Ethnicity, Sex, and Vagal Activity: Differences in Hemodynamics Underlying Long-Term Blood Pressure Regulation

DISSERTATION

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Abstract

Hypertension, or high blood pressure, is a leading cause for mortality and morbidity worldwide. When split by ethnicity, African American (AA) individuals are at a greater risk for the development of hypertension compared to Caucasian American (CA) individuals. It is thought that over the course of hypertension, higher cardiac output is typically responsible for initially higher BP, and as hypertension progresses, cardiac output normalizes and total peripheral resistance (TPR) increases. Autonomic nervous system (ANS) activity is thought to underlie the development of hypertension, including the aforementioned hemodynamic changes. Ethnic differences have been found in resting ANS and hemodynamic activity, and are thought to potentially underlie ethnic disparities. Moreover, sex differences in resting ANS activity and the development of hypertension have been reported. One common theme underlying ethnic and sex differences in ANS control is vagally-mediated (vmHRV), which is widely recognized as an index of parasympathetic nervous system (PNS) activity, and serves as an independent risk factor for hypertension. However, research has yet to examine how ethnicity, sex, and vmHRV may interact to produce different patterns of hemodynamics in long-term BP regulation. In the following study, prospective methods were used to investigate this complex relationship. I investigated hemodynamic patterns over the course of six years, with physiological measures taken at two time points: (1) Baseline/initial visit (“Time 1”) and; (2) follow up visit on an average of 6 years later (“Time 2”). I considered hemodynamic patterns from “Time 1” to “Time 2” in the full sample, in addition to split by ethnicity.
(AAs and CAs), by sex (males and females), and vmHRV at “Time 1”. A median split was conducted on “Time 1” vmHRV to create high and low vmHRV groups to show the impact of relative high and low vmHRV on hemodynamics over time. Results showed that in normotensive individuals, CAs show a relative normal aging of the cardiovascular system over time, characterized by increased BP over time via increased cardiac output and stable or decreased TPR, a pattern seen especially in CA males with higher vmHRV. In contrast, AAs showed a more deleterious pattern of cardiovascular activity, marked by increased BP via increases in TPR, a pattern seen especially in AA females with lower vmHRV. Overall these data suggest a similar outcome of higher BP, however this is achieved via different hemodynamic mechanisms as a function of ethnicity, sex, and resting PNS activity as indexed by baseline vmHRV. Based on these factors, implications for psychophysiological function, in addition to the development and treatment of hypertension, will be discussed.
To my “Grandad”
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Fields of Study

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Chapter 1: An Introduction

1.1 Synopsis

Between the years 2011 and 2014, the prevalence of hypertension, or dangerously-high resting blood pressure (BP), is estimated to have impacted upwards of 85 million US adults (Benjamin et al., 2017). Chronic or long-term high BP can lead to a number of disease states, including kidney and heart failure (Lackland and Weber, 2015; Pickering, 1952). As such, hypertension is considered a leading risk factor for mortality and morbidity not only in the US, but worldwide (Lopez, Mathers, Ezzati, Jamison, and Murray, 2006). When split by ethnicity, African American (AA) individuals are at a much greater risk for the development, and thus consequences, of hypertension (Benjamin et al., 2017; Karlamangla, Merkin, Crimmins, & Seeman, 2010). For example, AAs have an earlier onset of disease, greater general impairment, and worse prognosis (likely course of disease) due to hypertension compared to Caucasian American (CA) individuals (Mensah, Mokdad, Ford, Greenlund, & Croft, 2005). Over the course of hypertension, well documented changes in hemodynamic activity occur, also called blood flow parameters, that are likely mediated by activity of the autonomic nervous system (ANS; Julius and Nesbitt, 1996; Ellis and Julius, 1973; Lund-Johansen, 1994; Julius, 1971 Julius, 1991; Palatini and Julius, 2009).
Importantly, AAs and CAs have shown to differ at rest in these very hemodynamic measures in addition to ANS control of the heart; such differences have been proposed as mechanisms underlying such health disparities (Hill et al., 2015; Kemp et al., 2016). However how the course of hemodynamics may change as a function of ethnicity is not well understood. Additionally, males and females have been shown to differ in their ANS control of the heart at rest (Koenig and Thayer, 2016). While sex differences in the development of hypertension are well documented (Hogarth, Burns, Mackintosh, Mary, 2008; Hogarth, Mackintosh, Mary, 2007; Palatini, 2001; Palatini and Julius, 2009), how changes in hemodynamic activity may be impacted by both ethnicity and sex have not been adequately investigated.

One common theme underlying both ethnic and sex differences in ANS control is resting-state vagally-mediated heart rate variability (vmHRV), which is widely recognized as a psychophysiological index overall health and parasympathetic nervous system (PNS) activity (Thayer and Lane, 2000; Thayer, Ahs, Fredrikson, Sollers, and Wager, 2012). Importantly, low vagal (or PNS) activity serves as an independent risk factor for hypertension and other cardiovascular and health risks (Thayer and Lane, 2009; Thayer and Sternberg, 2006). Higher PNS activity can be compensatory when facing greater sympathetic (SNS) activity and subsequent increases in greater BP. Therefore, as PNS activity should dominate SNS activity, PNS activity has been implicated in the regulation of long-term BP (Guyenet, 2006; Hill, Thayer, Halbert, Hao, Robinson, Harshfield, and Kapuku, under review; Laio, Cai, Barnes, Tyroler, Rautaharju, Holme, and Heiss, 1996; Palatini, Longo, Zetta, Perkovic, Garbelotto, and Pessina, 2006).
Therefore, vmHRV may also contribute to hemodynamic patterns underlying potential ethnic and sex differences in long-term BP regulation, yet no study has attempted to understand how ethnicity, sex, and vmHRV may produce different patterns of hemodynamics in long-term BP regulation.

Utilizing archival data from an empirical prospective study, I investigated hemodynamic patterns over the course of six years, with physiological measures taken at two time points: (1) Baseline/initial visit (“Time 1”) and; (2) follow up visit on an average of 6 years later (“Time 2”). I considered hemodynamic patterns from “Time 1” to “Time 2” in the full sample, in addition to split by ethnicity (AAs and CAs), by sex (males and females), and vmHRV at baseline (high and low levels of vmHRV indexed at “Time 1”). In sum, I explored the complex impact of three major factors (ethnicity, sex, resting vmHRV) on the maintenance of BP over six years in normotensive young people. Such differences in hemodynamics over time between these various groups would have major psychophysiological implications for the course – and thereby treatment – of hypertension.

1.2 Blood Pressure Regulation and Hypertension: An Autonomic Nervous System Perspective

Hypertension is defined as a resting systolic pressure of greater than 140 mmHg (millimeter of mercury) and diastolic pressure greater than 90 mmHg (Benjamin et al., 2017). Hypertension can be classified as either primary or secondary. In most cases hypertension is primary or essential (Berglund, Andersson, and Wilhelmsen 1976; Danielson and Dammstrom, 1981), which is defined as chronic increased BP with an
unknown cause or origin. For many years, it has been proposed that genetic and/or lifestyle factors, such as environmental stressors (Zimmerman and Frohlich, 1990) and/or dietary and lifestyle factors (Geleijnse, Kok, and Grobbee, 2004), may underlie the development of essential hypertension. In contrast, secondary hypertension is defined as chronic increased BP with a known origin, such as kidney (renal) disease. Given the characteristics of secondary hypertension, potential treatments and cures are better identifiable. On the other hand, essential hypertension affects more individuals compared to secondary hypertension (Berglund et al., 1976; Danielson and Dammstrom, 1981), and is potentially more difficult to treat given that the mechanism may not be isolated.

Frontal brain regions such as the prefrontal cortex (PFC) and anterior cingulate cortex (for review, see Etkin, Egner, & Kalisch, 2011) exert an inhibitory influence on subcortical brain structures such as the amygdala, allowing the organism to adaptively respond to demands from the environment, and organize their emotional and behavioral responses effectively (Etkin et al., 2011; Lane, McRae, Reiman, Chen, Ahem, and Thayer, 2009; Urry et al., 2006). The reciprocal activity of these brain structures output at the ANS (autonomic nervous system). The ANS dually innervates peripheral organs, thereby regulating many important bodily systems, including the cardiac, respiratory, immune, and endocrine systems (for review, see Thayer and Lane, 2009). In the resting state, ANS influence is characterized by a relative dominance of the parasympathetic nervous system (PNS) over influences of the sympathetic nervous system (SNS; fight-or-flight; Sleight, 1997; Thayer and Lane, 2009; Thayer and Sternberg, 2006) – a pattern of adaptive activity that represents ANS balance. In contrast, autonomic imbalance is
characterized as a hyperactive SNS and hypoactive PNS at rest and is predictive of mortality and morbidity (Thayer et al., 2010; Wulsin, Horn, Perry, Massaro, and D’Angostino, 2015), including from hypertension (Brook and Julius, 2000). PNS activity is of particular importance as the vagus chronically inhibits SNS activity via the neurotransmitter acetylcholine. Thus, lower PNS activity is independently associated with a number of disease states, including cardiovascular disease and hypertension (see Thayer et al., 2010 for review). In sum, these physiological relationships lay the foundation for theories suggesting neural mechanisms as contributors to long-term BP regulation (Palatini and Julius, 2009).

For years, researchers have acknowledged the role of the ANS in hypertension. Specifically, the SNS has been long implicated in the development of hypertension such that it can begin early in life (Julius et al., 1991) and precedes the development of essential hypertension (i.e., borderline hypertension; Julius, Schork, and Schork, 1987; Julius et al., 1991; Palatini and Julius, 2009). It is well-known that increased cardiac output and heart rate (HR) are two characteristics of borderline or early hypertension (Fries, 1960; Lund-Johansen, 1980; Palatini and Julius, 2009). Cardiac output is determined by the product of HR and stroke volume, (for example, see Vatner and Boettcher, 1978; See Figure 1 for Diagram). Generally, these hemodynamic mechanisms are thought to underlie initial increases in BP (i.e., in borderline hypertensive individuals) mediated by a hyperactive SNS (Lund-Johansen, 1980). Overall, this state of SNS hyperactivity is thought to underlie increased HR and thus cardiac output, and subsequently greater BP in borderline hypertensive individuals (see Palatini and Julius,
The first empirical study to display the importance of the PNS in BP regulation tested the role of both beta-adrenergic receptors (receptors that the SNS interacts with to increase HR and BP) and nicotinic acetylcholine receptors (receptors that the PNS interacts with to decrease HR and BP) in determining BP (Julius et al., 1971). Eleven borderline hypertensive and 16 normotensive individuals first rested, and then were administered propranolol and atropine. Propranolol is considered an antagonist (blocker) of these beta receptors and thus, blocker of SNS influence. Atropine is an antagonist of the PNS system. Results showed borderline hypertensive individuals to indeed have high HR, cardiac output, and BP (systolic and diastolic) compared to those in the normotensive group at rest. When administered propranolol, cardiac output and HR decreased significantly in both groups, however borderline hypertensive individuals remained higher on all variables compared to normotensives. This result highlights the importance of the PNS – it is the lack of inhibitory control via the neurotransmitter acetylcholine that allows these group differences in cardiac output and HR to persist without direct SNS influence (Julius et al., 1971). Moreover, when atropine was administered, groups no longer differed on cardiac output and HR, however BP remained elevated. This suggests that cardiac output and HR are not necessarily maintaining higher BP in borderline hypertensive compared to normotensive individuals. Taken together, these results suggest that the PNS and SNS play important roles in the beginning stages of hypertension; however, this study also highlights the importance of PNS activity in regulating BP via inhibition.
Julius and colleagues (1971) proposed that a hyperkinetic state, marked by lower PNS activity accompanied by higher SNS activity, in borderline hypertensive individuals that maintain increased HR and cardiac output, thus maintaining increased BP (Julius et al., 1971; Palatini and Julius, 2009). One study showed that borderline hypertensive individuals in a hyperkinetic state were more likely to progress to essential hypertension six years later compared to borderline hypertensive individuals without such ANS abnormalities (Palantini, Longo, Zaetta, Perkovi, Garbelotto, and Pessina, 2006), thereby providing longitudinal evidence of the impact the ANS has on the course of hypertension.

