THE EFFECT OF GENDER AND PHYSICAL CAPACITY ON CARDIOVASCULAR CONTROL IN THE ELDERLY

By

Vanessa Castellano

(Under the direction of Kevin K. McCully)

ABSTRACT

This study examined the effect of gender and physical capacity on cardiovascular control in older adults. A 60° tilt at the waist lasting two minutes, and a six-minute walking test were administered in thirty-seven older adults aged 75 ± 4 years. Carotid and femoral blood flow, blood pressure and heart rate were measured continuously. There was a 15 % increase in heart rate and a 60% decrease in femoral blood flow upon tilt. Women had greater heart rate increases upon tilt. Despite a two fold range in walking distance no relationships were found between the response to tilt and physical capacity. In conclusion, a 60° tilt produced significant changes in carotid and femoral blood flow, heart rate and blood pressure. Heart rate and blood pressure showed the expected gender differences, while blood flow was not affected by gender. Physical capacity did not influence cardiovascular responses in a healthy elderly population.

INDEX WORDS: Cardiovascular control, postural challenge, carotid blood flow, physical capacity, gender, elderly

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DEDICATION

I would like to dedicate my work to Rosa and Andreu, my parents. Dad, as I grew up, you showed me what it means to have a strong work ethic. Mom, by your actions you have showed me how far tenacity can take me. Without those two attributes, I would have never made it here. Thank you for all your unconditional support throughout the years, and a life full of magnificent opportunities. No matter where I am, you are always close to me.

M'agradaria dedicar el meu treball a L'Andreu i la Rosa, els meus pares. Sense la heredada dedicacio al treball del meu pare i la tenacitat de la meva mare, no ho podria haver fet mai. Gracies per tot el vostre suport incondicional durant tots aquests anys, i una vida plena de grans reptes. No importa on sigui, perque sempre esteu aprop meu.

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Thank you Mom and Dad, Andreu and Ingrid for sacrificing absolutely everything for a girl that always dreamt of soccer, became a tennis player along the way, and is on her way to becoming a scientist. Us estimo molt!

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CHAPTER 1

INTRODUCTION

Age is associated with increased incidence of cardiovascular disease. Cardiovascular disease leads to reduced function and is the major cause of death in the U.S., accounting for nearly 900,000 deaths each year (1) . Even in the absence of cardiovascular disease, advanced age is associated with altered cardiovascular responses to physiological stress such as posture, and may lead to reduced function (2-5). However, it is important to note that these age-related changes are subject to large individual differences depending on physical fitness, as well as nutritional, socio-economical, and genetics (6). Thus, early detection of cardiovascular disease is critical to assure treatment, and prevent high levels of mortality in the elderly due to cardiovascular complications.

Detection of abnormal cardiovascular responses may serve as an early sign of cardiovascular disease. Previous studies may have missed any evidence of alterations and missed detection of disease while looking at the delayed responses of the cardiovascular system (7). The immediate response upon a postural stress is a sensitive measure that can be easily missed if measurements are not continuous (8-10). Moreover, by incorporating immediate responses as a measure upon a postural stress, the effect size will increase, making any possible abnormalities easier to detect.

It is widely documented that posture affects resting blood pressure, heart rate and other physiological mechanisms (2, 5, 7, 9, 11, 12). When the upright posture is assumed, blood pools in the extremities, and cardiac filling is reduced. This is also followed by a transient fall of blood pressure and the subsequent excitation of baroreceptors, which leads to increased sympathetic activity, reduced vagal outflow, and acceleration of the heart rate (7). Stimulation of catecholamines, activation of the renin-angiotensin-aldosterone system, and increases in cardiac output, peripheral resistance, venous return and volume expansion all function to bring about a prompt stabilization of blood pressure (13, 14). The regulation of the cardiovascular system occurs immediately in healthy individuals, adapting rapidly, and securing proper function after a postural stress. Therefore, a postural stress such as tilt, elicits a complex pattern of cardiovascular changes, and may reveal abnormalities if changes do not occur quickly (7, 14, 15).

Physical capacity is associated with increased cardiovascular function and reduced prevalence of cardiovascular disease (15-17). Physical capacity may also lower the reactivity of the cardiovascular system during a postural stress test (15, 18). Furthermore, exercise has been known to ameliorate some of the effects of aging, even though it will not slow down the aging process. For example, autonomic reflex capacity decreases due to aging, therefore impairing control of blood flow. Regular aerobic exercise can also prevent the age-associated loss in endothelium-dependent vasodilation (16, 19). This loss of vasodilation may represent an important mechanism by which regular aerobic exercise lowers the risk of cardiovascular disease and other cardiovascular risk factors (19). Physical capacity through its positive effects on biological processes can improve the effects of aging by regulating autonomic reflexes, improve endothelial function and ameliorate decreased cardiovascular capacity due to aging (20).

Gender has an important influence on cardiovascular reactivity. Barnett (21) found that gender may have an effect on autonomic control of the cardiovascular function. Furthermore, gender has been shown to be important in regulating blood pressure upon a postural stress, finding larger decreases of systolic blood pressure in men compared to women (10, 15, 22).In addition, women tend to have higher heart rates at rest and lower blood pressure than men (15). Consequently, the existing evidence points to possible differences between men and women during cardiovascular testing.

To summarize, aging is associated with increased cardiovascular disease and may be associated with altered cardiovascular responses. A postural challenge test can provide information about cardiovascular reactivity. Most importantly, the immediate response of the cardiovascular system will reveal if the cardiovascular system is functioning properly. In addition, various factors such as physical capacity and gender may influence cardiovascular reactivity. The purpose of the study is to evaluate the effects of gender and physical capacity on cardiovascular responses elicited by a postural challenge test in older adults.

Purpose Statement:

The purpose of this study is to determine if:

1) Physical capacity levels affect cardiovascular control upon a postural challenge
2) Gender influences cardiovascular control upon a postural challenge
3) Flow in large arteries, such as the carotid artery and the femoral artery, are useful in assessing cardiovascular control upon a postural challenge.
4) The immediate responses elicited by the cardiovascular system are a useful measure to evaluate cardiovascular control

Hypotheses:

It is hypothesized that:

1) Higher levels of physical capacity will be associated with better cardiovascular control:
    a) Smaller decreases in carotid blood flow upon tilt
    b) Smaller decreases in blood pressure and heart rate upon tilt
    c) Larger decreases in femoral blood flow in subjects upon tilt
    d) Faster reaction times for blood flow and cardiovascular variables upon tilt
2) Males and females will respond differently upon a postural stress, and will be explained by:
    a) Women will have greater increases in heart rate and will take longer to return to baseline upon a postural stress
    b) Women will show larger decreases in blood pressure than women upon a postural stress
    c) Women will have larger decreases in femoral blood flow upon a postural stress

Significance of the study:

The significance of the study is to understand various factors regarding cardiovascular function in the elderly. Specifically, to see if physical capacity helps maintain cardiovascular control, and to determine if males and females respond differently to a postural stress in terms of their cardiovascular system. This study could be also used to determine if changes in carotid and femoral blood flow can be used to determine cardiovascular control. If the study found changes in carotid and femoral blood flow are a good predictor of cardiovascular control, it could improve the accuracy of detecting cardiovascular disease. In addition, carotid and femoral blood flow continuous measurements will be provided, which have been scarcely measured immediately upon a postural stress. Typically, cardiovascular changes have been reported after a delayed period of time (1-5 minutes). In this study, the measurements will be recorded continuously to provide a measure of immediate and delayed responses. Examining the immediate responses will increase the effect size, and will provide detailed information of the cardiovascular adaptations upon tilt. Furthermore, gender and physical activity are two important factors that cannot be ignored while studying cardiovascular health. Studies have looked at gender, and physical capacity independently. However, physical capacity in particular, has been ignored while looking at cardiovascular responses upon tilt. This study, by measuring both the immediate and delayed responses upon tilt, may provide evidence that can be critical to improve cardiovascular testing, and determine if gender and physical capacity have an effect on cardiovascular control.

CHAPTER 2

REVIEW OF THE RELATED LITERATURE

Cardiovascular Function and Disease

Cardiovascular disease (CVD) is the nation's leading killer for both men and women among all ethnic groups(23). Unfortunately, almost 1 million Americans all ages die every year of CVD, accounting for 42% of all deaths. CVD includes dysfunctional conditions of the heart, arteries, and veins that supply oxygen to vital life-sustaining areas of the body(23, 24). Although early medical treatment and prevention are available, and a good portion of sudden heart attack patients are examined by a doctor 6 months prior the heart attack, predicting such disastrous events has been difficult to identify. In a study by Kuller (23), medical examination of 326 individuals who had received medical examinations within 6 months period before they died (from sudden heart attack) showed that not a single one of the 326 heart attacks were predicted by the physicians; Another interesting fact is that 86 of those patients died within seven days of their medical examination. Obviously, there is a need to find a more effective examination that will give us more information about cardiovascular disease.

Physiology and Importance of Age in Cardiovascular Function

The cardiovascular system goes through stressful modifications with age, which results in transformations in cardiovascular functions(25). An example of this is cardiovascular disease, which is an age-associated disease and its prevalence increases with age(1). The hardening of the arteries, or atherosclerosis is an inevitable part of the aging process.

Nobody is immune to some form of hardening of the arteries; however, for some people this process is more rapid than for others. This process occurs due to the constant passage of blood through arteries, where fatty material containing cholesterol or calcium is deposited in the most inner layer of the artery(26). This aging process is reflected most in the arteries of the heart and brain, but is also commonly seen in the arteries in the neck and legs (15). The clinical tests available to measure cardiovascular function are the mental, and physical stress test, with the ankle-brachial index and Doppler ultrasound used to assess the amount of blockage in the neck or legs. Unfortunately these tests may only diagnose a small percentage of future clinical events (15). A variety of other aging factors affect each individual differently. For instance, diet habits and physical conditioning may ameliorate age-related changes. Physical conditioning has a major influence on the cardiovascular system and has been found to delay or partially regress these changes (27). A few studies found that physically fit elderly subjects had the closest physiology to younger ones, although not quite the same, but significantly better than sedentary adults (28-30). These studies also pointed out aging may be secondary to deconditioning, exhibiting the major role of staying physically fit to carry a healthy lifestyle. Diet has also been shown to indirectly affect aging related changes. Avolio (31) found regional differences in arterial wall stiffness in populations with high salt intake compared to low salt intake in China. These examples support the idea that other variables can affect the cardiovascular system in positive or negative ways.

It is also important not to attribute abnormal symptoms in elderly patients as normal because they might be secondary to normal aging. For example, a common belief that was widely accepted for many years was that cardiac performance declined with age;

it is known now that individuals who are screened for coronary artery disease show no age-related decline in many important measures of cardiac performance (32). Another misconception was that the age-associated elevation of systolic blood pressure upon standing was normal regardless of its degree. The Framingham Study found that elevation of systolic blood pressure was associated with increased cardiovascular morbidity and mortality (33). The Systolic Hypertension in the Elderly Program also demonstrated that the treatment of systolic blood pressure above 160mmHg could be beneficial and reduce the incidence of stroke by 36%, and even reduce the incidence on non-fatal myocardial infarction by 27% (13). Since volume changes are not tolerated well by the elderly (13, 34), due to a high reliance on the Frank Sterling mechanism to augment cardiac output, a better knowledge of age-related cardiac dysfunction and cardiovascular physiology is necessary to understand what the elderly body needs in stressful situations for the cardiovascular system. Hence, age-related changes, although of an adaptive nature, need to be watched due to their possible negative consequences for the cardiovascular system, which can cause increased morbidity and pathologic potential (33).

