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EFFECTS OF MINDFULNESS AND STRESS MANAGEMENT ON NEUROCARDIOVASCULAR AND PSYCHOLOGICAL OUTCOMES

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EFFECTS OF MINDFULNESS AND STRESS MANAGEMENT ON NEUROCARDIOVASCULAR AND PSYCHOLOGICAL OUTCOMES

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ॐ भूर्भुव॒ स्सुव॑ः
तत्स॑ वि॒तुर्वरिण्यं॒
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धियो॒ यो नः॑ प्रचो॒दयात् ॥

List of Abbreviations:

cf- carotid-femoral
ABPM- Ambulatory Blood Pressure Monitor
AHA- American Heart Association
ANOVA- Analysis of Variance
AP- Augmentation Pressure
APA- American Psychological Association
AIx- Aortic Augmentation Index
AIx@75- Augmentation Index at 75 beats per minute
bpm- beats per minute
BAI- Beck Anxiety Inventory
BP- Blood Pressure
BMI- Body Mass Index
CBT- Cognitive Behavioral Therapy
CDC- Centers for Disease Control and Prevention
CVD- cardiovascular disease
DAP- Diastolic Arterial Pressure
ECG- Electrocardiogram
EQ- Experience Questionnaire
GAD- Generalized Anxiety Disorder
HPA- Hypothalamic- Pituitary- Adrenal
HR- Heart Rate
HRV- Heart Rate Variability
ICC- Intra class correlation
MAP- Mean Arterial Pressure
MBSR- Mindfulness-Based Stress Reduction
MM- Mindfulness Meditation
MS- Mental Stress
MSNA- Muscle Sympathetic Nerve Activity
NE- Norepinephrine
NPG- No Pandemic Group
PG- Pandemic Group
PP- Pulse Pressure
PTSD- Post Traumatic Stress Disorder
PWA- Pulse Wave Analysis
PWV- Pulse Wave Velocity
RCT- Randomized Controlled Trial
SAP- Systolic Arterial Pressure
SME- Stress Management Education
SNS- Sympathetic Nervous System
STAI- State and Trait Anxiety Inventory
WHO- World Health Organization

Abstract

There has been a higher prevalence of developing anxiety due to frequent episodes of stress among adults in recent years. Chronic anxiety can contribute to the prevalence of elevated blood pressure and hypertension. High anxiety and stress also contribute to overactivation of the sympathetic nervous system which can be quantified by increased muscle sympathetic nerve activity (MSNA). Sympathetic overactivation can lead to vasoconstriction and loss of arterial elasticity. Anxiety, MSNA, blood pressure, and arterial stiffness are all interconnected, thus studying these relationships is crucial to understand the underlying mechanisms for prevention and treatment of cardiovascular disease (CVD). Non-pharmacological and mind-body treatments such as mindfulness-based stress reduction (MBSR) and stress management education (SME) have gained popularity in the management of anxiety and CVD risk.

In ***Study 1,*** 19 volunteers (18-45 years) were randomized into 8-week MBSR or SME, where we monitored changes in anxiety, decentering, and arterial stiffness. There was a tendency for state anxiety to be reduced after MBSR (p=0.06), but carotid-femoral pulse wave velocity (cfPWV) did not change from pre to post in either condition. ***Study 2*** enrolled 27 volunteer participants (25±1 years) to determine how muscle sympathetic nerve activity (MSNA) and mean arterial pressure (MAP) reactivity influence post mental stress aortic augmentation index (AIx). The mental stress task significantly increased HR (Δ15±2 beats/minute), MAP (Δ14±1 mmHg), and perceived stress (Δ1.9±0.1 a.u.), while MSNA (Δ -13 to +20 bursts/min) was not significantly increased. The change in MAP during mental stress was a significant predictor (β=0.47; p=0.03) of the change in AIx (post-stress vs. baseline). Changes in MSNA and perceived stress were not predictors of mental stress-

related changes in AIx. ***Study 3*** examined how 8-week MBSR, or SME influenced anxiety and decentering in 36 volunteer participants. Nineteen participants completed the 8-week study prior to concerns over COVID-19 (no pandemic group = NPG), while 17 participants were affected by the stay-at-home order due to the pandemic (pandemic group = PG). Anxiety and decentering were measured before and after the 8-weeks of MBSR and SME. Trait anxiety was reduced in NPG/PG and MBSR/SME ($p<0.05$), while decentering was also improved in PG ($p<0.03$).

The results of these studies agree with previous studies that indicate how MBSR can help to reduce anxiety. However, MBSR does not appear to decrease arterial stiffness (cfPWV). Aim 2 challenges the concept that acute stress-induced changes in aortic augmentation index are directly linked to changes in MSNA. The changes in AIx were linked to changes in MAP, but not MSNA. Aim 3 provides indications of how MBSR and SME can reduce trait anxiety and improve the ability to decenter during a global health crisis like COVID-19.

Keywords: Mental stress, Anxiety, Decentering, Arterial Stiffness, Wave Reflections, Muscle Sympathetic Nerve Activity, Microneurography, Blood Pressure, COVID-19 Pandemic

1 Introduction:

1.1 Overview of this dissertation:

The focus of this dissertation is to review the mechanisms of cardiovascular diseases (CVD) and to determine the efficiency of mindfulness-based stress reduction (MBSR) which can be used as a management strategy for some CVD symptoms. An overview of the components of this dissertation can be seen in Figure 1 below.

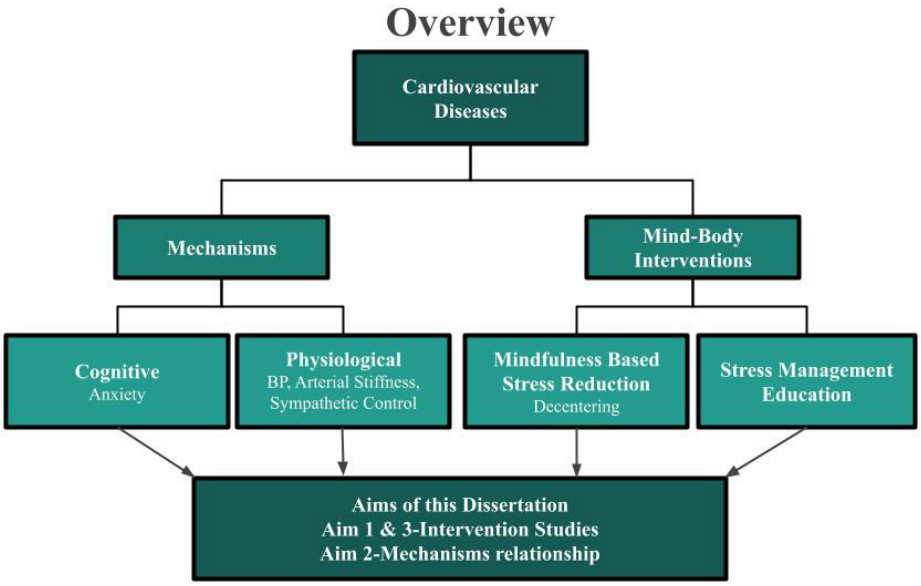


Figure 1. Schematic representation of the dissertation overview and the description of the three aims.

1.2 Prevalence of the cardiovascular diseases (CVD):

CVDs are one of the most common causes of morbidity and mortality in adults (1-4). CVD is commonly seen in aging adults which can lead to substantial disability. This is prevalent even today with great advances in technology for diagnosis and treatments of various CVDs. Moving into the 21st century, there has been greater improvements where a reasonable reduction in communicable diseases was observed (5). With changes in

lifestyle habits associated with easily available amenities to make daily activities convenient, there came the rise of many non-communicable diseases such as cancer, cardiovascular diseases, obesity, and others (6). With increased occurrence of CVDs, it poses a higher risk of mortality and morbidity among adults globally (5). Early detection and screening of individuals who are at moderate and substantial risk of CVDs is important. This could reduce the societal and healthcare burden of the disease (7).

A statement published in Nature suggested that it is estimated that CVD deaths will reach up to 23.6 million by 2030 when compared to 16 million in 2010 (1, 8). These statistical dynamics have altered in the last four decades where the risk of CVD was higher in developed and western countries such as North America and European Union but now have significantly also increased in developing countries (1). This is a sincere concern which must be addressed pertaining to the societal and healthcare burden of CVDs. Increased prevalence of CVD can be largely attributed to four major health related behaviors of frequent tobacco usage, poor diet choices, limited physical activity, and regular alcohol consumption of more than recommended daily allowance (5). Apart from these other factors, anxiety, elevated blood pressure, arterial stiffness and autonomic dysfunction can also play a significant role in increasing the chances of developing CVD.

1.3 Hypothesis and experimental approach:

CVDs are one of the most common health conditions affecting the quality of life and risk for mortality of people worldwide. For this reason, almost every aspect of CVD has been researched extensively for decades, and it is still ongoing. Very recently, some other mechanisms such as activation of the sympathetic nervous system and its connection to

CVD have gained the interest of researchers. This dissertation details how anxiety, the sympathetic nervous system, and arterial stiffness can impact an individual's health. The overview section provided details on the cognitive and physiological symptoms leading to CVD. I tried to connect the gaps in already defined mechanisms for CVD including stress, anxiety, blood pressure regulation, arterial stiffness and autonomic control for CVDs and newer non-pharmacological treatment methods for management of CVD. This dissertation is divided into sections elaborating on the three aims; the intervention studies which are aim 1 and 3 and mechanisms study which is aim 2. A detailed overview of the divisions of the three aims can be seen in Figure 2.

1.3.1 Aim 1:

The aim 1 intervention study (Figure 2) investigates the effects of MBSR and SME on anxiety, decentering, and arterial stiffness. This is the first study to our knowledge to investigate the effects of MBSR and SME on arterial stiffness. We hypothesized that 8-weeks of MBSR would reduce anxiety, improve decentering, and reduce arterial stiffness in the study sample.

1.3.2 Aim 2:

The mechanism study: aim 2 (Figure 2) investigated the MSNA, MAP, and aortic wave reflection responses to mental stress. Aortic augmentation index (AIx) was assessed during a baseline prior to mental stress, and then again 10 minutes after completion of a 5-min mental stress protocol. We hypothesized that blood pressure and muscle sympathetic nerve activity during mental stress would influence post stress aortic wave reflection (i.e., AIx).

1.3.3 Aim 3:

Finally, the aim 3 intervention study (Figure 2) investigated the effects of MBSR and SME on psychological health during the COVID-19 stay-at-home restrictions. The stay-at-home restrictions negatively impacted psychological health in many adults. We hypothesized that active engagement of individuals in interventions of MBSR and SME would have a positive impact on their psychological wellbeing during COVID-19 stay-at-home restrictions. This was quantified using measures of anxiety and decentering in the volunteer participants.

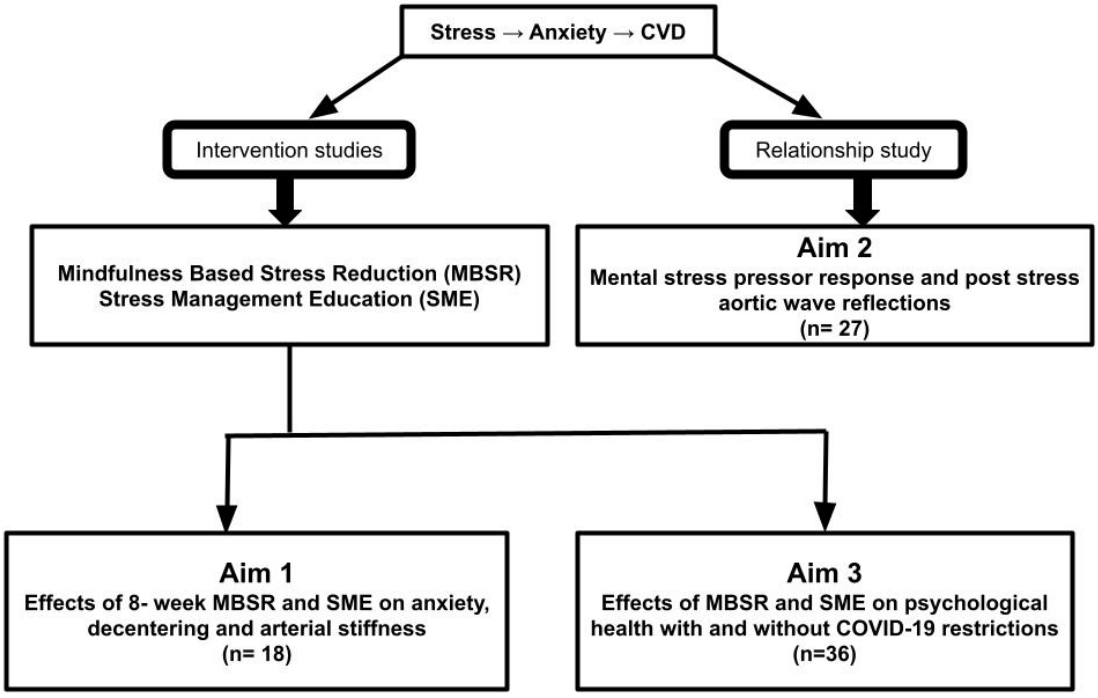


Figure 2. Overview of the three study aims of this dissertation.

This dissertation is part of a National Institutes of Health R15 project on "Mindfulness and Neural Cardiovascular Control in Humans" granted to Dr. John Durocher. The project proposed a sample size of 60 participants in total with a target of 30 to be randomized into MBSR and 30 into SME groups with a statistical power of 89% which was dependent on the muscle sympathetic nerve activity (MSNA) analysis. MSNA provides direct measures of postganglionic sympathetic nerve activity in humans. However, the total sample size of 60 was not achieved as the ongoing studies were impacted by the COVID-19 pandemic. Therefore, the sample size at the time of this dissertation was 44 adults. Details and descriptions of the study designs (i.e., aims) and results are discussed in Sections 3, 4 and 5 below.

1.4 Factors influencing CVD risk:

CVD risk factors are important to be addressed to prevent mortality and morbidity. There are various non-modifiable and modifiable risk factors which play a crucial role in the development and prevention of CVD. This section discusses the clinical risk factors and mechanisms of CVD. It includes defining the relationships and understanding the potential links between stress, anxiety, high blood pressure, arterial stiffness, and autonomic function. Each of these factors can contribute to current and future development of CVD.

1.4.1 Relationship between stress, anxiety, and CVD:

The Oxford dictionary defines stress as anything that causes a state of strain or tension (9). In relation to health, stress can be defined as something which is experienced

by an individual when there is excessive demand on the structures involved. This could be demonstrated as psychological or physical symptoms. Psychologically, stress is a feeling which causes adverse effects on a person's state of mind. Physically, stress can increase heart rate and blood pressure, and make a person more prone to illness.

Anxiety is defined as a "constant feeling of transient fear, uncertainty, and apprehension about the future" (10, 11). There are individual differences on how persistently an individual feels anxious in terms of the extent of their symptoms (10). Symptoms of anxiety include increased restlessness, constant fatigue, palpitations, increased sweating, changes in appetite and disruptive sleep (12). There is an interconnected relationship between the cognitive and physiological symptoms of stress leading to long term anxiety which can worsen several CVD risk factors. (13) Figure 3 outlines the relationship between the cognitive factors of stress and anxiety leading to physiological symptoms of CVDs.

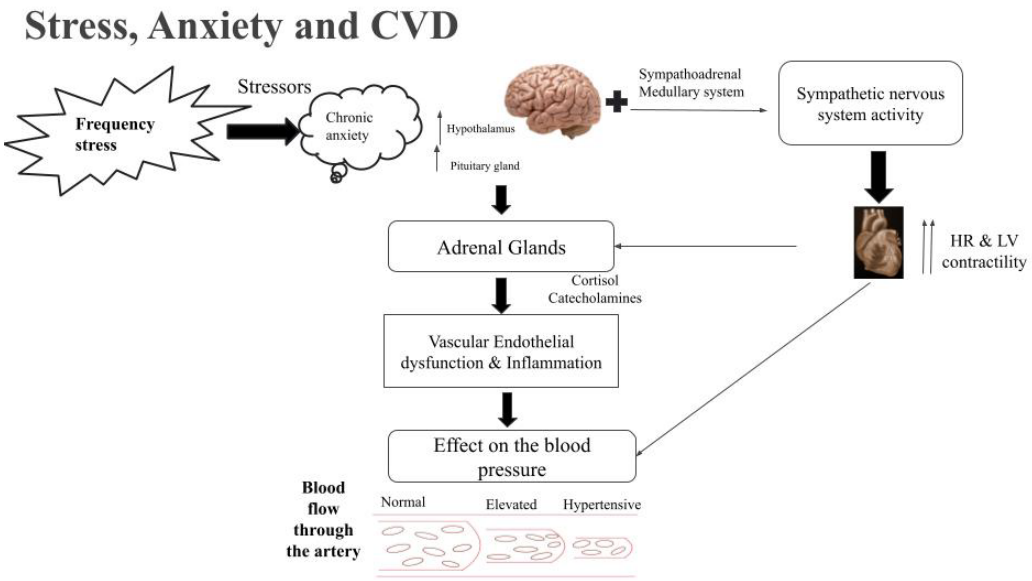


Figure 3. The relationship between stress, anxiety, and CVD by impacting the sympathetic, adrenal, and vascular systems.

1.4.1.1 Influence of central neural mechanisms in stress and anxiety:

Mental stress (MS) influences neural and cardiovascular health by increasing the Hypothalamus-Pituitary-Adrenal (HPA) axis activity responsible for regulating stress (14, 15). Persistent anxiety also works by increasing HPA axis activity and the risk of developing future hypertension and other CVDs (16-18). Chronic long-term anxiety pertaining to hypertension is an independent risk factor for cardiovascular mortality (8, 11, 16, 19). Figure 3 shows a schematic representation of the stress and anxiety response to CVD. Frequent short episodes of mental stress can lead to chronic anxiety even in the absence of stressors. Physiologically, along with activation of HPA axis, there is heightened response to sympathoadrenal medullary system. This increases the firing of sympathetic efferent fibers to target organs like the heart, blood vessels, and kidneys (14, 20-24). Figure 3 details two important mechanisms in describing the relationship between stress, anxiety, and CVD. First, an overactive HPA axis can influence the sympathoadrenal medullary system which leads to the fight-or-flight response and increased sympathetic activity affecting the heart by increasing the left ventricular contractility (10-12, 14, 15, 25). This contributes by increasing heart rate and impacting the blood flow through arteries. Second, the increased HPA axis can influence cardiovascular risk by causing an increase in catecholamine circulation in the plasma from the adrenal glands to cause increased blood pressure related to vascular endothelial dysfunction and inflammation (12, 26), which reversibly contributes to increased heart rate (21, 24), arterial stiffness (27, 28), and sympathetic activation (14).

Cognitively, stressed and anxious individuals are constantly hypervigilant as they overuse attentional resources ultimately impacting their performance (12, 29). Twenty independent studies involving almost a quarter million anxious adults found that the risk of fatality due to coronary heart disease and heart failure increased by 26% and 48% respectively (8), suggesting a linear relationship between long term chronic anxiety and hypertension (30). The mechanism postulated behind long term anxiety, hypertension, and CVD are heightened HPA axis and sympathomedullary system as outlined in Figure 3. Other potential mechanisms behind increased anxiety and risk of CVD includes lifestyle habits such as smoking, alcohol consumption, and decreased physical activity (10, 31). Acute anxiety can lead to increased cardiovascular reactivity to stress, and an elevated resting heart rate. Anxiety can affect heart rate variability (HRV), contribute to baroreflex dysfunction, and increase the ventricular repolarization rate (10, 21). Considering the increased prevalence of anxiety and its relationship with CVDs, it becomes essential that anxiety is being diagnosed and managed early to reduce the risk of developing severe symptoms affecting the quality of life (32).

1.4.1.2 Evaluation of anxiety in humans:

Anxiety is often part of everyday life where an individual may feel the strain of professional workload, before taking an exam, financial pressures, family demands, or any important change in life. However, a clinical diagnosis of anxiety disorder occurs when this feeling is persistent. Chronic anxiety can interfere with daily performance and affect the cognitive demands associated with completing daily life tasks. Anxiety can be

diagnosed as general anxiety disorder (GAD), panic disorder, phobia, post-traumatic stress disorder (PTSD) and social anxiety disorder (20, 33).

Anxiety is measured using subjective surveys or questionnaires where an individual rates or describes their symptoms on a Likert scale. However, subjective measurement of anxiety can be assessed using various screening and psychometric tools. Some of the commonly used questionnaires for quantifying severity of anxiety include Beck Anxiety Inventory (BAI) (34), Hamilton Anxiety Score (35), Spielberger State and Trait Anxiety Inventory (STAI) (36), and Generalized Anxiety Disorder 7-item scale (37). STAI is commonly used to diagnose anxiety in clinical population. A physical examination can be helpful in determining the presence of any other underlying condition which can cause symptoms of anxiety. STAI is discussed in detail in the next section as this dissertation utilized the Y1 and Y2 components as part of the experimental approach.

1.4.1.3 Spielberger state and trait anxiety Inventory (STAI) for adults:

Charles D. Spielberger, PhD, a clinical psychologist developed and validated the State and Trait Anxiety Inventory (STAI) for adults (36, 38-40). STAI is a 40 item self-reported questionnaire in which the form Y1 includes 20 items on a 4-point scale “not at all” to “very much so” for state anxiety rating and Y2 has 20 items on a 4-point scale from “almost never” to “almost always” for trait anxiety (38). The score ranges from 20-80 and a higher score corresponds to greater anxiety and is unfavorable. Seok, 2018 (41) measured the reliability of STAI and concluded that it has a Cronbach’s alpha of 0.85 indicating the tool is reliable in measuring anxiety levels (42). STAI also has an internal consistency of 0.86-0.95 and test- retest reliability of 0.65- 0.75 when measured within 2 months (38, 41, 43) concluding it has strong reproducibility.

State anxiety can be defined as anxiety which occurs at the present moment and can lead to activate the central nervous system. State anxiety can be defined the feeling of anxiety which is acute or temporary (42). State anxiety is typically a reaction which a person has to short term negative events occurring in their lives. Trait anxiety however, is more of a personality wherein the anxiety is embedded within a person's behavior due to chronic and sustained symptoms (42) and can otherwise be defined as anxiety in general and a hyperarousal state (42, 44, 45). Trait anxiety can also cause overactivity in the sympathetic nervous system (SNS) and lead to pathological conditions such as increased heart rate, blood pressure, and muscle sympathetic nerve activity (MSNA). Trait anxiety can also take longer to normalize after a stressor (42).

Spielberger defined anxiety as a one-dimensional phenomenon which is a combination of both state and trait anxiety. State anxiety is more of an acute response, whereas trait anxiety is more of a chronic response to repeated stress. Spielberger STAI for adults has been studied extensively in many populations. A study by Ferreira from 1983 (46) validated the use of STAI for anxiety by including 56 undergraduate students who were asked to perform in front of an audience and no audience. Hoge, 2013 (35) examined the effects of mindfulness-based stress reduction on STAI in 87 individuals with generalized anxiety disorders. These studies have been not only helpful in determining the extensive use of STAI for rating anxiety severity in humans but also its efficiency.

1.4.2 High blood pressure (BP) and CVD risk:

Among the major risk factors of CVD, elevated blood pressure is the strongest independent predictor (47-52). Individuals who have suffered with stroke or coronary heart

disease in their life often also have had high blood pressure (4, 51). Longitudinal studies such as the Framingham Heart study explored the various risk factors and Vasan, et al., in 2001 (47) strongly attributed systolic (SAP) and diastolic arterial blood pressures (DAP) to have a significant association to CVDs (47). This relationship was significant irrespective of other demographic characteristics like biological sex, age, and racial and ethnicities (47). Long term elevated blood pressure can lead to target organ damage to the kidneys, heart, and brain (53, 54).

Another commonly established mechanism of CVD related to blood pressure is vascular aging (55). Older individuals are at a higher prevalence of suffering from blood pressure related cardiovascular accidents. Age related changes in the blood vessels can contribute to further elevation in blood pressure. Older adults often sustain vascular, cardiac, and renal damage which causes increased beat-to-beat blood pressure for a prolonged period.

1.4.2.1 Measuring blood pressure in humans:

Blood pressure can be measured using a mercury tube like device called sphygmomanometer, and more recently automated blood pressure monitoring has become more popular to obtain standardized readings. The pressure readings are usually reported in the form of SAP and DAP. Ambulatory blood pressure monitoring (ABPM) is accepted as an efficient method for recording of arterial blood pressure especially at night, and during daily activities to predict the possibility of developing future hypertension. ABPMs can be used in addition to automated blood pressures at the physician's office (51), to better determine blood pressure patterns and actual CVD risk.

Guidelines for blood pressure are provided by organizations such as American Heart Association (AHA), Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO). In 2018, the AHA (52, 56) defined its new guidelines for arterial blood pressure. Maintaining normal blood pressure is crucial for functioning and should be less than 120 mmHg systolic and 80 diastolic mmHg. Elevated blood pressure is when systolic BP is between 120-129 mmHg and diastolic BP is less than 80 mmHg. In stage 1 high blood pressure (hypertension), systolic BP is between 130-139 or diastolic BP between 80-89 mmHg, and stage 2 high blood pressure (hypertension) ≥140/90 mmHg (52, 56). Hypertensive crisis is when the blood pressure is >180 and/or120 mmHg and can be life threating, requiring immediate medical attention. Early identification of elevated blood pressure gives clinicians the best chance to identify risk factors so that timely appropriate treatments can be provided to the patients.

1.4.2.2 Blood pressure regulation in humans:

When the left ventricle pumps blood into the periphery during the systole phase of cardiac cycle there is some resistance due to the pressure it exerts on the vessel walls and the viscosity of the blood itself (57, 58). When this resistance increases too much, there is difficulty for the blood to pass through the arteries and frequent long-term occurrence of this phenomenon can lead to high blood pressure. As mentioned earlier, high blood pressure is a challenge as it can lead to organ damage and eventually fatality. Arterial BP can be altered due many reasons such as exercising, diet, and aging. However, the change in BP depends on the cardiac output during each cardiac cycle, the elasticity in the central and peripheral arteries, sympathetic activity, and the peripheral vascular resistance (57-61).

Blood pressure is directly proportional to cardiac output and total peripheral resistance (62, 63). Therefore, understanding blood pressure mechanisms and regulation can help researchers to help define early management strategies for physicians and their patients.