In sum, a hyperactive SNS and a hypoactive PNS activity (i.e., autonomic imbalance) serves as a process underlying hemodynamic patterns (e.g., increased cardiac output, HR) seen in borderline hypertensive individuals, is a precursor of essential hypertension, and is overall characteristic of borderline hypertensive individuals in a hyperkinetic state (Julius et al., 1971; Palatini and Julius, 2009; Palantini et al., 2006).

Interestingly, should an individual progress from borderline hypertension to essential hypertension, this person’s hemodynamic profile will also change over the course of hypertension (Lund-Johansen, 1980; Lund-Johansen., 1989; Palantini et al., 2006). Specifically, as the course of hypertension continues, HR and cardiac output activity begins to normalize, however BP remains elevated via increased TPR. This hemodynamic transition from a state of high cardiac output to high TPR has been shown longitudinally (Julius and Nesbitt, 1996; Lund-Johansen, 1994). For example, one study showed that at a 10-year follow up, hypertensive individuals transitioned from increased cardiac output to decreased cardiac output and increased TPR, and this difference was
even more pronounced and consistent (across both rest and exercise) at the 20-year follow-up (Lund-Johansen, 1989). A well-known mechanism of this hemodynamic transition is the down-regulation of beta-adrenergic receptors which decreases SNS influence, and thus decreases HR. Decreased cardiac compliance, or how easily heart ventricles and vessels expand, occurs due to cardiac and vascular hypertrophy, or the thickening of heart ventricles and vessels. This decrease in cardiac compliance leads to a decrease in stroke volume, or the amount of blood pumped by the left ventricle each beat. Therefore, as both HR and stroke volume decrease, their product, cardiac output also decreases. Meanwhile, cardiac compliance is indicative of the stiffening of vessel walls, called vascular hypertrophy, which have a direct impact on TPR, or how resistant these vessels are to blood flow. Higher TPR at rest is associated with excessive vascular reactivity to vasoconstrictor stimuli such as stress. Therefore, a “resetting” of the SNS system in the course of hypertension occurs in tandem with this hemodynamic transition from high cardiac output to higher TPR, such that SNS hyperactivity as seen in borderline hypertension normalizes (via decreased beta-adrenergic receptor activity). Some propose that this change from increased beta-adrenergic SNS activity in borderline hypertensive individuals to apparently normal beta-adrenergic SNS activity in essential hypertension can best be explained within the conceptual framework of the “BP-seeking” properties of the brain (Palatini and Julius, 2009). In hypertension, the central nervous system seeks to maintain systemic BP at the higher level. Via both vascular hypertrophy and the down-regulation of beta-adrenergic receptors, less SNS activation is needed to
maintain vasoconstriction (Lund-Johansen, 1980; Lund-Johansen., 1989; Palantini and Julius, 2009; Palantini et al., 2006).

Mean arterial pressure (MAP) is an index of BP, and is determined by the product of cardiac output (CO) and TPR (MAP = CO * TPR; see Figure 1 for details). Therefore although MAP increases in the transition from borderline to essential hypertension, the underlying hemodynamics change from elevated cardiac output in borderline hypertension to elevated TPR in essential hypertension (Lund-Johansen., 1980; Lund-Johansen., 1989). It is important to note that BP elevations mediated by TPR increases are more deleterious in comparison to cardiac output mediated BP elevations, as mean BP is higher and can lead to end-organ damage (Fagard, Pardaens, Staessen, & Thijs, 1996; Mensah, Pappas, Koren, Ulin, Laragh, & Devereux, 1993).

*Figure 1. Diagram of Hemodynamics Determining Mean Arterial Pressure*
1.3 Physiological Mechanisms Underlying Long-Term BP Regulation: The Baroreflex

As mentioned, greater PNS activity may act as compensation for greater SNS activity. However as it relates to BP regulation, the PNS is involved directly in vasodilation via the baroreflex (Thrasher, 2006). Baroreceptors are responsible for adjusting cardiovascular activity in accordance with changes in BP. The baroreceptor reflex is comprised of three branches, each responsible for adjusting (i) inter-beat intervals (IBIs)/HR (ii) TPR, and (iii) stroke volume (SV) in accordance with changes in BP a process known as the baroreflex. Baroreflex sensitivity (BRS) can be defined as the magnitude of changes in cardiovascular activity in accordance with BP changes and baroreflex effectiveness (BEI) can be defined as the ratio of BP changes that elicit actual changes in cardiovascular activity. Anatomically, arterial baroreceptors are located in both the aortic arch and the carotid sinus (at the top of the common carotid sinus).

Baroreceptors are stretch sensitive – a change, either increase or decrease, in BP leads to a “reflex” firing of afferent signals from the baroceptors (via the vagus) to the brain, and an efferent signal is sent back to the body in an attempt to control stroke volume, IBIs, and TPR in accordance with these changes (See Figure 2 for illustration).

For example, an increase in BP (i.e., MAP; see “Hypertensive stimulus” column) leads to firing of baroreceptors that elicit an excitatory signal (via glutamate) in the nucleus tractus solitarius (NTS) to the caudal ventrolateral medulla (CVLM) that sends an inhibitory signal to the rostral ventrolateral medulla (RVLM). This signal leads to
greater release of acetylcholine via PNS activation, and inhibits firing of sympathetic preganglionic neurons. This leads to increased PNS activity and thus reduced SNS activity. This action decreases both cardiac output (via decreased HR and stroke volume) and TPR and thus, normalizes MAP.

Figure 2. Diagram of Baroreflex Afferents and Brain Stem Efferents via the ANS in Response to Stimuli

A decrease in BP would lead to a reduction in baroreceptor firing and therefore reverse responses at each step (For discussion, see Victor, 2015). Importantly, the baroreflex chronically inhibits action at the RVLM (firing of SNS nerves). Therefore, the baroreflex is directly involved in BP regulation via the vagus, which determines BP via vasodilation (i.e., TPR; See Figure 2, labeled as “TVC” or total vascular constriction) and cardiac output (i.e., via HR and stroke volume – labeled as “HR” and “SV” in Figure 1,
respectively). Longitudinally, research has shown BRS to predict BP 5 years later (Ducher, Fauvel, and Cerutti, 2006).
Chapter 2: Ethnic Differences in both Hypertension and Cardiac Activity

As previously mentioned, AAs are at an increased risk for hypertension compared to CAs (Benjamin et al., 2016). As it relates to hemodynamics, AA individuals typically show greater resting BP (Chaturvedi and McKeigue, 1993; Dorr, Brosschot, Sollers, and Thayer, 2007) and transition from normal to high levels of BP quicker (Hardy et al., 2017) in comparison to CA individuals. Strikingly, AAs show early signs of vascular dysfunction compared to CAs (Gaillard, Schuster, and Osei, 2009; Stein, Lang, Singh, He, and Wood; 2000; Kahn et al., 2002; Frohlich, 1990; Taherzadeh, Brewster, Van Montfrans, and VanBavel, 2010) marked by increased TPR (e.g., Dorr et al., 2007) which have been proposed to underlie ethnic differences in BP (for discussion, see Hill et al., 2015).

One physiological process thought to underlie these TPR mediated elevations in blood pressure is impaired vasodilation in AAs. Studies have shown that greater doses of acetylcholine, the primary inhibitory neurotransmitter secreted via the PNS, are needed in AAs to produce the same degree of vasodilation in CAs (Jones, Andrawis, & Abernethy, 1999; Taherzadeh et al 2010). Another study showed AA individuals to have increased vascular alpha-adrenergic responsivity and suggest that increased TPR is more easily achieved in AAs compared to CAs (Sherwood et al., 1995). Early on, studies focused on potential mechanisms that would increase BP, or more generally SNS activity, in AAs
and thus potentially lead to these increases in TPR over time. One popular proposed mechanism underlying increased hemodynamic activity is diet (e.g., Ferdinand and Armani, 2007) – some propose that increased salt intake in the AA culture may be the reason for increased BP (for discussion, see Dorr et al., 2007; and Williams and Mohammed, 2009). Nevertheless, studies have shown that despite both diet, exercise, and socioeconomic status, AAs remain at an increased risk for hypertension and other diseases (Gadegbeku, Lea, and Jamerson, 2005).

Strikingly, AAs also tend to have greater resting vagally mediated heart rate variability (vmHRV) – a well-known index of cardiac PNS activity – in comparison to CAs (see Hill et al., 2015 for meta-analysis). Indeed, I and others typically conceptualize PNS and SNS activity as two opposing entities, and this is not entirely accurate. Coactivation of the PNS and SNS may reduce the impact of increased SNS activity, as the PNS should “eventually” dominate the SNS as compensation. However, this increased PNS activity – or compensatory mechanism – cannot be effectively inhibiting SNS action in AAs as key hemodynamics, such as BP and TPR, remain elevated leading to higher disease risk compared to CAs (see Hill et al., 2015 for discussion). In other words, in AAs, the PNS does not seem to “eventually” dominate the SNS as one would theorize. This general finding (in addition to others) serves as evidence of impaired vasodilation; greater PNS activity is indicative of greater acetylcholine and should be associated with lesser TPR via vasodilation and therefore, lower BP (TPR). In sum, given the cardioprotective nature of the PNS, this pattern of increased resting alpha-adrenergic
SNS activity and PNS activity found in AAs compared to CAs is counterintuitive, and has been termed the “cardiovascular conundrum” (Hill et al., 2015).

For example, one study (Dorr et al., 2007) examined the impact of anger expression and inhibition on hemodynamics in AA compared to CA individuals. Participants engaged in both a racially-charged and neutral debate with a CA confederate. Results showed that all participants who inhibited their anger showed delayed recovery of TPR. However, CAs who expressed their anger showed faster recovery in comparison to AAs. In fact, AAs who expressed their anger showed greater BP via increased cardiac output and decreased vmHRV. In other words, psychological stress in AAs can lead to maladaptive patterns of hemodynamics, despite greater vmHRV. Researchers posit that higher PNS activity in AAs may not be as effective in decreasing SNS activity and thus elevations in BP mediated by TPR.