Ways to Measure Cardiovascular Function

The elderly is a very difficult group to study due to the high percentage of people having one or more chronic diseases. Early studies often missed occult disease because they used relatively insensitive measures such as medical history and medical examinations to screen their patients. With the emergence of non-invasive and simpler tests to detect cardiovascular dysfunction, more people are diagnosed early and will enjoy a better quality of life. Autonomic function testing is used to assess clinical tests in patients with a wide range of cardiovascular problems (35). The recognition that patients with cardiovascular disease may have important abnormalities of autonomic function has increased enormously the requirement for testing, both in clinical and research settings (36). There are many ways to measure cardiovascular disease, but the questions addressed are which test is the best and what can be improved in the existing tests. Research tests include measuring cardiovascular response to a stressor, including the cold pressor test, which although has been demonstrated to produce ischemia in subjects with coronary artery disease, it will only probably work in patients with severe degrees of coronary obstruction (6, 37); The emotional stress test has also been used, where mental arithmetic, puzzle solving or videotape watching are used to see how a person reacts to emotional challenges (38); Other tests have focused on exercise, postural stress or drug tests to measure cardiovascular responses to predict cardiovascular disease (2, 8, 21, 39, 40).

Head-up tilt testing has also made the diagnosis of unexplained syncope more accurate. It is very critical to observe the first responses elicited from the cardiovascular system, due to its quick adaptive responses. Such testing can confirm a clinical diagnosis, identify the pathophysiology, and aid in the selection of therapy for patients with syncope, or patients without detectable heart disease (41). Heart rate responses to postural changes have also provided a useful way of providing information. Minimal cardiac acceleration (<10 beats/min) in the face of hypotension suggests impaired baroreceptor reflexes, whereas tachycardia (>100 beats/min) may suggest volume depletion (41). Most cardiovascular autonomic function tests involve measurements of baroreflex activity, but unfortunately, adjustments of ongoing reflexes may modify possible hemodynamic differences caused by all sort of stimuli. James (42) found blood pressure changes in response to active standing in the clinic and in response to 60 degrees head-up tilt in the laboratory were significantly correlated, and Bloomfield (11), found that autonomic changes are nearly identical when comparing active and passive standing. Smith (43) also reported similar heart rate changes within the first 30 seconds of head up tilt and active standing. The upright posture acquired through the usage of these methods causes a fall in right atrial pressure, in left ventricular end-diastolic volume, and cardiac output. In normal subjects there might be an immediate modest fall in systolic and diastolic pressure (0-10mmHg) followed by recovery to baseline in systolic pressure and a rise in diastolic pressure (7-10mmHg), as well as an increase in heart rate (36).

Damaged cardiovascular control can also cause orthostatic intolerance (OH), which is common in the elderly and is associated with hypertension and decreased physical function (12, 44, 45). A survey conducted by Ooi (46), confirmed that more than 50% of elderly residents of retirement and nursing homes reported OH. Orthostatic intolerance is the development of disabling symptoms upon assuming an upright posture that are relieved partially by resuming the supine position, and it is defined as a drop in systolic pressure of 20mmHg or more upon assuming the upright position. Symptoms such as lightheadedness, dizziness, weakness, blurred vision, impaired concentration, and even loss of consciousness, may occur when cerebral perfusion is markedly impaired (6, 47).

In the elderly, it is well recognized that there is a reduced ability to adapt to orthostatic stress (24). There are reports of an alarming significant association between changes in systolic pressure from supine position to standing and a 4-year mortality rate, suggesting dose-response relationship in a cohort of Japanese American elderly men (48). For example, heart rate does not increase in response to orthostatic stress to the magnitude that it would in younger individuals. Patients with orthostatic hypotension also have a significantly smaller and slower HR rise in heart rate during the first 40 seconds of standing probably due to an autonomic reflex dysfunction. This failure of the autonomic system causes bradycardia and does not raise the total peripheral resistance (49). The failure of heart rate response to lowered venous return seems to be the primary event. Thereafter, cardiac output, blood pressure, and carotid arterial blood flow are reduced in that order (49).

In addition, the ratio between the ankle systolic to brachial systolic blood pressure (ankle-brachial index) can provide valuable information to determine if there is evidence of heart disease (50). Because the ankle systolic pressure varies with the central aortic pressure (but brachial does not), it is desirable to compare each ankle pressure measurement with the simultaneous aortic pressure. The ankle brachial index provides a general guide to the degree of functional disability in the lower extremity (51). In the absence of proximal arterial occlusive disease, the ankle-brachial system is always greater than 1, with a mean value of 1.11 ± 0.10 (52). In addition, compelling evidence by Vogt (53) and Newman (54) show that a reduction of more than 0.9 in the ankle-brachial index is associated with increased risk for cardiovascular disease and coronary heart disease morbidity and mortality. However, although the ankle-brachial index reflects overall severity of arterial occlusive disease in the lower extremity, it may overlap among values from patients with different clinical presentations (52). Therefore, the ankle-brachial index should be combined with another clinical information to determine the status of the patient's peripheral arterial health.

In conclusion, abnormalities in cardiovascular control may be obtained from a postural challenge test, and may help identify people at risk for stroke and other cardiovascular deficiencies (55).

Physical Capacity and Cardiovascular Disease

Peak physiological function occurs, for the most part, between 25-40 years of age (25). Aging affects physiological mechanisms such as cellular function, a decline in physical capacity, and systemic regulation. Training will not slow down the process, but will ameliorate the decline of these important mechanisms, along with increases in physical strength, maximal oxygen consumption and decreases in body fat (25). The capacity of the autonomic reflexes also seems to decrease, therefore impairing control of blood flow, and letting the aging process run its course. Physical capacity has many effects on biological processes, maximizing to full capacity all the physiological mechanisms encountered throughout a person's life. More important, exercise training has positive effects on cardiovascular disease risk factors, atherosclerosis, endothelial dysfunction, as well as improvements in body composition and plasma lipoprotein profiles. Ultimately, physical capacity will not stop the aging process, but it can help improve a person's quality of life.

A study by Streicher (9) explored the hemodynamic responses in active and inactive elderly subjects. The data was collected in the supine, sitting, standing and 70 degrees upright tilt positions over a ten-minute period (long term response). The results indicated that physically active older men had significantly lower resting heart rates and higher stroke volumes than inactive older men in all four positions. However, physically active and inactive older men reacted hemodynamically similar when looking at the long-term response in the sitting, standing and upright tilt position as compared with the supine. These results only looked at the long term cardiovascular responses of the elderly, and any possible abnormalities may have had disappeared after such a long period of time between measurements. Others have looked at the cardiovascular responses during a mental stress test between aerobically trained and sedentary individuals (15, 17, 56). Some studies reported that fit individuals compared to unfit ones show lesser cardiovascular reactivity (15, 56), while others found no significant differences between groups (17, 56).

In addition, regular exercise has also been known to lower systolic blood pressure and to lower resting heart rate, therefore proving its beneficial applications toward hypertension, and other cardiovascular diseases as well as improving the person's overall health. These conflicting results indicate that more studies need to be done to address the influence of physical capacity in older adults during a postural stress.

The Influence of Gender on Cardiovascular Control

Gender may influence cardiovascular autonomic control, which in turn may affect the ability to withstand cardiac events and respond to orthostatic stress (21, 57). Since gender may have a profound influence on the risk of cardiovascular disease and death, it is important to understand the effects of healthy aging and gender on autonomic control of the cardiovascular function (21). Beat-to-beat blood pressure dynamics have not been well studied, and it is not known whether changes in the autonomic regulation of beat-to-beat blood pressure are associated with hemodynamic impairment.

At all ages, women seem to have higher heart rates at rest but lower blood pressure than men (15). Interestingly, there are reports of females showing greater heart rate responses to stress than men do (57). On the other hand, men show greater decreases in systolic blood pressure when responding to stress than women (10, 15, 22), even with the possible attenuation of cardiovascular responses due to aging (58).

Measurements influenced by body size, such as the common carotid artery diameter have been known to be lower in women (59). However, common carotid artery distensibility, which reflects the properties of the arterial wall as a material, is no different between men and women (22). Multiple factors affecting the arterial tree differ between the two genders: estrogenic hormone levels in women affect arterial distensibility, which may fluctuate widely; other non-hormonal differences, such as discrepancies in body weight, heart rate, stroke volume, arterial compliance, may also affect systolic and diastolic blood pressure (60).

Ultimately, both men and women will respond to a cardiovascular stress by adapting their cardiovascular responses as quickly as possible. The differences in their mechanisms may be explained by different factors such as size, hormone levels, or even fitness. More information on the different mechanisms men and women use upon a postural stress is critical to understand and treat cardiovascular abnormalities that lead to cardiovascular disease.

Significance of Carotid and Femoral Blood Flow

The cardiovascular system depends on the major arteries to distribute blood that is pumped away from the heart to the various parts of the body. The carotid artery is responsible for carrying blood to the brain, and occlusion or irregular flow through it, could result in cerebral ischemia (59). Blood flow in the carotid artery is laminar, meaning that blood cells move in parallel lines. Slower velocities along the vessel wall and faster velocities near the lumen center may be seen in color-flow images of a duplex ultrasound device. Laminar flow may be disturbed by bifurcations, viscosity and tortuosity (59). The normal ranges of velocities in the common carotid artery have not been studied extensively, and velocities may vary with physiologic differences among individuals (61).

Femoral arterial flow is also laminar, and relatively uniform (62). Duplex ultrasound shows the triphasic velocity waveform associated with the lower arterial extremities. The initial high velocity, forward flow phase that results from cardiac systole is followed by a brief phase of reverse flow in early diastole and a final low-velocity, forward flow phase later in diastole (61). The reverse flow component is a consequence of the relatively high peripheral vascular resistance in the normal lower extremity arterial circulation (60). A loss of reversal flow typically occurs in normal limbs with the vasodilation that accompanies reactive hyperemia, limb warming or occlusion (62). Arterial lesions can also disrupt the spectral waveform by widening the spectral band, and changing the characteristic velocity and laminar flow (60, 61).

According to Kojo (63), carotid blood flow declines due to a postural challenge. Blood flow changes were measured every minute after tilt in children and adolescents with orthostatic intolerance, neurally mediated syncope and epilepsy. They also found that patients who found themselves dizzy after ten minutes of tilt also experienced longer times to reach maximum carotid blood flow (63). A low body negative stress also induced significant decreases in cerebral blood flow with elapsed time (49).

Age-related progressive decreases in basal whole-limb blood flow have been reported in various studies in a supine position (16, 64). These reductions are probably due to lower limb vascular conductance, which can have important implications for both function and disease risk in humans (65). These measurements were done at rest and during long periods of time in the supine position. Our study wants to find out what happens to the vasoconstrictors when there is a postural challenge, and if gender or physical activity affect the way they are controlled. Imadojemu (66), found that a 40° head up tilt in healthy subjects caused the femoral artery flow velocity to decrease (after the initial increase in blood flow), which is the anticipated response. A study by Morgan (67) found that after an orthostatic challenge, patients with rest pain in their legs had significant elevations of femoral blood flow compared to normal subjects. This study is hypothesizing similar outcomes, by expecting significant elevations of femoral blood flow if poor cardiovascular control is present. Thus, both carotid and femoral blood flow after tilt can provide information about the cardiovascular control in two critical areas of the human body: the head and the legs. Blood flow in the carotid has been shown to be abnormal if it is significantly reduced (59). In contrast, blood flow in the legs is a high resistance system, and it is abnormal if it remains elevated due to lack of vasoconstriction after a postural stress (68, 69).

