RACIAL DIFFERENCES IN CARDIOVASCULAR RESPONSES FOLLOWING AN ACUTE BOUT OF AEROBIC EXERCISE

BY

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DISSERTATION

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ABSTRACT

African-Americans (AA) are at greater risk than Caucasians (CA) for developing hypertension, cardiovascular disease, stroke and renal disease. An acute bout of moderate aerobic exercise causes a sustained reduction in blood pressure (BP), termed post-exercise hypotension (PEH) in CA. Histamine receptors 1 and 2 (H1R and H2R) have been shown to be responsible for post exercise vasodilation and associated PEH in Caucasians. It appears that AA women may not exhibit PEH following aerobic exercise. Hence, this study sought to determine the extent to which AA develop PEH, and the contribution of histamine receptors to PEH (or lack thereof) in this population. Forty-nine (9 AA men, 13 AA women, 14 CA men and 13 CA women) young and healthy subjects completed the study. Subjects were randomly assigned to take either a combined H1R and H2R antagonist (fexofenadine and ranitidine) or a control placebo followed by the other condition on the second visit between 3 pm to 8 pm. During study visits, subjects rested in the supine position for baseline BP, cardiac output, peripheral resistance and arterial stiffness measurements and 30 min, 60 min and 90 min after 45 min of treadmill exercise at 70% HRreserve. An acute bout of aerobic exercise increases DBP in young AA but not in CA. The underlying mechanism for the BP increases may be related to increases in brachial artery stiffness and sympathetic activation and but not to changes in cardiac output. Moreover, DBP is also elevated in AA after exercise with histamine receptor blockade.
Additionally, H1R and H2R blockade elicited differential responses in cardiac function and carotid artery between AA and CA following exercise, suggesting a potential role of histamine receptors in mediating post exercise BP in AA. Our study also indicates that central BP may better reflect the level of vascular burden in young AA than Brachial BP. The heightened BP and vascular responses to exercise stimulus may play a role in the pathogenesis of hypertension in AA.
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CHAPTER 1

INTRODUCTION

African-Americans are at greater risk than Caucasians for developing hypertension, cardiovascular disease, stroke and renal disease (Vita 2003). Even young, apparently healthy African-Americans, who exhibit comparable brachial blood pressure (BP) to their Caucasian peers, have higher central but similar peripheral BP and greater macro and microvascular dysfunction (Heffernan, Jae et al. 2008). This underscores the critical need for decreasing racial disparities in, and preventing the development of hypertension and hypertension related end-organ damage.

An acute bout of moderate aerobic exercise causes a sustained reduction in BP, termed post-exercise hypotension (PEH). PEH is usually due to a reduction in peripheral vascular resistance that is not completely offset by a rise in cardiac output (Halliwill 2001). Histamine receptors 1 and 2 (H1R and H2R) have been shown to be responsible for post exercise vasodilation and associated PEH in humans (McCord and Halliwill 2006).

The prolonged hypotensive effect of regular exercise training may be due to repeated instances of PEH (Liu, Goodman et al. 2012, Hecksteden, Grutters et al. 2013). PEH has been widely observed in both normotensive (Rossow, Yan et al. 2010) and hypertensive (Rueckert,
Slane et al. 1996) Caucasian men and women, with greater and more prolonged responses in hypertensives (Floras, Sinkey et al. 1989, Kenney and Seals 1993, Lizardo, Silveira et al. 2008). Thus, understanding the causes of PEH can serve as a model for understanding the effect of exercise and physical activity on blood pressure. Little information is available on PEH in African-Americans, but some evidence suggests PEH may be absent in this population (Pescatello, Bairos et al. 2003, Enweze, Oke et al. 2007) consistent with their higher risk for hypertension. However, the lack of PEH in those studies may have been a function of diurnal variation (Jones, George et al. 2008, Jones, Taylor et al. 2009), or lack of an adequate exercise stimulus.

The long term goal of this research is to determine the effect of exercise and physical activity on blood pressure as part of lifestyle prevention efforts to reduce racial disparities in hypertension and end-organ damage. The objective of this project is to determine the extent to which African-Americans develop PEH, and which mechanisms contribute to PEH (or lack thereof) in this population. The central hypothesis is that PEH is absent in African-Americans, but present in Caucasians, and that the lack of PEH in African-Americans is accounted for by reduced peripheral vasodilation. It is also possible that PEH in African-Americans, but not Caucasians, may manifest differentially depending on the site of BP measurement (aortic or brachial).
The primary aims of the present investigation are as follows:

**Aim 1:** To determine the extent that reductions in brachial and central BP differ between African-Americans and Caucasians.

We hypothesize that African-Americans will not exhibit post exercise hypotension in either brachial or central BP, while Caucasians will show a similar reduction in brachial and central BP after an acute bout of aerobic exercise.

**Aim 2:** To determine the extent of changes in peripheral vascular resistance and arterial stiffness following acute exercise, and the extent to which these changes differ between African-Americans and Caucasians. We hypothesize that African-Americans will show greater vascular resistance post exercise, coupled with greater arterial stiffness, but there will be no differences between races in cardiac output.

**Aim 3:** To determine the extent to which H1R and (H2R contribute to PEH in young African-Americans and the extent of differential changes in African-Americans and Caucasians. We hypothesize that H1R and H2R antagonists will blunt PEH in Caucasians while H1R and H2R antagonists will have no effect on BP in African-Americans.

**Significance**

It is well established that hypertension and hypertension related end-organ damage is much greater in African-Americans than in Caucasians (Vita 2003, Fields, Burt et al. 2004). The
disease burden of hypertension increases with age, although the disease process starts in childhood, and increased blood pressure and end-organ alterations are observed at a young age in African-Americans (Ferreira, Viana et al. 1999, Vita 2003, Din-Dzietham, Couper et al. 2004, Fields, Burt et al. 2004). Thus, there has been increased attention focused on early intervention and prevention, mostly through lifestyle interventions (Dennison, Post et al. 2007, Heffernan, Fahs et al. 2009), before end-organ damage occurs. The immediate and sustained BP-lowering effect of a single session of dynamic exercise holds promise in the prevention and treatment of hypertension (Kenney and Seals 1993, Thompson, Crouse et al. 2001). However, evidence shows that PEH may be absent in African-Americans (Pescatello, Bairos et al. 2003, Enweze, Oke et al. 2007). The contribution of this project is expected to be a detailed understanding of both the peripheral and central blood pressure response to acute exercise in African-Americans, including identifying the mechanisms responsible for these changes (or lack thereof). This contribution is significant because it is an important step in the process of understanding how exercise and physical activity affects blood pressure, and the potential mechanisms of those effects, in African-Americans. Such understanding will significantly advance the field and eventually lead to improved therapeutic approaches, including exercise and physical activity, that will prevent or minimize the deleterious effect of hypertension and end-organ damage. Recognizing that exercise and physical activity are important contributors to decreased morbidity
and mortality in the general population (Cornelissen and Fagard 2005, Kokkinos and Myers 2010), this study will increase our understanding of how exercise affects blood pressure in African-Americans. This may contribute to reducing the well documented health disparities between African-Americans and Caucasians.

**Innovation**

Studies of PEH in African-Americans to date have been limited by the research design employed. Most studies (Pescatello, Bairos et al. 2003, Enweze, Oke et al. 2007) have utilized relatively short exercise duration, thus limiting the possibility of observing PEH. Also, these studies have not tightly controlled for diurnal variation. This is important because it has now been shown that PEH is less likely to occur in the morning, but it is almost always present in the late afternoon in Caucasian population (Jones, George et al. 2008, Jones, Taylor et al. 2009). Thus, previous studies have been hampered by designs that do not clearly indicate if differences between African-Americans and Caucasians were due to actual physiologic differences or due to the design. Furthermore, little information is available on potential mechanistic differences regarding PEH between African-Americans and Caucasians. Thus, this study is innovative because the design will move the field beyond its current status, and address what mechanisms may account for the racial differences in PEH. Also, since BP differences between African-Americans depends on measurement site (Heffernan, Jae et al. 2007, Heffernan, Jae et al.
2008), this proposed project is innovative because we will evaluate PEH through both peripheral and central BP.
CHAPTER 2

LITERATURE REVIEW

2.1 Post Exercise Hypotension (PEH) in Caucasians

PEH was first documented by L Hill in 1897 as arterial pressure in men fell below normal resting pressures following a 400 yard dash (Hill 1897). However, it was not until the past few decades that substantial research was generated to examine the clinical implications and physiologic mechanisms behind this phenomenon (Halliwill, Dineno et al. 2003, Lockwood, Pricher et al. 2005, Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, Rossow, Yan et al. 2010).

PEH is defined as the decrease in blood pressure (BP) from baseline during recovery after exercise (Kenney and Seals 1993). PEH has been widely observed in both normotensive (Rossow, Yan et al. 2010) and hypertensive (Rueckert, Slane et al. 1996) Caucasian men and women, with greater and more prolonged responses in hypertensives (Floras, Sinkey et al. 1989, Kenney and Seals 1993, Lizardo, Silveira et al. 2008). Post stimulatory hypotension (PSH) refers to the same phenomenon when it is elicited by simulating exercise through electric stimulation of muscles in certain animal models. PEH/PSH has also been documented in normotensive (Yao,
Andersson et al. 1982) and spontaneously hypertensive rats (Overton, Joyner et al. 1988).

Limited data suggested that the degree of PSH may be related to the genetic predisposition of the animal to hypertension because PSH occurs in Dahl salt-sensitive rats but not in Dahl salt-resistant rats (Kenney, Morgan et al. 1991), suggesting there may be a genetic component to, or that salt sensitivity may impact PEH.

PEH has been noted after a variety of aerobic exercises including walking (Wilcox, Bennett et al. 1982, Wallace, Bogle et al. 1999), running (Floras, Sinkey et al. 1989, Hara and Floras 1992), cycling (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, Rossow, Yan et al. 2010), and arm ergometry (MacDonald, MacDougall et al. 2000). An acute bout of aerobic exercise between 40 and 70% of peak oxygen consumption (VO2peak) produces post-exercise hypotension (Kenney and Seals 1993, Pescatello and Kulikowich 2001). Longer bouts (45 min or more) of aerobic exercise consistently produce PEH (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, McCord and Halliwill 2006, Rossow, Yan et al. 2010), whereas shorter bouts may produce PEH, but less consistently in normotensive populations (Pescatello, Fargo et al. 1991, Cleroux, Kouame et al. 1992).

PEH has been found to persist for several hours after an exercise bout (Brandao Rondon, Alves et al. 2002). The prolonged hypotensive effect of regular exercise training may be due to repeated instances of PEH (Liu, Goodman et al. 2012, Hecksteden, Grutters et al. 2013), thus the
blood pressure response to acute exercise may provide important clinical and physiologic information. PEH is usually due to a reduction in peripheral vascular resistance that is not completely offset by a rise in cardiac output (Halliwill 2001). There is no significant sex difference in PEH following steady-state cycling, however, the mechanisms contributing to PEH differ between well-trained, but not untrained, men and women (McCord and Halliwill 2006, Rossow, Yan et al. 2010).

2.2 Hemodynamic Changes after Exercise

2.2.1 Vascular Conductance

Following aerobic exercise involving large muscle groups, there is an elevated systemic vascular conductance associated with vasodilatation in the vascular beds of previously active skeletal muscles and limited contribution from skin, splanchnic or renal circulations (Pricher, Holowatz et al. 2004, Wilkins, Minson et al. 2004, Endo, Shimada et al. 2012). However, vasodilatation is not limited to the exercising limbs. Following an acute bout of upright cycling exercise, the contribution of vascular conductance in the active limbs (legs) and non-active limbs (arms), kidneys and viscera to the total increase in vascular conductance were approximately 33 to 39%, 20 to 26%, 2 to 5% and 2 to 8%, respectively (Endo, Shimada et al. 2012). It was suggested that vasodilatation observed in non-exercised regions may be induced by an increase in cutaneous circulation. However, in this study the vascular conductance of the skin in the
fingertip was unchanged after exercise. In addition, Wilkins et al. failed to parallel the reduction in arterial pressure and changes in cutaneous vascular conductance in the chest, forearm, thigh and leg after upright cycling exercise (Wilkins, Minson et al. 2004). Thus, changes in cutaneous circulation do not appear to exert a major influence on PEH.

Sympathetic withdrawal and peripheral vasodilation (e.g. histamine-receptor mediated) are suggested to be the neural and peripheral component of the PEH, respectively (Halliwill 2001). Muscle sympathetic nerve activity was reduced post exercise with concurrent decrease in BP suggesting PEH is partly mediated by inhibition of sympathetic nerve activity to muscle vessels (Floras, Sinkey et al. 1989). Increases in systemic vascular conductance after exercise can also be diminished by blocking histamine receptors (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, McCord and Halliwill 2006). When single leg exercise was performed, histamine receptor-mediated vasodilation was restricted to the previously exercised limb (Barrett-O'Keefe, Kaplon et al. 2013). Therefore, sympathetic withdrawal was speculated to be the cause of increased vascular conductance in non-active regions (Barrett-O'Keefe, Kaplon et al. 2013).

2.2.2 Cardiac Function

During recovery from moderate intensity aerobic exercise, HR usually stays elevated for 15 to 30 min after the cessation of exercise and gradually returns to baseline values in the general
population (MacDonald, MacDougall et al. 1999, McCord and Halliwill 2006, Rossow, Yan et al. 2010, Endo, Shimada et al. 2012) (exceptions will be discussed later). This increase in HR then contributes to the increase in cardiac output following exercise.