Interestingly, our lab recently showed AAs and CAs to be similar in BRS of the IBI branch, but showed poorer TPR and IBI BEI (Williams et al., 2016). Moreover, the endothelium (the inner lining) of blood vessels utilizes nitric oxide to relax and promote vasodilation; endothelial-dependent arterial dilatation (EDAD) is a measure that represents nitric oxide mediated vasodilation. We also showed AAs to have decreased EDAD in comparison to EAs (Williams et al., 2017). In sum, there has been work illustrating a difference in physiological profiles between AAs and CAs in a resting state (e.g., Dorr et al., 2007; Hill et al., 2015). Higher vmHRV and TPR is typically seen in AAs and it has been proposed that greater vmHRV serves as compensation for greater TPR. Yet BP and TPR is not reduced in AAs and the risk for mortality and morbidity
from hypertension remains greater than that of CAs (Hill et al., 2015); therefore, this compensation may not be acting effectively. It appears that effectiveness in the TPR branch of the baroreflex, in addition to nitric oxide levels, are important mechanisms here. However, ethnic differences in hemodynamics underlying long-term BP regulation have not been adequately investigated, which would have implications for ethnic differences in the actual course of hypertension (from borderline to essential), particularly in the transition from high cardiac output to high TPR. Additionally, how PNS activity, as compensation for increases in BP, may further impact these potential differences has not been investigated.
Chapter 3: Sex Differences in Cardiac Activity and Hypertension

Similar to AAs and CAs, studies have shown women and men to differ in their physiological profiles. However, there are vast differences here. First, women tend to show higher resting HR in comparison to men, yet, women show a lower prevalence of hypertension and its associated consequences (Hogarth et al, 2007, 2008; Narkiewicz, Phillips, Kato, Hering, and Bieniaszeksji, 2005). Moreover, higher HR is more predictive of cardiovascular events in men compared to women. In fact, postmenopausal women with essential hypertension are thought to have similar risk of cardiac events compared to men, yet, these same women showed lesser SNS hyperactivity in comparison to men (Hogarth et al, 2008). A recent meta-analysis (Koenig & Thayer, 2016) found women to show greater resting vmHRV. This pattern of results – higher HR and vmHRV – in women is also thought to be counterintuitive (Koenig & Thayer, 2016).

In the context of hypertension, this result makes sense, as greater PNS activity can be cardioprotective against elevated BP due to elevated cardiac output, particularly in borderline hypertensive individuals. As mentioned, the action of the PNS can inhibit the SNS, thereby decreasing the risk of end-organ damage and other consequences of vascular hypertrophy (via the baroreflex) due to prolonged SNS activity. Therefore in women, higher vmHRV as compensation for higher HR appears effective as they do not show increased CVD, hypertension, or other disease risk compared to men.
In sum, while women and AAs show similar HR and vmHRV patterns in comparison to their counterparts, the consequences are very different. Greater vmHRV is thought to represent compensation in the face of greater SNS activity – women seem to be less likely to experience negative cardiac events despite increased HR. This suggests that, in coactivation in women, the PNS may indeed “eventually” dominate. In contrast, AAs remain at a greater risk for hypertension via increased TPR despite increased PNS activity. Overall women’s compensatory mechanism – increased vmHRV – appears effective at regulating SNS activity and serving as protection from cardiovascular events, whereas the compensatory mechanism in AAs does not appear as effective in reducing SNS activity, TPR, or hypertension risk.
Chapter 4: The Present Study

Hypertension and hypertension related disorders can lead to diseases (e.g., cardiovascular disease) that claim the lives of thousands of individuals per year in America – as previously mentioned, these numbers are proportionately greater in AAs compared to CAs (Benjamin et al., 2016). Low PNS activity, as indexed by low vmHRV, serves as an independent risk factor for hypertension and other diseases. Recent studies have shown vmHRV to predict BP years later independent of both sex and ethnicity (e.g., Hill et al., under review; Liao et al., 1996). This work and others (e.g., Julius et al., 1971) provide converging empirical evidence suggesting that the PNS plays an important role in the hemodynamic mechanisms responsible for maintaining long-term BP.

There is a hemodynamic transition that occurs in the development of hypertension – it is from a hyperkinetic state (high cardiac output) in borderline hypertension to a high vascular resistance state in essential hypertension (Lund-Johansen, 1980; Lund-Johansen., 1989; Julius et al., 1971; Palatini and Julius, 2009; Palantini et al., 2006). It is plausible that, as AAs show early signs of vascular dysfunction, TPR may be the primary mechanism responsible for increased BP over time compared to CAs. However, research has not yet investigated how hemodynamic patterns may differ as a function of ethnicity over time. Moreover, research has not yet considered how sex might further impact these differences. Finally, as greater resting vmHRV may represent a compensatory mechanism
for greater SNS activity with differential effectiveness across ethnicity (Hill et al., 2015) and sex (Koenig and Thayer, 2016), and vmHRV is an independent predictor of increased BP (Hill et al., under review), understanding how vmHRV further impacts potential differential hemodynamic patterns based on sex and ethnicity is also important.

In the following study, prospective methods were used to investigate this complex relationship. I investigated hemodynamic patterns over the course of six years, with physiological measures taken at two time points: (1) Baseline/initial visit (“Time 1”) and; (2) follow up visit on an average of 6 years later (“Time 2”). I considered hemodynamic patterns from “Time 1” to “Time 2” in the full sample, in addition to split by ethnicity (AAs and CAs), by sex (males and females), and vmHRV at “Time 1”. A median split was conducted on “Time 1” vmHRV to create high and low vmHRV groups to show the impact of relative high and low vmHRV on hemodynamics over time.

4.1 Hypotheses Regarding Baseline Group Differences

I hypothesized AAs to show greater BP (MAP), TPR, and vmHRV, but lower cardiac output, in comparison to CAs. I also expected greater HR and vmHRV to be present in women compared to men. Additionally, I expected that those with relatively lower vmHRV (low vmHRV group) at baseline to have greater BP and HR at baseline compared to those in the high vmHRV group. I expected AAs to show increased TPR and relatively stable cardiac output and thus, increased BP. In contrast, I hypothesized CAs to show increased BP as a function of increased cardiac output and decreased TPR. Thus, I expect to find evidence of the “cardiovascular conundrum” (higher TPR and higher PNS activity).
4.2 Hypotheses for Hemodynamics by Ethnicity and Resting-Baseline vmHRV

As it is theorized that AAs show early signs of vascular dysfunction compared to CAs (Hill et al., 2015), I expected all AAs to show greater BP characterized by increased TPR and stable or decreased cardiac output from Time 1 to Time 2. However, I expected this pattern of results to be particularly evident in AAs in the low vmHRV group (representing poorer compensation), but still significantly present in AAs in the high vmHRV group (representing less effective compensation).

I expected CAs to show greater BP over time, but not to the degree of AAs. Additionally, I expected CAs in the low vmHRV groups to show increased BP as a product of greater cardiac output and stable TPR, whereas CAs in the high vmHRV group should show a relatively smaller increase in BP as a product of greater cardiac output and decreases in TPR. Overall, I expected increased BP over time in all groups (as a function of aging), however I expected the magnitude of this increase in BP to be greater in AAs compared to CAs, especially in the low vmHRV group, and that TPR and cardiac output should characterize AAs and CAs increased BP, respectively.

4.3 Hypotheses for Hemodynamics by Ethnicity, Resting vmHRV, and Sex

In line with the above hypotheses, for AAs I expect for both males and females in the low vmHRV group to show increased BP over time via increased TPR and relatively stable cardiac output. According to prior theory, AA women in the low vmHRV group should show poorer compensation from both an ethnicity and sex perspective, therefore it is plausible that this demographic will show the greatest increase in BP characterized by TPR elevations and stable cardiac output. I expected for AA males in the high vmHRV
(less effective compensation) group to show a similar pattern as AAs in the low vmHRV group (poorer compensation). I made no specific hypotheses regarding AA female individuals in the high vmHRV group, as it is difficult to determine if AA females’ compensation (i.e., higher vmHRV) will be (more or less) effective.

I expected CA males in the low vmHRV group to show increased BP over time as a product of stable TPR and increased cardiac output. I expected CA males in the high vmHRV group to show no significant change in BP as both cardiac output and TPR should be decreased. As CA females in the low vmHRV group should show poorer compensation, I expected greater elevated BP (via increased cardiac output and stable TPR) compared to CA females in the high vmHRV group (effective compensation). I expected CA females in the high vmHRV group to show increased BP via increases in cardiac output and decreased TPR.

4.4 Overall Aim

In sum, I explored the complex impact of three major factors (ethnicity, sex, resting vmHRV) on the maintenance of two important parameters in determining BP, cardiac output and TPR, over six years in normotensive young people, as differences in hemodynamics between these various groups would have major psychophysiological implications for the course – and thereby both pharmacological and behavioral treatment – of hypertension.
Chapter 5: Methods

I utilized archival participant data collected at Augusta University in Augusta, GA. The study was approved by the institutional review committee. Following informed consent, all demographic, body, and physiological measurements were obtained by a female research assistant of the same ethnicity as the subject.

At the first-time point (Time 1) all demographic, body, hemodynamic, and cardiac measures were assessed. It is important to note that socioeconomic status (SES), also split by mother and father SES, was assessed at Time 1 using the Hollingshead Four-Factor Index of Socioeconomic Status. Such data was not available for all participants and thus is not included in the following analyses as it led to a much smaller sample size. For those who had such data, AAs showed significantly lesser SES compared CAs (AAs: mean = 34.96, standard deviation (SD) = 15.84; CAs: mean = 42.18, SD = 15.48; \( t_{(339)} = 7.22, p < .001 \)). Additionally, father’s education (AAs: mean = 4.70, SD = 1.29; CAs: mean = 5.16, SD = 1.26; \( t_{(280)} = 2.99, p = .003 \)) and SES (AAs: mean = 37.61, SD = 16.81; CAs: mean = 29.48, SD = 13.98; \( t_{(291)} = 4.46, p < .001 \)) was significantly higher in CAs compared to AAs. There was no difference between sexes or vmHRV group (each \( p > .121 \)). Finally, there was a significant difference between individuals with SES information and individuals without in the domain of smoking only (individuals with
SES: mean = 0.33, SD = 0.47; individuals without SES: mean = 0.48, SD = 0.50; $t_{(387)} = 2.10, p = .036$; all other comparisons were not significant.

During the second-time point (Time 2), some demographic, some body, all hemodynamic, and no cardiac measures (except HR) were assessed (see below for details).

### 5.1 Participants Demographics

In this study, 389 normotensive youths (mean age 23.2 ± 2.9 years; 211 females; 178 males) were recruited. Of the 389 participants, there were a total of 211 AA (mean age 23.6 ± 2.8 years; 128 females, 83 males) and 178 CA (mean age 23.7 ± 2.9 years) normotensive youth individuals. All individuals participated in two separate laboratory evaluations separated by an average of 6.32 years (minimum of 2.1, maximum of 8.2 years). Participants were initially aged between 15 to 32 years (mean demographics of the full sample shown in Table 1, split by ethnicity in Table 2).

### 5.6 Body and Demographic Evaluation

At time 1, participants’ height (in centimeters) and weight (in kilograms) were measured without shoes with a Health-O-Meter medical scale, which was calibrated daily. Body mass index (BMI) was calculated as weight/height$^2$. Waist circumference was also assessed in inches. Smoking was assessed using a yes/no dichotomy; no: having never smoked; and yes: have smoked at all. Medical histories were also recorded. At time 2, height, weight, BMI, and WC were assessed again.

