AEROBIC EXERCISE DOES NOT MODIFY CAROTID ARTERY STIFFNESS IN
SEDENTARY HEALTHY PRE-MENOPAUSAL WOMEN

by

EARL H. SCHWARK, II

(Under the Direction of Kevin McCully)

ABSTRACT

Cardiovascular disease remains the number one cause of death for women. Arterial stiffness has been used as a predictor of future heart disease. Arterial stiffness decreases with aerobic training in older men and women. The purpose of this study was to test whether a 14-week aerobic (stationary cycling) training program improves arterial stiffness in nine healthy pre-menopausal sedentary women. Measures of body composition (DXA), cardiorespiratory fitness (VO2peak) and carotid arterial stiffness, defined as beta stiffness index, compliance, and distensibility were measured before and after the training. Fitness improved by 9.4% (P=0.016), with no significant changes in body composition. Arterial stiffness did not change with training, pre 6.45±3.5 (U) to post 6.36±1.75 (U) (P=0.46). In conclusion, aerobic training does not appear to improve arterial stiffness in younger women whose arteries did not show increased stiffness pre-treatment.

INDEX WORDS: Arterial stiffness, Carotid artery, Compliance, Women, Exercise
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EARL H. SCHWARK, II

B.S., Western Michigan University, 2001

A Thesis Submitted to the Graduate Faculty of the University of Georgia in Partial Fulfillment of
the Requirements for the Degree

MASTERS OF SCIENCE

ATHENS, GEORGIA

2005
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EARL H. SCHWARK, II

Major Professor: Kevin McCully

Committee: Kirk Cureton
Harry DuVal

Electronic Version Approved:
Maureen Grasso
Dean of the Graduate School
The University of Georgia
May 2005
ACKNOWLEDGEMENTS

This project is the result of many efforts and I would like to note, in no particular order, some of those responsible for my success. I would like to thank my committee for help with this project and for all the opportunities they provided me in my time at UGA. Dr. Cureton for your support in my coming to UGA and passionate instruction in the classroom. Dr. DuVal for offering me a job and helping me learn all the science as well as the “other” that came with it. Dr. McCully for being a good scientist and a great guy; thanks for the ability to learn the process.

Much thanks to my parents and family for always being there to listen. A special thanks to Bill and Laurel Yen, all that you gave me made this project much easier. Especially, the place to stay, the car usage, the companionship and most of all the delicious FOOD. I’d be a skinny, uneducated, poor man without the two of you!!! Of course Lee Stoner, one of the few people that can understand me, even when I’m not speaking American or British! Thanks buddy.

To my great team of assistants, Michelle Habermehl, Lora Raines and Genevieve Olivier, thank you for all of your time and talents in the massive data collection, especially when I was assisting you!!!! Without question thanks to the resilience of my research subjects, without your ability to tolerate the bike seat and me, there would not have been a project.

Finally, a big nod of appreciation to Manning Sabatier. His help in design and implementation of the project was appreciated. His technical assistance and leadership in showing how to be fully dedicated to a project without losing sight of the big picture were necessities. Lastly, thanks for that mint chocolate chip brownie!!
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CHAPTER 1
INTRODUCTION

Structure of Thesis

Chapter one is a brief foundation for the reasons behind the study, the aims of the project and the hypotheses to be tested. Chapter two is a review of some of the relevant research on the topics of cardiovascular disease, fitness and arterial stiffness. Attention is drawn to the interrelation of fitness and arterial stiffness, highlighting how they can help define, modify and predict cardiovascular disease. Chapter three is one of the manuscripts from the data analysis of the aerobic training study, which will be submitted to Dynamic Medicine for publication. Chapter four presents the findings of the study with remarks on their importance and future use. Chapter five concludes the document with the list of references for all four preceding chapters.

Introduction

Cardiovascular disease (CVD) has been the number one cause of death in America for both men and women over the last 20 years (4). Many factors are associated with cardiovascular disease; some are used to measure the extent of disease, while others can predict likelihood of disease. Measures of arterial properties have been studied more frequently over the last few decades and are starting to come into favor as measures associated with and possibly predictive of CVD (5,13,22).

Arterial stiffness is one arterial property that is associated with CVD (22) and appears to be modifiable in some populations (10,17). Both central and peripheral arterial stiffness can be determined in vivo (5,22). Central stiffness, determined through measurements made at the
carotid artery may have a greater relationship with CVD as it may approximate the properties of the aorta itself (10). This site is also easy to measure as it is a superficial artery at an accessible location in most populations.

Changes in central arterial stiffness occur with aging (5), are independent of body composition changes (17) and appear to be affected by activity and fitness levels (17). Much of the work in this area has been done on older individuals using cross-sectional methods, primarily on men, with very few studies conducted on women (12). Healthy women and men alike have been studied infrequently using longitudinal designs that include an exercise intervention, especially in younger populations. Therefore, the purpose of this study was to explore the effects of an aerobic exercise training protocol on common carotid stiffness in sedentary women of varying size.

