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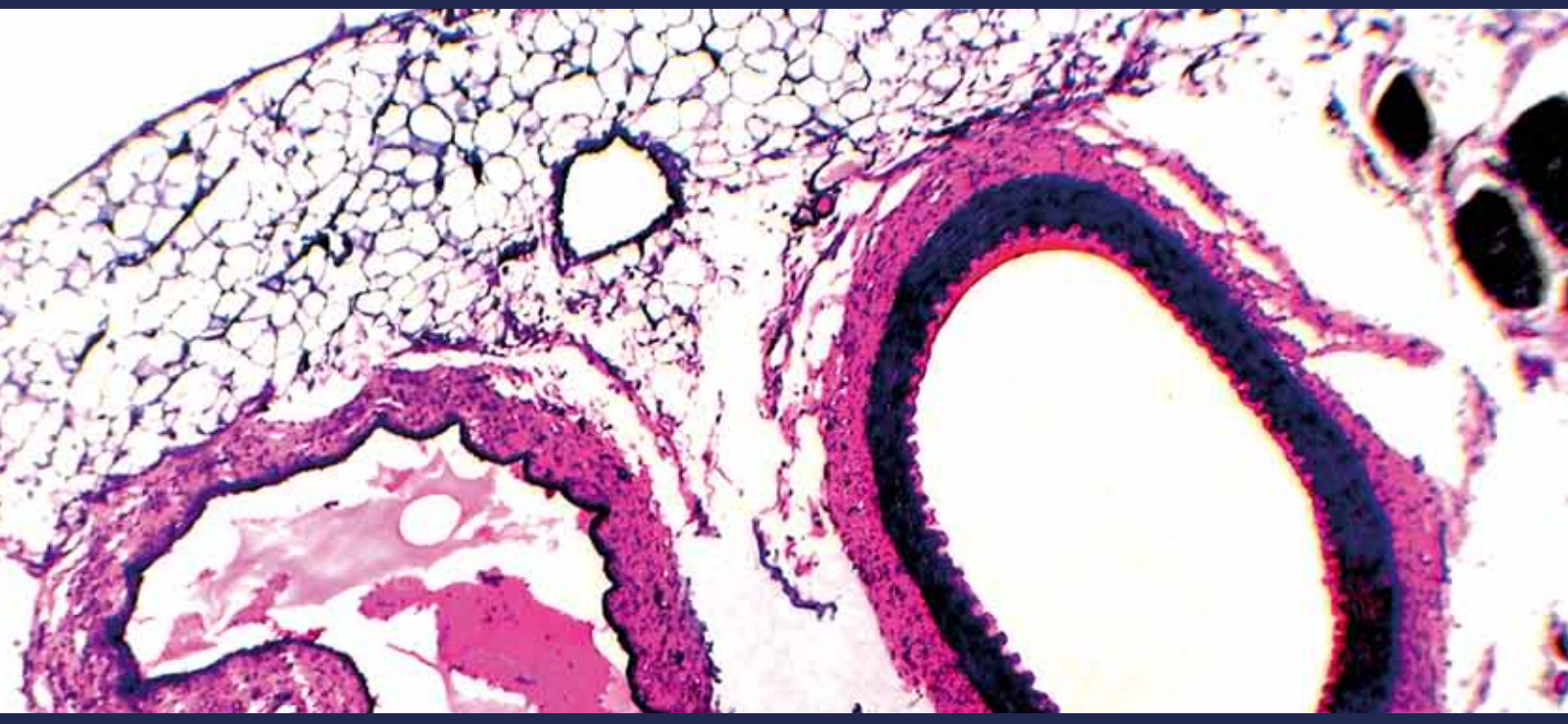
Hypertension: A Behavioral Medicine Perspective

Guest Editors: Tavis Campbell, Simon L. Bacon, Joel E. Dimsdale, and Douglas Carroll



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Editorial Board

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Editorial

Hypertension: A Behavioral Medicine Perspective

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Behavioral medicine is an interdisciplinary field concerned with the development and integration of behavioral and biomedical science, knowledge, and techniques relevant to health and illness and the application of this knowledge and these techniques to prevention, diagnosis, treatment, and rehabilitation. From a behavioral medicine standpoint, hypertension is a lifestyle disorder, aggravated by unhealthy diet, adiposity, excessive alcohol intake, and stress. The World Health Organization has identified hypertension as the number one risk factor for mortality worldwide [1]. Although considerable progress has been made in developing pharmacological treatments for hypertension, the underlying behaviors that contribute to the majority of hypertension in the first place (and which are also related to most chronic illnesses) continue to escalate. For example, in the USA, the Centers for Disease Control have been tracking increases in overweight and obesity on an annual level, and current estimates suggest that 33.8% [2, 3] of the US adult population is obese. Perhaps more troubling are the statistics for children in the USA, of whom 17% obese—nearly 3 times the number in 1980 [4]. Although there is clear consensus on the impact of behaviors such as exercise and nutrition on blood pressure, relatively little is known about how to motivate people to take up and consistently engage in these health behaviors. This is a striking knowledge gap because the first line of therapy for the treatment of hypertension is usually a recommendation that the patient modifies his/her lifestyle by, for example, changing diet or increasing physical activity. Despite considerable investigation, even less is known about how stress affects physiology to contribute to the hypertensive process or how stress affects blood pressure through effects on health behaviors. While there is substantial work left to be completed in behavioral medicine, we should, at the same time, recognize the progress the field has made in elucidating mechanisms through which lifestyle contributes to hypertension and in developing behavioral interventions for disease management.