### 5.7 Hemodynamic Measures
For hemodynamic assessment, all participants were escorted to a quiet temperature controlled room (20°C to 22°C) and fitted with a Dinamap Vital Signs Monitor (model 1864 SX; Criticon Inc., Tampa, Florida) for the measurement of BP. Participants were placed in a supine position and spontaneously breathing and were given standardized instructions to relax for 15 minutes and not to move or fall asleep. The inflatable cuff was wrapped around participants’ upper arm, and readings were automatically taken at 11, 13, and 15 minutes, during a 15-minute supine relaxation period. The average of the last 2 readings was used to represent one hemodynamic value per measure, per evaluation (at both Time 1 and Time 2). Primary hemodynamic measures of interest include TPR, cardiac output, and their product MAP. Secondary measures of interest include stroke volume and HR as determinants of cardiac output, and systolic and diastolic BP for completeness. The TPR index and cardiac output index were also computed; both TPR and cardiac output values were divided by total body surface area. Body surface area was calculated using the following calculation: body surface area = .007184 x weight\(^{0.425}\) x height\(^{0.725}\) (Du Bois and Du Bois, 1916; Verbraken, Van de Heyning, De Backer, Van Gaal, 2006).

5.8 Cardiac Measures

Continuous HR data was recorded using a BioZ impedance monitor (Cardio-Dynamics, San Diego, CA) at Time 1 only. Electrodes were placed (1) below the right clavicle, (2) on the left side of the abdomen (below the heart), (3) on the right side of the abdomen (4) at the notch of the throat, (5) at the sternum, (6) at the top of the neck, (7) and on the mid back. Participants’ successive inter-beat-intervals (IBI; time in
between r spikes, in milliseconds) were extracted and then analyzed using Kubios HRV analysis (Tarvainen, Niskanen, Lipponen, Ranta-aho, and Karialainen 2014), allowing for the calculation of frequency- and time-domain indices of resting HF-HRV. Artifacts within the IBI series were visually detected, and we applied an artifact correction level that would differentiate and remove artifacts (differing abnormal IBIs from the mean IBI; smoothing priors as a detrend method; see Tarvainen et al., 2014, for review) using a piecewise cubic spline interpolation method. The root mean square of successive differences (RMSSD) was calculated and is considered a reliable and valid measure of vmHRV. Using Fast Fourier Transformation, both low- (LF-HRV; 0.04-0.15 Hz) and high- (HF-HRV, 0.15-0.4 Hz) frequency power were calculated (Thayer et al., 2010; Task Force of the European Society of Cardiology, 1996). HF-HRV is a reliable and valid measure of vmHRV (i.e., Thayer, Hansen & Johnsen, 2010). HF-HRV and RMSSD were highly correlated in our sample ($r = .950, P < .001$). Because all results were virtually identical when analyses were conducted using both RMSSD and HF-HRV, HF-HRV was used as the primary index of vmHRV. A median split was conducted on (log-transformed) HF-HRV values to determine high and low vmHRV groups. It is important to note that median splits were conducted by ethnicity and sex given the previously reported differences found in resting vmHRV (Hill et al., 2015; Koenig and Thayer, 2016).

While many consider LF-HRV an index of PNS and SNS activity (Task Force, 1996), however, this position is not without controversy (e.g., Goldstein, Bentho, Park and Sharabi, 2011). The LF/HF ratio was also calculated, and is considered a valid proxy
for cardiac autonomic balance despite controversy surrounding the LF-HRV component (Williams et al., 2015, 2016). All cardiac measures, with the exception of HR, were assessed at Time 1 only; HR was assessed at both Time 1 and Time 2.

5.9 Statistical Analyses

All statistics were conducted using SPSS (ver. 19, IBM Chicago, IL, USA) and StatsSoft Statistica 6.0 (StatSoft, Inc., Tulsa, OK). Independent sample t-tests were used to examine ethnic, sex, and vmHRV group differences on all demographic, body, and hemodynamic measures for both Time 1 and Time 2, in addition to HRV measures for Time 1.

Multiple between-within factor analysis of variances (ANOVAs) were conducted. Between-factors included ETHNICTY (CA and AA), SEX (male and female), and HRV-GROUP (high and low vmHRV groups). The within factor was TIME, and dependent variables were HR and each of the hemodynamic measures, including systolic BP, diastolic BP, MAP, cardiac output index, stroke volume, and TPR index. It is important to note that both cardiac output and TPR, and their respective indexes, were included in group mean analyses, however only TPR and cardiac output indexes were included in the ANOVA tests as these measures better control for body surface area. Preplanned contrasts were used to evaluate hypothesized comparisons and pattern differences (from Time 1 to Time 2) in HR and hemodynamics between groups (Rosnow and Rosenthal, 1995). We computed r coefficients as measures of effect size (Rosnow, Rosenthal, and Rubin, 2000).

5.9.1 Covariates
All ANOVA models were also conducted controlling for age at Time 1, average time elapsed between age at Time 1 and Time 2, baseline BMI, change in BMI from Time 1 to Time 2, waist circumference at Time 1, and baseline smoking status. Statistics from these models are only included if results significantly differ when including covariates.
Chapter 6: Results

6.1 Sample Characteristics and Group Baseline Analyses

Participant demographics for the entire sample are presented in Table 1. Demographics are also presented split by ethnicity (Table 2), sex (Table 3), vmHRV group (Table 4). For the full sample at both time points, both systolic (Time 1 mean = 113; Time 2 mean = 116) and diastolic (Time 1 mean = 83, Time 2 mean = 89) BP mean values were below borderline hypertension values, validating that these subjects on a whole were normotensive throughout the experiment. Moreover, HR was within a healthy range of approximately 64 bpm for both time 1 and time 2. According to standards, our sample was considered overweight as they showed a mean BMI greater than 24.5 at both time points. One-hundred and thirty-four individuals reported some history of smoking (approximately 35% of the sample). Mean and standard deviations for all other variables are presented in Table 1.

6.1.1 Split by Ethnicity

Split by AAs and CAs, AAs showed significantly higher age at both time 1 ($t_{(387)} = -3.23, p < .001$) and time 2 ($t_{(387)} = -3.40, p < .001$), however there was no difference in the average time elapsed between time 1 and 2 ($t_{(387)} = -0.87, p = .436$). AAs showed significantly higher BMI at both time points in comparison to CAs (time 1: $t_{(387)} = -4.04, p < .001$; time 2: $t_{(387)} = -3.50, p = .001$).
At time 1, AAs also showed a significantly lower LF/HF ratio (t(387) = -3.23, p < .001). In addition, AAs showed greater systolic BP (t(387) = -4.42, p < .001), diastolic BP (t(387) = -5.98, p < .001), MAP (t(387) = -5.92, p < .001), TPR (t(387) = 2.49, p = .003), and TPR index (t(387) = -4.10, p < .001) in comparison to CAs.

At time 2, AAs showed significantly lower CO (t(387) = -3.23, p < .001) and CO index (t(387) = -4.49, p < .001) in comparison to CAs. AAs also showed significantly greater systolic BP (t(387) = -5.65, p < .001), diastolic BP (t(387) = -7.11, p < .001), MAP (t(387) = -6.88, p < .001), TPR (t(387) = 6.24, p < .001), and TPR index (t(387) = -6.66, p < .001) in comparison to CAs at time 2.

6.1.2 Split by Sex

Split by males and females, females showed significantly lower BMI at both time points in comparison to males (time 1: t(387) = -2.83, p = .005; time 2: t(387) = -2.94, p = .003). Significantly less women were smokers compared to men (t(387) = 4.08, p < .001).

At time 1, females showed significantly lower mean RR intervals (t(387) = 5.27, p < .001), lower LF power (t(387) = 2.83, p = .005), LF/HF ratio (t(387) = -3.21, p = .001), systolic BP (t(387) = 7.10, p < .001), MAP (t(387) = 3.44, p = .001), stroke volume (t(387) = 6.08, p < .001), cardiac output (t(387) = 2.50, p = .013), and TPR index (t(387) = 2.10, p = .036) compared to males. Women also showed significantly higher diastolic BP (t(387) = -2.02, p = .044) and HR (t(387) = -5.54, p < .001) in comparison to men at time 1.

At time 2, females showed significantly lower systolic BP (t(387) = 5.28, p < .001), MAP (t(387) = 2.81, p = .005), stroke volume (t(387) = 9.33, p < .001), cardiac output (t(387) = 5.87, p < .001), cardiac output index (t(387) = 2.23, p = .026) and TPR (t(387) = -3.41, p
= .001) compared to males. Women also showed significantly higher HR (t\(_{387}\) = -4.60, \(p < .001\)) in comparison to men at time 2.

6.1.3 Split by vmHRV Group

Split by high and low vmHRV groups, individuals in the high vmHRV showed significantly lower age both at time 1 (t\(_{387}\) = 3.31, \(p = .001\)) and time 2 (t\(_{387}\) = 3.57, \(p < .001\)) compared to the low vmHRV group. These groups did not differ on the average time elapsed between time 1 and 2 (t\(_{387}\) = -1.02, \(p = .307\)). The high vmHRV group showed a greater BMI at time 1 (t\(_{387}\) = 2.04, \(p = .042\)), but not time 2 (t\(_{387}\) = 1.81, \(p = .071\)). Waist circumference was smaller at both time points in individuals in the high compared to low vmHRV groups (time 1: t\(_{387}\) = 2.07, \(p = .039\); t\(_{387}\) = 2.14, \(p = .033\)). There was no significant difference between groups in the change of waist circumference from time 1 to time 2 (t\(_{387}\) = 0.31, \(p = .757\)).

At time 1, individuals in the high vmHRV exhibited higher RR intervals, HR, SDNN, (ln)RMSSD, LF-HRV, and HF-HRV compared to those in the low vmHRV group (each \(p < .001\)). Individuals in the high vmHRV group also showed lower HR (t\(_{387}\) = 9.91, \(p < .001\)), systolic BP (t\(_{387}\) = 2.73, \(p = .007\)), and cardiac output (t\(_{387}\) = 2.24, \(p = .025\)). Individuals in the high vmHRV group also showed significantly higher TPR (t\(_{387}\) = -4.00, \(p < .001\)) and TPR index (t\(_{387}\) = 3.28, \(p = .001\)) at time 1 compared to low vmHRV individuals.

At time 2, individuals in the high vmHRV group showed lower HR (t\(_{387}\) = 2.87, \(p = .004\)), systolic BP (t\(_{387}\) = 2.33, \(p = .020\)), MAP (t\(_{387}\) = 3.08, \(p = .002\)), cardiac output (t\(_{387}\) = 4.87, \(p < .001\)), and cardiac output index (t\(_{387}\) = 4.69, \(p < .001\)). Individuals in the
high vmHRV group also showed significantly higher TPR ($t_{(387)} = -4.00, p < .001$) and TPR index ($t_{(387)} = 3.28, p = .001$) at time 1 compared to low vmHRV individuals.

6.2 ANOVA Results: MAP as determined by TPR and cardiac output

6.2.1 Mean Arterial Pressure (MAP)

ANOVA results showed a significant main effect of SEX ($F_{(1,381)} = 70.75, r = .395, p < .001$) and ETHNICITY ($F_{(1,381)} = 56.82, r = .360, p < .001$), such that males and AAs showed higher total MAP in comparison to females and CAs, respectively. Results also showed a significant main effect of HRV-GROUP ($F_{(1,381)} = 11.66, r = .172, p < .001$), such that those in the high vmHRV group had significantly lower total MAP. A significant main effect of TIME (Figure 3) showed an increase in MAP over time in all participants ($F_{(1,381)} = 111.00, r = .474, p < .001$).