Heart rate, Blood pressure and Orthostatic Stress

Groedel's investigations in the early 1900s suggested that blood volume and the basic tone of blood vessels in man are adjusted in such a way as to ensure adequate cardiac filling when standing erect (70). Now, almost a century later, the mechanism of cardiovascular dynamic changes, and more specifically, heart rate and blood pressure regulation, are well understood. The regulation of blood pressure is usually described in terms of homeostasis (51), where although being constantly influenced by external stimulations, always displays the tendency to come back toward a reference set point. With the arrival of more sophisticated and accurate experimental techniques the interest has shifted from understanding homeostasis, to how long it takes for heart rate and blood pressure to adjust, and if it varies in different populations, such as age, gender or ethnic group (6, 7). Braune (71) found the minimum time to assess heart rate and blood pressure during active standing and passive tilt was 60 seconds. Wieling (72) also reported that analysis of the initial circulatory responses in the first 30 seconds after the onset of standing provides almost all the information that is necessary to determine abnormalities in orthostatic circulatory control. Furthermore, Braune (71) believed the best parameters with the highest sensitivity to sense cardiac autonomic dysfunction were shown by the initial increase of heart rate, and blood pressure within seconds.

Heart rate usually experiences a rapid increase upon a postural change, followed by a decrease before stabilizing at higher levels than baseline. Different factors may affect the rate of change and time an individual needs to adjust the cardiovascular system. According to Braune (71), mean HR activation caused by an orthostatic stress is attenuated with increasing age (12, 45, 71), but was unrelated to sex. The heart rate response in relationship to gender is controversial. A few studies have reported women have naturally higher baseline heart rates (7, 22) and significant higher heart rate increases (73) upon a postural challenge, whereas others reported no differences between men and women over time for heart rates (7).

The response of blood pressure to a postural stress has been used in epidemiological studies as a measure of cardiovascular reactivity. A few investigators have concluded that the difference between the supine and seated blood pressures is positively associated with subsequent development of systemic hypertension independent of the supine blood pressure (8, 74). For example, Sparrow (74) reported that a 10 millimeter per mercury (mmHg) or greater increase in diastolic blood pressure from the supine to a standing position significantly modified the effect of seated systolic blood pressure and diastolic blood pressure on the incidence of myocardial infarction in a cohort of middle-aged white men (8). Although some studies have not found any gender differences while looking at the cardiovascular responses due to a postural stress (75), several experimental studies have suggested a differential response of blood pressure upon a postural stress due to gender (22, 37, 76). In addition, physical activity and its effect on cardiovascular responses have not been studied much in the elderly population. Again, mixed results are encountered in the literature, where there are reports of increases in cardiovascular control in highly trained individuals (77, 78), as well as diminished or no effect on cardiovascular responses due to a postural stress after an endurance training program (79, 80). In addition, most of these studies were done on young adults, and using different stressors such as lower negative body pressure, 60-90º tilt, and standing.

In conclusion, more research needs to be conducted to elucidate differences in reactivity between males and females. Furthermore, the research needs to consider the effect of physical activity and gender after a postural stress test.

Summary of the Literature

The literature provided information on why: 1) Cardiovascular control is important 2) Cardiovascular disease has a higher prevalence with lack of physical activity 3) Physical capacity can improve regulation of the cardiovascular system 4) There may be gender differences in cardiovascular control 5) A postural challenge is a good way to measure cardiovascular control

CHAPTER 3

THE EFFECT OF GENDER AND PHYSICAL CAPACITY ON CARDIOVASCULAR CONTROL IN THE ELDERLY[1]

[1] Castellano, V., Olive, J.S., Stoner, L., Black, C., and McCully, K.K. To be submitted to Journal of Gerontology

ABSTRACT

Background. This study examined the effect of gender and physical capacity on older adults by means of a postural challenge test, a six-minute walking test, and a physical activity survey in thirty-seven older adults aged 75 ± 4 years.

Methods. Participants were tilted 60° at the waist while blood flow in the carotid artery and femoral artery, blood pressure and heart rate were measured continuously for two minutes. A 6-minute walking test was done in a 50-meter quiet corridor at the subject's own pace. The subjects also completed a physical activity survey. Peripheral vascular disease was assessed with ankle-brachial index measurements.

Results. Tilt resulted in a 20% increase in heart rate, a 22% decrease in systolic blood pressure, a 17% decrease in carotid blood flow and a 60% decrease in femoral blood flow. Heart rate and blood pressure responses to tilt showed the expected gender differences, while blood flow was not affected by gender. Physical capacity did not have a major effect on most cardiovascular responses upon tilt. A multiple regression showed immediate ($p<0.001$) and delayed ($p<0.05$) carotid VMAX responses were affected by physical capacity. The ankle-brachial exam showed only one subject had mild peripheral disease (ABI <0.9), indicating the population of the study was healthy.

Conclusion. A postural challenge elicited by a 60° head-up tilt produces significant changes in carotid and femoral blood flow, heart rate and blood pressure. In conclusion, a 60° tilt at the waist produces significant changes in carotid and femoral blood flow, heart rate and systolic blood pressure. Heart rate and blood pressure showed the expected gender differences, while blood flow was not affected by gender. Physical capacity did not influence cardiovascular responses to tilt in a healthy elderly population.

INTRODUCTION

Age is associated with increased incidence of cardiovascular disease. Cardiovascular disease leads to reduced function and is the major cause of death in the U.S., accounting for nearly 900,000 deaths each year (1). Even in the absence of cardiovascular disease, advanced age is associated with altered cardiovascular responses to physiological stress such as posture, and may lead to reduced function (2-5). However, it is important to note that these age-related changes are subject to large individual differences depending on physical fitness, as well as nutritional, socio-economical, and genetics (6). Thus, early detection of cardiovascular disease is critical to assure treatment, and prevent high levels of mortality in the elderly due to cardiovascular complications.

Detection of abnormal cardiovascular responses may serve as an early sign of cardiovascular disease. Previous studies may have missed any evidence of alterations and missed detection of disease while looking at the delayed responses of the cardiovascular system (7). The immediate response upon a postural stress is a sensitive measure that can be easily missed if measurements are not continuous (8-10). Moreover, by incorporating immediate responses as a measure upon a postural stress, the effect size will increase, making any possible abnormalities easier to detect.

It is widely documented that posture affects resting blood pressure, heart rate and other physiological mechanisms(2, 4, 7, 10-12). When the upright posture is assumed, blood pools in the extremities, and cardiac filling is reduced. This is also followed by a transient fall of blood pressure and the subsequent excitation of baroreceptors, which leads to increased sympathetic activity, reduced vagal outflow, and acceleration of the heart rate (7). Stimulation of catecholamines, activation of the renin-angiotensin-aldosterone system, and increases in cardiac output, peripheral resistance, venous return and volume expansion all function to bring about a prompt stabilization of blood pressure (13, 14). The regulation of the cardiovascular system occurs immediately in healthy individuals, adapting rapidly, and securing proper function after a postural stress. Therefore, a postural stress such as tilt, elicits a complex pattern of cardiovascular changes, and may reveal abnormalities if changes do not occur quickly(7, 14, 15).

Gender has an important influence on cardiovascular reactivity. Barnett (16) found that gender may have an effect on autonomic control of the cardiovascular function. Furthermore, gender has been shown to be important in regulating blood pressure upon a postural stress, finding larger decreases of systolic blood pressure in men compared to women (9, 15, 17). In addition, women tend to have higher heart rates at rest and lower blood pressure than men (15). Consequently, the existing evidence points to possible differences between men and women during cardiovascular testing.

Physical capacity is associated with increased cardiovascular function and reduced prevalence of cardiovascular disease (15, 18, 19). Physical capacity may also lower the reactivity of the cardiovascular system during a postural stress test (15, 20). Furthermore, exercise has been known to ameliorate some of the effects of aging, even though it will not slow down the aging process. For example, autonomic reflex capacity decreases due to aging, therefore impairing control of blood flow. Regular aerobic exercise can also prevent the age-associated loss in endothelium-dependent vasodilation (21, 22). This loss of vasodilation may represent an important mechanism by which regular aerobic exercise lowers the risk of cardiovascular disease and other cardiovascular risk factors (22). Physical capacity through its positive effects on biological processes can improve the effects of aging by regulating autonomic reflexes, improve endothelial function and ameliorate decreased cardiovascular capacity due to aging(23).

The purpose of the study was to evaluate the effects of gender and physical capacity on cardiovascular responses elicited by a postural challenge test in older adults. A 60° tilt at the waist was used to elicit cardiovascular responses including carotid and femoral blood flow, heart rate and blood pressure. Immediate (5-30 seconds) and delayed (2 minutes) responses to tilt were examined.

METHODS

Subjects

Thirty-seven older subjects volunteered to participate in the study between the ages of 69 and 82 years. Nineteen subjects were male and eighteen subjects were female. All subjects reported being Caucasian except for one female, who was an African-American. The subjects reported to the laboratory after eating a low fat meal, and did not take any medications the morning of the test. Eleven out of thirty-seven subjects took high blood pressure medication regularly, but did not take it the morning of the test. Only one subject was a smoker and eleven more reported being ex-smokers. Subjects were excluded from the study if they had a pacemaker, suffered from severe back pain, were under alpha blocker medication or were diagnosed with heart disease six months prior to participating in the study. The subjects were recruited from the Athens, Georgia community area through newspaper advertisements. All subjects participated in the study under their physician's consent. The study was conducted with the approval of the Institutional Review Board at the University of Georgia.

Protocol

The study included one testing session. The test was done at the University of Georgia Department of Exercise Science located in the Ramsey Student Center between 8:00-11:00 am in a quiet, comfortable room (temperature 20-22ºC). An informed consent form was signed and a medical history questionnaire used. Height and weight of the subjects were taken to calculate BMI. The subject rested for at least 10 minutes to allow stabilization, and then the testing procedure proceeded as follows:

Postural Challenge Test. The subject was placed in a supine position while preparations were made. Blood pressure and heart rate were measured continuously in the wrist by use of a Colin 7000 (Colin, Inc.). The Colin 7000 was not used in 12 subjects due to technical difficulties. In those subjects, automated blood pressures were taken every thirty seconds throughout the test with an Accutor 3 device (Datascope), and heart rate was measured continuously by an electrocardiogram using three electrodes placed carefully on the chest provided by the Biopac 1100 (Biopac, Inc). Blood flow measurements of the right carotid and the right femoral artery were measured continuously by use of a quantitative Doppler Ultrasound (Logiq 400 CL, General Electric). A linear array transducer was used with frequencies of 6-9 MHz. The imaging sites were located 2-3 centimeters distal to the carotid bifurcation in the right common carotid artery, and on the upper third of the thigh in the right superficial femoral artery. Resting diameter was measured in the axial view during diastole. Pulsed Doppler ultrasound was recorded in the longitudinal view using an insonation angle of 60°. The velocity gate was set to include the entire arterial diameter. Measurements were made continuously and averaged over one heartbeat. All data were saved to magnetic optical disks and a computer software program (Ammons

Engineering, Inc.) connected to a video signal and especially designed to collect continuous velocity data for storage and analysis. Baseline measurements were obtained for carotid blood flow, heart rate, and blood pressure during 5 minutes of quiet rest, followed by a quick rise (1.5-2 seconds) of the tilt table at the level of the waist to 60 degrees to elicit hemodynamic changes in blood flow, heart rate and blood pressure. The subject was in this position for 2 minutes while all measurements were being collected. The subject was then placed in the supine position until all measurements stabilized (>5minutes). When all the variables were stable, the subject was tilted at the level of the waist again, and this time the femoral artery blood flow was measured along with heart rate and blood pressure responses to the postural challenge. The order of carotid and femoral artery blood flow measurements were alternated throughout the whole experiment. Preliminary studies showed no order effect in repeated tilts.