The main focus of this special issue is to highlight the role of behavioral and psychological factors in the etiology, prevention, and treatment of hypertension. Two papers review mechanisms through which biobehavioral factors influence and are affected by increases in blood pressure. J. R. Jennings and A. F. Heim argue that findings from human neuroimaging suggest the brain is an early target for hypertension. W. Gerin and colleagues propose a model to explain the effects of cumulative exposure to stress (including ruminative stress) that leads, over time, to an upward resetting of the resting blood pressure, resulting in an increased risk of hypertension.

Another five papers in the issue examine the impact of sleep, anxiety, anger, depressed mood, and various health behaviors on blood pressure, blood pressure regulation, and endothelial function. These papers provide an excellent sense of current investigations into the impact of various candidate

psychological/behavioral factors on hypertension, as well as some of the intricacies and challenges involved in deriving clinically meaningful conclusions from this work.

The issue shifts focus to consider the impact of psychological interventions on blood pressure, with a review of a stress management intervention, meditation. While meditation techniques appear to produce small yet meaningful reductions in blood pressure, the review also points to serious methodological shortcoming and the need to attain a higher standard of quality, with more randomized controlled trial studies. Another paper suggests stress-activated gene $\times$ environment interactions may contribute to individual variability in blood pressure reductions from behavioral interventions.

A series of papers consider the uptake of behavioral medicine interventions, including self-monitoring of blood pressure in hypertension, a relatively simple and easily adopted activity that is associated with small but meaningful clinical improvements. The special issue ends with a provocative review of behavioral versus public health efforts to curb an obvious target for health behavior change, sodium consumption.

In highlighting some of the key areas of endeavor in the field of behavioral medicine, we hope to encourage readers to incorporate psychological and behavioral variables into their research on hypertension. Given the web of underlying causality, we believe that such an approach has considerable potential to inform efforts aimed at better understanding the causes, consequences, and treatment of hypertension.

Tavis Campbell
Simon L. Bacon
Joel E. Dimsdale
Douglas Carroll

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Review Article

Current Perspectives on the Use of Meditation to Reduce Blood Pressure

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Meditation techniques are increasingly popular practices that may be useful in preventing or reducing elevated blood pressure. We reviewed landmark studies and recent literature concerning the use of meditation for reducing blood pressure in pre-hypertensive and hypertensive individuals. We sought to highlight underlying assumptions, identify strengths and weaknesses of the research, and suggest avenues for further research, reporting of results, and dissemination of findings. Meditation techniques appear to produce small yet meaningful reductions in blood pressure either as monotherapy or in conjunction with traditional pharmacotherapy. Transcendental meditation and mindfulness-based stress reduction may produce clinically significant reductions in systolic and diastolic blood pressure. More randomized clinical trials are necessary before strong recommendations regarding the use of meditation for high BP can be made.

1. Introduction: Meditation Techniques as Treatments for Elevated Blood Pressure

According to worldwide estimates, hypertension affects approximately 1 billion people, resulting in 7.1 million attributed deaths per year [1]. In the United States, nearly half of all adults have blood pressure (BP), expressed in terms of systolic (SBP) over diastolic blood pressure (DBP), in the prehypertensive (SBP of 120–139 or DBP of 80–89) or hypertensive (SBP > 140 or DBP > 90) range [2, 3]. As one of the most widespread, least controlled diseases around the world, hypertension poses a threat to adults from all cultures and lifestyles. Factors such as improved treatment, pharmacologic interventions, preventative measures, and lifestyle changes have contributed to a 60% decrease in age-adjusted death rates from stroke and a 50% decrease in age-adjusted death rates from coronary heart disease in the United States since 1972. However, despite these improvements, BP control among American adults still remains suboptimal. For example, two-thirds of hypertensive individuals are not being controlled to recommended BP levels. Furthermore, approximately 30% of American adults are unaware of their hypertension, and over 40% of those with hypertension are not receiving treatment [3].

Current treatment guidelines for hypertension include antihypertensive medications and health-promoting lifestyle modifications such as weight reduction, the DASH eating plan (increased fruits and vegetables, and low fat dairy products with reduced saturated and total fat), reduced dietary sodium, increased physical activity, and moderation of alcohol consumption. Ideally, antihypertensive medications and lifestyle modifications successfully reduce BP to optimal levels. However, despite the effectiveness of antihypertensive medication [4], adherence to medication regimens is often poor and interferes with the goal of reducing BP [5, 6]. In addition, hypertensive medications can produce troublesome side effects such as insomnia, sedation, dry mouth, drowsiness, impotence, and headaches [4]. Due to difficulty

adhering, side effects, and prescription drug costs, hypertensive individuals may desire a nonpharmacologic intervention to avoid or complement their antihypertensive medication regimen. Therefore, whereas continued improvement in pharmacologic treatments is necessary, these advancements must be complemented by nonpharmacological approaches to BP control. Toward that end, mind-body interventions such as relaxation, stress management, and meditation—whether used alone or in combination with lifestyle modifications—have been evaluated as potential treatments for high BP (refer to Table 1 for an overview of the major types of mind-body interventions). Ample evidence exists regarding the effects of relaxation and stress management on BP to draw some conclusions, which are discussed below. However, less is known regarding the potential of meditation as an intervention for hypertension. The purpose of this focused paper is to evaluate the evidence that meditation is an effective intervention for lowering elevated BP (refer to Table 2 for a summary of studies in the literature search).