Prolonged strenuous aerobic exercise (e.g. Marathon running) induced systolic and diastolic dysfunction has been well documented and termed as cardiac fatigue (Shave, George et al. 2008, Fernhall, Fahs et al. 2012). However, recent evidence suggests that the decreased contractility measurements observed following prolonged aerobic exercise may be load-dependent and measurements that are less load-dependent contradict traditional views (Shave, George et al. 2008, Shave, George et al. 2009, Fernhall, Fahs et al. 2012). The varied response reflects the complexities of cardiac function and calls for a multimodal approach when assessing cardiac function following exercise. Unfortunately, very few studies reported detailed cardiac function measurements following a shorter bout (e.g. 1 hour) of moderate intensity aerobic exercise due to different methodology employed. Cardiac measurements in most studies assessing hemodynamic changes following moderate intensity exercise were estimated from either inert gas rebreathing method (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, McCord and Halliwill 2006) or impedance cardiography (Lacombe, Goodman et al. 2011) instead of echocardiography, therefore only SV was reported. SV is usually well maintained (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006) and is dependent on left
ventricular preload, afterload and cardiac contractility. Using echocardiographic measurements, our lab has shown decreased LV contractility after 1 hour of moderate cycling exercise; this effect is similar to that of prolonged exercise although the magnitude was much smaller in our case (Rifai, Douglas et al. 1999, Rossow, Yan et al. 2010).

Left ventricular preload has been shown to decrease after exercise as central venous pressure is reduced (Halliwill, Minson et al. 2000). However, our lab did not observe any evidence of decreased left ventricular preload in endurance-trained individuals because neither LV end diastolic volume nor diastolic tissue velocities changed significantly after exercise (Rossow, Yan et al. 2010). The maintained SV is likely due to decreased afterload because of deceased post exercise blood pressure.

2.2.3 Arterial Stiffness

Following an acute bout of maximal lower limb aerobic exercise, the recovery patterns of arterial stiffness in the upper and lower limbs were different (Naka, Tweddel et al. 2003, Ranadive, Fahs et al. 2012). Upper limb arterial stiffness (measured by PWV) was higher compared to baseline immediately post exercise (~3 min), and then decreased and remained below baseline by 60 min post exercise. In the lower (exercising) limb, arterial stiffness exhibited an early decrease after exercise and reached nadir at 10 min, and then gradually increased back to baseline by 60 min (Naka, Tweddel et al. 2003). Data from our lab also
showed differential changes in arterial stiffness following maximal lower limb exercise (Ranadive, Fahs et al. 2012). We found decreased lower limb arterial stiffness and maintained upper limb arterial stiffness. We also compared the arterial stiffness following an acute bout of maximal lower limb exercise verses upper limb exercise. Our results show that upper limb arterial stiffness decreased approximately 13% following arm exercise, while leg exercise had no significant effect on upper limb arterial stiffness. Conversely, lower limb arterial stiffness decreased (10.4%) and (13.2%) at 10 min of recovery following both maximal upper and lower limb cycling, respectively. This supports the possibility of discriminating between local and systemic consequences of exercise. A recent study conducted by New et al. also supported this notion (New, Reilly et al. 2013) as arterial stiffness in upper limb and lower limb changed differently following 30 min of cycling exercise. PWV in the upper limb was significantly decreased during 120 min recovery but not in the lower limb. The decrease in PWV in the upper limb was independent of the decrease in MAP. The discrepancy between changes in PWV in the upper limb and lower limb may be due to methodology. Previous research has shown that upper limb vascular bed is more responsive than lower limb vascular bed after exercise and pharmacological provocation with this methodology (Naka, Tweddel et al. 2006).
2.2.4 Wave Reflection

The early part of the central arterial pressure wave is generated by the left ventricular ejection wave. This forward-traveling pressure wave is dependent on ascending aortic stiffness and is not influenced by wave reflections. The augmented pressure is generated by the reflected wave from the lower body arriving during systole and adding to the forward-traveling pressure wave (Westerhof, Sipkema et al. 1972). This augmentation of the measured pressure wave can be estimated as an augmentation index (AIx). AIx is defined as the difference between the second and first peaks corresponding to systolic blood pressure (SBP) and expressed as a percentage of the PP. AIx is dependent on the elastic effects of the entire arterial tree, the velocity of the forward and reflected waves, and distance to the major reflecting site (Nichols, Denardo et al. 2008). Aging and hypertension associated progressive degeneration dilation of the aorta and increased stiffening causes an early return of pressure waves (Boutouyrie, Bussy et al. 1999, Mitchell, Parise et al. 2004).

Mixed results of changes in AIx during exercise recovery have been reported. Submaximal exercise at a heart rate of 100 bpm has been shown to decrease AIx in young individuals during exercise (Ahlund, Pettersson et al. 2008), while no significant reduction of AIx was observed after 30 min of aerobic exercise in older individuals (Tabara, Yuasa et al. 2007). Our lab also reported a significant sex effect for the change in AIx showing young women
exhibited a greater change than men after an acute bout of maximal aerobic exercise (Yan, Ranadive et al. 2013). Changes in AIX may not be necessarily associated with changes in central arterial stiffness because vasoactive drugs can change aortic AIX independently from changes in cPWV in healthy men (Kelly, Millasseau et al. 2001). Resting central arterial stiffness and AIX in men and women were also disassociated (Yan, Ranadive et al. 2013).

The disassociation between arterial stiffness and wave reflection is likely a factor of wave reflections altering the ventricular-vascular coupling not only through increased arterial stiffness and changed timing, but also through modifications in their amplitude. The majority of wave reflection as seen by the heart is attributable to the branching of the aorta at the celiac trunk, renal arteries and its terminal tapering (Mills, Gabe et al. 1970). Recent evidence suggests the traditional model may be over-simplified and that backward waves are likely compound waves consisting of echoes from many reflection sites (Westerhof and Westerhof 2012, Westerhof and Westerhof 2013). In an elastic aorta, the augmentation index is more likely to be related to the intensity of the reflected wave rather than to its velocity. This theory also suggests a disassociation between BP and wave reflection (Levenson, Pithois-Merli et al. 1990). Evidence from antihypertensive drugs supported this notion. Both fosinopril and atenolol produced similar reductions in ambulatory BP while fosinopril had greater beneficial effect on AIX compared to atenolol (Chen, Ting et al. 1995). This new theory challenges the traditional view on the
association between increased wave reflection and incidence of cardiovascular diseases (Weber, Auer et al. 2004). However, it is not known if the disassociations between AIx, BP and arterial stiffness would apply to exercise-induced hemodynamic changes.

2.3 Factors Affecting PEH

2.3.1 Exercise Intensity

Several studies were undertaken to examine the “dose-response” relationship between exercise intensity and PEH. Pescatello et al. (Pescatello, Fargo et al. 1991) examined the influence of one bout of light (40% of VO2max) and moderate (70%) cycle ergometry exercise for 30 min on PEH in hypertensive and normotensive subjects. No PEH was observed in the normotensive group while post exercise diastolic blood pressure and mean arterial pressure were lower by 7-8 mmHg for 12.7 hours in the hypertensive group, independent of exercise intensity. These results were supported by another study from the same lab, where the researchers examined the influence of one bout of light (40% of VO2max) and of moderate (60%) endurance exercise for 40 min on PEH in 49 middle-aged hypertensive men (Pescatello, Guidry et al. 2004). During a 45-min recovery period in the seated position and subsequent 9 h of ambulatory blood pressure monitoring, light exercise was comparable to moderate exercise in eliciting PEH in this population. Forjaz et al. also reported that varying exercise intensity from 30 to 80% of VO2peak
in young normotensive humans did not influence the magnitude of post exercise hypotension (Forjaz, Matsudaira et al. 1998).

By contrast, a bout of concurrent endurance and resistance exercise at moderate intensity resulted in a longer PEH for both systolic and diastolic blood pressure compared to light intensity in prehypertensive women (Takeshima, Rogers et al. 2004). Quinn et al. (Quinn 2000) also documented that exercise at 75% of VO2max appears to offer a more sustained and substantial reduction in both systolic blood pressure and diastolic blood pressure compared to a work bout at 50% of VO2max in 16 men and women with stage 1–2 hypertension from ambulatory blood pressure monitoring. Jones et al. suggested that post exercise reduction in BP was clinically similar 20 min following high intensity short duration exercise and moderate intensity longer duration exercise that were matched for total work done (Jones, George et al. 2007). It seems that the short term (20 min) post exercise reduction in arterial pressure is dependent on the exercise intensity and the associated total work. However, when BP was monitored for longer durations after exercise (~12h), the difference in the decrease in BP among different exercise intensities is less evident. Overall, we still lack a comprehensive relationship for exercise and PEH.
2.3.2 Recovery Posture

Reduction in BP during recovery from exercise has been studied using either a seated (Pescatello, Fargo et al. 1991, Forjaz, Matsudaira et al. 1998, Jones, Pritchard et al. 2008) or supine position (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006). Similar to data from the supine position recovery from aerobic exercise, reductions in total peripheral resistance and a small elevation in cardiac output were observed during seated recovery (Jones, Pritchard et al. 2008). The influence of recovery posture on PEH in normotensive men has also been examined (Raine, Cable et al. 2001, Senitko, Charkoudian et al. 2002). Changes in Heart rate and BP were not different between supine position and immediate measured after 5 min of 70° head-up tilt following an acute bout of aerobic exercise (Senitko, Charkoudian et al. 2002).

Similar reductions in MAP and changes in gross hemodynamic profile involving a reduction in total peripheral resistance and elevation in cardiac output were also observed during seated and supine recovery conditions following an acute bout of maximal aerobic exercise. However, in the seated recovery position, subjects had compromised venous return and stroke volume (Raine, Cable et al. 2001). Vascular resistance in the calf skin and total forearm was also markedly greater in the seated position compared to the supine position. These differences are likely to result from the prolonged gravitational stress from seated position compared to supine position.
However, these changes were offset by higher HR during recovery in the seated position, making the reduction in MAP under these two conditions similar.

2.3.3 Diurnal Variation

In most normotensive individuals, resting blood pressure is characterized by a nocturnal dip of 10-20% of the daytime level and a morning surge (Millar-Craig, Bishop et al. 1978). Jones et al. (Jones, Atkinson et al. 2006) compared BP reactivity to everyday physical activities and found the highest reactivity between 08:00 and 10:00 with a secondary rise in reactivity between 16:00 and 18:00. The same research group also examined the BP response to a controlled bout of exercise at different times of the day (Jones, George et al. 2008). Attenuated hypotensive effect was observed after morning aerobic exercise compared to afternoon exercise (Jones, Taylor et al. 2009). PEH was absent or even reversed when exercise was performed between 04:00 and 08:00, evidenced by increased rather than decreased diastolic BP and MAP during recovery from morning exercise. PEH was greatest in the afternoon coupled with lower total peripheral resistance (Jones, Pritchard et al. 2008).

2.4 Postulated Mechanisms Contributing to PEH

2.4.1 Baroreflex Resetting

Systolic blood pressure is tightly coupled to exercise intensity during aerobic exercise. Following exercise, blood pressure declines significantly and arterial baroreflex resetting to a
lower operation point is suggested to be responsible for this process (Hara and Floras 1992, Halliwill, Taylor et al. 1996). Muscle sympathetic nerve activity was decreased after exercise despite a drop in mean arterial pressure in hypertensive men (Floras, Sinkey et al. 1989). It suggests that PEH may be mediated in part by inhibition of sympathetic nerve activity to muscle vessels as a result of baroreflex resetting. In addition, Halliwill et al. (Halliwill, Taylor et al. 1996) found that for a given diastolic pressure, there is less muscle sympathetic nerve activity after exercise compared to sham protocol (no exercise) in normotensives.

2.4.2 Central Nervous System Mechanisms

Based on a series of experiments in animal models, Chen et al. (Chen, Munch et al. 2002, Chen, Bechtold et al. 2009) provided compelling evidence for the role of the central nervous system in mediating PEH. During exercise, muscle afferent fibers stimulate the release of substance P to activate a specific group of GABA (gamma-aminobutyric acid) interneurons in the NTS (nucleus tractus solitarii) to reset the baroreflex to a higher blood pressure (exercise pressor response). Binding of substance P to the neurokinin-1 receptor further triggers the receptor to undergo internalization, resulting in reduced inhibitory input to the second-order baroreceptive neurons in the NTS after exercise resulting in lower sympathetic activity, and hence lower blood pressure (Chen, Bechtold et al. 2009, Chen and Bonham 2010).
In addition, the hypotensive response to mild dynamic exercise was significantly attenuated with a blockade of cardiac afferents (Collins and DiCarlo 1993) and central arginine vasopressin within the central nervous system (Collins, Rodenbaugh et al. 2001), suggesting the role of cardiac afferents in mediating PEH. Cardiac receptors have an opiate synapse in the reflex pathway to sympathetic vasoconstrictors and the most likely location of the opiate synapse is in the NTS, which receives input from cardiac afferents (Burke and Dorward 1988). The prevention of PEH by blocking cardiac afferents (presumably to NTS) may occur because of blockade of central opioid receptors, which consequently abolishes the withdrawal of sympathetic vasoconstrictor tone after exercise (Hara and Floras 1992, Monnin 1992). Arginine vasopressin may contribute to PEH through the arginine vasopressin receptor-induced facilitation of cardiopulmonary reflexes (Applegate, Hasser et al. 1987) and/or resetting of the operating point of the arterial baroreflex (Hasser, Bishop et al. 1997).