Physical Capacity and Physical Activity. The distance covered during a six-minute walking test was a measure for physical capacity (24, 25). Physical activity was recorded in two different ways: Kilocalories spent during a typical week in the past month, and a frequency score of daily activities. The subjects completed a standard validated physical activity questionnaire for the elderly(26). The subjects were asked to recall the amount of physical activity they do in a typical week of the past month that were a part of their regular work and leisure routines. Two scores are reported in the Yale Physical Activity Survey: Total calories per week and a frequency of activity score computed from the amount of time they spent doing those activities. After completing the questionnaire, the subjects performed a six-minute walk test in a quiet corridor. The subjects walked back and forth in a 50-meter corridor for six minutes at their own pace, and distance walked was calculated. Uniform encouragement was provided throughout the six-minute walking test.

Ankle-Brachial Index: An Ankle-Brachial Index (ABI) test was performed with a PVL device (Biomedix, Inc.). The subject rested on a supine position for five minutes. While lying down, segmental pressures were recorded in the right arm (brachial artery) and both ankles (posterior tibial artery) with an 8Mhz probe. The ankle SBP was divided by the brachial SBP to calculate the ankle-brachial index (ABI<0.9 was used to indicate the presence of peripheral vascular disease) (27).

Statistics: Data are expressed as mean±SD. Independent samples t-test indicated that there were significant differences between males and females based on physical activity ($p = 0.001$). Based on this, a repeated measures analysis of covariance (ANCOVA) were conducted using SPSS (version 10.0) to characterize the response of the subjects to tilt (baseline-peak-two minutes), and to control for differences in physical activity between groups. Bonferroni pairwise comparisons were conducted for post-hoc analyses with familywise error set at 0.05. The assumption of sphericity was tested for and if violated was corrected by the Huynh-Feldt method. When it was appropriate, independent t tests were conducted to compare the means of the male and female groups. A regression analysis was also conducted, where gender and physical activity were entered directly, followed by the gender x physical activity interaction, to determine their independent effects on the dependent variables. When the interaction was not significant, it was removed and the main effects of gender and physical activity were tested. Pearson product moment correlations were conducted to determine relationships between variables. Differences were considered significant at values of <0.05.

RESULTS

Fifty-two older adults responded to a newspaper advertisement. Of those fifty-two, forty-six fit the criteria to be in the study. A doctor's consent was received for forty-one subjects, and thirty-seven older subjects (19 men and 18 women) with a mean age of 75 ± 4 years were tested. The physical characteristics, physical activity scores and ankle-brachial values of the subjects are shown in Table 1.

Table 1. Population Description, Physical Activity and Ankle-Brachial Index in Men and Women. (*p<0.05)

	Men (n = 18)	**Women (n = 17)**	**P value**
Age (yrs)	75.1 ± 4.2	74.9 ± 4.1	0.876
Height (cm)	174.6 ± 7.3	161.4 ± 6.2	p<0.001*
Weight (kg)	81.9 ± 11.5	70.9 ± 10.5	0.005*
BMI	26.9 ± 3	27.3 ± 5	0.732
Six-Minute Walk (m)	589 ± 83	490 ± 86	0.001*
Total energy spent (kcal/wk)	5157 ± 1791	4285 ± 1702	0.138
Frequency Activity Score	70 ± 19	54 ± 19	0.012*
Lowest ABI	1.25 ± 0.16	1.17 ± 0.15	0.147

Six-Minute Walk and Physical Activity Questionnaire. Males walked, in an average, 99 meters longer than females, and spent 20% more total energy expenditure than females (Table 1). The frequency score of leisure and physical activities in men was 16 points higher than in the females (Table 1).

Ankle-Brachial Index (ABI) Test. ABI ranged from 0.88 to 1.72. Ten subjects had ABIs of 1.4 or higher, and only one subject was <0.9. There were not any systemic differences in response to tilt in people with values above 1.4. The men had higher values than females in both right (1.32 ± 0.16 vs. 1.23 ± 0.15 respectively) and left legs (1.28 ± 0.16 vs. 1.18 ± 0.15 respectively), but these differences were not significant. The lowest ABI of the subjects were not significantly correlated to the cardiovascular responses upon tilt. The values of the lowest ABI between the two legs are reported in Table 1.

Heart Rate and Blood Pressure Responses to Tilt. A repeated measures ANCOVA was conducted to determine between males and females differences and within group differences for heart rate. The heart rate was significantly different between males and females, as well as significantly different within groups after tilt. The statistics were as follows: The ANCOVA indicated that there was a significant interaction between gender and HR for between group differences ($F(1.2, 37.2) = 4.461$, $p = 0.035$) indicating that males and females were different (Figure 1). Sphericity was tested and violated ($\varepsilon = 0.600$). Because there was an interaction main group effects were analyzed for males and females. Main group effects for women indicated that there were significant differences across time points and were corrected for sphericitiy ($\varepsilon = 0.573$) ($F(1.6, 17.2) = 34.219$, $p < 0.001$). Bonferroni post hoc analyses indicated that peak HR was significantly higher than baseline ($p < 0.001$) and 2 minute ($p < 0.001$) (Table 2). Main group effects for men indicated that there were significant differences across time points and corrected for sphericity ($\varepsilon = 0.559$) ($F(1.12, 19.02) = 17.225$, $p < 0.001$). Bonferroni post hoc analyses indicated that peak HR was significantly higher than baseline ($p = 0.001$) and 2 minute ($p = 0.005$), and baseline was significantly lower than 2 min ($p = 0.010$), but baseline and 2 minute only approached significance ($p = 0.072$) (Table 2).

A repeated measures ANCOVA was conducted to determine between and within group differences for systolic blood pressure. Systolic blood pressure was not significant between males and females, but was significant within groups. The statistics were as follows: Although approaching significance, the ANCOVA indicated that between group

Table 2. Heart Rate and Blood Pressure Tilt Response Values. *p<0.05 between peak and baseline, **p<0.05 between peak and 2 minutes, $^{\#}$p<0.05 between 2 minutes and baseline, $^{\$}$p<0.05 between men and women.

	Men	Women	P value	Number of subjects (male/fem)
Heart Rate Variables			0.035$^{\$}$	
Baseline (bts/min)	61 ± 9	68 ± 7	0.001*	19/18
Peak (bts/min)	70 ± 11	87 ± 14	0.005**	18/16
2-min (bts/min)	63 ± 9	69 ± 9	0.010$^{\#}$	19/18
SBP Variables			0.062	
Baseline (bts/min)	129 ± 16	146 ± 27	<0.001*	15/13
Peak (bts/min)	102 ± 21	96 ± 20	<0.001**	8/4
2-min (bts/min)	122 ± 18	136 ± 24	0.499	16/14
DBP Variables			0.930	
Baseline (bts/min)	70 ± 9	76 ± 15	0.224	15/13
Peak (bts/min)	56 ± 8	56 ± 8	0.224	8/6
2-min (bts/min)	63 ± 13	63 ± 13	0.224	15/13

differences were not significant, indicating that males and females had similar systolic blood pressure responses ($F(1, 9) = 4.539$, $p = 0.062$). Within group analyses indicated that there was a significant difference across time intervals ($F(2,20) = 27.481$, $p < 0.001$). Post hoc analyses indicated that peak systolic pressure was significant lower when compared to baseline ($p < 0.001$) and at 2 minutes ($p < 0.001$), but was not significant between baseline to 2 minutes ($p = 0.499$) (Table 2).

A repeated measures ANCOVA was conducted to determine between and within group differences for diastolic blood pressure. Diastolic blood pressure was not significant between males and females, nor significant within groups. The statistics were as follows: The ANCOVA indicated that between group differences were not significant indicating that males and females had similar diastolic blood pressure responses ($F(1, 12) = 0.008$, $p = 0.930$). Within group analyses indicated that there were not any significant differences across time intervals during the tilt ($\varepsilon = 0.787$) ($F(1.573, 18.881) = 1.622$, $p = 0.224$) (Table 2).

Timed Responses of Heart Rate and Blood Pressure. Table 3 shows time to peak values evaluated with an independent t test. Men showed significantly longer time than women to reach peak heart rate and diastolic blood pressure upon tilt. Blood flow values were not significant.

The Effect of Physical Capacity on Heart Rate and Blood Pressure Responses upon Tilt. Physical capacity by means of the six-minute walking test did not have an effect on the immediate ($t = -0.40$, $p = 0.692$) or delayed ($t = -1.435$, $p = 0.163$) heart rate responses (Figure 3). Blood pressure was only affected by physical capacity in the delayed response, although the effect was only significant when gender was not entered in the equation (t = -2.369, p = 0.027).

Table 3. Time to Peak Values upon 60° tilt in Men and Women. [$]p< 0.05 between men and women.

Time to Peak (sec)	Men	Women	P Value	Number of subjects (male/fem)
HR	8.6 ± 6.3	6.9 ± 9.0	0.001[$]	18/16
SBP	8.0 ± 3.7	9.1 ± 5.8	0.66	8/7
DBP	10.6 ± 5.5	5.6 ± 2.2	0.028[$]	9/8

Blood Flow Responses to tilt. A repeated measures ANCOVA was conducted to determine between and within group differences in blood flow.

Carotid Blood Flow Responses. The ANCOVA indicated that between group differences were not significant indicating that males and females had similar carotid blood flow responses (F (1, 33) = 1.620, p = 0.212). Within group analyses indicated that there was a significant difference across time intervals during the tilt (F (2, 68) = 50.176, p <0.001). Post hoc analyses indicated that peak blood flow was significantly lower than baseline (p <0.001) and at 2 minutes (p <0.001), and approached significance between baseline and 2 minutes (p = 0.088) (Table 4).

An ANCOVA was conducted to determine differences between and within for carotid maximum velocity (VMAX). The ANCOVA indicated that between group differences were not significant indicating that males and females had similar VMAX responses (F (1, 31) = 0.790, p = 0.381). Within group analyses indicated that there was a significant difference across time intervals during the tilt (ε = 0.516) (F (1.032, 33.033) = 81.359, p

<0.001). Post hoc analyses indicated that peak VMAX was significantly higher than baseline (p = 0.000) and at 2 minutes (p <0.001), and baseline was significantly lower than at 2 minutes (p <0.001) (Table 4).