2. Mind-Body Interventions

Relaxation therapies for hypertension have been evaluated for over 30 years with disappointing results. For example, the Hypertension Intervention Pooling Project found no treatment effect for SBP and a small effect for DBP [22]. In a study by Irvine and Logan, relaxation therapy produced effects equal to a group that received support therapy, and the relaxation group did not produce a larger decrease in BP [23]. Positive results sometimes observed for relaxation can often be explained by methodology [24]; that is, individuals with higher baseline BPs tend to benefit more than individuals with lower baseline BPs, and repeated monitoring of BP appears sufficient to reduce BP levels [24, 25]. Overall, relaxation techniques, the most common being progressive muscle relaxation (PMR), are not considered effective methods for treating hypertension [26]. Consequently, PMR can even be used as a control group for randomized controlled trials of other mind-body interventions.

In contrast, stress-management therapies have had some success reducing BP [27–30]. In a meta-analysis, multicomponent stress management treatments were more effective in reducing BP (13.5 mm Hg SBP and 3.4 mm Hg DBP) than sham treatments, whereas single-component therapies (e.g., relaxation alone) did not produce significant results [31]. Another meta-analysis reported that multicomponent stress-management therapies were more effective in reducing BP than single-component relaxation-based therapies [32]. The Canadian Coalition for High Blood Pressure Prevention and Control has recommended multicomponent stress management be considered for hypertensive individuals whose stress appears to contribute to their hypertension [30].

Despite the promise of multicomponent stress-management interventions, implementation has not been widespread. Historically, the field of behavioral medicine has taken a keen interest in the contribution of stress to elevations in BP. Naturally, evidence that stress contributes to elevated BP and hypertension was followed by attempts to treat stress in order to reduce BP. However, stress-management interventions for high BP are neither widely available nor commonly practiced. Although we cannot be certain, we speculate the association of stress management programs with mental health treatment may introduce stigma and reduce patient acceptance of stress-management approaches. The expense of treatment programs and relative scarcity of healthcare professionals qualified to provide stress management to patients with high BP may also contribute to the limited implementation of multicomponent stress management programs as a uniquely behavioral medicine solution to hypertension.

Another mind-body intervention for high BP is meditation. It appears to be a promising option, as meditation is portable and can be practiced independently of structured treatment programs, although evaluation in clinical trials obviously requires a clear treatment protocol. Meditation has less association with mental health stigma and may be a more acceptable intervention than stress-management treatments in many cultures.

The most widespread types of meditation interventions can be roughly grouped into mantra meditation, such as transcendental meditation (TM) and mindfulness meditation. Mindfulness meditation involves an attitude of openness, acceptance, and reflection rather than impulse and judgment toward the practitioner's current experiences, as well as the observation of thoughts, feelings, and the external world alike through calm, detached sensory awareness [33]. Mantra meditations focus on a word, phrase, or concept. The mantras often have soft sounds, like "Om," and these words are thought to produce different vibrations in different people, producing various effects on the individual [34]. In the TM technique, the mantras, which are used for sound value rather than meaning, become increasingly secondary in experience and eventually disappear, while self-awareness becomes primary in experience as the practitioner transcends to a state of pure consciousness [35].

Mindfulness—described as a calm awareness of one's body, mind, and environment that embodies an interaction between nonjudgmental acceptance and focuses on the present moment—has existed for over 2,500 years and can be found in numerous religions, cultures, meditation techniques, and psychotherapies [36]. Although it is the 7th step of the Noble Eightfold Path in Buddhism, there is nothing inherently religious about mindfulness as it is mostly taught completely independent from any religious doctrine. Mindfulness meditation research became formalized in 1979 when Dr. Jon Kabat-Zinn founded the MBSR program at University of Massachusetts-Amherst to treat the chronically ill [37]. Other practices and interventions that utilize the concept of mindfulness include yoga [38], acceptance and commitment therapy [39], dialectical behavior therapy [40], Tai Chi [41], and Qigong [42].

2.1. Transcendental Meditation. TM has been extensively studied as a meditation therapy for high BP. In one study, the feasibility and efficacy of TM and progressive muscle relaxation (PMR) were tested via a subgroup analysis by sex and level of hypertension risk in older African Americans [17]. Compared to control subjects who underwent lifestyle

Table 1: Major types of mind-body interventions.

