ABSTRACT

Title of Thesis: SIMILAR VASCULAR RESPONSES TO A HIGH-FAT MEAL, REGARDLESS OF RACE AND SOCIAL DETERMINANTS OF HEALTH

Cynthia Marie Weiner, Master of Arts, 2022

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Black individuals are at a higher risk for developing cardiovascular disease (CVD), including hypertension, compared to white individuals. Chronic low-grade inflammation contributes to hypertension by causing vascular dysfunction, including increased vascular resistance. Young, healthy, normotensive black individuals exhibit heightened inflammatory biomarkers at rest, a possible factor in the higher prevalence of hypertension seen within this population. Vascular function decreases transiently as a result of an acute inflammatory stimulus, such as with consumption of a high-fat meal (HFM). However, there is limited evidence regarding the racial differences in inflammatory and vascular responses to a HFM in young, healthy black and white individuals. Furthermore, there are limited data regarding the association between social determinants of health (SDH) factors and the physiological components of inflammation and vascular responses. Therefore, the goal of the present study was twofold: to evaluate the racial differences in inflammatory and vascular responses to a HFM and to evaluate the potential impact of SDH factors on these relationships.

Five black individuals (5 males, 21.2 ± 1.5 yrs) and 14 white individuals (7 males/7 females, 25 ± 4.1 yrs) completed the study. White individuals were significantly older than black individuals,

but were similar in fitness status (VO_2peak; 43.4 ± 10.8 ml/kg/min vs. 40.5 ± 5.9 ml/kg/min) and BMI (22.6 ± 2.9 kg/m^2 vs. 23.5 ± 3.3 kg/m^2). Black and white individuals exhibited similar vascular function, arterial stiffness, wave reflection, and hemodynamic variables (BP, HR) at baseline and following the HFM. Black individuals had a significantly lower total SDH score compared to white individuals, indicating lower SDH across seven domains assessed in the SDH questionnaire. However, SDH was not associated with any of the vascular measurements at baseline or following the HFM. Inflammation was not detected at baseline and following the HFM, as measured by a multiplex immunoassay. Therefore young, healthy black and white individuals maintain vascular function following a HFM, regardless of SDH status.

SIMILAR VASCULAR RESPONSES TO A HIGH-FAT MEAL, REGARDLESS OF RACE AND SOCIAL DETERMINANTS OF HEALTH

by

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Chapter 1: Introduction

A. Overview

Cardiovascular disease (CVD), which includes coronary heart disease, heart failure, stroke, and hypertension, is highly prevalent within the United States with reports indicating nearly half of all adults aged ≥ 20 years old as having CVD.[1] Furthermore, there are racial disparities present in the prevalence of CVD, including hypertension. The prevalence of CVD in individuals aged ≥ 20 years old is higher in black females (57%) and males (60%) as compared to white females (43%) and males (51%).[1] Similarly, the prevalence of hypertension is higher in black females (56%) and males (59%) as compared to white females (41%) and males (48%).[1] However, the cause of this disparity in hypertension prevalence has not been fully elucidated, but could be driven by social determinants of health (SDH). The SDH take a holistic approach to health, combining various factors that affect human health, and broadly include social, economic, and environmental factors.[2] These factors are further divided into economic stability, neighborhood and built environment, social and community context, health and healthcare, and education. Higher SDH indicates better holistic health, whereas lower SDH indicates lower holistic health. Importantly, previous studies show a negative association between individual SDH factors, such as educational attainment and income, and CVD risk.[2] Individual SDH factors have also been negatively associated with increased risk of hypertension, which is both a chronic disease and a risk factor for CVD.[3–5]

Hypertension is largely driven by a pro-inflammatory environment resulting in vascular dysfunction.[6,7] Heightened inflammation and vascular dysfunction are prevalent in normotensive, young healthy black individuals.[8,9] However, the effect of inflammation on the vasculature is difficult to study directly, therefore, a model of induced inflammation can be

used to study inflammation-driven vascular dysfunction. A high-fat meal (HFM) is one such model of inflammation which has been used in previous studies to induce inflammation[10–18] and/or vascular dysfunction.[16,18–29] Therefore, by using the HFM stimulus, potential mechanisms driving these racial differences in hypertension risk can be elucidated.

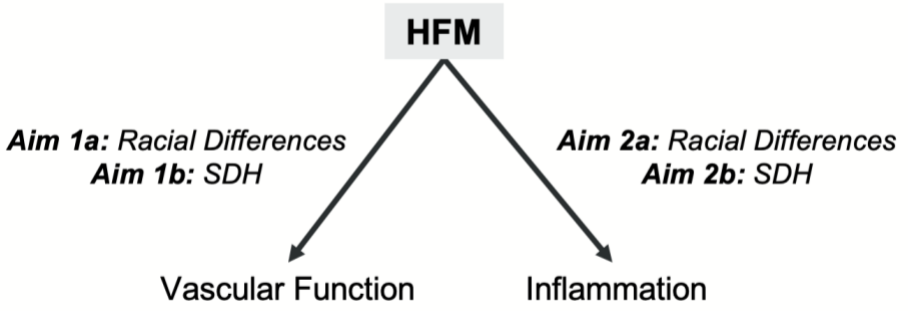


Figure 1. Research Aims. **Aim 1a** and **1b** will investigate the effects of race and SDH, respectively, on vascular function following the HFM. **Aim 2a** and **2b** will investigate the effects of race and SDH, respectively, on inflammation following the HFM.

B. Regulation of Blood Pressure and Hypertension

Hypertension is the clinical term for high blood pressure (BP), with BP being the force exerted on the artery walls during systole and diastole. Hypertension is defined by the American Heart Association as a systolic blood pressure (SBP) of between 130-139 mmHg or diastolic blood pressure (DBP) between 80-89 mmHg for Stage 1 hypertension and SBP of at least 140 mmHg or DBP of at least 90 mmHg for Stage 2 hypertension.[30]

BP regulation is highly complex and usually assumes multi-system involvement. The contribution of each system/reflex to BP regulation depends on the temporal aspect, i.e. either short-term, intermediate, or long-term.[31] The short-term mechanisms include the baroreceptor reflex, chemoreceptor reflex, and the central nervous system ischemic response.[31]

Baroreceptors, a type of mechanoreceptor, respond to stretch within the artery wall.[32] Baroreceptors are found in various places throughout the vasculature, including the carotid

sinus and the aortic arch.[32] These baroreceptors use a negative feedback loop. When the baroreceptors are stretched, as with higher BP, the sympathetic outflow is reduced to decrease vasoconstriction, thus decreasing BP and maintaining homeostasis.[33] When BP decreases, the opposite occurs in which the sympathetic output increases and causes vasoconstriction.

The endothelium, which lines the inside of arteries, is also an important factor in short-term BP regulation. It is important in multiple processes, including producing factors that regulate vascular tone, both vasoconstrictors and vasodilators.[34] The most potent vasodilator produced within the endothelium is nitric oxide (NO), which stimulates the smooth muscle surrounding the artery to relax, thus aiding in BP regulation.[34]

Long-term mechanisms for BP regulation include the renin-angiotensin-aldosterone system (RAAS) and antidiuretic hormone (ADH).[31] The renin-angiotensin-aldosterone system (RAAS) functions at the kidney level, regulating the blood volume by manipulating fluid retention within the kidney and ultimately regulating vascular resistance, therefore helping to maintain BP. [35]

Similar to RAAS, ADH also acts on the kidney. When baroreceptors sense low BP, the vagus nerve is stimulated, leading to the release of ADH from the hypothalamus. ADH then causes an increase in water retention within the kidney, thus increasing blood volume and pressure. When BP increases, ADH release is inhibited.[36]

C. Inflammation and Hypertension

The pathophysiological mechanisms of hypertension are complex because different components in each system/pathway can lead to hypertension.[33] However, inflammation is a critical driving component of hypertension as a result of its effects on vascular function.[6,7] Inflammation affects vascular function through multiple mechanisms: inflammation causes 1)

an increase in the permeability of the vasculature;[33] 2) an increase in reactive oxygen species (ROS), which scavenge other molecules and causes molecular damage[33]; and 3) the release of cytokines.[33]

Pro-inflammatory cytokines are signaling proteins that are released by various cells of the immune system, including macrophages, and promote inflammation.[37] These proteins ultimately cause an increase in the thickness of the resistance vessels, which are the small vessels within the periphery of the body that primarily control BP.[33] This in turn increases vascular resistance, causing an increase in BP.

In addition, ROS are produced by the innate and adaptive immune responses within the body and are chemically formed by the partial reduction of oxygen.[33,38] ROS are important in normal physiological signaling, but become pathological when they override the antioxidative system, especially during inflammation.[38,39] ROS are unstable and scavenge other substances, creating oxidizing compounds and ultimately leading to cellular/organ damage.[39] A prime example of ROS scavenging includes NO, which forms peroxynitrite.[39] Therefore, the scavenging action performed by ROS diminishes the vasodilatory capacity within the vasculature by decreasing the bioavailability of NO, leading to dysregulation of BP and eventually hypertension.

D. Vaccine and Intermittent Hypoxia as Models of Inflammation

As described above, there is a link between inflammation, vascular dysfunction and the development of hypertension. However, it is difficult to study chronic inflammation and its impacts on the vasculature directly. Therefore a model of inflammation can be used to induce inflammation and to study the effects on vascular reactivity. Reactivity refers to the ability of the artery to respond to a stressor to continue its normal function.

There are multiple potential ways to induce this acute inflammation and to study the resulting vascular reactivity. One potential method is through administering a vaccine. The typhoid, salmonella-typhi, and influenza vaccines have been shown to successfully induce inflammation.[40–44] In the study by Hingorani et al.,[40] microvascular (smaller "resistance" vessels) function was measured following the administration of the salmonella-typhi vaccine. The participants presented with a significantly lower vasodilator response to vasodilators (bradykinin and acetylcholine) in the forearm eight hours post vaccination, indicating acute microvascular dysfunction.[40] However macrovascular (large conduit artery) function remained similar at both post-vaccination timepoints (8 and 32 hours).[40]

Similar to the study by Hingorani et al.,[40] in the most recent study from our laboratory, administration of the influenza vaccine induced inflammation, as measured by a significant increase in interleukin 6 (IL-6) concentration, but macrovascular function, as assessed by flow-mediated dilation (FMD), remained similar at 24 and 48 hours post-administration.[41] In contrast, macrovascular function, as measured by FMD, significantly decreased 48 hours post-administration of the influenza vaccine in the study by Liuba et al., 2007.[42]

Along these lines, Clapp et al.[43] reported microvascular function also significantly decreased eight hours after typhoid vaccination.[43] In addition, this study reported a decreased response to the infusion of L-NMMA, an inhibitor of NO, with venous occlusion plethysmography (VOP), indicating reduced bioavailability of NO and therefore reduced ability to vasodilate.[43]

Furthermore, arterial stiffness, as assessed by pulse wave velocity (PWV), significantly decreased eight hours post-administration of the salmonella typhi vaccine.[44] Taken together,

vaccination leads to inflammation, thus impairing vascular function and increases arterial stiffness.

