect of sex and effect of training was similar across and within groups.

There were no significant differences between groups on self-reported mean METs from IPAQ (p>0.05). Accelerometry analysis was successfully recorded on seventy-four participants
(n=21 female marathoners, n=17 female controls, n=16 male marathoners, n=20 male controls). Accelerometry data indicated that the female marathoners had significantly more time spent in MVPA, steps per day, and moderate intensity minutes compared to the controls (Table 2; p<0.05), whereas male marathoners were similar to male controls on all indices (p>0.05). There was no significant sex by training interaction in physical activity levels, suggesting that 1) the effect of sex on levels of physical activity was similar between marathoners and controls and 2) the effect of training on levels of physical activity was similar between men and women (p>0.05).

**Resting Blood Pressure, Arterial Stiffness and Wave Reflections.**

Resting mean brachial SBP and DBP was significantly lower in females compared to males, irrespective of training status (Table 3; p<0.05). Brachial mean pressure was similar across groups and resting heart rate was significantly lower in both female and male marathoners compared to controls (Table 3; p<0.05). Mean aortic SBP, DBP, aortic PWV, Pf and Pb were all significantly lower in females compared to males (p<0.05), while aortic AIx and RM were significantly higher in females compared to males (p<0.05). When mean PWV was adjusted for differences in mean pressure, the sex effect in PWV was abolished (p>0.05). There were no significant sex x training interactions (p>0.05) suggesting similar sex differences in hemodynamics in both marathon and control groups and similar training effects in men and women.

**Ventricular Vascular Coupling: Arterial and Ventricular Elastance.**

Resting mean ESP was significantly higher in female marathoners compared male marathoners (p<0.05) and significantly lower in female controls compared to male controls (Table 3; p<0.05). Mean Ea was significantly higher in females compared to males irrespective of training status.
(p<0.05). There was also a significant effect of training in Ea with female marathoners having a lower Ea compared to female controls (p<0.05). For indices of Elv, Female marathoners and controls had higher mean Elv compared to both male marathoners and controls (p<0.05). Mean Ea/Elv was significantly lower in female marathoners compared to both recreationally active females and male counterparts (p<0.05).

3-D Echocardiography.

For 3D indices, females, regardless of training status had smaller mean LVM, EDV, ESV, SV, and Q but larger LVMI, compared to their male counterparts (Table 4; p<0.05). There was a training effect detected in mean LVMI (adjusted for 3D BSA) with female marathoners having slightly larger LVMI compared to controls (p<0.05). Female marathoners had larger mean LVMI compared to males, independent of training status (p<0.05). There was no main effect of sex or training on SV_{BSA} and Q_{BSA} (p>0.05). There were no sex, training or interaction effects detected in EF, 3D GLS, GCS, GAS, and GRS (p>0.05). When sex differences in mean LVMI were adjusted for mean PWV, brachial BP, aortic BP, AIx and RM sex differences in LVMI remained (p<0.05).

24-hour Ambulatory Central Hemodynamics.

Non-exercise control. 24-hour non-exercise mean SBP, MAP, DBP, aSBP, aDBP, PWV and aPP were lower in females compared to males regardless of training status (Table 5; p<0.05). Mean RM was significantly higher in females compared to males (p<0.05). 24-hour non-exercise mean HR was lower in female and male marathoners compared to the controls (p<0.05). 24-hour non-exercise mean PP, AIx, Pb, and Pf were similar across groups (p>0.05). There was a significant training effect for mean aSBP only in men, whereby male marathoners had higher aSBP compared to male controls (p<0.05), however, there was no significant interaction. There were
no significant sex by training interactions detected in resting 24-hour hemodynamics (p>0.05) suggesting that 1) the effect of sex on 24-hour hemodynamics was similar within marathoners and controls and 2) the effect of training on 24-hour hemodynamics was similar between men and women.

**Post-exercise.** 24-hour post-exercise, mean SBP, MAP, aSBP, aDBP and aPP were lower in females compared to males, regardless of training status (Table 6; p<0.05). 24-hour post-exercise, mean RM was significantly higher in females compared to males independent of training status. Also, 24-hour post-exercise mean HR was significantly lower in female and male marathoners compared to the controls. There were no differences in 24-hour post-exercise mean PP, PWV, AIx, Pb and Pf (p>0.05). There were no significant interactions detected in post-exercise 24-hour hemodynamics, suggesting that 1) the effect of sex on post-exercise 24-hour hemodynamics was similar within marathoners and controls and 2) the effect of training on 24-hour hemodynamics was similar between men and women.

When 24-hour non-exercise mean SBP, aSBP, aPP, PWV, MAP, AIx, Pb, Pf, and RM were compared to corresponding 24-hour post-exercise measures, there were no significant sex x training x time interactions (Table 6; p>0.05) suggesting that the effect of sex and training (across time) on non-exercise control day and post-exercise 24-hour hemodynamics was similar within marathoners and controls and between men and women, respectively.

**Vascular hemodynamic correlates of LV Structure and Function.**

**Females.** 24-hour PWV and 24-hour SBP were significantly associated with AS, RS and 3D-LVMI (Table 7; p<0.05). 24-hour RM were significantly associated with 3D-LVMI but not with LV strain indices. Ea was associated with LVMI, RS and AS but not with 24-hour SBP, aSBP, 24-hour AIx, 24-hour RM, or PWV (p<0.05). Elv was not associated with LVMI, 24-hour AIx,
24-hour SBP, aSBP or 24-hour RM, but was associated with 24-hour PWV, AS, and RS (p<0.05). Ea/Elv was associated with LVMI, AS, RS, 24-hour AIx and 24-hour PWV but not with 24-hour SBP or aSBP or RM (p<0.05).

**Males.** 24-hour PWV, 24-hour SBP, 24-hour aSBP, AIx, and RM, were not significantly associated with 3D-LVMI or LV function (Table 8; p>0.05). Ea was not associated with LVMI, 24-hour PWV, 24-hour AIx, RM, 24-hour SBP or aSBP, but was associated with RS, and AS (p<0.05). Elv and Ea/Elv was not associated with LVMI, 24-hour SBP, 24-hour AIx and RM but was associated with 24-hour PWV, RS, and AS (p<0.05).

**Discussion**

Using a cross-sectional design, we comprehensively examined sex differences in LV structure and function, 24-hour central hemodynamics and ventricular-vascular coupling in marathon runners and recreationally active adults. The main findings of this study were that: (1) female marathoners had larger LVMI and more optimal ventricular-vascular coupling compared to all other groups; (2) overall LV function was similar across all groups; and (3) females had lower central hemodynamic load than men irrespective of training status. Collectively, these findings suggest that although female marathoners had larger LVMI they did not have LV dysfunction, or increased central hemodynamic load and had better overall ventricular-vascular coupling. This finding suggests that cardiac hypertrophy in female marathoners was physiological and not pathological. Moreover, while there were sex differences in central hemodynamics, chronic marathon training and racing does not appear to reduce LV function, or increase central hemodynamic load in otherwise healthy middle-aged men and women, suggesting that running multiple marathons is not detrimental to cardiovascular health.
LV Structure. Endurance athletes engage in prolonged frequent exercise, eliciting repeated increases in heart rate, blood pressure, stroke volume and cardiac output, which lead to increases in cardiac mass and dimensions [97]. Thus, chronic endurance trained individuals such as marathon runners are observed to have larger LVMI compared to non-endurance trained individuals [99, 100, 103]. In the current study, female marathoners had larger LVMI compared to recreationally active women. Despite training studies that indicate attenuated cardiac hypertrophy in women in response to endurance training [17], we found cross-sectional differences in LVMI that are consistent with increased cardiac mass reported in endurance athletes [97].

An unanticipated finding in the current study was that female marathoners had larger LVMI compared to male counterparts. Previous studies have noted, both in the general population and in endurance athletes, that women have smaller LVMI and volume compared to men [17-23]. Reasons for our findings might be physiological or methodological. In our sample, the total marathons completed by female marathoners in the past 20 years was greater than the males and may have contributed to why there was only a training effect in females. Moreover, we utilized 3DE to assess cardiac geometry. LV dimensions obtained from 3DE differ when compared to geometries obtained from conventional 2DE as 3DE does not rely on the same inherent assumptions for calculation of volumes (i.e. the LV is an ellipse). Compared to 2DE, measures obtained from 3DE more closely approximate cardiac size determined by “gold standard” cardiac MRI [235]. Thus, use of 3DE may offer novel insight into sex-differences in cardiac adaptations with chronic exercise training. Additional studies are needed using 3DE to quantify cardiac hypertrophy in marathon runners.
**LV Function.** Previous studies show that LV function might be better in athletes and in marathoners compared to other athletes and controls [3, 54, 236]. In our study, female marathoners had similar LV function compared to female controls. Studies in male marathoners find increased LVMI might be associated with decreased cardiac function [217, 219]. Thus, it might be expected that because female marathoners had larger LVMI in our sample, that they would also have lower LV function than female controls, but LV function was not lower in female marathon runners. Our finding suggests that female marathoners have a larger LVMI but also preserved LV function. Thus, female marathoners appear to experience physiological cardiac enlargement in response to chronic marathon running.

Although female marathoners had larger LVMI, we observed that both female and male marathoners had similar cardiac function, as measured by 3D LV strain, irrespective of training status. Previous studies suggest women in the general population have better overall LV function compared to men [30, 127]. In contrast to our hypothesis, we found no significant sex differences in LV function. Only one study to date has used 3DE to assess LV function via strain analysies in male athletes [77], which in accordance with our study, concluded that endurance athletes had similar strain to controls [77]. More studies are needed to examine the impact of chronic marathon training on cardiac function using 3DE to confirm our findings. Our results suggest that middle-aged adults who regularly run multiple marathons each year, do not have reduced LV function.

**24-hour Central Hemodynamic Load.** Ventricular remodeling and cardiac function in endurance-trained individuals may be influenced by underlying central hemodynamic load.
Endurance exercise reduces arterial stiffness and pressure from wave reflections and thus is associated with reduced central hemodynamic load and better LV function [147-152]. However, some studies suggest that strenuous long-term endurance exercise training and acute endurance exercise may increase arterial stiffness and wave reflections [40, 41, 148, 153] in male marathon [40], and ultra-marathon [41] runners which may in turn have a detrimental effect on cardiac structure and function [177, 181, 182]. We found that both female and male marathoners had similar 24-hour arterial stiffness, blood pressure and wave reflections compared to recreationally active controls on both non-exercise and exercise days and this might explain similar LV function among groups. Our findings are in agreement with a few cross-sectional studies that note no differences in arterial stiffness and blood pressure between endurance athletes and controls [148, 158].

Our study is the first study to examine sex differences in 24-hour arterial stiffness, blood pressure and wave reflections in marathon runners. We found that females irrespective of training status had lower 24-hour arterial stiffness, blood pressure and higher wave reflections compared to males. Our finding is supported by previous studies that find sex differences in resting hemodynamics whereby women have lower overall hemodynamic load compared to men [31-33, 42]. Our study extends these sex differences to the marathon runner population. Moreover, even though female marathoners had larger LVMI, they did not have higher central hemodynamic load on both non-exercise and exercise days, further supporting the notion that adaptations in LVMI are likely physiological and not pathological.

**Ventricular-Vascular Coupling.** When we assessed ventricular-vascular coupling, a measure of the interaction between the LV and the arterial system to determine cardiac performance and
energetics, we found that female marathoners had better overall ventricular vascular coupling compared to both recreationally active controls and male counterparts. Adequate coupling between the LV and the arterial system is important as it results in optimal transfer of blood from the LV to the periphery without excessive changes in pressure [4]. Ventricular-vascular uncoupling with age in women has been linked to greater risk of heart failure with preserved ejection fraction [44, 48]. Thus, our findings suggest that aforementioned cardiac and vascular adaptations in female marathoners may contribute to more optimal overall ventricular-vascular coupling.

**Correlates of LV structure and function in men and women.** Based on the theoretical relationships between LVMI, LV function, central hemodynamic load and ventricular vascular coupling, we explored various hemodynamic correlates of LVMI and LV function in women and men. In women, a larger LVMI was correlated with lower arterial stiffness, better LV function and better ventricular vascular coupling. However, in men LVMI was not associated with LV function, or central hemodynamics. Our findings suggest clear sex differences in correlates of LV structure and function and this is supported by previous studies [48]. This finding also substantiates our finding in the current study that female marathoners had a larger LVMI that might be associated with lower central hemodynamic load and better ventricular vascular coupling.

**Physical Activity Levels**

In the current study, we objectively measured physical activity levels in both marathoners and recreationally active controls. We found that female marathoners spent significantly more time in
MVPA and had more steps/day compared to recreationally active females, while male marathoners had similar levels of MVPA and steps/day to male controls. Furthermore, we found that both female and male marathoners spent a similar amount of time in vigorous and moderate activity/day as compared to their recreationally active counterparts. It might be expected that since marathoners engage in frequent high volumes of endurance exercise that they would be more active than their recreationally active counterparts. However, our findings are similar to few studies that have found low physical activity levels in marathon runners [237]. Reasons for the similarities in physical activity levels between marathoners and controls might be explained by high levels of inactivity in marathoners, despite frequent exercise training. Although marathoners might run once a day, most days of the week, the rest of their day they might spend a significant amount of time not very active or sitting and thus, are very sedentary or inactive. Indeed, studies suggest that marathoners actually spend up to 10 hours a day sitting during the week [237]. Future studies are necessary to examine physical activity levels in marathoners compared to non-marathoners to determine the implications of these findings.

Limitations and Additional Considerations.

Study Strengths. By design we did not incorporate a true sedentary control group. Recreationally active individuals are much healthier than sedentary individuals, as sedentary behavior is associated with increased central hemodynamic load and disease [203, 204]. Thus, incorporating a recreationally active control group into the current study was a strength. Additionally, 3DE is a novel, reliable technique and is a more technologically sensitive measurement compared to 2DE that is used in previous studies.
**Study Limitations.** All participants in the current study self-reported being of European descent or white, thus our study results cannot be extrapolated to other races and ethnicities. Reasons for lack of diversity in our study might be due to the lack of diversity in recruitment area of Central New York, timing of study measures being during the work day, lack of transportation and access to the study facilities or family obligations. Future studies should examine racial/ethnic differences in cardiovascular adaptations to endurance exercise. There are also potential limitations in our exploration of the relationship between measurements of ventricular vascular coupling and LVMI, in regards to multicollinearity, as indices used to calculate ventricular vascular coupling are also used in the calculation of LVMI. However, our findings from tonometry and 24-hour oscillometry support the overall findings that a larger LVMI in female marathoners is not pathological. Lastly, it is important to note, that this study was cross-sectional in nature and thus, we only have one 3DE measurement on these participants and do not know the dynamic LV changes that could occur due to training. As a first study to utilize 3DE to characterize sex differences in LVM and LV function in individuals who have run multiple marathons, we believe are findings are still novel and informative.

**Implications.** The results of our study suggest that although female marathoners had larger LV mass, they had preserved LV function, lower central hemodynamic load and optimal ventricular-vascular coupling. Previous studies that examine male marathoners with similar cardiac adaptations show that a larger ventricle is associated with reduced function, and higher hemodynamic load [215-217]. Thus, female sex may confer a level of cardio-protection from possible cardiac mal-adaptations with habitual endurance exercise training. Understanding the ventricular-vascular response to regular endurance exercise may also have important clinical
implications for women as ventricular-vascular uncoupling with age in women has been linked to greater risk of heart failure with preserved ejection fraction [44, 48]. Recoupling with endurance exercise may offer an important therapeutic strategy to mitigate CVD risk in women [224].

**Conclusions.** The main findings of this study were that: (1) female marathoners had larger LVMI and better ventricular-vascular coupling compared to all other groups; (2) overall LV function was similar among all groups; (3) females had lower central hemodynamic load then men irrespective of training status. Our findings suggest that although female marathoners had larger LVMI they did not have LV dysfunction or increased central hemodynamics load and had better overall ventricular-vascular coupling. Moreover, while there were sex differences in central hemodynamics, chronic marathon training and racing does not appear to reduce LV function, or increase central hemodynamic load in otherwise healthy middle-aged men and women, suggesting that running multiple marathons is not detrimental to cardiovascular health.
Table 1: Characteristics of Marathoners and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41±5</td>
<td>42±5</td>
<td>42±5</td>
<td>42±4</td>
<td>0.83</td>
<td>0.75</td>
<td>0.27</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164±7*</td>
<td>165±6†</td>
<td>178±7</td>
<td>178±7</td>
<td>0.00</td>
<td>0.95</td>
<td>0.51</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62±8*</td>
<td>68±12†</td>
<td>82±12</td>
<td>81±3</td>
<td>0.00</td>
<td>0.37</td>
<td>0.20</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>22.7±3.1*</td>
<td>24.3±4.0†</td>
<td>29.7±4.7</td>
<td>29.5±4.7</td>
<td>0.00</td>
<td>0.31</td>
<td>0.20</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>76±8*</td>
<td>79±9†</td>
<td>89±11</td>
<td>90±8</td>
<td>0.00</td>
<td>0.21</td>
<td>0.33</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>23.1±6.2‡</td>
<td>28.9±9.3†</td>
<td>20.4±7.1†</td>
<td>22.0±7.0</td>
<td>0.00</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>3-Dimensional BSA (m²)</td>
<td>1.60±0.13*</td>
<td>1.67±0.15†</td>
<td>1.90±0.15</td>
<td>1.90±0.17</td>
<td>0.00</td>
<td>0.32</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Lipid Profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>187±23</td>
<td>198±35</td>
<td>197±40</td>
<td>196±42</td>
<td>0.54</td>
<td>0.55</td>
<td>0.45</td>
</tr>
<tr>
<td>High Density Lipoprotein (mg/dl)</td>
<td>72±15*</td>
<td>66±19†</td>
<td>56±13</td>
<td>53±17</td>
<td>0.00</td>
<td>0.17</td>
<td>0.67</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>84±7*</td>
<td>90±8†</td>
<td>96±8</td>
<td>94±8</td>
<td>0.00</td>
<td>0.13</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>89±34</td>
<td>117±86</td>
<td>113±58</td>
<td>109±55</td>
<td>0.49</td>
<td>0.41</td>
<td>0.25</td>
</tr>
<tr>
<td>Low Density Lipoprotein (mg/dl)</td>
<td>97±30*</td>
<td>114±32†</td>
<td>121±39</td>
<td>123±41</td>
<td>0.03</td>
<td>0.21</td>
<td>0.29</td>
</tr>
<tr>
<td>Non-High Density Lipoprotein (mg/dl)</td>
<td>115±28*</td>
<td>135±36†</td>
<td>141±41</td>
<td>143±44</td>
<td>0.03</td>
<td>0.18</td>
<td>0.27</td>
</tr>
<tr>
<td>Total Cholesterol/HDL (mg/dl)</td>
<td>2.7±0.9*</td>
<td>3.4±1.4†</td>
<td>3.7±1.1</td>
<td>4.2±2.0</td>
<td>0.00</td>
<td>0.06</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Red Blood Cell Profile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44±4</td>
<td>44±4</td>
<td>44±5</td>
<td>46±4</td>
<td>0.33</td>
<td>0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>13.0±1.1*</td>
<td>13.1±0.7†</td>
<td>14.3±1.3</td>
<td>14.6±1.1</td>
<td>0.00</td>
<td>0.35</td>
<td>0.91</td>
</tr>
</tbody>
</table>

BSA, Body Surface Area. †Significantly different than female controls; ‡Significantly different than male marathoners; ††Significantly different than male controls; Significance level at p<0.05. SxT interaction, Sex x Training Interaction.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marathon History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Marathon in last 20 years (#)</td>
<td>16.2±12.4</td>
<td>-</td>
<td>15.0±15.4</td>
<td>-</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Marathons in last 5 years (#)</td>
<td>10.7±10.0</td>
<td>-</td>
<td>9.2±8.2</td>
<td>-</td>
<td>0.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Marathons in last 3 years (#)</td>
<td>6.5±1.0</td>
<td>-</td>
<td>6.7±1.5</td>
<td>-</td>
<td>0.18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Marathons in last 1 year (#)</td>
<td>3.1±2.0</td>
<td>-</td>
<td>2.0±2.0</td>
<td>-</td>
<td>0.08</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average Marathon Finishing Time (hours)</td>
<td>4.0±0.6</td>
<td>-</td>
<td>3.7±0.8</td>
<td>-</td>
<td>0.08</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miles per week (miles)</td>
<td>40.8±5.0</td>
<td>-</td>
<td>42.1±3.0</td>
<td>-</td>
<td>0.10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average Running Pace (mph)</td>
<td>6-8mph</td>
<td>-</td>
<td>6-8mph</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lifetime Training Hours (hrs)</td>
<td>5616±1000</td>
<td>-</td>
<td>5200±900</td>
<td>-</td>
<td>0.30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Aerobic Fitness Levels</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO\textsubscript{2} max (ml/kg/min)</td>
<td>47.5±5.5\textsuperscript{‡}</td>
<td>38.6±8.1</td>
<td>53.4±6.1\textsuperscript{†}</td>
<td>49.8±6.9</td>
<td>0.00</td>
<td>0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>VO\textsubscript{2} Max (ml/FFM/min)</td>
<td>61.9±6.2\textsuperscript{‡}</td>
<td>53.7±8.9\textsuperscript{†}</td>
<td>66.9±7.1</td>
<td>63.4±7.4</td>
<td>0.00</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td>VO\textsubscript{2} Max Age Percentile (%)\textsuperscript{^}</td>
<td>97.5</td>
<td>77.5</td>
<td>99.0\textsuperscript{†}</td>
<td>78.0</td>
<td>0.32</td>
<td>0.04</td>
<td>0.50</td>
</tr>
<tr>
<td>Heart Rate max (bpm)</td>
<td>179±9\textsuperscript{*}</td>
<td>181±12</td>
<td>176±8\textsuperscript{†}</td>
<td>184±11</td>
<td>0.00</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Physical Activity Levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time spent in MVPA (min/day)\textsuperscript{^}</td>
<td>55±25\textsuperscript{†}</td>
<td>34±15</td>
<td>55±20</td>
<td>41±21</td>
<td>0.57</td>
<td>0.00</td>
<td>0.43</td>
</tr>
<tr>
<td>Mean Steps Per Day (#)\textsuperscript{^}</td>
<td>11679±4231\textsuperscript{‡}</td>
<td>8158±1910</td>
<td>9969±2114</td>
<td>9227±2772</td>
<td>0.87</td>
<td>0.00</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean Duration of Vigorous (min/day)\textsuperscript{^}</td>
<td>11.75±12.7</td>
<td>6.4±8.2</td>
<td>10.0±13.7</td>
<td>8.9±11.4</td>
<td>0.97</td>
<td>0.27</td>
<td>0.41</td>
</tr>
<tr>
<td>Moderate Intensity Minutes (min/day)\textsuperscript{^}</td>
<td>46.5±22.6\textsuperscript{‡}</td>
<td>27.2±13.3</td>
<td>41.8±22.7\textsuperscript{†}</td>
<td>33.4±16.0</td>
<td>0.55</td>
<td>0.00</td>
<td>0.72</td>
</tr>
<tr>
<td>Metabolic Equivalents (min/week)\textsuperscript{^}</td>
<td>6988±6704</td>
<td>2895±267</td>
<td>5543±4678</td>
<td>6908±11402</td>
<td>0.79</td>
<td>0.88</td>
<td>0.06</td>
</tr>
</tbody>
</table>