2.4.3 Cardiac Output

PEH is usually due to a reduction in peripheral vascular resistance that is not completely offset by a rise in cardiac output (Halliwill 2001) with the exception of one report in older hypertensive patients (Hagberg, Montain et al. 1987) and in endurance-trained men (Senitko, Charkoudian et al. 2002, Rossow, Yan et al. 2010). In older hypertensive patients, a reduction in cardiac output was primarily mediated by a decrease in stroke volume resulting from reduced
myocardial contractility because neither reductions in cardiac preload nor increases in cardiac afterload could be accounted for (Hagberg, Montain et al. 1987).

Mechanisms mediating PEH in endurance-trained men are different from endurance-trained women and non-trained individuals in that endurance-trained men do not exhibit the post exercise augmentation of systemic vascular conductance (Senitko, Charkoudian et al. 2002, Rossow, Yan et al. 2010). Their stroke volume was reported to be either maintained (Rossow, Yan et al. 2010) or decreased (McCord and Halliwill 2006) during the post exercise period. The different response of SV in endurance-trained men may be explained by reduced central venous pressure and resulted fall in cardiac preload. Although central venous pressure was not directly measured in endurance-trained men, it may be affected by systemic vascular conductance. The unchanged systemic vascular conductance in the endurance-trained men may compromise venous return after exercise. The resistance specifically comes from areas other than skeletal muscle because post exercise hyperemia still exists (Senitko, Charkoudian et al. 2002). SV may also be influenced by higher absolute workload in endurance-trained men. Although relative work is set at the same level, exercise capacity is highest in endurance-trained men compared to sedentary population and endurance-trained women. Absolute exercise workload is inversely associated with the change in SV after exercise (Senitko, Charkoudian et al. 2002). However, the mechanism behind this association remains unknown.
2.4.4 Peripheral Mechanisms

The contribution of various local vasodilator substances has been examined. Neither epinephrine (Wilcox, Bennett et al. 1987) nor potassium (Medbo and Sejersted 1990) were responsible for PEH. Alpha-adrenergic hyporesponsiveness does not contribute to PEH in humans as neither alpha-1 nor alpha-2 adrenergic receptor responsiveness was changed after exercise (Halliwill, Dinenno et al. 2003). Inhibition of nitric oxide synthase does not reduce PEH in humans (Halliwill, Minson et al. 2000). Prostaglandins do not seem to independently mediate PEH in humans either (Lockwood, Pricher et al. 2005). Histamine receptors have been shown to be responsible for post exercise vasodilation and associated PEH in humans, as a histamine 1 receptor (H1R) antagonist (fexofenadine) attenuates the early stages of PEH (30 min after aerobic exercise) (Lockwood, Wilkins et al. 2005) and a histamine 2 receptor (H2R) antagonist (ranitidine) attenuates the later stages of PEH (~60-90 min) (McCord, Beasley et al. 2006); the combined administration of H1R and H2R antagonists blunted both the early and later stages of PEH (McCord and Halliwill 2006).

2.4.5 Histamine and Histamine Receptors

Histamine is a known mediator of several biological reactions through differential expression of four types of histamine receptors (H1R, H2R, H3R and H4R). Histamine is released by mast cells and basophils through various immunological or non-immunological
stimuli. Non-immunological stimuli includes neuropeptides, cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases, hypoxia, chemical and physical factors (extreme temperatures and traumas), or alcohol (Maintz and Novak 2007). Histamine causes smooth muscle cell contraction, vasodilatation, increased vascular permeability and mucus secretion, tachycardia, alterations of blood pressure, and arrhythmias. The variable influences of histamine on specific vascular beds of vasoconstriction, vasodilation, or a combination of both, depend on the dose, route of administration, and animal species (Levi, Rubin et al. 1991).

H1R is also responsible for changes in vascular permeability as a result of cytoplasmic changes suggestive of contraction in endothelial cell (Majno, Shea et al. 1969); in synthesis of prostaglandin (McIntyre, Zimmerman et al. 1985); in platelet-activating factor synthesis (McIntyre, Zimmerman et al. 1985); and in nitric oxide release (Van de Voorde and Leusen 1983).

The activation of H2R regulates various functions of histamine including heart contraction, gastric acid secretion, cell proliferation, differentiation and immune response. H2R antagonists have provided evidence for a physiological role of histamine in gastric acid secretion (Black, Leff et al. 1985). In cardiac tissues of most animal species, high concentrations of histamine are present which can mediate positive chronotropic and inotropic impacts on atrial or ventricular tissues by H2R stimulation (Hescheler, Tang et al. 1987). Also H2R-mediated smooth muscle
relaxation has been documented in vascular smooth muscle and in airways (Foreman, Rising et al. 1985, Ottosson, Jansen et al. 1989).

While H3R is mainly localized in the CNS, H4R is primarily expressed in hematopoietic cells, indicating their function in neurotransmission and immunomodulation, respectively. The H3R is a recognized drug target for neuronal diseases, such as cognitive impairment, schizophrenia, sleep/wake disorders, epilepsy and neuropathic pain; a small number of selective H3R antagonists have passed clinical Phase II trials. Preclinical data strongly suggest its potential therapeutic exploitation in allergy, inflammation, autoimmune disorders and possibly cancer (Tiligada, Zampeli et al. 2009).

During allergic reactions to substances such as pollen, H1R on smooth muscle in the lung are stimulated and cause smooth muscle contraction (Khardori 2011). H1R antagonists (commonly referred to as antihistamines) are widely used in the treatment of allergies (Runge, Martinez et al. 1992). H2R antagonists are used to treat gastrointestinal disorders (Curwain and Turner 1981). H2R antagonists inhibit acid production by reversibly competing with histamine for binding to H2R present on parietal cells (Khardori 2011).

Second generation histamine antagonists do not appear to cross into the central nervous system or possess sedative actions (Khardori 2011). Histamine levels were not elevated after exercise compared to baseline levels (Lockwood, Wilkins et al. 2005, McCord, Beasley et al.)
Blockade of either H1R or H2R, or combined blockade of both H1R and H2R do not alter histamine release nor histamine concentration in plasma or in whole blood (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, McCord and Halliwill 2006). It is very intriguing that blocking histamine receptors abolishes PEH and PEH associated post exercise hyperemia without significant histamine spillover in circulatory histamine. In addition, histamine concentration in non-exercised muscle was unchanged (McCord 2007). It is possible that histamine was only released and metabolized locally in the exercising muscles. However, it is very difficult to determine histamine concentration in working muscles as it is metabolized quickly. Another potential explanation is that sensitivity of the histamine receptors is unregulated after exercise.

Oral ingestion of a H1R antagonist (540 mg of fexodenadine) or H2R antagonist (300 mg of ranitidine) does not cause non-specific cardiovascular effects in the absence of exercise stimulus. When these drugs were given under normal resting conditions, cardiac output, heart rate, blood pressure, leg blood flow and skin blood flow did not change (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006). However, PEH was blunted with histamine receptor blockade. The blunted PEH with histamine receptor blockade is associated with attenuated peripheral post exercise hyperemia and modestly attenuated systemic vascular conductance (McCord and Halliwill 2006). Histamine receptor associated post exercise vasodilatation is
restricted to the previously exercise muscle beds (Barrett-O'Keefe, Kaplon et al. 2013). On the other hand, histamine receptor blockade does not have any effect on heart rate, stroke volume, or cardiac output during recovery from exercise (McCord, Beasley et al. 2006).

Histamine 3 receptors (H3R) may cause vasodilation by inhibiting norepinephrine release (Molderings, Weissenborn et al. 1992) and H3R have been suggested to be located throughout tissues on presynaptic nerve terminals. It is speculated that H3R activation after exercise may cause impaired sympathetic outflow (Halliwill, Dinenno et al. 2003). Sympathetic vasoconstrictor outflow is impaired post-exercise independently of changes in alpha-adrenergic receptor responsiveness (Halliwill, Dinenno et al. 2003).

Because there is no H3R or H4R antagonist for use in human subjects, we can only speculate about the role of H3R. Based on the data from the combined administration of H1R and H2R antagonist study (McCord and Halliwill 2006), 80% of post exercise hyperemia response in active muscles was mediated by H1R and H2R with a smaller impact in non-exercised muscles. Even if H3R or H4R contributes to PEH, the contribution would be limited.

2.5 Higher Risk for Cardiovascular Disease in African-Americans

African Americans have a much higher prevalence of hypertension, cardiovascular disease and renal disease compared to their Caucasian counterparts (Lackland and Keil 1996,
Flack, Ferdinand et al. 2003, Vita 2003). Compared with Caucasians in the U.S., hypertension in African-Americans is characterized by higher incidence, earlier onset, longer duration, higher prevalence, and higher rates of hypertension-related mortality and morbidity (Flack 1995).

Hypertension is associated with arterial stiffness and vascular dysfunction (Arnett, Boland et al. 2000). Considering that both arterial stiffness and vascular dysfunction are independently associated with cardiovascular events (Laurent, Katsahian et al. 2003, Weber, Auer et al. 2004), and large artery stiffness is also associated with microvascular disease (Vita 2003), it is likely that these factors contribute to the higher risk of cardiovascular events in African-Americans.

2.6 Decreased Arterial Function Manifested in Young African-Americans

The greater risk of cardiovascular disease is evident even in young African Americans. Normotensive African Americans, as young as 21 years of age, have reduced arterial compliance (Zion, Bond et al. 2003). Din-Dzietham et al. documented stiffer carotid arteries in African Americans than their Caucasian counterparts, assessed with beta-stiffness from carotid ultrasonography (Din-Dzietham, Couper et al. 2004). Our lab has recently documented that 22 year old African American males exhibited higher aortic PWV compared to age and fitness matched Caucasians (Heffernan, Jae et al. 2007) indicating higher aortic stiffness in young African Americans. We also found that African Americans have higher central BP despite
similar brachial BP to their Caucasian counterparts (Heffernan, Jae et al. 2007). This is important because central BP is more prognostic than conventional brachial BP as central pressure more aptly reflects the load encountered by the heart (i.e., ventricular-vascular coupling) (McEniery, Yasmin et al. 2008). Thus brachial BP may neglect important information on the cardiovascular burden and response to therapy in African-American men. Vasodilatory capacity of resistance arteries is also reduced in young (22 and 29 yrs) African Americans, suggesting early onset of microvascular dysfunction as well (Bassett, Duey et al. 1992, Heffernan, Jae et al. 2008). Young African-Americans also have greater peripheral arterial resistance compared to their Caucasian peers (Walker, Bassett et al. 1992). All of these maladaptations in African-Americans are directly related to increased risk of hypertension and end-organ dysfunction (Chaturvedi, Bulpitt et al. 2004).

Mechanisms underlying the observed racial differences in vascular function may involve both endothelial-dependent and endothelial-independent vasodilatation, as forearm blood flow is significantly attenuated in young AA compared to CA men following various pharmacological infusions including isoproterenol, methacholine, acetylcholine, and sodium nitroprusside (Lang, Stein et al. 1995, Stein, Lang et al. 1997, Stein, Lang et al. 2000, Kahn, Duffy et al. 2002). Nitric oxide (NO) is tonically released from endothelial cells and is essential to the maintenance of vasodilator tone and homeostasis, which are adversely affected by CVD risk factors (Quyyumi
1998). Using invasive techniques, AA have been shown to have reduced NO bioactivity in forearm microcirculation coupled with reduced smooth-muscle vasodilator response to NO donors, and thus have more generalized vascular dysfunction than CA (Campia, Choucair et al. 2002).

Additional evidence from human umbilical vein endothelial cell (HUVEC) also supported this notion (Brown and Feairheller 2013). African Americans seem to have an EC phenotype characterized by heightened oxidative stress, reduced antioxidant capacity (Feairheller, Park et al. 2011) and potential for a heightened inflammatory phenotype (Brown, Feairheller et al. 2011). In addition, African American HUVEC exhibited greater basal inducible NOS (iNOS) protein expression levels, which could be caused by the greater oxidative stress and inflammation (Feairheller, Park et al. 2011).

Differential arterial stiffness responses in AA and CA may also be affected by structural factors like the composition of the arterial wall, including the contents of the extracellular matrix (Olivetti, Anversa et al. 1980). Arteries become wider and less elastic with reduction in arterial elastin and an increase in collagen content (Learoyd and Taylor 1966). Wall thickness of large arteries correlates well with the burden of generalized atherosclerosis and is a reliable predictor of coronary events (Rohani, Jogestrand et al. 2005). AA had greater mean aortic wall thickness than CA, and higher age-related mean maximal aortic wall thickness (Li, Kamel et al. 2004,
Rosero, Peshock et al. 2011). In addition, AA tend to have higher relative collagen content in the aorta than CA in between 30 and 69 years (Meyer AC 1965). AA also have a tendency to overgrow connective tissue in response to disease (Polednak 1974). Therefore, the higher content of collagen in aortic arterial walls in AA may affect elastic properties of the large arteries after exercise.