Induced inflammation using a vaccine model was associated with a decrease in NO bioavailability due to an increase in oxidative stress, causing a decrease in vascular function.[43] The inflammation resulting from vaccines is believed in part to come from the toll-like receptor (TLR) pathway, which activates the innate immune system.[45] TLR causes activation of the transcription factor nuclear factor kappa B (NF-kB), which is a transcription factor that controls various processes, including immune and inflammatory response.[45] Activation of NF-kB in turn leads to an increase in pro-inflammatory cytokines, including TNF-α and IL-6.[45]

Another *potential* model is intermittent hypoxia (IH). IH occurs during episodes of sleep-disordered breathing, such as obstructive sleep apnea (OSA).[46] OSA is associated with an increased incidence of various disorders, including hypertension.[46] Tamisier et al.[47] modeled the cyclic IH that occurs during OSA in humans by exposing healthy (non-OSA) participants to cyclic desaturation and reoxygenation during sleep. The study found an increase in SBP after two weeks and DBP after four weeks of this IH model in healthy humans.[47]

Hypoxia stimulates the peripheral chemoreceptor in the body, the carotid body.[48] The carotid body receives input from the carotid sinus nerve, which senses the blood oxygen content. In hypoxic states, this chemoreflex causes an increase in the nerve activity, leading to increased sympathetic activity, ventilation, and BP.[48] This ultimately leads to an increase in BP during sleep in individuals with IH, causing an increase in BP during the day as well.[48] This is due to increased sensitivity of the carotid body and thus an increase in sympathetic outflow, in which inflammation is believed to contribute.[48]

IH induces ROS and inflammation.[48] The ROS scavenge the NO, leading to a reduction in bioavailability of NO, and therefore contributing to the hypertension seen with IH. ROS also stimulate an increase in various factors including transcription factors, such as NF-kB.[46] NF-kB in turn causes inflammatory and immune responses, including the release of downstream products, such as TNF-α and IL-8.[46] Therefore, it may be possible to induce acute IH in healthy participants to model inflammation-induced hypertension.

However, it is important to note that research on IH-induced hypertension in humans is minimal due to confounding factors in OSA patients.[46] Most of the research has instead been conducted in rodent models. Using an IH protocol to test vascular reactivity in humans is a relatively new concept and is currently being tested in our lab (Human Integrative Physiology Lab).

E. High-Fat Meal as a Model of Inflammation

Consumption of a high-fat, high-calorie meal, often referred to in the literature as a high-fat meal challenge, induces acute inflammation in young, healthy individuals.[10–15,17–19,21,49–53] The inflammation induced by a HFM is thought to be due to the rise in triglycerides (TG) and/or the diffusion of lipopolysaccharides (LPS) into the system, as shown in Figure 2.[49] LPS is present in the membranes of gram-negative bacteria, which is thought to enter the system via chylomicrons with the influx of free fatty acids during digestion after an individual consumes a HFM. Both the heightened TG and LPS induce inflammation via similar pathways. Both stimulate receptors (TLR 2/4) that lead to an increase in transcription of NF-kB and resultant cytokines, such as IL-6.[49] The heightened inflammation in turn results in a decrease in the bioavailability of NO and, therefore, causes acute vascular dysfunction, as seen within previous studies.[16,18–29]

Compared to using a vaccine and IH to test vascular reactivity, the HFM has many advantages. 1) Temporal aspect: HFMs have been shown to induce inflammation and decrease vascular function within four hours of consumption. Based on previous studies, vaccines can take anywhere between eight hours and two days to show inflammatory and/or vascular effects.[40–44] 2) Applicability: Western culture promotes unhealthy eating habits, including high-fat and high calorie meals.[54] Administration of a vaccine and experiencing IH (unless with OSA diagnosis) is not as common as consumption of a high-fat/high calorie meal. 3) Feasibility: A HFM is inexpensive, easy to administer, and does not require any specialized equipment or medical personnel.

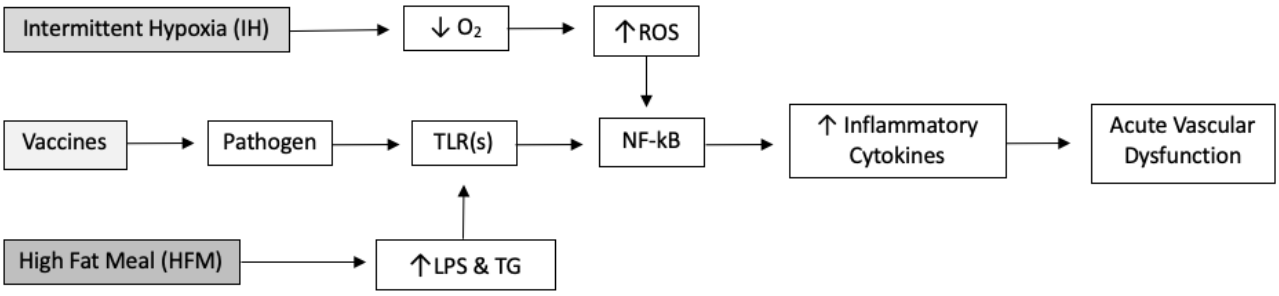


Figure 2. The shared pathways among models of inflammation. Toll-like receptor (TLR), oxygen (O_2), reactive oxygen species (ROS), nuclear factor kappa B (NF-kB), lipopolysaccharides (LPS), triglycerides (TG).

Chapter 2: Review of Literature

A. High-Fat Meal as a Model of Inflammation

Individuals in western society spend most of their day in a postprandial rather than a fasted state, regularly consuming high-fat, high calorie meals[55] contributing to the development of atherosclerosis, in which the increase in TG after a HFM (postprandial lipemia) causes an increase in inflammation.[56] Therefore, HFM research has become an important focus within the literature.

Previous HFM studies have used various meal compositions (including calorie content), administering the meal at varying times throughout the day, measuring varying postprandial timepoints and testing various conditions (including exercise protocols and the addition of antioxidants). Due to these variations in methodology, there are discrepancies among study results. Therefore, this review will focus on responses in young (average age 18-39 years old), healthy participants in the control condition (i.e. a HFM without preceding/post exercise or the addition of antioxidant(s)) to eliminate *some* confounding factors. Any discrepancies among results and potential mechanisms for these discrepancies in this target population will be discussed in more detail.

Before focusing on whether the HFM induces inflammation in previous literature, it is important to start with whether the HFM caused an increase in TG and/or LPS. As discussed in Chapter 1E, the proposed mechanism for HFM-induced inflammation is an increase in TG and/or LPS at the start of the signaling cascade that leads to an increase in inflammation (see Fig. 2).

TG concentration increases after an HFM in the young, healthy target population.[10,12,13,15,16,18–23,25,26,29,55–69] The timing of this increase in TG concentration varies,

with studies showing an increase in TG as early as 1 hour [12,58] to as long as 6 hours[19,27,57,66,67] postprandially. Many of these studies however, specifically see an increase in TG concentration beginning at 2 or 3 hours until the end of their study period (most commonly 4 or 6 hours).[13,16,18,19,21–23,25,27,29,55–57,59–63,66,67]

Unlike TG concentration that is measured in most of the previous HFM focusing on this target population, LPS (endotoxin) concentration has been less frequently measured. Postprandial endotoxemia, which is the accumulation of absorbed LPS, is facilitated by the absorption of fats within the small intestines.[58] The increase in LPS concentration has been seen in the HFM-only condition in young, healthy participants within 30 minutes to 5 hours postprandially.[53,56,58]

One potential limitation of comparing the timing of the TG and/or LPS responses in previous studies is due to the differing HFM compositions used within each study. Popular meals used as an HFM include frozen breakfast sandwiches, fast food meals, and liquid meals. These meals vary in fat content, fat composition (i.e. saturated vs. unsaturated fats), carbohydrate content, protein content, and overall nutrient content. These studies also differ in either set calorie content or whether the calorie content was standardized to the individual participant, using body surface area (BSA). However, the window of time to measure the increase in LPS and/or TG concentration generally remains similar within these previous studies and therefore provides information for adequate study design to capture the rise in LPS and/or TG concentration.

The increase in TG and/or LPS concentration have been theorized to cause the increase in inflammation. This increase in inflammation has been measured in previous HFM studies by

various inflammatory biomarkers, including the pro-inflammatory cytokine interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor α (TNF-α).

IL-6 has been commonly used to indicate an increase in inflammation after the HFM. The majority of studies indicate a significant increase in IL-6 concentration within the postprandial time-period (up to 6 hours),[10–16,18,62,70] while others failed to report an increase.[25,55,61] Discrepancies in the postprandial concentrations of IL-6 could result from varying methodology, including the time of day when the HFM was consumed.[25,55] However, despite these discrepancies, the HFM to be used in this proposed thesis study has been used previously to successfully increase inflammation postprandially, significantly increasing IL-6 concentration at hour 4.[70]

There are many additional biomarkers that have also been used in previous studies to measure acute inflammation, such as TNF-α and CRP. TNF-α concentration has been shown to either stay the same as baseline[10,13–15,56,58,61,62] or decrease following the HFM.[55] Thus, it is possible that TNF-α may be a less sensitive biomarker for indicating inflammation after an HFM than IL-6. For instance, previous studies that measured both IL-6 and TNF-α concentration observed a significant increase in postprandial IL-6, but not TNF-α.[13–15]

In addition, previous HFM studies indicate CRP is not a reliable biomarker for acute inflammation because it does not change significantly within the postprandial timeframe (~6 hours).[14,19,56,59,61,63,71] Studies suggest CRP peaks at ~48 hours, which is well outside of the HFM postprandial measurement window.[72]

Macrovascular Function

Inflammation after a HFM has also been associated with vascular function, depending on the study and which area/function of the vasculature was tested. Previous studies have assessed macrovascular function, which refers to large (conduit) artery function.