\textsuperscript{^}ACSM Guidelines Age Percentiles. Accelometry measured over a 7-day period; MVPA, Moderate to Vigorous Physical Activity. SxT interaction, Sex x Training Interaction. \textsuperscript{†}Significantly different than female controls; \textsuperscript{*}Significantly different than male marathoners; \textsuperscript{‡}Significantly different than male controls; Significance level at \( p<0.05 \).
Table 3: Resting Brachial Blood Pressure and Aortic Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114±10*</td>
<td>114±13†</td>
<td>125±9</td>
<td>124±8</td>
<td>0.00</td>
<td>0.74</td>
<td>0.94</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74±7*</td>
<td>75±8†</td>
<td>77±8</td>
<td>79±6</td>
<td>0.02</td>
<td>0.28</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean Pressure (mmHg)</td>
<td>88±7</td>
<td>88±9</td>
<td>93±8</td>
<td>93±6</td>
<td>0.12</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>51±6†‡</td>
<td>59±10†</td>
<td>49±7†</td>
<td>56±8</td>
<td>0.09</td>
<td>0.00</td>
<td>0.97</td>
</tr>
<tr>
<td>Aortic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>108±10*</td>
<td>107±14†</td>
<td>118±11</td>
<td>114±7</td>
<td>0.00</td>
<td>0.23</td>
<td>0.47</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74±6*</td>
<td>75±8†</td>
<td>77±7</td>
<td>79±6</td>
<td>0.01</td>
<td>0.21</td>
<td>0.91</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>6.2±1.0*</td>
<td>6.6±1.2†</td>
<td>7.2±1.1</td>
<td>6.8±1.0</td>
<td>0.01</td>
<td>0.96</td>
<td>0.07</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>27±11*</td>
<td>28±16†</td>
<td>15±16</td>
<td>14±13</td>
<td>0.00</td>
<td>0.58</td>
<td>0.56</td>
</tr>
<tr>
<td>RM</td>
<td>0.74±0.15*</td>
<td>0.68±0.15†</td>
<td>0.62±0.17</td>
<td>0.56±0.14</td>
<td>0.00</td>
<td>0.08</td>
<td>0.91</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>22±4*</td>
<td>20±6†</td>
<td>30±10†</td>
<td>26±5</td>
<td>0.00</td>
<td>0.02</td>
<td>0.42</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>16±3</td>
<td>13±4</td>
<td>18±5†</td>
<td>14±4</td>
<td>0.08</td>
<td>0.00</td>
<td>0.94</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>93±7*</td>
<td>90±10†</td>
<td>87±9†</td>
<td>97±9</td>
<td>0.00</td>
<td>0.42</td>
<td>0.79</td>
</tr>
<tr>
<td>Ea/Elv</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea</td>
<td>1.46±0.26*††</td>
<td>1.76±0.70†</td>
<td>1.43±0.50</td>
<td>1.43±0.40</td>
<td>0.01</td>
<td>0.01</td>
<td>0.79</td>
</tr>
<tr>
<td>Elv</td>
<td>2.30±0.62*</td>
<td>2.21±0.61†</td>
<td>1.71±0.71</td>
<td>1.81±0.64</td>
<td>0.01</td>
<td>0.45</td>
<td>0.70</td>
</tr>
<tr>
<td>Ea/Elv</td>
<td>0.67±0.20*††</td>
<td>0.93±0.36†</td>
<td>0.85±0.42</td>
<td>0.85±0.31</td>
<td>0.05</td>
<td>0.05</td>
<td>0.41</td>
</tr>
</tbody>
</table>

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PWV, pulse wave velocity; AIx, Augmentation Index; RM, Reflection Magnitude (Pb:Pf); Pf, Forward Pressure due to Wave Reflections; Pb, Backward Pressure due to Wave Reflections; Ea, arterial elastance; Elv, ventricular elastance; †Significantly different than female controls; *Significantly different than male marathoners; ‡Significantly different than male controls; Significance level at $p<0.05$. SxT interaction, Sex x Training Interaction.

Figure 4.1: LVMI
LVMI (g/m²)

Significantly different than male marathoners; †Significantly different than male controls; Significance level at $p<0.05$.

Figure 4.2: LV Area Strain
Table 4: 3-Dimensional Echocardiography: LV Structure and Function
### LV Structure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM (g)</td>
<td>120±9*</td>
<td>117±9†</td>
<td>130±15</td>
<td>129±15</td>
<td>0.00</td>
<td>0.30</td>
<td>0.94</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>107±17*</td>
<td>101±20†</td>
<td>137±26</td>
<td>132±32</td>
<td>0.00</td>
<td>0.15</td>
<td>0.69</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>43±11*</td>
<td>44±15†</td>
<td>64±20</td>
<td>60±20</td>
<td>0.00</td>
<td>0.64</td>
<td>0.43</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>64±11*</td>
<td>56±16†</td>
<td>73±18</td>
<td>73±20</td>
<td>0.00</td>
<td>0.16</td>
<td>0.21</td>
</tr>
<tr>
<td>SV/BSA (L/m²)</td>
<td>39±7</td>
<td>33±10</td>
<td>38±9</td>
<td>38±9</td>
<td>0.70</td>
<td>0.06</td>
<td>0.10</td>
</tr>
<tr>
<td>Q (L/min)</td>
<td>3.5±0.8*</td>
<td>3.7±1.0</td>
<td>3.8±0.89</td>
<td>4.3±1.3</td>
<td>0.04</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>Q/BSA (L/min/m²)</td>
<td>2.6±0.4</td>
<td>2.1±0.6</td>
<td>1.9±0.5</td>
<td>2.1±0.5</td>
<td>0.33</td>
<td>0.48</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### LV Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection Fraction (%)</td>
<td>60.2±6.9</td>
<td>56.1±10.4</td>
<td>53.5±9.9</td>
<td>54.9±8.5</td>
<td>0.26</td>
<td>0.40</td>
<td>0.10</td>
</tr>
<tr>
<td>3D Longitudinal Strain (%)</td>
<td>-17.8±4.2</td>
<td>-15.8±5.0</td>
<td>-15.7±2.9</td>
<td>-16.3±4.4</td>
<td>0.20</td>
<td>0.55</td>
<td>0.16</td>
</tr>
<tr>
<td>3D Circumferential Strain (%)</td>
<td>-17.3±3.9</td>
<td>-15.6±3.6</td>
<td>-15.8±3.2</td>
<td>-16.2±3.3</td>
<td>0.41</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>3D Area Strain (%)</td>
<td>-29.4±5.2</td>
<td>-25.8±6.5</td>
<td>-26.7±4.4</td>
<td>-26.9±5.8</td>
<td>0.28</td>
<td>0.31</td>
<td>0.23</td>
</tr>
<tr>
<td>3D Radial Strain (%)</td>
<td>51.5±15.6</td>
<td>44.2±14.5</td>
<td>43.7±10.3</td>
<td>45.6±12.0</td>
<td>0.25</td>
<td>0.21</td>
<td>0.34</td>
</tr>
</tbody>
</table>

BSA, Body Surface Area.; LVM, Left Ventricle Mass; LVMI, Left Ventricle Mass Index; EDV, End Diastolic Volume; ESV, End Systolic Volume; 3D, 3 dimensional. SV, Stroke Volume; Q, Cardiac Output; †Significantly different than female controls; *Significantly different than male marathoners; ‡Significantly different than male controls; Significance Level at p<0.05. SxT interaction, Sex x Training Interaction.

Figure 4.3: Non-exercise 24-hour aSBP
aSBP Rest (mmHg)

Female Marathoners  Female Controls  Male Marathoners  Male Controls

*Significantly different than male marathoners; †Significantly different than male controls; Significance Level at p<0.05
Table 5: Non-exercise 24-hour Central Hemodynamics

<table>
<thead>
<tr>
<th>Variable^</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>108±8*</td>
<td>111±10†</td>
<td>116±6</td>
<td>115±6</td>
<td>0.00</td>
<td>0.29</td>
<td>0.08</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>85±7*</td>
<td>88±9†</td>
<td>93±5</td>
<td>92±5</td>
<td>0.00</td>
<td>0.45</td>
<td>0.10</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>66±6*</td>
<td>68±8†</td>
<td>74±4</td>
<td>83±5</td>
<td>0.00</td>
<td>0.73</td>
<td>0.16</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>42±6</td>
<td>43±5</td>
<td>42±5</td>
<td>42±5</td>
<td>0.75</td>
<td>0.23</td>
<td>0.36</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>59±6∗†</td>
<td>66±8†</td>
<td>55±6†</td>
<td>61±6</td>
<td>0.00</td>
<td>0.00</td>
<td>0.85</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>116±9∗</td>
<td>113±11†</td>
<td>131±10†</td>
<td>124±9</td>
<td>0.00</td>
<td>0.03</td>
<td>0.22</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>72±6*</td>
<td>70±9†</td>
<td>79±7</td>
<td>74±17</td>
<td>0.02</td>
<td>0.12</td>
<td>0.47</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>49±9*</td>
<td>49±9†</td>
<td>56±9</td>
<td>51±7</td>
<td>0.00</td>
<td>0.11</td>
<td>0.15</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>16±12*</td>
<td>16±19†</td>
<td>13±4</td>
<td>12±5</td>
<td>0.16</td>
<td>0.91</td>
<td>0.81</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>5.9±0.5*</td>
<td>5.9±1.1†</td>
<td>6.2±0.5</td>
<td>6.0±0.5</td>
<td>0.05</td>
<td>0.92</td>
<td>0.24</td>
</tr>
<tr>
<td>RM</td>
<td>0.63±0.06*</td>
<td>0.67±0.04†</td>
<td>0.61±0.04</td>
<td>0.57±0.10</td>
<td>0.00</td>
<td>0.99</td>
<td>0.08</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>14±3</td>
<td>15±3</td>
<td>15±4</td>
<td>16±4</td>
<td>0.73</td>
<td>0.90</td>
<td>0.04</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>22±4</td>
<td>22±4</td>
<td>24±7</td>
<td>23±5</td>
<td>0.18</td>
<td>0.98</td>
<td>0.36</td>
</tr>
</tbody>
</table>

^All Variables expressed as AUC/relative to number of measurements. SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; DBP, Diastolic Blood Pressure; PP, Pulse Pressure; aSBP, Aortic Systolic Blood Pressure; aDBP, Aortic Diastolic Blood Pressure; aPP, Aortic Pulse Pressure; AIx, Augmentation Index; RM, Reflection Magnitude; Pb, Reflected Wave Pressure; Pf, Forward Wave Pressure. †Significantly different than female controls; *Significantly different than male marathoners; ‡Significantly different than male controls; Significance Level, p<0.05. SxT interaction, Sex x Training Interaction.
Figure 4.4: Post-exercise 24-hour aSBP

*aSBP Post-Exercise (mmHg)*

Female Marathoners  Female Controls  Male Marathoners  Male Controls

*Significantly different than male marathoners; †Significantly different than male controls; Significance Level at p<0.05*
Table 6: 24-hour Central Hemodynamics Post-Aerobic Exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>Sex xT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>108±7*</td>
<td>111±12†</td>
<td>115±6</td>
<td>114±6</td>
<td>0.00</td>
<td>0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>86±6*</td>
<td>88±10†</td>
<td>92±5</td>
<td>92±5</td>
<td>0.00</td>
<td>0.20</td>
<td>0.33</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>67±6*</td>
<td>68±10†</td>
<td>72±5</td>
<td>73±7</td>
<td>0.00</td>
<td>0.31</td>
<td>0.68</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>41±6</td>
<td>43±5</td>
<td>42±4</td>
<td>42±4</td>
<td>0.80</td>
<td>0.37</td>
<td>0.06</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>59±6‡</td>
<td>67±7†</td>
<td>54±7†</td>
<td>61±8</td>
<td>0.00</td>
<td>0.00</td>
<td>0.84</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>114±7*</td>
<td>113±11†</td>
<td>127±10</td>
<td>122±8</td>
<td>0.00</td>
<td>0.28</td>
<td>0.51</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>72±7*</td>
<td>67±7†</td>
<td>75±5</td>
<td>77±9</td>
<td>0.00</td>
<td>0.45</td>
<td>0.17</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>44±8*</td>
<td>46±5†</td>
<td>53±5</td>
<td>49±7</td>
<td>0.00</td>
<td>0.73</td>
<td>0.97</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>17±11</td>
<td>16±15</td>
<td>14±6</td>
<td>16±4</td>
<td>0.21</td>
<td>0.47</td>
<td>0.51</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>5.9±0.5</td>
<td>5.8±0.5</td>
<td>6.0±0.5</td>
<td>6.0±0.5</td>
<td>0.23</td>
<td>0.73</td>
<td>0.97</td>
</tr>
<tr>
<td>RM</td>
<td>0.62±0.06*</td>
<td>0.65±0.08†</td>
<td>0.60±0.05</td>
<td>0.58±0.10</td>
<td>0.00</td>
<td>0.92</td>
<td>0.06</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>13.6±3.5</td>
<td>14.2±2.6</td>
<td>13.4±2.6</td>
<td>12.7±3.8</td>
<td>0.22</td>
<td>0.93</td>
<td>0.19</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>21.6±5.0</td>
<td>21.8±3.0</td>
<td>22.1±3.9</td>
<td>21.7±4.8</td>
<td>0.80</td>
<td>0.94</td>
<td>0.61</td>
</tr>
</tbody>
</table>

^All Variables expressed as AUC/relative to number of measurements. SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; DBP, Diastolic Blood Pressure; PP, Pulse Pressure; HR, Heart Rate; aSBP, Aortic Systolic Blood Pressure; aDBP, Aortic Diastolic Blood Pressure; aPP, Aortic Pulse Pressure; AIx, Augmentation Index; RM, Reflection Magnitude; Pb, Reflected Wave Pressure; Pf, Forward Wave Pressure. ‡Significantly different than female controls; *Significantly different than male marathoners; †Significantly different than male controls; Significance Level, p<0.05. SxT interaction, Sex x Training Interaction.
Table 7: Vascular correlates of LV Structure and Function in Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area Strain</th>
<th>Radial Strain</th>
<th>24-hour PWV</th>
<th>3D LVMI</th>
<th>24-hour SBP</th>
<th>24-hour aSBP</th>
<th>24-hour Alx</th>
<th>24-hour RM</th>
<th>Ea</th>
<th>Elv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial Strain</td>
<td>-0.929*</td>
<td>0.346*</td>
<td>-0.348*</td>
<td></td>
<td>0.290*</td>
<td>-0.308*</td>
<td>0.168</td>
<td>-0.249</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour PWV</td>
<td>-0.440*</td>
<td>0.370*</td>
<td>-0.100</td>
<td></td>
<td>0.214</td>
<td>-0.237</td>
<td>0.080</td>
<td>-0.021</td>
<td>0.749*</td>
<td></td>
</tr>
<tr>
<td>3D LVMI</td>
<td>-0.316*</td>
<td>-0.317*</td>
<td>-0.213</td>
<td>0.202</td>
<td>-0.203</td>
<td>-0.035</td>
<td>0.134</td>
<td>0.076</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>24-hour aSBP</td>
<td>0.635*</td>
<td>-0.551*</td>
<td>0.184</td>
<td>-0.265*</td>
<td>0.195</td>
<td>0.115</td>
<td>0.123</td>
<td>0.075</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour Alx</td>
<td>-0.316*</td>
<td>0.317*</td>
<td>-0.213</td>
<td>0.202</td>
<td>-0.203</td>
<td>-0.035</td>
<td>0.134</td>
<td>0.076</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>24-hour RM</td>
<td>0.681*</td>
<td>-0.590*</td>
<td>0.303*</td>
<td>-0.334*</td>
<td>0.088</td>
<td>0.090</td>
<td>-0.693*</td>
<td>0.133</td>
<td>0.730*</td>
<td>-0.581*</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed).

2D, Two-dimensional
3D, Three-dimensional
LV, Left Ventricle
LVM, Left Ventricle Mass
BSA, Body Surface Area
24-hour values are AUC/relative
SBP, Systolic Blood Pressure

a, Aortic
Alx, Augmentation Index
RM, Reflection Magnitude
Table 8: Vascular correlates of LV Structure and Function in Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area Strain</th>
<th>Radial Strain</th>
<th>24-hour PWV</th>
<th>3D LVM</th>
<th>24-hour SBP</th>
<th>24-hour aSBP</th>
<th>24-hour AIx</th>
<th>24-hour RM</th>
<th>Ea</th>
<th>Elv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial Strain</td>
<td>-0.919</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour PWV</td>
<td>0.023</td>
<td>-0.191</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D LVMI</td>
<td>0.084</td>
<td>-0.024</td>
<td>-0.297</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hours SBP</td>
<td>0.048</td>
<td>-0.152</td>
<td>0.462*</td>
<td>-0.215</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hours aSBP</td>
<td>0.015</td>
<td>-0.126</td>
<td>0.146</td>
<td>-0.074</td>
<td>0.556*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour AIx</td>
<td>-0.179</td>
<td>0.126</td>
<td>-0.084</td>
<td>-0.044</td>
<td>-0.048</td>
<td>-0.084</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour RM</td>
<td>0.211</td>
<td>-0.285</td>
<td>-0.022</td>
<td>0.166</td>
<td>0.063</td>
<td>0.256</td>
<td>0.318*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea</td>
<td>0.399*</td>
<td>-0.399*</td>
<td>-0.034</td>
<td>-0.272</td>
<td>-0.141</td>
<td>-0.084</td>
<td>-0.181</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elv</td>
<td>-0.612*</td>
<td>0.653*</td>
<td>-0.375*</td>
<td>-0.210</td>
<td>-0.158</td>
<td>-0.060</td>
<td>-0.080</td>
<td>-0.078</td>
<td>0.241</td>
<td></td>
</tr>
<tr>
<td>Ea/Elv</td>
<td>0.835*</td>
<td>0.786*</td>
<td>0.550*</td>
<td>-0.091</td>
<td>0.142</td>
<td>0.156</td>
<td>-0.049</td>
<td>0.212</td>
<td>0.509*</td>
<td>-0.644*</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed).