Femoral Blood Flow Responses. The ANCOVA indicated that between group differences were not significant indicating that males and females had similar blood flow responses (F (1, 28) = 0.071, p = 0.792). Within group analyses indicated that there was a significant difference across time intervals during the tilt (F (2, 58) = 45.844, p <0.001) (Figure 2). Post hoc analyses indicated that peak blood flow was significantly lower than baseline (p = 0.002) and at 2 minutes (p = 0.002), as well as baseline being significantly higher than at 2 minutes (p = 0.001) (Table 4).

An ANCOVA was conducted for femoral VMAX, and indicated that between group differences were not significant indicating that males and females had similar blood flow responses (F (1, 27) = 2.955, p = 0.097). Within group analyses indicated that there was a significant difference across time intervals during the tilt (ε = 0.748)(F (1.496, 41.879)= 89.371, p <0.001). Post hoc analyses indicated that peak femoral VMAX was significantly lower than baseline (p <0.001) and at 2 minutes (p <0.001), as well as baseline significantly higher than at 2 min (p <0.001) (Table 4).

The Effect of Physical Capacity on Carotid and Femoral Blood Flow Responses upon Tilt. Physical capacity did not affect the immediate (t = 1.367, p = 0.181) or delayed blood flow responses upon tilt (t = 0.228, p = 0.778). However, there were effects on carotid VMAX responses upon tilt. Physical capacity had an effect on immediate carotid VMAX responses upon tilt when (t=3.629, p= .001). There was also a correlation of physical capacity to the immediate carotid VMAX responses ($r = 0.558$, $p < 0.001$) (Figure 4). When gender was not entered in the equation, physical capacity had an effect on the delayed carotid VMAX responses ($t=2.039$, $p= .050$). Physical capacity was also correlated to the delayed carotid VMAX responses($r = 0.334$, $p = 0.025$). The immediate or delayed femoral blood flow response was not affected by physical capacity($t = 1.11$, $p = 0.277$ and $t = -0.436$, $p = 0.666$ respectively).

Table 4. Carotid and Femoral Blood Flow Variables. *p<0.05 between peak and baseline, **p<0.05 between peak and 2 minutes, # p<0.05 between 2 minutes and baseline

	Men	Women	P value	Number of subjects (male/fem)
Carotid Blood Flow Variables			0.212	
Rest (m/s)	0.136 ± 0.04	0.114 ± 0.03	p<0.001*	18/18
Peak value (m/s)	0.114 ± 0.03	0.093 ± 0.03	p<0.001**	18/18
2-min value (m/s)	0.131± 0.03	0.110 ± 0.03	p<0.001#	18/18
Carotid VMAX Variables			0.381	
Rest (m/s)	0.747±0.15	0.644±0.16	p<0.001*	19/18
Peak value (m/s)	0.957±0.23	0.785±0.02	p<0.001**	19/17
2-min value (m/s)	0.792±0.17	0.660±0.18	p<0.001#	19/18
Femoral Blood Flow variables			0.792	
Rest (m/s)	0.024 ± 0.01	0.023 ± 0.01	0.002*	17/15
Peak value (m/s)	0.010 ± 0.01	0.009 ± 0.01	0.002**	17/14
2-min value (m/s)	0.021 ± 0.01	0.018 ± 0.00	0.001#	17/14
Femoral VMAX variables			0.097	
Rest (m/s)	0.773±0.13	0.788±0.28	p<0.001*	18/15
Peak value (m/s)	0.568±7.78	0.566±0.19	p<0.001**	18/14
2-min value (m/s)	0.651±0.13	0.663±0.22	p<0.001#	18/14

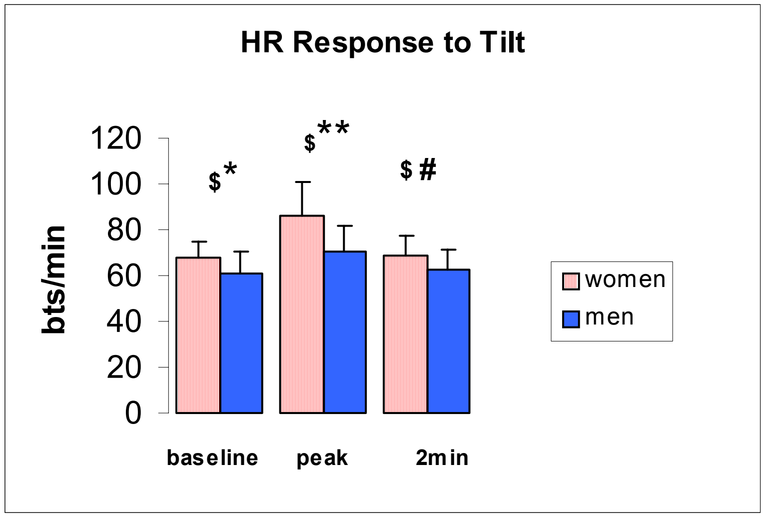

Figure 1. Tilt Response Values. *p<0.05 between peak and baseline, **p<0.05 between peak and 2 minutes, [#]p<0.05 between 2 minutes and baseline, [$]p<0.05 between men and women.

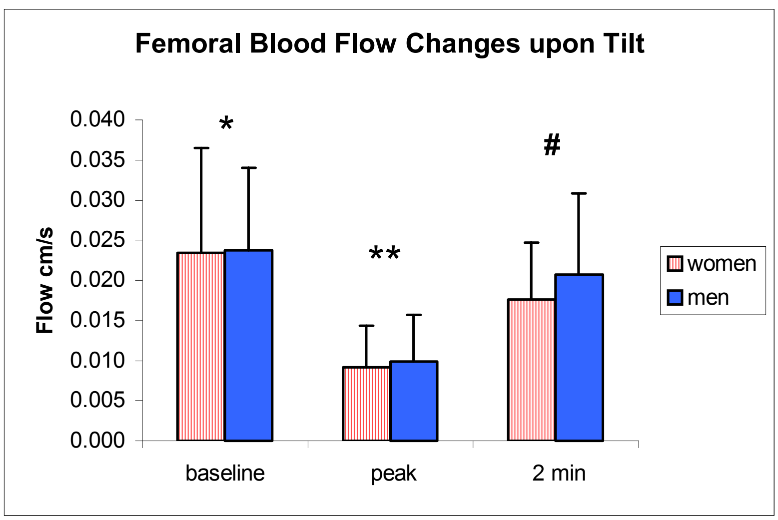

Figure 2. Femoral blood flow changes upon tilt. *P <0.05 between peak and baseline, **p< 0.05 between peak and 2 minutes, [#]p< 0.05 between 2 minutes and baseline

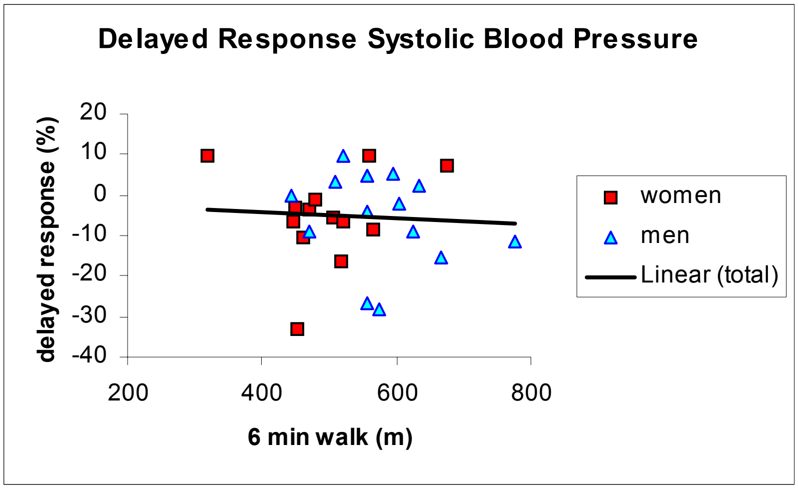

Figure 3. The regression analysis (t =-2.369, p = 0.027) and correlation between the six-minute walk and the delayed systolic blood pressure response (r = -0.443, p = 0.013) were statistically significant.

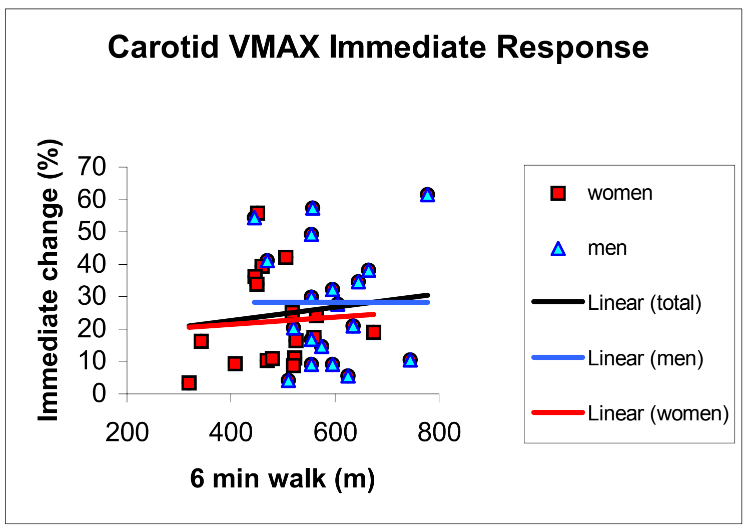

Figure 4. The regression analysis (t =3.629, p = .001) and correlation between the six-minute walk and immediate response of carotid VMAX (r = 0.558, p<0.001) were statistically significant.

DISCUSSION

The results indicated that there were significant differences in heart rate between males and females upon tilt. Females had a significantly higher heart rate increase and higher heart rate values at baseline. These findings are consistent with the literature, where in general, females tend to show larger resting heart rates than males (28), and larger increases in heart rate due to a postural stress (28-31, 32 , 33). These changes in heart rate may leave females more susceptible than men to larger changes in blood pressure in situations in which the autonomic function may be compromised (34, 35). Many female-differences in cardiovascular responses, even after menopause, have been shown to be estrogen-related, mediated through the endothelium-dependent factor nitric oxide (34-36). Although not significant, this study also found gender differences upon tilt in systolic and diastolic blood pressure. Females had larger decreases than males in both systolic and diastolic blood pressure. However, the low number of subjects in the blood pressure measurements may have prevented this study from finding any significant results reported in other studies (7, 28, 33, 37). Interestingly, differences between males and females were also found in heart rate and diastolic pressure time to peak. Males took 25% longer time than females to peak, whereas diastolic blood pressure took 48 % longer than females to peak. These faster responses shown by females may be explained due to previous reported smaller vasoconstriction in women during a postural challenge. Neither carotid or femoral blood flow experienced differences between males and females. Measurements of carotid or femoral blood flow regarding gender differences immediately after a postural stress have been scarce (6, 38). Other factors, such as carotid diameter or pulsatility have been known to differ between males and females (30). However, the results of this study indicate that there are not carotid or femoral blood flow differences upon tilt between males and females. Therefore, blood flow regulation through the carotid and femoral arteries ultimately adjusts swiftly to a postural challenge regardless of gender.

Contrary to what the study hypothesized, physical capacity of the subjects did not have a major effect on blood flow, blood pressure or heart rate immediate or delayed responses. However, physical capacity had a moderate significant effect on carotid VMAX immediate and delayed changes. VMAX is a potentially important but understudied hemodynamic parameter according to (39). Its increase may reflect the fast response of the cardiovascular system to adjust blood flow regulation after a postural challenge or larger heart rate contractility due to higher levels of physical capacity, but the carotid VMAX significance is still unknown. Furthermore, it is possible that even after a wide range of physical capacity, the population studied was not directly affected by physical capacity due to their normal health status. However, this relationship between physical capacity and cardiovascular responses may be different in well-trained or diseased populations in the elderly.