Macrovascular function is commonly assessed by flow-mediated dilation, or FMD. FMD measures the capacity of the brachial artery to vasodilate, which is largely NO mediated. Briefly, a cuff is placed on the forearm and an ultrasound probe is used to measure the baseline diameter of the brachial artery in the upper arm. Baseline diameter is taken for one minute, after which the forearm cuff is inflated to suprasystolic pressure to occlude blood flow for five minutes. The cuff is then released (deflated), which initiates a hyperemic response to the lower arm, causing the diameter of the brachial artery to vasodilate.

FMD is reported as the percent change in brachial artery diameter between baseline (pre) and the peak diameter post-forearm cuff occlusion.[73] Of note, special attention must be paid to any significant changes in baseline diameter that occurs during the FMD because this could drive any significant changes in the FMD reported.[73] One such factor that could influence this baseline diameter is insulin, which causes vasodilation.[74] Therefore, if a HFM contains large amounts of glucose, this could drive the baseline diameter higher and thus cause the percent change to appear lower.

Previous studies have shown varying results for FMD during the postprandial period after consumption of a HFM. The majority of the studies indicate a significant decrease in postprandial FMD during the HFM-only condition.[16,18–27,29,68] However, the baseline diameter is not reported for all of these previous studies, making it difficult to determine if any changes in baseline diameter might have affected the comparisons.[18,19,25]

Others studies have not reported a decrease in FMD during the postprandial time period.[65,66,69,75,76] The majority of these studies report similar baseline diameters at each measurement period.[66,69,75,76] However, in one study by Raitakari et al.,[65] the baseline diameter was significantly different between pre-meal and post-meal measurements, which could have affected the FMD comparison.[65]

Fitness status could be a confounding factor between these previous studies. In the study by Johnson et al.,[26] only the nonactive group exhibited a significant decrease in FMD postprandially whereas the active group did not.[26] This emphasizes the importance of accounting for fitness status, which many of these previous studies did not measure, when viewing these changes in FMD.

In addition, endothelial-independent vasodilation has also been assessed in previous studies to assess smooth muscle function. Smooth muscle refers to the muscle surrounding the artery which receives input to relax/contract and therefore cause vasodilation/vasoconstriction. Previous studies suggest endothelial-independent/ smooth muscle function is not altered with a HFM;[15,18,24,28,66] suggesting a major role of endothelial-driven mechanisms.

Arterial Stiffness

Due to the interplay between vascular function and arterial stiffness on the vasculature, arterial stiffness has also been assessed following a HFM. In the study by Lithander et al., 2013,[77] 20 healthy men (mean age 38 ± 14) consumed a HFM high in monounsaturated fats and a HFM high in saturated fats on two separate days.[77] Pulse wave velocity (PWV) and augmentation index (AIx) were measured at baseline and every 30 minutes up to 4 hours postprandially. Focusing on the high saturated fat meal, PWV significantly increased postprandially, but was no longer significant when corrected for the concomitant increase in

BP. AIx also increased significantly postprandially, but was no longer significant after correcting for an increase in heart rate and BP. However, postprandial arterial stiffness change vary among studies, with Fahs et.al. reporting no changes in PWV, AIx and carotid artery stiffness[76] while Augustine et. al. reported an increase only in peripheral PWV.[64]

B. Race, Social Determinants of Health, and Inflammation

Although race is not a biological concept, black individuals exhibit both higher rates of hypertension[1] as well as divergent vascular function compared to their white counterparts.[8] Increased vascular resistance has been observed in young, normotensive black individuals as compared to their white counterparts.[8] This increase in vascular resistance may indicate a decrease in the bioavailability of NO.[8] Additionally, pro-inflammatory cytokines in young, normotensive black individuals levels are higher as compared to white individuals.[9]

Specific SDH factors, such as higher educational levels and income, have been negatively associated with risk factors for CVD.[2] Other specific SDH factors, such as lower status occupation, higher levels of anger/hostility and the influence of the built environment on negative behavioral outcomes, have also been associated with an increased risk of hypertension.[3–5] Higher scores in the racism and discrimination categories (both negative SDH factors) have also been independently associated with higher ambulatory BP.[78] In addition, low socioeconomic status (a negative SDH factor) is associated with higher levels of CRP and IL-6, both proinflammatory cytokines and biomarkers of systemic inflammation.[79] Since higher chronic, low-grade inflammation is known to be a factor in the development of chronic diseases, this could be one factor driving the increased CVD and/or hypertension risk associated with these specific SDH factors. However, the association between SDH factors and inflammatory/vascular outcomes to an acute stimulus has not been evaluated nor commonly

accounted for when studying vascular differences between different populations. Therefore, by understanding the influence of SDH factors on inflammation and vascular function, it may elucidate factors driving the divergence in vascular function between black and white individuals.

Aims and Hypotheses

Aim 1a: To evaluate vascular function among young, healthy black individuals compared with white individuals following an inflammatory challenge using a HFM.

Aim 1a Hypothesis: Following induced inflammation, we hypothesized that black participants would have significantly lower postprandial vascular function as compared to white participants.

Aim 1b: To evaluate the association between SDH factors and vascular function in young, healthy black and white individuals following an inflammatory challenge using a HFM.

Aim 1b Hypothesis: Following induced inflammation, we hypothesized that higher SDH scores (i.e. better holistic health) would be positively associated with vascular function following the HFM.

Aim 2a: To evaluate circulating inflammatory biomarkers (IL-6) concentration among young, healthy black individuals compared with white individuals following an inflammatory challenge using a HFM.

Aim 2a Hypothesis: Following induced inflammation, we hypothesized that black participants would have significantly higher postprandial concentrations of the inflammatory biomarker IL-6 as compared to white participants.

Aim 2b: To evaluate the association between SDH factors and inflammatory biomarker (IL-6) concentration in young, healthy black and white individuals following an inflammatory challenge using a HFM.

Aim 2b Hypothesis: Following induced inflammation, we hypothesized that higher SDH scores (i.e. better holistic health) would be negatively associated with inflammatory biomarker (IL-6) concentration following the HFM.

Chapter 3: Methods

Experimental Design

The present comparative study involves two groups consisting of black and white individuals. Both groups underwent an exercise test and anthropometric measurements during the first visit. During the second visit, both groups underwent baseline vascular measurements and a baseline blood draw, a HFM, and subsequent vascular measurements (hourly; hours 1-4 postprandial) and blood draws (hour 2 and 4 postprandial).

Primary variables for inflammation were measured in the blood and consisted of IL-6 concentration. Primary variables for vascular function consisted of macrovascular function in terms of FMD. Secondary variables for the vasculature consisted of BP (using continuous BP monitoring in the form of a finger cuff), heart rate (using electrocardiogram), and wave reflection/arterial stiffness (using PWA and PWV).

IRB Approval

This study was approved by the Institutional Review Board at the University of Maryland, College Park. All study procedures and potential risks were explained to the participant in detail and all questions were answered prior to obtaining written informed consent. Participants were between the ages of 18-35 years old, weighed more than 110 pounds, had a calculated body mass index (BMI) less than 30 kg/m^2, had a BP lower than 140/90 mmHg, did not have a current or previous heart, lung or metabolic disease or diabetes, were not currently pregnant, had regular menstrual cycles (females), had not been sick in the past two weeks, were not users of tobacco or nicotine products, and were not currently taking any prescription medications (other than oral contraceptive pills where participants were tested during their placebo phase).

Experimental Overview

Participants were recruited from the University of Maryland, College Park campus. Study flyers were posted in dormitories, campus buildings, and cafeterias. Emails were distributed to various campus organizations as well as department listservs. In addition, brief presentations were conducted in undergraduate courses upon approval of the instructor.

Participants visited the lab for two different visits separated by at least 24 hours. Visit 1 began with informed consent followed by participant screening. Participants then completed a SDH questionnaire followed by anthropometric (body composition) measurements and a VO_2peak exercise test on a cycle ergometer (Parvo Medics, Salt Lake City, Utah) to determine cardiovascular fitness.

During Visit 2, individuals' baseline (fasted) vascular measurements (finger plethysmography, ECG, FMD, PWA, PWV) and venous blood draw were obtained. Participants were then given a liquid HFM to consume within 10 minutes. Vascular measurements were repeated at 1, 2, 3, and 4 hour/s postprandial. Venous blood samples of 60 mL were drawn at 3 time points (baseline (fasted), 2 hours, and 4 hours post HFM) for a total of 180 mL, from an antecubital vein by a trained research member using aseptic techniques.

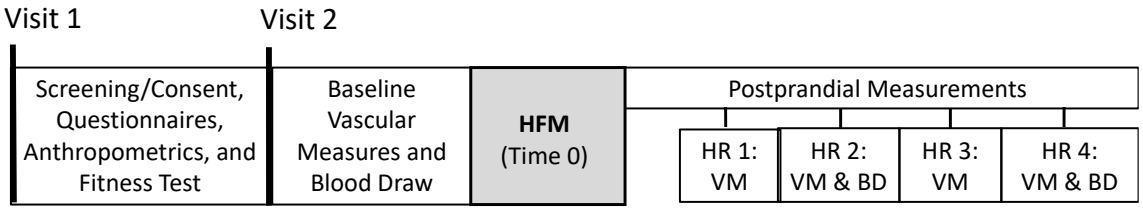


Figure 3. Visit timeline. High-fat meal (HFM), hour (HR), vascular measures (VM), blood draw (BD).

High Fat Meal

Participants were given a liquid HFM, which consisted of heavy whipping cream, sugar, chocolate syrup and non-fat powdered milk normalized to the subject's body surface area (BSA).

The ratio of ingredients was the same for each participant, with a total of 386 grams of meal per 2 m^2 of BSA. Approximately 84% of total calories were from fat for each meal. This specific HFM has been used successfully in previous HFM studies.[70,80]

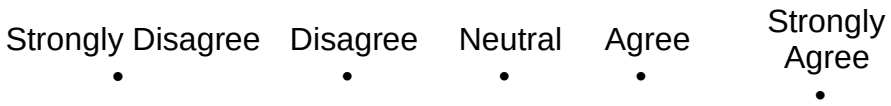
Social Determinants of Health Questionnaire

The social determinants of health questionnaire is a 7-item questionnaire which contains questions pertaining to economic stability, neighborhood and built environment, social and community belonging, health and health care, and education, as displayed below:

SDH Questions:

1. I feel as though I have access to good health care.
2. I feel as though I have access to complete/adequate nutrition.
3. I feel as though I have access to good education.
4. I feel as though I have access to good housing conditions.
5. I feel as though I live in a high stress environment.
6. I feel socially accepted at UMD (I belong).
7. [My family and I] are in a financially stable position.