2.7 African-Americans Have Augmented Sympathetic Tone and Sympathoexcitatory Responses

Cardiovascular hyperreactivity to stress is a major risk factor for hypertension, and African Americans exhibit an exaggerated blood pressure response to behavioral (Light and Sherwood 1989) and physiological (Bond, Mills et al. 1999) sympathoexcitation stress. Calhoun et al (Calhoun, Mutinga et al. 1993) have reported that during the cold pressor test, African Americans had higher systolic, diastolic and mean arterial blood pressure by 11 mmHg, 10 mmHg and 10 mmHg, respectively, when compared to Caucasians. Blood pressure response to cold stress has clinical significance in that normotensive individuals who are systolic hyperreactors (defined as a rise of 15 mm Hg in systolic blood pressure above baseline) have a 1.37 greater relative risk of developing hypertension than normal reactors (Kasagi, Akahoshi et al. 1995). The exaggerated blood pressure response may be a result of reduced beta adrenergic sensitivity and augmented alpha 1-adrenergic receptor sensitivity (Ray and Monahan 2002,
Lemogoum, Van Bortel et al. 2004), resulting in higher vascular resistance (Bond, Thompson et al. 1996). Consistent with this notion, African Americans have been shown to exhibit reduced peripheral arterial compliance response following an acute bout of maximal aerobic exercise compared to Caucasian men (Heffernan, Jae et al. 2007). Our lab has also shown that an acute bout of maximal cycling exercise elicited a small increase in central stiffness in African American men and women but a small decrease in central stiffness in Caucasian Americans, making the change in central stiffness significantly different between AA and CA. These differences cannot be attributed to resting differences in cardiovascular risk factors, as kidney function was normal, resting blood pressure and blood lipids did not differ between CA and AA, and we statistically controlled for differences in BMI (Yan, Ranadive et al. 2013).

2.8 Post Exercise Blood Pressure is Different in African Americans

It appears that African American women may not exhibit PEH following aerobic exercise. Headley et al (Headley, Keen et al. 1998) found that 40 min of walking at approximately 50-60% of the HRmax did not acutely lower the BP of middle-aged borderline hypertensive African American women who were not taking medication for their hypertension. Furthermore, systemic vascular resistance (SVR) increased in African American women but decreased in Caucasians following exercise. The SVR response in Caucasians was in accordance with previous literature, but the increase of SVR in African American women was unexpected.
Similarly, African American women with high-normal BP and stage I hypertension (Pescatello, Bairos et al. 2003) did not exhibit PEH whereas the Caucasian comparison group did. Instead, 30 minutes of cycling at 60% VO2 max exercise (with 5 min warm up and additional 5 min of cool-down) seemed to adversely increase BP in the African American women. In another study of young, normotensive African American women (Enweze, Oke et al. 2007), without a Caucasian control group, 30 min of cycling exercise at 60% VO2 peak produced post exercise recovery values that were not significantly different from baseline. The results in their study may be explained by unchanged cardiac output measured by electrical bioimpedance during recovery.

Our lab has shown that even an acute bout of maximal aerobic exercise elicited differential BP responses in Caucasians and African Americans (Yan, Ranadive et al. 2013). Changes in central SBP were greater in Caucasians than in African Americans, whereas the changes in brachial SBP were comparable in both groups.

Increased vasoconstriction and decreased vasodilation are likely to be another explanation for the diminished BP depressor influence of acute dynamic exercise in African American women with and without hypertension compared with Caucasian women. However, little or no information regarding vascular resistance and arterial compliance is available. Also, no information exists regarding possible mechanisms for the reduced drop in vascular resistance following exercise in African Americans. More importantly, research on PEH should be
performed during a standardized time of a day to avoid diurnal variations since post exercise hypotensive effects are reduced in the morning compared to the afternoon (Jones, George et al. 2008, Jones, Taylor et al. 2009), and this had not been done in earlier studies with African Americans. In addition, it would be important to have a control group of Caucasians to determine whether there is a lack of PEH or a lack of an adequate exercise stimulus.
CHAPTER 3

RESEARCH DESIGN AND METHODS

3.1 Participants

This study was approved by the University of Illinois Institutional Review Board and each subject gave informed, written consent before participation. Fifty-nine young (age range 18-33 yr), healthy individuals volunteered for this study and signed informed consent.

All subjects were free of cardiovascular, metabolic, renal or respiratory disease, and all were non-smokers. Subjects did not take any medications, including over-the-counter pain/anti-inflammatory medication or H1R and H2R antagonists. All of the subjects were in normal sinus rhythm, and had no history of arrhythmias. Subjects were self-defined as African-American or Caucasians, if they reported that both parents were of African descent or both parents were of Caucasian descent. Female subjects had negative pregnancy tests on study visits. All subjects were recruited from the local community or university population.

3.2 Study Design

This study employed a randomized, double-blind, counterbalanced design to test the effect of H1R and H2R blockade on PEH. A schematic of the study design is presented in Figure 3.1. Subjects underwent testing to determine peak oxygen uptake (VO₂peak) and a blood draw...
prior to randomization to placebo or histamine blockade. During blood draw visits, venous blood samples were obtained after an overnight fast (minimum 12 h fasting). On study days, subjects were given water with either a combined H1R- and H2R antagonist (fexofenadine and ranitidine) or a control placebo (lactose capsules), which served as placebo previously (Fahs, Yan et al. 2010) for the first visit (randomly determined) followed by the other condition on the second visit. Subjects were asked to abstain from caffeine, alcohol and exercise for at least 12 hours before each testing session. The parallel study visits were made between 3 pm to 8 pm (since exercise induced hypotension is most consistently observed at this time (Jones, George et al. 2008, Jones, Pritchard et al. 2008)). During study visits, subjects rested in the supine position for 10 min in a quiet and temperature-controlled (22 - 25°C) room, and then baseline (PRE) BP, cardiac output, peripheral resistance and arterial stiffness were assessed. After baseline measurements, subjects exercised on the treadmill for 45 min at 70% HRreserve determined from the VO2peak visit. Cardiovascular measurements were taken again at 30 min (P30), 60 min (P60) and 90 min (P90) after exercise. All pre- and post-exercise measurements were obtained with subjects in a supine position. Men were tested at least 5 days apart between two study visits. Women were tested during consecutive early follicular phases (days 1-5) of their menstrual cycle or placebo phases of the oral contraceptive cycle to control for the influence of hormone fluctuations (visits approximately 30 days apart).
more than adequate time for clearance of fexofenadine (half life ~ 12 h) (Russell, Stoltz et al. 1998) and ranitidine (half life ~ 2.6 h) (Garg, Eshelman et al. 1985).

Figure 3.1. A schematic of the study design showing the procedures for each visit. Study visits were randomized and all the subjects were counterbalanced for the order in which the blockade/placebo were administered.

3.3 H1R and H2R Blockade

H1R were blocked with 540 mg fexofenadine and H2R were blocked with 300 mg ranitidine. These amounts of fexofenadine and ranitidine have been shown to adequately block
H1R and H2R, respectively (Garg, Eshelman et al. 1985, Russell, Stoltz et al. 1998). Oral ingestion of a H1R antagonist (540 mg of fexodenadine) or H2R antagonist (300 mg of ranitidine) does not cause non-specific cardiovascular effects in the absence of an exercise stimulus. When these drugs were given under normal resting conditions, cardiac output, heart rate, blood pressure, leg blood flow and skin blood flow did not change in Caucasians (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006).

3.4 Measurements

3.4.1 VO$_2$peak Testing

Following a brief warm-up walking on the treadmill, subjects started walking for three minutes at Stage 1 with speed (2.74 km/hr) and grade of slope (10%). After 3 minutes into the test the speed was adjusted to 4.02 km/hr and the slope to 12%, after 6 minutes into the test the speed was adjusted to 5.47 km/hr and the slope to 14%, and so on following Bruce treadmill protocol. Heart rate was measured with a Polar Heart Rate Monitor (Polar Electro Oy, Oulu, Finland). Maximal heart rate (HRmax) for each subject testing was recorded. Expired air was analyzed with a Quark b2 breath-by-breath metabolic system (Cosmed, Rome, Italy). The test was terminated when subjects met three of the following five criteria: 1) a final rating of perceived exertion (RPE) score of 17 or greater on the Borg scale (scale 6-20), 2) a respiratory exchange ratio greater than 1.1, 3) no change in heart rate with a change in workload, 4) a
“plateau” (increase of no more than 150 ml) in oxygen uptake with an increase in workload, 5) volitional fatigue, defined as an inability to keep up with the treadmill speed.

3.4.2 Fasting Blood Measures

All blood draws were carried out in the morning with subjects in a fasted state for at least 12 hours. Fasting glucose was assessed via an oxygen rate method using a Beckman Coulter oxygen electrode (Beckman Coulter, Villapointe, France). Total cholesterol, high density lipoprotein cholesterol (HDL cholesterol), and triglycerides (TG) were measured using enzymatic techniques. Low density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedewald formula. Very low density lipoprotein cholesterol (VLDL cholesterol) was calculated by dividing triglycerides by 5.

3.4.3 Renal Function Assessment

Given known racial differences in renal function, estimated glomerular filtration rate (eGFR) was estimated from serum creatinine (sCR) in accordance with recommendations from the Laboratory Working Group of the National Kidney Disease Education Program (Myers, Miller et al. 2006). eGFR was estimated from the Modification of Diet in Renal Disease Study formula (Myers, Miller et al. 2006).

3.4.4 Anthropometrics

Height and weight were recorded as previously described (Heffernan, Jae et al. 2008).
3.4.5 Brachial Artery BP Assessment

Following 5 minutes of quiet supine rest in a dimly lit room, resting systolic blood pressure (Brachial SBP) and diastolic blood pressure (Brachial DBP) were measured with an automated oscillometric cuff following established guidelines (Melenovsky, Borlaug et al. 2007). All BP measurements were repeated and the average of the two values was recorded and used for analysis. If the values differed by \( \geq 5\text{mmHg} \), a third measurement was obtained and the two closest values were averaged. Brachial mean arterial pressure (Brachial MAP) was calculated as \( \frac{1}{3} \times \text{SBP} + \frac{2}{3} \times \text{DBP} \).

3.4.6 Carotid and Aortic BP

Applanation tonometry was performed using a high-fidelity strain-gauge transducer (SphygmoCor, AtCor Medical, Sydney, Australia) on the radial artery to obtain pressure waveforms. Aortic systolic blood pressure (Aortic SBP), diastolic blood pressure (Aortic DBP), mean arterial pressure (Aortic MAP) were derived from radial pressure waveforms as previously described (Heffernan, Jae et al. 2007).

Using a generalized validated transfer function (Pauca, O'Rourke et al. 2001), a central aortic pressure waveform was reconstructed from the radial artery pressure waveform to obtain Aortic SBP and Aortic DBP. This transfer function has been validated at rest and during exercise.
through invasive methods (Sharman, Lim et al. 2006). Aortic MAP was derived from integrating
the area under the central BP waveform.

Applanation tonometry was also performed using a high-fidelity strain-gauge transducer
(SphygmoCor, AtCor Medical, Sydney, Australia) on the carotid artery to obtain BP waveforms
and calibrated against brachial mean arterial and diastolic pressure to obtain carotid systolic
blood pressure (Carotid SBP), carotid diastolic blood pressure (Carotid DBP) and carotid mean
arterial pressure (Carotid MAP).

3.4.7 Pulse Wave Velocity (PWV)

PWV was measured following current guidelines (Van Bortel, Duprez et al. 2002). Values
from the carotid to the radial artery (Brachial PWV), carotid to the femoral artery (Central PWV)
and the femoral to superior dorsalis pedis (Femoral PWV) artery were obtained as previously
described (SphygmoCor, AtCor Medical, Sydney, Australia) (Heffernan, Jae et al. 2007). A
single high-fidelity strain-gauge transducer (Millar Instruments, Houston, TX, USA) was used to
sequentially obtain pressure waveforms between (1) the right common carotid and the right
radial artery, (2) the right common carotid and the right femoral artery, and (3) the right femoral
artery and the ipsilateral superior dorsalis pedis artery. Consecutive waveforms were captured for
a 10-s epoch. Simultaneous ECG gating, as a timing marker, was assessed via a 3-lead CM5
configuration and further used to obtain HR. The foot of the pressure wave was identified
automatically, removing potential observer bias, using an algorithm that detects the initial upstroke via a line tangent to the initial systolic upstroke point of the pressure tracing and an intersecting horizontal line through the minimum point (Chiu, Arand et al. 1991). This algorithm has been shown to be highly reproducible (Chiu, Arand et al. 1991). Distances from the suprasternal notch to the femoral artery, carotid artery, and femoral artery sampling site to the superior dorsalis pedis artery were measured as straight lines with a tape measure. The distance from the carotid artery to the sternal notch was then subtracted from the sternal-femoral segment to correct for differences in propagation direction along the arterial path length and taken as a measure of central arterial stiffness. Brachial PWV and Femoral PWV were taken as indices of peripheral arterial stiffness. Central PWV was taken as a measure of central/aortic stiffness.

Integral software assessed pulse wave quality (strength of pulse wave signal, pulse height variation, pulse length variation, and base line variation) and standard deviation of mean time differences (SphygmoCor, AtCor Medical, Sydney, Australia). This technique has been shown to be highly reproducible (Wilkinson, Hall et al. 2002).

3.4.8 Carotid and Femoral Artery Stiffness

The carotid artery and femoral artery were imaged via ultrasound (Aloka, Alpha 10, Tokyo, Japan) using a 7.5 MHz linear-array probe. Heart rate (HR) was recorded with a single lead
ECG. Once all data were recorded, the following equations were used to calculate the 2 parameters related to arterial stiffness in the carotid artery and femoral artery:

Pressure-strain elasticity modulus (Ep) = \[\frac{(P_1 - P_0)}{(D_{max} - D_{min})} \times D_{min}\]

\[\beta\text{-stiffness index (}\beta\text{ stiffness)} = \frac{\ln P_1 / P_0}{(D_{max} - D_{min}) / D_{min}}\]

where \(D_{max}\) and \(D_{min}\) are the maximum (systolic) and minimum (diastolic) diameters, and \(P_1\) and \(P_0\) are the highest (systolic) and lowest (diastolic) carotid pressures. Carotid BP was measured with applanation tonometry as described above and was used to calculate carotid arterial stiffness. Brachial BP was used to calculate femoral arterial stiffness measurements.