2D, Two-dimensional
3D, Three-dimensional
LV, Left Ventricle
LVM, Left Ventricle Mass
BSA, Body Surface Area
24-hour values are AUC/relative
SBP, systolic Blood Pressure
PP, Pulse Pressure
a, Aortic
AIx, Augmentation Index

Supplemental Table 9: Comparison of Non-exercise 24-hour hemodynamics to Post-AE hemodynamics
### Table of Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male marathoners (n=24)</th>
<th>Male controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>Time Effect</th>
<th>SxTxTime Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-exercise SBP (mmHg)</td>
<td>108±8</td>
<td>111±10</td>
<td>116±6</td>
<td>115±6</td>
<td>0.35</td>
<td>0.78</td>
<td>0.41</td>
<td>0.83</td>
</tr>
<tr>
<td>Post-AE SBP (mmHg)</td>
<td>108±7</td>
<td>111±12</td>
<td>115±6</td>
<td>114±6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise aSBP (mmHg)</td>
<td>116±9^*</td>
<td>113±11†</td>
<td>131±10</td>
<td>124±9</td>
<td><strong>0.00</strong></td>
<td>0.15</td>
<td>0.93</td>
<td>0.56</td>
</tr>
<tr>
<td>Post-AE aSBP (mmHg)</td>
<td>114±7^*</td>
<td>113±11†</td>
<td>127±10</td>
<td>122±8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise aPP (mmHg)</td>
<td>49±9^*</td>
<td>49±9†</td>
<td>56±9</td>
<td>51±7</td>
<td><strong>0.00</strong></td>
<td>0.73</td>
<td>0.15</td>
<td>0.21</td>
</tr>
<tr>
<td>Post-AE aPP (mmHg)</td>
<td>44±8^*</td>
<td>46±5†</td>
<td>53±5</td>
<td>49±7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise MAP (mmHg)</td>
<td>85±7</td>
<td>88±9</td>
<td>93±5</td>
<td>92±5</td>
<td>0.18</td>
<td>0.48</td>
<td>0.30</td>
<td>0.43</td>
</tr>
<tr>
<td>Post-AE MAP (mmHg)</td>
<td>86±6</td>
<td>88±10</td>
<td>92±5</td>
<td>92±5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise AIx (%)</td>
<td>16±12</td>
<td>16±19</td>
<td>13±4</td>
<td>12±5</td>
<td>0.09</td>
<td>0.45</td>
<td>0.31</td>
<td>0.20</td>
</tr>
<tr>
<td>Post-AE AIx (%)</td>
<td>17±11</td>
<td>16±15</td>
<td>14±6</td>
<td>16±4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise PWV (m/s)</td>
<td>5.9±0.5</td>
<td>6.1±1.1</td>
<td>6.2±0.5</td>
<td>6.0±0.5</td>
<td>0.32</td>
<td>0.83</td>
<td>0.41</td>
<td>0.95</td>
</tr>
<tr>
<td>Post-AE PWV (m/s)</td>
<td>5.9±0.5</td>
<td>5.8±0.5</td>
<td>6.0±0.5</td>
<td>6.0±0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise Pb (mmHg)</td>
<td>14±3</td>
<td>15±3</td>
<td>15±4</td>
<td>13.1±4</td>
<td>0.96</td>
<td>0.41</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Post-AE Pb (mmHg)</td>
<td>14±3</td>
<td>14±3</td>
<td>13±3</td>
<td>13±4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise Pf (mmHg)</td>
<td>22±4</td>
<td>22±4</td>
<td>24±7</td>
<td>23±5</td>
<td>0.30</td>
<td>0.98</td>
<td>0.36</td>
<td>0.51</td>
</tr>
<tr>
<td>Post-AE Pf (mmHg)</td>
<td>22±5</td>
<td>22±3</td>
<td>22±4</td>
<td>22±5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-exercise RM</td>
<td>0.63±0.06</td>
<td>0.67±0.04</td>
<td>0.61±0.04</td>
<td>0.57±0.10</td>
<td>0.38</td>
<td>0.81</td>
<td>0.70</td>
<td>0.46</td>
</tr>
<tr>
<td>Post-AE RM</td>
<td>0.62±0.06</td>
<td>0.65±0.08</td>
<td>0.60±0.05</td>
<td>0.58±0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^All Variables expressed as AUC/relative to number of measurements. SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; DBP, Diastolic Blood Pressure; PP, Pulse Pressure; HR, Heart Rate; aSBP, Aortic Systolic Blood Pressure; aDBP, Aortic Diastolic Blood Pressure; aPP, Aortic Pulse Pressure; AIx, Augmentation Index; PWV, Pulse-wave velocity; RM, Reflection Magnitude; Pb, Reflected Wave Pressure; Pf, Forward Wave Pressure. †Significantly different than female controls; *Significantly different than male marathoners; ‡Significantly different than male controls; Significance Level, p<0.05. SxT interaction, Sex x Training Interaction.
Chapter V: Summary, Future Directions and Conclusions

Over the past few decades there has been increased participation in endurance events, such as marathons. The impact of aerobic exercise on risk for CVD is well-established as beneficial for the cardiovascular system. However, there is some debate as to whether excessive endurance exercise, such as completing multiple marathons, is detrimental to the cardiovascular system. Some studies in male marathoners note adverse cardiac structural remodeling, ventricular contractile abnormalities [2, 3] coronary artery calcification and fibrosis [2, 3]. Despite, well-established sex differences in cardiovascular risk and physiology across the lifespan, and an increase in the number of women marathon participants, no studies have examined sex differences in the impact of chronic endurance exercise on cardiovascular system. Thus, our study examined sex differences in cardiovascular structure, function and vascular hemodynamics in marathon runners and recreationally active individuals.

Our initial hypotheses were largely unsupported by our findings (Figure 5.1). Unexpectedly, we found that female marathoners had larger relative LV and better ventricular vascular coupling compared to recreationally active females and male counterparts. Additionally, we found marathoners to have similar LV function and 24-hour hemodynamics compared to recreationally active controls. However, females irrespective of training status had lower overall hemodynamic load. This suggests that running multiple marathons does not appear to reduce LV function or increase hemodynamic load (i.e. blood pressure, aortic stiffness and wave reflections) in middle aged men and women. Upon further exploration, female marathoners also had significantly higher ventricular-vascular coupling, an index for myocardial performance and efficiency. Indeed, our data suggests that a larger LVMI in female marathoners was associated
with increased cardiac contractility and efficiency, lower hemodynamic stress, and preserved LV function.

**Figure 5.1: Theoretical Framework with Hypotheses and Findings.** Red indicates findings that did not support our hypotheses.

**Implications**

CVD is the leading cause of morbidity and mortality in women in the United States [195]. With increasing age, risk for CVD in women exceeds that in men [196]. It is expected that by 2020 approximately 20% of the population of the United States will be 65 years or older.
As women age, they experience greater increases in artery stiffness and hypertension compared to men, which contributes to reduced LV function and increased incidence of heart failure. Therefore, it is important that we examine how strategies to reduce risk for CVD, impact at risk populations, such as women.

Aerobic exercise is a well-established and effective lifestyle strategy to attenuate risk for CVD in women [198-200]. Over the past 30 years there has been a steady increase in the number of women racing competitive endurance events such as marathons. However, there is little research examining the effects of this chronic strenuous endurance exercise training on cardiovascular health in women. Recent research in men suggests the potential for adverse ventricular remodeling, coronary plaque, and myocardial fibrosis, which are associated with cardiac arrhythmias and sudden cardiac death [27-29].

The results of our study suggest that although female marathoners had larger LV mass, they had preserved LV function, lower central hemodynamic load and optimal ventricular-vascular coupling. Previous studies that examine male marathoners with similar cardiac adaptations show that a larger ventricle is associated with reduced function, and higher hemodynamic load. Thus, female sex may confer a level of cardio-protection from possible cardiac mal-adaptations with habitual endurance exercise training. Understanding the ventricular-vascular response to regular endurance exercise may also have important clinical implications for women as ventricular-vascular uncoupling with age in women has been linked to greater risk of heart failure with preserved ejection fraction [44, 48]. Recoupling with endurance exercise may offer an important therapeutic strategy to mitigate CVD risk in women [224].

**Future Directions**
Future studies stemming from this study might examine older marathoners (>50 years) to determine whether these sex differences extend into older age, particularly when women reach menopause. Prior to menopause women are expected to have lower cardiovascular risk than age-matched men [238]. Indeed, pre-menopausal women have lower hemodynamic stress compared to men [45, 238]. The results from our study confirm these previous findings and suggest that this is even true in female marathoners. However, risk for CVD in women shifts once women reach menopause. In post-menopausal women experience a larger reduction in vascular function and are at a two-fold increase for cardiovascular events after the age of 50 years, compared to men [238]. It would be compelling to determine whether chronic marathon running might prevent the menopause related increased in hemodynamic load. Equally, it would be interesting to determine if, similar to our findings, post-menopausal female marathoners have lower hemodynamic load compared to age-matched male marathoners.

We evaluated sex differences in LV structure and function based on one single echocardiography measure. A future study might follow up with the participants in the current study to re-evaluate their LV structure, function and hemodynamics to determine whether these sex differences persist in 3-6 months or even 3-5 years. We do not know how dynamic the changes to the LV are in response to endurance training or whether our results were actually due to the marathon training or random error. In order to truly confirm our results, we would ideally like to perform a follow-up study with the current study participants. Another study possibility would be to include a true sedentary control group, in addition to the recreationally active and marathon group. This might give us a broader spectrum for the type of changes that occur to the LV in response to no physical activity or exercise compared to moderate levels of activity to marathon training. Although this study would then incorporate six study groups and be a
substantial study design to take on, it would provide insight into sex differences in LV function and hemodynamics across exercise groups.

Furthermore, there is still limited research on sex differences in how chronic marathon running impacts the cardiovascular system beyond the level of the heart. For instance, we know there are physiological sex differences in the other systemic arteries, such as the leg (femoral) arteries that are readily impacted by marathon training. Systemic vascular health has implications for overall cardiovascular risk. Additionally, there are known sex differences in the cerebrovascular health and we currently do not know how chronic endurance exercise impacts cerebrovascular health. Cerebrovascular health has implications for overall cardiovascular risk, cerebrovascular disease and dementia. Thus, future studies might examine sex differences in femoral and cerebral hemodynamics in marathoners.

During the course of the data collection for this study we simultaneously collected additional data to preliminarily examine sex differences on the effect of chronic endurance training on systemic vasculature. More specifically, during the first study visit, we examined femoral arterial health and simultaneously measured medial cerebral artery hemodynamics (measurements of brain blood flow). The following is a summary of our additional findings stemming from our investigation of sex differences in cardiac adaptations to chronic endurance exercise. These findings will be the subject of future studies and publications that examine sex differences in cardiovascular adaptations to chronic endurance exercise.

**Preliminary Data 1: Sex Differences in Cerebral Blood Flow and Vascular Hemodynamics in Marathon Runners**

Aortic stiffness increases with aging and is associated with cognitive decline [239, 240]. Increases in aortic stiffness may lead to increased cerebral pulsatility, which is associated with
reduced cerebral perfusion [136] [241] and increased risk for cerebrovascular disease and dementia [136] [241]. Interestingly, across the lifespan women have lower arterial stiffness and better cerebral perfusion compared to men [242]. Regular physical activity reduces arterial stiffness [243]. Thus, aerobic exercise is a strategy to reduce aortic stiffness, and improve cerebral perfusion. Although aerobic exercise has a favorable effect on arterial stiffness, too much exercise may be detrimental to the vasculature. For instance, marathon runners, who engage in habitual aerobic exercise may have increased arterial stiffness [40]. In contrast, the results of our current study suggest that marathoners have similar aortic stiffness compared to their recreationally active counterparts. Nonetheless, females irrespective of training status had lower arterial stiffness and blood pressure compared to men. However, to date no study has examined sex differences in cerebral perfusion and arterial stiffness in an endurance-trained or marathon runner population [244]. Thus, the purpose of the current study was to examine aortic stiffness and cerebral blood flow in male and female marathon runners and recreationally-active controls.

Eighty-six marathon runners and recreationally active controls participated in the current study; n=19 male controls (age 41±4 years), n=23 male marathoners (age 42±5 years), n=25 female controls age (42±5 years), and n=19 female marathoners (42±5 years). Participants completed one visit to the Human Performance Laboratory, 12 hours fasted, no caffeine, alcohol or exercise.
Measures taken in addition to those already outlined in the current study (Chapter V) were:

1) common carotid artery (CCA) stiffness measured using eTracking. The carotid artery was imaged below the carotid bulb using ultrasound (ProSound α7, Aloka, Tokyo, Japan) and a 7.5- 10.0 MHz linear-array probe; 2) Middle cerebral artery (MCA) blood velocity (MnV), pulsatility index (PI) were measured using Transcranial Doppler (TCD) using a 2-MHz transcranial probe applied to the left temporal window. A one-way Analysis of Variance (ANOVA) determined mean differences within and between groups on main outcomes. Data were analyzed in SPSS (SPSS Inc., IBM; Chicago, IL) with a significance level set a priori at $p<0.05$.

The results from this data show that CBF MnV was similar between male marathoners and male controls ($Table 5.2$, 63±11 vs. 65±14 m/s, $p<0.05$) and female marathoners and female controls (80±15 vs. 74±14 m/s, $p<0.05$). Interestingly, CBF MnV was significantly higher in female marathoners compared to male marathoners (74±14 m/s vs. 63±11 m/s, $p<0.05$). Cerebral PI and aortic stiffness were similar between male marathoners and male controls (0.70±0.10 vs. 0.71±0.10 and 6.8±1.1 vs. 7.0±1.1 m/s, respectively, $p>0.05$) and female marathoners and female controls and (0.70±0.10 vs. 0.72±0.08 and 6.8±1.0 vs. 6.5±1.1 m/s, respectively, $p>0.05$). Cerebral PI and aortic stiffness were also similar between male and female marathoners (0.71±0.10 vs 0.70±0.10 vs. and 7.0±1.1 vs. 6.8±1.0 m/s, respectively, $p>0.05$).

In conclusion, male marathoners and male controls had similar aortic stiffness, cerebral
mean velocity and pulsatility. Female marathoners and female controls had similar aortic stiffness, cerebral mean velocity and pulsatility. Interestingly, female marathoners had significantly higher cerebral mean velocity compared to male marathoners. Thus, the current study suggests that regular participation in marathons is not detrimental or beneficial to arterial health or cerebral blood flow. Reasons that female marathoners may have better cerebral perfusion compared to male counterparts might be due to the protective effects of estradiol. Higher levels of estradiol are associated with increased systemic perfusion, improved arterial stiffness and increased cerebral perfusion. Notably, studies in post-menopausal women show with increasing age concomitant reductions in cerebral perfusion may be predominantly due to the absence of estrogen (10).

These data are similar to our findings that LV structure, function and hemodynamics were similar between marathoners and controls in both men and women. Additionally, similar to our findings regarding LVMI, female marathoners had better cerebral perfusion and cardiac performance compared to male marathoners. Increased cerebral perfusion in female marathoners may be associated with reduced risk for cerebrovascular disease and dementia. This is important as post-menopausal women have a two-fold risk for development of cardiovascular disease and development of dementia [226]. Thus, future studies are needed to determine whether these beneficial adaptations observed in female marathoners extend to post-menopausal women, when women lose the protective effects of estrogen.
Table 5.1: Cerebral and Carotid Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Male Marathoners (n=23)</th>
<th>Male Controls (n=19)</th>
<th>Female Marathoners (n=19)</th>
<th>Female Controls (n=25)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SXT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic SBP (mmHg)</td>
<td>114±10</td>
<td>109±12</td>
<td>111±13</td>
<td>110±12</td>
<td>0.00</td>
<td>0.74</td>
<td>0.94</td>
</tr>
<tr>
<td>Aortic DBP (mmHg)</td>
<td>77±7</td>
<td>75±7</td>
<td>74±6</td>
<td>76±7</td>
<td>0.02</td>
<td>0.28</td>
<td>0.86</td>
</tr>
<tr>
<td>Aortic PWV (m/s)</td>
<td>6.9±1.1</td>
<td>6.8±1.1</td>
<td>6.7±1.1</td>
<td>6.5±1.1</td>
<td>0.90</td>
<td>0.85</td>
<td>0.70</td>
</tr>
<tr>
<td>MCA MnV (cm/s)</td>
<td>62±11</td>
<td>65±14</td>
<td>79±15*</td>
<td>74±14</td>
<td>0.02</td>
<td>0.35</td>
<td>0.55</td>
</tr>
<tr>
<td>MCA PI</td>
<td>0.71±0.10</td>
<td>0.70±0.10</td>
<td>0.70±0.10</td>
<td>0.72±0.08</td>
<td>0.87</td>
<td>0.75</td>
<td>0.90</td>
</tr>
<tr>
<td>CCA IMT systole (mm)</td>
<td>0.47±.07</td>
<td>0.54±.13</td>
<td>0.50±.14</td>
<td>0.48±.11</td>
<td>0.39</td>
<td>0.30</td>
<td>0.09</td>
</tr>
<tr>
<td>CCA Diameter systole (mm)</td>
<td>5.15±0.36</td>
<td>4.98±0.43</td>
<td>5.79±0.41</td>
<td>5.83±0.42</td>
<td>0.00</td>
<td>0.30</td>
<td>0.14</td>
</tr>
<tr>
<td>CCA IMT End Diastole (mm)</td>
<td>0.44±0.06</td>
<td>0.49±0.09</td>
<td>0.48±0.16</td>
<td>0.46±0.10</td>
<td>0.72</td>
<td>0.63</td>
<td>0.10</td>
</tr>
<tr>
<td>CCA Diameter End Diastole (mm)</td>
<td>5.60±0.36</td>
<td>5.34±0.47</td>
<td>6.26±0.47</td>
<td>6.27±0.47</td>
<td>0.00</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>CCA PI</td>
<td>1.29±0.21</td>
<td>1.30±0.25</td>
<td>1.65±0.34</td>
<td>1.56±0.25</td>
<td>0.00</td>
<td>0.41</td>
<td>0.34</td>
</tr>
<tr>
<td>CCA MnV (cm/s)</td>
<td>40.7±5.7</td>
<td>42.3±5.6</td>
<td>36.4±6.1</td>
<td>50.7±58.9</td>
<td>0.73</td>
<td>0.10</td>
<td>0.29</td>
</tr>
</tbody>
</table>

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PWV, Pulse Wave Velocity; MnV, Mean Velocity; PI, Pulsatility Index; IMT, Intima Media Wall Thickness; CCA, Common carotid artery. *Significantly different than male marathoners, Significance, p<0.05.
Preliminary Data 2: Sex Differences in Femoral Hemodynamics in Marathon Runners

Shear Stress is the frictional force of blood on the arterial wall and it is essential for arterial adaptations to various stimuli [160, 245]. At rest, shear stress exhibits a pattern whereby during systole the blood travels towards the periphery (antergrade shear) and during diastole the blood travels back towards the heart (retrograde shear). Antegrade shear has anti-atherogenic effects on the vasculature [160], while increases in retrograde shear are associated with proatherogenic effects [245]. Increases in retrograde shear are associated with increased arterial stiffness in the systemic vasculature [233]. The vasculature in the lower limbs, such as the femoral arteries are more susceptible to increases in retrograde shear. Thus, it is crucial to prevent increases in retrograde shear to reduce risk for atherosclerosis.

Exercise is potent stimulus to augment blood flow, shear stress and thus, is beneficial to the vasculature. Exercise-trained arteries are notably larger in diameter and have attenuated retrograde blood flow and shear compared to sedentary individuals. Exercise is thus, a beneficial means to attenuate resting retrograde shear. Endurance athletes, such as, marathon runners, engage in chronic prolonged bouts of exercise and thus, experience prolonged increases in shear stress. Some studies suggest that prolonged shear stress, such as occurs with endurance exercise, are paradoxically associated with increased arterial stiffness. Whether marathon runners have increased retrograde shear is unknown.

Given that marathoners predominately stress and train their legs, examining femoral blood flow patterns in marathon runners might provide ideal insight into the effects of chronic endurance exercise on femoral artery hemodynamics. Interestingly, women are reported to have lower aortic stiffness, and lower retrograde blood flow compared to men. However, it is currently unknown whether there are sex differences in leg blood flow patterns in marathon
runners. Thus, the aim of this study was to examine sex differences in superficial femoral artery stiffness and shear patterns in marathoners and recreationally-active adults.

101 (53 female, 48 male) healthy marathon runners and recreationally active adults (35-50 years) participated in the current study. Participants completed one visit to the Human Performance Laboratory, 12 hours fasted, no caffeine, alcohol or exercise.

Measures taken in addition to those already outlined in the current study (Chapter V) were: 1) Femoral-Tibialis Anterior (Leg) Pulse Wave Velocity (PWV). Applanation tonometry of femoral and tibalis-anterior (ankle) pulse sites assessed pulse wave velocity as a measure of leg stiffness (SphygmoCor, AtCor Medical; Sydney, Australia); 2) Superficial Femoral Artery was imaged using Doppler ultrasound technology (ProSound α7, Aloka, Tokyo, Japan) The T- and R-wave diameter and intima-media thickness (IMT) measurements were taken from their respective image; 3) Systolic antegrade, systolic retrograde, and diastolic antegrade, and mean blood velocity ($V_m$) were measured with Doppler ultrasound. These variables were automatically calculated by the echo-tracking software. $V_m$ was computed with the following formula: $V_m = \int V(t)dt / FT$. $\int V(t)dt$ is the velocity-time integral of the velocity waveform, and FT is flow time; 4) Shear rate was calculated using the following formula: Shear rate = $4 \times (V_m / \text{Diameter})$. A one-way Analysis of Variance (ANOVA) determined mean differences within and between groups on main outcomes. Data were analyzed in SPSS (SPSS Inc., IBM; Chicago, IL) with a significance level set a priori at $p<0.05$.

The results from this data show that femoral-tibialis anterior PWV was significantly higher in males compared to females, independent of training status (Table 5.2; $p<0.05$). IMT in
end diastole was similar between males and females but significantly higher in male marathoners compared to male controls (p<0.05). IMT in end systole was similar between all groups (p>0.05). SFA diameter in end diastole and end systole was smaller in females than males but both marathoners had larger diameters compared to controls (p<0.05). There were no differences in antegrade and retrograde pulsatility index (PI) (p>0.05). Antegrade MnV was higher in females than males, independent of training status (p<0.05). Retrograde MnV and diastolic antegrade PI was significantly lower in female marathoners compared to both recreationally active females and men, independent of training status (p<0.05). Diastolic antegrade MnV was lower in females than males, irrespective of training status (p<0.05). Systolic and diastolic antegrade shear were higher in females than males (p<0.05). There were no differences in retrograde shear or oscillatory shear index (p>0.05).