Heart rate, systolic blood pressure, carotid blood flow and femoral blood flow significantly changed upon tilt. As expected, heart rate experienced a significant increase in heart rate upon tilt (28, 30-33, 37). Males showed a 15% increase and females showed a 26% increase upon tilt. The study demonstrated tilting at the waist was a useful measure provoking heart rate responses that were significant, regardless of lower absolute numbers than previously reported in other studies (7, 37). Furthermore, systolic blood pressure significantly decreased (22 ± 11mmHg) upon tilt, providing very similar numbers reported by previous studies (16, 33, 40) (41). Diastolic blood pressure did not significantly decrease upon tilt (7, 42). However, the low number of subjects (14) used due to technical difficulties during testing may have inhibited the expected changes in diastolic blood pressure found by many others (6-8, 30, 33, 40). In addition, carotid blood flow significantly decreased an average of 6 % immediately after tilt (26 seconds). In contrast, carotid VMAX took an average of 10 seconds to reach VMAX after tilt, which was 25% higher than at baseline. Carotid blood flow upon tilt has only been studied after long periods of tilt and in diseased populations (38, 43). Therefore, it is hard to compare these results with past ones since immediate responses may happen within the first 30 seconds after tilt. Femoral blood flow and femoral VMAX significantly decreased immediately after tilt (20% and 16 % respectively), slowly recovered, and stabilized at lower levels than baseline (44, 45). Femoral flow reached its lowest blood flow at 58 seconds, while femoral VMAX reached it sooner at 35 seconds. The decrease in femoral blood flow is due to an activation of the vasoconstrictor response caused by the initial rush of femoral blood flow immediately after tilt, preventing blood pooling after a postural stress (44, 46).

This study wants to point out that, due to the difficulties, a postural challenge test has been rarely assessed while looking at the carotid or femoral arterial blood flow immediately after tilt (47). Specifically, very few studies have measured carotid blood flow upon tilt. To our knowledge, blood flow has only been measured after a delayed period of time, and never immediately after tilt like in this study (38, 43). This study found the immediate response to tilt showed a bigger effect size then delayed responses. Furthermore, the carotid and femoral VMAX significantly increased and decreased respectively immediately upon tilt. As pointed out before, the significance of VMAX is not well understood, but it is clear that there were significant changes in VMAX velocity upon tilt and physical capacity had an effect on it.

Physical Capacity. The study collected three different physical activity measures: The six-minute walk test, total kilocalories per week, and a score of leisure and recreational activities reported by the subjects. The six-minute walk was used to be compared to blood flow, heart rate and blood pressure measures. The six-minute walk was chosen because reflects the physical capacity of the subjects more closely than the other two measures, and ultimately provides a measure of physical function (24, 25). In addition, the 6-minute walking test has been validated by high correlation with workloads, heart rate, and oxygen saturation when compared with standard bicycle ergometry and treadmill exercise (24, 25, 48). Furthermore, the 6-minute walking test improves testing effectiveness to assess capacity in an elderly population because it can be administered in all ability levels (25, 48). However, the physical activity survey by (26), indicated males and females spent a similar amount of kilocalories per week although their physical activity score were significantly different. This study believes self-reported activities did not reflect past physical activity and may have been bias toward the interviewer. Therefore, the six-minute walking distance was selected to be compared with the rest of the measures.

A multiple regression analyses revealed that the distance covered during the six minute walking test had an effect on delayed systolic blood pressure changes upon tilt. Higher levels of physical capacity were related to the recovery of back to baseline levels of systolic blood pressures after two minutes of head-up tilt. Thus, these results indicated systolic blood pressure recovered back to normal after being exposed to two minutes of a postural stress. Others have also indicated that physical capacity may affect blood pressure and postural tolerance in adults of all ages (6, 20, 28). In contrary to what we had expected, carotid blood flow or femoral blood flow were not directly affected by physical capacity upon a postural stress. The study encountered difficulties recording changes in blood flow immediately after tilt in some subjects, and whether that may be a factor or not, it may have helped understand in more detail the nature of blood flow dynamics upon tilt more in depth. Future studies should take this factor in consideration while measuring blood flow changes after a postural test. Instead, this study found that physical activity had a moderate effect on immediate and delayed VMAX responses. Fitter individuals recovered by immediately increasing VMAX carotid blood flow to the head showing a good adaptive response which led to proper blood irrigation after a postural challenge (Figure 5). The significance of VMAX has yet to be studied in more depth, but this interesting relationship between physical capacity and VMAX may provide more useful information in the future.

Even though the subjects had a range of physical capacity values, the study did not find major effects of physical capacity on cardiovascular responses to tilt. Others have found exercise training positively affect orthostatic tolerance and baroreflex control (49, 50). The lack of effect in our study may be explained by the normal health status of the population of this study. Future research is necessary in diseased or trained/untrained populations to reveal the significance of physical capacity in different elderly populations regarding blood flow and other cardiovascular responses upon tilt.

Ankle-Brachial Index and Race. The ankle-brachial index was used to provide a measure of peripheral vascular disease (51, 52). Only one subject had recordings lower than 0.9 (ABI of 0.88), indicating the population of the study was free of any major peripheral vascular disease. Ten subjects had an ABI > 1.4, indicating possible hardening of the arteries. However, our observations did not reveal a different pattern from these subjects in the other cardiovascular measurements. This study also included an African American female. Although race has been known to be a factor in cardiovascular responses to a postural stress (7), the subject was included in the study because her results did not change the outcome of the cardiovascular responses upon tilt.

The results of this study showed significant changes occur in the cardiovascular system upon tilt at the waist. Heart rate and blood pressure showed the expected gender differences, while blood flow was not affected by gender. Physical capacity did not influence cardiovascular responses in a healthy elderly population. Furthermore, physical capacity did not have an effect on blood flow measures, but did have a moderate effect on VMAX blood flow responses upon tilt. More information on carotid and femoral blood flow immediate responses would clarify if there are any differences between different populations upon tilt.

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REFERENCES

1. Burt VL, Whelton P, Roccella EJ, et al. Pervalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey. *Hypertension* 1995;25:305-313.
2. Caird FI, Andrews, G.R., Kennedy, R.D. The effect of posture on blood pressure in the elderly. *Br Heart J* 1973;35:527-530.
3. Jansen RW, Lenders JW, Thien T, Hoefnagels WH. The influence of age and blood pressure on the hemodynamic and humoral response of head-up tilt. *Journal of the American Geriatric Society* 1989;27:528-532.
4. Hainsworth R, Al-Shamma YM. Cardiovascular responses to upright tilting in healthy subjects. *Clin. Sci.* 1988;74:17-22.

5. Vargas E, Lye, M. Physiological responses to postural change in young and old healthy individuals. *Exp Gerontol* 1982;17:445-452.
6. Smith JJ, Ebert, T.J. General response to orthostatic stress. Circulatory response to upright posture. Boca Raton, F: CRC Press; 1990.
7. Goldstein IB, Shapiro D. The cardiovascular responses to postural change as a function of race. *Biological Psychology* 1994;23:172-186.
8. Nardo C, Chambless L, Light K, Rosamond W, Sharrett A, Tell G, et al. Descriptive epidemiology of blood pressure response to change in body position. *Hypertension* 1999;33:1123-1129.
9. Light KC. Differential responses to salt-interactions. In: Plenum, editor. Individual responses in cardiovascular response to stress. New York; 1995. p. 245-263.
10. Streicher W, Misner, J.E., Bloomfield, D.K., Massey, B.H. Hemodynamic responses to positional change in habitually physically active and inactive older men. *J Am Geriatr Soc* 1998;36(9):795-800.
11. Bloomfield DM, Kaufman ES, Bigger JT, Fleiss J, Rolnitzky L, Steinman R. Passive head-up tilt and actively standing up produce similar overall changes in autonomic balance. *American Heart Journal* 1997;134:316-320.
12. Fagard R, Thijs L, Amery A. Age and the hemodynamic response to posture and exercise. *American Journal of Geriatric Cardiology* 1993;2:23-40.
13. Sheperd JT. Circulation to skeletal muscle. Handbook of Physiology, The Cardiovascular system, Peripheral circulation and Organ Blood Flow. Bethesda, MD: Am Physiol. Soc.; 1993.
14. Wieling W. Orthostatic stress and autonomic function.: Oxford University Press; 1988.
15. Turner JR. Cardiovascular reactivity and stress: patterns of physiological response. New York; 1994.
16. Barnett SR, Morin RJ, Kiely DK, Gagnon M, Azhar G, Knight EL, et al. Effects of age and gender on autonomic control of blood pressure dynamics. *Hypertension* 1999;33:1195-1200.
17. Stoney CM, Davis, M.C., Matthews, K.A. Sex differences in physiological responses to stress in coronary heart disease: a causal link? *Psychophysiology* 1987;24:127-131.
18. Cox JP, Evans JF, Jamieson JL. Aerobic power and tonic heart rate responses to psychological stressors. *Personality and Social Psychology Bulletin* 1979;5:160-163.
19. Dinenno FAS, D.R., DeSouza, C.A., Tanaka, H. Age-related decreases in basal limb flow in humans: time course, determinants and habitual exercise effects. *J Physiol Mar* 2001;531(573-579).
20. Holmes DS, Roth DL. Association of aerobic fitness with pulse rate and subjective responses to psychological stress. *Psychophysiology* 1992;22:525-529.
21. Dinenno FA, Jones PP, Seals DR, Tanaka H. Limb flow and vascular conductance are reduced with age in healthy humans. *Circulation* 1999;100:164-170.
22. DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, et al. Regular aerobic exercise prevents and restores age-related declines in

endothelium-dependent vasodilation in healthly men. *Circulation* 2000;102:1351-1357.
23. Brooks GA, Fahey, T.D., Timothy, P.W., Baldwin, K.M. Exercise Physiology: Human bioenergetics and its applications; 2000.
24. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *American Journal of Respiratory and Critical Care Medicine* 1998;158:1384-1387.
25. Knox AJ, Morrison JF, Muers MF. Reproducibility of walking test results in chronic obstructive airways disease. *Thorax* 1988;43:388-392.
26. DiPietro JA EK, Todd KS. A survey for assessing physical activity among older adults. May. *Med Sci Sports Exerc.* 1993;25(5):628-42.
27. Vogt M, Cauley J, Newman A, Kuller L, Hulley S. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 1993;270:465-469.
28. Frey MA, Tomaselli CM, Hoffler WG. Cardiovascular responses to postural changes. Differences with age for women and men. *Journal of Clinical Pharmacology* 1992;34:394-402.
29. Shoemaker JK, Hogeman CS, Silber DH, Gray K, Herr M, Sinoway LI. Head-down-tilt bed rest alters forearm vasodilator and vasoconstrictor responses. *Journal of Applied Physiology* 1998;84(5):1756-1762.
30. Smulyan H, Asmar, R.G., Rudnicki, A., London, G.M., Safar, M.E. Comparative effects of aging in men and women on the properties of the arterial tree. *J. Am. Coll. Cardiol.* 2001;37:1374-80.
31. Abdel-Rahman AR, Merrill RH, Wooles WR. Gender-related differences in the baroreceptor reflex control of heart rate in normotensive humans. *Journal of Applied Physiology* 1994;77:606-613.
32. Girdler SS, Light KC. Hemodynamic stress responses in men and women examined as a function of female menstrual cycle phase. *International Journal of Psychophysiology* 1994;17:233-248.
33. Gotshall RW, Tsai PF, Bassett Frey MA. Gender-based differences to the cardiovascular response to standing. *Aviation, Space, and Environmental Medicine* 1991;62:855-859.
34. Volterrani M, Rosano, G., Coats, A., Beale, C, Collins, P. Estrogen acutely increases peripheral blood flow in post-menopausal women. *Am. J. Med.* 1995;99:119-122.
35. Williams JK, Adams, M.R., Klopfeinstein, H.S. Estrogen modulates responses of atherosclerotic coronary arteries. *Circulation* 1990;81:1680-1687.
36. Williams JK, Adams, M.R., Herrington, D.M., Clarkson, T.B. Short-term administration of estrogen and vascular responses of atherosclerotic coronary arteries. *J. Am. Coll. Cardiol.* 1992;29:452-457.
37. Shoemaker JK, Hogeman, C.S., Khan, M., Kimmerly, D.S., Sinoway, L.I. Gender affects sympathetic and hemodynamic response to postural stress. *Am. J. Physiol. Heart Circ. Physiol.* 2001;281:H2028-H2035.
38. Kojo M, Wada, M., Akiyoshi, K., Inutsuka, M., Izumi, T. . . , (), . Reduction of carotid artery blood flow in pediatric patients with syncope: evaluation with head-up tilt test. *Neuropediatrics* 2001;32(4):169-75.