**Study Aims**

The aims of the study were to:

1. Measure stiffness of the common carotid artery in sedentary women of varying BMI.
2. Conduct a 14-week aerobic training program with women of varying BMI.
3. Measure stiffness of the common carotid artery in women of varying BMI after a 14-week aerobic training program.

**Study Hypotheses**

It is hypothesized that:

1. Percent fat from DXA will be positively associated with central stiffness.
2. A 14-week aerobic training program will improve aerobic capacity without a change in percent fat calculated from DXA.
3. Participating in an aerobic training program will decrease central stiffness.
Significance of the Study

This study will assessed arterial stiffness in a population studied infrequently. Women represent a small part of the published literature and an even smaller part of studies that have looked at arterial stiffness. In addition, pre-menopausal women are studied infrequently using clinical measures like arterial stiffness. This will be one of the first looks at this measure in this population. While larger cross-sectional studies often estimate fitness and body composition, this study uses DXA and VO$_{2peak}$, which accurately quantify body composition and cardiorespiratory fitness. Using specific quantitative measures in a population infrequently studied will yield results that have the potential to be novel and informative.
CHAPTER 2
RELATED LITERATURE REVIEW

Cardiovascular Disease

A recent publication by the Centers for Disease Control presented a compilation of the leading causes of death based on death certificate reports. Heart disease is the number one cause of death for all persons, regardless of gender (4). The report also compared the data from 2001 to that from 1980; this comparison indicated that heart disease is unchanged as the leading cause of death.

Over this 20-year span, many aspects of heart disease have been studied in an attempt to determine treatment plans, as well as, prevention strategies. Significant work done in this area has developed a list of major risk factors used to help predict individuals at risk for heart disease. The American College of Sports Medicine has supported this movement and recently compiled a list of Coronary Artery Disease Risk Factor Thresholds used for exercise testing and exercise prescription (1). Other clinical guidelines are available to help predict likelihood of CVD, with lack of cardiorespiratory fitness common to most.

Cardiorespiratory Fitness

Physical inactivity is a risk factor for development of heart disease (1). Many methods are available to measure physical activity, all with positive and negative features. Many researchers choose to measure fitness instead of physical activity, as fitness is more easily quantified. Fitness itself is a generic term that has numerous definitions. Generally, fitness
refers to cardiorespiratory fitness, which is defined as the ability to perform dynamic exercise using large muscles at moderate-to-high intensity for prolonged periods (1).

**Cardiovascular Disease and Cardiorespiratory Fitness**

Fitness is an important health marker, as low levels of fitness relate to increased risk of heart disease and mortality (8). Ekelund et al. (8) studied the relationship between fitness and death from heart disease. They took 3,000 men between the ages of 30 and 70 and measured current risk factors, administered a treadmill test and then followed the men for an average of 8.5 years. The second stage heart rate and duration on a treadmill test determined fitness level. They concluded that a lower level of fitness was associated with a higher risk of death from coronary heart disease. This increased risk was independent of other risk factors (8).

**Measurement of Cardiorespiratory Fitness**

In the above study second stage heart rate and duration on the treadmill defined fitness, while these indirect estimations are used, determining fitness has historically relied on measurement of VO\(_2\)max. VO\(_2\)max is the maximal rate at which oxygen can be taken up into the blood (3). The maximal rate reached for each individual varies with the specifics of the test, as such; the maximal value obtained is relative to the conditions of the test used (11). It is necessary to define the modality used to elicit a VO\(_2\)max. Different modalities result in different VO\(_2\)max values due to different amounts of active muscle and the fitness level of those specific muscles. In general, a continuous progressive graded exercise test will elicit a VO\(_2\)max for the exercise modality used. This approach uses large muscle masses and leads to an efficient time to VO\(_2\)max, with reproducible conditions.
Improving Cardiorespiratory Fitness

Achieving an increase in cardiorespiratory fitness requires manipulating the frequency, intensity, time and type of exercise. Intensity is the most important variable related to an increase in overall cardiorespiratory fitness (7). Exercise training at intensities below 50 percent of VO₂max generally will not result in an increase in VO₂max (7), unless the person is deconditioned (1). Conversely, if intensity is set too high, it is difficult for individuals to adhere to the recommended program. The American College of Sports Medicine (1) recommends an intensity that elicits 60 to 80 percent of heart rate reserve to increase cardiorespiratory fitness.

The type of training or specificity of training is also important when considering improvements in VO₂max. In general, the muscles utilized during training will show the training adaptation. There does appear to be some cross over from trained muscles to the rest of the body as exercise training does have central effects (1). Specificity of training is also important in measuring the improvement in VO₂max. As described above the different modes of testing VO₂max, yield different VO₂’s due to the difference in active muscles. Measuring and training using the same type of exercise is the best way to capture an improvement in cardiorespiratory fitness.