Figure 3. Main Effect of TIME on Mean Arterial Pressure

![Figure 3. Main Effect of TIME on Mean Arterial Pressure](image)
A significant TIME by ETHNICITY interaction \( F(1,381) = 5.89, r = .123, p = .016; \) Figure 4) showed AAs to have a greater increase in MAP \( F(1,381) = 89.96, r = .437, p < .001 \) from Time 1 to Time 2 compared to CAs \( F(1,381) = 30.83, r = .437, p < .001 \).

**Figure 4. TIME by ETHNICITY Interaction for Mean Arterial Pressure**

There was also a significant TIME by HRV-GROUP \( F(1,381) = 4.61, r = .109, p = .032; \) Figure 5) that showed individuals in the low vmHRV group showed a greater increase in MAP \( F(1,381) = 80.92, r = .418, p < .001 \) from Time 1 to Time 2 compared to individuals in the high vmHRV group \( F(1,381) = 34.96, r = .289, p < .001 \).

Lastly, a significant TIME by SEX by ETHNICITY interaction showed AA males to have the greatest increase in MAP over time compared to all other groups, especially CA males \( F(1,381) = 9.28, r = .154, p = .002; \) Figure 5).
TIME by ETHNICITY by HRV-GROUP contrasts for MAP are shown in Figure 6. Preplanned contrasts showed that in the low vmHRV group, both CAs ($F(1,381) = 27.53$, $r = .259$ $p < .001$) and AAs ($F(1,381) = 28.80$, $r = .265$ $p < .001$) showed significant increases in MAP over time. In the high vmHRV group, both CAs ($F(1,381) = 6.96$, $r = .113$, $p = .008$) and AAs ($F(1,381) = 34.48$, $r = .288$ $p < .001$) also showed significant increases in MAP over time, however the increase in MAP was significantly stronger in AAs compared to CAs ($F(1,381) = 4.10$, $r = .102$, $p = .043$).
Figure 6. TIME by ETHNICITY by HRV-GROUP contrasts for MAP.

Figure 7. Patterns of MAP in males. Low vmHRV group is represented on the left, and high vmHRV on the right. Red lines indicate AAs, and blue lines indicate CAs.

Preplanned contrasts further showed that in the low vmHRV group, both CA males ($F_{(1,381)} = 9.47, r = .155 p = .002$) and AA males ($F_{(1,381)} = 28.80, r = .265 p < .001$) showed significant increases in MAP over time; however the increase in MAP was
significantly stronger in AA compared to CA males \( (F_{(1,381)} = 4.02, r = .102, p = .045) \). In the high vmHRV group, CA males did not show a significant increase in MAP over time \( (F_{(1,381)} = 2.10, r = .074, p = .149) \) whereas AA males do show a significant increase in MAP over time \( (F_{(1,381)} = 22.09, r = .234, p < .001) \). All contrasts regarding MAP in males are shown in Figure 7.

Figure 8. Patterns of MAP in females. Low vmHRV group is represented on the left, and high vmHRV on the right. Red lines indicate AAs, and blue lines indicate CAs.

All AA and CA women showed increases in MAP over time (low vmHRV, CA female: \( F_{(1,381)} = 18.32, r = .214, p < .001 \); high vmHRV, CA female: \( F_{(1,381)} = 5.22, r = .116, p = .022 \); low vmHRV, AA female: \( F_{(1,381)} = 28.70, r = .264, p < .001 \); high vmHRV, AA female: \( F_{(1,381)} = 12.46, r = .177, p < .001 \)). There were no significant differences between these trends as seen in males. All contrasts regarding MAP in females are shown in Figure 8.
6.2.2 Total Peripheral Resistance (TPR) Index

ANOVA results showed a significant main effect of ETHNICITY ($F_{(1,381)} = 58.64$, $r = .365$, $p < .001$), such that AA individuals as a group showed greater total TPR in comparison to CA individuals. Controlling for covariates, there was a significant TIME main effect, such that TPR increased over time ($F_{(1,381)} = 7.23$, $r = .136$, $p = .007$; Figure 9).

Figure 9. TIME Main Effect on TPR Index

There was a significant TIME by ETHNICITY interaction ($F_{(1,381)} = 6.26$, $r = .127$, $p = .013$; Figure 10), indicating that over time, CA individuals showed no significant change in TPR over time ($F_{(1,381)} = 1.84$, $r = .069$, $p = .175$), whereas AAs showed a significant increase in TPR over time ($F_{(1,381)} = 4.89$, $r = .113$, $p = .027$).
There was also an interaction between TIME and HRV-GROUP ($F_{(1,381)} = 11.76$, $r = .173$, $p < .001$; Figure 11), such that individuals in the low vmHRV group showed an increase in TPR over time, whereas individuals in the high vmHRV group showed a decrease over time.

TIME by ETHNICITY by HRV-GROUP contrasts for TPR are shown in Figure 12. Preplanned contrasts showed that in the low vmHRV group, AAs showed significant increases in TPR over time ($F_{(1,381)} = 10.42$, $r = .163$ $p = .001$), whereas CAs showed no significant linear trend ($F_{(1,381)} = 0.623$, $r = .040$ $p = .430$). In the high vmHRV group, CAs showed significantly decreased TPR ($F_{(1,381)} = 7.11$, $r = .135$ $p = .007$) and AAs showed no significant linear trend in TPR ($F_{(1,381)} = 0.16$, $r = .006$, $p = .889$).
Preplanned contrasts also showed no significant change in TPR over time in CA males (F(1,381) = 0.001, r = .001, p = .973) or AA males (F(1,381) = 2.64, r = .082, p = .105) in the low vmHRV group. In the high vmHRV group, CA males showed significantly lower TPR over time (F(1,381) = 4.96, r = .112, p = .027), whereas AA males showed no significant change (F(1,381) = 1.07, r = .05, p = .301). Here it is important to note that the slight, but not significant, upward change in TPR in the low vmHRV AA males is significantly different from the downward change seen in AA males in the high vmHRV group (F(1,381) = 3.56, r = .096, p = .05). All contrasts regarding TPR index in males are shown in Figure 13.
Figure 12. TIME by ETHNICITY by HRV-GROUP contrasts for TPR

Figure 13. Patterns of TPR in Males. Low vmHRV group is represented on the left, and high vmHRV on the right. Red lines indicate AAs, and blue lines indicate CAs.
In females, AA individuals in the low vmHRV group showed an increase in TPR over time ($F_{(1,381)} = 9.98, r = .159, p = .001$). No other changes were found to be significant (low vmHRV, CA female: $F_{(1,381)} = 1.16, r = .055, p = .281$; high vmHRV, CA female: $F_{(1,381)} = 2.38, r = .078, p = .123$; high vmHRV, AA female: $F_{(1,381)} = 1.10, r = .053, p = .293$). All contrasts regarding TPR index in females are shown in Figure 14.

Figure 14. Patterns of TPR in Females. Low vmHRV group is represented on the left, and high vmHRV on the right. Red lines indicate AAs, and blue lines indicate CAs.

6.2.3 Cardiac Output (Index)

ANOVA results showed a significant main effect of HRV-GROUP ($F_{(1,381)} = 14.31, r = .190, p < .001$) and ETHNICITY ($F_{(1,381)} = 11.51, r = .171, p < .001$), such that CAs and individuals in the low vmHRV group showed greater total cardiac output in comparison to AA males and high vmHRV individuals, respectively. There was also a
significant main effect of TIME such that cardiac output increased in all individuals over time ($F_{(1,381)} = 13.84, r = .187 p < .001; \text{Figure 15}$).

**Figure 15. Main Effect of TIME on Cardiac Output**

![Figure 15. Main Effect of TIME on Cardiac Output](image1)

There was a TIME by ETHNICITY interaction on the border of significance, such that CA individuals show a greater increase in cardiac output over time compared to AA.

**Figure 16. TIME by ETHNICITY Interaction of Cardiac Output**

![Figure 16. TIME by ETHNICITY Interaction of Cardiac Output](image2)
individuals ($F_{(1,381)} = 3.81, r = .099, p = .051$; Figure 16). There was also a significant interaction between TIME and HRV-GROUP such that there was a greater difference in cardiac output at Time 1 between high and low groups, compared to no difference at Time 2 ($F_{(1,381)} = 7.34, r = .137, p = .007$; Figure 17).

Figure 17. TIME by HRV-GROUP Interaction for Cardiac Output

![Graph showing TIME by HRV-GROUP Interaction for Cardiac Output]

TIME by ETHNICITY by HRV-GROUP contrasts for cardiac output are shown in Figure 18. Preplanned contrasts showed that in the low vmHRV group, both CAs ($F_{(1,381)} = 0.765, r = .044, p = .382$) and AAs ($F_{(1,381)} = 0.14, r = .019, p = .903$) showed no significant linear trend in cardiac output. In the high vmHRV group, CAs showed a significant increase in cardiac output over time ($F_{(1,381)} = 20.91, r = .228, p < .001$), whereas AAs showed no significant linear trend, although trending in an upward direction ($F_{(1,381)} = 2.95, r = .087, p = .086$).
Preplanned contrasts also showed that males in the low vmHRV group did not show any significant trends in cardiac output over time (low vmHRV, CA male: $F_{(1,381)} = 1.10, r = .053, p = .293$; low vmHRV, AA male: $F_{(1,381)} = 2.80, r = .085, p = .231$). Males in the high vmHRV all show a significant linear increase in cardiac output over time (high vmHRV, CA male: $F_{(1,381)} = 12.02, r = .174, p < .001$; high vmHRV, AA male: $F_{(1,381)} = 4.97, r = .113, p = .026$). All contrasts regarding cardiac output index in females are shown in Figure 19. Females in the low vmHRV showed no significant change in cardiac output (low vmHRV, CA female: $F_{(1,381)} = .05, r = .011, p = .809$; low vmHRV, AA female: $F_{(1,381)} = 1.77, r = .068, p = .184$). CA females in the high vmHRV group show a strong increase in cardiac output over time ($F_{(1,381)} = 9.00, r = .152, p = .002$), whereas AA females did not show a significant change ($F_{(1,381)} = 0.00, r = .001, p = .998$). All contrasts regarding cardiac output index in females are shown in Figure 20.
Figure 19. Patterns of Cardiac Output in Males. Low vmHRV group is represented on the left, and high vmHRV on the right. Red lines indicate AAs, and blue lines indicate CAs.

Figure 20. Patterns of Cardiac Output in Females. Low vmHRV group is represented on the left, and high vmHRV on the right. Red lines indicate AAs, and blue lines indicate CAs.
6.3 ANOVA Results: HR and Stroke Volume as Determinants of Cardiac Output

6.3.1 Heart Rate

ANOVA results showed a significant main effect of SEX ($F_{(1,381)} = 39.48, r = .306, p < .001$) and HRV-GROUP ($F_{(1,381)} = 56.90, r = .360, p < .001$) such that both females and individuals in the low vmHRV group had higher total HR (i.e., time 1 and 2 HR) in comparison to males and individuals in the high vmHRV group, respectively.