This questionnaire uses a Likert-type scaling method, measuring a positive or negative response to each question (strongly agree to strongly disagree):



Each question is scored on a scale from 1-5, with 5 being the "healthiest" or "best" answer. For all of the questions, except for question 5 (stress), a score of 5 was assigned to "strongly agree," with 1 assigned to "strongly disagree." For question 5 (stress), a score of 5 was assigned to "strongly

disagree" and a score of 1 to "strongly agree." The total SDH score was then calculated by adding the scores from each question, with the highest (or best) score being a 35.

Vascular Measurements

Beat-to-Beat Blood Pressure (Finger Plethysmography), and Electrocardiogram (ECG): A finger beat-to-beat BP cuff (finger plethysmography – AD Instruments) was placed on the participant's middle finger between the proximal and distal interphalangeal joints. Additionally, five electrodes were placed on the participant to record a single lead ECG tracing. One electrode was placed underneath the participant's collarbone on each shoulder and on both sides of the lower abdomen. The earth (ground) electrode was placed on the participant's calf. The finger beat-to-beat BP cuff and ECG electrodes were connected to the participants for 10 minutes of rest and during the duration of each vascular measurement. All physiological measures were interfaced with an AD Instruments data collection system for filtering and offline analysis.

Flow Mediated Dilation (FMD): The brachial artery capacity to dilate was assessed non-invasively using ultrasonography (Hitachi-Aloka Arietta 70). The brachial artery was imaged in longitudinal section, 5-10 cm above the placement of a usual BP cuff, using a high frequency (5-13 MHz) linear array probe. A BP cuff was placed on the forearm. The diameter of the brachial artery was measured for 1 minute at rest (baseline diameter), during a 5-minute ischemic stimulus where the BP cuff was rapidly inflated to 220 mmHg, and for 2.5 minutes following rapid deflation of the cuff (to determine peak diameter). Analysis of the FMD was carried out using a semi-automated edge detection software system (Quipu Cardiovascular Suite). Responses were calculated as percentage change in brachial artery diameter from baseline. If baseline diameters differed significantly between timepoints (baseline, hours 1, 2, 3, 4), FMD was allometrically scaled (if needed) to adjust for the influence of the baseline diameter as described in Atkinson et

al., 2013.[73] Briefly, the baseline and peak diameters are logarithmically transformed and allometrically scaled to the baseline diameter.

Pulse Wave Analysis (PWA) and Pulse Wave Velocity (PWV): PWA was conducted using brachial artery pressure waveforms which were measured in the supine position using a BP cuff (SphygmoCor, AtCor Medical). The SphygmoCor software measures the ascending aortic pressure wave and uses it to calculate several measurements, including aortic augmentation index (AIx), and central pulse pressure (CPP). PWV was measured using the same equipment. PWV uses the velocity of the blood travelling from the aorta to the femoral artery as an index of large artery compliance. A cuff was placed on the upper thigh of the right leg. The femoral pulse was palpated in the right upper thigh area and the distance was measured from femoral pulse to the thigh cuff. The carotid artery on the right side of the neck was then palpated. The distance between the suprasternal notch and carotid artery (pulse) was then measured with a measuring tape. The distance between the suprasternal notch and the thigh cuff was measured and these distances were entered into the program. This allows the program to determine the true distance between the two pulses (carotid and femoral) to perform velocity calculations. These distance measurements are needed to account for the femoral pulse being at a different location than the thigh cuff. The time was measured with a carotid applanation tonometer placed on the carotid artery and with inflation of the thigh cuff to capture BP waveforms at the carotid and femoral sites. PWV was calculated by the time the pressure waveform takes to transmit from femoral to carotid pulse sites and the distance between the two sites.

IL-6 Concentration

Blood was collected via venipuncture at each time-point (baseline, hour 2 postprandial, and hour 4 postprandial) in a 10 mL ethylenediaminetetraacetic acid (EDTA) tube. EDTA tubes

were centrifuged at 4°C for 20 minutes at 1800 x gravity. The plasma was then aliquoted into 1.5 mL microcentrifuge tubes and placed in a -80°C freezer until analysis, at which time samples were thawed at room temperature.

Plasma was used to evaluate IL-6 concentration to be consistent with previous HFM literature, as previous HFM studies predominantly evaluated IL-6 concentration in plasma.[10,13,15,18,55,59,70] This includes previous HFM studies conducted by our lab, which use the same HFM. Previous studies have noted differences in IL-6 concentration evaluated in plasma versus serum,[81] which indicates the need to be consistent for comparability purposes.

Baseline, 2 hours post-prandial, and 4 hours post-prandial IL-6 concentration were measured in plasma using a human multiplex immunoassay according to manufacturer instructions (ProcartaPlex; Invitrogen, Thermo Fisher, Waltham, MA). Sample dilutions were performed according to the manufacturer's' instructions for IL-6, with the addition of 5% fetal bovine serum (FBS). Samples were assayed in duplicate and their concentrations were measured using an Luminex MagPix System (Luminex, Austin, TX).

Statistical Analysis

Analyses were performed using GraphPad Prism. All data were assessed for normality and outliers via Shapiro-Wilk test and ROUT 1% method, respectively. For Aim 1a and 2a, repeated measures analysis of variance (ANOVA) was performed. Post-hoc analysis was performed if the repeated measures ANOVA was deemed significant. Pearson's correlation coefficient was performed for Aim 1b and 2b. Pearson's correlation coefficient was also performed to assess the correlation between the change in vascular function (FMD) following the HFM at hour 2 postprandial and fitness level (VO_2Peak). Aim by aim statistical analysis include:

Aim 1a: To evaluate the differences in macro-vascular function among young, healthy black individuals as compared to white individuals following an inflammatory challenge using a HFM.

The association between measures of vascular function/arterial stiffness (FMD, PWA, PWV) and race was assessed using 2x5 repeated measures ANOVA with race (black vs white) and HFM time-point (pre vs. post HFM; hour 1-4) as separate factors.

Aim 1b: To evaluate the association between SDH factors and macrovascular function in young, healthy black and white individuals following an inflammatory challenge using a HFM.

Correlations between total SDH score and vascular function was evaluated at baseline and at postprandial timepoints, including the change between postprandial and baseline (delta) using Pearson's correlation coefficient.

Aim 2a: To evaluate differences in circulating inflammatory biomarkers among young, healthy black individuals compared to white individuals following an inflammatory challenge using a HFM.

The measure of inflammation (IL-6) was assessed using 2x3 repeated measures ANOVA with factors as race (black vs white) and HFM time-point (pre vs. post HFM; hour 2 and 4) as separate factors. Correlation between inflammation (IL-6) and vascular function (FMD) was evaluated using Pearson's correlation coefficient and/or Spearman's Rho.

Aim 2b: To evaluate the association between SDH factors and inflammatory biomarker (IL-6) concentration in young, healthy black and white individuals following an inflammatory challenge using a HFM.

Correlations between total SDH score and inflammation were evaluated at baseline and postprandial timepoints, including the change between postprandial and baseline (delta) IL-6 concentration using Pearson's correlation coefficient and/or Spearman's Rho.

Sample Size and Power Considerations

Using means and SDs from four different studies, a sample of 16 participants in total was needed to detect 1 SD difference in primary outcome variable of FMD at 80% power and alpha = 0.05, suggesting we would be powered to detect a medium to large effect size (Cohen's d ~0.7). Based on the previous studies, 8 participants per group were needed to detect changes in the primary outcome variable. We would be powered to detect differences between groups with our proposed sample size of 20 total participants even if the true effect size is small to medium (d ~0.4) at the same alpha and power levels.

Chapter 4: Results

Participant Demographics and HFM

Participant characteristics of both groups are presented in Table 1. Five black (5 M) and 14 white (7 M/ 7 F) individuals completed testing. White individuals were significantly older than black individuals (25 ± 4.1 y vs. 21.2 ± 1.5 y; p= 0.01). Groups were similar in height, weight, BMI, resting systolic blood pressure (SBP), resting diastolic blood pressure (DBP), resting heart rate (HR), and fitness (VO_2Peak) (p>0.05). Groups were also similar in body surface area (BSA) and subsequent HFM kilocalories (p>0.05), as displayed in Table 2.

Table 1. Participant Demographics

	Black Individuals (n=5)	**White Individuals (n=14)**
M/F	5/0	7/7
Age (years)	21.2 ± 1.5	25 ± 4.1*
Height (cm)	177.2 ± 8.1	170.1 ± 9.8
Weight (kg)	73.8 ± 11.3	65.3 ± 9.3
BMI (kg/m^2)	23.5 ± 3.3	22.6 ± 2.9
SBP (mmHg)	120.8 ± 6.4	116.4 ± 7.4
DBP (mmHg)	68.2 ± 4.2	70 ± 6.5
HR (bpm)	52 ± 3.6	55.4 ± 9.4
VO_2Peak (ml/kg/min)	40.5 ± 5.9	43.4 ± 10.8

Data presented as means ± SD. M, male; F, female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. * indicates p<0.05 as compared with black individuals.

Table 2. High Fat Meal

	Black Individuals (n=5)	**White Individuals (n=14)**
BSA	1.9 ± 0.2	1.7 ± 0.2
HFM (Kcal)	1426.5 ± 118.8	1302.5 ± 115.8

Data presented as means ± SD. BSA, body surface area; HFM, high fat meal; Kcal, kilocalorie.

Aim 1a: No race differences in vascular function at baseline or following the HFM

Black and white individuals had similar vascular function (%FMD) at baseline (p>0.05). Within each group, %FMD and baseline diameter remained similar at hours 1-4 post HFM compared to baseline (p>0.05), as displayed in Table 3 and Figure 4. However, peak diameter was

significantly increased at 4 hours post HFM only in white individuals. There was no effect of time ($F(4, 78) = 0.5036$, $p=0.73$), race ($F(1, 78) = 0.1441$, $p= 0.14$), or the interaction of race x time ($F(4, 78) = 0.3446$, $p=0.85$) on %FMD outcomes. Δ%FMD, calculated by baseline subtracted from each post-timepoint, also remained similar within each group at hours 1-4 post HFM (Table 4). There was also no effect of time ($F(3, 58) = 0.04304$, $p=0.99$), race ($F(1, 58) = 2.786$, $p= 0.10$), or the interaction of race x time ($F(3, 58) = 0.1837$, $p=0.91$) on Δ %FMD outcomes.