Arterial Stiffness

Ultrasound measures of arterial properties are useful tools in the diagnosis and treatment of CVD (9,13). There is also evidence that these measures predict disease (5). One of these measures is arterial stiffness, which is linked to CVD (22). Van Popele et al. (22) reported on data from The Rotterdam Study, which is a population base cohort designed to assess risk factors for disease. Each subject had various non-invasive and invasive measurements of arterial properties done. Arterial stiffness, defined as the distensibility coefficient was measured at the
aorta and the common carotid artery (22). Their results showed a strong and independent relationship between arterial stiffness and all indicators of atherosclerosis (22).

**Non-Invasive Measurement of Arterial Stiffness**

Measurement of arterial stiffness is a complex endeavor in humans. Early work utilized invasive methods to assess vessel wall properties (21). Over the last 20 years, techniques using non-invasive designs can measure an in vivo artery in man (5,21). Local arterial stiffness assessment uses Doppler ultrasound to measure the diameter of the chosen artery over the cardiac cycle. These values are used in combination with blood pressure measurements to calculate stiffness. Blood pressure is taken either at the site of interest using applanation tonometry (12,15) or at a different site in the arterial tree, primarily the brachial artery (19).

Indexes of stiffness include cross-sectional compliance, distensibility coefficient, Young’s elastic modulus, pulse wave velocity and Beta stiffness index (5). Each index refers to a slightly different characteristic of the vessel, with some accounting for distending pressure (Beta stiffness index) or initial artery size (distensibility). For the purposes of this review, cross-sectional compliance, distensibility coefficient and beta stiffness index are explained.

Distensibility coefficient is defined as the change in volume per initial volume per change in pressure (12,17,20,21). Assuming that an in vivo artery does not lengthen during the cardiac cycle, the equation is re-written as the change in area per initial area per change in pressure DC=[(As-Ad)/Ad]/(Ps-Pd). It is useful in comparing arteries of different size as it accounts for the initial size of the artery (5). This becomes important when there are differences in subject characteristics pre treatment or in comparison of different populations, especially males and females as males generally have larger arteries.
Cross-sectional compliance describes the buffering capacity of vessel segments and is important for vascular function (5). It can be defined in terms of distensibility in that $CC = DC \times V$. The assumption of constant length is employed again to change the equation to $CC = DC \times A$, with $A$ representing initial area. Referring to the equation of $DC$ listed above, it can be seen that $CC = \frac{(As - Ad)}{(Ps - Pd)}$ (5,12,17).

Beta stiffness index accounts for changes in Petersen’s elastic modulus with changes in distending pressure (5). It employs the natural logarithm of the ratio of systolic to diastolic pressure to accomplish this task using the equation; $\text{Beta} = \ln\left(\frac{Ps}{Pd}\right)/\left(\frac{Ds - Dd}{Ds}\right)$. With $\ln$ indicating the natural logarithm, $Ps$ and $Pd$ describing systolic and diastolic blood pressure and $Ds$ and $Dd$ describing systolic and diastolic arterial diameter. The Beta stiffness index is unitless and may represent a way to compare across studies as the natural logarithm minimizes dependence on distending pressure (5). While there is agreement on the concepts behind these equations, it should be noted that the equations themselves vary based on the researcher.

**Fitness and Arterial Stiffness**

Arterial stiffness increases as a result of age (13) and studies are finding a relation between fitness and arterial stiffness (5). Tanaka et al. (17) recently published a report describing both the age related increase in arterial stiffness of the carotid artery and an interesting relationship to fitness. In this study, they conducted two protocols. First, 151 healthy men were grouped into 20-year age ranges. The fitness levels of the men were categorized as sedentary (no regular physical activity), recreationally active (light to moderate aerobic exercise more than three times per week), or endurance trained (vigorous aerobic exercise more than five times per week and involvement in local racing events. The results showed that there was a
smaller age related increase in arterial stiffness in the endurance trained men compared to the sedentary men (17).

The second protocol of the study looked at the effects of a short (12 week) aerobic training program on arterial stiffness in previously sedentary men. Here the investigators found a 25% increase in arterial compliance measured centrally at the common carotid artery. This change was independent of changes in body weight, percent fat or VO2max (17). They concluded that aerobic exercise might help reduce CVD by decreasing the age-associated decline in compliance in middle age men.

These results were found using male subjects. In 1998, two studies explored different markers of arterial stiffness in women (15,16). These studies found an age related increase in central arterial stiffness in women. One study found an attenuation of this decline in physically active women, as well as women on hormone replacement therapy HRT (15). In a separate study, there was an inverse association between increases in arterial stiffness and blood volume, stroke volume and cardiac output (16). Both studies used cross sectional designs to evaluate these phenomena.