39. Perret RS, Sloop, G.D. Increased peak blood velocity in association with elevated blood pressure. *Ultrasound Med Biol.* 2000;26(9):1387-91.
40. James MA, Potter, J.F. Orthostatic blood pressure changes and arterial baroreflex sensitivity in elderly subjects. *Age and Ageing* 1999;28:522-530.
41. Wieling W, Ten Harkel, A.D., Van Lieshout, J.J. Spectrum of Orthostatic disorders: classification based on an analysis of the short-term circulatory response upon standing. *Clin Sci* 1991(81):241-8.
42. Moore KI, Newton, K. Orthostatic heart rates and blood pressures in healthy young women and men. *Heart Lung* 1986;15:611-617.
43. Takeshita S, Nagai, H., Fujisawa, T., Sekine, Y, Yoshioka, S. . J. The usefulness of the measurement of carotid artery blood flow in patients with orthostatic dysregulation by pulsed-doppler evaluation. *Jpan. Pediat. Soc.* 1994;98:120-121.
44. Imadojemu VA, Lott ME, Gleeson K, Hogeman CS, Ray CA, Sinoway LI. Contribution of perfusion pressure to vascular resistance response during head-up tilt. *Am. J. Physiol. Heart Circ. Physiol.* 2001;281:H371-H375.
45. Morgan RH, Psaila, J.V., Stone, J., Carolan, G. Effect of postural change on common femoral artery blood flow, measured by duplex ultrasound, in normal subjects and patients with peripheral vascular disease. *J Biomed Eng May* 1991;13(3):244-8.
46. Schmidt-Truckass A, Schmid, A., Brunner, C., Schererer, N., Zach, G., Keul, J., Huonker, M. Arterial properties of the carotid and femoral artery in endurance-trained and paraplegic subjects. *J. Appl. Physiol.* 2000;89:1956-1963.
47. Smith JJ, Porth, C.M., Erickson, M. Hemodynamic response to the upright posture. *J Clin Pharmacol. May* 1994;34(5):375-86.
48. Guyatt GH, Sullivan MJ, Thompson PJ. The six-minute walk: A new measure of exercise capacity in patients with chronic heart failure. *Canadian Medical Association Journal* 1985;132:919-923.
49. Krieger EM, Da Silva, G.J., Negrao, C.E. Effects of exercise training on baroreflex control of the cardiovascular system. *Ann NY Acad Sci* 2001;490:338-347.
50. Geelen G, Greenleaf, J.E. Orthostasis: Exercise and exercise training. *Exerc Sport Sci Rev* 1993;21(201-230).
51. Zwiebel WJ. Introduction to vascular ultrasonography. Philadelphia: Saunders; 2000.
52. Yao J. Hemodynamic studies in peripheral arterial disease. *Br. J. Surg.* 1970;57:761-766.

CHAPTER 4

SUMMARY AND CONCLUSIONS

According to Smith (43), the currently difficult task of measuring carotid blood flow or cerebral blood flow during a postural change would be physiologically very useful to understand and possibly diagnose cardiovascular disease. This study attempted to assess arterial blood flow changes, as well as heart rate and blood pressure upon a postural change in the elderly. In addition, gender differences and physical capacity measured by a six-minute walk test were closely analyzed.

Thirty-seven men and women participated in this study. A postural stress test measured by a 60° tilt at the level of the waist lasting 2 minutes was performed to determine if carotid and femoral blood flow, heart rate and blood pressure experienced any changes. A six-minute walking test, and physical activity survey for the elderly were administered. Lastly, an ankle-brachial index test was given to the participants.

The results indicated that there were significant differences in heart rate between males and females upon tilt. Females had a significantly higher heart rate increase and higher heart rate values at baseline. These findings are consistent with the literature, where in general, females tend to show larger resting heart rates than males (81), and larger increases in heart rate due to a postural stress (37, 39 , 60, 81-83). These changes in heart rate may leave females more susceptible than men to larger changes in blood pressure in situations in which the autonomic function may be compromised (68, 84). Many female-differences in cardiovascular responses, even after menopause, have been shown to be estrogen-related, mediated through the endothelium-dependent factor nitric oxide (68, 69, 84). Although not significant, this study also found gender differences upon tilt in systolic and diastolic blood pressure. Females had larger decreases than males in both systolic and diastolic blood pressure. However, the low number of subjects in the blood pressure measurements may have prevented this study from finding any significant results reported in other studies (7, 37, 73, 81). Neither carotid or femoral blood flow experienced differences between males and females. Measurements of carotid or femoral blood flow regarding gender differences immediately after a postural stress have been scarce (6, 63). Other factors, such as carotid diameter or pulsatility have been known to differ between males and females (60). However, the results of this study indicate that there are not carotid or femoral blood flow differences upon tilt between males and females. Therefore, blood flow regulation through the carotid and femoral arteries ultimately adjusts swiftly to a postural challenge regardless of gender.

Physical capacity of the subjects did not have a major effect on blood flow, blood pressure or heart rate immediate or delayed responses. However, physical capacity had a moderate significant effect on carotid VMAX immediate and delayed changes. VMAX is a potentially important but understudied hemodynamic parameter according to (85). Its increase may reflect the fast response of the cardiovascular system to adjust blood flow regulation after a postural challenge or larger heart rate contractility due to higher levels of physical capacity. Further studies are needed to understand the importance of carotid VMAX significance upon tilt. Furthermore, it is possible that even after a wide range of physical capacity, the population studied was not directly affected by physical capacity due to their normal health status. However, this relationship between physical capacity and cardiovascular responses may be different in well-trained or diseased populations in the elderly.

In conclusion, a 60° tilt at the waist produces significant changes in carotid and femoral blood flow, heart rate and systolic blood pressure. Heart rate and blood pressure showed the expected gender differences, while blood flow was not affected by gender. In addition, physical capacity did not affect any of the main variables indicating the cardiovascular response to tilt may not be affected by physical capacity. Future experiments should look at the significance of VMAX and its relationship to physical capacity. In addition, more information is needed on continuous measurements of carotid and femoral blood flow in all populations. Specifically, to determine if diseased and healthy populations react differently after a 60° tilt at the waist.

CHAPTER 5

LITERATURE CITED

1. Burt VL, Whelton P, Roccella EJ, et al. Pervalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey. *Hypertension* 1995;25:305-313.
2. Caird FI, Andrews, G.R., Kennedy, R.D. The effect of posture on blood pressure in the elderly. *Br Heart J* 1973;35:527-530.
3. Jansen RW, Lenders JW, Thien T, Hoefnagels WH. The influence of age and blood pressure on the hemodynamic and humoral response of head-up tilt. *Journal of the American Geriatric Society* 1989;27:528-532.
4. Vargas E, Lye, M. Physiological responses to postural change in young and old healthy individuals. *Exp Gerontol* 1982;17:445-452.
5. Hainsworth R, Al-Shamma YM. Cardiovascular responses to upright tilting in healthy subjects. *Clin. Sci.* 1988;74:17-22.
6. Smith JJ, Ebert, T.J. General response to orthostatic stress. Circulatory response to upright posture. Boca Raton, F: CRC Press; 1990.
7. Goldstein IB, Shapiro D. The cardiovascular responses to postural change as a function of race. *Biological Psychology* 1994;23:172-186.
8. Nardo C, Chambless L, Light K, Rosamond W, Sharrett A, Tell G, et al. Descriptive epidemiology of blood pressure response to change in body position. *Hypertension* 1999;33:1123-1129.
9. Streicher W, Misner, J.E., Bloomfield, D.K., Massey, B.H. Hemodynamic responses to positional change in habitually physically active and inactive older men. *J Am Geriatr Soc* 1998;36(9):795-800.
10. Light KC. Differential responses to salt-interactions. In: Plenum, editor. Individual responses in cardiovascular response to stress. New York; 1995. p. 245-263.
11. Bloomfield DM, Kaufman ES, Bigger JT, Fleiss J, Rolnitzky L, Steinman R. Passive head-up tilt and actively standing up produce similar overall changes in autonomic balance. *American Heart Journal* 1997;134:316-320.
12. Fagard R, Thijs L, Amery A. Age and the hemodynamic response to posture and exercise. *American Journal of Geriatric Cardiology* 1993;2:23-40.
13. Sheperd JT. Circulation to skeletal muscle. Handbook of Physiology, The Cardiovascular system, Peripheral circulation and Organ Blood Flow. Bethesda, MD: Am Physiol. Soc.; 1993.
14. Wieling W, Ten Harkel, A.D., Van Lieshout, J.J. Spectrum of Orthostatic disorders: classification based on an analysis of the short-term circulatory response upon standing. *Clin Sci* 1991(81):241-8.
15. Turner JR. Cardiovascular reactivity and stress: patterns of physiological response. New York; 1994.