In conclusion, marathoners had larger femoral arteries compared to the recreationally active adults. Femoral artery stiffness was higher in men compared to women. Although female marathoners had lower retrograde blood flow compared to both recreationally active females and males, retrograde shear was similar between all groups. Females overall had higher antegrade blood flow and shear compared to males. This data suggests that running multiple marathons does not increase retrograde blood flow or shear stress and thus, may not be pro-atherogenic. Moreover, females irrespective of training status had lower leg stiffness, higher antegrade blood flow and shear, suggesting women may have better arterial function, and reduced risk for systemic atherosclerosis. Reasons for why women have higher antegrade blood flow and shear stress might be due to the presence of estrogen which is known to potentiate the production of nitric oxide and other vasoactive substances to promote arterial vasodilation and augment shear stress [180].
Similar to the findings of our larger scale study, marathon running does not appear to augment pro-atherogenic shear patterns in the femoral artery and is thus, not associated with increased atherosclerosis. Females regardless of training status have better leg blood flow, higher shear rates and lower leg artery stiffness. Future studies should incorporate indices of artery function to confirm these findings and examine femoral blood flow patterns in post-menopausal women to determine whether these findings extend to an older population that is at an increased risk for atherosclerosis.
Table 5.2: SFA Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral-tibialis Anterior PWV (m/s)</td>
<td>4.2±3.0*</td>
<td>5.3±3.7*</td>
<td>5.8±4.3^</td>
<td>7.2±3.8</td>
<td>0.03</td>
<td>0.15</td>
<td>0.79</td>
</tr>
<tr>
<td>SFA IMT End Diastole (mm)</td>
<td>0.39±0.06</td>
<td>0.39±0.08</td>
<td>0.42±0.10^</td>
<td>0.36±0.06</td>
<td>0.96</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>SFA Diameter End Diastole (mm)</td>
<td>5.30±0.52^^</td>
<td>4.98±0.45*</td>
<td>6.79±0.53</td>
<td>6.46±0.82</td>
<td>0.00</td>
<td>0.00</td>
<td>0.85</td>
</tr>
<tr>
<td>SFA IMT End Systole (mm)</td>
<td>0.39±0.06</td>
<td>0.38±0.06</td>
<td>0.40±0.07</td>
<td>0.37±0.08</td>
<td>0.91</td>
<td>0.32</td>
<td>0.57</td>
</tr>
<tr>
<td>SFA Diameter End Systole (mm)</td>
<td>5.48±0.61^^</td>
<td>5.18±0.51*</td>
<td>6.95±0.60^</td>
<td>6.63±0.83</td>
<td>0.00</td>
<td>0.01</td>
<td>0.88</td>
</tr>
<tr>
<td>SFA PI Systolic Antegrade</td>
<td>1.70±0.14</td>
<td>2.15±2.34</td>
<td>1.71±0.15</td>
<td>1.71±0.12</td>
<td>0.35</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>SFA-MnV Systolic Antegrade (cm/s)</td>
<td>38.5±6.5*</td>
<td>38.0±8.5*</td>
<td>34.8±5.2</td>
<td>35.1±5.1</td>
<td>0.01</td>
<td>0.95</td>
<td>0.85</td>
</tr>
<tr>
<td>SFA-PI Retrograde (cm/s)</td>
<td>1.34±1.1</td>
<td>1.12±0.23</td>
<td>1.26±0.55</td>
<td>1.14±0.30</td>
<td>0.81</td>
<td>0.17</td>
<td>0.64</td>
</tr>
<tr>
<td>SFA-MnV Retrograde (cm/s)</td>
<td>15.7±2.2^*</td>
<td>18.1±3.9</td>
<td>18.4±4.3</td>
<td>19.2±3.9</td>
<td>0.04</td>
<td>0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>SFA-PI Diastolic Antegrade (cm/s)</td>
<td>0.76±0.27^*</td>
<td>0.85±0.36</td>
<td>0.95±0.28</td>
<td>0.89±0.31</td>
<td>0.05</td>
<td>0.98</td>
<td>0.35</td>
</tr>
<tr>
<td>SFA-MnV Diastolic Antegrade (cm/s)</td>
<td>9.2±2.5^*</td>
<td>8.6±1.7</td>
<td>9.8±1.4</td>
<td>10.1±1.6</td>
<td>0.01</td>
<td>0.48</td>
<td>0.15</td>
</tr>
<tr>
<td>Systolic Antegrade shear (/s)</td>
<td>281.0*</td>
<td>293.4*</td>
<td>218.7</td>
<td>211.8</td>
<td>0.04</td>
<td>0.18</td>
<td>0.65</td>
</tr>
<tr>
<td>Retrograde Shear (/s)</td>
<td>118.5</td>
<td>145.4</td>
<td>108.4</td>
<td>118.9</td>
<td>0.10</td>
<td>0.15</td>
<td>0.75</td>
</tr>
<tr>
<td>Diastolic Antegrade Shear (/s)</td>
<td>67.2^*</td>
<td>66.4^*</td>
<td>56.4</td>
<td>60.9</td>
<td>0.05</td>
<td>0.25</td>
<td>0.65</td>
</tr>
<tr>
<td>Oscillatory Shear Index</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.40</td>
<td>0.85</td>
<td>0.86</td>
<td>0.96</td>
</tr>
</tbody>
</table>

PWV, Pulse Wave Velocity; SFA, superficial femoral artery; IMT, Intima thickness; PI, Pulsatility Index; MnV, Mean Velocity; *Significantly different than males; ^Significantly different than controls, p<0.05.
Additional Considerations: Impact of Race and Ethnicity.

In the current study, all participants self-reported Caucasian (i.e. White or of European Descent) as their race/ethnicity. This may be reflective of the actual race/ethnic make-up of marathon race participation. In the United States, it is reported that 90% of marathon finishers are White, 5.1% Hispanic, 3.9% Asian/Pacific Islander, and 1.6% Black [223]. Reasons for a lack of diversity in the marathon running population may be due to specific barriers to participation and/or social and cultural stereotypes that surround sport participation and success.

Some barriers to marathon race participation might be 1) access to training programs, gym facilities, and coaches; 2) cost of race participation and training equipment; 3) time to train due to family or job obligations (as a few examples). Additionally, social and cultural stereotypes exist with regards to sport participation and success. In particular, some cultures perceive that only certain sports are performed by certain races or ethnicities. Similarly, some cultures perceive they will only have success in certain sports based on the stereotypes projected from society and culture (i.e. professional sports). Efforts through scholarships, education, and increased access to training opportunities should be made to reduce the diversity gap in marathon race participation.

Moreover, there are well-established racial and ethnic differences in risk for cardiovascular disease (CVD) across the lifespan [246]. Risk for CVD and CVD mortality is higher in blacks compared with white counterparts [246]. Interestingly, despite Hispanics having a higher risk for CVD they have a lower overall CVD mortality compared to [247] non-Hispanic counterparts. Asians/Pacific Islanders have lower CVD risk and mortality but a higher risk for stroke [248]. These racial and ethnic differences in CVD risk and mortality might stem from well-established racial and ethnic differences in vascular function. In particular, studies in
African Americans have shown that African Americans have higher blood pressure [250], arterial stiffness [251] and development of heart failure [252] earlier in life compared with white Americans, and this is apparent across the life span [251, 253, 254]. Additionally, African Americans have been reported to have an exaggerated blood pressure response to acute exercise which might impact heightened risk for CVD [255]. Both resting and exercise related cardiovascular function is less clear in Asian and Hispanic populations. Future studies are necessary to examine the racial and ethnic differences in cardiovascular responses to endurance exercise. In regards to the current study, future studies are necessary to discern the effect of chronic endurance exercise (i.e. marathons) on cardiovascular function and risk for CVD in a multi-ethnic population.
Conclusion

The main findings of this study were that: (1) female marathoners had larger LVMI and better ventricular-vascular coupling compared to all other groups; (2) overall LV function was similar among all groups; (3) females had lower central hemodynamic load then men irrespective of training status. Our findings suggest that although female marathoners had larger LVMI they did not have LV dysfunction or increased central hemodynamics load and had better overall ventricular-vascular coupling. Thus, female marathoners experienced physiological not pathological cardiac hypertrophy. Moreover, while there were sex differences in central hemodynamics, chronic marathon training and racing does not appear to reduce LV function, or increase central hemodynamic load in otherwise healthy middle-aged men and women, suggesting that running multiple marathons is not detrimental to cardiovascular health.
Summary of Findings

- Female marathoners had larger LVMI and better ventricular-vascular coupling compared to all other groups.
- Overall LV function was similar among all groups.
- Females had lower central hemodynamic load than men irrespective of training status.
- Female marathoners had larger LVMI; they did not have LV dysfunction or increased central hemodynamics load and had better overall ventricular-vascular coupling.
- Chronic marathon training and racing does not appear to reduce LV function, or increase central hemodynamic load in otherwise healthy middle-aged men and women.
- Running multiple marathons is not detrimental to cardiovascular health in middle-aged men and women.
Appendix

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TO: Kevin Heffernan  
DATE: April 12, 2017  
SUBJECT: Expedited Protocol Review - Approval of Human Participants  
IRB #: 17-135  
TITLE: *Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise*  

The above referenced protocol was reviewed by the Syracuse University Institutional Review Board for the Protection of Human Subjects (IRB) and has been given expedited approval. The protocol has been determined to be of no more than minimal risk and has been evaluated for the following:

1. the rights and welfare of the individual(s) under investigation;  
2. appropriate methods to secure informed consent; and  
3. risks and potential benefits of the investigation.

The approval period is **April 11, 2017** through **April 10, 2018**. A continuing review of this protocol must be conducted before the end of this approval period. Although you will receive a request for a continuing renewal approximately 60 days before that date, it is your responsibility to submit the information in sufficient time to allow for review before the approval period ends.

Enclosed are the IRB approved date stamped consent and/or assent document/s related to this study that expire on **April 10, 2018**. The IRB approved date stamped copy must be duplicated and used when enrolling new participants during the approval period (may not be applicable for electronic consent or research projects conducted solely for data analysis). Federal regulations require that each participant indicate their willingness to participate through the informed consent process and be provided with a copy of the consent form. Regulations also require that you keep a copy of this document for a minimum of three years after your study is closed.

Any changes to the protocol during the approval period cannot be initiated prior to IRB review and approval, except when such changes are essential to eliminate apparent immediate harm to the participants. In this instance, changes must be reported to the IRB within five days. Protocol changes must be submitted on an amendment request form available on the IRB web site. Any unanticipated problems involving risks to
subjects or others must be reported to the IRB within 10 working days of occurrence.

Thank you for your cooperation in our shared efforts to assure that the rights and welfare of people participating in research are protected.

Katherine McDonald IRB Chair

DEPT: Exercise Science, 820 Comstock Ave. – Rm. 201 CC: Kan Liu, Wesley Lefferts, Jacqueline Augustine, Jacob DeBlois, Robert Voelker
DATE: August 1, 2017

TO: Kan Liu, MD, PhD
FROM: SUNY Upstate IRB

SUBMISSION TYPE: Amendment/Modification
PROJECT TITLE: [1005999-4] Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise

UPSTATE IRB #: 2017-0

ACTION: APPROVED
APPROVAL DATE: August 1, 2017
EXPIRATION DATE: March 12, 2018
REVIEW TYPE: Expedited Review

Thank you for your submission of Amendment/Modification materials for this project. The SUNY Upstate IRB has APPROVED your submission. The materials submitted were reviewed in accordance with Federally-defined categories of expedited review outlined in 45 CFR 46.110(b) and 21 CFR56.110(b).

All research must be conducted in accordance with this approved submission. As the Principal Investigator, you are responsible for the overall conduct of this research study.
Please note that any modifications to the project as approved must be reviewed and approved by this committee prior to initiation (unless the change is required to eliminate an immediate hazard to the subjects).

Where obtaining informed consent/permission/assent is required as a condition of approval, be sure to assess subject capacity in every case, and continue to monitor the subject's willingness to be in the study throughout his/her duration of participation. Only use current, Upstate-stamped forms in the consent process and retain a complete copy of each signed form with your study records. Consent must be obtained and documented prior to the initiation of any study procedures. Provide each participant with a complete copy of the signed consent document.

Report All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTED adverse events promptly to this office, per the IRB policy. All FDA and sponsor reporting requirements should also be followed.

Report any COMPLAINTS regarding this project to this office.

You are reminded that you must apply for, undergo review, and be granted continued approval for this study before March 12, 2018 in order to be able to conduct your study in an uninterrupted manner. If you do not receive approval before this date, you must cease and desist all research involving human subjects, their tissue and their data until such time as approval is granted.

If you have any questions, please contact Jean DeCicco at 315-464-4317 or deciccoj@upstate.edu. Please include your project title and reference number in all correspondence with this committee.

Documents in this submission:

- Amendment/Modification-Form-AmendmentRequest_7-28-17.doc(UPDATED:07/31/2017)
- ConsentForm-1005999Upstateconsentformver07282017.docx(UPDATED:07/31/2017)
- RegistrationFormforIRBReview-RegistrationFormforIRBReview(UPDATED:07/26/2017)

Unless otherwise stated, all documents submitted in previous packages have been approved by the SUNY Upstate IRB.
Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise

We are inviting you to participate in a research study run by Dr. Kevin Heffernan, PhD, Dr. Kan Liu MD, PhD, and Mrs. Jacqueline Augustine, MS. Involvement in the study is voluntary, so you may choose to participate or not to participate. This informed consent and authorization form explains the study to you and what your participation will entail. Please feel free to ask questions about the research if you have any. We will be happy to explain anything in more detail if you wish.

PURPOSE
Over the past three decades, the number of marathon finishers has increased from 25,000 in 1976 to 550,636 in 2015. An all-time high of 43% of marathon finishers are women. The increase in marathon participation is likely associated with the vast knowledge that exercise is beneficial for the heart. Even though exercise is beneficial for the heart, questions exist about whether years of long-term endurance exercise may predispose individuals to cardiovascular disease. We are interested in examining the effects of long-term (>5 years) endurance exercise, such as running, on the cardiovascular system and major blood vessels throughout the body. The way the heart adapts to endurance marathon training and racing may differ between men and women. In response to endurance training female athletes display smaller hearts compared to male athletes even after adjusting for body size and lean body mass. Despite the increased participation of women in endurance events such as marathon races, no studies have included women. Thus, little is known regarding the effect of endurance training on the heart in women compared to men.

The purpose of this study is to examine heart size and function in endurance-trained men and women and compare the results to recreationally active healthy men and women. We
are also interested in examining why there might be sex differences in heart size and function in endurance-trained athletes. Therefore, we will also examine 24-hour blood pressure and artery function to determine if 24-hour blood pressure and artery function may explain sex differences in heart size and function in endurance trained men and women.

The goal of the study is to improve our understanding of the role of long-term endurance exercise in improving the health and function of the heart in men and women who regularly participate in marathons. This study will be one of the first to examine sex differences in cardiovascular adaptations to chronic endurance exercise training.

GENERAL STUDY INFORMATION:

If you choose to participate in this study, you will visit the Syracuse University Exercise Science Laboratory, located in the Women's Building at Syracuse University three times for health screening and for the exercise portions of the study. You will also need to visit SUNY Upstate Medical University, University Hospital Echocardiography Lab, one time for an imaging study of your heart. Each visit will take approximately 60-90 minutes. The total time for study participation is approximately 4 ½ to 6 hours.

100 participants (25 endurance trained men, 25 endurance trained women; 25 recreationally active men, 25 recreationally active women) will be enrolled in this study. All participants will be 35 to 50 years of age. Additionally, women participants must be premenopausal and not using hormonal contraception (e.g. oral pill, Depo-Provera, IUD, transdermal patch, that contain hormones: estrogen/progesterone in varying levels) as indicated by the health history questionnaire and menstrual history questionnaire.

Inclusion Criteria

You are being asked to participate in the current study because you are a male or female between the ages of 35-50 years old and an otherwise healthy (defined as not having any of the conditions described below) regular marathon runner who fits all of the following criteria:

- Currently training for a marathon race
- Completed ≥1 marathon per year over the course of the past ≥5 years
- Regularly run ≥25 miles per week, runs 5-7 times per week on average, approximately ≥6 mph (≤10 minutes/mile)
- Engage in ≤1-2 extensive strength training sessions per week

You may also be asked to participate if you are between the ages of 35-50 years and an otherwise (defined as not having any of the conditions described below) healthy recreationally active individual who fits all of the following criteria:

- Not currently training for a half marathon or marathon race
- Never completed marathon and if you have, the marathon was completed ≥20 years ago

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• Regularly exercise 2-3 times per week for ≤30 minutes (i.e. walk, jog, run ≤10 miles per week, cycle, swim, aerobic, strength training) at a moderate to easy intensity
• Do not regularly participate in races or competitions.

**Exclusion Criteria**

You may be *excluded* from the study participation for any of the following reasons:

• Current and/or previous Smoker
• Known Cardiovascular disease (as indicated on Health History Questionnaire as diagnosed hypertension and/or peripheral artery disease)
• Body Mass Index (BMI) >35 kg/m², indicating obesity
• Hypertension defined as blood pressure >140/90 mmHg
• Hyperlipidemia defined as >200 mg/dl total cholesterol or >150 mg/dl LDL
• Poor circulation (low ankle brachial index, ≤ 0.9)
• Diagnosed atherosclerosis by a physician (as indicated on the Health History Questionnaire as diagnosed peripheral artery disease or indicated by low ABI from the study physician)
• A cardiac event in the past 6 months (as determined by Health History Questionnaire)
• Thyroid disorder
• Type II diabetes (defined as >110 mg/dl fasting glucose)
• Orthopedic injury preventing you from exercising such as, ankle sprain, knee injury, stress fracture, torn/sprained ligaments/tendons
• Kidney disease (previously diagnosed and/or blood, protein in the urine as indicated by urine sample provided at screening)
• Low cognitive function or dementia (>78 seconds, Trails A, >273 seconds, Trails B, paper cognitive test provided during screening)
• Arrhythmias (abnormal heart beat as determined by 12 lead electrocardiogram and study physician)
• Depression (score of >16 on CES-D)
**STUDY PROCEDURES:**

**Study Design Overview**

Time between Visit 1 to Visit 3 ≤ 7 days

- VISIT 1
  - ~1 hour
  - >12 hours fasted
  - >24 hours no exercise
  - Questionnaires
  - Blood Lipids
  - Arterial stiffness
  - 3 Dimensional Body surface area, Body fat %
  - Give Heart rate monitor, accelerometer
  - Fit and give blood pressure monitor
  - 12-lead ECG

- VISIT 2
  - ~1 hour
  - Fitness test on treadmill
  - Bring back blood pressure monitor

- VISIT 3
  - ~1.5 hours
  - >12 hours fasted
  - Controlled Exercise day in the laboratory
  - Perform a 30 minute run at 60-70% of Heart rate max on treadmill
  - Pre- and post-exercise vascular measures
  - Give blood pressure monitor

- VISIT 4
  - ~1 hour
  - ABI
  - Upstate 3-dimensional echocardiography
  - Heart size and function

**Study Design.** An overview of the study design is depicted in Figure 1 above. This study will consist of 4 study visits. Visits 1-3 (Syracuse University, Exercise Science Department) will be scheduled within 7 days to avoid potential changes in cardiovascular measures that may occur with changes in exercise training and/or hormonal changes due to the menstrual cycle. Visit 4 (SUNY Upstate Medical University) will be scheduled within 2 weeks of Visit 1. The total time for study participation is approximately 4 ½ to 6 hours.

**Visit 1: Informed Consent and Health Screening Visit: Syracuse University, Exercise Science Laboratory (~1 hour)**

- Prior to the health screening visit you will be given the consent form which will detail all study procedures. You will fill out and sign this consent form if you would like to participate in this study.

- For the health screening visit we ask you to arrive first thing in the morning ≥12 hours fasted (i.e. no food, caffeine, or alcohol for the past 12 hours). We ask this so that we can accurately measure your cholesterol, blood pressure, body composition, and blood sugar to determine overall health status for further participation in the study (described further below). A light snack will be provided after this visit.

- We also ask that you arrive to the laboratory ≥24 hours post-exercise to avoid changes in artery function associated with exercise.
• Female participants will be asked to arrive at the laboratory during the early follicular phase of their menstrual cycle also known as Days 1-7 of the menstrual cycle which is the week of their menses period (you can come into the laboratory the day of the start of your period up to 7 days after the start of your period).

• To determine if you are eligible for the study you will be given a detailed health history questionnaire, menstrual history questionnaire, marathon and running history questionnaire, a sleep and physical activity questionnaire and a depression questionnaire. Additionally, we will measure your height and weight using a stadiometer and electronic scale, in the same manner typically done at the doctor’s office.

• We will also have you perform a brief paper cognitive test to assess basic brain function to ensure you do not have dementia or poor cognitive function.

• We will ask you to give us a small urine sample so that we can check the function of your kidneys and your hydration status at the time of the visit. We will provide a small sample container and escort you to the restroom.

• We will also perform a 12-Lead electrocardiogram reading of your heart rhythm. This will test the electrical activity of your heart. For this test, you will be asked to lie down (on your backs) on the exam table. You will be encouraged to lie still and relax your muscles. 10 Electrodes (round stickers, ~2 inches in diameter) will be placed on the your body, 1 on each wrist, 1 on each ankle, and 6 on your chest. Prior to electrode placement each location will be cleaned with a alcohol swab and air dried to ensure ideal signal through the electrodes. Short wires will connect the electrodes to a machine that tells us your heart’s rhythm. Each reading will be de-identified and the de-identified data will be electronically sent to the study physician (Dr. Kan Liu) to be read to make sure you are medically cleared to perform the exercise tests.