1.4.2.3 Negative feedback loop mechanism:

It is essential that our body continuously remains in the state of homeostasis. Whenever there is a change in arterial blood pressure, this can be sensed by the baroreflex to normalize the blood pressure and maintain homeostasis. Blood pressure regulation in humans operates through negative feedback mechanisms. Changes in arterial blood pressure is detected by baroreceptors in the carotid arteries and aortic arch (64). These baroreceptors can sense the changes in blood pressure through fall or rise in the amount of stretch placed on them. To react to the change in blood pressure, baroreceptors can signal the autonomic nervous system to excite or inhibit the parasympathetic or sympathetic divisions (65, 66). When there is fall in blood pressure, the baroreceptors cause increased sympathetic activity to increase left ventricular contractility, heart rate thereby and vasodilation improving the blood flow through the arteries. The opposite happens in case of high blood pressure, where the sympathetic control to the heart and blood vessels is decreases and parasympathetic control increased. This is commonly known as the negative feedback mechanism (58, 60, 62, 66, 67). Other systems such as Renin-Angiotensin-Aldosterone system, and Antidiuretic Hormone also play a role to regulate blood pressure more so in the long-term.

1.4.3 Arterial stiffness and CVDs:

Some of the newer noninvasive methods of detecting CVD risks factors include ultrasound, ankle brachial index, arterial stiffness, and wave reflections (68, 69). Arterial stiffness is one of the independent markers of CVDs (7, 68-71). For the purpose of this dissertation, arterial stiffness and wave reflections are discussed in detail. Arterial stiffness affects the tunica media, the muscular layer within the artery and the loss of mechanical properties of the arterial wall leading to stiffening and loss of elasticity (7, 72). Normally, arterial stiffness increases with age or predisposing health conditions. Some of the causes of early stiffness include hypertension, diabetes, and smoking (7, 73-75). Arterial stiffness is measured non-invasively via pulse wave velocity (PWV). PWV measures the speed of pulse propagating through the arterial tree and stiffness in the artery increases the velocity of this pulse. Carotid-femoral PWV (cfPWV) is the most validated method used for measurement of arterial stiffness. Measurement of cfPWV values is a strong predictor of heart failure, stroke and other CVDs when adjusted for sex, age, SAP, DAP, smoking history, diabetes, and antihypertensive therapy (7, 70, 73). A cfPWV of >10 m/sec is an indicator of hypertension mediated organ damage and requires further medical evaluation for risks of CVD (7, 70).

1.4.3.1 Mechanisms contributing to arterial stiffness:

Arteries when compliant, help with the blood flow from the heart to the target organs (70, 74). Healthy arteries provide a cushioning effect to the circulating blood and carry needed oxygen and nutrients to the tissues of the body. They can sense pressure through the baroreceptor reflex which can cause resistance to the blood flow (64). This is possible

as the tunica media which is smooth muscle in the artery provides a contracting (or vasoconstricting) force to regulate pressure. The arteries are also made of elastin and collagen, which helps them to expand and accommodate the flowing blood without excessive increases in blood pressure. With normal aging or arterial diseases, there is loss of elastin and collection of thicker collagen fibers which increased stiffening and loss of elasticity (76, 77). Stiff arteries cause excess resistance to blood flow which increases chance of developing cardiovascular diseases such as hypertension, chronic kidney disease and strokes (76, 78, 79). Arterial stiffness can be estimated using an SphygmoCor System (AtCor Medical, Sydney, Australia) as depicted below in Figure 4 (72). Arterial stiffness is measured using a procedure called applanation tonometry where the artery is flattened, but not blocked, in between the probe and the underlying tissue such as bone as shown in Figure 5. Peripheral arterial tonometry has a strong test-retest reliability (ICC= 0.74) which can be used to assess vascular dysfunction in different populations (80).

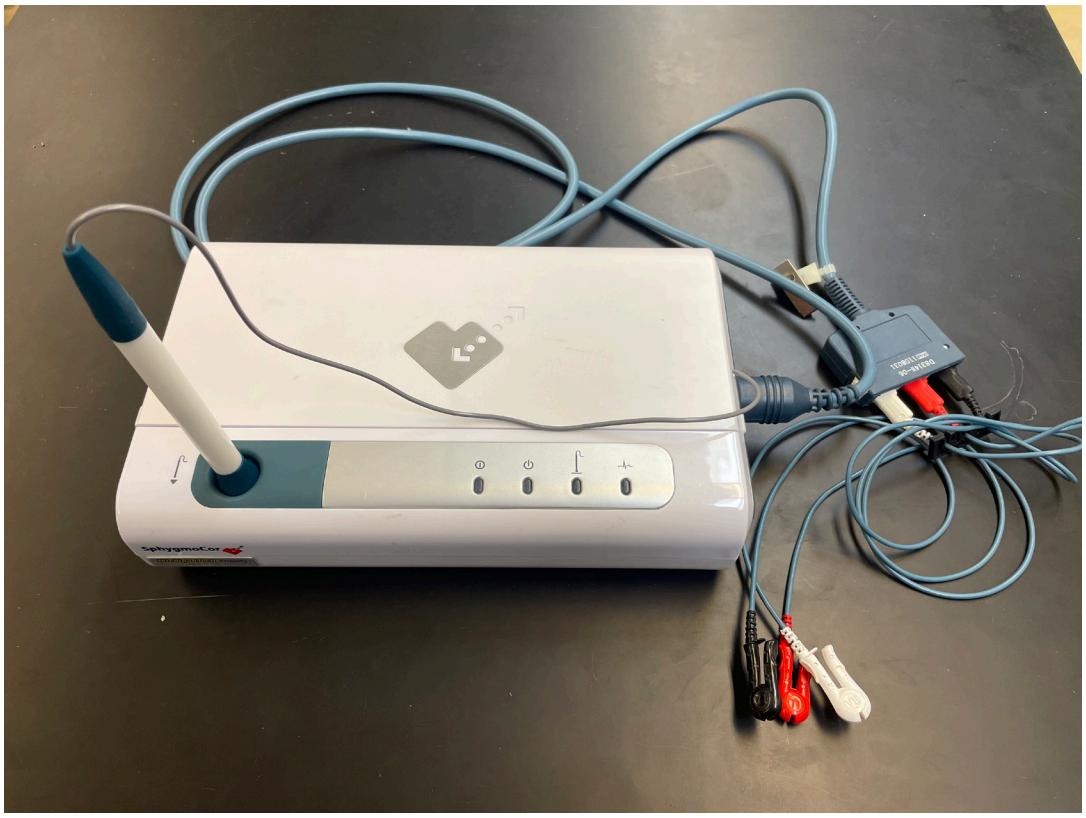


Figure 4. SphygmoCor equipment used for estimating arterial stiffness. The left side of the picture also shows the tonometer probe which is placed on the artery and the right side of the picture displays the 3-lead ECG.

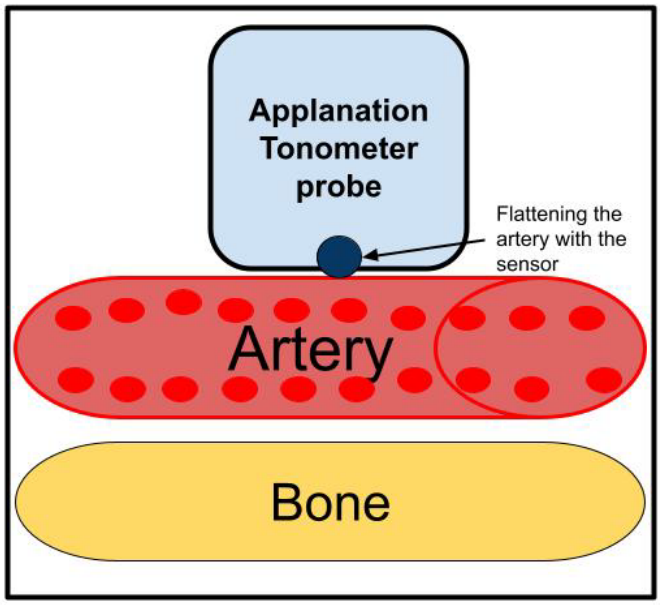


Figure 5. Visual representation of the applanation tonometry technique which is used to record pulse waves during PWA and PWV.

1.4.3.2 Assessing pulse wave velocity (PWV):

Arterial stiffness estimated with PWV non-invasively using applanation tonometry gated to the R-waves from a 3-lead ECG as shown below in Figure 6. PWV is a gold standard measurement for arterial stiffness (69, 72, 73). When left ventricular contracts in systole, it generates the forward propagated wave form from the aorta and a pulse known as the PWV (7, 27, 55, 70, 72, 73). PWV can be measured between central arteries such as the carotid and femoral (75) and peripheral arteries in the arms and legs (28). Description of carotid-femoral PWV (cfPWV) for central artery stiffness is shown in Figure 6 where the distance is measured from the suprasternal notch to carotid artery and suprasternal notch to femoral artery to determine the delay in the pulse velocity when gated with EGC. The tonometer probe is then placed at the each of the arteries in sequence and the

measurement is taken for 10 cardiac cycles and the order is then reversed (i.e., femoral then carotid). The values for PWV are obtained by the following equation:

$$\textbf{Pulse Wave Velocity (PWV)} = \frac{\textbf{Distance (m)}}{\textbf{Time (s)}}$$

Distance is the length traveled by pulse and T is the delay in the pulse travel time (Figure 6). The values are provided in m/s. Measurements for PWV can also be taken mathematically using the Frank Bramwell-Hill and Moens-Korteweg equations both of which use the elastic and fluid density changes in the blood vessel wall (81, 82). Carotid to femoral (i.e., central) PWV has a very strong test-retest reliability with ICC= 0.9 (83) and Cronbach's alpha of 0.97 (83, 84) making it a highly reproducible technique.

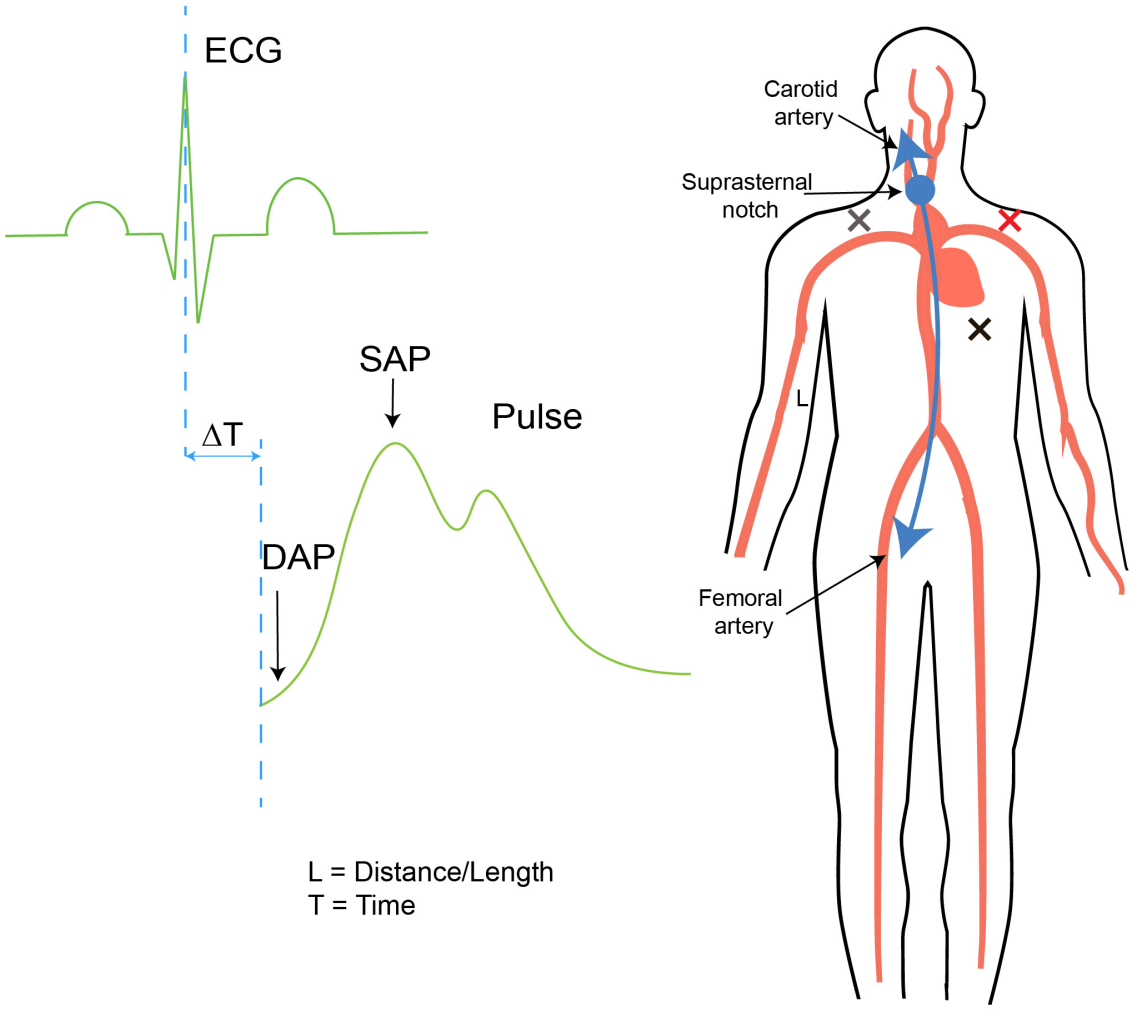


Figure 6. Shows the pulse propagation. The right side of the picture shows the distance from the heart to the carotid artery and the heart to the femoral artery. The picture also shows the placement of the 3-lead ECG as marked by the three "X's." The left side of the figure shows the time delay of the pulse when gated with ECG.

1.4.3.3 Assessing aortic wave reflection:

PWV is considered as the most validated measurement of arterial stiffness, but wave reflections via PWA recordings have gained attention of researchers as a surrogate for estimating arterial stiffness. Wave reflections measures the pulse waves generated in the proximal aorta (55, 85, 86). This was first determined by O'Rourke in 1989 and since then many clinical trials have been conducted which has confirmed its wide use for diagnosing

arterial diseases (55, 87, 88). PWA identifies the pressure wave form from the heart passes through the arterial tree and can be measured in the periphery, most commonly at the radial artery (86, 89) just proximal to the thumb. This can be done by measuring Pulse Wave Analysis (PWA) using a SphygmoCor (Figure 4) and applanation tonometry (Figure 5) without the need to gate to ECG recordings.

In young healthy individuals, the aorta is quite elastic and complaint. The aorta generates a forward propagating wave during left ventricular contraction. Usually, there is an alteration in the forward wave form and the wave reflection. The forward wave form is reflected from the periphery to the heart comes back to aorta during the end of systole or beginning of diastole. When this reflected wave comes back to the aorta or heart during diastole, it increases the coronary blood flow for the heart to efficiently pump blood through next cardiac cycles. In stiff arteries, this forward propagated waveform arrives early at aorta during systole which causes lack of coronary perfusion and can contribute to myocardial ischemia. This mechanism is visually represented in Figure 7, where the forward propagating and backward reflecting waves are shown with respect to the phase of cardiac cycle.

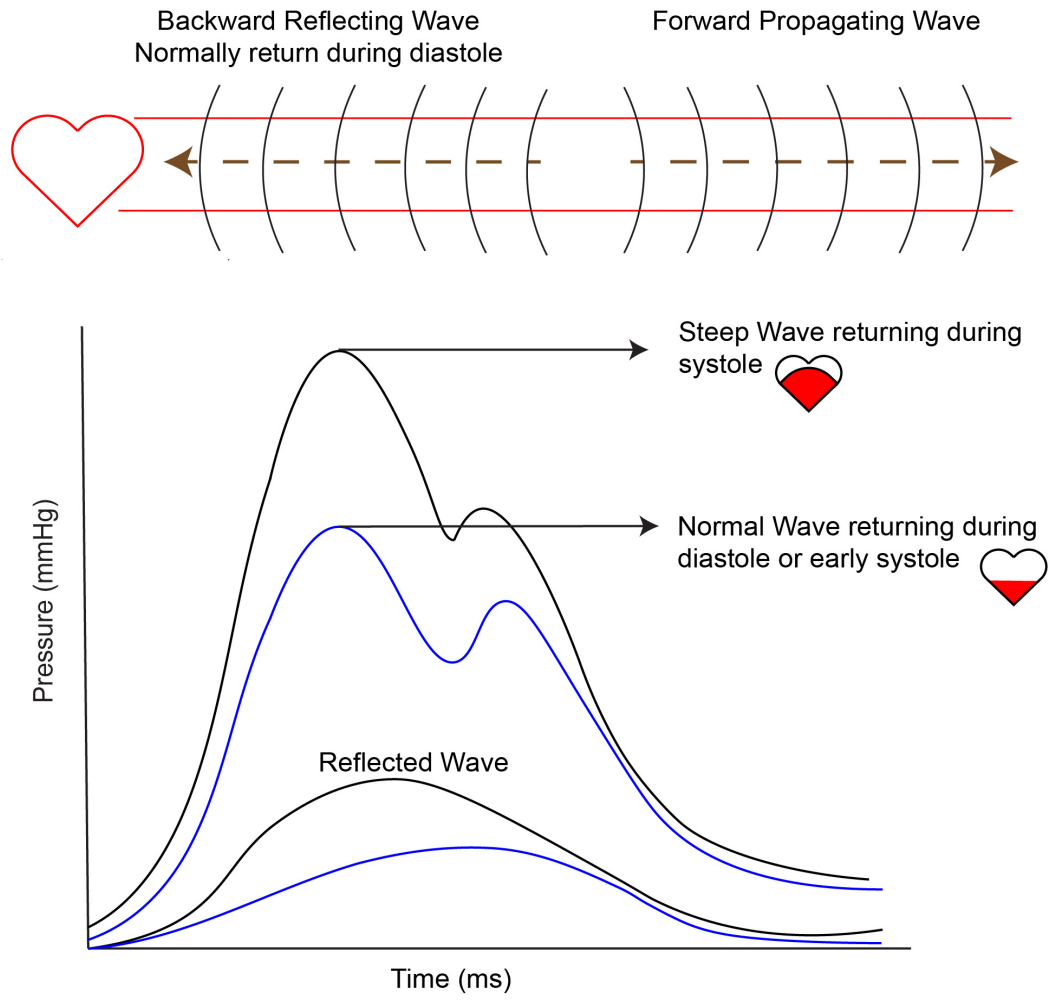


Figure 7. Pulse wave propagation in the arterial tree. The blue wave represents the normal waveform, and the black wave represents steep wave with early return.

Figure 8 below describes the distinct phases of aortic pressure waveform. There is an initial (SAPi) or incident wave formation related to systolic blood pressure. However, there is another peak wave form which is generated which causes the peak systolic pressure (SAPp). The difference between the initial wave and the peak wave is known as the augmented pressure (AP). Aortic pressure is calculated by measuring augmentation index or AIx. AIx is a newer an indirect method of estimating arterial stiffness by measuring the

aortic pressure waveforms. AIx is calculated by dividing AP by PP (Pulse Pressure) and is reported as a percentage (%).

$$\textbf{\textit{A}ugmentation Index (AIx \%)} = \frac{\textbf{Augmentation Pressure (AP)}}{\textbf{Pulse Pressure (PP)}} \times \textbf{100}$$

Higher values on AIx indicate that the wave returned earlier from the periphery which can predict arterial stiffness. AIx is also dependent on heart rate, and it is further normalized at 75 beats per minute to get values for AIx at 75 beats per minute (bpm) (75, 90). AIx is commonly used to measure PWA and has a strong reproducibility (86, 89, 91, 92) with ICC= 0.74-0.8 (91, 93). AIx measured using a SphygmoCor can be used to predict CVD risk.

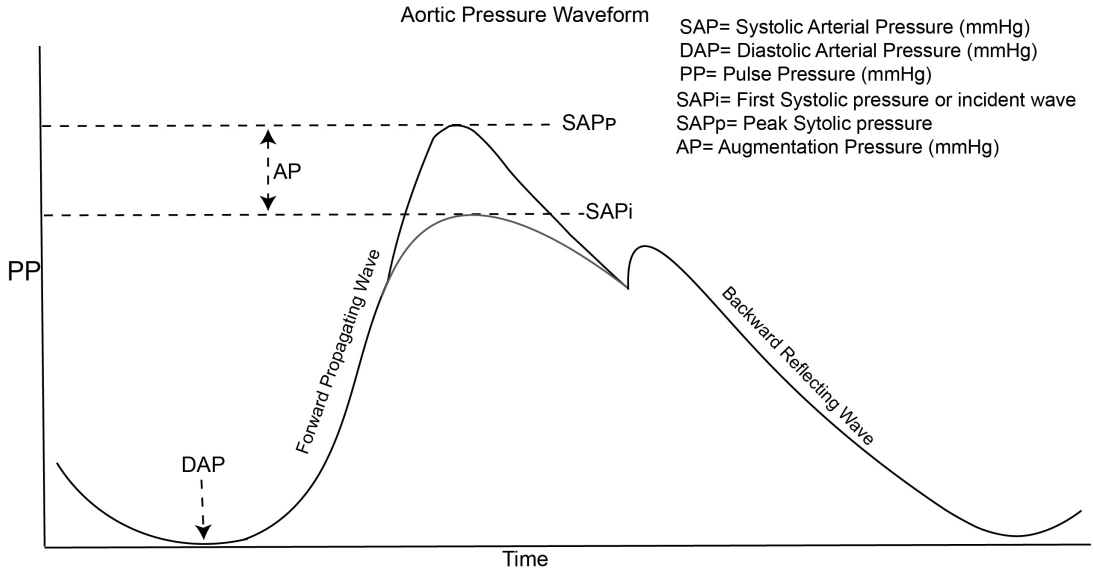


Figure 8. Description of the distinct phases of an aortic pressure waveform generated after left ventricular contraction. Adapted from O'Rourke, 1989 (72).

1.4.4 Autonomic function, sympathetic activity, and CVD:

The sympathetic nervous system (SNS), a component of the autonomic nervous system is responsible for maintaining left ventricular contractility, blood vessel wall diameter (61, 94) which thereby regulates blood pressure (60, 61, 67, 95). The peripheral blood vessels are innervated by the SNS, and the overactivity of these nerve fibers can lead to vascular vasoconstriction around the target organs (Figure 10). It is crucial that the organs receive continuous flow of blood to prevent any long-term damage. Constant vasoconstriction can lead to impaired blood pressure regulation and chronically elevated blood pressure (96). An overactive SNS can cause increased heart rate and left ventricular hypertrophy (96). Studies on SNS overactivity in young adults show that they have higher chances of developing hypertension and other cardiovascular diseases (60, 61). Hence, it becomes critical to investigate the SNS and autonomic control to help prevent the risk of cardiovascular diseases.

1.4.5 Methods to evaluate the SNS:

SNS in humans can be measured using various methods such as the norepinephrine (NE) spillover rate to plasma and urine NE. But the scope of this dissertation is to discuss the methodology of recording muscle sympathetic nerve activity (MSNA) measured via microneurography to provide direct measures of sympathetic activity.

1.4.5.1 Microneurography to record MSNA:

Microneurography is a direct recording of sympathetic nerve traffic from the peripheral muscular nerve supplying the vascular beds (97-100). Microneurography was first used by Hagbarth and Valbo in 1965 (Swedish neurophysiologists) and then by Sundlöf and Wallin from the same laboratory (97-101). They were the first to record

impulses from a conscious alert human which helped to determine the sympathetic neural control at target organs (99, 100).

Microneurography is used to measure the sympathetic outflow to the to the vascular beds, mostly to arterioles (small arteries). Sympathetic signals can be recorded from nerves innervating the muscle such as the peroneal nerve which is known as MSNA and/or skin nerves known as skin sympathetic nerve activity (SSNA). The neurogram can be obtained from afferent or efferent fibers at single or multiunit post ganglionic fibers in peripheral muscle nerves (102). Our laboratory obtains recordings from multiunit post-ganglionic efferent fibers of the peroneal, or common fibular nerve. Microneurography is a technique in which the target nerve is impaled percutaneously and actively manipulated for obtaining signals. The recording comes from the peripheral nerves to muscle and skin (97, 102). The signals are obtained in the form of a polygraph and audio signals. The audio signals along with the graphic representation of the nerve discharges help in discrimination the neural signals obtained from the muscle nerve vs. those obtained from a skin nerve. The advantage of microneurography is that the recordings can be done in conscious alert humans (98, 100). Microneurography is also highly reproducible in between testing session with ICC = 0.8 (20, 103-105).

1.4.5.2 Microneurography technique:

Microneurography is a direct measure of recording the muscle sympathetic nerve activity (MSNA). Microneurography records the signals from the post ganglionic fibers using a technique in which a tungsten microelectrode is inserted in the peroneal nerve behind the knee (26, 100, 102). Figure 9 shows the electrode placement in the peroneal

nerve. The tungsten microelectrode is insulated at the shaft with an epoxy resin throughout with a diameter of 100-200µm (102). The tip is uninsulated which is 1 µm in diameter. A reference ground electrode is placed 2-3 cm by the side of the of the recording electrode. MSNA is generated from the efferent nerve fiber which sends sympathetic signals to the nerves controlling the peripheral vasculature (97). Prior to electrode insertion, the nerve is located using a stimulator to cause a lateral foot twitch via activation of the peroneal muscles. Then the microneurographer uses the audio signals on the oscillator and the amplifier to listen for an insertion burst once the uninsulated tip of the electrode enters the peroneal nerve.