Major types of mind-body interventions	Subtypes	Description	Setting	Certification to administer	Dose	Standardization
Relaxation therapy	Progressive muscle relaxation (PMR), biofeedback, relaxation-assisted biofeedback, autogenic training	Uses relaxation techniques to achieve physical and mental relaxation, often coupled with breathing exercises or mental imagery	Group or individual	Varies (health professionals, psychologists, therapists, etc.)	Varies (e.g., weekly sessions with homework assignments)	Not standardized
Stress-management therapy	N/A	Adjusts behavioral and psychological responses to stress through cognitive behavioral interventions	Group or individual	Varies	Varies	Not standardized
Zen meditation	N/A	Focuses attention on counting deep breaths or koans (riddles irresolvable by logic) to cultivate awareness	Mostly individual	Zen practitioner	Varies	Not standardized
Transcendental meditation (TM)	N/A	Takes attention beyond normal thinking processes until thought is transcended and a state of pure consciousness is achieved, beginning with repetition of a mantra	Mostly individual	Certified instructor through the Maharishi Vedic Education Foundation	Technique learned in a 7-step course or through personal instruction, practiced 15–20 min twice/day	Standardized
Mindfulness-based stress reduction (MBSR)	N/A	Uses meditation and stress-management techniques, including mindfulness skills, such as coping, sitting meditation, and yoga, to improve physical and emotional well-being	Group sessions with individual practice	Varies	8 weekly 2.5 hr. sessions, with at least 45 min. of daily practice 6 days/week, concluding with an 8 hr. mindfulness retreat with a therapist	Standardized

Table 2: Literature search overview.

Meditation study overview	Sample size, population	Intervention/dose	Control	Length of baseline, no. of BP readings	Randomized, blinded	Therapists' training	Results	F/U
Mindfulness [7]	70 (normotensive, female posttreatment cancer patients, age ≥18)	8 wk. MBSR	Passive (waitlist)	3 readings taken at 3-min. intervals	Not randomized, NR if blinded	Clinical psychologist with over 10 yrs. of experience	No significant difference in BP between MBSR group and control; when patients were analyzed by "higher BP" and "lower BP" groups based on BP readings at week 1, "higher BP" MBSR participants had lower SBP compared to controls at week 8	None
Mindfulness [8]	121 (African American ninth graders, resting SBP between 50th and 95th percentiles)	Life skills training, health education, or Breathing Awareness Meditation (BAM), with 10-min. in-school and at-home sessions every day for 3 mos.	None	4 readings taken within 10 min. (first reading discarded) over 3 consecutive days	Randomized, single-blind	Health/physical education teachers trained and certified by program instructors	Only the BAM group showed significant decreases in 24-hour SBP	3 mos.
Mindfulness [9]	166 (African American ninth graders, resting SBP between 50th and 95th percentiles)	Botvin LifeSkills Training or BAM, with 10-min. in-school and at-home sessions every day for 3 mos.	Active (health education)	3 readings taken within 10 min. (first reading discarded) over 3 consecutive days	Randomized, NR if blinded	Health education teachers trained by program instructors	BAM group showed greatest decreases in SBP, changes in overnight SBP, DBP, and heart rate (significant group differences)	None
Mindfulness [10]	56 (adults aged 30–60 yrs., 91% Caucasian, BP in the prehypertensive range, 120–139 mm Hg SBP, or 80–89 mm Hg DBP, unmedicated)	MBSR for 8 wks.	Active (PMR training)	3 readings taken at 5-min. intervals, followed by 2 additional measurements within 2 wks.	Randomized, single-blind	MBSR and PMR therapists	MBSR produced significant decreases in clinic SBP (by 4.9 mm Hg) and DBP (by 1.9 mm Hg)	None

Table 2: Continued.

Meditation study overview	Sample size, population	Intervention/dose	Control	Length of baseline, no. of BP readings	Randomized, blinded	Therapists' training	Results	F/U
TM [11]	35 (adolescents with high normal BP aged 15–18 yrs., 34 African Am., 1 Caucasian Am., resting SBP ≥85th and ≤95th percentile)	TM, with 15 min meditation sessions twice/day for 2 mos.	Active (health education)	3 consecutive occasions, length of baseline NR	Randomized, NR if blinded	NR	TM group showed greater decreases in resting SBP and in SBP during acute stressor	None
TM [12]	60 (African American adults, aged >20 years; with high normal BP of 130–139/80-85, stage 1 hypertension BP of 140–159/90–99, or stage II hypertension BP of 160–179/100–109)	TM for 6–9 mos. (average intervention period of 6.8 ± 1.3 mos.)	Active (CVD risk factor prevention education program)	3 readings taken at each of 3 consecutive visits (last 2 visits were averaged)	Randomized, single-blind	Certified instructors from the African American community	Both groups had significant decreases in BP (TM group by 7.77 ± 10.34 mm Hg SBP and 3.5 ± 7.6 mm Hg DBP, control group by 6.74 ± 12.8 SBP and 5.9 ± 8.6 DBP), but only the BP decrease in TM group was associated with corresponding decrease in carotid intima-media thickness)	None
TM [13]	39 (normotensive Caucasian Am. male adults, mean age of 24.6 yrs.)	TM for 4 mos.	Active (cognitive-based stress education)	BP measured every 4 min. for 20 min.	Randomized, single-blind	Qualified TM instructor	TM decreased ambulatory DBP by 4.8 ± 2.4 mm Hg (8.8 ± 3.0 mm Hg in high-compliance subgroup)	None
TM [14]	298 (university students, BP <140/90 and > 90/60 mm Hg, with 159 in a hypertension risk subgroup for having SBP>130 mm Hg, DBP>85 mm Hg, or other risk factors)	TM for 3 mos.	Passive	3 readings taken at 1-min. intervals (last 2 readings were averaged)	Randomized, single-blind	Research staff and TM instructional staff	In the hypertension risk subgroup, TM significantly reduced SBP by 5.0 mm Hg and DBP by 2.8 mm Hg; reductions in overall sample were not significant. TM produced significant improvements in total psychological distress, anxiety, depression, anger/hostility, and coping.	None
TM [15]	100 (African American adolescents aged 16.2 ± 1.3 yrs., with high normal SBP)	TM for 4 mos.	Active (health education control with lifestyle education sessions)	Readings taken from 6AM–11PM every 20 min. (daytime) and 11PM-6AM every 30 min. (nighttime) over 24 hrs.	Randomized, NR if blinded	NR	TM group showed greater declines in daytime SBP ($P < 0.04$) and DBP ($P < 0.06$) compared to the health education control group	4 mos.