Moreau, et al. (12) performed a continuation of this work in women in 2003. This investigation used both cross-sectional and interventional components to compare three groups of post-menopausal women. They studied women that were sedentary and endurance trained not on HRT and sedentary women on HRT. Pre-menopausal women served as controls. The training intervention focused on the sedentary post-menopausal women on HRT to see if there was an additive effect of the training to the HRT effect on arterial compliance. The 12-week walking program increased arterial compliance in the postmenopausal women to the level of the pre-menopausal women (12).
Ferreira et al, (10) as part of the Amsterdam Growth and Health Longitudinal Study, reported another look at arterial compliance and fitness in women in 2003. This project is a longitudinal study that started with a group of 450 boys and girls in 1976. During the examination periods, each subject received numerous tests of health, including routine maximal treadmill tests, and most recently measurements of arterial properties. Ferreira and colleagues reported on the longitudinal changes in VO$_2$max and their relationship to arterial properties of the carotid, brachial and femoral arteries (10). They found that changes in VO$_2$max from adolescence and young adulthood to adulthood were associated with changes in arterial stiffness. In addition, physical activity levels showed associations with arterial properties at the sites measured. They concluded that a more physically active lifestyle that starts in adolescence or young adulthood could have a significant impact on arterial stiffness, potentially leading to a decrease in CVD (10).

The published literature indicates that CVD is still a devastating and deadly disease. CVD is linked to fitness, age and many other factors used to gauge severity and predict likelihood of disease. Of utmost importance is determining safe and effective prevention strategies that use non-invasive and benign methods of assessment. Arterial stiffness is a measure that is safe to use and allows for detailed descriptions of the arterial tree. Work in this area has focused on a narrow range of populations. Information is emerging from this research that exercise does reduce the amount of stiffness in middle aged and older populations. These results are not generalizable to all ages as the arterial tree changes over the lifespan. There is a need to explore the relationship between arterial stiffness and fitness in a younger population in order to assess the effects of exercise on this non-invasive marker of CVD.
CHAPTER 3

AEROBIC EXERCISE DOES NOT MODIFY CAROTID ARTERY STIFFNESS IN SEDENTARY HEALTHY PRE-MENOPAUSAL WOMEN\textsuperscript{1}

\textsuperscript{1} Schwark EH 2\textsuperscript{nd}; Sabatier, M; Lewis, R; McCully, KK.
To be submitted to Dynamic Medicine.
AEROBIC EXERCISE DOES NOT MODIFY CAROTID ARTERY STIFFNESS IN
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Abstract

Cardiovascular disease remains the number one cause of death for women. Arterial stiffness has been used as a predictor of future heart disease. Arterial stiffness decreases with aerobic training in older men and women. The purpose of this study was to test whether a 14-week aerobic (stationary cycling) training program improves arterial stiffness in nine healthy pre-menopausal sedentary women. Measures of body composition (DXA), cardiorespiratory fitness (VO2peak) and carotid arterial stiffness, defined as beta stiffness index, compliance, and distensibility were measured before and after the training. Fitness improved by 9.4% (P=0.016), with no significant changes in body composition. Arterial stiffness did not change with training, pre 6.45±3.5 (U) to post 6.36±1.75 (U) (P=0.46). In conclusion, aerobic training does not appear to improve arterial stiffness in younger women whose arteries did not show increased stiffness pre-treatment.

INDEX WORDS: Arterial stiffness, Carotid artery, Compliance, Women, Exercise

Introduction

Cardiovascular disease (CVD) has been the number one cause of death in America for both men and women over the last 20 years (4). Many factors are associated with cardiovascular disease; some are used to measure the extent of disease, while others can predict likelihood of disease. Measures of arterial properties have been studied more frequently over the last few
decades and are starting to come into favor as measures associated with and possibly predictive of CVD (5,13,22).

Arterial stiffness is one arterial property that is associated with CVD (22) and appears to be modifiable in some populations (10,17). Both central and peripheral arterial stiffness can be determined in vivo (5,22). Central stiffness, determined through measurements made at the carotid artery may have a greater relationship with CVD as it may approximate the properties of the aorta itself (10). This site is also easy to measure as it is a superficial artery at an accessible location in most populations.

Changes in central arterial stiffness occur with aging (5), are independent of body composition changes (17) and appear to be affected by activity and fitness levels (17). Much of the work in this area has been done on older individuals using cross-sectional methods, primarily on men, with very few studies conducted on women (12). Healthy women and men alike have been studied infrequently using longitudinal designs that include an exercise intervention, especially in younger populations.