Table 3. Vascular Function

Black Individuals (n=5)	Baseline (0HP)	1HP	2HP	3HP	4HP
%FMD	5.76 ± 4.29	6.83 ± 2.15	6.03 ± 1.57 (n=4)	5.95 ± 2.48	5.76 ± 4.92
BL D (mm)	3.99 ± 0.30	4.09 ± 0.25	4.29 ± 0.22 (n=4)	4.04 ± 0.23	4.17 ± 0.43
Peak D (mm)	4.21 ± 0.20	4.36 ± 0.22	5.06 ± 0.91 (n=4)	4.28 ± 0.21	4.40 ± 0.27
White Individuals (n=14)	Baseline (0HP)	1HP	2HP	3HP	4HP
%FMD	4.61 ± 2.97 (n=13)	6.7 ± 2.22 (n=12)	6.34 ± 3.43 (n=13)	7.02 ± 3.49 (n=13)	7.15 ± 3.7 (n=13)
BL D (mm)	3.68 ± 0.44 (n=13)	3.69 ± 0.46 (n=12)	3.83 ± 0.54 (n=13)	3.8 ± 0.58 (n=13)	3.77 ± 0.61 (n=13)
Peak D (mm)	3.84 ± 0.45 (n=13)	3.94 ± 0.47 (n=12)	4.07 ± 0.56 (n=13)	4.07 ± 0.61 (n=13)	4.03 ± 0.61 (n=13)*

Data presented as means ± SD. %FMD, flow mediated dilation percentage; BL D, baseline diameter; Peak D, peak diameter; mm, millimeters; HP, hours post HFM. * indicates $p<0.05$ as compared with baseline within each group.

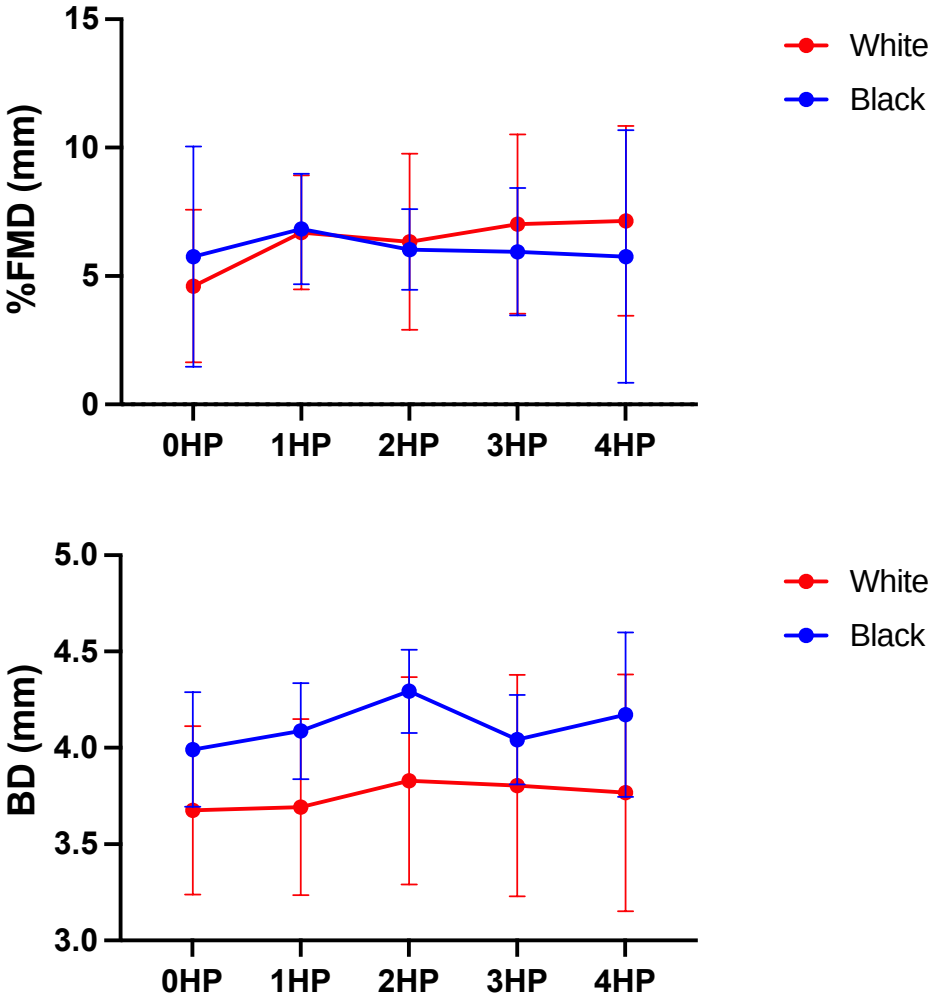


Figure 4. Vascular Function. Data presented as means ± SD. FMD, flow-mediated dilation; BD, baseline diameter; HP, hours-post HFM. * indicates $p<0.05$ as compared with 0HP (baseline) within each group.

Table 4. Δ FMD

Black Individuals (n=5)	1HP	2HP	3HP	4HP
Δ %FMD	1.07 ± 4.39	0.63 ± 4.76 (n=4)	0.19 ± 4.03	0.001 ± 4.88
White Individuals (n=14)	1HP	2HP	3HP	4HP
Δ %FMD	2.10 ± 2.81 (n=11)	1.70 ± 3.62 (n=12)	2.13 ± 3.76 (n=12)	2.92 ± 3.87 (n=12)

Data presented as means ± SD. Δ%FMD, baseline flow-mediated dilation subtracted from each post-timepoint. * indicates $p<0.05$ as compared with baseline within each group.

Hemodynamic Variables

There was no effect of time, race, or interaction of race x time on DBP ($p>0.05$). In black individuals, SBP remained similar and DBP decreased significantly at 2 hours post HFM ($p= 0.008$) compared to baseline. In white individuals, SBP significantly increased at hour 4 compared to baseline (SPB, $p= 0.028$), whereas DBP remained similar. There was no effect of time, race, or interaction of race x time on SBP ($p>0.05$).

There was no effect of time, race, or interaction of race x time on HR, AIx, AIx75, or PWV outcomes ($p>0.05$ for all). In black individuals, HR, AIx, AIx75, and PWV remained similar to baseline ($p>0.05$), as shown in Table 5 and Figures 5-10. In white individuals, HR significantly increased at hour 1 ($p=0.014$) and 4 ($p= 0.013$). AIx significantly decreased at hour 1 compared to baseline ($p= 0.043$). AIx75 and PWV remained similar ($p>0.05$).

There was no effect of time, race, or interaction of race x time on ΔSBP, ΔDBP, ΔAIx, ΔAIx75, ΔHR, or ΔPWV outcomes ($p>0.05$ for all). Delta data for the hemodynamic variables are displayed in Table 6.

Table 5. Blood Pressure and Arterial Stiffness

Black Individuals (n=5)	Baseline (0HP)	1HP	2HP	3HP	4HP
HR (bpm)	52 ± 4	60 ± 9	61 ± 9	61 ± 7	59 ± 7
SBP (mmHg)	120.8 ± 6.38	124.20 ± 13.81	122 ± 15.08	123 ± 9.11	124.20 ± 7.73
DBP (mmHg)	68.20 ± 4.21	64.20 ± 5.26	63.8 ± 4.15*	70 ± 10.65	68.8 ± 3.7
AIx (AU)	-0.60 ± 2.51	-3.20 ± 3.7	-4.8 ± 6.1	-5 ± 5.34	-4.20 ± 6.18
AIx75 (AU)	-12.20 ± 2.39	-9.8 ± 6.1	-11.40 ± 7.13	-12.2 ± 5.81	-12.6 ± 5.03
PWV (m/s)	5.24 ± 1.04	5.43 ± 0.67 (n=3)	5.35 ± 0.71 (n=4)	5.45 ± 0.5 (n=4)	5.53 ± 0.79 (n=4)
White Individuals (n=14)					
HR (bpm)	55 ± 9	63 ± 11	59 ± 8	59 ± 10	62 ± 13
SBP (mmHg)	116.36 ± 7.38	119.5 ± 8.62	119.23 ± 9.20 (n=13)	120.07 ± 8.98	121.29 ± 7.84*
DBP (mmHg)	70 ± 6.48	69.64 ± 6.23	69.38 ± 7.08 (n=13)	69.43 ± 7.02	71 ± 5.38
AIx (%)	0.71 ± 8.05	-5.36 ± 8.55*	-2.08 ± 9.12 (n=13)	-1.14 ± 10.84	-5.79 ± 10.84
AIx75 (%)	-8.57 ± 9.75	-11.21 ± 8.76	-9.69 ± 10.94 (n=13)	-8.86 ± 11.43	-12.07 ± 9.59
PWV (m/s)	5.37 ± 0.75	5.41 ± 0.87	5.28 ± 0.53 (n=13)	5.36 ± 0.69	5.56 ± 0.73

Data presented as means ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AIx, augmentation index; AIx75, augmentation index normalized to a heart rate of 75 bpm; PWV, pulse wave velocity; HP, hours post HFM. * indicates $p<0.05$ as compared to baseline at each timepoint within each group.

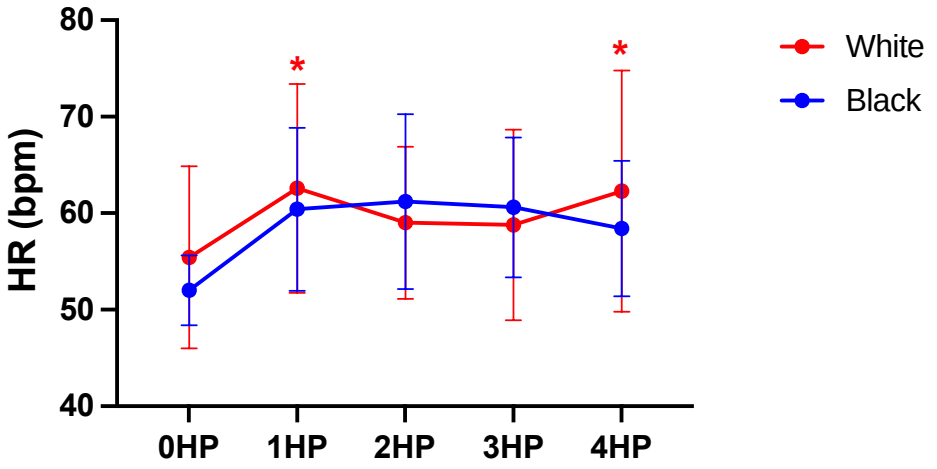


Figure 5. Heart rate responses. Data presented as means ± SD. HR, heart rate; HP, hours post. * indicates p<0.05 as compared with 0HP (baseline) within each group.