Table 2: Continued.

Meditation study overview	Sample size, population	Intervention/dose	Control	Length of baseline, no. of BP readings	Randomized, blinded	Therapists' training	Results	F/U
TM-based [16]	41 (adults aged 22–62 yrs., with essential hypertension, unmedicated, ≥100 mm Hg arterial pressure)	SRELAX group received training over 5 wkly. sessions based on TM (including mantra), with 15–20 min meditation sessions twice/day	Both passive and active (NSRELAX placebo group had same training, no mantra)	5 readings taken at 1 min. intervals	Randomized, single-blind	Experienced TM instructor	Both SRELAX and NSRELAX modestly decreased BP, with significant decrease only in DBP	3 mos.
TM or relaxation [17]	127 (hypertensive African Am. adults aged 55–85 yrs., SBP ≤179 mm Hg, DBP 90–104 mm Hg)	Transcendental Meditation (TM) or progressive muscle relaxation (PMR), with 1 wk. initial instruction and 1.5 hr. monthly followups for 3 mos.	Active (lifestyle modification)	4 readings over 1-2 mos.	Randomized, single-blind	NR	TM significantly decreased BP in both women (SBP by 10.4 mm Hg, DBP by 5.9 mm Hg) and men (SBP by 12.7, DBP by 8.1); PMR only decreased DBP significantly in men (by 6.2)	3 mos.
TM or relaxation [18]	127 (African Am. adults aged 55–85 yrs., with mild hypertension, SBP ≤189 mm Hg, DBP 90–109 mm Hg, final baseline BP ≤179/104 mm Hg)	TM or PMR, with 1 wk. initial instruction and 1.5-hr. monthly followups for 3 mos.	Active (lifestyle modification)	3 readings taken at one visit	Randomized, single-blind	Africa Am. instructors qualified to teach either TM or PMR	TM decreased SBP by 10.7 mm Hg, DBP by 6.4 mm Hg (both significantly greater decreases than those in PMR)	3 mos.
TM or relaxation [19, 20]	150 (African Am. adults, mean age of 49 ± 10 yrs., SBP 140 to 179 mm Hg, DBP 90–109 mm Hg)	TM or PMR	Active (conventional health education)	3 readings taken within 1 hr. at each of 5 sessions over 1 mo.	Randomized, single-blind	NR	TM decreased SBP by 3.1 mm Hg, DBP by 5.7 mm Hg (greatest decrease of all groups); TM decreased use of antihypertensive medication (relative to increases in other groups)	1 yr.
TM, mindfulness, or relaxation [21]	72 (elderly retirement-age adults, mean age of 81 yrs.)	TM, mindfulness training (MF), or mental relaxation	Passive	3 readings taken at 2-min. intervals (only SBP reported)	Randomized, single-blind	21 trained instructors (professionals, graduate students, and college seniors)	TM decreased SBP by 12.4 mm Hg (greatest decrease of all groups), and survival rate was 100% (compared to the second highest, 87.5% in MF) after 3 yrs.	3 yrs.

modification education only, TM produced significant declines in BP after 3 months for both men (by 12.7 mm Hg SBP and 8.1 mm Hg DBP) and women (by 10.4 mm Hg SBP and 5.9 mm Hg DBP). In contrast, women practicing PMR failed to show significant declines, while men practicing PMR experienced significant declines solely in DBP (by 6.2 mm Hg) [17]. An earlier randomized controlled trial of TM by the same authors reported that 20 elderly patients who were treated with TM exhibited a 12.4 mm Hg drop in SBP, compared to a 2.4 mm Hg reduction for patients in the control group [21].

The short-term efficacy of TM and PMR in treating mild hypertension was also evaluated in 127 African American men and women aged 55 to 85 years, compared with a lifestyle modification education control program [18]. TM reduced SBP (10.7 mm Hg) and DBP (4.7 mm Hg), which was significantly greater than those observed for relaxation (4.7 mm Hg SBP and 3.3 mm Hg DBP). Between the two stress-reducing approaches, TM was about twice as effective as PMR. Later, Schneider and colleagues [19] conducted another study following African American hypertensive individuals over one year while they underwent TM, PMR, or conventional health education classes as a control. The TM group experienced greater decreases in SBP and DBP than the PMR or control groups, as well as reduced use of antihypertensive medication, relative to increases for PMR and the control group. Consequently, the TM program may be particularly useful in the long-term treatment of hypertension in African Americans, for whom many of these effects have been demonstrated. Schneider and colleagues also conducted a recent meta-analysis, which revealed that, compared with combined controls, the TM group showed substantial decreases in all-cause mortality, cardiovascular mortality, and cancer-related mortality [20].