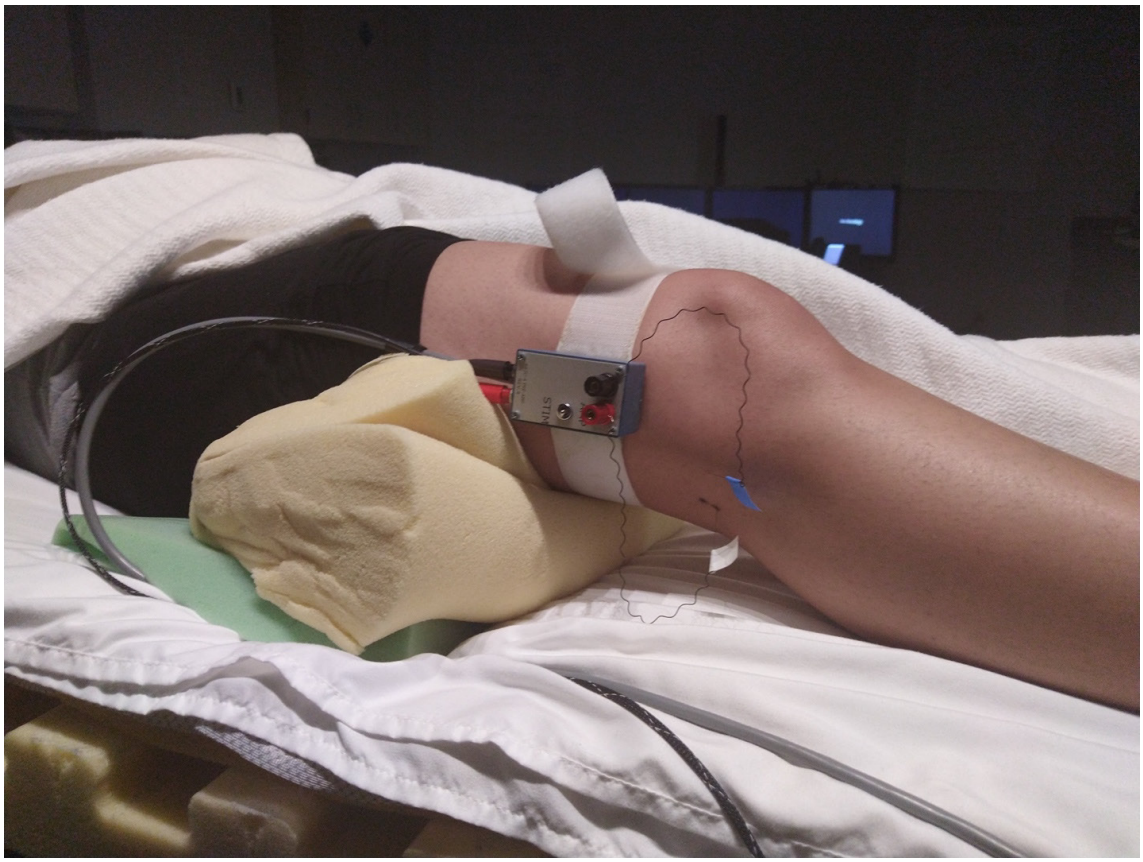


Figure 9. The electrode placement in the peroneal nerve for microneurography testing in conscious humans.

The MSNA is gated with continuous heart rate using ECG, beat-to-beat blood pressure using finger plethysmograph and respiration using a respiratory belt as depicted below in Figure 10. MSNA is quantified as spontaneous activity from efferent fibers generated in the form of bursts/minute, bursts/100 heart beats, burst amplitude and total activity. MSNA can be altered by changes in reflex action due to breathing and alteration in blood pressure. MSNA typically increases when the blood pressure decreases and vice versa so that the systemic blood pressure is regulated in a homeostatic range (60, 61, 102). MSNA is also altered in conditions such as Valsalva maneuver, deep breathing, mental stress task, cold pressor test, lower-body negative pressure, tilt table test, orthostatic changes, and isometric handgrip tests (106). MSNA responses to these tests can be commonly used to evaluate autonomic function. Higher MSNA influences pressure in the arteries by contributing to vasoconstriction which can lead to changes in blood pressure (96) (Figure 10).

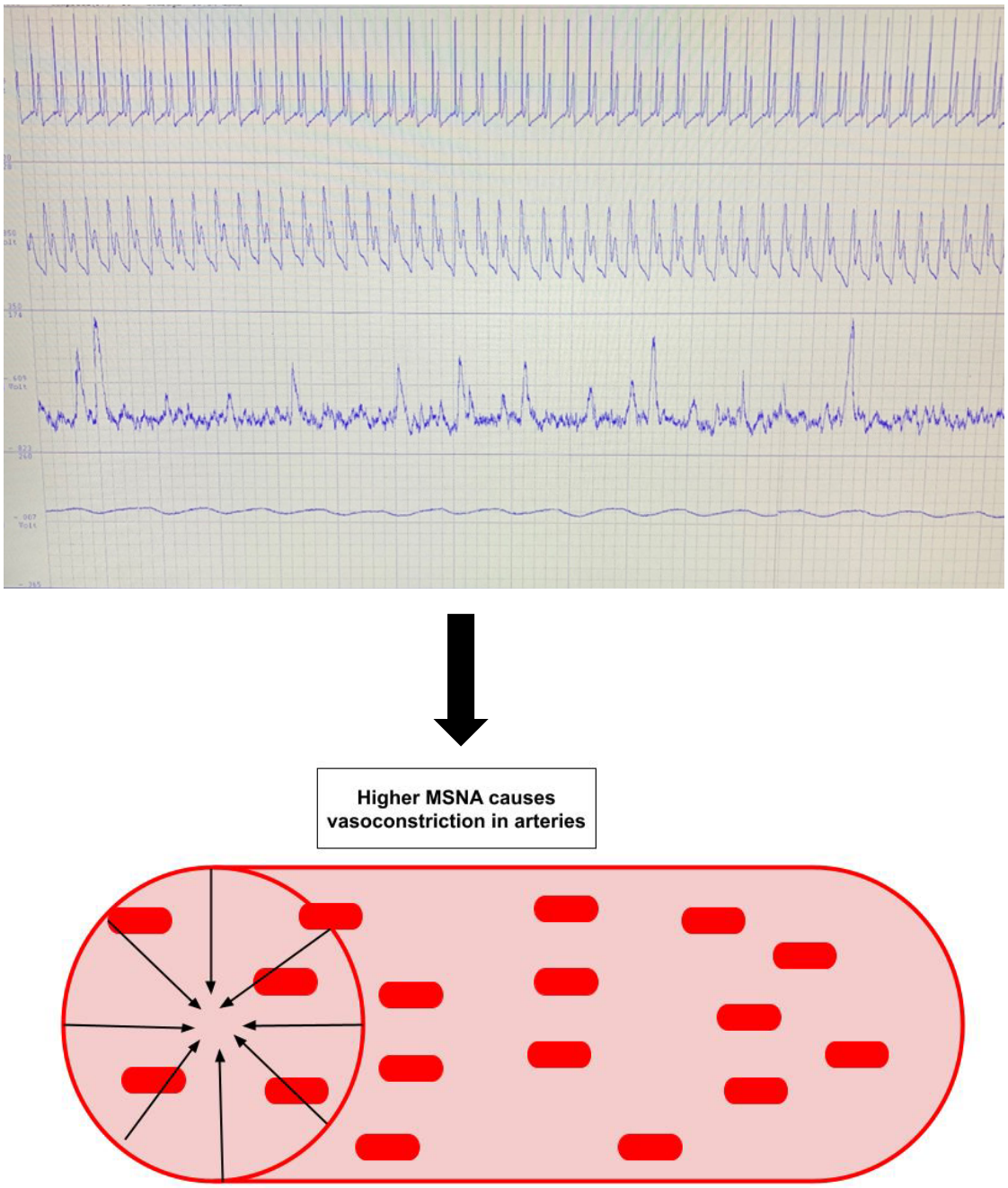


Figure 10. Shows the continuous recordings of ECG, BP, MSNA and respiration during microneurography testing and the influence of MSNA on vasoconstriction in the arteries.

Physiological differences in MSNA are observed in different biological sex, age, sleep deprivation, physical activity levels and other pre-existing conditions such as congestive heart failure, chronic kidney disease, coronary artery disease, stroke, multiple sclerosis, brain injuries and others (107-109). Hence, evaluating the role of MSNA in different conditions becomes essential to know the underlying disease mechanisms and when defining the best treatment strategies.

1.4.5.3 Baroreflex sensitivity:

The baroreceptors in the aortic arch and the carotid sinus are sensitive to changes in blood pressure (64). The baroreflex is a negative feedback mechanism wherein the decrease in blood pressure induces tachycardia and sends signals to the sympathetic nervous system to increase the blood pressure by increasing vasoconstriction and cardiac output. This is also described in section 1.4.2.3 as a negative feedback loop. Cardiovagal baroreflex sensitivity is measured using continuous ECG and beat to beat blood pressure and presented as a linear slope between RR interval and the systolic blood pressure (21, 106). This method is excellent in measuring the autonomic function because it is non-invasive in nature and provide accurate values. Sympathetic baroreflex sensitivity is a method commonly used by our laboratory which examines the changes in DAP and changes in MSNA by binning changes in DAP into 3 mmHg bins. The spontaneous DAP-MSNA slope method is clearly described in Durocher et al. (21).

1.4.5.4 Beat-to-beat blood pressure:

Blood pressure recording obtained by continuous recordings is sometimes utilized to estimate autonomic function. Noninvasive methods of testing blood pressure variability (BPV) include finger plethysmography (110) in which infrared rays are passed through arteries to determine pressure. Finger plethysmography can be measured using Finometer (Finapres Medical Systems, Amsterdam, Netherlands) and it accurately describes the changes in the circulation generated by beat-to-beat blood pressure in the periphery. Blood pressure variability using finger plethysmography can also give some estimate of the sympathetic control of the peripheral blood vessels (110, 111).

1.5 Interconnected relationship:

The above-mentioned factors have been individually addressed in detail for their mechanisms and their roles in CVD development. However, it is worth noting that all these mechanisms have an interconnected relationship to one another. Figure 11 shows how the four primary CVD factors evaluated in this study are linked to one another.

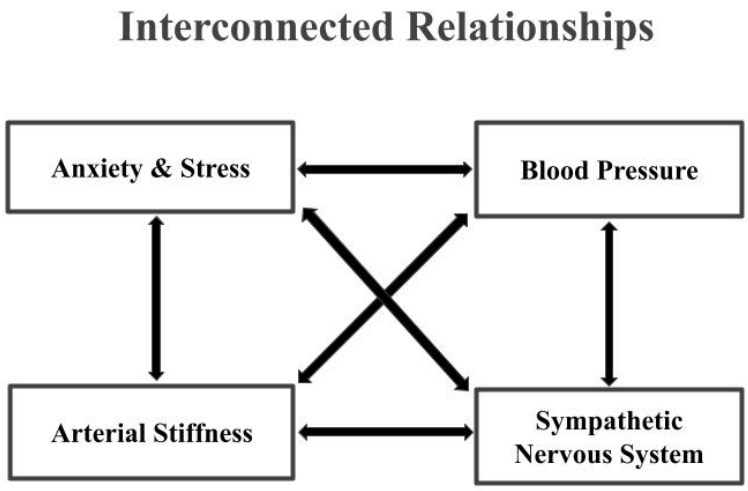


Figure 11. Schematic representation of the interconnected relationship between the risk factors.

2 Prevention and Management of CVD:

To prevent and manage CVD, a combination of pharmacological as well as non-pharmacological interventions are essential. It is important to note that the medical management for CVD is the first line of treatment. However, patients and healthcare professionals are moving from pharmacological treatment due to extensive side effects, lack of adherence, and accessibility to medications by patients. These factors are making other alternative methods more advantageous, and non-pharmacological methods may often be used as proactive preventative strategies. This section discusses non-pharmacological methods and lifestyle adherence in detail for CVD prevention and risk factor management.

2.1.1 Lifestyle modification strategies

Individuals with predisposition to CVD are also at risk of developing other conditions such as diabetes, myocardial infarction, peripheral artery diseases, stroke, heart attacks and others (112, 113). The treatment is twofold in this case with drug management along with lifestyle modification (32). Four major lifestyle strategies that can reduce CVD risk are briefly outlined below.

2.1.1.1 Smoking cessation:

Smoking is considered as an independent risk factor of CVD which increases the rate of mortality and morbidity due to CVD (31, 113, 114). Individuals are advised to stop smoking regardless of any history of CVD, their age and sex. Smoking poses acute risk on the cardiovascular system and cessation of smoking leads to immediate and longer

reduction in risk factors. It is essential to educate individuals regarding the benefits of quitting smoking and hazardous negative effects it poses on the body.

2.1.1.2 Obesity management:

Excess abdominal fat and fat around the organs is a major risk factor of CVD (113). Excessive fat deposition in the body contributes to development of atherosclerotic plaques which can lead to myocardial ischemia in the future. Therefore, managing optimal weight based on height, sex and age is important to prevent the risks of developing CVD (115). The target weight of an individual is often based on body mass index (BMI) guidelines and waist circumference measurements. It is essential that weight management incorporates strategies which can return the BMI within the normal range and does not cause rebound weight gain. Management for obesity should focus on physical activity and dietary changes.

2.1.1.3 Dietary changes:

CVD patients can benefit from dietary changes in their routine (56). The focus of this lifestyle modification depends on maintaining optimal levels of sodium consumptions of less than or up to 2300 mg per day recommended by CDC, and also specific cholesterol levels (116), high fiber foods, and alcohol intake as further described below. Individuals who are at high risk of CVD due to elevated blood pressure are often prescribed a DASH diet (117). The DASH diet includes foods rich in nutrients such as potassium, magnesium, calcium. It is also encouraged that these individuals consume food which is low in sodium, saturated fats, and excess sugars. Individuals are asked to maintain their cholesterol and triglycerides levels to prevent risk of developing atherosclerosis (118). The AHA suggests that the total cholesterol should be less than 150 mg/dL (56). Along with this, the

consumption of alcohol should also be monitored. Excessive alcohol intake can lead to high blood pressure and elevated triglyceride synthesis in the liver. It is recommended that men have 2 or less alcoholic drinks per day, and that women consume 1 or less per day (56).

2.1.1.4 Physical activity:

Physical activity in any form is critical for prevention of CVD risk factors. A sedentary lifestyle can increase body fat and lead to obesity. This can further contribute to other risk factors or diseases such as high cholesterol, metabolic syndrome, diabetes, glucose intolerance, and hypertension. Regular physical activity can promote cardiovascular health by improved vascular and endothelium function, ejection fraction, cardiac output, and reduced blood lipid levels (5, 113, 119). Physical activity can also reduce mental stress, and releases endorphins in the body which can alleviate mood and cause cognitive function to improve. Regular exercise causes the heart to pump blood efficiently during each cardiac cycle and to increase coronary perfusion. Exercise guidelines for CVD prevention should be based on the FITT (Frequency, Intensity, Time, and Type) principle (120-122). The American College of Sports Medicine (ACSM) has specific guidelines for exercise prescription for CVD such as hypertension, myocardial infarction, coronary artery diseases and other metabolic syndromes (120-122).

2.1.2 Stress-reducing techniques:

The relationship between how the mind interacts with the body has been studied extensively. Mind-body models have discussed the importance of the mind as a separate structure responsible for various physiological or physical output in our body (123, 124). Various mind-body interventions have been commonly used as stress-reducing treatment strategies and this section discusses the details of a few of those techniques.

The mind-body concept has been widely discussed in ancient Greece, India and even in religions like Buddhism (123). The main structure is based on the mind-body problem. This is defined as our conscious or mental state which leads to events in our physical state (123). Stress is considered as an event occurring in our mind which can lead to dysfunctions in the periphery. Stressful events in our body can lead to various physical ailments, including increased heart rate, blood pressure, and respiratory rate (21). Hence, there has been an increase in popularity to use mind-body interventions for treating various conditions (125). Rosenkranz, 2016 (126) evaluated mind-body interactions in asthma patients by comparing the effects of chronic low versus high stress life events to their symptoms. They concluded that chronic stress individuals had increased inflammatory markers which accounted for exacerbation in triggering their asthmatic symptoms. Thus, it becomes essential to address the importance of how the mind can impact physiological responses and evaluate its effects.

Progressive relaxation therapy, cognitive behavioral therapy, meditation, stress management, and yoga are some of the examples of mind-body interventions (127). The goal of these methods is to provide strategies to reduce stress. These methods use different approaches such as in progressive relaxation therapy, the individual is asked to cause voluntary contraction in the muscles and then release it. This causes the muscles to further reduce the symptoms of stress. Cognitive behavioral therapy (CBT) uses methods which cause ways in which a thinking is changed (127). This impacts an individual's approach towards their psychological problems which can impact quality of life such as anxiety, substance abuse, eating disorders. Meditation is a method which can be used in various forms to intentionally increase conscious awareness and to improve attention and concentration. Yoga is also considered a form of physical activity which uses various postures to improve flexibility, strength, and concentration (128).

2.1.2.1 Mind- body intervention using mindfulness meditation (MM):

Meditation is one of the ancient practices in eastern cultures. Its origin backs to Indian, Buddhist, and Chinese history. In the late 20th century, meditation became popular in the western world and now is extensively used. Mindfulness is an ancient mental awareness technique which promotes being conscious of what is happening around you in that moment (129-133). Mindfulness teaches an individual to be aware of their thoughts, emotions and feelings without being overly judgmental about them (134, 135). In the last five decades, mindfulness has been researched extensively to determine its efficacy and benefits in varied populations suggesting that it is a versatile technique with a range of health benefits. Mindfulness has been used frequently to help patients suffering from not only psychological ailments such as stress, anxiety, and depression to name a few but also from physical and physiological symptoms (136). One positive aspect of meditation is it doesn't require supervision or expertise, and it can be practiced almost anywhere. Meditation is widely accepted in society and doesn't typically carry social stigma. Mindfulness principles can be defined as paying attention to create awareness in the present moment in a non-judgmental way (129, 130, 133, 134, 137) as shown in Figure 12.

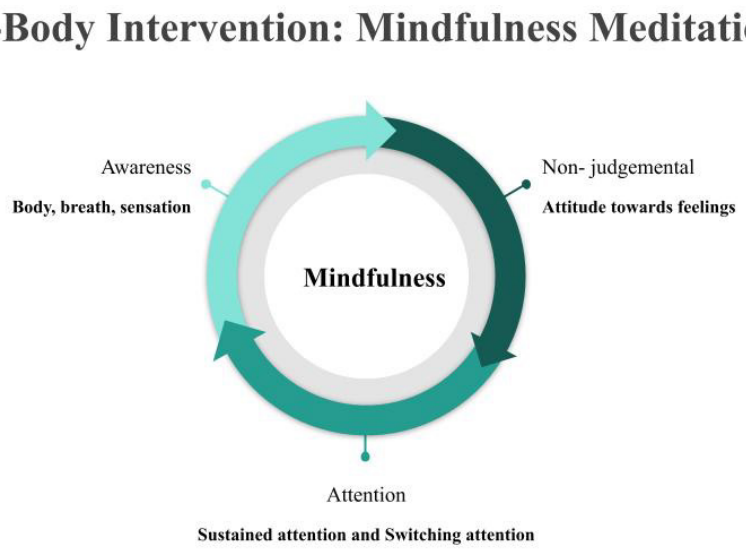


Figure 12. Three operational principles of mindfulness meditation.

In cognitive processing, mindfulness meditation utilizes attentional resources, mainly executive functioning and networks by activating the centers in the cortex (138). The cognitive mechanism of mindfulness uses introspection of body awareness and conscious breathing works by activating the salience network of the attentional resources and particularly the bottom-up mechanisms of attentional network and working memory (138). The mindfulness attentional component works by maintaining sustained attention to breath awareness and switching attention by bringing the thoughts back to breath awareness when the mind starts to wander (Figure 12).

Mindfulness Based Stress Reduction, or MBSR, is a specific form of mindfulness meditation defined by Dr. John Kabat- Zinn in the 1970s at University of Massachusetts at Amherst. Kabat-Zinn formed a structured 8-week course of MBSR initially for chronic pain, which was later used in various psychological disorders such as anxiety, depression,

and sleep (Figure 13) and physical disorders like cardiovascular diseases such as blood pressure, obesity and weight management (139), organ transplants (140), cancer, irritable bowel syndrome and many others (140, 141). MBSR use is not limited to use in diseased conditions, but it is also frequently used in healthy populations as a brain training modality for improving attention, working memory, and executive functioning (142). The MBSR (129, 134, 135, 143) group participates in meditation, body scanning and light yoga during a ~2.5-hour class every week for 8-weeks which was led by a trained expert. Figure 13 provides a schematic representation of the 8-week MBSR intervention. The focus of the MBSR group was multifaceted. The sessions included information on the principles of mindfulness meditation, stress physiology and its association to anxiety, and how practicing mindfulness can help to manage stress and related symptoms in daily life. MBSR participants also did ~45 minutes of daily home practice. MBSR participants were enrolled for a course on CANVAS© (Instructure, Inc.) which had uploaded assignments such as videos, a daily diary, and reading assignments from the book "Full Catastrophe Living" by Dr. Jon Kabat-Zinn (144). The MBSR group also participates in a silent retreat on one Saturday and practiced walking meditation, mindful eating, and the above-mentioned activities.

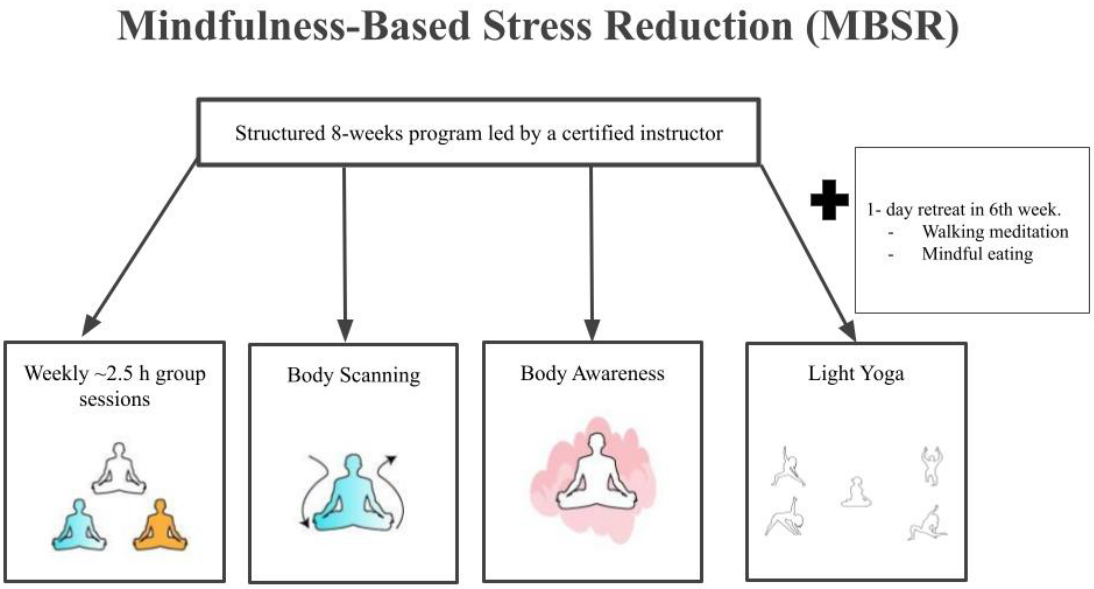


Figure 13. Conceptual figure showing the different components of 8-week MBSR course.

Mindfulness is a subjective parameter and can be rated and quantified using questionnaires. Some of the commonly used mindfulness scales include Five Facets of Mindfulness Questionnaire (145), Toronto Mindfulness Scale (146), the Mindfulness Attention Awareness Scale (147), Freiburg Mindfulness Inventory (148), Kentucky Inventory of Mindfulness Skills (149), and Philadelphia Mindfulness Scale (150). These scales are widely used and validated in different samples and populations for their effective use.

Recent studies have shown positive effects of mindfulness for not only psychological but also for cardiovascular disorders. It is known that stress can increase the risk of CVD. Stress causes an increase in the fight or flight response and over activity of sympathetic nervous system (15) which can increase the risk for CVD. Kingston, 2006 (136) studied 42 university students in a RCT on effectiveness of mindfulness in pain

tolerance, mood, blood pressure and pulse rate. They reported mindfulness improved pain tolerance because of attainment of mindfulness skills and reduced diastolic arterial pressure (DAP). In other studies, laboratory induced stress procedures have been shown to rapidly increase in heart rate, blood pressure, and the SNS, but reduce activity of the parasympathetic nervous system (PNS) (20, 22, 27). Stress also causes increased contractility in the left ventricle and peripheral blood vessels constriction (151). Mindfulness can help reduce the subjective rating on an individual's stress response which can thereby benefit the cardiovascular system (151). Mindfulness causes the mind to calm, reduce anxiety, reduced secretion of circulating cortisol, and could potentially divert the autonomic functioning towards the parasympathetic division. Mindfulness also reduces the response to stress via hypothalamic pituitary axis responsible for SNS activity (138). Overall, the neuroendocrine, inflammatory, vascular responses to stress are reduced with continued practice of mindfulness and since then, there has been extensive research on the effect of mindfulness as a stress reducing technique.

Park et al., 2014 (109) measured the effects of acute mindfulness meditation (MM) on muscle sympathetic nerve activity (MSNA) in 15 hypertensive African America males with chronic kidney disease. They measured cardiovascular and sympathetic responses during 14 minutes of mindfulness meditation (MM) compared to 14 minutes of BP education which served as the control group. The results of this study showed that, their participants had reduced BP, heart rate and MSNA from minute 10-14 during MM group compared to control. This study concluded that MM can acutely affect sympathetic nerve activity which can thereby help to reduce other cardiovascular variables.

Mindfulness literature is quite extensive with respect to its usage in different disorders. Nijjar, 2014 (152) evaluated the effects of 8-week MBSR on heart rate variability (HRV) in 20 healthy participants. They concluded that MBSR training improved HRV via improved cardiac sympatho-vagal balance in their study participants compared to control. Another study by Wolever, 2012 (139) investigated the effects of MBSR and yoga-based stress reduction program to reduce stress at workplace. They enrolled 239 employees working at a national insurance company to practice mindfulness at work. The results showed a significant reduction in the level of perceived stress, and improved sleep, heart rate, breathing, mood and productivity at workplace.

Hall, 2018 (153) evaluated mindfulness intervention in 101 university students on depression, anxiety, and sleep dysfunction. The results showed reduction in depression and anxiety symptoms compared to controls. It also improved their participant's subjective sleep latency and efficiency. Another pilot study enrolled 20 women in age range of 48-74 years with diagnosis of cardiac disorders such as angina, hypertension, cardiovascular conditions, valve disorders and compared the 8-week MBSR to control program on anxiety, emotional control, coping tendencies. The women in the MBSR group had improvement in anxiety scores, regulation in emotion, significant coping mechanism comparing to the control participants. The literature shows that mindfulness can be a great tool in managing many psychological and physiological symptoms. This dissertation has also used MBSR as an intervention for management of neural and cardiovascular parameters which will be discussed further in sections below.