3.4.9 Leg Blood Flow

The diameter of the femoral artery was determined from digital B-mode ultrasound images (Aloka, Alpha 10, Tokyo, Japan) while the ultrasound probe was placed on the skin surface 2-3 cm proximal to the bifurcation of the femoral artery. The mean diameter was calculated from \(D_1\) and \(D_0\) weighted to the percentage of time spent at each diameter in the cardiac cycle: \(D_{mean} = (1/3)D_{max} + (2/3)D_{min}\). The mean blood velocity (MBV) in the femoral artery was measured by using pulse Doppler ultrasonography (Aloka, Alpha 10, Tokyo, Japan) and was taken immediately after diameter measurements.

Mean limb blood flow (Q) was calculated from the mean velocity and area using the formula: \(Q (mL/min) = MBV \pi r^2 60\), where MBV is the mean velocity of the blood (cm*s\(^{-1}\)), r
is the mean radius of the artery during the cardiac cycle (cm), and 60 is a constant ($s \cdot min^{-1}$) to convert the calculated flow from milliliters per second to milliliters per minute. The mean radius of the artery was calculated from the diameter assuming the artery is circular ($r = D_{\text{mean}}/2$). This value was doubled to represent both legs. Femoral vascular conductance (FVC) was calculated as flow for both legs/brachial MAP and expressed as $ml \cdot min^{-1} \cdot mmHg^{-1}$.

### 3.4.10 Cardiac Echocardiography

Cardiac output (CO) and stroke volume (SV) were assessed using two-dimensional echocardiography via ultrasound (Aloka, Alpha 10, Tokyo, Japan). With subjects in the left lateral position, measurements were obtained using the four-chamber apical view. The interior endocardial border of the left ventricle was manually traced during both end systole and end diastole. Volumes were measured using Simpson’s rule. SV was calculated by subtracting end systolic volume from end diastolic volume. CO was calculated as HR multiplied by SV. Systemic vascular conductance (SVC) was calculated as CO/brachial MAP and expressed as $ml \cdot min^{-1} \cdot mmHg^{-1}$. 
3.5 Exercise Protocol

Exercise was performed in a temperature-controlled room (22 - 25°C) and water was allowed ad libitum. The aerobic exercise protocol required subjects to exercise continuously for 45 min at 70% HRreserve, which has consistently been shown to cause PEH (Floras and Wesche 1992, Rueckert, Slane et al. 1996). Up to 10 min of warm-up was employed to ensure subjects reached their target HR. Subjects were asked to keep their HR at target HR±5 bpm during exercise. HR and RPE were recorded every 10min during exercise and average HR (ave_HRex) and average RPE (ave_RPEex) were calculated. Water intake during exercise (water_ex) and during the study visit (water_total) was measured. Body weight was measured at the end of the study visit to determine fluid loss.

3.6 Statistical Analysis

All data is presented as mean ± SE. Descriptive variables and baseline hemodynamic variables were analyzed with t-tests for possible racial differences. Three way repeated-measures analysis of variance (ANOVA) was used to test for possible condition, race, time and their interaction effects. Post-hoc t-tests were conducted if the initial ANOVA yielded significance. We also conducted these probes using ANCOVAs controlling for VO2peak. Statistical
significance was set at p < 0.05. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.
CHAPTER 4

RESULTS

4.1 Subject Characteristics

Of the 59 subjects initially recruited, 49 (9 AA men, 13 AA women, 14 CA men and 13 CA women) subjects completed the study. Ten subjects (3 AA men, 3 AA women, 2 CA men and 2 CA women) dropped out of the study following the initial visit because they were unwilling to continue.

Subject characteristics are shown in Table 1. VO$_{2\text{peak}}$ was significantly lower in AA compared to CA (p<0.05) and eGFR was significantly higher in AA compared to CA (p<0.05). There were no significant differences between AA and CA in other anthropometrics or fasting blood measures. Almost all of the subjects were recreationally active (except 1 AA male) with average exercise time of between 1-12 hours per week.

4.2 Exercise

Exercise data are shown in Table 2. Both AA and CA experienced significant fluid loss (p<0.05). Fluid loss, ave$_{HRe}$, ave$_{RPEex}$, water$_{ex}$ or water$_{total}$ were not different between control and blockade days. Fluid loss, ave$_{HRe}$, ave$_{RPEex}$, water$_{ex}$ or water$_{total}$ were also
not different between CA and AA on either control or blockade days. Ave_HRex in either CA or AA was not significantly different from 70%HRreserve goal in either condition.

4.3 Hemodynamics

The hemodynamics from baseline to 90 min post exercise are shown from Fig 4.1 to Fig 4.8.

4.3.1 Preexercise Hemodynamics

Supine resting hemodynamics was not different between control and blockade days. In control condition, there was no significant difference between AA and CA at rest. However, in blockade condition, AA exhibited significantly lower SV (p<0.05; Fig. 4.4B) and lower SVC (p<0.05; Fig. 4.5D) compared to CA.

4.3.2 Post Exercise Hypotension

Fig. 4.1 to Fig. 4.3 shows Carotid, Brachial and Aortic BP at baseline and at 30 min, 60 min and 90 min following acute exercise. There was no significant three-way interaction, two-way interaction or main effect of histamine blockade (condition) for Carotid SBP (Fig. 4.1A and 4.1B). There were a significant main effect of time and main effect of race for Carotid SBP (p<0.05; Fig. 4.1A and 4.1B). Overall, Carotid SBP (averaged across group and condition) decreased significantly across time (from 110 ± 2 to 109 ± 2 to 107 ± 1 to 106 ± 1 mmHg, time
effect p<0.05). Overall Carotid SBP (averaged across time and condition) was also higher in AA compared to CA (111 ± 2 vs. 105 ± 2 mmHg, race effect p<0.05).

There was no significant three-way interaction, condition by time interaction, condition by race interaction or main effect of histamine blockade for Carotid DBP (Fig. 4.1C and 4.1D). There were a significant race by time interaction, a significant main effect of time and a main effect of race and for Carotid DBP (p<0.05; Fig. 4.1C and 4.1D). Carotid DBP increased significantly more in AA (from 65 ± 1 to 66 ± 1 to 66 ±1 to 69 ± 1 mmHg) than in CA (62 ± 1 to 63 ± 1 to 62 ± 1 to 64 ± 1 mmHg) over time (race by time interaction p<0.05). Carotid DBP also increased significantly across time (averaged across groups and condition, from 63 ± 1 to 64 ± 1 to 64 ± 1 to 66 ± 1 mmHg, time effect p<0.05). Overall Carotid DBP (averaged across time and condition) was also higher in AA compared to CA (66 ± 1 vs. 63 ± 1 mmHg, race effect p<0.05).

There was no significant three-way interaction, condition by time interaction, condition by race interaction or main effect of histamine blockade for Carotid MAP (Fig. 4.1E and 4.1F). There were a significant race by time interaction, a significant main effect of time and a main effect of race and for Carotid MAP (p<0.05; Fig. 4.1E and 4.1F). Carotid MAP increased in AA (from 80 ± 1 to 81 ± 1 to 81 ±1 to 82 ± 1 mmHg) but not in CA (77 ± 1 to 77 ± 1 to 76 ± 1 to 77 ± 1 mmHg) over time (race by time interaction p<0.05). Carotid MAP increased significantly
across time (from 79 ± 1 to 79 ± 1 to 78 ± 1 to 80 ± 1 mmHg, time effect p<0.05). Carotid MAP was also higher in AA compared to CA (81 ± 1 vs. 77 ± 1 mmHg, race effect p<0.05). There was no significant three-way interaction, two-way interaction, main effect of race or main effect of histamine blockade for Brachial SBP (Fig. 4.2A and 4.2B). There was a significant main effect of time for Brachial SBP (p<0.05; Fig. 4.2A and 4.2B). Overall, Brachial SBP (averaged across group and condition) decreased across time (from 115 ± 1 to 113 ± 1 to 112 ± 1 to 113 ± 1 mmHg, time effect p<0.05).

There was no significant three-way interaction, race by condition interaction, main effect of race or main effect of histamine blockade for Brachial DBP (Fig. 4.2C and 4.2D). There were a significant race by time interaction and a significant main effect of time for Brachial DBP (p<0.05; Fig. 4.2C and 4.2D). Brachial DBP increased significantly in AA (from 65 ± 1 to 66 ± 1 to 66 ±1 to 69 ± 2 mmHg) but not in CA (63 ± 1 to 63 ± 1 to 63 ± 1 to 64 ± 1 mmHg) over time (race by time interaction p<0.05). Brachial DBP (averaged across condition) increased significantly more in the blockade condition (from 63 ± 1 to 65 ± 1 to 65 ± 1 to 67 ± 1 mmHg) than in the control condition (from 64 ± 1 to 65 ± 1 to 64 ± 1 to 66 ± 1 mmHg) over time (condition by time interaction p<0.05). Overall, Brachial DBP (averaged across group and condition) increased significantly across time (from 64 ± 1 to 65 ± 1 to 65 ± 1 to 66 ± 1 mmHg, time effect p<0.05).
There was no significant three-way interaction, two-way interaction, main effect of race or main effect of histamine blockade for Brachial MAP (Fig. 4.2E and 4.2F). There was a significant main effect of time for Brachial MAP (p<0.05; Fig. 4.2E and 4.2F). Overall, Brachial MAP (averaged across group and condition) increased significantly across time (from 81 ± 1 to 81 ± 1 to 82 ± 1 mmHg, time effect p<0.05).

There was no significant three-way interaction, two-way interaction, main effect of race or main effect of histamine blockade for Aortic SBP (Fig. 4.3A and 4.3B). There was a significant main effect of time for Aortic SBP (p<0.05; Fig. 4.3A and 4.3B). Overall, Aortic SBP (averaged across group and condition) changed across time (from 95 ± 1 to 95 ± 1 to 94 ± 1 to 96 ± 1 mmHg, time effect p<0.05).

There was no significant three-way interaction, two-way interaction or main effect of histamine blockade for Aortic DBP (Fig. 4.3C and 4.3D). There were a significant main effect of time, and main effect of race for Aortic DBP (p<0.05; Fig. 4.3C and 4.3D). Overall, Aortic DBP (averaged across group and condition) increased across time (from 64 ± 1 to 65 ± 1 to 65 ± 1 to 66 ± 1 mmHg, time effect p<0.05). Overall Aortic DBP (averaged across time and condition) was also higher in AA compared to CA (67 ± 1 vs. 63 ± 1 mmHg, race effect p<0.05).

There was no significant three-way interaction, two-way interaction or main effect of histamine blockade for Aortic MAP (Fig. 4.3E and 4.3F). There were a significant main effect of
time, and main effect of race for Aortic MAP (p<0.05; Fig. 4.3E and 4.3F). Overall, Aortic MAP (averaged across group and condition) changed significantly across time (from 78 ± 1 to 78 ± 1 to 77 ± 1 to 79 ± 1 mmHg, time effect p<0.05). Overall Aortic MAP (averaged across time and condition) was also significantly higher in AA compared to CA (80 ± 1 vs. 77 ± 1 mmHg, race effect p<0.05).

4.3.3 Cardiac Parameters

There was no significant three-way interaction, two-way interaction or main effect of histamine blockade for SV (Fig. 4.4A and 4.4B). There were a significant main effect of time and main effect of race for SV (p<0.05; Fig. 4.4A and 4.4B). Overall, SV (averaged across group and condition) increased significantly across time (from 61 ± 2 to 63 ± 2 to 63 ± 2 to 62 ± 2 ml, time effect p<0.05). Overall SV (averaged across time and condition) was also significantly lower in AA compared to CA (59 ± 2 vs. 65 ± 2 ml, race effect p<0.05).

There was no significant three-way interaction, two-way interaction, main effect of histamine blockade or main effect of race for HR (Fig. 4.4C and 4.4D). There was a significant main effect of time for HR (p<0.05; Fig. 4.4C and 4.4D). Overall, HR (averaged across group and condition) increased significantly across time (from 63 ± 1 to 66 ± 1 to 65 ± 1 to 65 ± 1 ml, time effect p<0.05).
There was no significant three-way interaction, race by condition interaction, race by time interaction, main effect of race or main effect of histamine blockade for CO (Fig. 4.4E and 4.4F). There was a significant condition by time interaction and a main effect of time and for CO (p<0.05; Fig. 4.4E and 4.4F). CO increased significantly less in the blockade condition (from 3.9 ± 0.1 to 4.2 ± 0.1 to 4.0 ± 0.1 to 3.9 ± 0.1 L/min) than in the control condition (from 3.7 ± 0.1 to 4.1 ± 0.1 to 4.0 ± 0.1 L/min) over time (condition by time interaction p<0.05).

Overall, CO (averaged across group and condition) increased significantly across time (from 3.8 ± 0.1 to 4.1 ± 0.1 to 4.1 ± 0.1 to 4.0 ± 0.1 L/min, time effect p<0.05).

### 4.3.4 Vascular Conductance

There were no significant changes, no significant group differences or differences due to histamine receptor blockade for femoral VC (Fig. 4.5A and 4.5B).