In another study [16], unmedicated patients with hypertension underwent TM-based training (treatment group), TM-based training without a mantra (placebo control group), or no training (no-treatment control group). Compared with the no-treatment controls, modest BP declines were observed in both the treatment and placebo control groups, with DBP percentage showing a significant decrease [16]. The similarity in effectiveness of TM training and TM training without a mantra could be attributed to the fact that both were in effect "meditation" groups or that changes in BP were due to another factor. A meta-analysis that only included high-quality assessments—as determined by 11 factors, which included participant selection, randomization, blinding, full description of the therapeutic intervention, and appropriate measurements of BP—found TM, compared to controls, associated with clinically meaningful reductions of 4.7 and 3.2 mm Hg in SBP and DBP, respectively [43]. TM has also appeared to reduce carotid arteriosclerosis in African Americans [12] and a 4.8 mm Hg drop in ambulatory DBP among white males treated with TM [13].

A study assessing the effects of TM on BP, psychological distress, and coping among university students was also the first randomized clinical trial to demonstrate that TM significantly increased coping and reduced BP in association with lessened psychological distress in a hypertension risk subgroup. The TM program may decrease the risk for developing hypertension in young adults [14]. TM also reduced resting BP among adolescent African Americans with high normal BP (with a resting SBP $\geq$85th and $\leq$95th percentile) over two months, with larger declines than those in a health education control group, demonstrated during both at rest and during acute laboratory stressors [11]. In another study on African American adolescents with high normal systolic BP, the 4-month TM group showed greater declines in daytime SBP ($P < 0.04$) and DBP ($P < 0.06$) compared to the health education control group, further exhibiting a beneficial impact of TM in youth at risk for hypertension. This study is of particular interest due to its utilization of ambulatory 24-hour BP monitoring, which not only tends to be relatively free of placebo effects and to be highly reproducible but also records BP regularly over a prolonged time period in the participants' natural environments, thus increasing sensitivity to changes in average BP and providing a more reliable measure of overall BP [15]. Ambulatory studies like the one produced here by Barnes and colleagues are valuable because they generate the potential to measure treatment effects out of the laboratory and in day-to-day life, which may allow generalization of treatment effects.

2.2. MBSR. Mindfulness-based stress reduction (MBSR), a subset of mindfulness meditation that has been standardized and manualized, is said to treat depression and anxiety, lower stress, and treat health conditions like hypertension. MBSR is a program that utilizes meditation and stress management techniques. Originally founded by Dr. Jon Kabat-Zinn, The Center for Mindfulness in Medicine, Health Care, and Society at the University of Massachusetts Medical School (http://www.umassmed.edu/cfm/) has treated over 19,000 patients with MBSR.

MBSR was originally developed and used in a behavioral medicine setting for individuals with chronic pain [44] and typically consists of eight 2.5-hour weekly group sessions. These sessions contain instruction and practice in mindfulness meditation, as well as conversations of stress, coping, and homework assignments. Students learn a range of mindfulness skills including body scan exercises, sitting meditation, and yoga exercises. Homework consists of practicing these skills for at least 45 minutes per day, 6 days per week, in addition to practicing mindfulness skills during group meetings. The program concludes with an 8-hour intensive mindfulness retreat with a therapist. During and after the program, students are encouraged to pay mindful, nonjudgmental attention to daily activities like walking, eating, and talking. One goal is for participants to see that most sensations, emotions, and thoughts are short-lived and do not require immediate suppression.

Recent studies have evaluated the effectiveness of MBSR for reducing BP, as well as breathing awareness meditation (BAM), a primary exercise in MBSR, in producing declines in BP among differing populations. In one study, 121 African American ninth graders (with a resting SBP >50th percentile and <95th percentile) underwent BAM, life skills training, or health education [8]. Among the three behavioral intervention approaches, only BAM produced significant decreases

in 24-hour SBP. Another study also conducted among 166 African American ninth graders at increased risk for essential hypertension compared the treatment effects of BAM, the Botvin LifeSkills Training, or a health education control [9]. Significant group differences emerged, with the BAM group exhibiting the greatest decreases in SBP, DBP, and heart rate.

MBSR has also shown some potential for lowering BP in individuals with elevated BP. A recent study comparing the effects of MBSR versus PMR on prehypertensive adults found that MBSR produced significant reductions in SBP and DBP. A 4.9 mm Hg reduction in clinic SBP was observed in the MBSR group compared to 0.7 mm Hg in the PMR group, and MBSR produced a 1.9 mm Hg reduction in DBP compared to a 1.2 mm Hg increase for PMR [10]. The results were qualitatively similar to reductions in BP reported in a meta-analysis of TM [45], as well as the reduction observed in the PREMIER trial of comprehensive lifestyle modification for high BP [46]. In another study, adult female posttreatment cancer patients who underwent MBSR did not experience significant differences in BP compared to the waitlist control group [7]. However, when patients were analyzed by "higher BP" and "lower BP" groups through a median split based on BP readings during the first week of treatment, "higher BP" MBSR participants had lower SBP compared to controls at the end of the MBSR program. Given the normotensive sample and preliminary results due to methodological limitations of the study (e.g., results may have been an effect of regression to the mean), more well-designed trials are needed to evaluate the utility of MBSR in reducing clinically elevated BP [7].