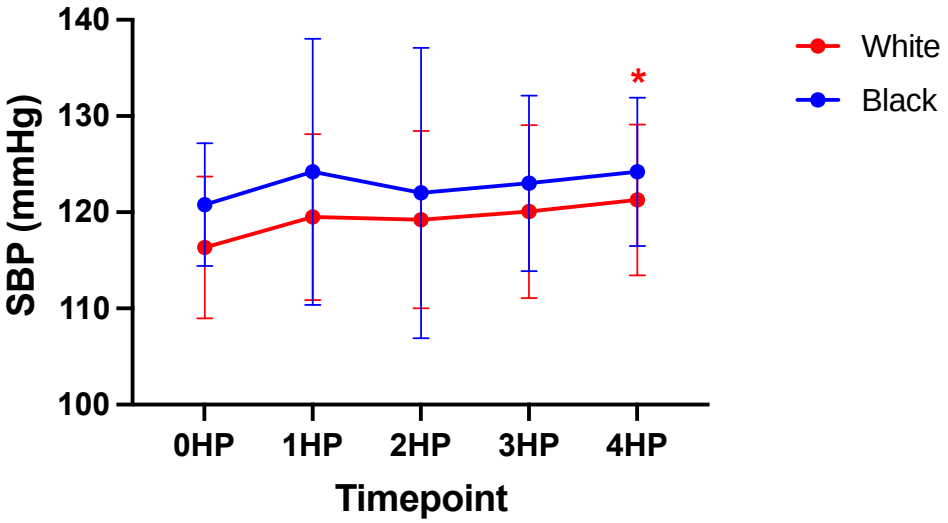


Figure 6. Systolic blood pressure responses. Data presented as means ± SD. SBP, systolic blood pressure; mmHg, millimeters of mercury; HP, hours post. * indicates p<0.05 as compared with 0HP (baseline) within each group.

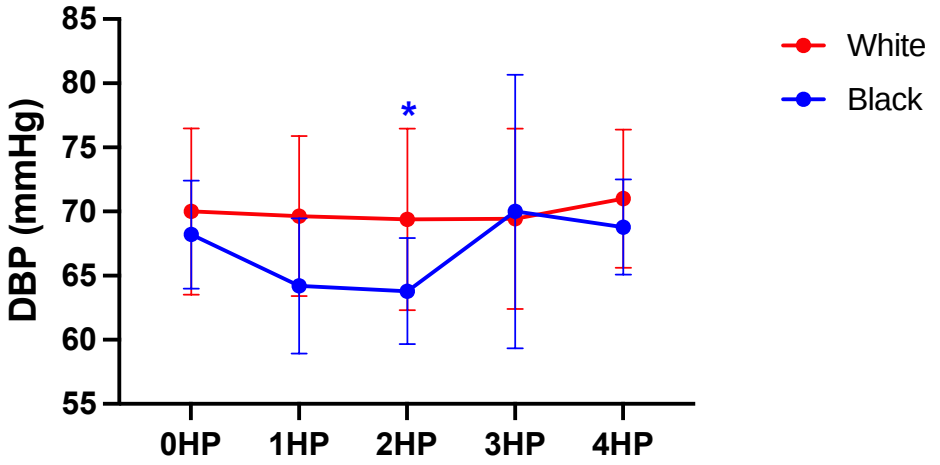


Figure 7. Diastolic blood pressure responses. Data presented as means ± SD. WH, white individuals; BL, black individuals; BP, blood pressure; mmHg, millimeters of mercury; HP, hours post. * indicates p<0.05 as compared with 0HP (baseline) within each group.

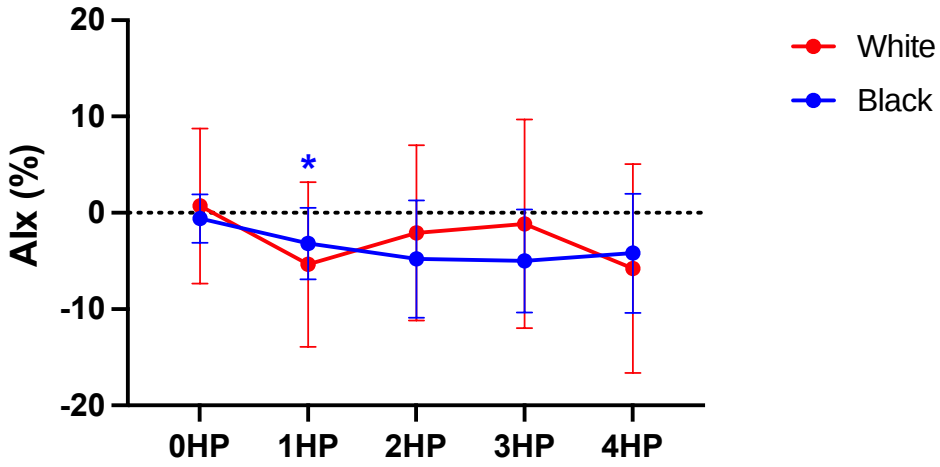


Figure 8. Augmentation index responses. Data presented as means ± SD. AIx, augmentation index; HP, hours post. * indicates p<0.05 as compared with 0HP (baseline) within each group.

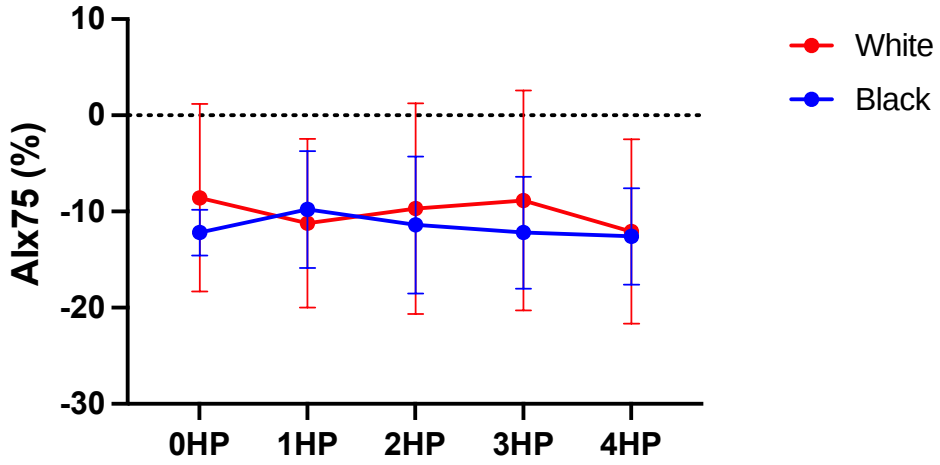


Figure 9. Augmentation index normalized to 75 bpm responses. Data presented as means ± SD. AIx75, augmentation index normalized to 75 bpm; HP, hours post. * indicates p<0.05 as compared with 0HP (baseline) within each group.

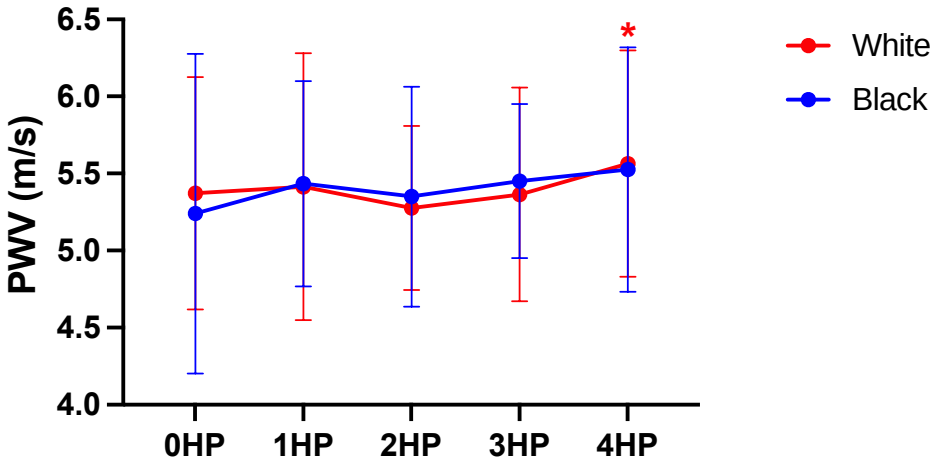


Figure 10. Pulse wave velocity responses. Data presented as means ± SD. PWV, pulse wave velocity; m/s, meters per second; HP, hours post. * indicates p<0.05 as compared with 0HP (baseline) within each group.

Table 6. Δ BP and Δ Arterial Stiffness

Black Individuals (n=5)	1HP	2HP	3HP	4HP
Δ HR	8.4 ± 5.86	9.2 ± 6.76	8.6 ± 5.5	6.4 ± 4.83
Δ SBP (mmHg)	3.4 ± 9.66	1.2 ± 10.13	2.2 ± 3.56	3.4 ± 3.58
Δ DBP (mmHg)	-4 ± 6.82	-4.4 ± 1.52	1.8 ± 8.98	0.6 ± 2.51
Δ AIx (AU)	-2.6 ± 3.65	-4.2 ± 5.07	-4.4 ± 4.04	-3.6 ± 6.02
Δ AIx75 (AU)	2.4 ± 5.41	0.8 ± 6.42	0 ± 4.74	-0.4 ± 5.98
Δ PWV	0.33 ± 1.08 (n=3)	-0.08 ± 1.24 (n=4)	0.03 ± 0.88 (n=4)	0.1 ± 1.28 (n=4)
White Individuals (n=14)				
Δ HR	7.14 ± 7.68	4.69 ± 4.89 (n=13)	3.36 ± 6.65	6.86 ± 7.28
Δ SBP (mmHg)	3.14 ± 6.06	2.85 ± 5.51 (n=13)	3.71 ± 8.92	4.93 ± 5.97
Δ DBP (mmHg)	-0.36 ± 4.58	0.08 ± 3.93 (n=13)*	-0.57 ± 4.43	1 ± 2.99
Δ AIx (AU)	-6.07 ± 7.95	-2.46 ± 9.94 (n=13)	-1.86 ± 8.56	-6.5 ± 9.52
Δ AIx75 (AU)	-2.64 ± 9.18	-0.23 ± 10.71 (n=13)	-0.29 ± 9.85	-3.5 ± 8.23
Δ PWV (m/s)	0.04 ± 0.55	-0.02 ± 0.41 (n=13)	-0.01 ± 0.5	0.19 ± 0.33

Data presented as mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; AIx, augmentation index; AIx75, augmentation index normalized to a heart rate of 75 bpm; HR, heart rate; PWV, pulse wave velocity; HP, hours post HFM. * indicates $p<0.05$ as compared to black individuals at each timepoint.