There was also a significant SEX by HRV-GROUP interaction ($F_{(1,381)} = 4.61, r = .109, p = .032$), such that there is a greater difference between high and low vmHRV women in total HR ($F_{(1,381)} = 50.27, r = .341, p < .001$) compared to that between low and high vmHRV males ($F_{(1,381)} = 13.65, r = .186, p < .001$). A significant TIME by HRV-GROUP interaction ($F_{(1,381)} = 34.18, r = .287, p < .001$) showed that the difference in HR between high and low vmHRV groups is greater at Time 1 in comparison to Time 2.

Preplanned contrasts showed in the low vmHRV group, CA males had a significant decrease in HR from Time 1 to Time 2 ($F_{(1,381)} = 5.48, r = .119, p = .020$); AA males showed no significant change in HR over time ($F_{(1,381)} = 0.53, r = .037, p = .467$). In the high vmHRV group, CA males showed a significant increase in HR ($F_{(1,381)} = 6.82, r = .132, p = .009$), whereas AA males again showed no significant change in HR over time ($F_{(1,381)} = 2.67, r = .083, p = .106$). For women in the low vmHRV group, both CA ($F_{(1,381)} = 5.62, r = .120, p = .018$) and AA ($F_{(1,381)} = 9.04, r = .152, p = .003$) women significantly decreased HR over time. For women in the high vmHRV group, CA women showed a significant increase in HR over time ($F_{(1,381)} = 5.36, r = .117, p = .021$), but not significantly so in AA women ($F_{(1,381)} = 5.23, r = .116, p = .073$).
6.3.2 Stroke Volume

ANOVA results showed a significant main effect of SEX \((F_{(1,381)} = 80.46, r = .417, p < .001)\) and ETHNICITY \((F_{(1,381)} = 4.51, r = .108, p = .034)\), such that women and AAs showed lesser total SV in comparison to men and CAs, respectively. There was also a significant main effect of TIME such that SV was significantly higher at Time 2 compared to Time 1 in all participants \((F_{(1,381)} = 40.93, r = .311, p < .001)\).

There was a significant TIME by SEX interaction such that while both men and women showed a significant increase in SV over time, this relationship is stronger in men than women \((F_{(1,381)} = 6.69, r = .131, p = .010)\). There was also a TIME by ETHNICITY interaction such that both AAs and CAs show an increase in SV over time, however this relationship is stronger in CAs than in AAs \((F_{(1,381)} = 5.44, r = .118, p = .020)\). It is important to note that this interaction is no longer significant when controlling for the aforementioned covariates. Additionally, there was a significant SEX by ETHNICITY by HRV-GROUP interaction such that CA and AA males in the low vmHRV showed a greater difference in SV in comparison to women, who do not differ as a function of ethnicity at low levels of vmHRV \((F_{(1,381)} = 7.34, r = .137, p = .007)\). No differences were found in the high vmHRV group \((F_{(1,381)} = 3.11, r = .089, p = .078)\).

Preplanned contrasts showed that all males showed a significant increase in SV over time (low vmHRV, CA male: \(F_{(1,381)} = 17.66, r = .210, p < .001\); high vmHRV, CA male: \(F_{(1,381)} = 11.07, r = .168, p < .001\); low vmHRV, AA male: \(F_{(1,381)} = 5.72, r = .122, p = .017\); high vmHRV, AA male: \(F_{(1,381)} = 6.38, r = .128, p < .012\)). In women in the low vmHRV group, CA females show a significant increase in SV over time \((F_{(1,381)} = \)
4.63, \( r = .110, \ p = .032 \)); a pattern not found in AA females (\( F_{(1,381)} = 0.99, \ r = .051, \ p = .319 \)). Increased SV over time is also evident in CA females in the high vmHRV group (\( F_{(1,381)} = 5.91, \ r = .123, \ p = .015 \)) but not AA females in the high vmHRV group (\( F_{(1,381)} = 0.14, \ r = .019, \ p = .702 \)).

6.4 ANOVA Results: Systolic and Diastolic Blood Pressure

6.4.1 Systolic Blood Pressure

ANOVA results showed a significant main effect of SEX (\( F_{(1,381)} = 70.75, \ r = .395, \ p < .001 \)) and ETHNICITY (\( F_{(1,381)} = 56.82, \ r = .360, \ p < .001 \)), such that men and AAs showed higher total systolic BP in comparison to women and CAs, respectively. Results also showed a significant main effect of HRV-GROUP (\( F_{(1,381)} = 11.66, \ r = .172, \ p < .001 \)), such that those in the high vmHRV group had significantly lower total systolic BP.

There was a significant TIME by ETHNICITY interaction (\( F_{(1,381)} = 5.19, \ r = .116, \ p = .023 \)), such that AAs had a greater increase in systolic BP over time compared to CAs. There was also a significant TIME by ETHNICITY by SEX interaction, such that CA females (\( F_{(1,381)} = 5.25, \ r = .117, \ p = .022 \)), AA males (\( F_{(1,381)} = 16.17, \ r = .201, \ p < .001 \)), and AA females (\( F_{(1,381)} = 9.18, \ r = .153, \ p = .002 \)) all show significantly increased systolic blood pressure over time. However there was no significant linear trend found in CA males (\( F_{(1,381)} = 0.01, \ r = .005, \ p = .904 \)).

Preplanned contrasts showed that neither CA males in the low (\( F_{(1,381)} = 0.48, \ r = .035, \ p = .560 \)) nor high (\( F_{(1,381)} = 0.48, \ r = .035, \ p = .489 \)) vmHRV group showed any significant change in systolic BP over time. Results also showed AA males to have
increased systolic BP over time in both the low \((F_{(1,381)} = 6.21, r = .126, \ p = .013)\) and high \((F_{(1,381)} = 10.30, r = .162, \ p = .001)\) vmHRV groups. AA women in the high vmHRV group also showed significantly increased systolic BP over time \((F_{(1,381)} = 5.87, r = .123, \ p = .016)\). Trends are not significant in CA females with low \((F_{(1,381)} = 3.63, r = .097, \ p = .057)\) or high \((F_{(1,381)} = 1.76, r = .071, \ p = .185)\) vmHRV, and AA women with low vmHRV \((F_{(1,381)} = 3.45, r = .094, \ p = .064)\).

6.4.2 Diastolic Blood Pressure

ANOVA results showed a significant main effect of ETHNICITY \((F_{(1,381)} = 59.93, r = .368, \ p < .001)\) and HRV-GROUP \((F_{(1,381)} = 8.89, r = .151, \ p = .003)\), such that AAs and individuals in the low vmHRV group have greater total diastolic BP in comparison to CAs and individuals in the high vmHRV group, respectively. A significant TIME main effect showed diastolic BP was significantly higher over time in all participants \((F_{(1,381)} = 21.17, r = .229, \ p < .001)\). Controlling for the aforementioned covariates, this TIME main effect is no longer significant \((F_{(1,375)} = 1.11, r = .054, \ p < .292)\).

Results also showed a SEX by HRV-GROUP interaction, such that the difference between males in the high and low vmHRV group on diastolic BP \((F_{(1,381)} = 127.17, r = .500, \ p < .001)\) was greater than the difference between high and low vmHRV women \((F_{(1,381)} = 26.67, r = .255, \ p < .001)\). Results also showed a significant interaction between TIME and SEX \((F_{(1,381)} = 7.25, r = .137, \ p = .007)\), such that the change in diastolic BP over time was significantly greater in men than in women.
Preplanned contrasts indicate increased diastolic BP over time in CA males (low
vmHRV group: $F_{(1,381)} = 26.67, r = .255, p < .001$; high vmHRV group: $F_{(1,381)} = 14.11, r$
= .188, $p < .001$), AA males (low vmHRV group: $F_{(1,381)} = 39.52, r = .306, p < .001$;
high vmHRV group: $F_{(1,381)} = 53.34, r = .350, p < .001$), CA females (low vmHRV
group: $F_{(1,381)} = 21.74, r = .232, p < .001$; high vmHRV group: $F_{(1,381)} = 4.35, r = .106, p$
= .037), and AA females (low vmHRV group: $F_{(1,381)} = 42.29, r = .316, p < .001$; high
vmHRV group: $F_{(1,381)} = 11.33, r = .169, p < .001$).
Chapter 7: Discussion

The present investigation sought to understand the complex relationship between ethnicity, sex, and vmHRV on long-term blood pressure regulation in normotensive individuals. At baseline, vmHRV did not significantly differ between AAs and CA as seen previously (Hill et al., 2015), however results were trending in the direction of AAs showing greater vmHRV compared to CAs. Additionally, females showed significantly greater HR in comparison to men at both time points, however males and females did not differ in baseline vmHRV as seen previously (Koenig and Thayer, 2015). Notably and in line with my hypotheses and previous reports (Hill et al., 2015; Koenig and Thayer, 2015). AAs and females showed a lower LF/HF ratio compared to CAs and males. This suggests that both AAs and females show greater PNS activity relative to SNS activity (Williams et al., 2015; 2016) compared to their respective counterparts. Therefore the current sample’s physiological characteristics were in line with my group hypotheses. These results showed the previously observed pattern of increased PNS activity and increased TPR in AA’s, the so-called “cardiovascular conundrum”.

As expected, BP (MAP) increased for the full sample over time; this was characterized by stable TPR and increased cardiac output over time; increased cardiac output was marked by stable HR and increased stroke volume. However, when considered by ethnicity, AAs indeed showed increased TPR and decreased cardiac output
over time, equaling a significantly higher increase in BP compared to CAs. In contrast, CAs showed increased BP marked by increased cardiac output and decreased TPR compared to AAs. Interestingly, increased cardiac output in CAs was characterized by an increase in stroke volume compared to a relative decrease in stroke volume over time in AAs. These results are in line with my hypotheses and support the idea that ethnicity is a crucial factor that may differentiate hemodynamics underlying long-term BP regulation.

When considered by both ethnicity and vmHRV, results showed that CAs with high vmHRV or good compensation, showed increased MAP, but to a lesser degree than all other groups. These increases were characterized by decreased TPR and increased cardiac output. CAs in the low vmHRV group (poorer compensation) showed increased BP over time, but stability in both cardiac output and TPR. In contrast, AAs in the low vmHRV group showed the strongest increase in BP, marked by increased TPR and stable cardiac output. AAs in the high vmHRV group showed increased BP over time, but stability in both cardiac output and TPR, similar to CAs in the low vmHRV group. These results also support my hypothesis, and suggest that poor compensation, as indexed by resting vmHRV, is particularly harmful for AAs as it may lead to increased BP via TPR elevations. However better compensation (i.e., high vmHRV) does not appear entirely beneficial for BP elevations in AAs, but does appear beneficial in avoiding elevated TPR.

**7.1 Discussion of Hemodynamic Patterns Split by Ethnicity, Sex, and vmHRV**

When further considered by both sex and vmHRV, CA males in the low vmHRV group showed no significant change in cardiac output over time as a function of lower HR and higher stroke volume (although the trend in cardiac output is in the upward
direction). CA males in the low vmHRV group also showed no significant change in TPR. Although statistically stable on both TPR and cardiac output, CAs in the low vmHRV group showed increased BP over time, but not to the degree of AA males in the low vmHRV group as expected. Hemodynamics for this group are diagramed in Figure 21.