3. Methodological Considerations

A report on meditation techniques conducted by the United States Agency for Healthcare Research and Quality (AHRQ) evaluated the methodological quality of 286 randomized controlled trials employing meditation practices in a variety of populations [33]. Studies were evaluated using the Jadad scores, as the Jadad scale is the most commonly used assessment scale of methodological quality of randomized controlled trials in health care research [47]. Scores (on a scale of 1–5, from lowest to highest methodological quality) are based on reported method of randomization, double-blinding, and description of withdrawals and dropouts, with low scores indicating a higher risk of bias [48]. The quality of meditation trials was evaluated to be poor overall, with only 14% being rated high quality (i.e., Jadad scores ≥ 3 points); the studies reviewed were found to have too many qualitative or observational reports, limited descriptions of participant characteristics (including if the inclusion criteria required an official diagnosis of prehypertension or hypertension), small sample sizes, inadequately described blinding procedures and randomization, lack of control groups, insufficient followup periods, limited reporting of intention-to-treat statistical analyses, and inadequately described losses to followup [33]. Furthermore, much of the research published on specific forms of meditation has been conducted by the organizations that create or disseminate those specific forms of meditation. Although the methodological quality of this research is improving, meditation techniques should be tested by independent research teams who have no association with organizations promoting a particular approach to meditation. Recent additions to the literature have increasingly adhered to the CONSORT recommendations (Consolidated Standards of Reporting Trials; 49). There are many methodological improvements that can be made. For example, conflict of interest and researcher bias can be minimized by collaborative efforts with outside institutions having independent oversight of data collection and analysis, independent replication, rigorous blinding, allocation concealment, randomization, and selection of a suitable control condition.

4. Future Directions and Studies

Future research targeting meditation interventions must begin by adequately defining the role of mindfulness or other concepts and components in meditation and delineating intentions for applications to the study population. Meditation treatments should be standardized and manualized as much as possible to ensure maximal external validity. Additionally, similarities and differences between kinds of meditation interventions should be highlighted within publications. The role of mindfulness and meditation in a given intervention should be explained. Furthermore, assessments that target measurements of the construct, mindfulness, and the process through which mindfulness is achieved, meditation, should be refined and psychometrically validated in medical populations and healthy controls.

Future studies should clearly outline their inclusion and exclusion criteria, with efforts to extend meditation interventions to hypertensive individuals who otherwise belong to understudied populations. Including a variety of populations makes the examination of potential moderators such as ethnicity possible. Aims should include using larger sample sizes and continuing with the disease-specific approach to interventions, implying the use of strict inclusion criteria requiring participants must be diagnosed with either prehypertension or hypertension to participate. There may need to be a better selection of control protocols, with preference given to similar interventions that have been validated to not produce the results experimenters expect to find (or not) in the experimental condition. In addition, studies defining dose response would be substantially beneficial in helping not only to confirm the correlation-effect link, but also to determine how much of an intervention produces both statistically and clinically significant effects. This would facilitate wider dissemination and scalability.

Procedural and statistical methodology must be explicitly outlined so the studies can be critiqued and replicated and so articles published from the studies can be included in reviews and meta-analyses. With improved adoption of the CONSORT guidelines [49], better systematic comparisons of effects of different mindfulness interventions can be established. Hopefully, as the methodology and reporting of these studies is strengthened and clarified, scientists will be able to adopt more experimental designs, ultimately optimizing the ability to make causal inferences.

Meditation is an intervention for hypertension and prehypertension that is perhaps best characterized as being in its adolescence. There is clearly considerable promise, with a variety of studies demonstrating efficacy in the short-term reduction of BP similar to that achieved with single-agent drug therapy. On the other hand, many of these studies are potentially biased due to lack of blinding, inadequate baseline measurements of BP, and limited followup. All meditation techniques are not created equal, and few studies have directly compared one technique to another. More importantly, there has been essentially no evaluation to determine what may be the essential components of a putatively successful methodology or if an entire "standard" approach is required. This has major implications for scalability, particularly in resource-limited settings where both clinical staff time and patient meditation environment and time may be constrained. Hypothesis-driven mechanistic studies are rare and, if well conceived and executed, could dramatically advance the field. Potential mechanisms of action include alterations in the autonomic nervous system, with changes in the sympathovagal balance favoring the latter. Perhaps meditation affects mood in hypertensives; in other settings depression has been associated with physical inactivity and altered eating patterns, both of which may affect BP.

Hypertension is paradigmatic of a chronic disease, with clinical sequelae typically developing after years of elevated BP. Long-term followup, after the acute intervention is complete but, while the patient is still employing meditative techniques, is essential. Perhaps "booster doses" of instruction will be required. While prima facie meditation would appear to be free of side effects, few studies have systematically evaluated their presence and consequences. It is possible that the most significant side effect may be procedural, where meditation is simplistically viewed only as an alternative or substitute for antihypertensive drugs. Pharmacotherapy of hypertension frequently involves multiple drugs, particularly in those with substantially elevated baseline pressure. It is unlikely that meditation will be effective as monotherapy in all (and perhaps most of) patients with established hypertension. A therapeutic approach of multimodality treatment, wherein meditation is truly viewed as complementary to drug treatment, is an important underexplored area, with the potential to expand the number of individuals who could both benefit from meditative techniques and achieve improved BP control.