• We will then estimate your body composition (percent body fat) using a BodPod and 3-D body scanner that will require you to wear tight fitting, minimal clothing for greatest accuracy in estimations. You will be asked to sit quietly in a chamber that resembles a giant egg for approximately two, 60-second intervals. This machine measures your body volume to estimate body fat. This device does not fill with water and you will not be getting wet during this procedure. For the 3-D body scanner we will have you stand in the middle of the scanner in the same outfit you wear for the BodPod and 3 laser-guided cameras will scan down your body from head to toe. These lasers are not dangerous and will not damage your eyes, if your eyes are sensitive however, we will invite you to close your eyes for the scan. The scan takes approximately 10 seconds for the cameras to move from your head to your toes.

• We will measure your blood pressure in both arms. We will place a blood pressure cuff around both your left and right upper arms (biceps) and they will inflate and deflate slowly. This is the same measurement that is often done at the Doctors office during a routine visit. We will take this measurement while you are lying down.

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- We will also measure your hemoglobin/hematocrit, cholesterol, and glucose, by obtaining a few small drops of blood from your fingertip (finger prick). These tests require that you arrive >12 hours fasted.

- Next, we will measure blood pressure at specific blood vessels in the body. To do so, we will take a small tonometer (a small pen-like device that senses pressure) and press it gently against the carotid artery (neck), radial artery (wrist), femoral artery (upper leg/hip), and ankle (anterior tibialis). We will do this while simultaneously measuring your heart rate from electrodes placed on your ribs and shoulder. We can use these pressure waves to calculate how stiff your blood vessels are.

- As you leave the screening visit we will send you home with a small physical activity monitor, heart rate monitor and a 24-hour blood pressure monitor (further instructions attached).

- The physical activity monitor is less than 2 inches in length and will measure how much you move throughout the week. You will be instructed to wear a stretchy belt that will allow the monitor to sit snug against your right hip. We ask that you wear the activity monitor for 24 hours for a full 7 days, only removing it when involved in water activities such as showering/bathing and swimming (activity/training log will be provided).

- We ask that you wear the heart rate monitor for each and every training/exercise session for 7 days. We will also ask you to wear the 24-hour blood pressure monitor for the duration of 24 hours following your visit and not to engage in exercise while wearing this device. Please do not wear the monitor in water activities such as showering/bathing and swimming.

- Depending on your health status determined from the answers you provide on the health questionnaires (i.e. exercise tolerance and previous health history) we may ask you to contact your physician and receive permission to continue with the exercise portion of the study on subsequent visits. We will require you to obtain clearance from your physician to participate in the exercise portion of the study if you are in this group (≥2 cardiovascular risk factors). If you are unable to obtain clearance from your physician you will not be allowed to participate in the exercise visits. All screening test results will be reviewed by Jacqueline Augustine and Dr. Liu to determine if you can continue in the study. Test results which may indicate a health problem and which may exclude you from study participation will be shared with you so you can follow-up with your primary health care provider.

Visit 2: Cardiorespiratory Fitness (exercise) Test: Syracuse University, Human Performance Laboratory (~1 hour)

- For the first exercise visit we ask you to arrive not having eaten > 3 hours and to bring shorts and a T-shirt. Intense exercise may upset your stomach if you have recently eaten. We also ask that you refrain from exercising or consuming alcohol or caffeine (including caffeinated coffee, tea, soda or energy drinks) on the day that you come into the lab.

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• We will first prepare you for the cardiorespiratory fitness test. We will have you walk on the treadmill and then rest. At this time, we will explain the exercise protocol to you.

• The cardiorespiratory fitness test will consist of a running exercise, starting at a very low intensity for warm-up, and increasing exercise intensity with time. We will increase the intensity of exercise by increasing your running speed and the grade (incline) of the treadmill. We will ask you to give a maximal effort and run until you cannot run for any longer. The goal of this test is to measure how much oxygen your body can consume during exercise. The more oxygen you can take in, the more fit you are. We will instruct you to continue exercising as long as you can. The test will end whenever you believe you cannot exercise any harder. If you are ever uncomfortable or concerned, you may end the test and stop exercising at any time. The exercise test will usually last somewhere between 10-20 minutes.

• During the exercise test we will measure the following...
  o Your blood pressure on the upper arm.
  o The oxygen delivery to your calf muscle using a small sensor enclosed in a compressive stocking.
  o Your heart rate using a thin strap that will be placed directly on the skin around your chest.
  o The amount of oxygen you are consuming using a small device that is worn as a headset with a facemask.
  o How hard you think you are working using a scale ranging from 6 (no work) to 20 (working as hard as you can).

• After ending the test, we will have you cool down and recover briefly by exercising at a very low intensity for 3-5 minutes before dismissing you.

• We will provide you with a snack and water following the test.

Visit 3: Acute exercise: Syracuse University, Human Performance Laboratory (~1.5 hours)

• For the second exercise visit we ask you to arrive >12hours fasted (i.e. no food, caffeine, or alcohol for the past 4 hours) and to wear shorts and a T-shirt. At this visit we will measure your blood vessel health, and blood pressure, both before, and after, 30-minutes of moderate-intensity running/walking exercise on a treadmill.

• First, we will measure your blood pressure in the same manner as the previous visits. This is the same measurement that is often done at the Doctors office during a routine visit. We will take this measurement both while you are sitting, and while you are lying down.

• Next, we will measure blood pressure at specific blood vessels in the body. To do so, we will take a small tonometer (a small pen-like device that senses pressure) and press
it gently against the carotid artery (neck), radial artery (wrist), femoral artery (upper leg/hip), and anterior tibialis artery (ankle). We will do this while simultaneously measuring your heart rate from electrodes placed on your ribs and shoulder. We can use these blood pressure waves to calculate how stiff your blood vessels are.

- Next, we will measure your neck and leg blood flow and brain blood flow using two non-invasive (no needles, no blood) techniques, Doppler ultrasound and blood flow sensors. We are interested in not only how endurance exercise affects the cardiovascular system but also the major blood vessels throughout the body, such as your neck, leg, and brain. Ultrasound probes will be placed on your neck, upper leg/thigh and on the side of your face (near your temple, between your eye and ear) to assess neck and leg artery stiffness and blood flow and brain blood flow. Additionally, a blood flow sensors will be placed on the forehead and secured with a headband to assess brain blood flow.

- Once you have completed the resting artery measures, we will remove our instruments and you will begin the 30-minute exercise bout. The running/walking intensity will be set at a workload to approximately 60-70% of your heart rate maximum (determined from visit 2).

- During the 30-minute running exercise bout we will measure blood pressure, heart rate, how hard you think you are working, and how much oxygen you are breathing in using the same techniques from the cardiorespiratory fitness test.

- After completing the exercise bout, we will have you return to the testing table and let you recover for approximately 5 minutes while we set our instruments back up. After that, we will repeat the same measures from before exercise for 25-30 minutes following the exercise bout (blood pressure, leg, neck and brain blood flow).

- We will also provide you with water throughout the visit and a snack to be consumed after the exercise is performed.

- Once the measurements are complete, we will remove our instruments and we will then give you the same 24-hour blood pressure monitor you received at Visit 1 to be worn for another 24-hours and only taken off while showering or coming in contact with water. You will be asked to refrain from exercise while wearing the monitor and to bring it back within 48 hours of visit 3. You will then be permitted to leave.

- This exercise visit will take approximately 90 minutes to complete (15-20 minutes pre-testing, 30 minutes’ exercise, 30-minutes post-exercise).

- If you wish to withdraw from the study at any time, you are free to do so.

Visit 4: 3-dimensional Echocardiography Visit: SUNY Upstate Medical University, 6th Floor Echo Laboratory (~1 hour)

- For the fourth and final visit, you will meet Jacqueline Augustine, researcher, in the lobby of Upstate University Hospital. You will be escorted to the Echocardiography laboratory to have a non-invasive, 3-dimensional echocardiography of your heart. This
procedure will be performed by a certified echocardiography technician/researcher and accompanied by Dr. Liu.

- The imaging of your heart will be non-invasive (no needles, no blood) using a Doppler ultrasound technique, which is very similar to the probe used to measure your neck and leg blood flow during Visit 3 at Syracuse University. An ultrasound probe will be placed on the left side of your chest. The technician will take 1-2 images of your heart.

- We will also measure ankle-brachial index (ABI), which measures your artery function. This is a non-invasive test that will compare the blood pressure at your ankles with the blood pressure at your arm. This procedure indicates how good your circulation is throughout your body. A low ankle-brachial index is an indicator of poor circulation and potential for peripheral artery disease. If a low ABI is detected you may be excluded from the study.

- This visit to the echocardiography lab will take approximately 30 minutes, however, the total duration of the visit to Upstate University Hospital will take ~1 hour with parking, arrival and imaging.

**RISKS & DISCOMFORTS:**

- There are some risks associated with portions of this study.

- We will use a small amount of gel to help us measure your brain blood flow. There is minimal risk of gel getting into your eye when we measure brain blood flow due to the small amount of gel used in this technique. Nonetheless, we will remind you to remain still as we take these measures to ensure that the gel does not come into contact with your eye. The gel is water-based and is designed for eye exams so in the event some comes in contact with your eye the discomfort should be minimal and temporary and can be rinsed out easily. We will escort you quickly to a sink to rinse out your eye if discomfort occurs.

- You may experience discomfort from the finger stick to test your blood lipids, cardiac function, inflammation, hematocrit and hemoglobin. This will only be done two or three times and no more than that. We will use different fingers each time to reduce discomfort. If desired we can also place ice on the finger prior to the finger stick to reduce discomfort from the pinch.

- There is a small risk of infection associated with the finger stick. However, we will reduce this risk by ensuring that equipment is clean and sterile and the finger stick technician will wear lab coat, gloves, will clean the finger with alcohol swabs and will clean the area with a disinfectant wipe afterwards.

- You will be asked to come to Visit 1 (≥12 hours fast) and 3 (≥12 hours fasted) following a fast. It is possible that you may experience some gastrointestinal discomfort by the end of testing from feelings of hunger or experience symptoms of low blood sugar such as, feeling faint or dizzy. Although this is not anticipated, as many people do not consume food for large breaks during the day, we will provide a light snack at the completion of testing (granola bar) if you are hungry. It is important that we have

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participants arrive fasted because food consumption can greatly affect vascular function based on the timing and content of the meal.

- There are risks associated with exercise.
  
  - There is a small risk of losing consciousness following intense exercise. We will minimize this risk by having you “cool-down” following the cardiorespiratory fitness test at visit 2. This will prevent the blood from staying down in your legs and will reduce the risk of light-headedness or dizziness after exercise. Additionally, we will ask you communicate directly with us if you feel any light-headedness so that we can take appropriate precautions.
  
  - Any type of exercise may, in rare instances, lead to heart attack, stroke or death; however, this is unusual, especially in adults free of known cardiovascular disease, free of any signs or symptoms of cardiovascular disease, and with few major risk factors of cardiovascular disease. Thus, risks associated with exercise are low in healthy, middle-aged adults. Our multi-stage screening process will help us ensure that exercise is appropriate and safe for you. The multi-stage screening process will let us identify any pre-existing conditions or abnormalities that might limit exercise. By design, our exclusion criteria and extensive health screening prior to the exercise visits (visit 2 and 3) will remove you from participating if you are a high-risk individual.
  
  - Based on our criteria however, you may be a moderate-risk individuals (i.e. you have >2 cardiovascular risk factors). The odds are, if you have high blood pressure you will fall into this moderate-risk group. As mentioned previously, we will require you to obtain clearance from your physician to participate in the exercise portion of the study if you are in this moderate-risk group (>2 cardiovascular risk factors). If you are unable to obtain clearance from your physician you will not be allowed to participate in the exercise visits.
  
  - It should be noted that exercise is widely recommended by health organizations as a lifestyle modification to reduce the negative effects of cardiovascular disease, even in moderate-risk populations with high blood pressure. Our multi-stage screening process and physician clearance steps will ensure that you will only engage in exercise if it is appropriate and safe for you, thus these risks should be minimal should you be cleared for the exercise portions of the study.
  
  - Communicating with the researcher throughout the protocol will reduce risks.
  
  - It is possible that we may find out something about your health that you did not know about. In the event we discover any significant medical abnormalities during the course of your participation in this study, we will inform you and your primary care physician, if you wish. If you do not have a primary physician, an appropriate referral will be made.
  
  - If at any point, you are uncomfortable or feel pain anywhere, please tell us immediately.

**BENEFITS:**

- There is no direct benefit to you for participating in this research study; however, the

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information learned may help others in the future.

- You will receive information on your blood pressure, cholesterol level, body composition, aerobic fitness, cognitive function, heart structure and function. **These tests are not being used to diagnose a medical/health problem (NOT for medical/clinical purposes). These tests are being performed for research purposes only.** If you have high blood pressure, high cholesterol, high blood glucose, depression, or blood in your urine we will inform you to go the university health center or your health care provider. If an abnormality is detected on the 3D echocardiography, low ABI is detected or an abnormal heart rhythm is observed, you will be referred to the cardiologist, lead physician on this study, Dr. Kan Liu.

**VOLUNTARY PARTICIPATION:**

Your participation in this study is entirely voluntary and you may refuse to participate or discontinue participation at any time without penalty or loss of benefits to which you would normally be entitled. Your decision about whether or not to participate in the study will not affect your relationship with Syracuse University or SUNY Upstate Medical University.

**STUDY WITHDRAWAL:**

- At any time, you may remove yourself from the study without giving any reason.
- If you are a student, withdrawing from the study will not affect your grade in courses in any way.
- Exercise is not appropriate for all individuals based on their health status. This study has a multi-stage process where we may exclude you from participating in the exercise portions of the study. Throughout this process, you may be excluded from the study based on answers to the questionnaires administered in the screening visit, if you have low kidney function (determined from the urine test), very low cognitive function (determined from the basic cognitive function test on visit 1), high depressive symptomology (determined from a questionnaire), and very high cholesterol or blood sugar (determined from blood tests). We may also exclude you if...
  - We find that you regularly experience any signs or symptoms that suggest you may have a medical condition and your health care provider is not aware that you are experiencing these symptoms. We will exclude you from the study and ask that you contact your health care provider.
  - You have recently sustained a concussion.
  - You have high blood pressure (systolic pressure >140, diastolic pressure >90 mmHg) and are not undergoing medical treatment for it. We will exclude you and ask that you follow up with your health care provider.
  - You have an abnormal blood pressure response to exercise during visit 2.

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- You have >2 cardiovascular risk factors and your physician does not give you, or you do not obtain, clearance to exercise.

- If you are experiencing any signs or symptoms of a serious/significant health condition (i.e. severe chest pain, leg pain, dizziness, feelings of heart palpitations) we will contact emergency medical services immediately and you will not be able to participate in the study.

The researchers may take you out of the study at any time with or without your agreement. This may happen if:

- It is in your best medical interest to stop your participation
- You are not able to follow the study instructions
- The study is cancelled

**COSTS/PAYMENTS:**

- There will be no costs to you for participating in this study.

- You will receive monetary compensation for your time. You may receive up to $25.00 for participating in this study. You will receive $5 for completing screening/Visit 1, $5 completing physical activity monitoring/at-home blood pressure and completing visit 2, $5 completing visit 3, $10 for completing Visit 4 ($5 for completing the echocardiogram and $5 for Upstate parking fees upon completion of Visit 4). If you remove yourself, or are excluded, from the study prior to completing all visits, you will only be compensated for the visits/procedures that were completed. If you withdraw or are excluded from the study at visit 2 or 3, your compensation will be pro-rated depending on what stage of the visit you had completed.

**IN CASE OF INJURY:**

In the event of illness or physical injury resulting from taking part in this research study, medical treatment will be provided at University Hospital. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by SUNY Upstate Medical University or Syracuse University. SUNY Upstate Medical University and Syracuse University have no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

**CONFIDENTIALITY OF HEALTH INFORMATION FOR RESEARCH:**

If you agree to participate in this research, identifiable health information about you will be used and shared with others involved in this research. For you to be in this research we need your permission to collect and share this information. When you sign this consent form at the end, it means that you have read this section and authorize the use and/or sharing of your protected health information as explained below.

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Your protected health information will be kept confidential. Your identity will not be revealed in any publication or presentation of the results of this research.

- **The research records from this study will be confidential.** Confidentiality means that it is our responsibility to keep any information you provide private and safe. Although we have taken steps in order to maximize and maintain confidentiality, *it is important to understand that confidentiality cannot be guaranteed in lab settings.*

- Only members of the trained research staff for this study with training in research ethics may look over your research records.

- The paperwork, results and records will be kept in a locked filing cabinet that only the researchers with training in research ethics will have access to.

- You will be given a study identification number (coded numbers, known only by primary researchers) and this will be entered into all research computers used to collect your blood pressure and blood flow. Your name will not appear anywhere on these computers or the data output from these computers.

- All information stored on computers requires a password access it. Only members of the research team with training in research ethics will have this password.

- The data and research record will be stored for up to 10 years.

- **Your individual results will not be used in any way (we will average all results and display group averages only when presenting findings in papers and presentations)**
  
  - If at any point you wish to withdraw yourself from the study you may.
  
  - You do not give up any of your legal rights by participating in this study.

**QUESTIONS:**

If you have any questions about the research, or in the event of a research-related injury, please contact Kan Liu, MD at (315) 464-9335, Jacqueline Augustine at (860) 508-8996, Kevin Heffernan, PhD at (315) 443-9801. If you have any questions about your rights as a research subject, please contact the SUNY Upstate Medical University Institutional Review Board Office at (315) 464-4317 or the Syracuse University Institutional Review Board Office at (315) 443-3013.

By signing below you indicate that you have read and fully understood this informed consent form. You are fully aware of the purpose and procedures of this study as well as the risks, discomforts, and benefits associated with the experimental protocol and that you sign this document freely and voluntarily.

All of my questions have been answered, I am 18 years of age or older, and I wish to participate in this research study. I have received a copy of this consent form.

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Signature of participant

Date

Printed name of participant

Signature of researcher

Date

Printed name of researcher
CONSENT & AUTHORIZATION FORM

STUDY TITLE: Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise

UPSTATE MEDICAL UNIVERSITY PRINCIPAL INVESTIGATOR:

Kan Liu, PhD, MD
750 East Adams Street, Syracuse, NY 13210
6th Floor University Hospital
315-464-5735

SYRACUSE UNIVERSITY PRINCIPAL INVESTIGATOR:

Kevin Heffernan, PhD
820 Comstock Avenue, Syracuse, NY 13210
Syracuse University, Women’s Building, Room 201
315-443-9801

INTRODUCTION:

Please read this form carefully. It tells you important information about a research study. A member of the research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called “subjects.” This term will be used throughout this consent form.

We are inviting you to participate in a research study run by Dr. Kan Liu MD, PhD, Dr. Kevin Heffernan, PhD and Mrs. Jacqueline Augustine. Involvement in the study is voluntary, so you may choose to participate or not to participate. This informed consent and authorization form explains the study to you and what your participation will entail. Please feel free to ask questions about the research if you have any. We will be happy to explain anything in more detail if you wish.

BACKGROUND/PURPOSE:

Over the past three decades the number of marathon finishers has increased from 25,000 in 1976 to 550,636 in 2015. We are interested in examining the effects of long-term endurance exercise, such as running, on the heart. Even though exercise is considered to be beneficial for the heart, questions exist with regards to whether years of long-term endurance exercise may predispose individuals to cardiovascular risk. Interestingly, the way the heart adapts to endurance training and racing may differ between men and women. However, despite the increased participation of women in endurance events such as, marathon races, very few studies have included women. Thus, little is known regarding the effect of endurance training on the heart in women compared to men.
The purpose of this study is to examine heart size and function in endurance-trained men and women and compare the results to recreationally active healthy men and women. We are also interested in examining why there might be sex differences in heart size and function in endurance-trained athletes. Therefore, we will also examine 24-hour blood pressure and artery function to determine if 24-hour blood pressure and artery function may explain sex differences in heart size and function in endurance trained men and women.

GENERAL STUDY INFORMATION:
If you choose to participate in this study, you will visit the Syracuse University Exercise Science Laboratory, located in the Women’s Building at Syracuse University three times for health screening and for the exercise portions of the study. You will also need to visit SUNY Upstate Medical University, University Hospital Echocardiography Lab, one time for an imaging study of your heart. Each visit will take approximately 60-90 minutes.

100 participants (25 endurance trained men, 25 endurance trained women; 25 recreationally active men, 25 recreationally active women) will be enrolled in this study. All participants will be 35 to 50 years of age. Additionally, women participants must be premenopausal and not using hormonal contraception (e.g. oral pill, Depo-Provera, IUD, transdermal patch, that contain hormones: estrogen/progesterone in varying levels) as indicated by the health history questionnaire and menstrual history questionnaire.

Inclusion Criteria
You are being asked to participate in the current study because you are a male or female between the ages of 35-50 years old and an otherwise healthy regular marathon runner who fits the following criteria:

- Currently training for a marathon race
- Completed ≥1 marathon per year over the course of the past ≥5 years
- Regularly run ≥25 miles per week, runs 5-7 times per week on average, approximately ≥6 mph (≤10 minutes/mile)
- Engage in ≤1-2 extensive strength training sessions per week

You may also be asked to participate if you are between the ages of 35-50 years and an otherwise healthy recreationally active individual who fits the following criteria:

- Not currently training for a half marathon or marathon race
- Never completed marathon and if you have, the marathon was completed ≥20 years ago
- Regularly exercise 2-3 times per week for ≤30 minutes (i.e. walk, jog, run ≤10 miles per week, cycle, swim, aerobic, strength training) at a moderate to easy intensity
- Do not regularly participate in races or competitions.