Therefore, the purpose of this study was to explore the effects of an aerobic training program on central arterial stiffness in healthy young women. The primary aim was to enroll young (25-40 years) women in a training program designed to increase fitness without changing body composition and measure arterial stiffness before and after the 14-week program. We hypothesized that fitness would increase and this change would be associated with a decrease in arterial stiffness.
Methods

Subjects

Nine healthy pre-menopausal female volunteers (44% minority) were studied before and after a 14-week aerobic training intervention. All subjects were sedentary (<1 exercise session per week in the last 3 months) and ranged in body size (BMI 19-30). Prior to inclusion, all subjects denied known cardiovascular disease and obese subjects received physician clearance. Procedures were approved by the Human Subjects Institutional Review Board of the University of Georgia and all participants provided written informed consent.

Testing Procedures

We conducted two testing sessions during the last week of the follicular phase of subjects’ ovarian cycles (based on self-report), before and after the 14 weeks of aerobic training. Testing session one consisted of body habitus measurements; including height, weight, waist and hip circumference, and a dual energy x-ray absorptiometry (DXA) scan. Maximal aerobic capacity ($VO_{2peak}$) was also assessed during testing session one. The second session measured the systolic and diastolic diameter of the common carotid artery, as well as, systolic and diastolic blood pressure of the brachial artery. Central arterial stiffness was calculated from these four measures.

Measuring Maximal Aerobic Capacity

Oxygen consumption was assessed using open circuit spirometry with a Parvo Medics TrueOne 2400 Metabolic Measurement System (Parvo Medics, Inc., Salt Lake City, UT). A Monark ergometer was used for the graded exercise test, with the Quinton Q Stress EKG recorder continuously measuring heart rate. Borg’s Rating of Perceived Exertion was measured during each stage of the test, while blood pressure was measured (auscultation) before, during
(every other stage) and after exercise. The test consisted of 2 minutes of sitting rest on the ergometer, 4 minutes of no resistance pedaling (warm-up), and then 15-watt increases every minute. Cadence was set at 60 rpm and kept constant with use of a standard metronome. Davis et al. (6) used a similar protocol on a Monark ergometer to elicit maximal tests from a diverse group of sedentary men and women. The same exercise physiologists conducted all tests.

The criteria used for VO2max attainment was a plateau in oxygen consumption with an increase in workload (18). As not all of the subjects achieved this criteria, the test was labeled VO2peak if two of the following three indications were seen, respiratory exchange ratio above 1.15, BORG’s RPE of 19 or 20 or a maximum heart rate within 10 beats/min of age predicted maximum (14). VO2peak quantified state of training and fitness, as such; it was expressed as a function of fat free mass (ml/kg FFM/min), with the fat free mass determined by DXA.

Body Composition Measurements

Percent body fat, total fat and lean mass were assessed using DXA (Delphi A, Hologic Inc., Bedford, MA) in the Clinical and Sports Nutrition Lab of the University of Georgia. The same trained observer conducted and analyzed each scan. Height and weight were used to calculate Body Mass Index (BMI) (kg/m²). Waist and hip measurements from the narrowest circumference of the torso and the largest circumference of the gluteal region determined waist to hip ratio.

Determining Central Arterial Stiffness

Subjects refrained from caffeine, alcohol and high fatty foods preceding the measurements. All tests were done at the same time of day pre and post training to minimize circadian variation. Upon entering the lab, subjects assumed a supine position and had blood pressure measured at the left brachial artery using an automated blood pressure system.
(Datascope, Mahwah, NJ). Subjects remained supine for at least 10 minutes before ultrasound testing began; this time was extended if the blood pressure readings were unstable. Blood pressure was collected every 4-5 minutes during the test, as well as, immediately before and after ultrasound imaging of the right common carotid. Averaged systolic and diastolic readings from the left brachial artery estimated common carotid pressure. This method is used by others (2,22) and may be more reliable than applanation tonometry given the range in body weights of the population studied (19).

B-mode imaging captured the common carotid artery approximately 2-6 cm proximal to the carotid bifurcation using a LogiQ 400CL (General Electric, Rainbow City, AL) with a 7-13 MHz linear-array ultrasound transducer. Magnification and focal zone settings were adjusted to optimize imaging of the proximal and distal vessel wall. Subjects maintained a relaxed partial exhaled state for the duration of the ultrasound imaging. A fifteen second B-mode video file was recorded by a computer using a video capture device (ADS technologies, Cerritos, CA, U.S.A.). Video files were collected at 30 frames per second and converted into JPEG images for analysis. These images were measured offline using semi-automated edge-detection software custom written to interface with National Instruments. Diameters from seven to ten cardiac cycles were included in the analysis. Cross-sectional compliance, distensibility and beta stiffness index were calculated from the measured diameters and pressures.