2.1.2.2 Mindfulness and Decentering:

Decentering is one of the newer concepts in the cognitive arena and can impact a person's psychological wellbeing. Decentering is defined as an ability to move away from one's own thoughts and emotions in a conscious state of mind (137, 154, 155). Decentering can also be defined as an ability to observe oneself in an objective and third-person perspective (154). Decentering is crucial factor required for healthy living and can be linked to a person's mindfulness ability. With decentering, individuals can differentiate between their thoughts and reality. Decentering is a metacognitive ability which can be improved by various mind-body interventions such as mindfulness training (137, 156). Decentering is usually attained in adulthood and requires some practice and training. Some interventions like mindfulness and decentering go hand in hand. Individuals who are skilled and experts in mindfulness also typically possess a better ability to decenter. Decentering can be measured using an 11-item tool called the Experiences Questionnaire (EQ) (157) which includes a Likert type scale ranging from 1-5, with 1 being never or rarely true and 5 being often or always true. The total score for EQ ranges between 0-55 with a higher score indicating better ability to decenter. The EQ is commonly used for measuring decentering and has a Cronbach's alpha of 0.89 (157, 158).

2.1.2.3 Mind-body intervention using stress management education (SME):

Stress management is one of the popular ways to manage psychological disorders such as anxiety (33, 35, 159). This method provides an understanding of the physiology behind stress, creating awareness and incorporating methods which can help reduce the impact of stress. Stress management education (SME) is an 8-week course developed by

Dr. Elizabeth Hoge from Georgetown University School of Medicine. The SME course has been utilized in multiple clinical trials as an active control group (33, 35, 159). Dr. Hoge developed the modules of SME to match the duration and parameters with MBSR but removed the mindfulness component from SME. The principles of SME focus on explaining the stress physiology in a group session and teaching coping strategies for stress (35, 159). SME sessions are led by specialists where they explain the importance of lifestyle modification such as nutrition, exercise, sleep, time management, altruism, volunteering and their potential to help manage everyday stress. SME sessions also include completing daily readings from the book "Why Zebras Don't Get Ulcers" by Robert Sapolsky (160), and low intensity resistance band training as at home assignments. The design of SME course includes an all-day retreat with the trainer at the end of the 6th week of interventions. The SME group also participates in volunteering activities in the community, resistance training, and studied altruism during the all-day retreat (Figure 14). Stress management education is gaining popularity in workplaces, education institutes and specialized schools for managing everyday stress among individuals of every age group.

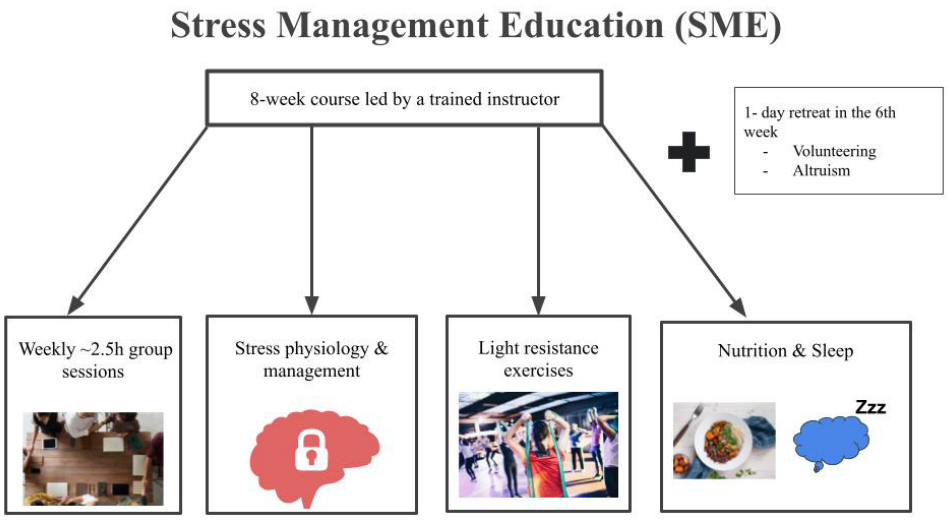


Figure 14. Conceptual diagram explaining the details of the structured 8-weeks SME course.

3 STUDY 1: Effects of 8-weeks MBSR and SME on decentering, anxiety, and arterial stiffness: a pilot randomized controlled trial

3.1 Introduction

Mindfulness based stress reduction (MBSR); a commonly used form of mindfulness meditation (MM) is attributed as a stress reduction technique. The use of MBSR has expanded and now it is frequently used for managing symptoms of psychological disorders such as anxiety, depression, addiction, eating disorders (143, 161-163), and physiological conditions impacting the cardiovascular system such as heart rate and blood pressure (151, 152, 164).

Mindfulness found its popularity in the last couple of decades, but the research has been limited in terms of truly determining its efficacy due to lack of active control groups. Many previous studies have either used no control group or a waitlist group to determine if MBSR had any effect on their participants. These studies demonstrate that even when MBSR is effective in their population the usage of the technique still cannot be generalized due to lack of comparisons with control group. Recently, Dr. Elizabeth Hoge, a faculty member, and medical doctor from the Department of Psychiatry at Georgetown University's School of Medicine developed stress management education (SME) as an active control group used in conjunction with MBSR to compare the efficiency of MBSR (33, 35, 159).

MBSR has been compared with SME mainly in individuals who manifest psychological issues such social anxiety, generalized anxiety disorders (GAD), post-traumatic stress disorders (PTSD), and depression (33, 35). Future anxiety prevalence

increases when there are frequent stressful events leading to a constant state of worry. Improvements in anxiety after practicing MBSR have been attributed to an individual's improved ability to decenter (156, 159).

Neurophysiologists have recently gained substantial interest in mindfulness to learn the mechanism through which physiological changes occur after the practice mindfulness, particularly the neural and cardiovascular parameter affected by chronic stress. Frequent stress and anxiety heighten the sympathetic nervous system by increasing the fight or flight response by activating the HPA Axis. Long term anxiety is a result of being chronically stressed which often negatively influences cardiovascular health (16, 101). This response can directly impact the contractility in the left ventricle and/or peripheral arteries through neuro-endocrine hormones that can increase heart rate, blood pressure, and arterial stiffness (27). It is postulated that mindfulness increases awareness, and the practice of slow deep breathing causes decreased sympathetic and increased parasympathetic activity to help reduce blood pressure and heart rate (152, 165). However, there is limited trials comparing MBSR vs SME on neural and cardiovascular variables. Most of the MBSR and cardiovascular research report improved heart rate, and blood pressure (109, 151) but no comparisons can be found on the influence of MBSR on arterial stiffness. Stiffening in the arteries can occur because of endothelial dysfunction and circulating catecholamines within the blood vessels (27, 90). Arterial stiffness has a direct relationship with blood pressure (76) and these factors are essential in maintaining the integrity of the arterial wall elasticity and essential to prevent future risk of developing CVDs.

It is undeniable that there is some association of chronic diseases to stress. Stress can cause chronic conditions and can negatively affect cardiovascular health. There is an

interconnected relationship between CVD health and stress, and understanding the mechanisms becomes critical to provide appropriate treatments to the patients. Many clinical trials have established that MBSR is effective for improvement of mental wellbeing. Hoge et al., have conducted various RCTs comparing the benefits of MBSR with SME in those with anxiety disorders (33, 35, 159). Even with extensive research on mindfulness dating back >50 years in different population groups and disorders, there is no evidence of effectiveness of MBSR on elastic properties and stiffness in the arteries. One study conducted by Gainey et al., 2016 (166) reported improvement in PWV in 23 study participants after walking meditation when compared with traditional treadmill walking.

To our knowledge no study has directly measured the influence of 8-weeks MBSR on central arterial stiffness measured through pulse wave velocity (PWV). Therefore, the primary aim of this study is to measure the changes in central arterial stiffness measured through cfPWV after 8-weeks of MBSR or SME. The secondary aim of this study is to compare 8-weeks of MBSR and SME regarding changes in anxiety and decentering. We hypothesize that MBSR group will have reduced cfPWV, anxiety and an increased ability to decenter after 8-weeks compared with SME.

3.2 Methods:

3.2.1 Participants:

The study participants were volunteers from Michigan Technological University and the surrounding communities in the Upper Peninsula Michigan. All participants were within the age of 18-45 years and had elevated resting blood pressure of ≥120/80 mmHg

according to 2018 guidelines of the American Heart Association (AHA). Participants reported to the Clinical and Applied Physiology Laboratory at Michigan Technological University to evaluate their eligibility criteria. Other exclusion criteria included having diabetes, hypertension, or autonomic conditions and participants should be otherwise healthy and did not suffer from any psychological issues to participate in the study. The participants were excluded if they were taking any cardiovascular medication, had a body mass index of $\geq 30 kg/m^2$ and/or were smokers. They were also asked to abstain from alcohol, caffeine, and exercise for 12 hours and food for 3 hours before any laboratory testing. The study was approved by the Institutional Review Board of Michigan Technological University and procedures for testing adhered to Declaration of Helsinki. The study procedures were explained to all potential participants before they provided their informed consent and before any testing.

3.2.2 Study instruments and materials:

On the testing days, the participants completed self-reported psychometric tools on decentering and anxiety. The Spielberger State and Trait Anxiety Inventory (STAI) for adults was used to measure state and trait anxiety and the Experiences Questionnaire (EQ) was used to measure ability to decenter.

Blood pressure readings were taken on the brachial artery of the right arm using automated sphygmomanometer (Omron HEM-907XL; Omron HealthCare Kyoto, Japan). An average of three readings were taken with one-minute rest period in between. Arterial stiffness was estimated using carotid to femoral Pulse Wave Velocity (cfPWV) by using a SphygmoCor (AtCor, Sydney, Australia) CPVH System. Heart rate was recorded using the

3-lead ECG connected to the SphygmoCor to gate the PWV reading with the R-waves of the ECG. The ECG recording is taken as to determine the time delay in the velocity of the pulse to reach the peripheral arterial point after the left ventricle has contracted and ejected the blood. The PWV recording is taken for 10 cardiac cycles with clear upstrokes on the waveform to be acceptable for analysis. We used the average of two consecutive readings that had less than a 1 m/s variability between readings. Body mass index was calculated by using a Tanita wall mounted height rod and Tanita BC-418 scale for height and weight, respectively.

3.2.3 Protocol:

3.2.3.1 Pretesting:

Participants reported to the laboratory following testing day guidelines. Their demographic details such as age, sex, height, and weight were measured to determine their eligibility for the study. All the participants completed a questionnaire on their general health such any cardiovascular conditions, pacemakers, smoking, alcohol status, caffeine intake, exercise history for 12 hours prior and food consumption 3 hours prior to coming for screening. Female participants also reported information about their ovarian cycle including the number of days since the start of their last menstruation, use of contraceptives, and typical number of days in each complete cycle. The research assistant measured their seated blood pressure after 5 minutes of quiet sitting. Measurements were taken three times with a rest period of 1 minute in between on three non-consecutive days. Averages of nine total readings were taken, and all the participants had a seated clinical blood pressure of ≥120/80 mmHg to qualify for the study.

On the laboratory testing day, the participants were then asked to complete all forms and questionnaires. They then laid supine and an average of another 3 blood pressure readings were taken and ECG was connected to calibrate the SphygmoCor system. Applanation tonometry was used to measure carotid femoral PWV (cfPWV) for central arterial stiffness (72). For cfPWV, the distance between suprasternal notch to carotid artery and suprasternal notch to femoral artery were recorded to the nearest millimeter for calibrating the system. This will help in determining the delay in the pulse velocity after the left ventricle has ejected the blood and the time it takes to reach the artery. To record the cfPWV, the SphygmoCor tonometer probe is first placed on the carotid site, then at femoral site, and then the order is reversed to get two quality recordings at each site. The pulse wave recordings are taken for approximately 10 cardiac cycles at each point. The SphygmoCor software provides a PWV measurement in m/s and an average of the two readings is taken for final analysis.

3.2.3.2 Interventions:

After determining eligibility of all the participants, they were randomized into 8-weeks of either mindfulness-based stress reduction (MBSR) designed by Dr. John Kabat Zinn (132, 134, 135, 144, 167) or stress management education (SME) led by trained individuals. Detailed description of the 8-week course is discussed in section 2.1.2

3.2.3.3 Post testing:

All the participants underwent the same testing procedures as pretesting after 8-weeks of intervention. They were tested for anthropometric measures, blood pressure, cfPWV, STAI and decentering.

3.2.4 Study Design:

The study is a randomized controlled trial where MBSR is the intervention/experimental group, and the SME is the active control group used to compare the effects of MBSR. The comparisons were done as between subject factor for MBSR and SME and within subject for pre and post 8-weeks of interventions for cfPWV, STAI, decentering, and blood pressure.

3.2.5 Randomization procedure:

The study followed the CONSORT guidelines for randomization procedure. Appendix 1 provides a flow diagram with details of the study participants. Once the participant's eligibility for the study was determined, they were randomly assigned into the MBSR or SME group. Randomization was done by the primary investigator of the study where they randomly generated the number on the web for all the participants who will were assigned to MBSR and SME. It must be noted that, it is not possible for the investigators to blind the participants to whether they were practicing MBSR or SME. They were only informed about their randomization after the pretesting was complete and they were starting with the interventions.

3.2.6 Statistical analysis:

Independent sample t-tests were used to compare the demographic data presented in Table 1. A 2×2 Mixed Factor Analysis of Variance (ANOVA) was used to compare means from pre to post testing for within group and the effects of intervention (MBSR and SME) for between group comparison. Data are reported as mean ± standard deviation. Critical value was set at alpha <0.05 (2-tailed). IBM SPSS version 26 (IBM® SPSS®, Armonk, NY) was used to conduct statistical analysis. Origin Pro2021®b was used to generate figures. Tests for normality were completed prior to parametric statistical analyses.

The details on the step-by-step laboratory testing sequence are provided in Figure 15.

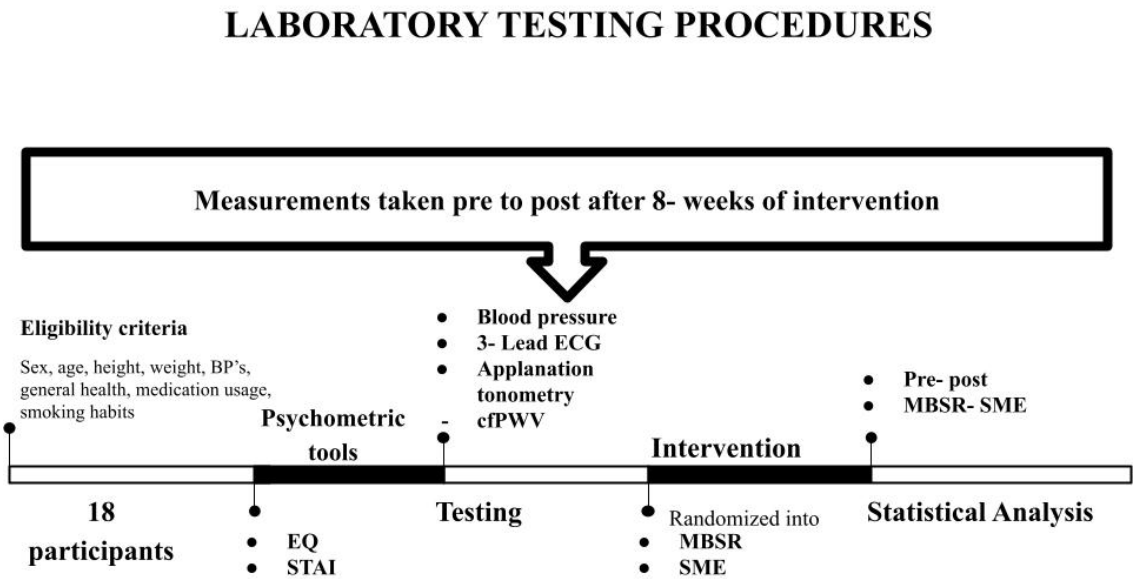


Figure 15. Description of the laboratory testing procedure and protocol for aim 1.

3.3 Results:

Eighty-seven participants were assessed for the eligibility and 68 were excluded from the study for not meeting the study criteria. Appendix 1 includes CONSORT flow diagram with participant details. Finally, 19 volunteer participants enrolled in the study and one participant dropped out while the group sessions were ongoing due to lack of available time. Eighteen individuals (13 males, 5 females) completed the 8-weeks of MBSR or SME and were included in the final analysis. Table 1 details the demographic variables and the initial clinical seated blood pressures. Baseline demographic variables had no significant difference for the 9 participants in each group.

Table 1. Demographic details of all the study participants.

Scores are represented as mean ± SD

Variables	MBSR (n=9)	SME (n=9)	*p*
Age (years)	26.88±9.93	22.44±2.45	0.21
Height (cm)	175.57±11.50	174.32±11.48	0.81
Weight (kg)	82.36±14.87	80.16±12.61	0.73
BMI (m/kg^2)	26.54±2.70	26.26±2.46	0.82
Resting SAP (mmHg)	125.33±6.78	129.77±12.91	0.37
Resting DAP (mmHg)	79.11±12.37	77.44±10.01	0.75
Resting HR (bpm)	75.44±12.25	74.55±11.01	0.87

cm = centimeters, kg = kilograms, BMI = body mass index, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, HR = heart rate, bpm = beats per minute

There were no significant differences in anxiety or decentering as shown below in Table 2. The results show a non-significant decrease in state anxiety score ($F\ (1, 13)$ = 4.1, p= 0.06 and η_p^2 of 0.2, 95% CI ranged from 25.2- 35.2). No main effects for interaction

between time (pre-post) × group (MBSR and SME) with F (1, 13) = 2, p= 0.18 and η_p^2 of 0.1 There was a non-significant decrease in state anxiety in MBSR (-Δ4.8±1.9 a.u.) and SME (-Δ0.9±1.6 a.u.) groups Table 2 provides descriptions of the changes in scores for state anxiety.

Trait anxiety also had no significant main effects for time after 8-weeks of intervention with MBSR and SME (*F (1, 15)* = 0.006, p= 0.9, η_p^2= 0, CI= 29- 42) and no significant interaction between time × group (*F (1, 15)* = 0.8 p= 0.3, η_p^2= 0.052).

Finally, there was no significant difference seen in decentering before and after 8-weeks of MBSR and SME (*F (1, 16)* = 0.9, p= 0.3, η_p^2= 0.05, CI= 33.6-50). There was also no significant interaction for time × group (*F (1, 16)* = 0.07, p= 0.7, η_p^2= 0.004).

Table 2. Changes in STAI and decentering in MBSR and SME group before and after 8-weeks.

Scores are represented as mean ± SD

Group of Variables	Pre	Post	Δ	Cohen's d	*p*
MBSR State n=7	28.57±5.06	23.57±3.35	-5.00±1.71	1.16	0.06
SME State n=9	34.55±11.86	33.66±10.27	-0.89±1.59	0.08	0.86
MBSR Trait n=8	34.62±11.32	31.75±8.66	-2.87±2.66	0.28	0.57
SME Trait n=9	39.88±11.02	38.33±10.46	-1.55±0.56	0.14	0.76
MBSR Decentering n=9	44.22±6.74	45.33±5.56	1.11±1.18	0.18	0.70
SME Decentering n=9	36.44±4.95	37.44±5.27	1.00±0.32	0.19	0.68

cfPWV = carotid-femoral pulse wave analysis, MBSR = mindfulness-based stress reduction, SME = stress management education, Δ = change from pre to post

There was no significant change in cfPWV after 8-weeks of intervention (*F (1, 16)* = 0.6, *p*= 0.4, η_p^2 of 0.03, 95% CI = 5- 5.8). Figure 16 shows no changes in cfPWV from pre to post in MBSR (Δ= -0.01±0.48, Cohen's d= 0.01 and *p*= 0.97) and SME (Δ= -0.27±0.09, Cohen's d= 0.38 and *p*= 0.42). The figure also shows the changes in each individual score for all the participants in each group who completed the study. No significant main effects were observed for time x intervention (MBSR vs SME) after 8 weeks with *F (1, 16)* = 1.2, *p*=0.2 and η_p^2 0.07.

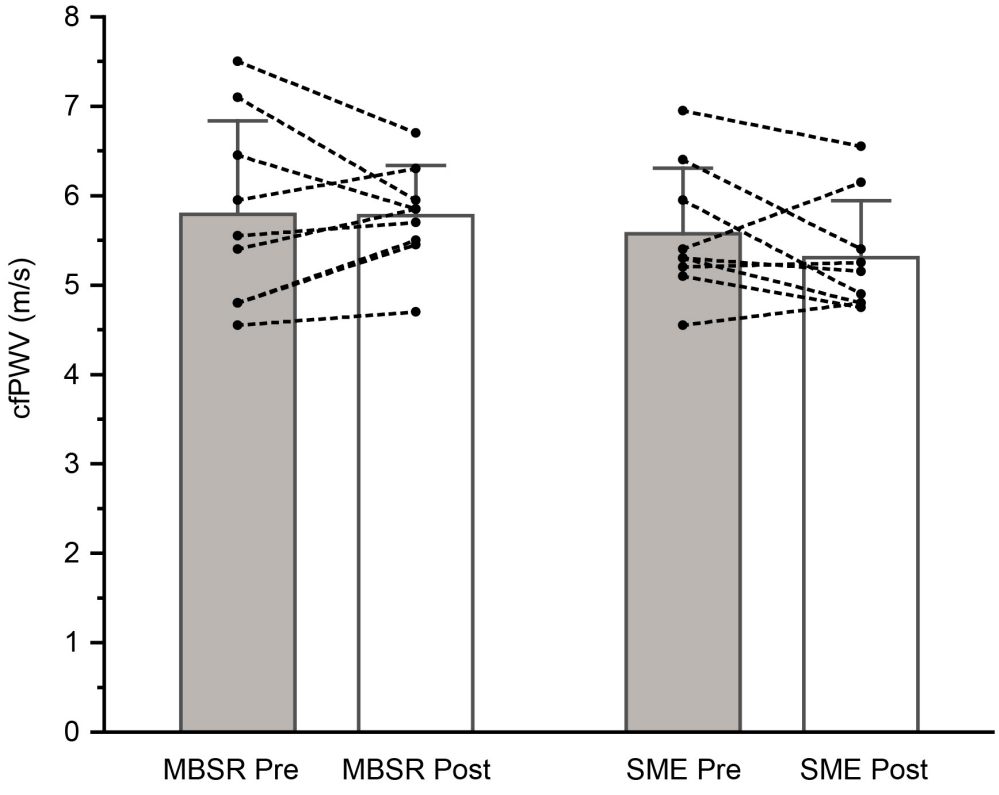


Figure 16. cfPWV in MBSR and SME groups from pre to post (after 8-weeks). The bar graph shows the average scores for pre and post, whereas the line graph shows changes in the scores for individual participants.

3.4 Discussion:

This was the first study to evaluate the effects of 8-week MBSR and SME on arterial stiffness measured via cfPWV. It has been previously established that mind-body interventions such as MBSR can have a varied but positive influence on psychological health and physical wellbeing. Some cardiovascular changes have also been observed with practice of MBSR with effects on heart rate and blood pressure. However, there was limited exploration on arterial stiffness with MSBR. This study tried to bridge that gap and investigated the effects of MBSR on cfPWV, but no changes were observed in cfPWV from before to after MBSR or SME. There was also no change in anxiety or decentering from pre to post, however there was a large effect size for state anxiety from before to after MBSR as shown in Table 2.

3.4.1 MBSR, anxiety and decentering:

MBSR and SME have been previously compared for effects on anxiety and decentering (35, 159). Multiple trials conducted by Hoge et al., have reported positive effects of MBSR in social anxiety disorders, GAS and PTSD (33, 35, 159). They have also reported benefits of MBSR in improving the ability to decenter (159). Various RCT's conducted by Hoge et al., had a moderate to large sample sizes in their studies and the current study only has nine participants in each group which was not sufficient to detect any changes. However, this study did show non-significant trends for reduction in state anxiety after 8-weeks of MBSR suggesting the efficiency of the MBSR intervention regarding improved psychological well-being.

3.4.2 MBSR and its effects on stress related CVD:

The cardiovascular system is considered as an initial target to respond to the effects of stress and anxiety. As noted earlier, stress when not controlled causes anxiety which influences the neuro-endocrine system by activating the HPA axis and sympathetic nervous system causing release of catecholamines, specifically norepinephrine (27). With persistent high serum catecholamine levels, there can be endothelial dysfunction (27, 73, 90), and inflammation measured using the levels of interleukins (IL-6) (20). As previously discussed, MBSR is an excellent stress reducing technique in managing the symptoms of stress and anxiety.

The damaging effects of anxiety on cardiovascular health have been recently recognized. Zieff, 2017 (130) interpreted how mindfulness practice has evolved over the years and hypothesized how meditation might be able to buffer stress and reduce the risk for CVD through mechanisms such as arterial stiffness. Zieff, 2017 (130) suggests mindfulness can alleviate chronic stress related physiological symptoms such as activating the PNS and inhibiting the HPA axis and SNS. Stress causes inflammation in the arteries, which eventually leads to arterial diseases including atherosclerosis which is high risk CVD. Mindfulness may attenuate the SNS and reduce inflammation and vascular dysfunction by reducing the circulating stress hormones which assist in preventing major cardiovascular complications (109, 151, 152, 164, 166, 168, 169) Regular mindfulness meditation can also normalize heart rate (151) and blood pressure with the practice of slow and deep breathing by targeting the autonomic nervous system (109, 141, 152, 165, 170).

3.4.3 MBSR and changes in arterial stiffness:

The integral properties of arteries can be affected by stress related changes. There is continuous circulation of stress hormones mainly catecholamines when there is frequent stress leading to chronic anxiety. This can contribute to endothelial damage and vascular dysfunction and linked to changes in elastic properties of the arteries measured through cfPWV. Gainey et al., 2016 did not directly measure the effects of MBSR on PWV, but they investigated the effects of walking meditation compared to traditional treadmill walking. They reported reduction of ~10% in PWV after walking meditation in study participants suggesting that mindfulness positively influences arterial stiffness. In the present study we did not detect a reduction in cfPWV after 8-weeks of MBSR or SME, but this should be further studied in a larger population.