Exclusion Criteria
You may be excluded from the study participation for any of the following reasons:

- Known Cardiovascular disease
• BMI >35 kg/m², indicating obesity
• Hypertension >140/90 mmHg
• Hyperlipidemia >200 mg/dl total cholesterol, >150 mg/dl LDL
• Diagnosed atherosclerosis by a physician
• A cardiac event in the past 6 months
• Thyroid disorder and diabetes (>110 mg/dl glucose)
• Orthopedic Injury preventing exercise such as, ankle sprain, knee injury, stress fracture, torn/sprained ligaments/tendons
• Kidney disease

STUDY PROCEDURES:

Study Design Overview
Time between Visit 1 to Visit 4 ≤ 3 weeks

Visit 1: Informed Consent and Health Screening Visit: Syracuse University, Exercise Science Laboratory (~1 hour)

Visit 2
~1 hour
• 12 hours fasted
• >24 hours no exercise
• Questionnaires
• Blood Lipids
• Arterial stiffness
• 3 Dimensional Body surface area, Body fat %
• Give Heart rate monitor, accelerometer
• Fit and give blood pressure monitor

Visit 3
~1.5 hours
• >12 hours fasted
• Controlled Exercise day in the laboratory
• Perform a 30 minute run at 60-70% of Heart rate max on treadmill
• Give blood pressure monitor

Visit 4
~1 hour
• Upstate 3-dimensional echocardiography
• Heart size and function

Study Design. This study will consist of 4 study visits. Visits 1-3 (Syracuse University, Exercise Science Department) will be scheduled within 7 days to avoid potential effects of training and hormonal changes due to the menstrual cycle. Visit 4 (SUNY Upstate Medical University) will be scheduled within 2 weeks of Visit 1. The total time for study participation is approximately 4 ½ to 6 hours.
• Prior to the health screening visit you will be given and explained the consent form which will detail all study procedures. You will fill out and sign this consent form if you would like to participate in this study.

• For the **health screening visit** we ask you to arrive first thing in the morning ≥12 hours fasted (i.e. no food, caffeine, or alcohol for the past 12 hours). We ask this so that we can accurately measure your cholesterol, blood pressure, body composition, and blood sugar to determine overall health status for further participation in the study (described further below). A light snack will be provided after this visit.

• We also ask that you arrive to the laboratory ≥24 hours post-exercise to avoid changes in artery function associated with exercise.

• Female participants will be asked to arrive at the laboratory during the early follicular phase of their menstrual cycle also known as Days 1-7 of the menstrual cycle which is the week of their menses period (you can come into the laboratory the day of the start of your period up to 7 days after the start of your period).

• To determine if you are eligible for the study you will be given a detailed health history questionnaire, menstrual history questionnaire, marathon and running history questionnaire, a sleep and physical activity questionnaire and a depression questionnaire. Additionally, we will measure your height and weight using a stadiometer and electronic scale, in the same manner typically done at the doctor’s office.

• We will also have you perform a brief paper cognitive test to assess basic brain function.

• We will ask you to give us a small urine sample so that we can check the function of your kidneys and your hydration status at the time of the visit. We will provide a small sample container and escort you to the restroom.

• We will then estimate your body composition (percent body fat) using a BodPod and 3-D body scanner that will require you to wear tight fitting, minimal clothing for greatest accuracy in estimations. You will be asked to sit quietly in a chamber that resembles a giant egg for approximately two, 60-second intervals. This machine measures your body volume to estimate body fat. For the 3-D body scanner we will have you stand in the middle of the scanner in the same outfit you wear for the BodPod and 3 laser-guided cameras will scan down your body from head to toe. These lasers are not dangerous and will not damage your eyes, if your eyes are sensitive however we will invite you to close your eyes for the scan. The scan takes approximately 10 seconds for the cameras to move from your head to your toes.

• We will measure your blood pressure in both arms. We will place a blood pressure cuff around both your left and right upper arms (bicep) and they will inflate and deflate slowly. This is the same measurement that is often done at the Doctor’s office during a routine visit. We will take this measurement both while you are sitting, and while you are lying down.

• We will also measure your hemoglobin/hematocrit, cardiac function, cholesterol, glucose, and whole-body inflammation by obtaining a few small drops of blood from your fingertip (finger prick). These tests require that you arrive >12 hours fasted.

• Next, we will measure blood pressure at specific blood vessels in the body. To do so, we will take a small tonometer (a small pen-like device that senses pressure) and press it gently against
the carotid artery (neck), radial artery (wrist), and femoral artery (upper leg/hip). We will do this while simultaneously measuring your heart rate from electrodes placed on your ribs and shoulder. We can use these pressure waves to calculate how stiff your blood vessels are.

- As you leave the screening visit we will send you home with a small physical activity monitor, heart rate monitor and at-home 24-hour blood pressure monitor (further instructions attached)

- The physical activity monitor is less than 2 inches in length and will measure how much you move throughout the week. You will be instructed to wear a stretchy belt that will allow the monitor to sit snug against your right hip. We ask that you wear the activity monitor for 24 hours for a full 7 days, only removing it when involved in water activities such as showering/bathing and swimming (activity/training log will be provided).

- We ask that you wear the heart rate monitor for each and every training/exercise session for 7 days. We will also ask you to wear the 24-hour blood pressure monitor for the duration of 24 hours following your visit and not to engage in exercise while wearing this device. Please do not wear the monitor in water activities such as showering/bathing and swimming.

- Depending on your health status determined from the answers you provide on the health questionnaires we may ask you to contact your physician and receive permission to continue with the exercise portion of the study on subsequent visits.

- All screening test results will be reviewed to determine if you can continue in the study. Test results which may indicate a health problem and which may exclude you from study participation will be shared with you so you can follow-up with your primary health care provider.

**Visit 2: Cardiorespiratory Fitness (exercise) Test: Syracuse University, Human Performance Laboratory (~1 hour)**

- For the first exercise visit we ask you to arrive not having eaten within the past 3 hours. Intense exercise may upset your stomach if you have recently eaten. Therefore, we ask you to refrain from exercising or consuming alcohol or caffeine (including caffeinated coffee, tea, soda or energy drinks) on the day that you come into the lab.

- We will first prepare you for the cardiorespiratory fitness test. We will have you walk on the treadmill and then rest. At this time, we will explain the exercise protocol to you.

- The cardiorespiratory fitness test will consist of a running exercise, starting at a very low intensity for warm-up, and increasing exercise intensity with time. We will increase the intensity of exercise by increasing the speed that you are running at and then at later stages in the test the grade (incline) of the treadmill will increase slightly until you cannot run for any longer. The goal of this test is to measure how much oxygen your body can consume during exercise. The more oxygen you can take in, the more fit you are. We will instruct you to continue exercising as long as you can. The test will end whenever you believe you cannot exercise any harder. If you are ever uncomfortable or concerned you may end the test at any time. The exercise test will usually last somewhere between 10-20 minutes.

- During the exercise test we will measure the following...
Your blood pressure on the upper arm.

The oxygen delivery to your calf muscle using a small sensor enclosed in a compressive stocking.

Your heart rate using a thin strap that will be placed directly on the skin around your chest.

The amount of oxygen you are consuming using a small device that is worn like a small backpack with a facemask (see image on the left).

How hard you think you are working using a scale ranging from 6 (no work) to 20 (working as hard as you can).

- After ending the test, we will have you cool down and recover briefly by exercising at a very low intensity for 3-5 minutes before dismissing you.
- We will provide you with a snack and water following the test.

Visit 3: Acute exercise: Syracuse University, Human Performance Laboratory (~1.5 hours)

- For the second exercise visit we ask you to arrive >4 hours fasted (i.e. no food, caffeine, or alcohol for the past 4 hours) and to wear shorts and a T-shirt. At this visit we will measure your blood vessels, blood pressure, and brain function both before, and after, 30-minutes of moderate-intensity running/walking exercise.

- First, we will measure your blood pressure in the same manner as the previous visits. This is the same measurement that is often done at the Doctors office during a routine visit. We will take this measurement both while you are sitting, and while you are lying down.

- Next, we will measure blood pressure at specific blood vessels in the body. To do so, we will take a small tonometer (a small pen-like device that senses pressure) and press it gently against the carotid artery (neck), radial artery (wrist), and femoral artery (upper leg/hip). We will do this while simultaneously measuring your heart rate from electrodes placed on your ribs and shoulder. We can use these pressure waves to calculate how stiff your blood vessels are.

- Next, we will measure your neck and leg blood flow and brain blood flow using two non-invasive (no needles, no blood) techniques, Doppler ultrasound and blood flow sensors. Ultrasound probes will be placed on your neck, upper leg/thigh and on the side of your face (near your temple, between your eye and ear) to assess neck and leg artery stiffness and blood flow and brain blood flow. Additionally, a blood flow sensors will be placed on the forehead and secured with a headband to assess brain blood flow.

- Once you have completed the resting artery measures we will remove our instruments and you will begin the 30-minute exercise bout. The running/walking intensity will be set at a workload to approximate 60-70% of your heart rate maximum (determined from visit 2).

- During the 30-minute running exercise bout we will measure blood pressure, heart rate, how hard you think you are working, and how much oxygen you are breathing in using the same techniques from the cardiorespiratory fitness test.
• After completing the exercise bout, we will have you return to the testing table and let you recover for approximately 5 minutes while we set our instruments back up. After that we will repeat the same measures from before exercise (cardiac function, blood markers, blood pressure, blood flow, cognitive function).

• Once the measurements are complete, we will remove our instruments and we will then give you the same 24-hour blood pressure monitor you received at Visit 1 to be worn for another 24-hours and only taken off while showering or coming in contact with water. You will be asked to refrain from exercise while wearing the monitor and to bring it back within 48 hours of visit 3. You will then be permitted to leave.

• This exercise visit will take approximately 90 minutes to complete (15-20 minutes pre-testing, 30 minutes’ exercise, 30-minutes post-exercise).

• If you wish to withdraw from the study at any time you are free to do so.

**Visit 4: 3-dimensional Echocardiography Visit: SUNY Upstate Medical University, 6th Floor Echo Laboratory (~1 hour)**

• For the fourth and final visit, you will meet Jacqueline Augustine, researcher, in the lobby of Upstate University Hospital. You will be escorted to the Echocardiography laboratory to have a non-invasive, 3-dimensional echocardiography of your heart. This procedure will be performed by a certified echocardiography technician/researcher and accompanied by Dr. Liu.

• The imaging of your heart will be non-invasive (no needles, no blood) using a Doppler ultrasound technique, which is very similar to the probe used to measure your neck and leg blood flow during Visit 3 at Syracuse University. An ultrasound probe will be placed on your chest near the left side of your chest. The technician will take 1-2 images of your heart.

• We will also measure ankle-brachial index (ABI), which measures your artery function. This is a non-invasive test that will compare the blood pressure at your ankles with the blood pressure at your arm. This procedure indicates of how good your circulation is throughout your body.

• This visit to the echocardiography lab will take approximately 30 minutes, however, the total duration of the visit to Upstate University Hospital will take ~1 hour with parking, arrival and imaging.

A University Hospital (UH) medical record will not be created for you as a participant in this study. If you already have a medical record at UH, we will not add the tests being done for this study to your UH medical record. A copy of your test results will be kept in Dr. Liu's study records; therefore, if you want a copy of the test results, please contact Dr. Liu at Liuk@upstate.edu or (315) 464-9335.

**RISKS & DISCOMFORTS:**

• There are some risks associated with portions of this study.
• We will use a small amount of gel to help us measure your brain blood flow. There is minimal risk of gel getting into your eye when we measure brain blood flow due to the small amount of gel used in this technique. Nonetheless, we will remind you to remain still as we take these measures to ensure that the gel does not come into contact with your eye. The gel is water-based and is designed for eye exams so in the event some comes in contact with your eye the discomfort should be minimal and temporary and can be rinsed out easily. We will escort you quickly to a sink to rinse out your eye if discomfort occurs.

• You may experience discomfort from the finger stick to test your blood lipids, cardiac function, inflammation, hematocrit and hemoglobin. This will only be done two or three times and no more than that. We will use different fingers each time to reduce discomfort. If desired we can also place ice on the finger prior to the finger stick to reduce discomfort from the pinch.

• There is a small risk of infection associated with the finger stick. However, we will reduce this risk by ensuring that equipment is clean and sterile and the finger stick technician will wear lab coat, gloves, will clean the finger with alcohol swabs and will clean the area with a disinfectant wipe afterwards.

• You will be asked to come to Visit 1 (≥12 hours fast) and 3 (≥12 hours fasted) following a fast. It is possible that you may experience some gastrointestinal discomfort by the end of testing from feelings of hunger or experience symptoms of low blood sugar such as, feeling faint or dizzy. Although this is not anticipated, as many people do not consume food for large breaks during the day, we will provide a light snack at the completion of testing (granola bar) if you are hungry. It is important that we have participants arrive fasted because food consumption can greatly affect vascular function based on the timing and content of the meal.

• There are risks associated with exercise.
  
• There is a small risk of losing consciousness following intense exercise. We will minimize this risk by having you “cool-down” following the cardiorespiratory fitness test at visit 2. This will prevent the blood from staying down in your legs and will reduce the risk of light-headedness or dizziness after exercise. Additionally, we will ask you communicate directly with us if you feel any light-headedness so that we can take appropriate precautions.

• Any type of exercise may, in rare instances, lead to heart attack, stroke or death; however, this is unusual, especially in adults free of known cardiovascular disease, free of any signs or symptoms of cardiovascular disease, and with few major risk factors of cardiovascular disease. Thus, risks associated with exercise are low in healthy, middle-aged adults. Our multi-stage screening process will help us ensure that exercise is appropriate and safe for you. The multi-stage screening process will let us identify any pre-existing conditions or abnormalities that might limit exercise. By design, our exclusion criteria and extensive health screening prior to the exercise visits (visit 2 and 3) will remove you from participating if you are a high-risk individual.

• Based on our criteria however, you may be a moderate-risk individuals (i.e. you have >2 cardiovascular risk factors). The odds are, if you have high blood pressure you will fall into this moderate-risk group. As mentioned previously, we will require you to obtain clearance from your physician to participate in the exercise portion of the study if you are in this moderate-risk group (>2 cardiovascular risk factors). If you are unable to obtain
clearance from your physician you will not be allowed to participate in the exercise visits.

- It should be noted that exercise is widely recommended by health organizations as a lifestyle modification to reduce the negative effects of cardiovascular disease, even in moderate-risk populations with high blood pressure. Our multi-stage screening process and physician clearance steps will ensure that you will only engage in exercise if it is appropriate and safe for you, thus these risks should be minimal should you be cleared for the exercise portions of the study.

- Communicating with the researcher throughout the protocol will reduce risks.

- It is possible that we may find out something about your health that you did not know about. In the event we discover any significant medical abnormalities during the course of your participation in this study, we will inform you and your primary care physician, if you wish. If you do not have a primary physician, an appropriate referral will be made.

- If at any point, you are uncomfortable or feel pain anywhere, please tell us immediately.

**BENEFITS:**

- There is no direct benefit to you for participating in this research study; however, the information learned may help others in the future.

- You will receive information on your blood pressure, cholesterol level, body composition, aerobic fitness, cognitive function, heart structure and function. However, **These tests are not being used to diagnose a problem (NOT for medical/clinical purposes). These tests are being performed for research purposes only.** If you have high blood pressure, high cholesterol, high blood glucose, depression, or blood in your urine we will inform you to go to the university health center or your health care provider. If an abnormality is detected on the 3D echocardiography, low ABI is detected or an abnormal heart rhythm is observed, you will be referred to the cardiologist, lead physician on this study, Dr. Kan Liu.

**VOLUNTARY PARTICIPATION:**

Your participation in this study is entirely voluntary and you may refuse to participate or discontinue participation at any time without penalty or loss of benefits to which you would normally be entitled. Your decision about whether or not to participate in the study will not affect your relationship with Syracuse University or SUNY Upstate Medical University.

**STUDY WITHDRAWAL:**

- At any time, you may remove yourself from the study without giving any reason.

- If you are a student, withdrawing from the study will not affect your grade in courses in any way.

- Exercise is not appropriate for all individuals based on their health status. This study has a multi-stage process where we may exclude you from participating in the exercise portions of the study. Throughout this process, you may be excluded from the study based on
answers to the eligibility survey, the questionnaires administered in the screening visit, if you have low kidney function (determined from the urine test), very low cognitive function (determined from the basic cognitive function test on visit 1), high depressive symptomology (determined from a questionnaire), and very high cholesterol or blood sugar (determined from blood tests). We may also exclude you if…

- We find that you regularly experience any signs or symptoms that suggest you may have a medical condition and your health care provider is not aware that you are experiencing these symptoms. We will exclude you from the study and ask that you contact your health care provider.
- You have recently sustained a concussion.
- You have high blood pressure (systolic pressure >140, diastolic pressure >90 mmHg) and are not undergoing medical treatment for it. We will exclude you and ask that you follow up with your health care provider.
- You have an abnormal blood pressure response to exercise during visit 2.
- You have >2 cardiovascular risk factors and your physician does not give you, or you do not obtain, clearance to exercise.
- If you are experiencing any signs or symptoms of a serious/significant health condition (i.e. severe chest pain, leg pain, dizziness, feelings of heart palpitations) we will contact emergency medical services immediately and you will not be able to participate in the study.

The researchers may take you out of the study at any time with or without your agreement. This may happen if:

- It is in your best medical interest to stop your participation
- You are not able to follow the study instructions
- The study is canceled

**ALTERNATIVES:**

If you decide not to participate in this research study, you will not have any of the above procedures done for research purposes.

**NEW INFORMATION:**

You will be informed in a timely manner if new information that could affect your willingness to continue participation in this study becomes available.

**COSTS/PAYMENTS:**

- There will be no costs to you for participating in this study.
• You will receive monetary compensation for your time. You will receive $5 for completing the health screening visit, $5 for completing the physical activity and at-home blood pressure monitoring, $5 for completing the cardiopulmonary fitness test, and $5 for completing the final exercise visit along with at-home blood pressure monitoring and $5 and parking fees and $5 for completion of the echocardiogram. If you remove yourself, or are excluded, from the study prior to completing all visits, you will only be compensated for the visits/procedures that were completed. If you withdraw or are excluded from the study at visit 2 or 3, your compensation will be pro-rated depending on what stage of the visit you had completed.

QUESTIONS:

If you have any questions about the research, or in the event of a research-related injury, please contact Kan Liu, MD at (315) 464-9335, Jacqueline Augustine at (860) 508-8996, Kevin Heffernan, PhD at (315) 443-9801. If you have any questions about your rights as a research subject, please contact the SUNY Upstate Medical University Institutional Review Board Office at (315) 464-4317 or the Syracuse University Institutional Review Board Office at (315) 443-3013.

IN CASE OF INJURY:

In the event of illness or physical injury resulting from taking part in this research study, medical treatment will be provided at University Hospital. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by SUNY Upstate Medical University or Syracuse University. SUNY Upstate Medical University and Syracuse University have no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

CONFIDENTIALITY OF RECORDS AND AUTHORIZATION TO USE/SHARE PROTECTED HEALTH INFORMATION FOR RESEARCH:

If you agree to participate in this research, identifiable health information about you will be used and shared with others involved in this research. For you to be in this research we need your permission to collect and share this information. Federal law protects your right to privacy concerning this information.

When you sign this consent form at the end, it means that you have read this section and authorize the use and/or sharing of your protected health information as explained below. Your signature also means you have received a copy of Upstate’s Notice of Privacy Practices. The Notice of Privacy Practices should be given to each subject at the time consent for participation in the study is obtained.

Individually identifiable health information under the federal privacy law is considered to be any information from your medical record, or obtained from this study, that can be associated with you, and relates to your past, present, or future physical or mental health or condition. This is referred to as protected health information.
Your protected health information will be kept confidential. Your identity will not be revealed in any publication or presentation of the results of this research.

Why is it necessary to use/share your protected health information with others?
The main reason to use and share your health information is to conduct the research as described in this consent form. Your information may also be shared with people and organizations that make sure the research is being done correctly, and to report unexpected or bad side effects.

In addition, we may be required by law to release protected health information about you; for example, if a judge requires such release in a lawsuit, or if you tell us of your intent to harm yourself or others.

What protected health information about you will be used or shared with others as part of this research?
We may use and share the results of tests, questionnaires, and interviews. We may also use and share information from your medical and research records. We will only collect information that is needed for the research.

Who will be authorized to use and/or share your protected health information?
The researchers, their staff and the staff of Upstate Medical University and Syracuse University participating in the research will use your protected health information for this research study. In addition, the Upstate Institutional Review Board (IRB) and the Syracuse University IRB, committees responsible for protecting the rights of research subjects, and other Upstate Medical University, Syracuse University, or University Hospital staff who supervise the way the research is done may have access to your protected health information.

The researchers and their staff will determine if your protected health information will be used or shared with others outside of Upstate Medical University and Syracuse University for purposes directly related to the conduct of the research.

With whom would the protected health information be shared?
Your protected health information may be shared with:

- Federal agencies that supervise the way the research is conducted, such as the Department of Health and Human Services’ Office for Human Research Protections, or other governmental offices in the US or other countries, as required by law.