**Training Intervention**

All subjects engaged in cycle training at the University of Georgia Fitness Center on Schwinn Airdyne ergometers. The first 4-6 sessions consisted of self-selected intensity to familiarize each subject with the stationary cycle and to determine appropriate work loads based on individual heart rate responses. After the initial familiarization period, each session consisted
of resting heart rate and blood pressure assessment, 5 minutes of warm-up, 40 minutes of interval training, 5 minutes of cool down, a brief lower body stretching session and post heart rate and blood pressure recordings. The 40 minutes of interval work were divided into twenty, two-minute segments that alternated between low and high intensity zones, designed to elicit 60 and 85 percent of heart rate reserve, respectively. The guide for the intensity of exercise was percent of heart rate reserve, as it closely reflects percent of oxygen uptake (1). Heart rates were recorded during low and high intensity zones with progression in workload as needed. An exercise physiologist conducted and supervised each session.

Statistical Analysis

Statistical analyses were conducted using paired t-tests to compare baseline scores with post treatment scores. Data are presented as mean ± SD, with statistical significance set at P<0.05.

Results

Nine subjects are included in the statistical analysis. Twelve participants started the exercise training intervention, with ten completing the study. The two drop-outs did so early in the training, citing medical reasons unrelated to the study. Of the 10 finishers, one subject was excluded due to low adherence (<50%). Table 1 shows the physical characteristics of the nine subjects included in the analysis.

Training Intervention

Figure 3.1 shows heart rate and oxygen consumption during an aerobic session for one participant. Oxygen uptake was measured during the entire bout of exercise. The graph shows a close mirror between percent heart rate reserve and percent oxygen uptake (R² = 0.94),
supporting our use of heart rate to monitor intensity. Average adherence to the program was 79%, representing an average attendance of 34 sessions over the 14 weeks.

Cardiorespiratory Fitness

$\text{VO}_{2\text{peak}}$ increased by 9.4% ($P=0.02$) following training (Figure 3.2). There was a trend toward an increase in maximal workload ($P=0.06$). At baseline, all subjects reported a perceived exertion of 18 or above and achieved a respiratory exchange ratio above 1.15 (Table 3.2). There was no evidence of increased effort during post-treatment testing, as there were no significant increases in maximal heart rate, rating of perceived exertion or respiratory exchange ratio. In addition, rate pressure product, defined as systolic pressure multiplied by heart rate, decreased (25,700 vs. 23,400, $P=0.01$) at stage six (115 Watts) of the graded exercise test.

Arterial Properties

There were no changes in arterial stiffness, as defined by Beta stiffness index, cross-sectional compliance and distensibility coefficient ($P=0.46, 0.46, 0.20$). Table 3.3 shows the mean values before and after training with corresponding $P$ values for the measured and calculated arterial properties. None of the measured arterial properties showed significant differences after aerobic training. At baseline and after training, there was a moderate effect of age on carotid compliance (Figure 3.4).

Discussion

This study represents one of few longitudinal studies of arterial stiffness in healthy women. Arterial stiffness was unchanged after the 14-week aerobic training intervention. While others have found increases in compliance after similar training (12,17), the samples used were of older populations, with mean subject ages of 53 and 58 years, respectively. Subjects in their 50’s most likely had significant age-related reductions in arterial compliance. The present study
used a younger population, mean age 32 years, probably free of any age-associated decreases (13).

To our knowledge, this is the first longitudinal study to examine arterial compliance in women without age or disease associated decreases in arterial compliance pre-treatment. Our findings confirm previous cross sectional work that showed a similar level of compliance between sedentary, recreationally active and endurance trained young men, mean age 28, (17). A similar conclusion was reached when sedentary and active young women (mean age 28) were compared (15).

Our subjects showed an increase in VO2peak of 9.4% (ml/kgFFM/min), which was expected based on the intensity and frequency of the training (7). This increase corresponded to an average change in fitness classification from poor to fair using classifications reported in the Cooper Fitness Instructor manual. This indicates a reduction in overall CVD risk. In addition, the training elicited a significant decrease in waist/hip ratio (P=0.019), indicating a decrease in CVD risk. In spite of these reductions in CVD risk, arterial compliance, a marker of CVD risk (5,13) remained unchanged. This could be indicating that there is a ceiling effect on arterial compliance, in that normotensive healthy young arteries are at maximum compliance. This is supported by the cross-sectional work mentioned above (12,17) and the present findings.

Two difficulties arise when attempting to compare values of arterial stiffness across studies. First, while there is consensus on the concept behind the measure, there are differences in the final equations used to calculate arterial stiffness (5,12,13,17,19,20). There are differing decisions on what needs to be included in the formula and what assumptions are made to assess an in vivo artery non-invasively. The second area of difficulty is in the reporting of the arterial
stiffness measures. Different units used when reporting results leads to confusion when attempting to interpret the results from different studies. Comparing different reported units derived from different equations is confusing and potentially misleading.