3.5 Study Limitations:

One of the limitations of this study is attributed to the small sample size which reduced the power of the study. This pilot study accounts for only 9 participants in each group who completed the study. Another limitation of the current study is that we had mainly young male participants. It is known that young males respond to cardiovascular changes differently when compared with young females, and middle to older aged adults.

3.6 Conclusion

Even though this study did not reveal significant results, this study was the first to evaluate the effects of MBSR on arterial stiffness (cfPWV) Figure 15. We did not observe significant changes in state anxiety, trait anxiety or decentering, but there was a large effect

size for state anxiety from before to after MBSR. The reduction in state anxiety would be consistent with larger studies that have studied the benefits of MBSR in several clinical populations.

3.7 Future directions:

Future studies should also test blood inflammatory markers and include other methods such as flow mediated dilation to understand vascular changes after MBSR. At cellular and molecular levels, studies can be conducted on measuring the ratio of elastin and collagen after the practice of MBSR. Future studies should also include a diverse group of men and women to best evaluate the effects of MBSR on stress related CVD risk factors.

4 STUDY 2: Mental stress pressor response and post stress aortic wave reflection

4.1 Introduction:

The American Institute of Stress reports that the country is going through a national mental health crisis attributed to increased stress due to the recent trends in events (13, 24, 25, 171). It is difficult to escape from the overwhelming feeling of stress which is experienced in daily life and the recent occurrence of COVID-19 pandemic has caused an enormous number of uncertainties in people which has accounted for a higher prevalence of anxiety. A recent survey of Stress in America™ by the American Psychological Association (APA) emphasized the direct interaction between mind and body and how psychological symptoms of stress can be seen as a physical response (171).

Mental stress is a result of not only external stimuli such as stressors from the workplace and family, but also internal stimuli such as biochemical and physiological responses (172). When the relationship between external and internal stimuli causes imbalance, there is higher incidence of developing stress. Hans Selye, an endocrinologist first defined stress as a "nonspecific response of the body to any demand" (13). Individuals in a state of eustress, can be defined as experiencing sufficient or optimal stress which is important for performance of everyday tasks. It is essential that the human body remains in the state of homeostasis to maintain important bodily functions, but allostatic load can lead to imbalanced homeostasis and difficulty in coping with the stressful situation (173). When the amount of stress exceeds the normal limits, it is referred to as distress, which can be harmful in many ways both psychologically and physiologically. The imbalance between these factors can precipitate the level of stress in an individual which can

negatively influence physical wellbeing and cardiovascular health, even from bouts of acute mental stress.

The negative influence of acute mental stress on heart rate, blood pressure, and perceived stress have been reported by Carter et al., 2008 (24), Durocher et al., 2011 (21), and many others. Their results indicated a consistent increase in blood pressure, heart rate, and perceived stress during mental stress, but the muscle sympathetic nerve activity (MSNA) responses are variable. Mental stress (MS) can increase, decrease, or show no change in MSNA (22). Durocher et al., 2011 (21), who studied 32 young healthy adults, reported that blood pressure and MSNA increased during MS compared to baseline as shown in Figure 17. Their recordings were completed during a 5-minute supine rest, 5-minute mental arithmetic stress task, and 5-minute recovery. The figure below is a representative recording from a single participant and there is a variable MSNA response to MS as mentioned above.

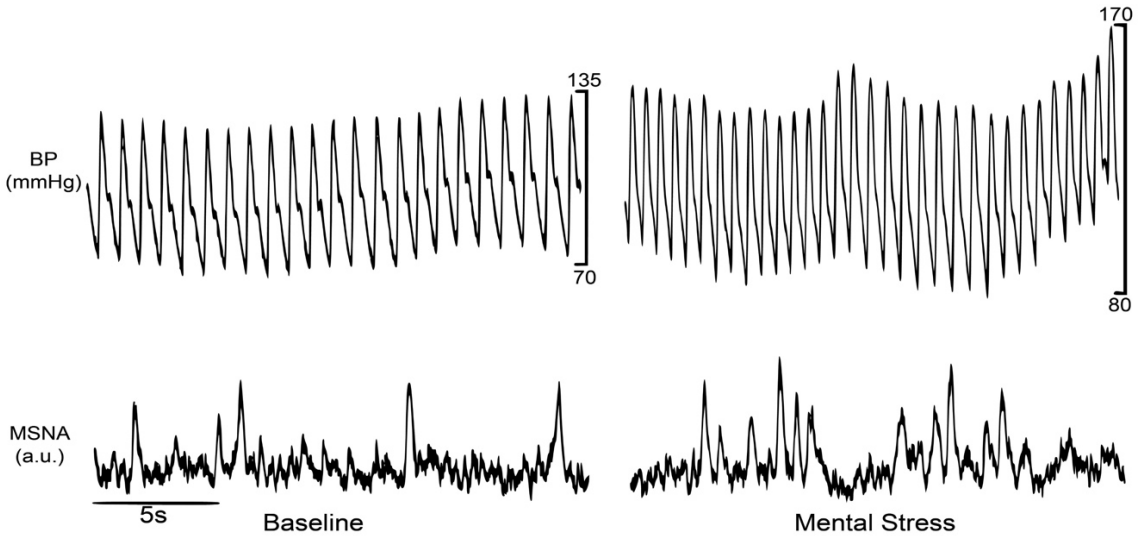


Figure 17. Cardiovascular and neural responses to mental stress from Durocher et al., 2011 (21).

Mental stress (MS) can contribute to endothelial dysfunction and mental stress reactivity increases cardiovascular risk by causing an elevation in aortic wave reflection even one hour after laboratory induced mental arithmetic task (27). Aortic wave reflections are estimated using aortic augmentation index (AIx) which is an indicator for large artery and aortic stiffening (72, 174, 175). Large artery stiffness and arterial wave reflections are independent risk factors of developing cardiovascular diseases (27, 79). Elasticity of arteries are affected by other factors such as increasing age, obesity, diabetes, hypertension, high cholesterol, and a family history of coronary artery disease (174). In normal healthy arteries, the wave reflection is slow and has low pulsatility, whereas in stiff arteries the wave reflection timing is fast and premature which causes high pulsatility (79). Normally, in compliant arteries, the reflected wave travels back to the aorta during diastole which helps with coronary perfusion, but with stiffness, it causes early return of the pulses during systole, which is problematic as there will not be enough perfusion to the myocardium during the next cardiac cycle (28, 79).

Frequent stress is also problematic as it keeps an individual in a heightened state of fight or flight by over activating the HPA axis continuously and causes chronic anxiety which is evident even in the absence of the stressor. Perceived stress is an indicator of subjective rating of stress on a 5-point Likert Type Scale with 0 being not stressful and 4 being very, very stressful (176). This scale was frequently used by Carter and colleagues in their work on influence of MS on cardiovascular health. In one of their previous works, they compared the effects of MS with negative pictures related to emotional stress responses in which the participants were shown negative pictures, neutral pictures and

mental stress using arithmetic task (24). Perceived stress rating was higher in subjects during mental stress compared with negative pictures (3 ± 0 a.u vs. 2 ± 0 a.u, $P < 0.001$).

The primary objective of the present study to determine if the muscle sympathetic nerve activity (MSNA) and mean arterial pressure (MAP) reactivity to mental stress influence post mental stress aortic augmentation index (AIx). The secondary aim of this study is to determine if there is a relationship between perceived stress and post MS AIx.

4.2 Methods:

4.2.1 Participants:

The study participants were selected from Michigan Technological University and the surrounding communities. The participants were selected from the age group of 18-45 years who had elevated blood pressure as described by the AHA guidelines. The sample size for the study was based on predicting a 3 bursts/min change in MSNA with 80% power, which resulted in a sample size estimate of 48 participants for MSNA data. However, COVID-19 stay-at-home restrictions limited the in-person data collection in the laboratory which limited our sample size.

The participants reported to the Clinical and Applied Physiology Laboratory at Michigan Technological University to be screened for study eligibility. Potential participants were excluded if they were taking any cardiovascular medication, had a body mass index of >30 kg/m^2 and/or were smokers. They were also asked to abstain from alcohol caffeine and exercise for 12 h and food for 3 h before any laboratory testing. The study was approved by the Institutional Review Board of Michigan Technological University and procedures for testing adhered to Declaration of Helsinki. The study

procedures were described to all participants who voluntarily signed their informed consent before any testing.

4.2.2 Study instruments and equipment:

On the laboratory testing day, the participants reported to the research laboratory at Michigan Technological University. Their seated and supine brachial blood pressure measurements were taken using an automated sphygmomanometer (Omron HEM-907XL; Omron HealthCare Kyoto, Japan). The supine blood pressures were used to calibrate the SphygmoCor (AtCor, Sydney, Australia) prior to performing pulse wave analysis which is used for calculating the aortic augmentation index (AIx). AIx is expressed as augmentation pressure divided by pulse pressure and the values are obtained as a percentage. Detailed description of the separate phases in aortic pressure waveform are described in Figure 8.

$$\textbf{\textit{A}ugementation Index (AIx \%)} = \frac{\textbf{Augmentation Pressure (AP)}}{\textbf{Pulse Pressure (PP)}} \times \mathbf{100}$$

Microneurography measurements were taken in a dim lit room with an ambient temperature of 22-24 Cº with no surrounding noise. Microneurography was used to directly record muscle sympathetic nerve activity (MSNA). MSNA recordings were completed as multi fiber recordings by percutaneously inserting as tungsten microelectrode in the peroneal nerve. A reference electrode was inserted 2-3 cm from the recording electrode. The neurogram was generated in the form of a polygraph and auditory recording with electrodes connected to the amplifier and preamplifier with a total gain of 80,000 and band pas filtered to 700-2000 Hz. The recordings obtained were satisfactory if the generated

neurogram has spontaneous synchronous bursts and were analyzable with 3:1 signal to noise ratio, 0.5s search window and expected 1.3s burst latency derived from the marked R-wave. The spontaneous sympathetic burst was acceptable if the amplitude and frequency of bursts increased with end-expiratory apnea and no change in bursts with sudden yelling or clapping done by the investigator. MSNA recordings were gated to continuous recordings of blood pressure, heart rate and respiration. Beat to beat arterial pressure was performed using a method known as finger plethysmography by a Finapres® NOVA (Finapres Medical Systems, Amsterdam, The Netherlands). Arterial blood pressures were reported as systolic, diastolic, and mean values from the NOVA system. Heart rate measurements were taken using a three-lead electrocardiogram (ECG).

4.2.3 Study Design:

4.2.3.1 Protocol:

Participants' demographic details such as age, sex, height, and weight were measured. All the participants completed a questionnaire on their general health such any cardiovascular conditions, pacemakers, smoking, alcohol status, caffeine intake, exercise history for 12 h prior and food consumption 3 h prior to coming for screening. Female participants also reported their menstrual cycle, pregnancy, and hormonal contraceptive usage history. Figure 18 outlines the laboratory testing sequence. The research assistant measured participants' seated blood pressures after 5 minutes of quiet sitting. Measurements were taken three times with a rest period of 1 minute in between on three non-consecutive days. An average of the nine total readings were used to ensure all the participants had a seated clinical blood pressure of ≥ 120/80 mmHg to qualify for the study. Other exclusion criteria included having diabetes, hypertension, and autonomic conditions.

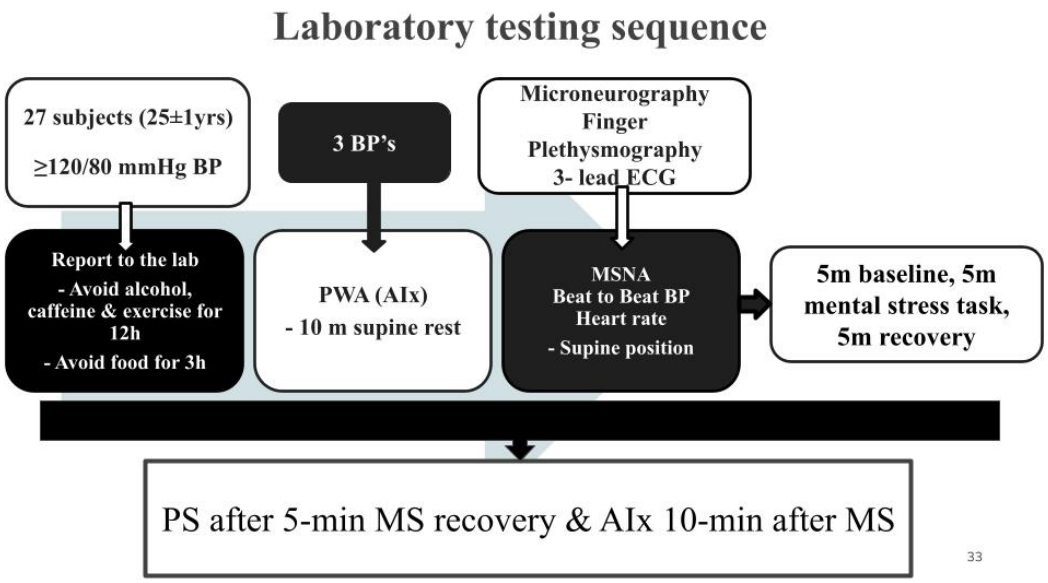


Figure 18. The timeline of events, screening criteria, and tasks involved for data collection.

The PWA recordings were taken two separate times with an operator index of ≥75% to be acceptable for analysis. The operator index determines the quality of the pulse wave recordings taken by the investigator which considers the consistency of the wave heights and quality of the pulse waves over 10 cardiac cycles. PWA recordings were completed after 10 minutes of supine rest. After the PWA measurements, the participants were equipped for microneurography, 3-lead ECG and continuous BP recording.

The mental stress (MS) protocol included 5 minutes of supine baseline, 5 minutes of mental arithmetic task and 5 minutes of supine recovery. The mental stress was induced in the laboratory using an arithmetic task which included serial subtraction of 6 or 7 from a 2- or 3-digit number (14, 20-23, 177). The participants had to answer quickly and accurately. Incorrect responses were immediately corrected by the researcher, and they were given a new random number to subtract from. Immediately after the 5-minutes of recovery from the mental arithmetic task, the participants were asked to subjectively rate

their perceived stress once on a Likert type scale from 0-4 (24, 176). After the 5 minutes of supine recovery, brachial blood pressures were again obtained in triplicate. PWA recordings were taken immediately after the brachial blood pressures which was approximately 10-minutes post mental stress.

4.2.3.2 Data analysis:

PWA data was obtained as AIx (%) from the SphygmoCor software (178) and the values were taken as the average of the two recordings. Autonomic data was recorded in WINDAQ software and imported in WinCPRS (Absolute Aliens, Turku, Finland) to make the waveforms (21). The WinCPRS software detected the R-waves and the ones which were not detected were marked manually by the researcher for the recording. Next, all the BP waveforms were marked. MSNA bursts were detected automatically by the software after all the R-waves and blood pressure markings were complete. MSNA was quantified for analysis as bursts frequency (bursts/minute). MSNA data was analyzed and edited by a single experienced researcher (J. Durocher) who was blinded to the participant identification to avoid bias.

4.2.3.3 Statistical Analysis:

Normality tests were completed prior to parametric statistical analyses. Paired t-tests were used to compare means at baseline and during mental stress for HR, BP, and MSNA. Change in MAP, MSNA and HR was calculated as the difference during MS vs. baseline values. Change in AIx was calculated as the difference between baseline and post MS AIx taken 10 minutes after completion of MS. Two-tailed Pearson correlations were conducted

to determine the relationship between MSNA, MAP, perceived stress and AIx. We used standard multiple regression with change in AIx as the dependent variable and changes in MSNA, MAP, and perceived stress as the independent variables. Means were considered significantly different when $p<0.05$. Data was analyzed using commercial statistical software IBM SPSS version 28 (IBM® SPSS®, Armonk, NY). Graphs were generated using OriginPro® 2021b.

4.3 Results:

Twenty-seven (25±1 years) volunteers completed the study. Table 3 displays the demographic details as well as the baseline blood pressure and heart rate values for all the participants.

Table 3. Demographics and baseline cardiovascular variables of study participants.

Values expressed as mean ± SD

Age (years)	24.41±5.71
Height (cm)	173.92±9.97
Weight (kg)	77.66±12.83
BMI (kg/m^2)	25.58±2.87
SAP (mmHg)	126.45±11.13
DAP (mmHg)	74.70±11.45
MAP (mmHg)	91.97±10.13
HR (bpm)	72.61±10.04

cm = centimeters, kg = kilograms, BMI = body mass index, SAP = systolic arterial pressure, DAP= diastolic arterial pressure, MAP = mean arterial pressure, HR = heart rate

Mental stress significantly increased HR, MAP, and perceived stress from baseline ($p<0.05$). The mental arithmetic task increased HR ($\Delta 15 \pm 9$ bpm), MAP ($\Delta 14 \pm 6$ mmHg) and perceived stress ($\Delta 1.9 \pm 0.7$ a.u). Mean MSNA values were not significantly changed from baseline to during mental stress. However, MSNA showed a range of changes among individual participants from -13 to +20 bursts / minute with mean and SD of 2 ± 9 bursts/minute during mental stress.

Pearson correlation analysis showed that there was no relationship between the changes in MSNA and change in AIx post MS with R = -0.31 and p = 0.18 as shown in Figure 19. Regression analysis indicated that ΔMSNA during mental stress was not a significant predictor for ΔAIx post MS recovery (**β** = -0.39 and p=0.08).

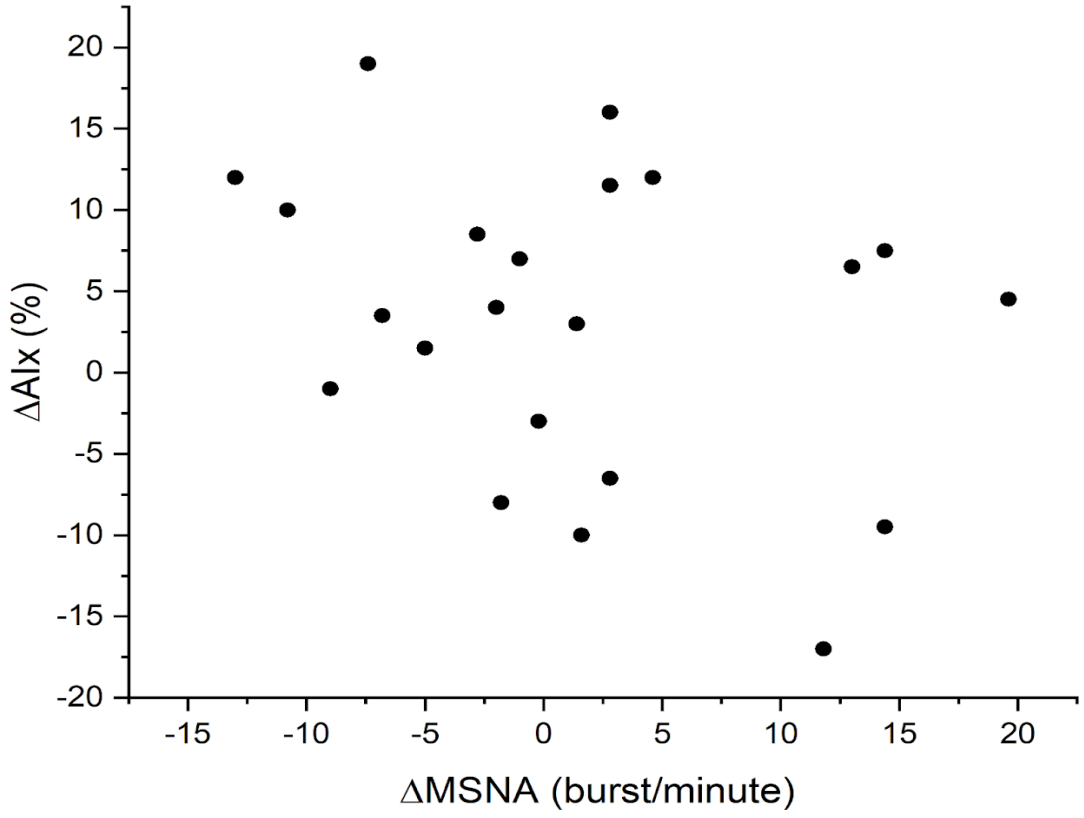


Figure 19. Shows no relationship between ΔMSNA during 5-minute MS task and ΔAIx post MS recovery.

Pearson correlational analysis revealed no relationship between perceived stress and ΔAIx with R = 0.08 and p = 0.7 as shown in Figure 20. Regression analysis indicated that perceived stress was not a significant predictor for post MS ΔAIx (**β** = 0.31 and *p*=0.17).

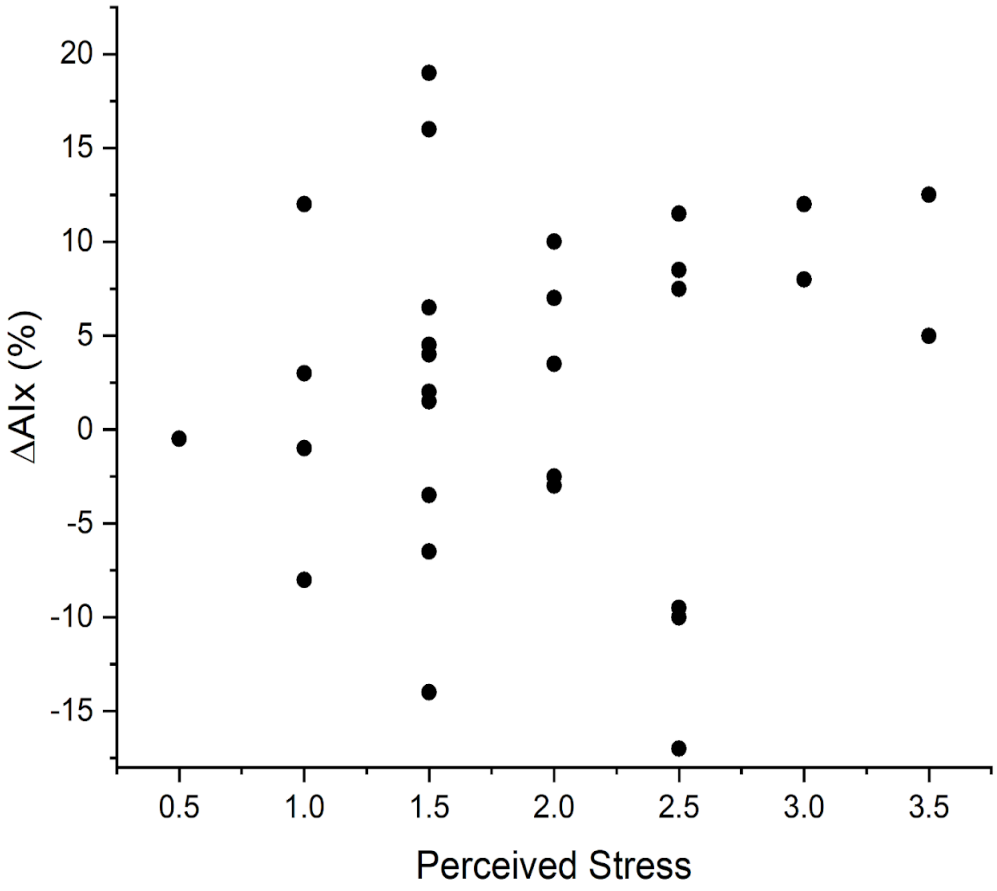


Figure 20. Shows no relationship between perceived stress and ΔAIx post MS.

Finally, there was a moderate correlation between ΔMAP & ΔAIx. Pearson correlation analysis between ΔMAP & ΔAIx showed a positive association with R=0.460, and p=0.024 (Figure 21). Linear regression analysis indicated that ΔMAP during mental stress was a significant predictor for post MS recovery ΔAIx with **β** = 0.47 and p=0.03.

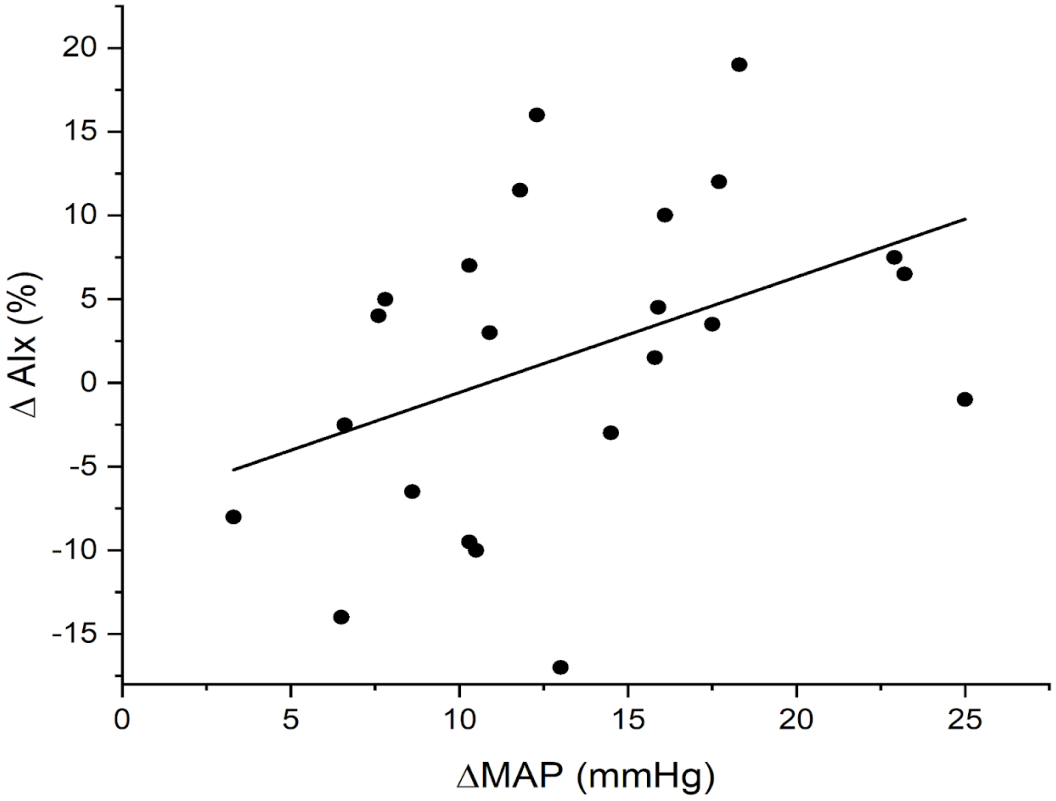


Figure 21. Shows relationship between ΔMAP during 5-minutes MS and ΔAIx post MS.