All reasonable efforts will be used to protect the confidentiality of your protected health information. However, not all individuals or groups have to comply with the Federal privacy law. Therefore, once your protected health information is disclosed (leaves Upstate Medical University), the Federal privacy law may not protect it.

For how long will your protected health information be used or shared with others?
There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be used and analyzed for many years and it is not possible to determine when this will be complete.
Can you withdraw your authorization to collect/use/share your protected health information?  
You always have the right to withdraw your permission (revoke authorization) for us to use and share your health information, by putting your request in writing to the investigator in charge of the study. This means that no further private health information will be collected. Once authorization is revoked, you may no longer participate in this research activity, but standard medical care and any other benefits to which you are entitled will not be affected. Revoking your authorization only affects uses and sharing of information obtained after your written request has been received, but not information obtained prior to that time.

Even after you withdraw your permission, Upstate Medical University and Syracuse University may continue to use and share information needed for the integrity of the study; for example, information about an unexpected or bad side effect you experienced related to the study.

Can you have access to your health information?

At the end of the study, you have the right to see and copy health information about you in accordance with the SUNY Upstate Medical University policies; however, your access may be limited while the study is in progress.

CONSENT TO PARTICIPATE IN RESEARCH & AUTHORIZATION TO USE AND SHARE PERSONAL HEALTH INFORMATION:

- I have read this information and this study has been explained to me.
- It has been written in a language that I understand.
- All my questions about the study have been answered to my satisfaction.

I hereby give my consent to participate in this research study and agree that my personal health information can be collected, used and shared by the researchers and staff for the research study described in this form. I will receive a signed copy of this consent form.

____________________________________  ______________  
Signature of subject  Date

___________________________________________  ______________  
Signature of Person Obtaining Consent/Authorization  Date

_________________________________________  
Name of Person Obtaining Consent/Authorization
Human Performance Lab Health Screening Form

Date__________
Age _______
Gender ______

Please answer the following questions as honestly as you can. Your patterns of responses will determine whether you may participate in the study.

**Known Diseases (Medical Conditions)**

1. List the medications and dietary supplements you take on a regular basis. (Include prescription and non-prescription, aspirin vitamins/minerals, nutrition supplements [Ensure, Boost, etc.])
   
   ______________________________________________________________________________________
   ______________________________________________________________________________________
   ______________________________________________________________________________________

Please underline or highlight or bold your answers to indicate “Yes” or “No” to the questions below:

2. Has your health care provider ever told you have diabetes? No Yes
3. Do you have acute or terminal illness (if so, please explain below)? No Yes
4. Have you ever had a stroke, heart attack or heart trouble? No Yes
5. Has your health care provider ever told you that you have a heart murmur? No Yes
6. Have you had a head injury in the past 3 months? No Yes
7. Do you have asthma /take asthma medication? No Yes
8. Has your health care provider ever told you that you have kidney or liver disease? No Yes
9. Has your health care provider ever told you that you have chronic pulmonary or respiratory disease? No Yes
10. Has your health care provider ever told you that you have peripheral artery disease? No Yes
11. Has your health care provider ever told you that you have high blood pressure? No Yes
12. Has your health care provider ever told you that you have high cholesterol? No Yes
13. Do you smoke cigarettes on a daily basis?   No   Yes

If yes to #13, how many packs per day _________________

If yes to #13, how long have you been smoking _________________

14. Have you lost or gained weight in the previous 6 months?   No   Yes

If yes, how much weight? _______

15. Has a first degree relative (e.g. father, mother, sister, brother, or child) suffered from a heart attack or diagnosed cardiovascular disease?   No   Yes

<table>
<thead>
<tr>
<th>Relative</th>
<th>Age</th>
<th>Did they pass away?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

16. Do you often have pains in your heart, chest, neck, jaw, arms or other areas especially during exercise?   No   Yes

17. Do you regularly get pains in your calves or lower legs during exercise which are not due to soreness or stiffness?   No   Yes

18. Do you experience swelling or accumulation of fluid in or around your ankles? No   Yes

19. Do you often feel faint or have spells of severe dizziness during exercise?   No   Yes

20. Do you often get the feeling that your heart is beating faster, racing, or skipping beats, either at rest or during exercise?   No   Yes

21. If you answered YES to question(s) 17-21, does your health care provider know that you have this/these symptom(s)?   No   Yes

22. If you answered YES to question(s) 16-20, are you currently experiencing this/these symptom(s) RIGHT NOW?   No   Yes

23. With which hand do you write?   Left   Right

24. How do you define your race/ethnicity? _________________________________
25. What is the highest grade/level of schooling/education completed?

8th Grade        Some HS        HS        some college       college        graduate school

26. Have you ever lost consciousness before during any daily activity?  No  Yes
   If you answered YES to question 31, please explain below.

27. On a scale of 1-5 (1= not anxious at all; 5= very anxious) how anxious do you feel during a
typical Doctor’s office visit?  1  2  3  4  5

Please underline or highlight or bold your answers to indicate “Yes” or “No” to the
questions below:

28. Additional:

<table>
<thead>
<tr>
<th>Allergies</th>
<th>Fibromyalgia</th>
<th>Polio</th>
<th>Flu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Attention Deficit</td>
<td>Reflux or Ulcers</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>Glaucoma</td>
<td>Liver Disease</td>
<td>Concussion</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Lupus</td>
<td>Bone Disease</td>
<td>Eczema</td>
</tr>
<tr>
<td>Asthma</td>
<td>Meningitis</td>
<td>Leg/foot Ulcers</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Chronic Lyme Disease</td>
<td>Diverticulitis</td>
<td>Headaches/Migraine</td>
</tr>
<tr>
<td>Chronic</td>
<td>Gout</td>
<td>Infection</td>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>Thyroid</td>
<td>Cold</td>
<td>Kidney Stones</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>(underactive/overactive)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blood pressure history

3. Have you ever been told you have high blood pressure (i.e. hypertension)?  No  Yes

4. Have you ever been diagnosed with high blood pressure by your physician?  No  Yes
   If yes, how long have you been living with high blood pressure? ________________
5. Are you currently taking prescription medication to treat/control your blood pressure? No
   Yes
   
   If yes, what kind of medication are you taking? ____________

   What dose? ____________

   Approximately how long have you been taking this medication? ____________

   Has your medication or your dose changed in the past 4-6 weeks? No Yes

6. Have you had trouble medically controlling your blood pressure (i.e. been on multiple medications)?
   No Yes

**Marathon History**

*Please underline or highlight or bold your answers to indicate “Yes” or “No” to the questions below:*

1. Have you ever completed a Marathon? No Yes
2. Are you currently training for a marathon race? No Yes
   a. If Yes, When is the marathon race? ____________
3. How many marathons have you completed in the past 1 year? ______
4. How many marathons have you complete in the past 3 years? ______
5. How many marathons have you completed in the past 5 years? ______
6. If you have completed any marathons in the past 5 years, please list the names of the races, year completed, and your finishing time
   __________________________________________________________
   __________________________________________________________
7. How many marathons have you completed in the past 20 years? ______
8. How many marathons have you completed in your lifetime? ______

9. On Average how many miles/week do you run? (circle one)
   <10 10-25 25-35 35-45 >45

10. On average how fast do you normally run? (circle one)
<5-6mph (>10 min/mile)  6-8mph (7:30-10:00 min/mile)  >8mph (<7:30 min/mile)

11. On average how many times a week do you run? (circle one)

   0   1-2   3-5   5-7

12. How many times a week do you perform extensive strength training sessions?

   0   1-2   3-5   5-7

13. Do regularly compete in road races or running competitions?  No  Yes

**Regular Exercise History**

1. Do you currently exercise on a regular basis?  No  Yes

2. Please rate your exercise level on a scale of 1 to 5 (5 indicating very strenuous) for each age range to your present age:

   15-20 _______  21-30 _______  31- 40 _______  41-50 _______  50 & older _______

3. Were you a high school and/or college athlete?

   If yes, please specify:

   ________________________________________________________________

4. Approximately how much time per week do you engage in exercise?

   Minutes/day: _______________  Days/week: _______________

5. Are you currently involved in regular endurance (cardiovascular) exercise?  No  Yes

   If yes, specify the type of exercise(s):

   ________________________________________________________________

   Days/week: ___________  Minutes/day: ___________

   Rate your perception of the exertion during your endurance/cardiovascular exercise (circle the number):

   (1) Light  (2) Fairly Light  (3) Somewhat Hard  (4) Hard

6. Are you currently involved in regular strength building (weight lifting) exercise?
If yes, specify the type of exercise(s):
_______________________________________________

Days/week: ___________ Minutes/day: ___________

Rate your perception of the exertion during your strength building exercise (circle the number):

(1) Light (2) Fairly Light (3) Somewhat Hard (4) Hard

7. How long have you been exercising regularly? ________ months ________ years

8. Do you participate in any sport, or recreational activities?

If yes, please specify the sports/activities
____________________________________________________________
____________________________________________________________

Menstrual Status (answer these questions only if you are a female)

1. Do you currently experience a regular menstrual cycle (i.e. period)? No Yes
   If no, approximately how many years ago did you have a regular menstrual cycle (10-12 a year)?_________
   If yes, approximately how many periods in a year do you have? _______
   Approximately how many days between periods? _______
   What was the approximate date of your last menstrual period?_____________

2. Has the time between your menstrual cycles changed at all recently? No Yes
   Has the length differed by >7 days? No Yes
   Has the length between cycles been >60 days (2 months)? No Yes

3. Have you ever experienced menstrual irregularity? No Yes
   Please describe (i.e. number of skipped menses, or prolonged menses):
   __________________________
   Approximately how long did this occur? Are you experiencing this currently?______________
4. Are you currently amenorrheic? 
   No    Yes

5. Have you gone through menopause (defined as no menstrual cycle/period for more than 12 months without any other possible causes)?
   No    Yes

6. Do you currently experience any of the following? Circle all that apply 
   No    Yes

<p>| | | | |</p>
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</table>

15. Do you use oral contraceptives? 
   If yes, for how long have you been using? ____________
   Which kind? ______________________
   What dose? ______
   Do you take the withdrawal/Placebo pills? ____________

16. Do you use Depo-Provera for birth control? 
   If yes, for how long have you used this method? ____________

17. Do you use hormone replacement therapy? 
   If yes, for how long have you been using? ____________
   Which kind? ______________________
   What dose? ______

18. If you are not currently taking a form of contraception or hormone replacement, have you ever been on any contraception and if so for how many years? 
   No    Yes
   a. How long ago did you discontinue use of contraception or hormone replacement?
**7-Day Exercise Training Log**

**Please make sure to wear your Heart Rate monitor that was given to you for the next 7 days DURING your training sessions**

**Day 1 Date:**

What time did you workout? ______________ What was your workout? ______________
How long did you work out for? _____________ If you ran how many miles did you run? _____
What was your average pace? ______________

**Day 2 Date:**

What time did you workout? ______________ What was your workout? ______________
How long did you work out for? _____________ If you ran how many miles did you run? _____
What was your average pace? ______________

**Day 3 Date:**

What time did you workout? ______________ What was your workout? ______________
How long did you work out for? _____________ If you ran how many miles did you run? _____
What was your average pace? ______________

**Day 4 Date:**

What time did you workout? ______________ What was your workout? ______________
How long did you work out for? _____________ If you ran how many miles did you run? _____
What was your average pace? ______________

**Day 5 Date:**

What time did you workout? ______________ What was your workout? ______________
How long did you work out for? _____________ If you ran how many miles did you run? _____
What was your average pace? ______________

**Day 6 Date:**

What time did you workout? ______________ What was your workout? ______________
How long did you work out for? _____________ If you ran how many miles did you run? _____
What was your average pace? ______________

**Day 7 Date:**


What time did you workout? ______________
What was your workout? ________________
How long did you work out for? __________
If you ran how many miles did you run? ____
What was your average pace? ____________
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ days per week

☐ No vigorous physical activities → Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?

_____ hours per day

_____ minutes per day

☐ Don’t know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ days per week

☐ No moderate physical activities → Skip to question 5

4. How much time did you usually spend doing moderate physical activities on one of those days?
Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?
   _____ days per week
   □ No walking → Skip to question 7

6. How much time did you usually spend walking on one of those days?
   _____ hours per day
   _____ minutes per day
   □ Don’t know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the last 7 days, how much time did you spend sitting on a week day?
   _____ hours per day
   _____ minutes per day
   □ Don’t know/Not sure

This is the end of the questionnaire, thank you for participating.
PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.
Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?
   BED TIME ___________

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   NUMBER OF MINUTES ___________

3. During the past month, what time have you usually gotten up in the morning?
   GETTING UP TIME ___________

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)
   HOURS OF SLEEP PER NIGHT ___________

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .
   a) Cannot get to sleep within 30 minutes
      Not during the past month____  Less than once a week____  Once or twice a week____  Three or more times a week____

   b) Wake up in the middle of the night or early morning
      Not during the past month____  Less than once a week____  Once or twice a week____  Three or more times a week____

   c) Have to get up to use the bathroom
      Not during the past month____  Less than once a week____  Once or twice a week____  Three or more times a week____

   d) Cannot breathe comfortably
      Not during the past month____  Less than once a week____  Once or twice a week____  Three or more times a week____

   e) Cough or snore loudly
      Not during the past month____  Less than once a week____  Once or twice a week____  Three or more times a week____

   f) Feel too cold
      Not during the past month____  Less than once a week____  Once or twice a week____  Three or more times a week____
6. During the past month, how would you rate your sleep quality overall?
   Very good ___________
   Fairly good __________
   Fairly bad ___________ 
   Very bad ____________

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?
   Not during the past month____   Less than once a week____   a week____   times a week____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
   Not during the past month____   Less than once a week_____  a week____   times a week____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
   No problem at all ____________
   Only a very slight problem __________
   Somewhat of a problem ____________
   A very big problem ____________

10. Do you have a bed partner or room mate?
No bed partner or room mate __________
Partner/room mate in other room __________
Partner in same room, but not same bed __________
Partner in same bed __________
If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring
   Not during the past month____   Less than once a week_____   Once or twice a week_____   Three or more times a week_____

b) Long pauses between breaths while asleep
   Not during the past month____   Less than once a week_____   Once or twice a week_____   Three or more times a week_____

c) Legs twitching or jerking while you sleep
   Not during the past month____   Less than once a week_____   Once or twice a week_____   Three or more times a week_____

d) Episodes of disorientation or confusion during sleep
   Not during the past month____   Less than once a week_____   Once or twice a week_____   Three or more times a week_____

e) Other restlessness while you sleep; please describe________________________________________
   ________________________________________________________________
   Not during the past month____   Less than once a week_____   Once or twice a week_____   Three or more times a week_____

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**CES-D Depression Inventory**

**INSTRUCTIONS:** For each statement, please circle the number in the column that best describes how you have been feeling *in the past week*.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or a moderate amount of the time (3-4 days)</th>
<th>Most or all of the time (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I was bothered by things that usually don’t bother me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>I did not feel like eating; my appetite was poor.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>I felt that I could not shake off the blues, even with the help from family or friends.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>I felt that I was just as good as other people.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>I had trouble keeping my mind on what I was doing.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>I felt depressed.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>I felt that everything I did was an effort.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>I felt hopeful about the future.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>I thought my life had been a failure.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>I felt fearful.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>My sleep was restless.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>I was happy.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>I talked less than usual.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>I felt lonely.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>People were unfriendly.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>I enjoyed life.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>I had crying spells.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>I felt sad.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>I felt that people dislike me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>I could not get “going”.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Anyone with suicidal urges should seek immediate consultation with a qualified psychiatrist or psychologist.
Activity Monitor Log

Please wear the physical activity monitor taped to the middle part of your thigh. Please wear this monitor during all waking and sleeping hours. **Remove the monitor before any water activity** (i.e. swimming, bathing, showering) and **document the time and duration that it was off of your body**.

EXAMPLE DAILY LOG

**Monday**

**Woke up at: 6:30AM**

**Went to bed at: 10:30PM**

<table>
<thead>
<tr>
<th>Please indicate time interval when monitor was not worn (i.e. &quot;8:05-8:25AM - shower&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:45-7:00AM - shower</td>
</tr>
<tr>
<td>5:30-5:40PM - shower after exercise</td>
</tr>
<tr>
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<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

**Monday**

**Woke up at:**

**Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
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</tbody>
</table>

Tuesday

Woke up at:  
Went to bed at:  

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
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</tbody>
</table>

Wednesday

Woke up at:  
Went to bed at:  

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Thursday

Woke up at:  
Went to bed at:  

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>
Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

... 

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Friday

Woke up at:

Went to bed at:

Saturday

Woke up at:

Went to bed at:

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Sunday

Woke up at:
Went to bed at:

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower")

Other notes:
The Keep Your Heart Running Study
The Exercise Science Department at Syracuse University is recruiting participants for a research study

To examine sex differences in the effect of endurance exercise (such as a marathon) on heart and blood vessel health.

You are eligible if you are 35-50 years old:
- Regularly participate in marathon races
- Are healthy recreationally-active adult
- Do not smoke, do not have diabetes, kidney disease, or cardiovascular disease

What do you have to do?
- Visit 1: Health Screening to determine eligibility and receive body fat testing, body composition testing, 7-day physical activity, heart rate monitoring (1 hour)
- Visit 2: Perform a maximal exercise test on a treadmill to determine fitness level (1 hour)
- Visit 3: Perform an easy 30 minute walk/run on the treadmill (1 hour)
- Visit 4: Receive a non-invasive three dimensional echocardiography image of your heart at SUNY Upstate Medical University (1 hour)

You may receive up to $25 compensation for completing the full study

All research will take place on the main campus of Syracuse University with one visit to the 6th floor of SUNY Upstate Medical University (on site, no cost for parking), Human Performance Laboratory, 820 Comstock Avenue, Women’s Building, SUNY Upstate Medical University, 750 E. Adams St, Echocardiography Lab

For more information, please contact us: Jaimse@syr.edu or 315-443-4540
Facebook Page Recruitment
We are requesting a study Facebook page aimed at expanding our recruitment efforts in order to reach more potential participants. We plan to use the Facebook page to post information about our study and use Facebook’s business outreach features where we would pay a small fee to increase our page’s exposure (in order to increase webpage traffic). The attached screenshots of the Facebook page represent our current working page, which will not get published (i.e. go public) until approval has been received. We still plan to use our flyers/SU news posts, this is meant to supplement our current recruiting efforts.
## Study Design Schematic

### Study Design

**Time between Visit 1 to Visit 4 ≤ 3 weeks**

**Time between Visit 1 to Visit 3 ≤ 7 days**

<table>
<thead>
<tr>
<th>VISIT 1</th>
<th>VISIT 2</th>
<th>VISIT 3</th>
<th>VISIT 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>~1 hour</td>
<td>~1 hour</td>
<td>~1.5 hours</td>
<td>~1 hour</td>
</tr>
<tr>
<td>12 hours fasted</td>
<td>VO2 Max test on</td>
<td>Controlled</td>
<td>Upstate 3-</td>
</tr>
<tr>
<td></td>
<td>treadmill</td>
<td>Exercise day in</td>
<td>dimensional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the laboratory</td>
<td>echocardiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(LVM, STE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24 hours no</td>
<td>Bring back</td>
<td>Perform a 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mobil-o-graph</td>
<td>minute run at</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-70% of HR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>max on treadmill</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D BSA, Body fat</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Give HR monitor,</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Fit and give Mobil-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>o-graph</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Two-Dimensional Echocardiography: LV Structure and Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Sex Effect</th>
<th>Training Effect</th>
<th>SxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LV Structure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (g)</td>
<td>120±20</td>
<td>118±25</td>
<td>176±51</td>
<td>158±32</td>
<td>0.00</td>
<td>0.24</td>
<td>0.50</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>74±15</td>
<td>67±21</td>
<td>86±3</td>
<td>83±17</td>
<td>0.00</td>
<td>0.24</td>
<td>0.58</td>
</tr>
<tr>
<td>LVM/EDV</td>
<td>59±12</td>
<td>55±17</td>
<td>61±20</td>
<td>66±11</td>
<td>0.12</td>
<td>0.59</td>
<td>0.27</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>94±17</td>
<td>94±18</td>
<td>121±31</td>
<td>119±24</td>
<td>0.00</td>
<td>0.74</td>
<td>0.99</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>39±7</td>
<td>48±15</td>
<td>47±13</td>
<td>42±13</td>
<td>0.00</td>
<td>0.26</td>
<td>0.73</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>57±11</td>
<td>62±17</td>
<td>74±21</td>
<td>73±15</td>
<td>0.00</td>
<td>0.83</td>
<td>0.46</td>
</tr>
<tr>
<td>SV/BSA (L/m²)</td>
<td>38±7</td>
<td>32±10</td>
<td>37±9</td>
<td>37±9</td>
<td>0.75</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>Q (L/min)</td>
<td>3.1±0.8</td>
<td>4.0±1.1</td>
<td>3.8±0.9</td>
<td>4.3±1.2</td>
<td>0.05</td>
<td>0.23</td>
<td>0.35</td>
</tr>
<tr>
<td>Q/BSA (L/min/m²)</td>
<td>1.8±0.4</td>
<td>2.3±0.6</td>
<td>1.9±0.5</td>
<td>2.2±0.5</td>
<td>0.40</td>
<td>0.50</td>
<td>0.20</td>
</tr>
<tr>
<td>IVS (cm)</td>
<td>0.82±0.10</td>
<td>0.80±0.09</td>
<td>0.94±0.13</td>
<td>0.90±0.08</td>
<td>0.00</td>
<td>0.11</td>
<td>0.67</td>
</tr>
<tr>
<td>PWD (cm)</td>
<td>0.82±0.10</td>
<td>0.80±0.09</td>
<td>0.95±0.14</td>
<td>0.89±0.09</td>
<td>0.00</td>
<td>0.19</td>
<td>0.49</td>
</tr>
<tr>
<td>LVDd (cm)</td>
<td>4.50±0.37</td>
<td>4.53±0.37</td>
<td>4.97±0.54</td>
<td>4.98±0.44</td>
<td>0.00</td>
<td>0.99</td>
<td>0.88</td>
</tr>
<tr>
<td>LVDs (cm)</td>
<td>3.05±0.30</td>
<td>3.00±0.24</td>
<td>3.35±0.38</td>
<td>3.35±0.38</td>
<td>0.00</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td>RWT</td>
<td>0.37±0.06</td>
<td>0.36±0.04</td>
<td>0.38±0.06</td>
<td>0.36±0.04</td>
<td>0.34</td>
<td>0.15</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>LV Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>62.9±7.4</td>
<td>64.4±5.4</td>
<td>62.6±6.0</td>
<td>61±6.3</td>
<td>0.17</td>
<td>0.80</td>
<td>0.39</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>33.4±6.8</td>
<td>34.1±3.9</td>
<td>35.3±10.8</td>
<td>33.0±4.4</td>
<td>0.79</td>
<td>0.38</td>
<td>0.45</td>
</tr>
<tr>
<td>2D Peak Global Strain (%)</td>
<td>-21.3±2.3</td>
<td>-25.9±24.4</td>
<td>-20.1±2.7</td>
<td>-19.4±2.1</td>
<td>0.18</td>
<td>0.50</td>
<td>0.36</td>
</tr>
</tbody>
</table>