Figure 21. Changes in hemodynamics overtime for CA males in the low vmHRV group

CA females in the low vmHRV group (Figure 22) showed no significant change in cardiac output, as a function of lower HR and higher stroke volume, or TPR over time. Yet, CA females in this group showed increased BP over time despite stability in TPR and cardiac output. These data partially fit my hypothesis. However I expected that poorer compensation in these women would lead to increased BP with clear increases in cardiac output; results did not show such a pattern. In fact, effect sizes indicate a trend upwards in TPR in these CA women, although not significant. AA females in the low vmHRV group also showed stable cardiac output, but marked by decreased HR and stable stroke volume over time.
CA males in the high vmHRV group (Figure 23) showed increased cardiac output via increased HR and increased stroke volume. CA males in the high vmHRV group showed significantly lesser TPR over time. Increased cardiac output and decreased TPR lead to no significant change in BP over time, thereby showing a pattern of hemodynamic activity associated with the most adaptive outcome (no change in BP) in all groups. These data partially support my hypothesis, but further suggest that CA males with high PNS activity may avoid BP increases via significantly increased cardiac output and decreased TPR.

CA females in the high vmHRV group (Figure 24) showed increased cardiac output via increased HR and increased stroke volume. CA females in this group trended downwards in TPR, but this trend was not significant. Thus, increase cardiac output and
relatively stable TPR lead to increased BP over time as expected. These results likely reflect an effective compensatory mechanism.

*Figure 23. Changes in hemodynamics over time in CA males in the high vmHRV group*

*Figure 24. Change in hemodynamics over time in CA females in the high vmHRV group*
AA males in the low vmHRV group (Figure 25) had stable HR and increased stroke volume over time, leading to no significant change in cardiac output. AA males in the low vmHRV group did not show a significant increase in TPR, although results showed a trend in this direction (p = .10). Therefore, AA males in the low vmHRV showed significantly increased BP over time as a function of stable cardiac output and TPR, however importantly, BP elevations were higher in AAs compared to CAs in this group. These data partially fit my hypothesis regarding AAs males in the low vmHRV group, as poorer compensation (i.e., lower vmHRV) seems to lead to steeper increases in BP over time characterized by stable cardiac output and increased TPR, although this trend is not statistically significant.

Figure 25. Changes in hemodynamics in AA males in the low vmHRV group

Female AAs in the low vmHRV group (Figure 26) also showed significantly increased TPR over time; stability in cardiac output and increased TPR lead to increased BP over time in this group. These results fit my hypothesis, as females in the low
vmHRV group may lack compensation from both an ethnic and sex perspective, and thus, show elevated BP characterized by sizable increases in TPR.

AA males in the high vmHRV group (Figure 27) showed increased cardiac output via increased stroke volume and stable HR. AA males in the high vmHRV group showed no significant change in TPR, although it is important to note, that the trend was a decrease in TPR over time. As cardiac output, but not TPR, was increased in these individuals, BP increased over time. These results are not in line with my hypothesis; I predicted that although compensation is present here, it may not be effective in decreasing early signs of vascular dysfunction given the aforementioned health disparities. Yet, AA males in the high vmHRV group showed increased BP via cardiac output, and not TPR, suggesting that in AA males, compensation (i.e., higher vmHRV) may help buffer vascular dysfunction thought to be present in AAs. In fact, AA males in the high vmHRV group show similar hemodynamic patterns as general theoretical perspectives of long-term BP regulation. This suggests that the progression to essential hypertension via increased TPR may be slowed in AA males with higher HRV.
AA females in the high vmHRV group (Figure 28) showed no change in cardiac output, marked by no change in HR or stroke volume. AA females in the high vmHRV group did not show a significant trend in TPR, however the trend was moving upward in contrast to the non-significant downward trend found in CA females in the high vmHRV group. Stability in both TPR and cardiac output lead to increased BP in AA females in the high vmHRV group. Importantly, as the trends between CA and AA females in the low vmHRV go in opposite directions (AA females upward trend, CA females downward trend; $p = .063$), it is likely that increased BP in AA females is related more to the vascular resistance than in CA females.
In sum, these data suggest that as BP increases over time, a combination of ethnicity, sex, and resting vmHRV can determine the underlying hemodynamic-regulation of such increases. All increases in BP are not equal – our data suggest that AAs, especially females with low vmHRV, may experience elevations in BP primarily due to increases in TPR instead of cardiac output as shown by their CA counterparts. BP elevations due to increased TPR are more deleterious in comparison to those due to increased cardiac output (Fagard et al., 1996; Mensah et al., 1993), and is characteristic
of individuals with essential hypertension (Lund-Johansen, 1980; Lund-Johansen, 1989; Palantini et al., 2006), yet, this sample was of normotensive individuals. This provides a concrete basis for the impact that early vascular dysfunction in AAs can have on BP over time. It is important to note one exception – AA males in the high vmHRV – showed hemodynamic patterns similar to CAs, that is, increased BP likely due to increased cardiac output, but interestingly only via increased stroke volume. This makes sense, as greater stroke volume is typically associated with lesser vascular pressure (via lower afterload, see Implications section for more details) and although not significant, AA males in the high vmHRV group also showed a trend downward in TPR, possibly reflecting some degree of effectiveness in the presence of this compensatory mechanism. Implications for physiological and psychological well-being are discussed next.

7.2 Implications

7.2.1 Water and Salt Retention in Long-Term BP Regulation

As previously mentioned, it is well documented that cardiac output is increased in borderline hypertensive individuals. Therefore, dating back at least 50 years, cardiac output has been a primary target in decreasing BP in both borderline and essential hypertension. Cardiac output is determined by the product of HR and stroke volume. Stroke volume is determined by three factors: (i) preload: the degree to which the left ventricle is stretched prior to contraction (ii) contractility: representing the force for which heart is able to contract; and (iii) afterload: pressure both heart ventricles must generate to pump blood into aortic and pulmonary valves. For example, one popular treatment in hypertension is a beta-blocker such as propranolol (see Victor, 2015 for
These beta-blockers are antagonists aimed at decreasing SNS activity by decreasing the impact of epinephrine on beta-adrenergic receptors, and thus, decreasing stroke volume and HR by decreasing contractility. While such treatments may decrease BP acutely, it is far from a long-term solution (Victor, 2015). The issue here is that these very beta-receptors are downregulated over the course of hypertension, thereby leading to decreased SNS activity, or epinephrine release, to elicit a proper flight or fight response. Therefore, the body’s natural response to long-term elevated BP and beta-blockers may work in tandem to treat, but not cure, hypertension.

Thus, one popular model of hypertension proposes that decreasing preload is a key factor in decreasing cardiac output and thus, BP in hypertensive individuals. Specifically, researchers have demonstrated that increased salt intake and therefore fluid retention increases stroke volume, and thus cardiac output, and subsequently BP (Guyton et al., 1972; Guyton, 1991). Therefore, another “first-line” of treatment in hypertension is a diuretic, or a pill that induces urination in an attempt to rid the body of extra salts and liquids. This work therefore identifies hypertension and the long-term regulation of BP as a process primarily involving the kidney’s (renal disease). In sum, Guyton’s model proposes that ANS activity is important in hypertension, however it is increased fluid, either via diet (salt) or kidney dysfunction, is the primary mechanism underlying both borderline and essential hypertension.

However, little empirical evidence shows increased fluid volume in hypertensive individuals (e.g., Julius, Schork, and Schrok, 1987). In fact, studies have shown decrease plasma volume, resulting in a higher hematocrit, which is a ratio of red blood cells and
plasma levels, in both borderline (Julius, Pascual, Reilly, and London, 1971) and essential (Tarazi, Frohlich, and Dustan, 1968) hypertensive individuals. This is important, as Guyton’s model could best explain increased BP borderline hypertension, where cardiac output is increased, possibly via preload. However research has also shown that increased blood volume did not accompany increased cardiac output in borderline hypertensive individuals (Julius et al., 1971a). In this study, both SNS and PNS blockades impacted cardiac output, but fluid volume was not changed. Therefore, this model seems most applicable in secondary hypertension, where kidney disease or failure may actually be the cause of increased BP. Another study showed that renal denervation (i.e., removing influence of the kidney’s) showed no significant change in BP (Bhatt et al., 2014). Despite conflicting evidence, this is a model of hypertension that many physicians use today. Therefore, many hypertensive individuals with normal kidney function are often incorrectly prescribed diuretics (Thrasher, 2006). In fact, there are a number of medications that are commonly prescribed to borderline hypertensive patients rarely help in the long-term, with many patients becoming resistant to such medications over time (Thrasher, 2006). Thus, it appears that given this new understanding of hemodynamics underling increased BP, as scientists, we may need to reevaluate how we approach treatments in hypertension, and more importantly, reevaluate our understanding of the primary mechanism underlying increased BP. While Guyton’s model of hypertension gained much attention, other mechanisms have been proposed underlying long-term BP regulation, particularly the baroreflex.

7.2.2 Alternative Models of BP regulation: The Baroreflex

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As early as 1948, the baroreflex was thought to play a role in both long-term and short-term BP regulation, as a study using animals first showed that vascular hypertrophy lead to decreased BRS (via less stretching), which was though to maintain increases in long-term BP (Volhard, 1948). Despite empirical evidence since then, a study in 1973 showed that sino-aortic denervation (SAD), or removing the influence (afferents) of the baroreflex for 2 weeks in dogs showed an increase in BP in the first week, and then a decrease back to levels of the control dogs by the second week (Cowley, Liard, and Guyton, 1973). By the fifth week, BP in these dogs fell below the control dogs’ BP. This was considered a primary test of the baroreflex, and thus, provided evidence that the baroreflex could not be involved in long-term BP regulation (Cowley et al., 1973).

However, the method of SAD has recently come into question, suggesting that it is not the best method of displaying chronic baroreceptor firing (Thrasher 2002; Thrasher 2006). Specifically, studies have shown neural changes to occur days following SAD, such that an unknown inhibitory mechanism at the NTS following chronic baroreflex loss occurs, thereby returning SNS activity and BP levels back to normal (Ito and Sved, 1997; Schreihofer, Ito, and Sved, 2005). This is likely the reason that SAD only increases BP for a maximum of two weeks. Another method has been proposed such that removing influence from only one side of baroreceptors allows for the neural mechanisms to stay in place, but much less efficiently (as only half of the receptors are firing in response to BP changes). This new method showed increased BP over a longer time (5 weeks) compared to SAD (2 weeks). More importantly, those with only half of their baroreceptors removed showed increased BP that also fell during the first week, but remained increased over
time in comparison to those with their baroreflex intact (Schreihof, et al., 2005). While
the first study (Cowley et al., 1973) provided evidence that the baroreflex was not
involved in long-term BP regulation, this seems to be a function of methodological
issues. Overall, decades of research suggest that the baroreflex, mediated by the vagus
(PNS) and associated brain structures, are likely primary determinants of long-term BP
regulation (see Victor et al., 2015 for review).