Aim 1b: No association between SDH and vascular responses to the HFM

White individuals reported significantly better (higher score for) nutrition access ($p= 0.043$), housing conditions ($p<0.001$), financial stability ($p= 0.001$), and total SDH score ($p<0.001$) compared to black individuals, as shown in Table 7. There were no relationships between baseline SBP, DBP, AIx, AIx75, PWV, or FMD and SDH total score ($p>0.05$). There were no relationships between ΔSBP, ΔDBP, ΔAIx, ΔAIx75, ΔHR, ΔPWV, or Δ%FMD and SDH total score ($p>0.05$), as shown in Table 8. Delta (Δ) values for each vascular measurement were calculated as baseline subtracted from 3-hour post timepoint.

Delta (Δ) values for each vascular measurement were also calculated as baseline subtracted from 4-hour post timepoint, which no associations with SDH total found (data not shown).

Table 7. Social Determinants of Health Questionnaire

	Black Individuals (n=5)	**White Individuals (n=14)**
Health Care	4.4 ± 0.5	4.7 ± 0.5
Nutrition	3.8 ± 0.8	4.8 ± 0.4*
Education	4.6 ± 0.5	4.9 ± 0.4
Housing	3.2 ± 0.8	4.7 ± 0.5*
Stress (Less)	2.8 ± 0.4	3.4 ± 1.3
Acceptance	3.8 ± 0.8	4.5 ± 0.7
Financial Stability	2.6 ± 0.9	4.4 ± 0.9*
Total Score	25.2 ± 1.6	31.4 ± 3.03*

Data presented as means ± SD. * indicates $p<0.05$ as compared to black individuals at each timepoint.

Table 8. Correlations between Social Determinants of Health and Vascular Measures

Total Participants (N=19)	**SDH Total**
ΔSBP (mmHg)	0.44
ΔDBP (mmHg)	0.09
ΔAIx (AU)	0.43
ΔAIx75 (AU)	0.34
ΔHR	-0.1
ΔPWV	0.13
Δ%FMD	-0.02

SBP, systolic blood pressure; DBP, diastolic blood pressure; AIx, augmentation index; AIx75, augmentation index normalized to a heart rate of 75 bpm; HR, heart rate; PWV, pulse wave velocity; FMD, flow-mediated dilation. Δ is 3HP – Baseline for each vascular measure. *indicates $p<0.05$. Pearson's correlation.

Aim 2a & 2b: IL-6 concentration at baseline and following the HFM

IL-6 concentration was measured in a total of n=13 participants and remained unchanged (undetectable) following the HFM.

Chapter 5: Discussion

The novel findings of the study are: 1) Black and white individuals exhibit similar vascular function and hemodynamic responses to a HFM; 2) SDH factors do not correlate with these vascular and hemodynamic responses; 3) There were no significant changes in the inflammatory cytokines following the HFM.

Vascular Function

%FMD did not decrease in either black and white individuals following the HFM. Both black and white individuals exhibited similar vascular function at baseline, with similar FMD percentages between groups. These findings are in contrast to the study by Campia et al. 2002,[8] in which FMD percentage was significantly lower among black individuals compared to white individuals.[8] However, the participants within this study were on average older in both groups (mean age of 37 yrs) compared to black (21.2 ± 1.5 yrs) and white individuals (25 ± 4.1 yrs) in the current study.

In addition, neither race, time, nor the interaction of race and time were associated with changes in FMD following the HFM. Therefore, vascular function was maintained within each group, with no race differences in response to the HFM. This is similar to the findings by Sapp et al. 2021,[41] in which vascular function was maintained in both black and white young, healthy individuals following acute inflammation in the form of a vaccine.[41] Similar results were also seen in postmenopausal women, where FMD was similar at baseline and following a HFM in both black and white individuals.[82]

Physically active individuals maintain vascular function (FMD) following a HFM compared to inactive individuals who exhibit a decrease in FMD.[26] Interestingly, the majority of previous studies that reported a decline in FMD following the HFM did not report fitness

level.[16,18,19,21,23–25,27,29,68] It is therefore possible that the study population in the current study might have had a higher fitness (higher VO2max) on average than in previous studies. Previous literature indicates exercise training decreases pro- and increases anti-inflammatory cytokines, [83] as well as increases antioxidant defenses.[84] In addition, fitness improves overall vascular function predominantly via improved production of NO.[85] The participants within this study had a wide range of fitness levels, which may explain the variation in vascular responses to the HFM. To this point, interestingly, within the current study, VO2max is directly correlated (R^2= 0.34, p= 0.02) with the change in ΔFMD at hour two with more fit individuals experiencing an increase in FMD at hour two following the HFM as shown in Figure 11 below. This observation is contrary to the hypothesis that HFM would decrease vascular function. Therefore, the fitness of the participants could help explain the variability in the FMD responses to the HFM (i.e. responders vs. non-responders) as shown in Figure 4.

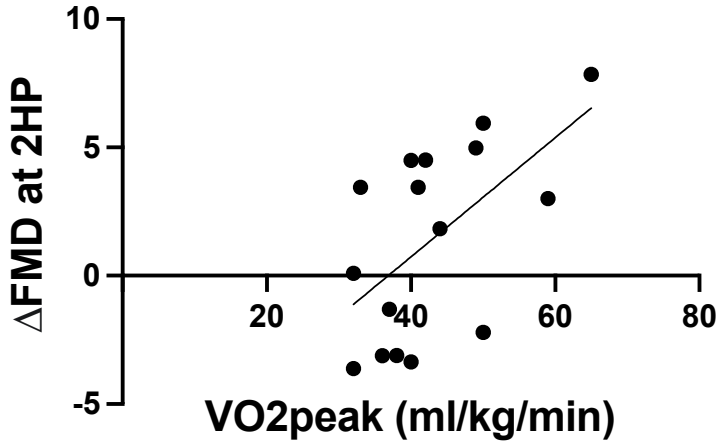


Figure 11. Correlation between ΔFMD at hour 2 with fitness status. ΔFMD, change in flow-mediated dilation at hour 2 post-HFM from baseline; VO2peak, peak rate of oxygen consumption.

Another important consideration when comparing the current study to previous studies is the sex of the participants. Sex differences in FMD response to the HFM were shown in the study by Harris et al[86] where men experienced a significant decrease in %FMD following the HFM whereas premenopausal women did not.[86] In the current study, both men and women's %FMD's were similar at baseline and remained similar following the HFM when both white and black individuals were combined by sex. Although the participants were similar in age and body composition to the Harris et al study,[86] fitness status was not reported in the previous study. In the current study, fitness category was similar between men and women, which could explain the discrepancy between study results.

This study was unable to recruit black women, which could impact our sex differences analysis. However, the FMD responses were also analyzed between white men and black men-only. White and black men had similar fitness and similar FMD responses to the HFM (data not shown). This would suggest homogeneity in the fitness status and responses within the male group, thus supporting the sex differences analysis. However, future studies should include black women to determine if their FMD responses to an HFM are similar to white women.

Another important aspect as compared to the previous literature in terms of FMD is the baseline brachial artery reactivity. The baseline FMDs in the current study were 5.76% in black individuals and 4.61% in white individuals. However, previous HFM studies have reported a baseline FMD ranging from 6.9% to 20%. [16,19–21,23,25,27,29] The higher baseline FMD could plausibly explain the decrease following the HFM in the previous literature as compared to the current study where we might have observed a "basement effect." However, two studies had similar baseline %FMD (5.05%, 5.1%) to the current study, but both found a significant decrease in FMD following the HFM.[18,22] In the study by Tucker et al,[22] the VO2max was similar to the

study groups (41.6 ml/kg/min in Tucker et al[22] vs. 40.5 ml/kg/min and 43.4 ml/kg/min in the current study), however, the HFM was 1,250 calories not standardized to body size.[22] It is, therefore, possible that smaller participants were consuming a significantly higher energy meal compared to other participants. In the current study, the HFM was standardized to BSA to help mitigate this issue. In the other study, Esser et al. 2013[18] neither reported fitness status nor standardized the meal to body size.[18] Therefore, it is difficult to compare the results of this study, where protocols for both fitness status and standardization of meal were followed.

The healthy profile of the participants - fitness, age and the ability to maintain vascular function after the HFM relates to the concept of redundancy in physiology. The concept is documented in detail in the review by Joyner and Dempsey from 2018,.[87] but in general, the body has many redundant mechanisms to maintain homeostasis during various types of physiological stress, in this case, vascular function with an acute inflammatory stressor in the form of a HFM. Although NO is a major contributor to vasodilation, and the bioavailability of NO could be maintained in this population following the HFM, multiple other vasodilators (hydrogen peroxide; H_2O_2, adenosine triphosphate; ATP, prostacyclin; PGI_2) can also maintain vascular function if NO bioavailability decreases.[34] This is important because although FMD is predominantly NO-mediated, other compensatory mechanisms could be more involved in vasodilation with an acute inflammatory stressor, allowing sufficient vasodilation to occur.[88] This also raises the question if the contribution of the various vasodilators differ by race or SDH status at baseline and following an acute inflammatory stressor, which could form the basis of future studies.

Hemodynamic Measurements

At baseline, both black and white individuals had similar SBP, DBP, and HR. Changes in HR, DBP, and SBP following the HFM were not different between races and time points, nor the interaction of race and time.

An increase in SBP following the HFM has been shown in some, [18,57] but not all previous studies that include SBP as a measurement.[69,76] HR has also been shown to increase[18] or remain similar following the HFM.[69,76] However, DBP has remained the same[18,69,76] or decreased[57] following the HFM. Within the current study, DBP significantly decreased at hour 2 in black individuals only. Interestingly, the majority of previous studies have not reported the HR and BP responses following the HFM.[16,19–25,27,29,61,65,66,68,75] Similar to the present findings, in a previous study from our laboratory, baseline SBP and DBP were similar between black and white individuals following acute inflammation in a vaccine model.[41]

As stated above, most of the previous HFM studies do not report HR and BP measurements, therefore sex differences in these responses are not known. However, due to the differences in composition of the study groups, sex analysis of these hemodynamic measurements was also performed. Women's DBP and HR were similar to men at baseline, with SBP higher in men. However, the interaction of sex and time did not influence the DBP, SBP, or HR responses to the HFM.