There was no significant three-way interaction, two-way interaction, main effect of histamine blockade or main effect of race for SVC (Fig. 4.5C and 4.5D). There was a significant histamine blockade by time interaction and main effect of time for SVC (p<0.05; Fig. 4.5C and 4.5D). SVC (averaged across group) increased significantly less in the blockade condition (from 48 ± 1 to 52 ± 2 to 50 ± 2 to 48 ± 1 ml.min-1.mmHg-1) than in the control condition (from 47 ± 1 to 50 ± 2 to 51 ± 2 to 50 ± 2 ml.min-1.mmHg-1) over time (condition by time interaction
p<0.05). Overall, SVC (averaged across group and condition) increased significantly across time (from 47 ± 1 to 51 ± 1 to 51 ± 1 to 49 ± 1 ml.min⁻¹.mmHg⁻¹, time effect p<0.05).

4.3.5 Pulse Wave Velocity

There was no significant three-way interaction, race by condition interaction, condition by time interaction, main effect of histamine blockade or main effect of race for Brachial PWV (Fig. 4.6A and 4.6B). There were a significant race by time interaction and main effect of time for Brachial PWV (p<0.05; Fig. 4.6A and 4.6B). Brachial PWV increased significantly in AA (from 7.1 ± 0.2 to 7.5 ± 0.2 to 7.5 ± 0.2 to 7.7 ± 0.2 m/s) but not in CA (from 7.3 ± 0.2 to 7.1 ± 0.2 to 7.3 ± 0.2 to 7.2 ± 0.2 m/s) over time (race by time interaction p<0.05). Overall, Brachial PWV (averaged across group and condition) increased significantly across time (from 7.2 ± 0.1 to 7.3 ± 0.2 to 7.4 ± 0.2 to 7.5 ± 0.2 m/s, time effect p<0.05).

There were no significant interactions or main effects on either Central PWV (Fig. 4.6C and 4.6D) or Femoral PWV (Fig. 4.6E and 4.6F).

4.3.6 Carotid and Femoral Artery

There was no significant three-way interaction, race by condition interaction, race by time interaction, main effect of histamine blockade or main effect of race for Carotid Ep (Fig. 4.7A and 4.7B). There were a significant condition by time interaction and a main effect of race and for Carotid Ep (p<0.05; Fig. 4.7A and 4.7B). Carotid Ep decreased significantly in the
blockade condition (from 67 ± 4 to 68 ± 3 to 60 ± 2 to 61 ± 3 kPa) but increased then decreased significantly in the control condition (from 60 ± 2 to 68 ± 3 to 60 ± 2 to 61 ± 3 kPa) over time (condition by time interaction p<0.05). Overall Carotid Ep (averaged across time and condition) was also higher in AA compared to CA (68 ± 3 vs. 57 ± 3 kPa, race effect p<0.05).

There was no significant three-way interaction, race by condition interaction, race by time interaction, main effect of histamine blockade or main effect of race for Carotid Beta stiffness (Fig. 4.7C and 4.7D). There were a significant control by time interaction and a main effect of race and for Carotid Beta stiffness (p<0.05; Fig. 4.7C and 4.7D). Carotid Beta stiffness (averaged across group) changed significantly in the blockade condition (from 5.8 ± 0.3 to 5.3 ± 0.2 to 5.6 ± 0.2 to 5.3 ± 0.3) than in the control condition (from 5.3 ± 0.2 to 6.0 ± 0.3 to 5.4 ± 0.2 to 5.4 ± 0.2) over time (condition by time interaction p<0.05). Overall Carotid Beta stiffness was also higher in AA compared to CA (5.9 ± 0.3 vs. 5.1 ± 0.3, race effect p<0.05).

There were a significant time by condition by race interaction, a condition by time interaction, a condition by race interaction and main effect of time, for Carotid diastolic diameter (p<0.05; Fig. 4.7E and 4.7F). There was no significant race by time interaction, main effect of histamine blockade or main effect of race for Carotid Dmin. Carotid Dmin increased significantly from PRE to P30 (p<0.05), from PRE to P60 (p<0.05), from PRE to P90 (p<0.05) and from P30 to P90 (p<0.05) in the control condition (Fig. 4.7E). Carotid Dmin increased
significantly from PRE to P60 (p<0.05), and from PRE to P90 (p<0.05) from P30 to P60 (p<0.05), and from P30 to P90 (p<0.05) in the blockade condition (Fig. 4.7F). Carotid Dmin in AA was significantly higher in the blockade condition compared to the control condition at PRE (p<0.05; Fig. 4.7E and 4.7F). Carotid Dmin in CA was significantly lower in the blockade condition compared to the control condition at P30 (p<0.05; Fig. 4.7E and 4.7F). AA had significantly higher Carotid Dmin compared to CA at P30 and P90 in blockade condition (p<0.05; Fig. 4.7F), but no racial differences were found in control condition (Fig. 4.7E).

There was no significant three-way interaction, race by condition interaction, race by time interaction or any main effects for Femoral Ep (Fig. 4.8A and 4.8B). There was a significant condition by time interaction for Femoral Ep (p<0.05; Fig. 4.8A and 4.8B). Femoral Ep (averaged across group) increased significantly at P90 in the blockade condition (from 72 ± 7 to 71 ± 6 to 73 ± 7 to 82 ± 9 kPa) but increased significantly at P30 in the control condition (from 71 ± 5 to 84 ± 7 to 71 ± 6 to 72 ± 6 kPa, condition by time interaction p<0.05).

There was no significant three-way interaction, race by condition interaction, race by time interaction or any main effects for Femoral Beta stiffness. There was a significant condition by time interaction for Femoral Beta stiffness (p<0.05; Fig. 4.8C and 4.8D). Femoral Beta stiffness increased significantly at P90 in the blockade condition (from 6.2 ± 0.6 to 6.0 ± 0.5 to
6.3 ± 0.6 to 6.8 ± 0.7) but increased significantly at P30 in the control condition (from 6.1 ± 0.4 to 7.2 ± 0.6 to 6.2 ± 0.5 to 6.0 ± 0.5) over time (condition by time interaction p<0.05).

There was no significant three-way interaction, race by condition interaction, race by time interaction, main effect of histamine blockade or main effect of race for Femoral Dmin (Fig. 4.8E and 4.8F). There was a significant condition by time interaction and a main effect of time for Femoral Dmin (p<0.05; Fig. 4.8E and 4.8F). Femoral Beta stiffness increased significantly more in the blockade condition (from 7.6 ± 0.2 to 7.8 ± 0.2 to 7.9 ± 0.2 to 8.2 ± 0.2) than in the control condition (from 7.6 ± 0.2 to 7.9 ± 0.2 to 7.7 ± 0.2 to 7.9 ± 0.2 mm) over time (condition by time interaction p<0.05). Overall, Femoral Dmin (averaged across group and condition) increased significantly across time (from 7.6 ± 0.2 to 7.8 ± 0.2 to 7.8 ± 0.2 to 8.0 ± 0.2 mm, time effect p<0.05).

Exit interviews conducted with subjects at the conclusion of testing showed that the subjects were unable to distinguish between treatment conditions.
## Figures and Tables

### Table 4.1. Subject characteristics

<table>
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<tr>
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<th>AA (n=22)</th>
<th>CA (n=27)</th>
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<tr>
<td>Age (yrs)</td>
<td>21 ± 1</td>
<td>23 ± 1</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
<td>73.4 ± 3.0</td>
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<td>BMI (kg/m2)</td>
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<tr>
<td>VO$_{2}$peak (ml/kg/min) ‡</td>
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<td>HRmax (bpm)</td>
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<td>190 ± 2</td>
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<td>70%HRRreserve (bpm)</td>
<td>154 ± 1</td>
<td>151 ± 1</td>
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<tr>
<td>eGFR (ml.min$^{-1}$1.73 m$^{-2}$) ‡</td>
<td>113 ± 4</td>
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<td>Glucose (mg/dl)</td>
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<td>TG (mg/dl)</td>
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<td>Total cholesterol (mg/dl)</td>
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<td>VLDL cholesterol (mg/dl)</td>
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<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>98 ± 4</td>
<td>108 ± 6</td>
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</table>

Values are mean ± SE.  ‡P < 0.05 significant race differences

VO$_{2}$peak – Peak Oxygen consumption; HRmax – maximal heart rate; BMI – body mass index; TG - triglyceride; HDL - high density lipoprotein; VLDL - very low density lipoprotein; LDL - low density lipoprotein; eGFR - estimated glomerular filtration rate.
Table 4.2. Exercise hemodynamic and water intake

<table>
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<th>Control AA (n=22)</th>
<th>Control CA (n=27)</th>
<th>Blockade AA (n=22)</th>
<th>Blockade CA (n=27)</th>
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<tr>
<td>ave_HRex (bpm)</td>
<td>153 ± 1</td>
<td>152 ± 1</td>
<td>153 ± 1</td>
<td>152 ± 1</td>
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<tr>
<td>ave_RPEex (bpm)</td>
<td>12 ± 0</td>
<td>12 ± 0</td>
<td>12 ± 0</td>
<td>12 ± 0</td>
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<tr>
<td>water_ex (ml)</td>
<td>236 ± 34</td>
<td>311 ± 48</td>
<td>196 ± 27</td>
<td>297 ± 48</td>
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<tr>
<td>water_total (ml)</td>
<td>393 ± 40</td>
<td>498 ± 59</td>
<td>389 ± 27</td>
<td>518 ± 69</td>
</tr>
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<td>Fluid loss (%)</td>
<td>-0.9 ± 0.1 §</td>
<td>-1.0 ± 0.2 §</td>
<td>-0.7 ± 0.2 §</td>
<td>-1.0 ± 0.1 §</td>
</tr>
<tr>
<td>Fluid loss (kg)</td>
<td>-0.7 ± 0.1 §</td>
<td>-0.7 ± 0.1 §</td>
<td>-0.6 ± 0.1 §</td>
<td>-0.7 ± 0.1 §</td>
</tr>
</tbody>
</table>

Values are mean ± SE. § P < 0.05 significantly different from 0

ave_HRex – average HR during exercise; ave_RPEex – average RPE during exercise; water_ex – water intake during exercise; water_total – total water intake during study visit; Fluid loss (%) – percent change in body weight from PRE to P90; Fluid loss (kg) – absolute change in body weight from PRE to P90
Figure 4.1. Figure 1. Carotid SBP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B).
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition.
§ Significant main effect of time (p<0.05).
‡ Significant main effect of race (p<0.05).

**Carotid DBP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).**

No significant three-way interaction.
No significant condition by time or condition by race interaction.
# Significant race by time interaction (p<0.05).
No significant main effect of condition.
§ Significant main effect of time (p<0.05).
‡ Significant main effect of race (p<0.05).

**Carotid MAP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H₁R and H₂R blockade condition (F).**

No significant three-way interaction.
No significant condition by time or condition by race interaction.
# Significant race by time interaction (p<0.05).
No significant main effect of condition.
§ Significant main effect of time (p<0.05).
‡ Significant main effect of race (p<0.05).
Figure 4.2. Brachial SBP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H$_1$R and H$_2$R blockade condition (B).
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).

**Brachial DBP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).**
No significant three-way interaction.
No significant race by condition interaction.
No significant main effect of condition or main effect of race.
# Significant race by time interaction (p<0.05).
* Significant condition by time interaction (p<0.05).
§ Significant main effect of time (p<0.05).

**Brachial MAP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H₁R and H₂R blockade condition (F).**
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).
Figure 4.3. Aortic SBP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B). No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).

**Aortic DBP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).**
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition
§ Significant main effect of time (p<0.05).
‡ Significant main effect of race (p<0.05).

**Aortic MAP at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H₁R and H₂R blockade condition (F).**
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition
§ Significant main effect of time (p<0.05).
‡ Significant main effect of race (p<0.05).
Figure 4.4. SV at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B).
SV at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B).
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition
§ Significant main effect of time (p<0.05).
‡ Significant main effect of race (p<0.05). AA also had significantly lower SV compared to CA at PRE in the blockade condition (p<0.05).

HR at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).
No significant three-way interaction.
No significant two-way interaction.
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).

CO at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H₁R and H₂R blockade condition (F).
No significant three-way interaction.
No significant race by condition or race by time interaction.
* Significant condition by time interaction (p<0.05).
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).
Figure 4.5. Femoral vascular conductance (VC) at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B).

There were no significant changes, no significant group differences or differences due to histamine blockade.

Systemic vascular conductance (SVC) at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).

No significant three-way interaction.

No significant race by condition or race by time interaction.

* Significant blockade by time interaction.
No significant main effect of condition or main effect of race.

§ Significant main effect of time (p<0.05).

‡ AA had significantly lower SVC compared to CA at PRE in the blockade condition (p<0.05).
Figure 4.6. Brachial PWV at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H1R and H2R blockade condition (B).
No significant three-way interaction.
No significant race by condition or condition by time interaction.
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).
# Significant race by time interaction (p<0.05).

Central PWV at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).
There were no significant effects.

Femoral PWV at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H₁R and H₂R blockade condition (F).
There were no significant effects.
Figure 4.7. Carotid Ep at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B). No significant three-way interaction.
No significant race by condition or race by time interaction.

* **Significant condition by time interaction (p<0.05).**

No significant main effect of condition or main effect of time.

‡ **Significant main effect of race (p<0.05).**

**Carotid Beta stiffness at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H₁R and H₂R blockade condition (D).**

No significant three-way interaction.

No significant race by condition or race by time interaction.