Limitations of this study include a small sample size, lack of a control group and no reported reproducibility of arterial stiffness measures. The small sample size did not allow for statistical analysis of race or body composition parameters, but it did allow for utilization of DXA and VO2peak measurements, costly and technical measurements often missing from larger epidemiological based studies. A limitation to the study is that I did not have a control group. If the control group became significantly less compliant over the study, then no improvement in compliance with the training program would have been a positive outcome. However, this would have required a decrease in compliance over 14 weeks in the control group that was considerably larger than what I found in my cross-sectional measurements. Another limitation is a lack of reproducibility assessment of the technique used to obtain carotid compliance. Our lab has done formal investigations into our techniques at other artery sites and found good reproducibility. In addition, all observations were made by the same blinded observer after the conclusion of the post training measurements to minimize variability.

In conclusion, we found an improvement in fitness after our training intervention that was not associated with a subsequent decrease in arterial stiffness. This is most likely a result of limited increases in arterial stiffness of our study. We utilized a healthy and relatively young population to assess the impact of aerobic exercise on a healthy unimpaired artery. Our findings indicate that exercise may be more beneficial in decreasing arterial stiffness in populations that already have stiff arteries, such as the older populations study by others (12,17). Based on our evidence there appears to be a basement level for arterial stiffness in the healthy artery.
Table 3.1: Subject Characteristics Before and After Training.

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>32</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Height (meters)</td>
<td>1.6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.1</td>
<td>64.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>24.9</td>
<td>25.0</td>
<td>0.38</td>
</tr>
<tr>
<td>DXA % Fat</td>
<td>34.5</td>
<td>33.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
<td>41.6</td>
<td>42.5</td>
<td>0.053</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>22.6</td>
<td>21.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Waist to Hip Ratio</td>
<td>22.6</td>
<td>21.9</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Table 3.2: Physiological measures collected at peak exercise.

<table>
<thead>
<tr>
<th></th>
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<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ml/kg/min)</td>
<td>29.4±5.9</td>
<td>32.2±4.2</td>
</tr>
<tr>
<td>(ml/kgFFM/min)</td>
<td>44.7±5.9</td>
<td>48.5±4.2</td>
</tr>
<tr>
<td>Maximum Workload (watts)</td>
<td>162±23</td>
<td>175±26</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>182±10</td>
<td>182±14</td>
</tr>
<tr>
<td>Rating of Perceived Exertion</td>
<td>18.8±0.7</td>
<td>18.9±0.6</td>
</tr>
<tr>
<td>Respiratory Exchange Ratio</td>
<td>1.23±0.06</td>
<td>1.20±0.04</td>
</tr>
</tbody>
</table>
Table 3.3: Arterial Properties Before and After Training

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest Hr (bpm)</td>
<td>78±13</td>
<td>77±17</td>
<td>0.37</td>
</tr>
<tr>
<td>Systolic BP (SBP)</td>
<td>113±15</td>
<td>113±14</td>
<td>0.45</td>
</tr>
<tr>
<td>Diastolic BP (DBP)</td>
<td>70±8</td>
<td>68±9</td>
<td>0.23</td>
</tr>
<tr>
<td>ΔP (SBP-DBP)</td>
<td>43.1±9.2</td>
<td>45.4±6.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Systolic Diameter (mm) (Ds)</td>
<td>6.4±0.4</td>
<td>6.7±0.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic Diameter (mm) (Dd)</td>
<td>5.9±0.5</td>
<td>6.1±0.5</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔD (Ds-Dd)</td>
<td>0.51±0.15</td>
<td>0.52±0.11</td>
<td>0.38</td>
</tr>
<tr>
<td>B Stiffness Index</td>
<td>6.45±3.5</td>
<td>6.36±1.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Carotid Compliance</td>
<td>1.19±0.44</td>
<td>1.17±0.33</td>
<td>0.46</td>
</tr>
<tr>
<td>Distensibility</td>
<td>4.53±2.14</td>
<td>4.07±1.34</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\[
 \ln(Ps/Pd)/[(Ds-Dd)/Dd]
\]

\[
 \pi \times (2d \times \Delta d + \Delta d^2) \div (4 \Delta P)
\]

\[
(2\Delta d^3 + \Delta d^2) / (\Delta P \cdot d^2)
\]
Figure 3.1: Oxygen uptake and heart rate recordings over 50 minutes of cycling. Boxes on x axis represent stage of protocol, i.e., warm-up and cool-down (white), low zone (grey) or high zone (black). The outline around the recordings represents the ACSM recommended training intensity of 60-85% of maximal oxygen uptake or Heart Rate Reserve. Note that using either VO2 or Heart Rate, training intensity remained in the target zone throughout the training session.

Figure 3.2: VO2peak expressed relative to total mass (A) and fat free mass (B), before and after the aerobic training program. Values are means ± SD. Note that aerobic training resulted in a significant increase in VO2peak.
Figure 3.3: Arterial stiffness calculated as Cross-sectional Compliance (A), Distensibility Coefficient (B) and Beta Stiffness Index (C) before and after training. Values are means±SD. Note that regardless of the method used to calculate stiffness, there were no significant changes after training.
Figure 3.4: Relationship between age and carotid compliance before (blue) and after (red) training. A moderate effect of age was seen in the ten year age range.