The regression model summary is shown as R= 0.603, R squared= 0.364, *F (3, 16)* =3.052, p= 0.059, and unstandardized coefficients by AIx= -13.212 + (0.647* ΔMAP) + (-0.394*ΔMSNA) + (3.762* Perceived Stress).

Table 4. Correlation coefficients and p-values (1- tailed).

Pearson Correlation	ΔAIx	ΔMAP	ΔMSNA	PS
ΔAIx	1	0.46(0.01)	-0.31(0.09)	0.07(0.35)
ΔMAP	0.46(0.01)	1	-0.09(0.35)	-0.14(0.24)
ΔMSNA	-0.31(0.09)	-0.09(0.35)	1	0.41(0.03)
PS	0.07(0.35)	-0.14(0.24)	0.41(0.03)	1

Δ = Delta or change, AIx = Augmentation Index, MSNA = Muscle Sympathetic Nerve Activity, MAP = Mean Arterial Pressure, PS = Perceived Stress

4.4 Discussion:

The results of the current study display three important findings. First, changes in aortic wave reflection (AIx) after mental stress are linked to MAP responses during MS. Second, no relationship was observed between change in MSNA and change in post MS AIx. Finally, the AIx response was not linked to the perceived stress response. We further discuss these primary findings below.

4.4.1 Sympathetic and cardiovascular responses to MS:

Mental stress (MS) using arithmetic task has been widely used as a measure for laboratory induced stress protocol (14, 20, 23, 179) with strong reproducibility. Fonkoue et al., 2015 (20) reported high test-retest reliability for MS in different variables including MSNA (ICC= 0.87), MAP (ICC= 0.74) and HR (ICC= 0.91) indicating high test-retest reliability.

MS is known to directly influence cardiovascular variables such as blood pressure, and heart rate, arterial compliance but also neural parameters such as sympathetic overactivity (14, 20, 22, 23, 27, 177, 179). Therefore, it is commonly used laboratory measure to better understand autonomic regulation in humans. However, it must be noted that sympathetic responses to MS are highly variable across individuals (21, 22). Compared with other laboratory induced stress protocols MS is advantageous in terms of its easy administration.

4.4.2 Aortic wave reflection and MS:

Even acute bouts of mental stress can cause negative changes in aortic wave reflection which could remain effectual even one hour after the mental stress task is completed. Vlachopoulos et. al, 2005, (27) was among the first to report this and showed negative effects of MS on aortic pressure waveforms in 19 young healthy individuals. They measured the effects of MS on AIx at 0, 5, 15, 30, 45 and 60 minutes after completing the task. The results indicate that the aortic wave reflection (AIx) was elevated during MS and peaked immediately at 0 minutes after MS ($p<0.05$). Kume et al., 2020 (28) also reported increased segmental arterial stiffness from heart to brachium, heart to ankle, and brachium to ankle following acute mental stress. Lydakis et al., 2008 (175) studied 15 subjects and found that aortic augmentation was increased after only 2 minutes of MS. All these studies indicate that MS can have a negative influence on AIx during and after the MS protocol. Our results indicate that the change in AIx post mental stress is attributed to the blood pressure response during mental stress. This unfavorable effect of mental stress might be

attributed to following mechanisms a) circulating catecholamines, b) endothelial dysfunction, and c) vascular inflammation.

4.4.3 MAP and MS:

Mental stress has an influence on cardiovascular reactivity measured by recording heart rate and beat-to-beat blood pressure. Heart rate and blood pressure is increased during MS measured using continuous recordings as reported earlier by Carter et al., 2005 (23) and Fonkoue et al., 2016 (179) .The results of the present study are consistent and indicate the negative influence of MS directly on the systems controlling the regulation of blood pressure and heart rate (21, 22, 179). Minakuchi, et.al., 2013 (110) also evaluated the effects of MS on autonomic functioning and blood pressure using finger plethysmography and confirmed MS has an influence on the sympathetic nervous and cardiovascular systems. The current study also evaluated the influence of MS on cardiovascular responses using beat-to-beat blood pressure values from finger plethysmography.

4.4.4 Blood pressure and AIx responses:

There is a bidirectional association between blood pressure and aortic stiffness. Increases in blood pressure can cause increased stiffening in the arteries and vice versa. Previously, it was confirmed that blood pressure affected central arterial stiffness measured using PWV (70, 71, 75, 76, 180). This was demonstrated in one of the longitudinal Framingham Heart study on aortic stiffness, central hemodynamics and blood pressure by Kaess, et al., 2012 (181). They also reported that higher blood pressure is linked increased augmentation index (AIx) but not central artery stiffness in their large sample. Another

study by Gedikli, et al., 2010 (75) also reported similar results in 85 subjects. They reported increased AIx@75 to be significantly correlated with prehypertension suggesting a relationship between blood pressure and aortic wave reflections. Evidence suggests that this relationship exists because changes in blood pressure weakens the vascular elastic properties due to inflammation and stress hormones leading to changes in aortic pressure wave form (27, 73, 75). Blood pressure increases can influence aortic waveform pulsatility which was also observed in the current study. MAP during mental stress was a significant predictor for changes in post MS AIx which helps to further link changes in AIx to changes in MAP during acute cognitive stress.

4.4.5 MSNA and AIx responses:

Overactive sympathetic nervous system firing can increase blood pressure, perfusion pressure, cardiac output, and cardiac hormones like epinephrine and norepinephrine (22, 23, 101). Mental stress shows some inconsistency in its influence on MSNA. Carter et al., 2005 (23) and Durocher et al., 2011 (21), reported that MSNA can have a variable response to MS. Mental stress can increase, decrease, or cause no change in MSNA (22). The current study showed that mental stress did not significantly increase MSNA. Carter et al., 2008 (24) compared the effects of mental stress, neutral pictures and negative pictures on MSNA responses and the results show that mental stress increased MSNA compared to negative pictures. The present study tested whether changes in MSNA during MS would increase post MS changes in AIx, however no relationship was observed between changes in MSNA and AIx. This warrants further investigation on the effects of MS on MSNA and post recovery AIx with a larger sample.

4.4.6 Perceived stress not linked to AIx:

An early study by Callister et al., 1992 (176) first defined the 0 to 4 scale for perceived stress and linked the sympathetic responses to mental stress using the perceived stress scale. However, later studies have not duplicated the link between perceived stress and MSNA responses to cognitive or emotional stress (24). One of the goals of the present study was to determine if the changes in AIx after mental stress were linked to perceived stress. However, our results did not show any connection between the levels of stress perceived during MS and the changes in AIx.

4.5 Study limitations:

One of the limitations of this study was it being underpowered. The power analysis indicated a sample size of 48 participants but due to COVID-19 restrictions and cancelation of on-campus laboratory testing, our data collection was halted and led to a smaller sample size. The small sample size may have limited our ability to detect relationships that may exist with a larger sample size.

4.6 Conclusion:

Our novel but preliminary results indicate that the increase in post MS AIx is attributed to the pressor response during MS. Previous researchers have speculated that the underlying mechanisms is related to increased HPA and sympathoadrenal medullary system to cause catecholamine circulation in the plasma, endothelial dysfunction and vascular inflammation leading to changes in blood pressure response and increased stiffening in the artery (27, 182, 183). However, no relationship was observed between

sympathetic activity or perceived stress and aortic wave reflection after mental stress in the present study.

4.7 Future directions:

This study did not compare differentiation between effects of MS on cardiovascular variables in different biological sexes or in different age groups. Most participants enrolled in this study were young males and the results indicated that MAP was a predictor for aortic augmentation index (AIx) after mental stress (MS). This could be observed as young men have higher prevalence of developing cardiovascular conditions than young women. Therefore, the results of this study cannot be generalized to women. Future studies could incorporate a larger sample to increase the power of the study and include a diverse group of participants. One area to direct these studies could include having an equal number of men and women in the study to explore the sex differentiation to mental stress and cardiovascular responses.

5 STUDY 3. Effects of MBSR and SME on Psychological Health With and Without COVID-19 Restrictions

5.1 Introduction:

The spread of the novel coronavirus named COVID-19 from the family of SARS-COV-2 originated from Wuhan in the Hubei province of China. In late December of 2019, the virus quickly spread through the country and within weeks the contagious virus crossed the international borders affecting millions (184-188). Since early 2020, there has been disruption of normal routines in the lives of people in the United States due to the restrictions with spread of novel coronavirus (189, 190). The spread of infection had increased in the United States, which forced governments to impose people across the country to follow stay-at-home orders. In March 2020, the first case of COVID-19 was reported in the state of Michigan and the governor declared the state of emergency forcing mandatory causing closures of businesses, universities, and government offices.

The mandatory state-at-home regulations which remained in action for the first time in early 2020 for approximately 4 months during the peak period of pandemic forced people to adjust to the new environment at their own homes and limited interaction with the outside world. This left people feeling anxious due to prolonged hours indoors, lack of social interaction, monetary losses due to unemployment, and the risk of getting infected by the virus (191-194). These many factors can contribute to increased anxiety, and long-term anxiety can affect the physiological and psychological well-being (159). While there were individuals who were directly infected by the virus, there was another group of people who suffered with mental health concerns pertaining to stay-at-home mandates leading to anxiety, stress, or depression.

Long term anxiety is linked to multiple cardiovascular risks such as elevated blood pressure, heart attacks and strokes (8). Since the beginning of the pandemic, there has been significant progress to address infection, and measures have been taken to reduce disease transmission. However, the mental health of the people impacted by the stay-at-home regulations due to the pandemic has not been fully addressed (191). While there were many researchers who studied the direct effects of COVID-19 infection on pathological states, there were few research studies which focused on understanding the potential influence of social isolation, and stay-at-home mandates during the COVID-19 lockdown on psychological health.

For example, Liu, 2020 (195) conducted a survey on people affected by COVID-19 and noted that ~44% of people were suffering from anxiety due to constantly being stressed and following the stay-at-home regulations (196). Benke, 2020 (197) reported higher incidence of anxiety in approximately 4335 younger individuals following stay-at-home orders in Germany. Similarly, Bigalke, 2020 and colleagues (187) also reported increased anxiety due to the uncertainties and new adjustments with the stay-at-home orders during the pandemic. Sex differences in self-reported anxiety was evaluated in 103 participants impacted by the COVID-19 stay-at-home regulations in the United States. Only 50% of males reported anxiety compared to 80% females during COVID-19 stay-at-home restrictions indicating the sex differences in anxiety during the pandemic.

Stress reducing techniques such as MBSR and SME have been commonly used to reduce the impact of anxiety in daily life (132, 140, 143, 159, 167). However, with COVID-19 restrictions, people were forced to follow stay-at-home mandates and the reported incidence of psychological health concerns drastically increased due to lack of social

engagement, isolation, and loneliness. Most studies incorporating mindfulness during COVID-19 for managing mental health has focused on online training and in person trainings separately and with limited control group comparison. One study on teachers used a combination of in-person and online 8-week mindfulness training for mental health concerns during peak COVID-19 lockdown in Italy. Mindfulness training improved anxiety, depression, empathy, and mental wellbeing in the study (185).

Mindfulness has been extensively researched for its efficacy in various psychological and physiological health concerns. Therefore, the primary aim of this study was to investigate the effects of MBSR and SME on state and trait anxiety before and during the COVID-19 pandemic restrictions. The secondary aim of the study was to determine the effect of MBSR and SME on the ability to decenter, both before and during COVID-19 restrictions. We hypothesized that participants enrolled in MBSR would reduce anxiety (state and trait) and improve decentering before and during COVID-19 restrictions.

5.2 Methods:

5.2.1 Participants:

The study participants were selected from Michigan Technological University and Houghton, Hancock, Baraga, Keweenaw communities from the Upper Peninsula of Michigan. The participants were selected from the age group of 18-45 years who had elevated blood pressure as described by the revised American Heart Association guidelines in 2018. Screening procedures included excluding anyone with pre-existing conditions such as hypertension, diabetes, or autonomic dysfunction. Individuals were also excluded if they took any cardiovascular medication. None of our study participants had been

medically diagnosed with any mental health condition. All our participants were non-smokers, and they abstained from caffeine, alcohol, and exercise for at least 12 hours and food for 3 hours before testing. Female participants could not be pregnant, and qualifying female participants provided information on their use of hormonal or birth control prescriptions and their typical menstrual cycle length.

This study had two groups. In the non-pandemic group (NPG), the participants completed the interventions and testing face to face before the beginning of COVID-19. The pandemic group (PG) participants did not have stay-at-home regulations for the pretesting and first 4-weeks of MBSR or SME and underwent in person testing and data collection. The last 4 weeks in PG were online sessions due to COVID-19 stay-at-home restrictions imposed by the state of Michigan, and cancellation of in-person meetings and closure of the Michigan Technological University campus in March 2020. None of our participants during the stay-at-home regulations were infected with COVID-19 while participating in the study. Table 5 reports baseline demographic details and questionnaire scores in the NPG and PG groups, and the MBSR and SME treatments.

The study design is a randomized control trial, and all participants were randomized into the intervention group of MBSR or active control group SME. A researcher explained all study procedures to each participant and their required availability to attend sessions for the interventions. The study was approved by the Institutional Review Board of Michigan Technological University. Testing and study procedures adhered to the Declaration of Helsinki. Signed informed consent was obtained from all the participants before any data collection.

5.2.2 Randomization:

The study participants from the NPG and PG groups were randomized into treatment of MBSR and SME (detailed explanation of participants in each group in Figure 22). The randomization was done by the primary investigator of the study allotting participants into treatment (MBSR and SME) via generating a random number on the web for the two treatments. The randomization followed the CONSORT guidelines (See Appendix 3 for the flow diagram). Due to the nature of the clinical trial and the interventions used it in the study, it was not possible to blind the participants of the treatment they were receiving during the study (either MBSR or SME).

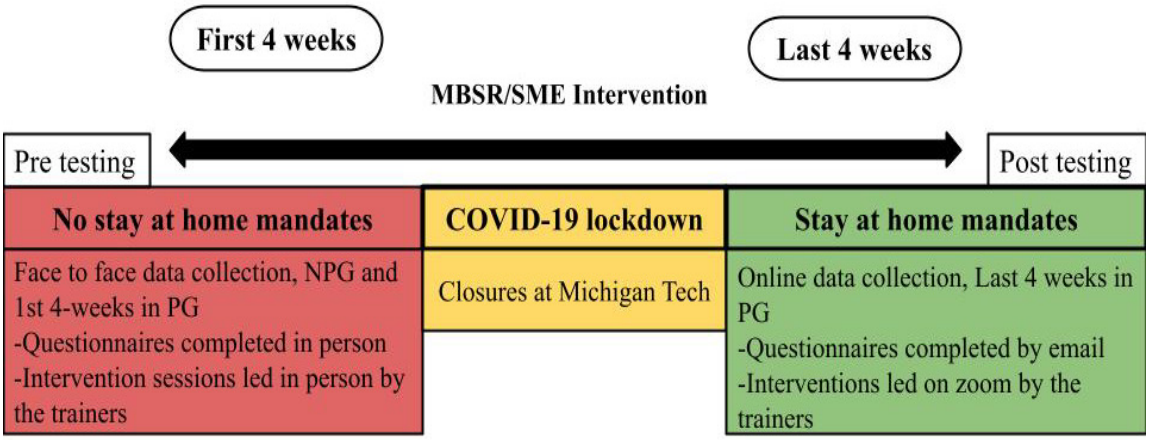


Figure 22. Visual representation of the study timelines based on the COVID-19 stay-at-home mandates in Michigan, and the data collection procedures.

5.2.3 Study instruments:

Before the interventions started, all participants completed the Experiences Questionnaire (EQ) on decentering (157) and the Spielberger state and trait anxiety inventory (STAI) for adults (36). Detailed description of the EQ can be found in section 2.1.2.2 and STAI in section 1.4.1.3.

5.2.4 Protocol:

The study used the structured 8-week MBSR (129, 134, 135, 143) intervention designed by Dr. Jon Kabat Zinn. SME was used as an active control. Detailed description of the sequence of the 8-weeks course is discussed in section 2.1.2. NPG had all face-to-face sessions and completed the protocol before the COVID-19 pandemic. The PG group had the first four weeks as face-to-face sessions and the last four weeks as online sessions using Zoom© video conferencing due to the stay-at-home mandates in Michigan. Detailed description of the study procedures during COVID-19 stay-at-home is shown in Figure 21. As the all-day retreat in PG happened during the closure of our campus, the participants completed the activities at their homes or places which were accessible for them with proper social distancing measures. All participants completed the STAI and decentering questionnaires before and after 8-weeks.

5.2.5 Study Design:

This study is a randomized control trial with an intervention/experimental group (MBSR) and an active control group (SME). Comparisons for effects of MBSR and SME before

and after 8-weeks were done as within subject design and between NPG and PG as between subject design.

5.2.6 Statistical analysis:

Independent t-tests were conducted to determine differences in the baseline demographics, state, and trait anxiety and decentering for group (NPG-PG) and treatment (MBSR-SME). The primary analysis incorporated a 2 × 2 × 2 (treatment × time × group) repeated measures mixed model Analysis of Variance (ANOVA) to compare the effects of MBSR and SME on state-trait anxiety and decentering from before to after the 8-week interventions. NPG and PG groups were entered as a between-subjects factor. Paired sample t-tests were used to compare pre and post values if the repeated measures ANOVA was significant for differences in MBSR and SME in NPG and/or PG. The data in the results are presented as means ± standard deviation. Significance level was set at $\alpha<0.05$ (2-tailed). Statistical analyses were completed using IBM SPSS version 26 (IBM® SPSS®, Armonk, NY). OriginPro® 2021b was used to generate graphs.

5.3 Results:

A total of 42 participants were initially enrolled for the study with 6 participants dropping out of the study due to personal reasons (detailed description given in CONSORT flow diagram in Appendix 3). Finally, 36 participants within the age group of 18-45 years (28 males, 6 females, and 1 non-binary) completed the study. Figure 23 shows the total number of participants in each group and the randomization procedure. Table 5 displays the mean and standard deviation for participants' age in years and body mass index in

kg/m^2, clinical seated blood pressure, anxiety and decentering for NPG and PG participants.

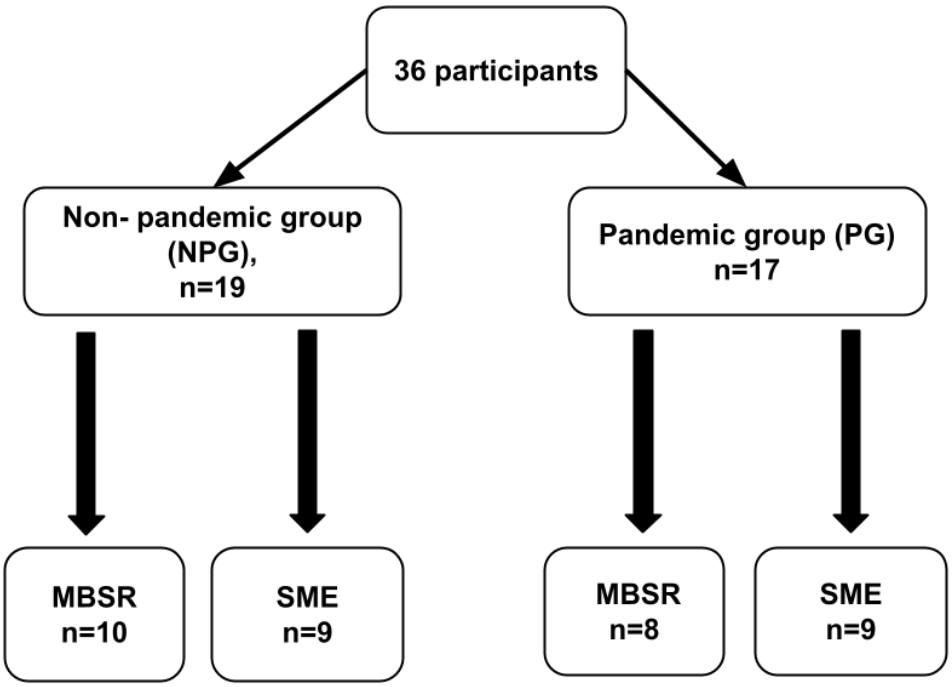


Figure 23. Randomization of participants into MBSR or SME.

Table 5. Baseline demographic details for the NPG and PG groups.

Values expressed as mean ± standard deviation.

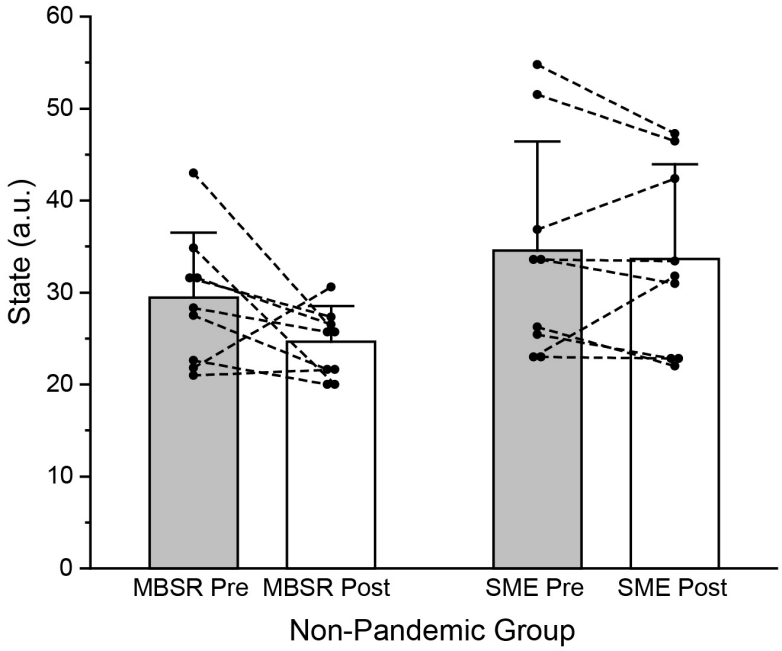
Group	**NPG (n=19)**			**PG (n=17)**		
Treatment	**MBSR**	**SME**	***p***	**MBSR**	**SME**	***p***
Age (years)	26.50±9.44	22.44±2.45	0.22	24.25±2.60	24.22±2.81	0.98
Height (cm)	175.08± 10.95	174.32±11.48	0.88	172.40±7.27	168.65±14.04	0.50
Weight (kg)	80.97±14.69	80.16±12.61	0.90	72.80±12.33	73.95±13.24	0.85
BMI (kg/m^2)	26.24±2.72	26.26±2.46	0.98	24.35±2.39	25.12±2.95	0.56
SAP (mmHg)	124.30±7.18	129.77±12.91	0.26	124.00±11.63	121.77±14.37	0.73
DAP (mmHg)	76.80±13.76	77.44±10.01	0.90	68.25±8.9	71.44±8.88	0.47
Heart Rate (bpm)	76.50±12.03	74.55±11.01	0.71	69.12±8.16	64.44±7.23	0.22
Decentering (a.u)	44.100±6.36	36.44±4.95	0.10	38.12±4.51	38.22±6.26	0.97
State Anxiety (a.u)	29.10±6.74	34.55±11.86	0.22	31.62±5.34	32.22±7.22	0.85
Trait Anxiety (a.u)	34.00±10.53	39.88±11.02	0.25	37.25±11.85	35.12±9.62	0.70

NPG = non-pandemic group, PG = pandemic group, MBSR = mindfulness-based stress reduction, SME = stress management education, BMI = body mass index, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, cm = centimeters, kg = kilograms.

5.3.1 Anxiety:

ANOVA results indicate there was no change in state anxiety during the pandemic when the participants engaged in MBSR or SME for 8-weeks as shown in Figure 24 (*F (1, 13)* = 0.1, *p*=0.2, $\eta_p^{2=}$0.1).

A.



B.

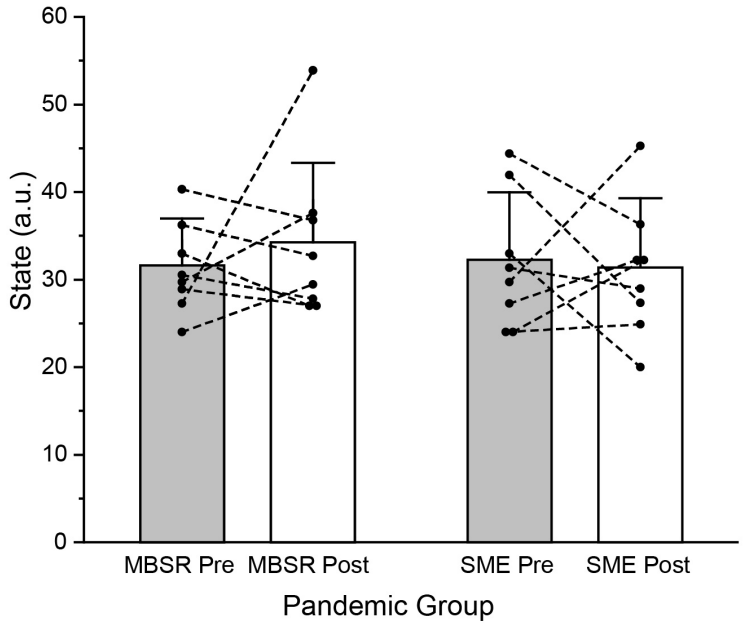
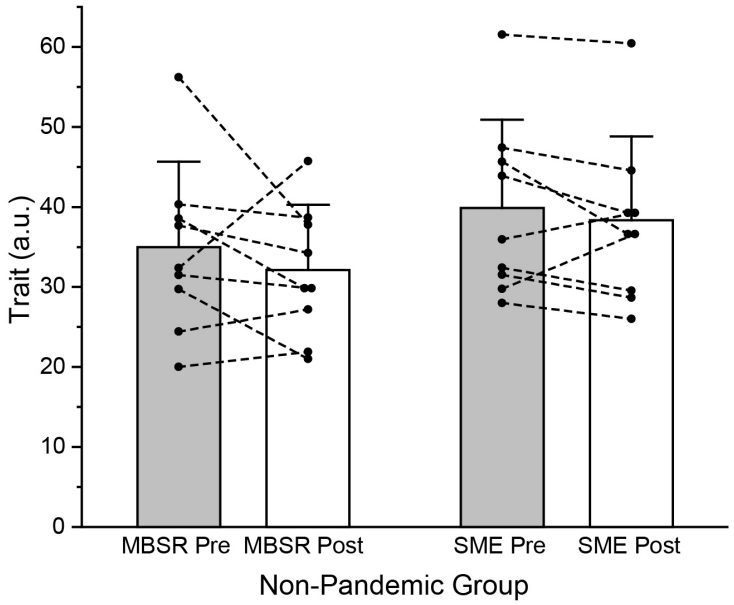


Figure 24. State anxiety scores before and after 8-weeks of MBSR and SME A) shows state anxiety scores in NPG participants after 8-weeks of MBSR/SME. B) shows state anxiety scores in PG participants after 8-weeks of MBSR/ SME. The bar graph shows the average scores for pre and post, whereas the line graph shows changes in the scores for individual participants.