* **Significant condition by time interaction (p<0.05).**

No significant main effect of condition or main effect of time.

‡ **Significant main effect of race (p<0.05).**

**Carotid diastolic diameter (Dmin) at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H₁R and H₂R blockade condition (F).**

§ **Significant time by blockade by race interaction (p<0.05).** Post-hoc analyses revealed that AA had significantly higher Carotid Dmin compared to CA at P30 and P90 in the blockade condition (p<0.05), but no racial differences were found in the control condition.

No significant race by time interaction.

* **Significant blockade by time interaction (p<0.05).**

& **Significant blockade by race interaction (p<0.05).** Post-hoc analyses revealed that Carotid Dmin in AA significantly higher in the blockade condition compared to control condition at PRE (p<0.05). Carotid Dmin in CA significantly lower in the blockade condition compared to control condition at P30 (p<0.05).

No significant main effect of condition or main effect of race.

§ **Significant main effect of time (p<0.05).** Post-hoc analyses revealed that Carotid Dmin increased significantly from PRE to P30 (p<0.05), from PRE to P60 (p<0.05), from PRE to P90 (p<0.05) and from P30 to P90 (p<0.05) in the control condition. Carotid Dmin increased significantly from PRE to P60 (p<0.05), and from PRE to P90 (p<0.05) from P30 to P60 (p<0.05), and from P30 to P90 (p<0.05) in the blockade condition.
Figure 4.8. Femoral Ep at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (A) and H₁R and H₂R blockade condition (B).
No significant three-way interaction.
No significant race by condition or race by time interaction.
* Significant condition by time interaction (p<0.05).
No significant main effects.

Femoral Beta stiffness at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (C) and H$_1$R and H$_2$R blockade condition (D).
No significant three-way interaction.
No significant race by condition or race by time interaction.
* Significant condition by time interaction (p<0.05).
No significant main effects.

Femoral diastolic diameter (D$_{min}$) at baseline and at 30 min, 60 min and 90 min following aerobic exercise in the control condition (E) and H$_1$R and H$_2$R blockade condition (F).
No significant three-way interaction.
No significant race by condition or race by time interaction.
* Significant blockade by time interaction showing greater vasodilatation in the blockade condition (p<0.05).
No significant main effect of condition or main effect of race.
§ Significant main effect of time (p<0.05).
CHAPTER 5
DISCUSSION

This is the first study to examine racial differences in brachial and central BP following an acute bout of aerobic exercise with and without histamine blockade in young normotensive AA and CA men and women. Our major new and novel findings were: (1) exercise acutely increased DBP during recovery; without histamine blockade, DBP was significantly higher following exercise in AA than CA, likely due to lower systemic vascular resistance in AA with no differences between groups in CO; (2) differential responses between central and peripheral BP were found post exercise. There was a significant higher Carotid SBP in AA compared to CA but no racial differences in Brachial or Aortic SBP following exercise; and (3) Brachial, Carotid and Aortic DBP were all higher in AA compared to CA in the histamine blockade condition following exercise. This suggests that histamine receptors may have a greater influence on PEH in AA compared to CA. Our data show that AA exhibit altered BP control not only at rest (which has been shown in previous studies) but also following exercise, consistent with an increased risk of hypertension. The AA group in our study was also less fit than CA. However, after adjusting for cardiorespiratory fitness levels, none of the results were altered, suggesting that our findings
were not driven by differences in cardiovascular fitness levels. This finding is also consistent with prior research in PEH (Senitko, Charkoudian et al. 2002).

**Responses without histamine blockade**

Increases in DBP of ~10mmHg or more during and after exercise have been considered an abnormal BP response because it represents an unstable form of hypertension, and may be associated with coronary artery disease (Akhras, Upward et al. 1985). AA have been shown to exhibit cardiovascular hyper-reactivity to stress with an exaggerated blood pressure response to both behavioral and physiological sympathoexcitation (Bond, Mills et al. 1999). AA have also been shown to have higher systolic and diastolic BP during submaximal dynamic exercise compared to CA (Walker, Bassett et al. 1992). We did not measure BP during exercise, thus we cannot compare our data with those of Walker et al (Walker, Bassett et al. 1992). However, our data are consistent with a greater stress induced BP response in AA compared to CA.

Post exercise hypotension is well documented in CA, but several studies have reported either unchanged or increased BP following exercise in AA (Pescatello, Bairos et al. 2003, Enweze, Oke et al. 2007). Enweze et al. (Enweze, Oke et al. 2007) found no PEH in young, normotensive AA women 1 hour after cessation of 30 min of moderate-intensity cycling exercise. Furthermore, Pescatello et al. (Pescatello, Bairos et al. 2003) monitored daytime BP by ambulatory BP monitoring after 40 min of moderate-intensity upright cycling exercise. The
mean daytime SBP after exercise was increased in both normotensive and hypertensive AA women while no change was found in DBP. In contrast, exercise lowered SBP and DBP in hypertensive CA women but did not have any effect on SBP or DBP in CA with normal BP. Thus, prior studies support the notion that AA women do not exhibit PEH following moderate intensity endurance exercise. Our data provide partial support for these findings as carotid, brachial and aortic DBP and MAP increased in AA, but not CA following exercise. However, SBP was decreased in both AA and CA (at 60 min), which is in contrast to previous findings. It is possible that controlling for the diurnal influence on PEH by testing our subjects only in the afternoon-evening may have accounted for this difference. Although our data support the notion of an overall (MAP) lack of PEH in AA, we also found a lack of PEH in our CA subjects (MAP), which is in contrast to earlier studies (Senitko, Charkoudian et al. 2002, Lockwood, Pricher et al. 2005, Lockwood, Wilkins et al. 2005).

Post exercise BP is modulated by changes in peripheral vascular resistance and CO (Kenney and Seals 1993). The overall (both groups combined) increase in Brachial DBP at 90 min post exercise was primarily driven by the higher DBP in AA. Central hemodynamics did not contribute to the differential DBP responses because changes in CO following exercise were not different between AA and CA. Thus, differential changes in peripheral or systemic vascular resistance/conductance likely caused the greater increase in DBP in AA.
Although previous studies have demonstrated significant contribution of the lower limbs in mediating post exercise BP changes (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006, McCord and Halliwill 2006), femoral vasodilatation and femoral arterial stiffness do not seem to contribute to racial differences in BP changes after exercise in our study. As expected we did observe increases in Systemic VC following exercise, but there was no significant increase in Femoral VC in either AA or CA, even though both groups had increased femoral arterial diameter. In contrast to our hypothesis, Femoral and Systemic VC were also not different between AA and CA following exercise, and both AA and CA increased systemic VC. Since VC was slightly higher in CA throughout (although not significant) this may have accounted for the reduced change in DBP and MAP in CA compared to AA. Headley and colleagues (Headley, Keenan et al. 1998) found that 40 min of walking at approximately 50-60% of HRmax did not acutely lower the BP of middle-aged borderline hypertensive AA women who were not taking medication for their hypertension. Furthermore, Systemic vascular resistance (SVR) increased in AA women but decreased in CA following exercise. They further demonstrated that the differential responses were possibly due to higher rennin levels and downstream vasoactive substances in AA women. The discrepancy between their study and ours is probably due to the different subject population. Our subjects were young and normotensive. We did not measure
rennin or Endothelin-1 levels in our study but Endothelin-1 levels have been shown to be higher in hypertensive AA compared to normotensives of the same race (Ergul, Parish et al. 1996).

The different recovery patterns of arterial stiffness in the upper and lower limbs we observed were in accordance with previous studies (Naka, Tweddel et al. 2003, Ranadive, Fahs et al. 2012). It has been shown that the upper limb vascular bed is more responsive than lower limb vascular bed after both exercise and pharmacological provocation (Naka, Tweddel et al. 2006). Upper limb arterial stiffness decreased approximately 13% following arm exercise, while leg exercise had no significant effect on upper limb arterial stiffness. Conversely, lower limb arterial stiffness decreased (10.4%) and (13.2%) at 10 min of recovery following both maximal upper and lower limb cycling, respectively. This supports the possibility of discriminating between local and systemic consequences of exercise. Our data thus suggest that AA exhibit a different systemic response to exercise in terms of arterial stiffness, since AA increased brachial PWV while there was no change in CA, while central and femoral PWV were unchanged in either group. Our findings are in support of those of Heffernan et al. (Heffernan, Fahs et al. 2009), who showed that AA but not CA, increased brachial artery stiffness following 6 weeks of resistance exercise training.

It is possible that increased brachial artery stiffness and the absence of PEH in AA are related to sympathetic activation or compromised sympathetic withdrawal. Since muscle
sympathetic nerve activity (MSNA) was reduced post exercise with concurrent decreases in BP, PEH may be partly mediated by a reduction of sympathetic nerve activity to muscle vessels (Floras, Sinkey et al. 1989, Halliwill, Taylor et al. 1996). Thus, sympathetic withdrawal has been speculated to be the cause of increased vascular conductance in non-active regions (Barrett-O'Keefe, Kaplon et al. 2013).

At similar levels of MSNA in AA and CA, normotensive AA have less reduction in blood pressure than CA (Lang, Stein et al. 1997, Muszkat, Sofowora et al. 2004). Lang et al. observed that AA have reduced hypotensive responses to the alpha1-adrenergic receptor agonist clonidine compared with CA peers, despite similar central sympathoinhibition (Lang, Stein et al. 1997). AA also had exaggerated cardiovascular hyper-reactivity compared to CA, which may be a result of reduced beta adrenergic sensitivity and augmented alpha1-adrenergic receptor sensitivity (Lemogoum, Van Bortel et al. 2004). Thus, it is possible that differences in adrenergic activity may at least partially explain differences in PEH between AA and CA in our study.

Sympathetic stimulation is also accompanied by a reduction in arterial distensibility, by exerting vasomotor control in small resistance arteries and also by directly modulating large artery function (Wallin and Charkoudian 2007). Aortic stiffness is positively associated with MSNA in healthy men (Swierblewska, Hering et al. 2010). Large artery stiffness may also interfere with autonomic regulation by impairing carotid baroreflex sensitivity (Gribbin,
Pickering et al. 1971). Conversely, acute withdrawal of sympathetic tone caused decreased large artery stiffness, as demonstrated in sympathectomized rats (Mangoni, Mircoli et al. 1997), and also in healthy and atherosclerotic subjects during brachial plexus or subarachnoid anesthesia or one month after removal of the lumbar sympathetic chain (Failla, Grappiolo et al. 1999). Thus, it is possible that the differential responses in brachial stiffness observed between AA and CA in our study may be due to differential sympathetic responses to exercise, or differences in sympathetic withdrawal following exercise.

Although it was suggested that splanchnic, renal, or cutaneous circulation has limited contribution to post exercise BP regulation in CA, we cannot rule out their potential contribution to PEH in AA. Previous research has shown no differences between AA and CA hypertensive patients with respect to the hemodynamic characteristics of the splanchnic or renal circulation (Frohlich 1990, Rockstroh, Schmieder et al. 1997). However, AA patients showed a significant positive correlation between the levels of mean arterial pressure and renal vascular resistance while no such correlation was found in CA (Frohlich 1990). In addition, at any level of mean arterial pressure or total peripheral resistance, renal blood flow was significantly less and renal vascular resistance was significantly greater in the AA patients (Frohlich 1990).

In our study, both AA and CA had normal kidney function because eGFR in both groups were well above normal values. National Kidney Disease Education Program recommends
reporting eGFR values greater than or equal to 60 mL/min/1.73 m², and not as an exact number when using the Modification of Diet in Renal Disease Study (MDRD) equation. There are several considerations for this recommendation. First, the MDRD Study equation has been most extensively evaluated in people with chronic kidney disease and reduced GFR, and is less accurate for persons with normal or mildly impaired kidney function (Lin, Knight et al. 2003, Rule, Gussak et al. 2004). Secondly, quantification of eGFR values below 60 mL/min/1.73 m² has more clinical implications for classification of kidney function than values above this level. Considering that AA had higher eGFR than CA in our study, it is less likely that reduced renal blood flow in AA may contribute to reduced PEH.

Racial difference in DBP was not likely due to differences in hydration status or exercise stimulus because water intake and HR during exercise were not different between CA and AA. Regardless of the cause, the greater increase in DBP in AA is an intriguing finding and deserves follow-up in future studies. The clinical significance of identifying high-risk patients by the increased DBP following exercise in AA should be interpreted with caution. What has been identified as a clinically abnormal increase in DBP was observed during or immediately (up to 5 min) after exercise and the magnitude of increase was greater compared to our study (10~15mmHg vs. 5mmHg) (Akhras, Upward et al. 1985). It is not yet known whether the increase in DBP in AA is associated with higher risk of hypertension and coronary artery disease.
Therefore, the use of an exercise test as a means of early prediction of hypertension still requires methodological development and confirmation.