Overall, the current data and our recent studies support the idea of long-term BP
regulation by the baroreflex (Victor, 2015; Thrasher, 2006; Ducher et al., 2006). Our
prior investigations support this idea as they implicate a less effective baroreflex in
adjusting TPR (Williams et al., 2016) and decreased nitric oxide (Williams et al., 2017)
as two mechanisms underlying increased resting BP in AAs. In the current study, the
hemodynamics underlying long-term BP regulation is different based on ethnicity and
PNS activity, suggesting that the interaction between the baroreflex and the vagus as
compensation for BP increases, is important in regulating long-term BP, especially in
AAs. However future research is needed to understand the mechanism underlying these
ethnic disparities in BEI and EDAD. It is possible that higher vmHRV as a compensatory
mechanism in AAs may help mitigate some of these deficiencies. Evidence in the current
investigation supports this possibility, as AAs with greater vmHRV did not show
increased TPR over time, but did show increased BP marked primarily by increases in
cardiac output. However, future research is needed to further investigate these claims. It
is important to note that while vmHRV may alter hemodynamics underlying long term
BP regulation in AAs, increases in BP remained larger compared to CAs with higher vmHRV (p = .04).

Regarding treatment, it appears that the baroreflex should be the primary mechanism targeted in decreasing BP in hypertensive individuals, and particularly the BEI of the TPR branch in AAs. At the very least, treatments in hypertension should be further tailored to the individual based on their ethnicity, sex, and autonomic profiles.

7.2.3. Physiological Compensation as Psychological Compensation

In the current data, CA males with in the high vmHRV showed the most adaptive hemodynamic patterns over time, characterized as increased cardiac output but no significant change in BP accompanied by decreases in TPR, representing effective compensation (i.e., higher vmHRV; Thayer et al., 2009). CA males in the low vmHRV group showed increased BP over time as a function of increased cardiac output and stable TPR. This suggest that although PNS activity is lower in these individuals, the activity present is effective enough to protect against increased TPR. CA females in both the high and low vmHRV group exhibited increased BP over time, this was not due to increases in TPR, and instead due to increased cardiac output. However notably, low vmHRV-group CA females’ upward trend in TPR was different (p = .06) than the trend downward seen in CA females in the high vmHRV. This suggests that although there were not mean differences in vmHRV between men and women, at least in CA women, this differential pattern of TPR may serve as evidence that the previously identified compensatory mechanism in women also applies to hemodynamics in long-term BP regulation, specifically in regulating TPR. In sum, CAs seem to follow a pattern of long-term BP
regulation that follows the Julius hyperkinetic model (Julius, 1971; 1991) in that cardiac output increases can lead to increases in BP, and potentially, lead to a hyperkinetic state in borderline hypertension (Palatini and Julius, 2009). In contrast, AA females in the low vmHRV group showed the most maladaptive patterns in hemodynamic activity over time, characterized by increased BP marked by increased TPR. Yet neither TPR nor cardiac output significantly increased in AA females with high vmHRV, suggesting that although BP increases remain evident, they are not likely due to normal aging. This provides evidence that greater vmHRV as compensation in AA women that may be beneficial for a healthier aging of the cardiovascular system by minimizing early signs of vascular dysfunction. In AA males with high vmHRV, increased BP over time is marked by increased cardiac output and in AA males with lower vmHRV, elevated BP is marked by increased TPR. Here, higher vmHRV in AA males also seems beneficial at minimizing signs of early vascular dysfunction (non-significant downward trend in TPR over time).

Overall and from a physiological perspective, the compensatory mechanism – higher vmHRV – is especially necessary for AA individuals in working to avoid early signs of vascular dysfunction and thus, end-organ damage and a greater risk for mortality and morbidity from hypertension. However it is important to note that this compensation displayed in these groups only minimizes early signs of vascular dysfunction, as they still show increased BP and even more so in comparison to their CA counterparts.

Interestingly, researchers have also proposed that greater vmHRV not only represents physiological compensation but also psychological compensation, and that such compensation is particularly important for both AAs and women.
From an ethnicity standpoint, AAs seem to be predisposed to the physiological conditions (i.e., increased BP, TPR early in life; Gadegbeku et al., 2005) under which hypertension is identified, developed, and maintained. Therefore, research has evaluated how psychological factors such as ethnic or racial discrimination may contribute to ethnic disparities in health (Williams and Mohammed, 2009). Racial stressors uniquely and negatively affect individuals of color, particularly AAs in comparison to CAs (Pascoe & Smart Richman, 2009; Steele & Aronson, 1995). Converging evidence has linked such stressors with deleterious psychological and physiological outcomes, including cardiovascular disease and hypertension, in AAs (see Brondolo, Brady Ver Halen, Pencille, Beatty, & Contrada, 2009; Schmader, Johns, & Forbes, 2008; and Williams & Mohammed, 2009, for reviews). Therefore, racial stressors are thought to be important factors underlying ethnic health disparities. As AAs show greater mean vmHRV compared to CAs (Hill et al., 2015), it is proposed that greater vmHRV reflects a psychological compensatory mechanism in response to the physiological impact of these unique social stressors and environmental challenges in AAs (Dorr et al., 2007; Hill et al., 2015; Williams et al., in press). In support of this idea a recent investigation showed that in 11,989 individuals, Black Brazilians showed greater resting vmHRV in comparison to both mixed (Brown Brazilians) individuals and White Brazilians, and this relationship was mediated by experiences of discrimination (i.e., darker skin tone associated with greater experiences of discrimination associated with higher resting vmHRV; Kemp et al., 2016). It is important to note that although AAs may display increased vmHRV, these alterations do not protect against the physiological effects of discrimination (Hill et al.,
2017; Williams et al., in press Williams et al., under review). Whereas Kemp et al. (2016) showed ethnic discrimination to be the mechanism underlying higher resting vmHRV between ethnic groups, another set of studies showed that that within AAs only, greater perceived ethnic discrimination was associated with lower resting vmHRV (Hill et al., 2017; Williams et al., in press). In another example, stereotype threat (ST) occurs when a cue(s) in the environment brings to mind, either consciously or unconsciously, a negative group-based stereotype for which the individual belongs to; ST is defined as being at risk of confirming such a negative stereotype (Aronson, Burgess, Phelan, & Juarez, 2013; Burgess, Warren, Phelan, Dovidio, & van Ryn, 2010; Steele & Aronson, 1995). ST has also been shown to both increase BP (Blascovich, Spencer, Quinn, and Steele, 2001) and decrease vmHRV in AAs (Williams et al., under review). Taken together, these studies support the idea that unique psychosocial factors negatively impact physiology in AAs. Yet, also seems to underlie ethnic differences in resting vmHRV (Kemp et al., 2016), suggesting that physiological compensation at rest seen in AAs may also have psychological influence.

From a sex differences standpoint, as women typically show greater mean vmHRV compared to men (Koenig and Thayer, 2016), researchers have begun to suggest that these differences in vmHRV between men and women are likely due to neural mechanisms (Williams et al., under review). From a structural perspective, a recent meta-analysis (Ruigrok et al., 2014) found that on average, men had a larger amygdala (in volume) compared to women, whereas women showed larger frontal brain structures, including the PFC, in comparison to men. From a functional perspective, imaging studies
have identified sex differences in the upregulation and downregulation of negative emotions; a set of reports found women to show more frontal lobe and amygdala (Gardner, Carr, Macgregor, Felmingham, 2013) activity in comparison to men in response to negative stimuli (see Stevens & Hamann, 2012, for meta-analysis). Lesser activity in frontal brain regions and more activity in the amygdala are typically associated with lower vmHRV and greater HR, and vice versa (Thayer et al., 2012). Thus, considering the aforementioned brain structural and functional sex differences, it is not surprising that research has identified that men and women differ in vmHRV (Koenig and Thayer, 2016). Some propose that in women but not men, greater frontal brain activation (both at rest and in response to negative stimuli) may represent psychological compensation in response to increased amygdala activity, potentially mediated by greater feelings of depression/anxiety (Drevets, 1999, Koenig & Thayer, 2016; Thayer, Rossy, Ruiz-Padial, Johnsen, 2003; Thayer, Smith, Rossy, Sollers, & Friedman, 1998; Nolen-Hoeksema, 2001; Piccinelli & Wilkinson, 2000; Lewinsohn, Gotlib, Lewinsohn, Seeley, & Allen, 1998). In sum, it is possible that increased vmHRV not only signifies compensation from a physiological perspective, but also a psychological perspective in both AAs and women particularly.

Taking into account both sex and ethnicity, prior theory (Dorr et al., 2007; Hill et al., 2015; Koenig and Thayer, 2016; Williams et al., in press; Williams et al., under review) would suggest that low vmHRV AA females may not have the necessary physiological compensation for physiological consequences (e.g., increased TPR) of unique psychological stressors such as racial stressors (e.g., discrimination) often faced
by AAs, and/or feelings of anxiety or depression often faced by women (Nolen-Hoeksema, 2001; Piccinelli & Wilkinson, 2000). Therefore, maladaptive hemodynamic patterns seen in AA females with poor compensation, as indexed by low vmHRV, unfortunately make sense. However it is important to note, that the potential impact of unique psychological stressors on SNS activity in the absence of compensation over time is speculative. Nevertheless, these findings highlight the importance of greater PNS activity as physiological compensation in decreasing TPR in addition to the ineffectiveness of this mechanism in minimizing elevated BP in AAs – future research should address how (un)successful psychological compensation potentially impacts hemodynamic activity.

7.3 Limitations and Future Directions

One limitation of the current investigation is that participants were normotensive and thus, I can only make conclusions based on long-term normotensive BP regulation, and not BP regulation during borderline or essential hypertension. Therefore, discussions regarding the development of hypertension are somewhat speculative, but very much related with important implications for hypertension. Nevertheless, future investigations should work to understand the possible differential hemodynamics and therefore outcomes in individuals based on ethnicity, and further by sex and vmHRV.

Another limitation of the current investigation is that it did not include measures of the unique stressors previously mentioned, such as ethnic discrimination. Future investigations should keep in mind the potential psychological mechanisms potentially underlying these differential hemodynamic patterns. A final limitation of the current
study that socioeconomic status (SES) information was not included in the current analysis. SES is proposed to be an influential variable in the experience of discrimination and other related stressors thus, future studies should examine the current relationship while considering SES. It is important to note that although SES is an important factor in racial stressors, it has not previously explained the ethnic health disparities gap (Williams and Muhammed, 2013) and has not been shown to be influential enough to mitigate the profound increases in BP in AAs compared to CAs (Hill et al., under review).

7.4 Conclusions

AAs are at a far greater risk for mortality and morbidity from hypertension and other related diseases in comparison to CAs (Benjamin et al., 2017). The current results suggest that in normotensive individuals, CAs show a relative normal aging of the cardiovascular system over time, characterized by increased BP over time via increased cardiac output and stable or decreased TPR, a pattern seen especially in CA males with higher vmHRV. In contrast, AAs showed a more deleterious pattern of cardiovascular activity, marked by increased BP via increased TPR, a pattern seen especially in AA females with lower vmHRV. Overall these data suggest a similar outcome of higher BP, however this is achieved via different hemodynamic mechanisms as a function of ethnicity, sex, and resting PNS activity as indexed by resting vmHRV. I conclude with stressing the importance of considering ethnicity, sex, and PNS activity in both long-term BP regulation and thus, potentially the development and treatment of hypertension.
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Hypertension, 8(4), S103-7.
Appendix A: Tables
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Table 1. Sample Demographics.
### Table 2. Sample Demographics Split by Ethnicity

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Table 3. Sample Demographics Split by Sex
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*Table 4. Sample Characteristics Split by vmHRV*