Trait anxiety was decreased in both groups (NPG and PG) after 8-weeks of MBSR and SME (Figure 25), *F (1, 13)* =5.00, p <0.04, and η_p^2 = 0.2. Significant differences were found between MBSR and SME in NPG and PG (*F (1, 13)* =5.71, p<0.03 and $\eta_p^2$of 0.3). MBSR had decreased trait anxiety (NPG = -Δ5.2 ± 4.78 a.u, PG = -Δ6.3 ± 1 a.u, and 95% CI; 2.5-9.2) but no difference was found in SME (NPG = -Δ1.5 ± 0.8 a.u, PG = - Δ 1.3 ± 4 a.u, 95% CI; 2.6-4.4).

A.



B.

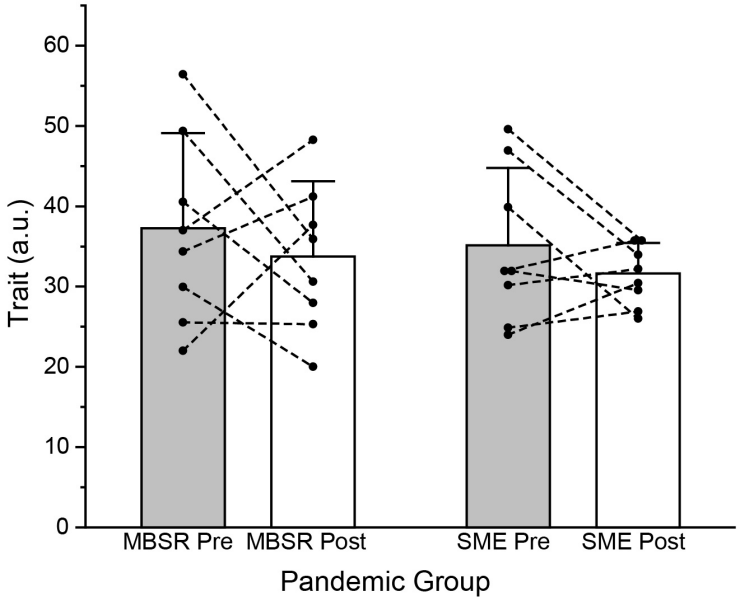
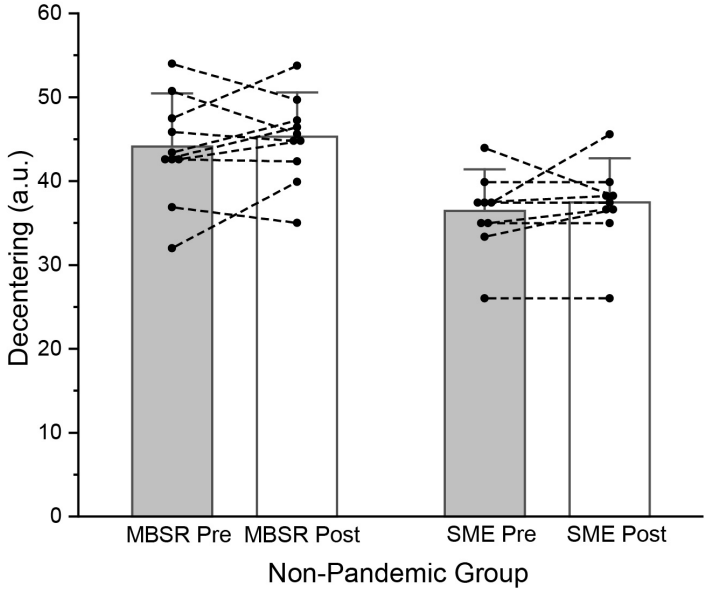


Figure 25. Trait anxiety scores from before to after 8- weeks of MBSR and SME. A) differences in trait anxiety scores in NPG after 8-weeks of MBSR/SME. B) differences in trait anxiety scores in PG after 8-weeks of MBSR/ SME. The bar graph shows the average scores for pre and post, whereas the line graph shows changes in the scores for individual participants.

5.3.2 Decentering:

Changes in decentering in PG can be seen in Figure 26. ANOVA results revealed that decentering improved after 8-weeks in PG (*F (1, 15)* = 24.14, $p<0.001$, η_p^2 =0.6). There was a significant difference ($p<0.03$ and of η_p^2 of 0.3) for treatment (MBSR-SME), treatment x group (NPG-PG) and time × group. MBSR (Δ3.4 ± 0.9 a. u, *t* (-4.8) and 95% CI; 1.7-5.2) and SME (Δ5.6 ±1.6 a.u., *t* (-3.8) and 95% CI; 2.1-9.1) had increased decentering after 8-weeks.

A.



B.

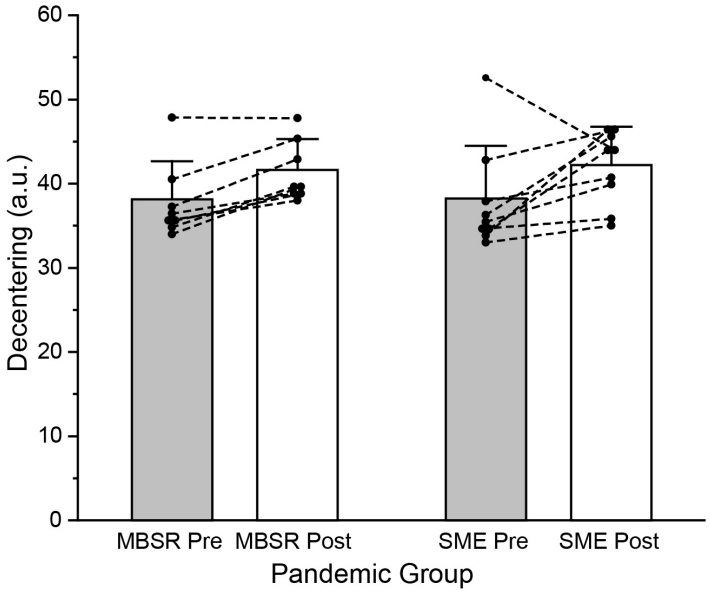


Figure 26. Decentering scores before and after 8-weeks of MBSR and SME. A) decentering scores in NPG after 8-weeks of MBSR/SME. B) differences in decentering scores in PG after 8-weeks of MBSR/SME. Increase in decentering score only in PG in both MBSR and SME groups after 8-weeks. The bar graph shows the average scores for pre and post, whereas the line graph shows changes in the scores for individual participants.

5.4 Discussion:

The present study offers three new findings regarding the effectiveness of MBSR and SME during a global health crisis. First, MBSR and SME which have been previously used as a method to reduce anxiety symptoms, reduced the level of trait anxiety during the pandemic. Second, the results also showed participants had an improved ability to decenter and observe their emotions from third person perspective when they were involved in MBSR or SME during the stay-at-home period in the spring of 2020. Third, there was no increase in state anxiety for participants actively engaged in MBSR and SME. These results are encouraging as individuals have reported the negative influence of COVID-19 pandemic on their psychological health and our study participants did not show negative influence of the pandemic when they were engaged in stress reducing techniques. MBSR which has been previously studied extensively for many psychological ailments also proved to be a helpful tool to managing negative mental health during the stay-at-home restrictions due to the pandemic. The 8-weeks MBSR and SME, both helped the study participants combat the issue of social isolation by engaging in the group sessions in face to face and online formats.

5.4.1 Trait anxiety:

The COVID-19 pandemic impacted lives in many ways which has been a challenge for the society. Initial studies from China, Italy, Hong Kong, United States, and other countries during restrictions suggested that the stress and anxiety levels were increased during the peak COVID-19 pandemic (178, 184, 185, 187, 191-193, 196, 198). Since the

outbreak of COVID-19, there has been advances in research focusing on the importance of stress reduction techniques such as mindfulness interventions and psychological wellbeing during the pandemic (184, 186, 193, 199). Many studies have utilized online mindfulness training to combat the negative health impacts (193, 195, 199). Some studies have also used online (186, 193, 200) and/or face to face method (184, 185) of delivering the 8-week MBSR course for management of anxiety and related mental health concerns during the COVID-19 pandemic. The current study was able to successfully complete the 8-week course using mix of face-to-face and online methods and proved advantageous in managing psychological health before and even during the COVID-19 pandemic.

Anxiety was observed to be highly prevalent during the COVID-19 stay-at-home regulation and lockdown due to the isolation and lack of social interaction (194, 197, 201-205). State anxiety is defined as how you feel currently and trait anxiety can be defined as the constant state of apprehension and worrying and is defined as how we feel generally in terms of being anxious (38, 143). Mind-body stress reducing interventions have been useful for reducing anxiety levels and particularly the structured 8-weeks MBSR has been beneficial in improving the symptoms of anxiety caused due to home isolation and the feeling of loneliness during the stay-at-home COVID-19 lockdown. In the current study, there was reduction in trait anxiety both before and during the pandemic when the participants engaged in stress reducing interventions of MBSR and SME. The results suggest MBSR training would be beneficial to help with COVID-19 pandemic and related stay at home regulations causing anxiety symptoms. This study specifically highlights that the individuals who participated in MBSR during the pandemic did not have higher anxiety levels caused because of lockdown and stay at home regulations.

Engaging in MBSR has been beneficial for psychological health before the emergence of pandemic, but it also proved beneficial during the uncertainties of the pandemic. A similar study (35) was previously conducted using the same intervention protocols as the current study, but the Beck Anxiety Inventory (BAI) was used to assess anxiety. The BAI is an anxiety scale focused on measuring the cognitive, somatic, and affective symptoms (143). They found significant reduction in BAI, and the MBSR group had a greater decrease than SME. The current study used STAI as an anxiety scale which measured two separate attributes namely state and trait which subjectively measures the state of feeling the anxiety symptoms (36).

An early study by Zhu, 2021 (193) conducted in China measured anxiety during peak COVID-19 and incorporated mindfulness as the intervention. They used mindfulness experience and self-practice as a method for comparison to pandemic related, anxiety, stress, distress, and depression. Distress can be defined as a psychological state where the stress makes it difficult to undergo tasks of everyday life and affects performance (13). The results of the study showed that individuals who were beginners in practicing mindfulness had better improvement in anxiety compared to individuals who were experienced (p<0.001). They also noted that younger individuals who were between ages 25-30 years had more anxiety during the pandemic compared to older individuals who were more than 60 years of age. The current study also had participants enrolled during the pandemic that were tested during the peak of stay-at-home restrictions in Michigan and all our participants were young adults. This study used the 8-week structured course over the method of self-

practice and experience suggesting the benefits of actively engaging in the MBSR group sessions can positively influence anxiety levels even during the times of global pandemic.

The mechanisms through which stress reducing interventions benefit psychological health can be debated. For example, Bergen-Cico & Cheon, 2014 (206) conducted a study to analyze the potential effects of mindfulness training on trait anxiety. They recruited 202 undergraduate and graduate students and they concluded that the reduction in trait anxiety was due to an increase in mindfulness skill. The current study did show trait anxiety was reduced in both groups (NPG and PG) with 8-weeks of MBSR. However, trait anxiety was not reduced from pre to post treatment in SME in the NPG, but was significantly reduced from pre to post treatment in SME in the PG. This may suggest how important weekly sessions were to participants during social isolation. A point to be noted with the results is that the baseline state and trait anxiety were not significantly different between the groups (NPG and PG) which could suggest that our study participants did not suffer from high anxiety at the beginning of the study and the improvements in anxiety scores were due to participation in treatments. To summarize, MBSR may be an effective tool to manage and prevent anxiety and it is also beneficial in unconventional times such as during the global health crisis of COVID-19 pandemic.

5.4.2 Decentering:

Decentering is a metacognitive ability which has multiple constructs and can be influenced by interventions such as mindfulness. Hoge, 2013 (35) conducted a RCT where they incorporated MBSR and SME protocols in individuals with general anxiety disorders. They conducted an analysis between decentering, MBSR and SME protocols. Hoge et al.,

2013 suggested that decentering and mindfulness is an ability which is developed through practice and helps with managing the symptoms of anxiety in everyday life (159). Mindfulness skill helps in honing the ability to decenter which cumulatively can help manage negative mental health concerns such as high anxiety levels. Kessel et al., 2016 (207) noted that decentering is an important concept when discussing treatment for psychological health, and its absence can cause development of mental health issues. Their study tested 55 individuals and measured the effects of decentering on psychological health.

The concept of decentering has been extensively studied of as metacognitive capacity which enables humans to become more aware of their anxiety symptoms and higher metacognitive monitoring ability can help manage their everyday tasks without being stressed or even developing chronic anxiety (137, 207). Higher decentering capabilities lets a person be more adaptive to the stress and manage it efficiently to avoid developing symptoms of anxiety and mindfulness assists with improving the decentering capabilities (156). The principles through which MBSR improves decentering is thought to be through awareness and acceptance which is essential for a person to identify when understanding the nature of their own emotions and feelings (156, 159, 208, 209). In the current study, the participants in NPG and PG had no difference in the baseline decentering score suggesting their decentering abilities were similar. The decentering was improved only in the PG and not in the NPG after 8-weeks of MBSR and SME. This difference suggests that the metacognitive capability of decentering is present in humans regardless of practicing mind-body interventions and as suggested by mindfulness and decentering research its effectiveness can be improved by continual practice (137, 156, 159, 208, 209)

5.5 Study limitations:

One of the limitations of this study is the small sample size. The study also did not control for what activities the participants were involved in apart from engaging in the study including exercising, diet modification or other mind-body interventions. There is also no direct evidence of whether the participants completed each of their home practice sessions.

5.6 Conclusion:

A pandemic like COVID-19 can negatively impact the mental health of people. This can be due to spending longer time in isolation, social distancing, quarantining, and closures of workplaces and schools. However, the results of this study demonstrated that if there is engagement in interventions such as MBSR or SME, the negative impacts can be reduced, specifically by reducing trait anxiety and improving the ability to decenter. These results indicate that adults who engage in stress reducing techniques such as MBSR or SME during COVID-19 restrictions report better psychological well-being. The results of this study are promising and suggest that MBSR and SME can benefit psychological health in everyday life, but also during the time of global health crisis.

5.7 Future directions:

Future studies may focus on exploring sex differences, middle and older age groups to compare the effects of no pandemic and pandemic with engagement in MBSR and SME. Future work could also include following up with the study participants a month or more

after the 8-week protocol of MBSR to explore the duration or carry over effects of the treatment.

6 Summary:

Stress and anxiety have become a common everyday phenomenon which can affect the productivity and performance of an individual. The effects are not just limited to psychological health but can also affect a person physiologically. This dissertation has aimed to answer questions pertaining to the relationships between anxiety, stress and progression of cardiovascular diseases (11, 210). Aim 1 expanded more on the effects of MBSR and SME on anxiety and decentering which have been previously validated. It also investigated if MBSR or SME could reduce arterial stiffness which has not been previously investigated. The results on arterial stiffness were non-significant, thus further research is needed. Aim 2 was to determine the relationship between MAP, MSNA and AIx post mental stress. This study concluded that MS related changes in AIx were blood pressure dependent. Finally, aim 3 investigated the effects of actively engaging in MBSR and SME during the COVID-19 health crisis and if it helped individuals with reducing anxiety and improving decentering. The results of these studies are valuable as anxiety and stress have become very common and therefore increase the chances for developing associated cardiovascular symptoms.

Non-pharmacological methods are becoming more and more popular in treatment of chronic diseases. These studies outline some ways which can be useful with minimal adverse effects if any in managing psychological and physical health. Stress-reducing techniques are beneficial as they are relatively low cost, can be easily administered and require minimal supervision if performed correctly. These methods also have benefits over other methods as they don't usually require specialized equipment or expertise. Some future directions from this dissertation include studying these variables with a larger

sample size. Future studies may also want to explore if the effects of these stress reduction interventions are different between men and women. Hormones interact in many ways and expanding more into this could provide insights into how different sexes react to engaging in MBSR and SME. These studies could also be replicated in middle aged and older individuals. CVDs are a common occurrence in older individuals and defining the mechanisms and non-pharmacological ways to treat them could be helpful in managing symptoms.

The scope of this dissertation could be expanded by conducting studies on MBSR and SME as a crossover design. The participants in these studies were randomized only into one group and the crossover studies could shed some light on how the participants interacted when they engaged in both MBSR, and SME interventions compared with only one. Other studies should also include follow up and longitudinal studies where the participants have practiced mindfulness for a longer duration. Expanding into these studies for their responses to MBSR can provide an insight into its efficiency in broader populations.

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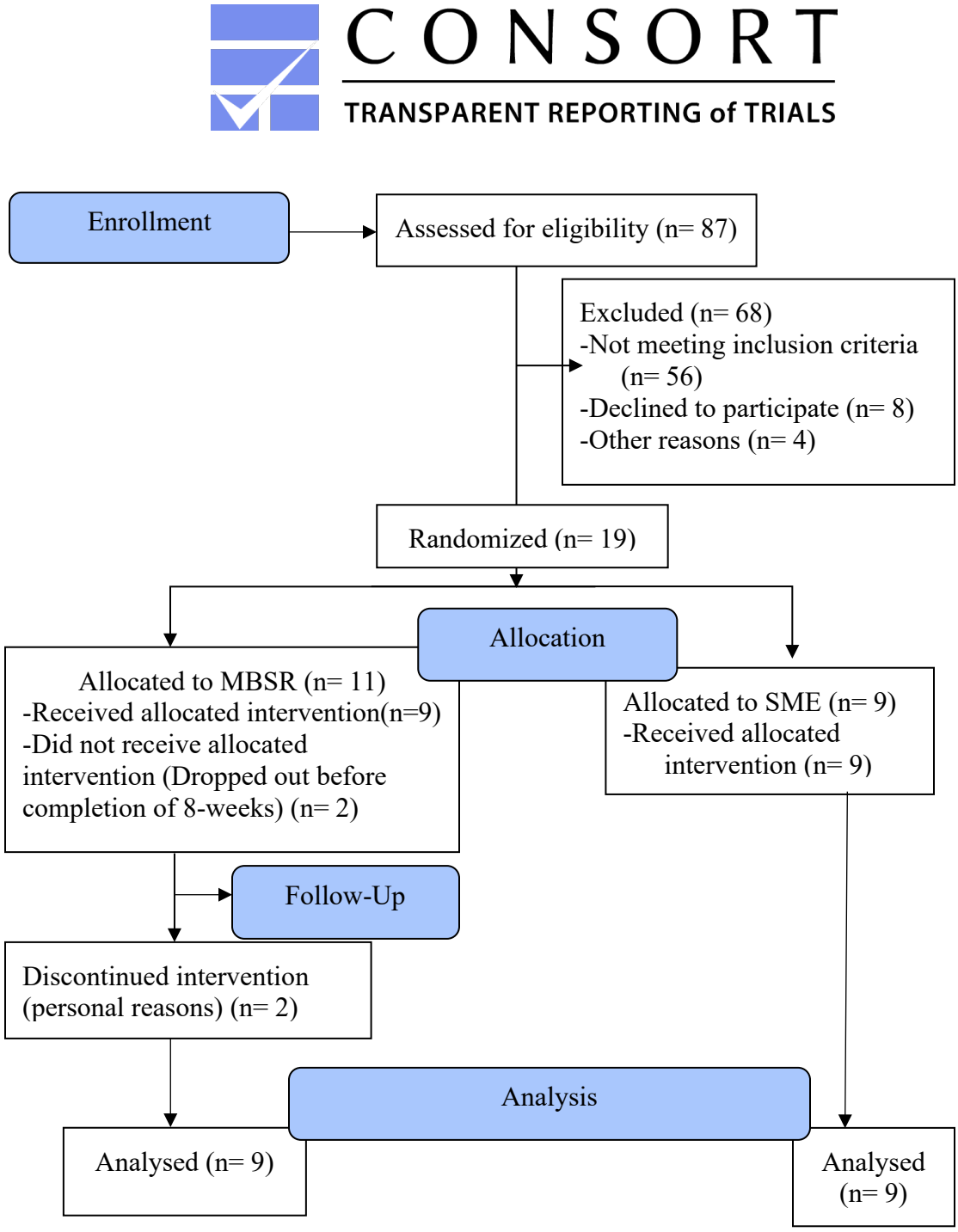
A Appendix:

A.1 STUDY 1:

A.1.1 CONSORT Flow Diagram with description of participants:



A.1.2 Raw data for carotid- femoral Pulse Wave Analysis:

Group	Pre cfPWV	Post cfPWV
MBSR	5.95	6.3
SME	5.3	4.8
MBSR	7.5	6.7
MBSR	6.45	5.85
SME	5.1	4.75
MBSR	4.8	5.45
MBSR	4.55	4.7
MBSR	4.8	5.5
SME	5.3	5.15
SME	5.95	4.9
SME	5.2	5.25
SME	6.4	5.4
SME	5.4	6.15
MBSR	7.1	5.95
SME	4.55	4.8
MBSR	5.55	5.7
SME	6.95	6.55
MBSR	5.4	5.85

A.1.3 Descriptive Statistics for cfPWV:

Descriptive Statistics

	Group	Mean	Std. Deviation	N
PrecfPWV	MBSR	5.4278	.94045	9
	SME	5.5667	.73101	9
	Total	5.4972	.82024	18
PostcfPWV	MBSR	5.4778	.70848	9
	SME	5.3056	.64053	9
	Total	5.3917	.66116	18

A.1.4 ANOVA for cfPWV:

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Time	Pillai's Trace	.035	.576[b]	1.000	16.000	.459
	Wilks' Lambda	.965	.576[b]	1.000	16.000	.459
	Hotelling's Trace	.036	.576[b]	1.000	16.000	.459
	Roy's Largest Root	.036	.576[b]	1.000	16.000	.459
Time * Group	Pillai's Trace	.072	1.250[b]	1.000	16.000	.280
	Wilks' Lambda	.928	1.250[b]	1.000	16.000	.280
	Hotelling's Trace	.078	1.250[b]	1.000	16.000	.280
	Roy's Largest Root	.078	1.250[b]	1.000	16.000	.280

Multivariate Tests[a]

Effect		Partial Eta Squared
Time	Pillai's Trace	.035
	Wilks' Lambda	.035
	Hotelling's Trace	.035
	Roy's Largest Root	.035
Time * Group	Pillai's Trace	.072
	Wilks' Lambda	.072
	Hotelling's Trace	.072
	Roy's Largest Root	.072

a. Design: Intercept + Group
Within Subjects Design: Time

b. Exact statistic

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
Time	1.000	.000	0	.	1.000

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Epsilon[b] Huynh-Feldt	Lower-bound
Time	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + Group
Within Subjects Design: Time

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Sphericity Assumed	.100	1	.100	.576	.459
	Greenhouse-Geisser	.100	1.000	.100	.576	.459
	Huynh-Feldt	.100	1.000	.100	.576	.459
	Lower-bound	.100	1.000	.100	.576	.459
Time * Group	Sphericity Assumed	.218	1	.218	1.250	.280
	Greenhouse-Geisser	.218	1.000	.218	1.250	.280
	Huynh-Feldt	.218	1.000	.218	1.250	.280
	Lower-bound	.218	1.000	.218	1.250	.280
Error(Time)	Sphericity Assumed	2.787	16	.174		
	Greenhouse-Geisser	2.787	16.000	.174		
	Huynh-Feldt	2.787	16.000	.174		
	Lower-bound	2.787	16.000	.174		

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Partial Eta Squared
Time	Sphericity Assumed	.035
	Greenhouse-Geisser	.035
	Huynh-Feldt	.035
	Lower-bound	.035
Time * Group	Sphericity Assumed	.072
	Greenhouse-Geisser	.072
	Huynh-Feldt	.072
	Lower-bound	.072
Error(Time)	Sphericity Assumed	
	Greenhouse-Geisser	
	Huynh-Feldt	
	Lower-bound	

A.1.5 Raw data for state anxiety inventory for adults

Group	Pre State	Post State
MBSR	26	.
SME	27	22
MBSR	28	22
MBSR	32	28
SME	34	34
MBSR	23	20
MBSR	35	20
MBSR	29	26
SME	37	43
SME	26	23
SME	55	48
SME	23	32
SME	23	23
MBSR	43	.
SME	52	47
MBSR	21	22
SME	34	31
MBSR	32	27

A.1.6 Descriptive Statistics for state anxiety:

Descriptive Statistics

	Intervention	Mean	Std. Deviation	N
PreState	MBSR	28.6667	5.53775	6
	SME	34.5556	11.86498	9
	Total	32.2000	10.01570	15
PostState	MBSR	23.8333	3.60093	6
	SME	33.6667	10.27132	9
	Total	29.7333	9.47528	15

A.1.7 ANOVA for State Anxiety:

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.
Time	Pillai's Trace	.241	4.122[b]	1.000	13.000	.063
	Wilks' Lambda	.759	4.122[b]	1.000	13.000	.063
	Hotelling's Trace	.317	4.122[b]	1.000	13.000	.063
	Roy's Largest Root	.317	4.122[b]	1.000	13.000	.063
Time * Intervention	Pillai's Trace	.131	1.959[b]	1.000	13.000	.185
	Wilks' Lambda	.869	1.959[b]	1.000	13.000	.185
	Hotelling's Trace	.151	1.959[b]	1.000	13.000	.185
	Roy's Largest Root	.151	1.959[b]	1.000	13.000	.185

Multivariate Tests[a]