16. Dinenno FAS, D.R., DeSouza, C.A., Tanaka, H. Age-related decreases in basal limb flow in humans: time course, determinants and habitual exercise effects. *J Physiol Mar* 2001;531(573-579).
17. Cox JP, Evans JF, Jamieson JL. Aerobic power and tonic heart rate responses to psychological stressors. *Personality and Social Psychology Bulletin* 1979;5:160-163.
18. Holmes DS, Roth DL. Association of aerobic fitness with pulse rate and subjective responses to psychological stress. *Psychophysiology* 1992;22:525-529.
19. DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthly men. *Circulation* 2000;102:1351-1357.
20. Brooks S, Faulkner J. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Americal Journal Physiology* 1990;258:C436-C442.
21. Barnett SR, Morin RJ, Kiely DK, Gagnon M, Azhar G, Knight EL, et al. Effects of age and gender on autonomic control of blood pressure dynamics. *Hypertension* 1999;33:1195-1200.
22. Stoney CM, Davis, M.C., Matthews, K.A. Sex differences in physiological responses to stress in coronary heart disease: a causal link? *Psychophysiology* 1987;24:127-131.
23. Kuller L, Lilienfeld A, Fisher R. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. *Circulation* 2000;34:1056-1068.
24. Lipsitz L. Orthostatic hypotension in the elderly. *N Engl J Med* 1989;321:952-957.
25. Brooks GA, Fahey, T.D., Timothy, P.W., Baldwin, K.M. Exercise Physiology: Human bioenergetics and its applications; 2000.
26. Dwyer JH. Genes, blood pressure, and African heritage. *The Lancet* 1995;8972:346-392.
27. Josephson RA, and S. Fannin. Physiology of the aging heart. Clinical cardiology of the elderly. Armonk, NY: Futura publishing Co; 1994.
28. Forman DE, Manning WJ, Hauser R. Enhanced left ventricular diastolic filling associated with long-term endurance training. *Journal of Gerontology* 1992;47:M56-M58.
29. Heath GW, Hagberg JM, Ali A, Ehsani A, Holloszy JO. A physiological comparison of young and older endurance athletes. *J. Appl. Physiol.* 1981;51:634-640.
30. Seals DR, Hagberg, J.M., Hurley, B.F. Endurance training in older men and women: Cardiovascular response to exercise. *J Appl Phys* 1984;57:1024-1029.
31. Avolio AP, Fa-Quan D, Wei-Qiang. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: Comparison between urban and rural communities in China. *Circulation* 1985;71:202-210.
32. Rodeheffer RJ, Gerstenblith, G., Becker, L.C. Exercise cardiac output is maintained with advancing age in healthy human subjects. *Circulation* 1984;69:203-213.
33. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension: The Framingham study. *Circulation* 1980;61:1179-1182.
34. Shannon R, Wei, J., Rosa, R. . T. The effect of age and sodium depletion on cardiovascular response to orthostasis. *Hypertension* 1986;8:438-443.

35. Sarno AJ, Pearson, M.A., Nabors-Oberg, R., Sollers, J.J., Thayer, J.Y. Autonomic changes during orthostasis: a time frequency analysis. *Biomed Sci Instrum* 2000;36:251-6.
36. Sneddon J. Cardiovascular autonomic function testing. In: Measurements in Cardiology. London: the Parthenon Publishing Group; 1999.
37. Gotshall RW, Tsai PF, Bassett Frey MA. Gender-based differences to the cardiovascular response to standing. *Aviation, Space, and Environmental Medicine* 1991;62:855-859.
38. Gerber LM, Halberstein RA. Blood pressure: Genetic and environmental influences. *Human Biology* 1999;71:467-473.
39. Girdler SS, Light KC. Hemodynamic stress responses in men and women examined as a function of female menstrual cycle phase. *International Journal of Psychophysiology* 1994;17:233-248.
40. Fagard R, Bielen E, Hespel P, Lijnen P, Staessen J, Vanhees L, et al. Physical exercise in hypertension. In: Laragh J, Brenner B, editors. Hypertension: pathophysiology, diagnosis, and management. New York: Raven Press, Ltd.; 1990. p. 1985-1998.
41. Gornick CC. Clinical cardiology in the elderly. Armonk, NY: Futura publishing; 1994.
42. James MA, Potter, J.F. Orthostatic blood pressure changes and arterial baroreflex sensitivity in elderly subjects. *Age and Ageing* 1999;28:522-530.
43. Smith JJ, Porth, C.M., Erickson, M. Hemodynamic response to the upright posture.
J Clin Pharmacol. May 1994;34(5):375-86.
44. Robbins AS, Rubenstein, L.Z. Postural hypotension in the elderly. *Journal of the American geriatric society* 1984;32:769-774.
45. Grossmann M. The peculiarities of the orthostasis reaction in advanced age. *ZFA* 1988(43):279-83.
46. Ooi WL, Barret, s., Hossain, M., Kelly-Gagnon, M., Lipstiz, L.A. Patterns of orthostatic blood pressure change and their clinical correlates in a frail, elderly population. *JAMA* 1997;277:1299-1304.
47. White NJ. Heart-Rate changes on standing in elderly patients with orthostatic hypotension. *Clin Sci* 1980;58:411-413.
48. Masaki. Orthostatic Hypotension predicts mortality in elderly men. *Circulation* 1998;98:2290-2295.
49. Sekiguchi K. Hemodynamic and hormonal correlates with exposure to lower body negative pressure after 12 hours head-down tilt. *Aviat. Space Environ. Med* 1993;64:599-605.
50. Vogt M, Cauley J, Newman A, Kuller L, Hulley S. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 1993;270:465-469.
51. Guyton AC. Textbook of Medical Physiology. Philadelphia: WB Saunders; 1991.
52. Yao J. Hemodynamic studies in peripheral arterial disease. *Br. J. Surg.* 1970;57:761-766.
53. Vogt M, Cauley J, Kuller L, Nevitt M. Functional status and mobility among elderly women with lower extremity arterial vascular disease: the study of osteoporotic fractures. *J. Am. Geriatr. Soc.* 1994;42:923-929.

54. Newman A, Sutton-Tyrrell K, Vogt M, Kuller L. Morbidity and morality in hypertensive adults with a low ankle/arm blood pressure index. *JAMA* 1993;270:487-489.
55. Eigenbrodt ML, Rose, K.M., Couper, D.J, Arnett, D.K., Smith, R., Jones, D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study. *Stroke* 2000(10):2307-13.
56. Hollander BJ, Seraganian P. Aerobic fitness and psychophysiological reactivity. *Canadian Journal Of Behavioral Science* 1984;16:257-261.
57. Watanabe M, Mano, K., Watanabe, H., Koike, Y. Effects of age and sex on orthostatic change in blood pressure in normal persons. *Rinsho Shinkeigaku* 1996;36:1175-8.
58. Hofsten A, Elmfeldt D, Svardsudd K. Age-related differences in blood pressure and heart rate responses to changes in body position. *Blood Pressure* 1999;8:220-226.
59. Zwiebel WJ. Introduction to vascular ultrasonography. Philadelphia: Saunders; 2000.
60. Smulyan H, Asmar, R.G., Rudnicki, A., London, G.M., Safar, M.E. Comparative effects of aging in men and women on the properties of the arterial tree. *J. Am. Coll. Cardiol.* 2001;37:1374-80.
61. Schmidt-Truckass A, Schmid, A., Brunner, C., Schererer, N., Zach, G., Keul, J., Huonker, M. Arterial properties of the carotid and femoral artery in endurance-trained and paraplegic subjects. *J. Appl. Physiol.* 2000;89:1956-1963.
62. Masuda Hb, H., Glagoiv, S., Zarins, C.K. Artery wall restructuring in response to increased flow. *Surg Forum* 1989;40:285-286.
63. Kojo M, Wada, M., Akiyoshi, K., Inutsuka, M., Izumi, T. . . , (), . Reduction of carotid artery blood flow in pediatric patients with syncope: evaluation with head-up tilt test. *Neuropediatrics* 2001;32(4):169-75.
64. Dinenno FA, Jones PP, Seals DR, Tanaka H. Limb flow and vascular conductance are reduced with age in healthy humans. *Circulation* 1999;100:164-170.
65. Jorfelt L, Wahren J. Leg blood flow during exercise in man. *Clin. Sci.* 1971;41:459-473.
66. Imadojemu VA, Lott ME, Gleeson K, Hogeman CS, Ray CA, Sinoway LI. Contribution of perfusion pressure to vascular resistance response during head-up tilt. *Am. J. Physiol. Heart Circ. Physiol.* 2001;281:H371-H375.
67. Morgan RH, Psaila, J.V., Stone, J., Carolan, G. Effect of postural change on common femoral artery blood flow, measured by duplex ultrasound, in normal subjects and patients with peripheral vascular disease. *J Biomed Eng May* 1991;13(3):244-8.
68. Volterrani M, Rosano, G., Coats, A., Beale, C, Collins, P. Estrogen acutely increases peripheral blood flow in post-menopausal women. *Am. J. Med.* 1995;99:119-122.
69. Williams JK, Adams, M.R., Herrington, D.M., Clarkson, T.B. Short-term administration of estrogen and vascular responses of atherosclerotic coronary arteries. *J. Am. Coll. Cardiol.* 1992;29:452-457.
70. Groedel T. Circulation. Washington, D. C.: American Physiological Society; 1908.
71. Braune S, Auer, A., Schulte-Monting, J., Schwerbrock, S., Lucking, C.H. Cardiovascular parameters: sensitivity to detect autonomic dysfunction and influence of age and sex in normal subjects. *Clin Auton Res* 1996;6(1):3-15.

72. Wieling W, and Shepherd, J.T. nitial and delayed circulatory responses to orthostatic stress in normal humans and in subjects with orthostatic intolerance. *nitial and delayed circulatory responses to orthostatic stress in normal humans and in subjects with orthostatic intoleranc* 1992;11:69-82.
73. Shoemaker JK, Hogeman, C.S., Khan, M., Kimmerly, D.S., Sinoway, L.I. Gender affects sympathetic and hemodynamic response to postural stress. *Am. J. Physiol. Heart Circ. Physiol.* 2001;281:H2028-H2035.
74. Sparrow Dt, C.P., Rossner, B., Weiss, S.T. postural changes in diastolic blood pressure and the risk of myocardial infarction. *Circulation* 1984;70:533-7.
75. Moore KI, Newton, K. Orthostatic heart rates and blood pressures in healthy young women and men. *Heart Lung* 1986;15:611-617.
76. Schondor R, Low, P.A. gender related differences in the cardiovascualr response to tilt in normal subjects. *Clin Auton Res* 1992;2:183-7.
77. Barney JA, Ebert TJ, Groban L, Farrell A, Hughes CV, Smith JJ. Carotid baroreflex responsiveness in high-fit and sedentary young men. *Journal of Applied Physiology* 1988;65:2190-2194.
78. MacDonald M, Tarnopolsky M, Green H, Hughson R. Comparison of femoral blood gases and muscle near-infrared spectroscopy at exercise onset in humans. *J. Appl. Physiol.* 1999;86:687-693.
79. Raven PB, Rohm-Young, D., Blomquist, C.G. Physical fitness an dcardiovascualr response to lower negative pressure. *J Appl Physiol* 1992;56:138-144.
80. Seals D, Hagberg J. The effect of exercise training on human hypertension: a review. *Med. Sci. Sports Exer.* 1984;16:207-215.
81. Frey MA, Tomaselli CM, Hoffler WG. Cardiovascular responses to postural changes. Differences with age for women and men. *Journal of Clinical Pharmacology* 1992;34:394-402.
82. Shoemaker JK, Hogeman CS, Silber DH, Gray K, Herr M, Sinoway LI. Head-down-tilt bed rest alters forearm vasodilator and vasoconstrictor responses. *Journal of Applied Physiology* 1998;84(5):1756-1762.
83. Abdel-Rahman AR, Merrill RH, Wooles WR. Gender-related differences in the baroreceptor reflex control of heart rate in normotensive humans. *Journal of Applied Physiology* 1994;77:606-613.
84. Williams JK, Adams, M.R., Klopfeinstein, H.S. Estrogen modulates responses of atherosclerotic coronary arteries. *Circulation* 1990;81:1680-1687.
85. Perret RS, Sloop, G.D. Increased peak blood velocity in association with elevated blood pressure. *Ultrasound Med Biol.* 2000;26(9):1387-91.