Figure 3.5: Beta Stiffness Index and the relation to age. Dashed arrows represent extrapolation of the data to the age range studied by others. This extrapolation shows a pronounced effect of aerobic training on arterial stiffness.
CHAPTER 4
SUMMARY AND CONCLUSIONS

I conducted a 14-week aerobic training program in healthy young (mean 32 years) women and measured arterial stiffness before and after the program. We found an improvement in fitness after the 14-week aerobic training intervention that was not associated with a subsequent decrease in arterial stiffness. This was contrary to our hypothesis. There are two possible reasons for this conclusion. It was the correct collection and interpretation of the data or there was significant and misleading measurement error.

In addressing this concern, comparison of my study to the literature needs to be done. The first aspect of the study that could result in conclusions contrary to the published literature is the difference in populations studied. This study looked at arterial stiffness in a younger age group than that previously studied by others (12,17). Our younger age group is believed to be free from age-associated increases in arterial stiffness (13) and our selection process eliminated the possibility of disease related increases in arterial stiffness. Our utilization of a healthy and relatively young population allows for assessment of a healthy unimpaired artery. Our findings indicate that exercise may be more beneficial in decreasing arterial stiffness in populations that already have stiff arteries, such as the older populations study by others (12,17).

Another source of error relates to the collection of the measures, specifically, arterial stiffness and VO2peak. Arterial stiffness requires measurement of four properties, systolic and diastolic diameters and pressures. While some researchers use applanation tonometry to measure
pressure of the left carotid while imaging the right, it is acceptable to use the brachial artery as a substitute for carotid pressure. We used the latter measure in our study. This technique has been used by others and does not require transfer functions or adjustments for hold down force.

Another property of arterial stiffness is an expected decrease in compliance with age. While this is expected, it was surprising to see a moderate effect in our sample due to the small age range of our subjects (27-37 years) (Figure 3.4). In addition, it is generally believed that the increase with age occurs around the beginning of the 4th decade. Using Beta Stiffness Index to quantify stiffness, there is once again the expected change with age (increase). If the data is extrapolated to older ages, the relationship between aerobic exercise and stiffness found by others is seen (Figure 3.5 dashed lines). This supports that our measurements of arterial stiffness yielded expected outcomes and further supports our conclusions.

Our other main measure was VO₂peak and it yielded an expected increase of 9.4%. The training program set out to elicit a varying intensity between 60-85% VO₂peak, which would result in a 10-15% increase in VO₂peak based on previous research. Due to less than perfect adherence to the program, frequency of training was below the programmed 3 days per week for some subjects (average attendance 79%). Working at just below the programmed amount coincides with showing an increase at the bottom end of the predicted. Another aspect of our training that matches expected results is the finding that those with lower VO₂peak’s at baseline had a greater increase in VO₂peak. This is an expected outcome when looking at most variables, especially VO₂peak.

What is interesting is that I believe this is the first longitudinal study to address arterial stiffness in healthy pre-menopausal women before and after an aerobic training intervention. This is an important distinction as we acutely increased fitness to better explore the changes in
fitness and stiffness. There was a significant decrease in waist to hip ratio, even though percent fat was unchanged. This is probably due to a near statistically significant increase in fat free mass (P=0.053), centered on the legs/hips, main muscles used for cycling. Increasing cardiorespiratory fitness and decreasing waist to hip ratio are changes that indicate decreases in cardiovascular disease (CVD) risk and are used clinically to assess and predict CVD. Since arterial stiffness is believed to be a marker and predictor of CVD, it is surprising that it did not change, given the other reductions in risk.

A lack of a decrease in arterial stiffness may be explained by a basement level of stiffness in the healthy artery. Arteries in a normotensive and otherwise healthy young person potentially have all the buffering capacity needed to handle homeostasis. This explains why exercise training would not increase the capacity beyond that required for proper maintenance of the arterial tree. Looking at what is happening with other markers of arterial health would add more information into the effects of exercise on arteries of a healthy young person. Flow mediated dilation and vaso-active range are two examples of tests that show different functions of the arteries and may yield interesting results.

In conclusion, conducting training studies on free-living humans is a difficult and time-consuming task. Yet it offers the best look at what changes occur with acute changes in fitness. This is useful in assessing what effects exercise has on overall health. This study found that exercise does not have the same effect on young arteries as it does on older stiffer arteries. Increased knowledge in this area will help to determine the best time to start assessing arterial stiffness.
CHAPTER 5
REFERENCES


2. **Aggoun Y, Bonnet D, Sidi D, Girardet JP, Brucker E, Polak M, Safar ME and Levy BI.**


7. **de Vries H.** Physiology of Exercise for Physical Education and Athletics. 1980