Effect		Partial Eta Squared
Time	Pillai's Trace	.241
	Wilks' Lambda	.241
	Hotelling's Trace	.241
	Roy's Largest Root	.241
Time * Intervention	Pillai's Trace	.131
	Wilks' Lambda	.131
	Hotelling's Trace	.131
	Roy's Largest Root	.131

a. Design: Intercept + Intervention
Within Subjects Design: Time

b. Exact statistic

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
Time	1.000	.000	0	.	1.000

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Epsilon[b] Huynh-Feldt	Lower-bound
Time	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + Intervention
Within Subjects Design: Time

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F
Time	Sphericity Assumed	58.939	1	58.939	4.122
	Greenhouse-Geisser	58.939	1.000	58.939	4.122
	Huynh-Feldt	58.939	1.000	58.939	4.122
	Lower-bound	58.939	1.000	58.939	4.122
Time * Intervention	Sphericity Assumed	28.006	1	28.006	1.959
	Greenhouse-Geisser	28.006	1.000	28.006	1.959
	Huynh-Feldt	28.006	1.000	28.006	1.959
	Lower-bound	28.006	1.000	28.006	1.959
Error(Time)	Sphericity Assumed	185.861	13	14.297	
	Greenhouse-Geisser	185.861	13.000	14.297	
	Huynh-Feldt	185.861	13.000	14.297	
	Lower-bound	185.861	13.000	14.297	

A.2 STUDY 2:

A.2.1 Raw data for correlational and regression analysis:

Delta MSNA	Delta AIx	Delta MAP	Delta HR	Perceived stress
13	6.5	23.2	10	1.5
14.4	7.5	22.9	6.2	2.5
.	-3.5	.	.	1.5
.	12.5	.	.	3.5
-0.2	-3	14.5	10.1	2
4.6	.	6	13.9	2.5
-2.8	8.5	.	.	2.5
-1.8	-8	3.3	2.2	1
-7.4	19	18.3	37.8	1.5
.	-0.5	.	.	0.5
.	-2.5	6.6	8	2
2.8	11.5	11.8	20	2.5
.	5	7.8	9.9	3.5
-5	1.5	15.8	25.9	1.5
11.8	-17	13	29.9	2.5
.	8	.	.	3
4.6	12	.	20.1	3
2.8	-6.5	8.6	12.2	1.5
.	-14	6.5	14	1.5
-10.8	10	16.1	13.8	2
14.4	-9.5	10.3	5.6	2.5
19.6	4.5	15.9	10	1.5
-9	-1	25	23.3	1
1.4	3	10.9	17.2	1
.	11.5	.	.	.
.	2	.	.	1.5
-1	7	10.3	30.4	2
1.6	-10	10.5	7	2.5
-13	12	17.7	7.1	1
-6.8	3.5	17.5	15.5	2
2.8	16	12.3	9	1.5
-2	4	7.6	6.5	1.5

A.2.2 Descriptive statistics for Aim 2:

Descriptive Statistics

	Mean	Std. Deviation	N
Delta_AIx	2.0741	9.07204	27
Delta_MAP	13.5833	6.58580	24
Delta_MSNA	1.3800	9.17087	20
Perceived_Stress	1.8704	.75438	27

A.2.3 Correlation analysis:

Correlations

		Delta_AIx	Delta_MAP	Delta_MSNA	Perceived_Stress
Pearson Correlation	Delta_AIx	1.000	.460	-.311	.077
	Delta_MAP	.460	1.000	-.091	-.149
	Delta_MSNA	-.311	-.091	1.000	.416
	Perceived_Stress	.077	-.149	.416	1.000
Sig. (1-tailed)	Delta_AIx	.	.012	.091	.351
	Delta_MAP	.012	.	.351	.244
	Delta_MSNA	.091	.351	.	.034
	Perceived_Stress	.351	.244	.034	.
N	Delta_AIx	27	24	20	27
	Delta_MAP	24	24	20	24
	Delta_MSNA	20	20	20	20
	Perceived_Stress	27	24	20	27

A.2.4 Regression Analysis:

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	Perceived_Stress, Delta_MAP, Delta_MSNA[b]	.	Enter

a. Dependent Variable: Delta_AIx

b. All requested variables entered.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.603[a]	.364	.245	7.88415

a. Predictors: (Constant), Perceived_Stress, Delta_MAP, Delta_MSNA

b. Dependent Variable: Delta_AIx

ANOVA[a]

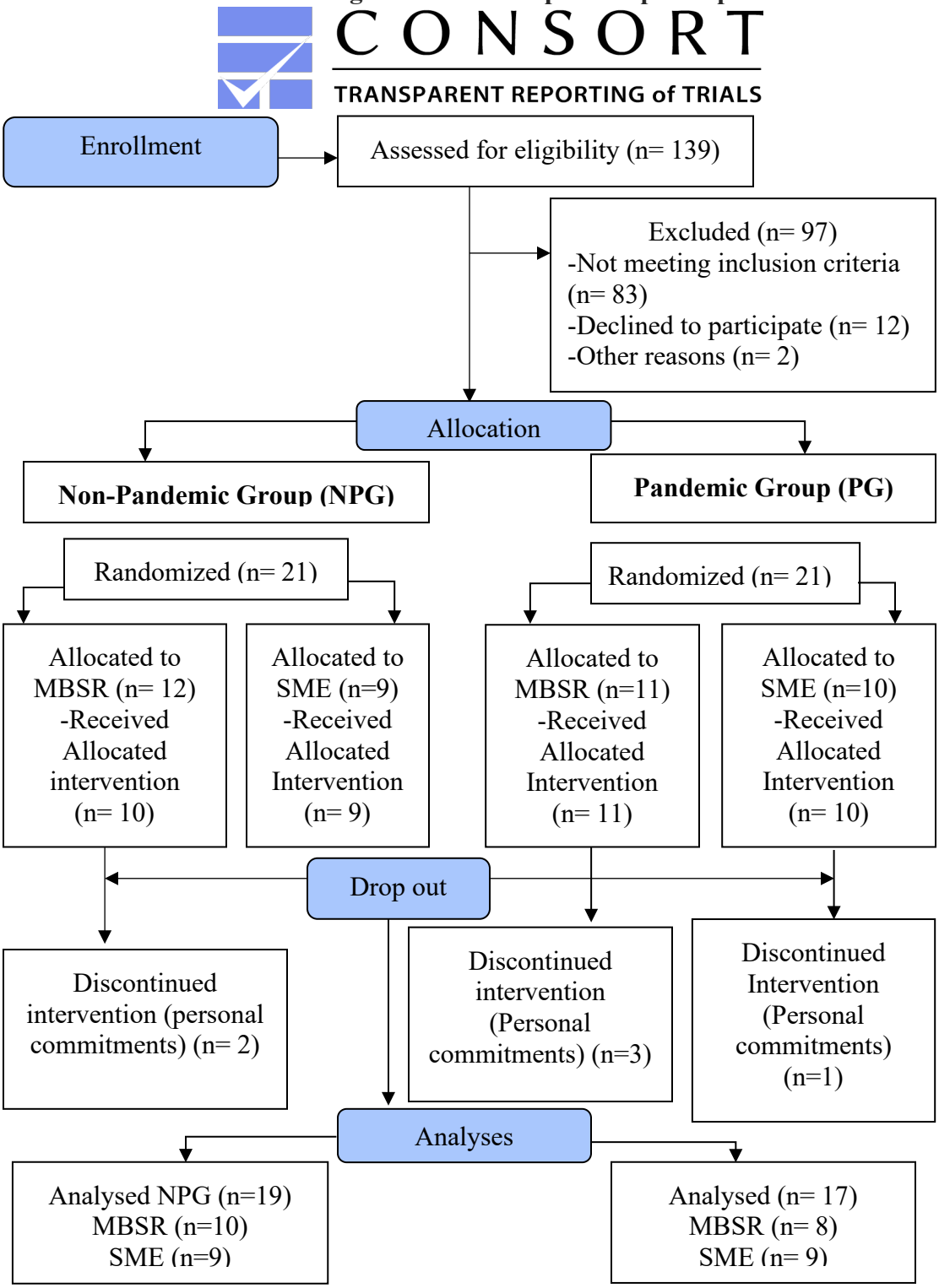
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	569.180	3	189.727	3.052	.059[b]
	Residual	994.558	16	62.160		
	Total	1563.738	19			

a. Dependent Variable: Delta_AIx

b. Predictors: (Constant), Perceived_Stress, Delta_MAP, Delta_MSNA

A.3 STUDY 3:

A.3.1 CONSORT Flow Diagram with description of participants:



A.3.2 Raw data for the demographic details for MBSR/SME and NPG/PG:

Intervention	Group	Height	Weight	BMI	Age	SAP	DAP	MAP	HR
MBSR	NPG	167.6	81.6	29.0	45	122	75	90.7	48
MBSR	NPG	180	85.7	26.5	22	135	76	95.7	85
MBSR	NPG	182.9	92.1	27.5	20	125	68	87	80
MBSR	NPG	165.1	57.6	21.1	19	126	81	96	82
MBSR	NPG	185.4	101.2	29.4	22	125	69	87.7	69
MBSR	NPG	170.6	68.4	23.5	23	115	56	75.7	86
MBSR	NPG	158	69.3	27.8	19	130	101	110.7	91
MBSR	NPG	176	71.9	23.2	29	121	76	91.0	73
MBSR	NPG	195	102.5	27.0	24	112	68	82.7	77
MBSR	NPG	170.2	79.4	27.4	42	132	98	109.3	74
SME	NPG	180	94.3	29.1	25	130	78	95.3	65
SME	NPG	180.3	84.8	26.1	21	117	73	87.7	67
SME	NPG	190.5	86.2	23.7	23	150	91	110.7	78
SME	NPG	170	85.3	29.5	27	125	79	94.3	67
SME	NPG	171	71.2	24.3	21	123	62	82.3	71
SME	NPG	159	57.6	22.8	21	119	74	89.0	84
SME	NPG	179.8	80.7	25.0	24	125	83	97.0	84
SME	NPG	155.4	66.6	27.6	20	126	66	86.0	61
SME	NPG	182.88	94.8	28.3	20	153	91	111.7	94
MBSR	PG	175	73.5	24.0	26	145	79	101.0	79
MBSR	PG	175.3	79.8	26.0	22	127	56	79.7	65
MBSR	PG	171	78	26.7	21	118	56	76.7	65
MBSR	PG	186	97	28.0	27	129	70	89.7	67
MBSR	PG	167	67.6	24.2	22	123	69	87.0	64
MBSR	PG	167.6	59.42	21.2	25	112	70	84.0	78
MBSR	PG	175.3	67.1	21.8	28	108	66	80.0	57
MBSR	PG	162	60	22.9	23	130	80	96.7	78
SME	PG	157	58	23.5	26	111	64	79.7	57
SME	PG	175.3	80.7	26.3	26	134	80	98.0	66
SME	PG	155	70	29.1	23	115	86	95.7	71
SME	PG	189	104	29.1	21	139	73	95.0	51
SME	PG	159	67	26.5	23	146	74	98.0	70

SME	PG	177	70	22.3	28	114	72	86.0	61
SME	PG	148	69.4	23.4	28	105	71	82.3	62
SME	PG	177.8	80.3	25.4	21	111	55	73.7	72
SME	PG				22	121	68	85.7	70

A.3.3 Raw Data from Experience Questionnaire (Decentering):

Group	Cond	Pre Decentering	Post Decentering
NPG	MBSR	46	45
NPG	SME	38	39
NPG	MBSR	32	40
NPG	MBSR	43	47
NPG	SME	38	38
NPG	MBSR	48	54
NPG	MBSR	44	48
NPG	MBSR	43	43
NPG	SME	35	35
NPG	SME	40	40
NPG	SME	26	26
NPG	SME	35	37
NPG	MBSR	43	45
NPG	SME	38	46
NPG	MBSR	37	35
NPG	SME	34	37
NPG	MBSR	54	50
NPG	SME	44	39
NPG	MBSR	51	46
PG	SME	38	41
PG	SME	33	35
PG	MBSR	41	46
PG	MBSR	35	40
PG	MBSR	36	38
PG	MBSR	37	39
PG	SME	35	36
PG	SME	34	47
PG	MBSR	38	43
PG	MBSR	48	48
PG	SME	35	44

PG	SME	43	47
PG	MBSR	34	40
PG	SME	36	40
PG	MBSR	36	39
PG	SME	37	46
PG	SME	53	44

A.3.4 Descriptive statistics for Decentering:

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
MBSR_Pre_Dec	NPG	43.3333	6.24500	9
	PG	38.1250	4.51782	8
	Total	40.8824	5.96744	17
MBSR_Post_Dec	NPG	45.2222	5.56277	9
	PG	41.6250	3.66206	8
	Total	43.5294	4.97641	17
SME_Pre_Dec	NPG	36.4444	4.95255	9
	PG	36.3750	3.11391	8
	Total	36.4118	4.06292	17
SME_Post_Dec	NPG	37.4444	5.27046	9
	PG	42.0000	4.78091	8
	Total	39.5882	5.42055	17

A.3.5 ANOVA for Decentering:

Multivariate Tests[a]

Effect		Sig.	Partial Eta Squared	Noncent. Parameter
treatment	Pillai's Trace	.007	.397	9.885
	Wilks' Lambda	.007	.397	9.885
	Hotelling's Trace	.007	.397	9.885
	Roy's Largest Root	.007	.397	9.885
treatment * Condition	Pillai's Trace	.020	.311	6.786
	Wilks' Lambda	.020	.311	6.786
	Hotelling's Trace	.020	.311	6.786
	Roy's Largest Root	.020	.311	6.786
time	Pillai's Trace	.000	.617	24.145
	Wilks' Lambda	.000	.617	24.145
	Hotelling's Trace	.000	.617	24.145
	Roy's Largest Root	.000	.617	24.145
time * Condition	Pillai's Trace	.022	.303	6.506
	Wilks' Lambda	.022	.303	6.506
	Hotelling's Trace	.022	.303	6.506
	Roy's Largest Root	.022	.303	6.506
treatment * time	Pillai's Trace	.614	.017	.265
	Wilks' Lambda	.614	.017	.265
	Hotelling's Trace	.614	.017	.265
	Roy's Largest Root	.614	.017	.265
treatment * time * Condition	Pillai's Trace	.228	.095	1.578
	Wilks' Lambda	.228	.095	1.578
	Hotelling's Trace	.228	.095	1.578
	Roy's Largest Root	.228	.095	1.578

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
treatment	1.000	.000	0	.	1.000
time	1.000	.000	0	.	1.000
treatment * time	1.000	.000	0	.	1.000

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Epsilon[b] Huynh-Feldt	Lower-bound
treatment	1.000	1.000
time	1.000	1.000
treatment * time	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + Condition
Within Subjects Design: treatment + time + treatment * time

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F
treatment	Sphericity Assumed	272.472	1	272.472	9.885
	Greenhouse-Geisser	272.472	1.000	272.472	9.885
	Huynh-Feldt	272.472	1.000	272.472	9.885
	Lower-bound	272.472	1.000	272.472	9.885
treatment * Condition	Sphericity Assumed	187.061	1	187.061	6.786
	Greenhouse-Geisser	187.061	1.000	187.061	6.786
	Huynh-Feldt	187.061	1.000	187.061	6.786
	Lower-bound	187.061	1.000	187.061	6.786
Error(treatment)	Sphericity Assumed	413.469	15	27.565	
	Greenhouse-Geisser	413.469	15.000	27.565	
	Huynh-Feldt	413.469	15.000	27.565	
	Lower-bound	413.469	15.000	27.565	
time	Sphericity Assumed	152.824	1	152.824	24.145
	Greenhouse-Geisser	152.824	1.000	152.824	24.145
	Huynh-Feldt	152.824	1.000	152.824	24.145
	Lower-bound	152.824	1.000	152.824	24.145
time * Condition	Sphericity Assumed	41.177	1	41.177	6.506
	Greenhouse-Geisser	41.177	1.000	41.177	6.506
	Huynh-Feldt	41.177	1.000	41.177	6.506
	Lower-bound	41.177	1.000	41.177	6.506
Error(time)	Sphericity Assumed	94.941	15	6.329	
	Greenhouse-Geisser	94.941	15.000	6.329	
	Huynh-Feldt	94.941	15.000	6.329	
	Lower-bound	94.941	15.000	6.329	
treatment * time	Sphericity Assumed	1.618	1	1.618	.265
	Greenhouse-Geisser	1.618	1.000	1.618	.265
	Huynh-Feldt	1.618	1.000	1.618	.265
	Lower-bound	1.618	1.000	1.618	.265
treatment * time * Condition	Sphericity Assumed	9.618	1	9.618	1.578
	Greenhouse-Geisser	9.618	1.000	9.618	1.578
	Huynh-Feldt	9.618	1.000	9.618	1.578
	Lower-bound	9.618	1.000	9.618	1.578
Error(treatment*time)	Sphericity Assumed	91.441	15	6.096	
	Greenhouse-Geisser	91.441	15.000	6.096	

A.3.6 Paired T-test for Decentering:

T-Test - Decentering in PG

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	MBSR_Pre_Dec	38.1250	8	4.51782	1.59729
	MBSR_Post_Dec	41.6250	8	3.66206	1.29474
Pair 2	SME_Pre_Dec	36.3750	8	3.11391	1.10093
	SME_Post_Dec	42.0000	8	4.78091	1.69031

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	MBSR_Pre_Dec & MBSR_Post_Dec	8	.893	.003
Pair 2	SME_Pre_Dec & SME_Post_Dec	8	.499	.208

Paired Samples Test

		Paired Differences			
					95% Confidence ...
		Mean	Std. Deviation	Std. Error Mean	Lower
Pair 1	MBSR_Pre_Dec - MBSR_Post_Dec	-3.50000	2.07020	.73193	-5.23073
Pair 2	SME_Pre_Dec - SME_Post_Dec	-5.62500	4.20671	1.48730	-9.14190

Paired Samples Test

		Paired ...			
		95% Confidence Interval of the ...			
		Upper	t	df	Sig. (2-tailed)
Pair 1	MBSR_Pre_Dec - MBSR_Post_Dec	-1.76927	-4.782	7	.002
Pair 2	SME_Pre_Dec - SME_Post_Dec	-2.10810	-3.782	7	.007

A.3.7 Raw data for State and Trait Anxiety Inventory for Adults:

Group	Cond	Pre State	Post State	Pre Trait	Post Trait
NPG	SME	27	22	28	26
NPG	MBSR	28	22	39	30
NPG	MBSR	32	28	25	28
NPG	SME	34	34	48	45
NPG	MBSR	23	20	30	21
NPG	MBSR	35	20	57	38
NPG	MBSR	29	26	32	30
NPG	SME	37	43	46	37
NPG	SME	26	23	33	30
NPG	SME	55	48	62	61
NPG	SME	23	32	30	37
NPG	MBSR	22	31	38	35
NPG	SME	23	23	32	29
NPG	MBSR	43	26	41	39
NPG	SME	52	47	44	40
NPG	MBSR	21	22	20	22
NPG	SME	34	31`	36	40
NPG	MBSR	32	27	33	46
PG	SME	42	28	47	34
PG	MBSR	24	30	22	38
PG	MBSR	33	27	30	20
PG	MBSR	41	37	35	42
PG	MBSR	29	27	26	26
PG	SME	28	33	32	36
PG	SME	24	25	25	27
PG	MBSR	28	54	37	49
PG	MBSR	37	33	41	28
PG	SME	33	20	32	30
PG	SME	32	29	40	26
PG	MBSR	30	38	50	31
PG	SME	30	46	31	33

PG	MBSR	31	28	57	36
PG	SME	24	33	50	36
PG	SME	45	37	24	31

A.3.8 Descriptive statistics for trait anxiety:

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
MBSR_Pre_Trait	NPG	35.6250	11.51319	8
	PG	39.4286	10.93705	7
	Total	37.4000	11.01817	15
MBSR_Post_Trait	NPG	30.3750	6.73875	8
	PG	33.1429	9.94030	7
	Total	31.6667	8.19117	15
SME_Pre_Trait	NPG	41.3750	10.78276	8
	PG	33.0000	8.12404	7
	Total	37.4667	10.25299	15
SME_Post_Trait	NPG	39.8750	10.03476	8
	PG	31.7143	4.11154	7
	Total	36.0667	8.68057	15

A.3.9 ANOVA for trait anxiety:

Multivariate Tests[a]

Effect		Sig.	Partial Eta Squared	Noncent. Parameter
treatment	Pillai's Trace	.458	.043	.584
	Wilks' Lambda	.458	.043	.584
	Hotelling's Trace	.458	.043	.584
	Roy's Largest Root	.458	.043	.584
treatment * Condition	Pillai's Trace	.033	.305	5.710
	Wilks' Lambda	.033	.305	5.710
	Hotelling's Trace	.033	.305	5.710
	Roy's Largest Root	.033	.305	5.710
time	Pillai's Trace	.043	.278	5.004
	Wilks' Lambda	.043	.278	5.004
	Hotelling's Trace	.043	.278	5.004
	Roy's Largest Root	.043	.278	5.004
time * Condition	Pillai's Trace	.900	.001	.016
	Wilks' Lambda	.900	.001	.016
	Hotelling's Trace	.900	.001	.016
	Roy's Largest Root	.900	.001	.016
treatment * time	Pillai's Trace	.206	.120	1.770
	Wilks' Lambda	.206	.120	1.770
	Hotelling's Trace	.206	.120	1.770
	Roy's Largest Root	.206	.120	1.770
treatment * time * Condition	Pillai's Trace	.852	.003	.036
	Wilks' Lambda	.852	.003	.036
	Hotelling's Trace	.852	.003	.036
	Roy's Largest Root	.852	.003	.036

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
treatment	1.000	.000	0	.	1.000
time	1.000	.000	0	.	1.000
treatment * time	1.000	.000	0	.	1.000

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

	Epsilon[b]	
Within Subjects Effect	Huynh-Feldt	Lower-bound
treatment	1.000	1.000
time	1.000	1.000
treatment * time	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + Condition
Within Subjects Design: treatment + time + treatment * time

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F
treatment	Sphericity Assumed	51.011	1	51.011	.584
	Greenhouse-Geisser	51.011	1.000	51.011	.584
	Huynh-Feldt	51.011	1.000	51.011	.584
	Lower-bound	51.011	1.000	51.011	.584
treatment * Condition	Sphericity Assumed	498.344	1	498.344	5.710
	Greenhouse-Geisser	498.344	1.000	498.344	5.710
	Huynh-Feldt	498.344	1.000	498.344	5.710
	Lower-bound	498.344	1.000	498.344	5.710
Error(treatment)	Sphericity Assumed	1134.589	13	87.276	
	Greenhouse-Geisser	1134.589	13.000	87.276	
	Huynh-Feldt	1134.589	13.000	87.276	
	Lower-bound	1134.589	13.000	87.276	
time	Sphericity Assumed	191.430	1	191.430	5.004
	Greenhouse-Geisser	191.430	1.000	191.430	5.004
	Huynh-Feldt	191.430	1.000	191.430	5.004
	Lower-bound	191.430	1.000	191.430	5.004
time * Condition	Sphericity Assumed	.630	1	.630	.016
	Greenhouse-Geisser	.630	1.000	.630	.016
	Huynh-Feldt	.630	1.000	.630	.016
	Lower-bound	.630	1.000	.630	.016
Error(time)	Sphericity Assumed	497.304	13	38.254	
	Greenhouse-Geisser	497.304	13.000	38.254	
	Huynh-Feldt	497.304	13.000	38.254	
	Lower-bound	497.304	13.000	38.254	
treatment * time	Sphericity Assumed	71.458	1	71.458	1.770
	Greenhouse-Geisser	71.458	1.000	71.458	1.770
	Huynh-Feldt	71.458	1.000	71.458	1.770
	Lower-bound	71.458	1.000	71.458	1.770
treatment * time * Condition	Sphericity Assumed	1.458	1	1.458	.036
	Greenhouse-Geisser	1.458	1.000	1.458	.036
	Huynh-Feldt	1.458	1.000	1.458	.036
	Lower-bound	1.458	1.000	1.458	.036
Error(treatment*time)	Sphericity Assumed	524.875	13	40.375	
	Greenhouse-Geisser	524.875	13.000	40.375	

A.3.10 Paired t-test for trait anxiety:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	MBSR_Pre_Trait	36.2353	17	10.99164	2.66586
	MBSR_Post_Trait	32.8824	17	8.51383	2.06491
Pair 2	SME_Pre_Trait	36.1176	17	10.34337	2.50864
	SME_Post_Trait	35.1765	17	8.54572	2.07264

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	MBSR_Pre_Trait & MBSR_Post_Trait	17	.339	.183
Pair 2	SME_Pre_Trait & SME_Post_Trait	17	.748	.001

Paired Samples Test

		Paired Differences			
					95% Confidence ...
		Mean	Std. Deviation	Std. Error Mean	Lower
Pair 1	MBSR_Pre_Trait - MBSR_Post_Trait	3.35294	11.39595	2.76392	-2.50631
Pair 2	SME_Pre_Trait - SME_Post_Trait	.94118	6.91439	1.67699	-2.61388

Paired Samples Test

		Paired ...			
		95% Confidence Interval of the ...			
		Upper	t	df	Sig. (2-tailed)
Pair 1	MBSR_Pre_Trait - MBSR_Post_Trait	9.21220	1.213	16	.243
Pair 2	SME_Pre_Trait - SME_Post_Trait	4.49623	.561	16	.582

A.3.11 Mean ± Standard Deviation for NPG/PG and MBSR/SME groups:

			State	Trait	Decentering
NPG (n=19)	**MBSR**	**Pre**	29.44±7.05	35.00±10.65	44.10±6.36
		Post	24.66±3.84	32.11±8.17	45.30±5.25
		Δ	-4.78±3.21	-2.89±2.48	1.2±1.11
	SME	**Pre**	34.55±11.86	39.88±11.02	36.44±4.95
		Post	33.66±10.27	38.33±10.46	37.44±5.27
		Δ	-0.89±1.59	-1.55±0.56	-1±0.32
PG (n=17)	**MBSR**	**Pre**	31.62±5.34	37.25±11.85	38.12±4.51
		Post	34.25±9.06	33.75±9.36	41.62±3.66
		Δ	2.63±3.72	-3.50±2.49	3.50±0.85
	SME	**Pre**	32.25±7.72	35.12±9.62	38.22±6.26
		Post	31.37±7.90	31.62±3.81	42.22±4.52
		Δ	-0.88±0.18	-3.50±5.81	4.00±1.74

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