As stated previously, this study was unable to recruit black women, which could impact our sex differences analysis. However, the hemodynamic responses were also analyzed between white men and black men-only. The hemodynamic responses to the HFM were similar between black and white men. This would suggest homogeneity within the male group, thus supporting the sex differences analysis. However, future studies should include black women to determine if their hemodynamic responses to an HFM are similar to white women.

Arterial Stiffness and Wave Reflection

Due to the complex interplay of stiffness, wave reflection, and function on the vasculature, arterial stiffness and wave reflection were evaluated at baseline and following the HFM. Wave reflection and arterial stiffness were similar between black and white individuals at baseline, evaluated using AIx, AIx75, and PWV. This is in contrast to some previous studies, which show increased arterial stiffness at baseline in young black individuals compared to white.[89–91] In the study by Heffernan et al,[89] central PWV was higher in black men (7.3 ± 0.3 m/s) compared to white men (5.7 ± 0.3 m/s), both of which are higher than the PWV seen in the current study (black individuals: 5.24 ± 1.04 m/s; white individuals: 5.37 ± 0.75 m/s).[89] The study participants were similar in age and BP, but were lower in fitness and higher in BMI compared to black and white individuals in the current study. The fitness status and body composition may have played a role in the differences in arterial stiffness at baseline shown between black and white individuals within the previous study, but not seen in the current study. In addition, if white men and black men are compared within the current study, arterial stiffness (AIx75 and PWV) is still similar between groups.

Similar results were shown in the study by Ashraf et al 2012,[90] with higher PWV and AIx75 in black individuals (men and women combined) compared to white. However, inflammation (CRP concentration) and BMI were higher in black individuals compared to white individuals in this study.[90] There are known associations between BMI and inflammation with vascular dysfunction, which may have compounded these results. In addition, fitness status was not measured.

In contrast, Liang et al 2019[91] showed increased PWV (when adjusted for MAP) in black women compared to white women, but not in men.[91] However, other variables, such as BMI, were

greater among black men and women compared to white, which could impact these results. Comparison between the Liang et al.[91] study and the current study is difficult due to our male-only black study group. However, as mentioned above, black men and white men had similar arterial stiffness at baseline in the current study.

The results of the current study are similar to those of Breet et al. 2017,[92] in which black and white individuals (men and women combined) had similar arterial stiffness as measured by PWV (adjusted for MAP).[92] Although the PWV was higher (black individuals: 6.31 ± 0.04 m/s; white individuals: 6.38 ± 0.04 m/s) than the PWV seen in the current study (black individuals: 5.24 ± 1.04 m/s; white individuals: 5.37 ± 0.75 m/s).

The current study is one of the first studies to examine race differences in arterial stiffness following an acute inflammatory stimulus. Unpublished data on arterial stiffness from the study reported in Sapp et al 2021[41] showed similar arterial stiffness following a vaccine in both black and white individuals.

Overall, arterial stiffness and wave reflection have been examined less following a HFM than vascular function. Similar to the current study, Lithander et al 2013[77] showed similar PWV (corrected for changes in BP) and AIx (corrected for HR) following a HFM.[77] Similar results were reported in Fahs et al,[76] with no changes in PWV, AIx, and carotid artery stiffness following a HFM.[76] Augustine et al 2014[64] also reported no changes in central PWV following a HFM.[64]

Therefore, the findings of similar arterial stiffness following a HFM are similar to previous literature. Arterial stiffness can be impacted by a multitude of factors, including the composition of the arterial wall (elastin/collagen), BP, ROS/inflammation, and endothelial dysfunction.[93] Change in the composition of the arterial wall would be unlikely due to the acute nature of the HFM. Similarly, BP remained similar following the HFM. ROS/inflammation and endothelial

dysfunction would therefore be likely causes for an increase in arterial stiffness following the HFM. Based on the results of the FMD, endothelial (vascular) function is maintained following the HFM, regardless of inflammation/ROS. Therefore, arterial stiffness remaining similar is plausible within the study because endothelial (vascular) function is not impacted by the HFM in these young, healthy individuals.

Similar to hemodynamic measures, sex differences in arterial stiffness and wave reflection responses to a HFM have been less studied. However, due to the composition of the participant groups, these variables were also analyzed by sex. AIx, AIx75, and PWV were similar at baseline between women and men. There was no effect of sex, time or the interaction of sex and time on responses to the HFM. Similarly, white and black men exhibited similar AIx, AIx75, and PWV at baseline and following the HFM. Future studies will need to determine if similar responses in arterial stiffness are seen in black women following a HFM.

Social Determinants of Health and Vascular Measures

White individuals indicated better overall SDH compared to black individuals by obtaining a higher SDH total score on the SDH questionnaire. This is consistent with previous reports documenting racial disparities between white and black individuals in SDH.[94] Specifically, white individuals reported significantly higher (better) access to complete/adequate nutrition, good housing conditions, and financial stability than reported by black individuals.

It is difficult to examine each component of SDH separately due to the connected nature of the determinants influencing one another. For instance, racial disparities in diet quality have been documented previously in black and white individuals, with a previous report from 1988 to 2014 suggesting better diet quality among white individuals compared to black individuals.[95] Improved diet quality over time (from 1999-2000 to 2009-2010) has also been reported among

white individuals, but not in black individuals.[96] Diet quality may be confounded by a multitude of factors, including socioeconomic status (SES) and nutrition access, both of which are higher among white individuals.[94] Access to good housing condition is closely connected with SES, and can impact nutrition access as well. Previous studies report better housing conditions in white individuals compared to black individuals.[94] Therefore, the results of the SDH questionnaire are consistent with previous literature citing improved SDH, including nutrition, housing, and financial stability, in white individuals compared to black individuals.

Both white and black individuals reported similar access to good healthcare and education, stress levels, and social acceptance at UMD. There are known racial disparities in both access to healthcare, education, and stress.[94,97,98] However, it is important to note the impact being a student at UMD might have on the responses of the SDH. For example, the individuals are all in higher education (undergraduate or graduate) with access to the health center on campus. Additionally, overall stress levels may be confounded by the stress of college, which can vary between participants. The feeling of belonging at UMD may also be impacted by the demographics of this particular University, with a higher population of black individuals compared to the majority of other colleges within the US.

Shifting from the known racial disparities in individual SDH factors to SDH as a whole, previous studies have shown individuals with lower SDH are at higher risk for CVD as well as risk factors for CVD, such as hypertension.[99] However, SDH was not associated with any of the vascular measurements at baseline within the current study. As mentioned previously, the participants within this particular study were young adults and healthy (no CVD risk factors). Age and CVD risk factors are tied to vascular function. It is possible that the participants were able to maintain their vascular function (and other vascular parameters) due to their health status. It is also

possible that the effects of negative SDH do not appear until later in life, when the body is less able to accommodate for these changes.

In addition, vascular changes following the HFM were not associated with the SDH total score. Again, the participants within this study were young and healthy. Their bodies may be able to adapt to systemic changes to maintain vascular function/homeostasis. It would be interesting to see if this study was repeated in older individuals with differences in SDH. It is possible that with an older aged study group (and probable CVD risk factors), SDH may be associated with changes in the vasculature following the HFM.

Induced Inflammation

IL-6 concentration was not detected in the baseline or post-HFM samples. It is possible that the specific immunoassay used was not sensitive enough to detect the IL-6 concentration at baseline or following the HFM. Previous literature indicates small changes in inflammation induced from the HFM, from approximately 0.75-2 pg/mL concentration at baseline to approximately 2-4 pg/mL post-HFM.[10,12–16,18,62,70] The study by Brandauer et al used the same HFM as in the current study, with the IL-6 concentration approximately 0.8 pg/mL at baseline, increasing to approximately 1.0 pg/mL post-HFM.[70] Although the immunoassay used in the current study listed the sensitivity of as low as 0.2 pg/mL, the standard curve started at 12 pg/mL, meaning that the samples were likely undetectable.

Similar to vascular function following induced inflammation, the possible small changes in IL-6 concentration with induced inflammation in a young, healthy population is in line with the concept of physiological redundancy.[87] A young, healthy individual is able to maintain homeostasis with physiological stressors, such as acute inflammation through various mechanisms, including anti-inflammatory pathways.

Chapter 6: Conclusions, Limitations, and Future Directions

Conclusions

Young, healthy black and white individuals exhibited similar vascular function, arterial stiffness, wave reflection, and hemodynamic measures at baseline and following an acute inflammatory stimulus in the form of a HFM. White individuals exhibited higher (better) SDH compared to black individuals. However, vascular measures (function, stiffness, wave reflection, hemodynamic measures) were not correlated with SDH at baseline or in response to the HFM. Additionally, inflammation, measured by IL-6 concentration, was not detectable at baseline or following the HFM, potentially due to low concentrations in these young, healthy individuals.

Limitations

The current study includes some limitations. One limitation is the study population, where the participants were all students at the University of Maryland, College Park. This could suggest homogeneity of the study population and the findings may not be applicable to non-students. Additionally, only five male black individuals, and no black females comprised the black study group due to recruitment and scheduling challenges. Additionally, the method used to detect the IL-6 concentrations may not have been sensitive enough to measure these low concentrations. In addition, diet was not assessed in the current study, with previous studies suggesting diet impacts the vascular responses to a HFM.

Future Directions

Although the influences of SDH are not seen in the current study, it is possible that this is due to the participants within this study being young and healthy. Their body may be able to adapt to systemic changes to maintain vascular function/homeostasis. Future studies should assess these associations in middle-aged/older individuals with differences in SDH. It is possible that with an

older aged study group (and probable CVD risk factors), SDH may be associated with changes in the vasculature following the HFM.

In addition, future studies should examine both pro-inflammatory, anti-inflammatory, and ROS following the HFM. By measuring only pro-inflammatory biomarkers, we are unable to obtain a full picture of the body's response to the HFM and the potential influence each may play on the vasculature. It would also be interesting to view the vascular function response to the HFM as a ratio to the response in inflammation. In other words, view the HFM inflammatory and vascular responses on average within a study group, but also view these responses on an individualistic level. If one individual has more inflammation following the HFM, but maintains vascular function, this is different from someone who has less of an inflammatory response, but a greater decrease in vascular function following the HFM. Future studies should therefore take this into account when analyzing their results.

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