Future research is also warranted to examine the association between changes in BP after an acute bout of aerobic exercise and the chronic effect of aerobic exercise training on BP in AA. Two recent studies suggested the association between the magnitude of PEH and training-induced decrease of blood pressure in CA (Liu, Goodman et al. 2012, Hecksteden, Grutters et al. 2013). This finding implies the clinical relevance of PEH in CA and makes the magnitude of PEH after an acute bout of exercise a promising candidate for the prediction of individual blood pressure–related training efficacy. Considering the antihypertensive effect of aerobic exercise training in AA (Kokkinos, Narayan et al. 1995), the positive correlation between PEH and decreases in BP after exercise training may not apply to in AA. Conversely, AA may benefit from exercise training from decreased cardiac hyperactivity. A 16.2 mmHg decrement in mean systolic BP and an 11.5 mmHg decrement in mean diastolic BP were detected during the post-training submaximal exercise tests (Bond, Stephens et al. 2002). It’s intriguing whether aerobic exercise training has any effect on PEH in AA. Aerobic exercise training may, therefore, reduce the risk of hypertension in normotensive African-American males by the mechanism of a reduction in TPR
Another novel finding in our study was that differential responses between central and peripheral BP were found post exercise. There was a significantly higher Carotid SBP in AA compared to CA but no racial differences in Brachial or Aortic SBP following exercise. It is increasingly recognized that BP measured in the brachial artery may not be representative of aortic BP and that measurement of central (i.e., aortic or carotid) BP may be a better predictor of cardiac load and cardiovascular risk (Protogerou, Papaioannou et al. 2007). Williams et al. (Williams, Lacy et al. 2013) demonstrated that brachial and central pressure showed different diurnal patterns, which were not modulated by BP-lowering therapy, with relatively higher night-time central pressures. Antihypertensive drugs have been shown to decrease central blood pressure and subsequent improved clinical outcomes despite no effect on brachial artery pressures (Williams, Lacy et al. 2006). Evidence from high dietary salt intake increasing carotid systolic BP in young healthy men despite minimal changes in brachial BP also supported this notion (Starmans-Kool, Stanton et al. 2011).

Earlier work from our lab has shown that resting aortic BP was elevated in AA despite comparable brachial BP at rest (Heffernan, Jae et al. 2008). We have also demonstrated that changes in Aortic SBP following an acute bout of maximal aerobic exercise was greater in AA and CA despite comparable changes in Brachial SBP (Yan, Ranadive et al. 2014). Although we did not find any differential responses between Aortic and Brachial BP following an acute bout
of submaximal exercise in our present study, carotid SBP was higher in AA supporting that central artery BP may respond differently in AA compared to CA following exercise.

Consistent with previous reports, it appears that the decrease in SBP was likely due to increases in Systemic VC despite a small increase in CO (Kenney and Seals 1993, Rossow, Yan et al. 2010). However, the decrease of SBP was significant at 60 min post exercise, yet relatively small (~2 mmHg). It is unlikely this is a result of an insufficient exercise stimulus because the exercise intensity and duration was shown to consistently elicit PEH in prior studies (Kenney and Seals 1993, Pescatello and Kulikowich 2001). The less pronounced PEH in our study may be due to the nature of our young and healthy subject population. This is in agreement with the literature suggesting that the magnitude of PEH is greater in subjects with a higher initial BP level (Forjaz, Tinucci et al. 2000, Pescatello, Guidry et al. 2004) and several studies has suggested that PEH was only observed in young males with hypertension but not in age-matched normotensive males (Floras and Senn 1991, Wallace, Bogle et al. 1997). A similar observation was made in the only study available comparing racial differences in PEH including both CA and AA groups. Exercise lowered SBP and DBP in hypertensive CA women but did not have any effect on SBP or DBP in CA with normal BP (Pescatello, Bairos et al. 2003). The lack of PEH in CA observed in these studies may due to methodology. The prolonged measurement period of ambulatory blood pressure monitoring (22 h) following exercise may mask the acute hypotensive effect of exercise.
Indeed, several studies showed a ~4-5 mmHg decrease in MAP following 60 min of moderate intensity cycling exercise in young normotensive individuals up to 90 min during recovery (Senitko, Charkoudian et al. 2002, Lockwood, Pricher et al. 2005, Lockwood, Wilkins et al. 2005). There was also evidence of 1.2 mmHg decrease in BP in young and healthy individuals following 120 min of moderate intensity running (Liu, Thomas et al. 2013).

Surprisingly, we failed to observe decreases in MAP in CA up to 90 min following exercise. The discrepancies in findings between previous studies and ours may be due to the “placebo effect”. A relevant reduction of BP in placebo-treated control groups is a phenomenon often observed in pharmacological studies of hypertension (Preston, Materson et al. 2000). The subjects in the present study were given identical capsules of either placebo or histamine receptor blockades on two separate study days. The ingestion of novel capsules (even placebos) might elicit sympathoexcitatory responses and elevated BP. Subjects in our study may also exhibit higher cardiovascular reactivity from being exposed to various testing measurements in the lab setting. However, it should be noted that cardiovascular reactivity in the lab is correlated with field cardiovascular reactivity (Turner, Sherwood et al. 1994). Lastly, our study has a larger sample size (50) compared to most other studies (Senitko, Charkoudian et al. 2002, Lockwood, Pricher et al. 2005, Lockwood, Wilkins et al. 2005).
Influence of H1R and H2R antagonists

To our knowledge, this is the first study to compare racial differences in brachial and central BP following exercise with and without histamine blockade in AA and CA. Brachial, Carotid and Aortic DBP were all higher in AA compared to CA in the H1R and H2R blockade condition following exercise.

Baseline differences between AA and CA in SV and SVC were evident after the administration of H1R and H2R blockade but not during the placebo condition. Interestingly, histamine receptor antagonists does not seem to cause non-specific cardiovascular effects in the absence of exercise stimulus in CA. Intravenous infusion of H1R (hydroxyzine) or H2R (cimetidine) antagonist or a combination of the both antagonists did not alter HR or BP in CA subjects (Kaliner, Sigler et al. 1981). Oral ingestion of a H1R antagonist (540 mg of fexodenadine) or H2R antagonist (300 mg of ranitidine) also did not change CO, HR, BP, leg blood flow and skin blood flow under normal resting conditions (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006). The mechanism responsible for lower SV and SVC in AA after H1R and H2R blockade in our current study at rest is not clear. It is possible that AA is more responsive to H1R and H2R blockade compared to CA. Infusion of histamine has been shown to increase cardiac contractility as percentage cardiac fractional shortening increased from 38.2 ± 4.1 to 53.5 ± 3.6% and mean fiber shortening velocity increased from 1.31 ± 0.19 to 1.99 ± 0.22
cm/s. These changes were both greatly reduced by H2R blockade along with H1R blockade (Watkins, Dargie et al. 1982). This may explain why SV was also consistently lower in AA compared to CA during recovery from exercise during H1R and H2R blockaded trial in our study. It is possible that AA had decreased cardiac contractility in response to the H1R and H2R blockades even at rest without infusion of additional histamine and the hypo-responsiveness to H1R and H2R blockade remained during post exercise recovery.

There were no racial differences in femoral arterial stiffness or diastolic diameter during histamine receptor blockade. At 30 min after exercise however, the femoral artery was stiffer yet more dilated in the control condition. The change of femoral arterial stiffness seems to coincide with the change pattern of femoral diastolic diameter. However, in the H1R and H2R blockade condition, femoral arterial stiffness did not change while diastolic diameter was increased throughout 90 min post exercise recovery.

This result was somewhat unexpected, because in previous studies, H1R and H2R blockade contributed to blunted vasodilatation post exercise (Lockwood, Wilkins et al. 2005, McCord, Beasley et al. 2006). It has been known for a long time that the action of histamine on vascular smooth muscle may vary depending on the tissue and species (Levi, Rubin et al. 1991). Additionally, the variable influences of histamine are known to be location and concentration
dependent. Even in a segmental vessel, heterogeneity of the response to histamine has been described (Yu, Su et al. 1992).

Our differential findings between the carotid and femoral artery support this notion. Carotid arterial stiffness changed similarly to femoral arterial stiffness in the control condition with an increase at 30 min and decreased afterwards. However, in the H1R and H2R blockade condition, arterial stiffness was slightly decreased at the 30 min post exercise. Increased carotid arterial diameter was observed in both the control condition and in the H1R and H2R blockade condition. H1R and H2R blockade also elicited differential responses in the carotid artery between AA and CA. The extent of carotid arterial dilation was greater post exercise in AA compared to CA in the H1R and H2R blockade condition, whereas no racial difference was found for the control condition.

Little is known about the mechanism underlying the different effects of histamine on different tissues. It has been postulated that the histamine receptor distribution at different sites of the artery may contribute to the differential responses (Zawinka, Resch et al. 2004). It was also suggested that the vasodilator actions of histamine were at least partially dependent on nitric oxide (NO) (Gross 1981). NO is tonically released from endothelial cells and is essential to the maintenance of vasodilator tone and homeostasis, which are adversely affected by CVD risk factors (Quyyumi 1998). Using invasive techniques, AA have been shown to have reduced NO
bioactivity in the forearm microcirculation coupled with reduced smooth muscle vasodilator response to NO donors (Campia, Choucair et al. 2002). Forearm blood flow is also significantly attenuated in young AA compared to CA men following various pharmacological infusions including isoproterenol, methacholine, acetylcholine, and sodium nitroprusside (Lang, Stein et al. 1995, Stein, Lang et al. 1997, Stein, Lang et al. 2000, Kahn, Duffy et al. 2002). Additional evidence from human umbilical vein endothelial cells (HUVEC) also supported this notion (Brown and Feairheller 2013). AA seem to have an EC phenotype characterized by heightened oxidative stress, reduced antioxidant capacity (Feairheller, Park et al. 2011) and potential for a heightened inflammatory phenotype (Brown, Feairheller et al. 2011). In addition, AA HUVECs exhibited greater basal inducible NOS (iNOS) protein expression levels, which could be caused by the greater oxidative stress and inflammation (Feairheller, Park et al. 2011). Considering the notable differences in endothelial-dependent and endothelial–independent vascular dysfunction in AA compared to CA, it is possible that NO plays a crucial role in mediating the differential effects of H1R and H2R antagonists between AA and CA.

Limitations

We acknowledge potential limitations of the present study, which include the noninvasive assessment of central aortic pressure, rather than direct measurement. Central blood pressures,
although derived from a transfer function, are valid both at rest and following exercise, as shown by validation compared to invasive techniques (Sharman, Lim et al. 2006).

We did not control for socioeconomic status, however, we recruited most of our subjects from university students and therefore they had a similar level of education.

Finally, we acknowledge that the absolute difference in BP between AA and CA, although statistically significant, is numerically small, and further work is required to evaluate its clinical impact.
CHAPTER 6

SUMMARY AND CONCLUSIONS

We studied changes in BP following an acute bout of aerobic exercise in AA and CA with and without H1R and H2R blockade and explored peripheral and central hemodynamic responses. We tested the hypothesis that the extent of reductions in brachial and central BP differ between African-Americans and Caucasians. Our results suggested that brachial SBP was significantly decreased 60 min following an acute bout of aerobic exercise without any racial differences between AA and CA. However, Brachial DBP was significantly increased 90 min following exercise with greater values in AA compared to CA. The increase of Brachial DBP at 90 min post exercise was contrary to our hypothesis and led to a significant increase in Brachial MAP from 60 min to 90 min following exercise. Aortic BP exhibited similar trends compared to Brachial BP. Furthermore, differential responses between central and peripheral BP were found post exercise in CA and AA. There was a significantly higher Carotid SBP in AA compared to CA but no racial differences in Brachial or Aortic SBP following exercise.

We have also tested the hypothesis that AA would show greater vascular resistance (less vascular conductance) post exercise, coupled with greater arterial stiffness, but there would be no differences between races in CO. In agreement with this hypothesis, we observed that the
changes in CO were not different between races, suggesting central hemodynamics were not
difference between AA and CA. In contrast to our hypothesis, Femoral or Systemic VC was not
different between AA and CA following exercise in the control condition. We did observe an
increase in overall Systemic VC following exercise as expected. Our data also suggest that AA
exhibit a different systemic response to exercise in terms of arterial stiffness, since AA increased
brachial PWV while there was no change in CA, while central and femoral PWV were
unchanged in either group.

Lastly, we hypothesized that H1R and H2R antagonists would blunt PEH in CA while H1R
and H2R antagonists would have no effect on BP in AA. H1R and H2R blockade did not impact
Brachial or Aortic SBP in either CA or AA. However, Brachial DBP increased more in the
blockade condition. In addition, Brachial and Aortic DBP was higher in AA compared to CA in
the blockade condition 1 hour following exercise. Systemic VC exhibited greater increases in the
control condition compared to the H1R and H2R blockade condition. Brachial arterial stiffness
increased after exercise in the H1R and H2R blockade condition. Carotid and femoral arterial
vessel dilation was also affected by H1R and H2R antagonist. Increased femoral arterial diameter
was only observed up to 30 min following exercise in the control condition but dilated femoral
artery was sustained during the 90 min measurement period in the H1R and H2R blockade
condition, resulting greater vessel dilation in the blockade condition. Increased carotid arterial
diameter was sustained in both the control condition and the H1R and H2R blockade condition. Increased carotid vessel diameter was greater in AA compared to CA in the blockade condition whereas no racial differences were found in the control condition. There were no racial differences in femoral stiffness. AA had higher carotid stiffness during recovery both in the control and blockaded condition.

In conclusion, an acute bout of aerobic exercise increases DBP in young African Americans but not in Caucasians. The underlying mechanism for the BP increases may be related to increases in brachial artery stiffness and sympathetic activation and but not to changes in cardiac output. Moreover, DBP is also elevated in AA after exercise with histamine receptor blockade. However, H1R and H2R blockade elicited differential responses in cardiac function and carotid artery between AA and CA following exercise, suggesting a potential role of histamine receptors in mediating post exercise BP in AA. Our study also indicates that central BP may better reflect the level of vascular burden in young African Americans than Brachial BP. The heightened BP and vascular responses to exercise stimulus may play a role in the pathogenesis of hypertension in AA.
REFERENCES