BSA, Body Surface Area; LV, Left Ventricle Mass; LVMI, Left Ventricle Mass Index; EDV, End Diastolic Volume; ESV, End Systolic Volume; SV, Stroke Volume; Q, Cardiac Output; EF, Ejection Fraction; IVS, Interventricular Septum; LVDd, Left Ventricle Diameter in Diastole; PWD, Posterior Wall Diameter; LVDs, Left Ventricle Diameter in Systole; RWT, Relative Wall Thickness. Significance Level at p<0.05. SxT interaction, Sex x Training Interaction.
### Average Non-Exercise 24-hour Ambulatory Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Gender Effect</th>
<th>Training Effect</th>
<th>GxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>113±10</td>
<td>116±10</td>
<td>122±6</td>
<td>120±6</td>
<td>0.00</td>
<td>0.28</td>
<td>0.07</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89±7</td>
<td>92±9</td>
<td>97±5</td>
<td>97±5</td>
<td>0.00</td>
<td>0.31</td>
<td>0.11</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>69±7</td>
<td>72±9</td>
<td>77±5</td>
<td>77±6</td>
<td>0.00</td>
<td>0.40</td>
<td>0.23</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>44±7</td>
<td>44±5</td>
<td>44±5</td>
<td>44±4</td>
<td>0.98</td>
<td>0.56</td>
<td>0.21</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>62±7</td>
<td>69±9</td>
<td>57±6</td>
<td>64±6</td>
<td>0.00</td>
<td>0.00</td>
<td>0.78</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>120±8</td>
<td>121±11</td>
<td>135±10</td>
<td>128±6</td>
<td>0.00</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>71±6</td>
<td>72±8</td>
<td>79±5</td>
<td>78±6</td>
<td>0.00</td>
<td>0.72</td>
<td>0.39</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>49±9</td>
<td>48±7</td>
<td>52±4</td>
<td>53±3</td>
<td>0.00</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>6.0±0.5</td>
<td>6.1±0.5</td>
<td>6.3±0.4</td>
<td>6.2±0.4</td>
<td>0.02</td>
<td>0.93</td>
<td>0.15</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>13.6±2.3</td>
<td>14.3±1.8</td>
<td>13.2±1.5</td>
<td>13.2±1.5</td>
<td>0.07</td>
<td>0.11</td>
<td>0.12</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>21.0±3.1</td>
<td>21.6±2.1</td>
<td>21.6±2.8</td>
<td>21.4±1.8</td>
<td>0.75</td>
<td>0.37</td>
<td>0.19</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; MAP, Mean arterial pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; HR, heart rate; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure; PWV, pulse wave velocity; Pb, backward wave pressure; Pf, forward wave pressure.
Average Non-Exercise Control 24-hour Ambulatory Day Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Gender Effect</th>
<th>Training Effect</th>
<th>GxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>117±9</td>
<td>121±11</td>
<td>127±7</td>
<td>125±7</td>
<td>0.00</td>
<td>0.48</td>
<td>0.04</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93±7</td>
<td>96±10</td>
<td>103±6</td>
<td>101±6</td>
<td>0.00</td>
<td>0.49</td>
<td>0.07</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73±7</td>
<td>75±9</td>
<td>82±6</td>
<td>81±7</td>
<td>0.00</td>
<td>0.54</td>
<td>0.19</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>44±7</td>
<td>5±5</td>
<td>45±6</td>
<td>43±5</td>
<td>0.73</td>
<td>0.80</td>
<td>0.18</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65±7</td>
<td>72±9</td>
<td>60±6</td>
<td>66±7</td>
<td>0.00</td>
<td>0.00</td>
<td>0.90</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>121±10</td>
<td>122±12</td>
<td>137±12</td>
<td>130±7</td>
<td>0.00</td>
<td>0.18</td>
<td>0.08</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>75±7</td>
<td>76±9</td>
<td>84±6</td>
<td>83±7</td>
<td>0.00</td>
<td>0.91</td>
<td>0.54</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>46±6</td>
<td>45±4</td>
<td>54±4</td>
<td>56±5</td>
<td>0.00</td>
<td>0.28</td>
<td>0.06</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>6.0±0.5</td>
<td>6.2±0.5</td>
<td>6.2±1.4</td>
<td>6.4±0.5</td>
<td>0.33</td>
<td>0.43</td>
<td>0.96</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>12.8±2.7</td>
<td>13.6±2.04</td>
<td>12.7±1.5</td>
<td>12.4±1.8</td>
<td>0.10</td>
<td>0.20</td>
<td>0.06</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>20.6±3.5</td>
<td>21.3±2.3</td>
<td>21.4±2.7</td>
<td>20.8±2.3</td>
<td>0.78</td>
<td>0.53</td>
<td>0.07</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; MAP, Mean arterial pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; HR, heart rate; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure; PWV, pulse wave velocity; Pb, backward wave pressure; Pf, forward wave pressure.
Average Non-Exercise Control 24-hour Ambulatory Night Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male Controls (n=24)</th>
<th>Gender Effect</th>
<th>Training Effect</th>
<th>GxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>106±10</td>
<td>108±11</td>
<td>112±7</td>
<td>111±5</td>
<td>0.02</td>
<td>0.45</td>
<td>0.15</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83±9</td>
<td>84±9</td>
<td>88±5</td>
<td>88±5</td>
<td>0.01</td>
<td>0.69</td>
<td>0.31</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>64±8</td>
<td>64±9</td>
<td>69±4</td>
<td>68±6</td>
<td>0.00</td>
<td>0.95</td>
<td>0.58</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>43±6</td>
<td>44±6</td>
<td>43±5</td>
<td>43±4</td>
<td>0.74</td>
<td>0.36</td>
<td>0.15</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>56±7</td>
<td>64±9</td>
<td>53±7</td>
<td>60±8</td>
<td>0.03</td>
<td>0.00</td>
<td>0.84</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>120±9</td>
<td>117±8</td>
<td>133±10</td>
<td>127±6</td>
<td>0.00</td>
<td>0.02</td>
<td>0.44</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>68±6</td>
<td>69±9</td>
<td>76±8</td>
<td>73±8</td>
<td>0.00</td>
<td>0.49</td>
<td>0.42</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>52±6</td>
<td>48±5</td>
<td>57±5</td>
<td>55±4</td>
<td>0.08</td>
<td>0.03</td>
<td>0.50</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>5.8±0.5</td>
<td>6.0±0.4</td>
<td>6.2±0.4</td>
<td>6.1±0.4</td>
<td>0.06</td>
<td>0.77</td>
<td>0.27</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>15.5±7.3</td>
<td>15.9±2.7</td>
<td>13.7±2.1</td>
<td>14.3±1.8</td>
<td>0.07</td>
<td>0.49</td>
<td>0.99</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>21.6±3.0</td>
<td>22.1±2.9</td>
<td>21.2±2.9</td>
<td>21.8±2.3</td>
<td>0.84</td>
<td>0.08</td>
<td>0.44</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; MAP, Mean arterial pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; HR, heart rate; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure; PWV, pulse wave velocity; Pb, backward wave pressure; Pf, forward wave pressure.
Average Post-exercise 24-hour Ambulatory Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male controls (n=24)</th>
<th>Gender Effect</th>
<th>Training Effect</th>
<th>GxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>112±8</td>
<td>115±11</td>
<td>120±7</td>
<td>120±6</td>
<td>0.00</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89±7</td>
<td>91±10</td>
<td>96±5</td>
<td>96±6</td>
<td>0.00</td>
<td>0.22</td>
<td>0.56</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70±7</td>
<td>71±9</td>
<td>75±5</td>
<td>77±7</td>
<td>0.00</td>
<td>0.26</td>
<td>0.96</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>43±7</td>
<td>44±5</td>
<td>45±5</td>
<td>43±4</td>
<td>0.60</td>
<td>0.79</td>
<td>0.07</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>62±6</td>
<td>69±7</td>
<td>57±7</td>
<td>64±8</td>
<td>0.00</td>
<td>0.00</td>
<td>0.98</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>120±8</td>
<td>120±12</td>
<td>135±12</td>
<td>130±7</td>
<td>0.01</td>
<td>0.30</td>
<td>0.40</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>73±7</td>
<td>71±7</td>
<td>79±6</td>
<td>80±8</td>
<td>0.00</td>
<td>0.83</td>
<td>0.32</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>32±5</td>
<td>34±4</td>
<td>33±4</td>
<td>32±4</td>
<td>0.28</td>
<td>0.38</td>
<td>0.02</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>6.0±0.5</td>
<td>6.1±0.6</td>
<td>6.3±0.6</td>
<td>6.2±0.4</td>
<td>0.12</td>
<td>0.93</td>
<td>0.73</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>13.3±2.4</td>
<td>14.4±1.8</td>
<td>13.3±1.7</td>
<td>12.7±2.1</td>
<td>0.04</td>
<td>0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>20.7±3.1</td>
<td>21.5±2.2</td>
<td>21.9±2.9</td>
<td>21.1±1.9</td>
<td>0.48</td>
<td>0.68</td>
<td>0.06</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; MAP, Mean arterial pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; HR, heart rate; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure; PWV, pulse wave velocity; Pb, backward wave pressure; Pf, forward wave pressure.
### Average Post-Exercise Ambulatory Day Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
<th>Male Marathoners (n=24)</th>
<th>Male controls (n=24)</th>
<th>Gender Effect</th>
<th>Training Effect</th>
<th>GxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>117±8</td>
<td>121±12</td>
<td>125±7</td>
<td>124±6</td>
<td>0.00</td>
<td>0.45</td>
<td>0.14</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>93±7</td>
<td>96±10</td>
<td>101±6</td>
<td>100±6</td>
<td>0.00</td>
<td>0.52</td>
<td>0.31</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74±7</td>
<td>75±9</td>
<td>81±7</td>
<td>80±7</td>
<td>0.00</td>
<td>0.64</td>
<td>0.63</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>44±7</td>
<td>45±5</td>
<td>45±5</td>
<td>44±5</td>
<td>0.80</td>
<td>0.61</td>
<td>0.11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>66±6</td>
<td>73±8</td>
<td>61±7</td>
<td>69±8</td>
<td>0.00</td>
<td>0.00</td>
<td>0.81</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>120±12</td>
<td>121±12</td>
<td>135±11</td>
<td>130±7</td>
<td>0.00</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>78±8</td>
<td>74±8</td>
<td>83±7</td>
<td>83±7</td>
<td>0.00</td>
<td>0.31</td>
<td>0.43</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>43±5</td>
<td>47±4</td>
<td>52±4</td>
<td>47±5</td>
<td>0.45</td>
<td>0.76</td>
<td>0.22</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>6.2±0.5</td>
<td>6.2±0.6</td>
<td>6.4±0.5</td>
<td>6.3±9.4</td>
<td>0.14</td>
<td>0.64</td>
<td>0.81</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>12.6±2.2*</td>
<td>13.5±1.8</td>
<td>12.7±1.6</td>
<td>11.8±2.3</td>
<td>0.07</td>
<td>0.64</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>20.4±3.2</td>
<td>21.1±2.3</td>
<td>21.6±2.8</td>
<td>20.6±2.4</td>
<td>0.45</td>
<td>0.91</td>
<td><strong>0.05</strong></td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; MAP, Mean arterial pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; HR, heart rate; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure; PWV, pulse wave velocity; Pb, backward wave pressure; Pf, forward wave pressure.
Average Post-exercise 24-hour Night Hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female Marathoners (n=28)</th>
<th>Female Controls (n=25)</th>
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<th>Male Controls (n=24)</th>
<th>Gender Effect</th>
<th>Training Effect</th>
<th>GxT Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>106±9</td>
<td>108±10</td>
<td>111±7</td>
<td>113±7</td>
<td>0.00</td>
<td>0.16</td>
<td>0.56</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83±8</td>
<td>84±9</td>
<td>87±5</td>
<td>89±7</td>
<td>0.00</td>
<td>0.16</td>
<td>0.83</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>64±8</td>
<td>64±9</td>
<td>67±5</td>
<td>70±7</td>
<td>0.00</td>
<td>0.21</td>
<td>0.33</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>42±6</td>
<td>44±6</td>
<td>45±5</td>
<td>43±2</td>
<td>0.36</td>
<td>0.62</td>
<td>0.35</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>56±7</td>
<td>62±8</td>
<td>51±7</td>
<td>58±10</td>
<td>0.01</td>
<td>0.00</td>
<td>0.92</td>
</tr>
<tr>
<td>aSBP (mmHg)</td>
<td>118±11</td>
<td>117±11</td>
<td>135±14</td>
<td>132±13</td>
<td>0.03</td>
<td>0.49</td>
<td>0.81</td>
</tr>
<tr>
<td>aDBP (mmHg)</td>
<td>70±6</td>
<td>67±8</td>
<td>74±8</td>
<td>75±9</td>
<td>0.00</td>
<td>0.70</td>
<td>0.33</td>
</tr>
<tr>
<td>aPP (mmHg)</td>
<td>48±5</td>
<td>50±6</td>
<td>60±6</td>
<td>57±3</td>
<td>0.00</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>5.9±0.4</td>
<td>5.9±0.6</td>
<td>6.2±0.6</td>
<td>6.0±0.5</td>
<td>0.17</td>
<td>0.60</td>
<td>0.50</td>
</tr>
<tr>
<td>Pb (mmHg)</td>
<td>13.9±2.4</td>
<td>15.9±3.0</td>
<td>14.2±2.7</td>
<td>14.1±1.6</td>
<td>0.17</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Pf (mmHg)</td>
<td>20.8±2.8</td>
<td>22.1±3.1</td>
<td>21.9±3.4</td>
<td>21.8±1.9</td>
<td>0.44</td>
<td>0.19</td>
<td>0.13</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; MAP, Mean arterial pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; HR, heart rate; aSBP, aortic systolic blood pressure; aDBP, aortic diastolic blood pressure; aPP, aortic pulse pressure; PWV, pulse wave velocity; Pb, backward wave pressure; Pf, forward wave pressure.
References


Curriculum Vitae
Jacqueline A. Augustine
Syracuse University; Department of Exercise Science
820 Comstock Avenue
Syracuse, NY 13244; (860)-508-8996
Email: Jaimse@syr.edu

EDUCATION

2018  Ph.D. Science Education, Exercise Science
Syracuse University, Syracuse, NY
Advisor: Kevin Heffernan
Dissertation: Sex Differences in Cardiovascular Adaptations to Chronic Endurance Exercise.

2014  M.S. Exercise Science
Syracuse University, Syracuse, NY
Advisor: Kevin Heffernan
Thesis: Vascular Function in Trained Females

2011  B.A. Psychology, Biology-Psychology Concentration
The College of the Holy Cross, Worcester, MA
Thesis: Rate of Carbon Dioxide Production Is Not a Valid Measure of Behavioral Energetics in Species with Poorly Developed Aerobic Metabolism: Spiders as an Example

TEACHING EXPERIENCE

2018- Assistant Professor of Kinesiology, SUNY Cortland
Department of Kinesiology

2016-2017 Adjunct Instructor, Human Physiology, SUNY Upstate Medical University, College of Health Professions, Physician Assistant Studies
Guest Lecturer: Research Design, Masters in Clinical Research Course

2016 Graduate School Most Outstanding Teaching Assistant Award

2015 Certificate of University Teaching from Syracuse University

2011-Present Research Assistant and Supervisor in The Human Performance Laboratory
Mentored undergraduate and graduate students in the laboratory

2012-Present Teaching Assistant, Syracuse University, Department of Exercise Science, School of Education, Syracuse, NY
Designed syllabi, designed laboratory exercises, guest lectured, graded assignments
Introduction to Exercise Science Recitation
Exercise Physiology Laboratory
Motor Behavior Across the Lifespan

2013    Summer Teaching Assistant, Syracuse University, Department of Exercise Science, School of Education, Syracuse, NY
         Exercise Physiology, High School Student

2013    Guest Lecturer, Syracuse University Exercise Physiology
         “Cardiovascular Physiology,” Exercise Physiology
         “Sports Nutrition,” Exercise Physiology

RESEARCH EXPERIENCE

2011-2018    Researcher in The Human Performance Laboratory
              Syracuse University, Syracuse, NY

2010    Student Research Fellowship, Heart Failure Unit, Cardiology Department,
              Hartford Hospital, Hartford, CT

Research Project: Novel Findings of Upregulation of Neutrophil Gelatinase-B Lipase (NGAL) in the Myocytes of Advanced Heart Failure Patients

2009-11    Student Research Assistant, Animal Physiology Laboratory, Biology Department, The College of the Holy Cross, Worcester, MA

PEER REVIEWED PUBLICATIONS


Augustine JA, Jae SY, Heffernan KS. The Relationship between cardiorespiratory fitness and aortic stiffness in women with central obesity, *Journal of Women’s Health*, 2014.


NATIONAL PRESENTATIONS AND ABSTRACTS


• Lefferts WK, Augustine JA, Nunemacher KN, Heffernan KS. No Sex Differences in Cardiovascular Response to Mental Stress in Older Adults. Northern American Artery Conference, Chicago, IL 2016.


• Spartano NL, Augustine JA, Lefferts WK, Hughes WE, Morse BG, Martin ED, Gump BB, Heffernan KS. “Physical Activity is Associated with Attenuated Carotid Blood


REGIONAL PRESENTATIONS AND ABSTRACTS


- Nunemacher K, Augustine JA, Lefferts WK, Barreira T, Heffernan KS. “Physical Activity Mediates the Relationship Between Sleep Quality and Vascular Health in Older Adults.” Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 6-7, 2015.
• **Augustine JA, Lefferts WK, Spartano NL, Hughes WE, Gump BB, Heffernan KS. “Physical Function, Cognitive Function, and Aortic Stiffness in Older Adults” Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburg, PA, October 31-November 1, 2014.


* Slide Presentation, ^Award Recipient

**GRANTS**

2013-18 School of Education Travel Grant ($400)
2013-18 Graduate Student Organization ($350)
2016 School of Education Sydney Young Research Grant ($2700)
2016 School of Education Creative Research Grant ($1000)
2015 Phi Kappa Phi Academic Honor’s Society “Love of Learning” Grant ($500)

**AWARDS**
2018  Syracuse University, Neuroscience Research Abstract Award, Second Place
2016  Graduate School Most Outstanding Teaching Assistant Award
2015  Certificate of University Teaching
2015  Mid-Atlantic Regional American College of Sports Medicine Doctoral Student Research Finalist
2014  Mid-Atlantic Regional American College of Sports Medicine Doctoral Student Research Finalist
2013  Mid-Atlantic Regional American College of Sports Medicine Masters Student Research Finalist
2012  Mid-Atlantic Regional American College of Sports Medicine Masters Student Research Finalist
2011-2012  Syracuse University School of Education Dean’s Scholarship (1 year tuition)

COMMUNITY AND PROFESSIONAL SERVICE
2012-Present  Future Professoriate Program (FPP)
2014-Present  Women in Science and Engineering (WISE) Program, Syracuse University
2013-Present  American Heart Association Walk, Syracuse, NY
2012-2014  Consultant for Syracuse University NCAA Division I Women’s Soccer Team
2013  Search Committee for Assistant Professor of Physical Education, Exercise Science Department, Student Representative

PROFESSIONAL MEMBERSHIP
2012-Present  American College of Sports Medicine (ACSM)
2012-Present  Mid-Atlantic Regional American College of Sports Medicine (MARC)
2013-Present  Phi Kappa Phi Honor’s Society, Syracuse University Chapter
2013-Present  American Heart Association (AHA)
2013-Present  National Science Teacher’s Association (NSTA)

PROFESSIONAL CERTIFICATIONS
2013-Present  American Red Cross, Adult and Pediatric CPR/AED/First Aid