Perhaps the greatest potential benefits of meditation techniques in the treatment of individuals with hypertension are in developing countries. Many of these countries are experiencing large population growth and with the increasing penetration of a Western lifestyle come both increased caloric and sodium intake and decreased physical activity. In these circumstances, cardiovascular diseases, particularly hypertension, are assuming increased prevalence. Meditation techniques, if they can be delivered efficiently and effectively, may prove to be valuable tools to treat the growing epidemic of hypertension, particularly if they eliminate the inconveniences of laboratory monitoring or prescription refills and indeed have few and rare side effects.

It is our hope that this overview of meditation techniques has highlighted prior successes, outlined the limitations existent in the field today and provided inspiration and guidance to move the field forward with mechanistic, specifically detailed, and long-term studies in the future.

Considering the current healthcare system in the United States, it is possible for mindfulness interventions to be implemented as both prevention and treatment programs (pending confirmation of their effectiveness). Most mindfulness interventions can be taught in a group format, which reduces the cost on participants and the burden on clinicians. As more treatments are standardized and their efficacy can be demonstrated in clinical trials, insurance companies may be more inclined to fund mindfulness training. Longitudinal studies must also be executed to determine if mindfulness can act as a protective factor against an array of psychosocial and medical ailments. Positive results may indicate that mindfulness interventions could produce a clinically significant resiliency or protection against problems requiring care from mental health and medical professionals. As a promising construct in complementary and alternative medicines, there is a strong possibility that mindfulness could become a component of effective interventions designed to prevent hypertension and lower suboptimal BP.

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Research Article

The Relationship between Multiple Health Behaviours and Brachial Artery Reactivity

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Background. The effects of smoking, alcohol consumption, obesity, and a sedentary lifestyle on endothelial function (EF) have only been examined separately. The relative contributions of these behaviours on EF have therefore not been compared. *Purpose*. To compare the relative associations between these four risk factors and brachial artery reactivity in the same sample. *Methods*. 328 patients referred for single-photon emission computed tomography (SPECT) exercise stress tests completed a nuclear-medicine-based forearm hyperaemic reactivity test. Self-reported exercise behaviour, smoking habits, and alcohol consumption were collected and waist circumference was measured. *Results*. Adjusting for relevant covariates, logistic regression analyses revealed that waist circumference, abstinence from alcohol, and past smoking significantly predicted poor brachial artery reactivity while physical activity did not. Only waist circumference predicted continuous variations in EF. *Conclusions*. Central adiposity, alcohol consumption, and smoking habits but not physical activity are each independent predictors of poor brachial artery reactivity in patients with or at high risk for cardiovascular disease.

1. Introduction

Poor endothelial function (EF) predicts future cardiovascular events [1] and is thought to be influenced by several behavioural risk factors for cardiovascular disease (CVD) including smoking, physical activity, obesity, and alcohol consumption. Thus, poor EF may mediate some of the risks for CVD created by these behaviours. For example, current smokers have been found to have lower EF than those who have never smoked [2–6]. Furthermore, smoking has been shown to induce an acute decrease in EF [4, 7]. To our knowledge, however, there has only been one study that has examined the relationship between lifetime smoking and EF [8]. While this study found that pack/years were inversely related to EF, the generalizability of these results may be limited given the narrow age range of its participants (20–28 years).

Cross-sectional studies have found that sedentary participants display reduced EF compared with athletes [9–11], though inconsistencies have been noted [12, 13]. While some interventions to increase physical activity have been found to have a positive impact on EF [12, 14–24], others have failed to do so [25–28]. To our knowledge, only two studies have examined the relationship between EF and physical activity in moderately active participants; one study found a significant effect of physical activity on EF in children [29], while the other did not find a relationship in adults [30].

While obesity is influenced by several factors, including physical activity, caloric consumption has been found to be

the most important predictor of weight loss or gain and caloric restriction to be the most effective means of inducing weight loss [31–33]. As such, although "obesity" is not a behaviour per say, here it will be considered a proxy of long-term excess caloric consumption. Cross-sectional studies have observed obese and overweight participants, classified according to BMI, have worse EF compared to normal weight controls [34–37]. Intervention studies using either gastric bypass surgery [38] or a low-calorie diet [39, 40] have also reported weight loss to result in improvements in EF. However, only one study to date has examined the relationship between obesity and EF in participants with a wide range of BMIs, finding that both overweight and obese individuals have worse EF than normal weight controls [41].

The effect of alcohol consumption on EF is equivocal. While studies comparing alcoholics to nonalcoholic controls have reported alcoholics to have significantly lower EF [42–44], the impact of moderate amounts of alcohol on EF is uncertain. Acute wine consumption has generally been observed to have a positive impact on EF [45–47] though one study found no difference in EF when pairing a glass of red wine versus a control beverage with a high-fat meal [48]. Furthermore, the equivalent of one drink's worth of ethanol has resulted in no acute change in EF [49], while four drinks' worth of ethanol resulted in a significant acute decrease in EF [50]. There has been only one published report on the relationship between moderate alcohol consumption and EF. In this study of 108 men with coronary artery disease, those who drank 1–3 drinks/day had significantly better EF than abstainers, suggesting an inverted J-shaped relationship between alcohol consumption and EF [51].

While the effects of smoking, physical activity, obesity, and alcohol consumption on EF have been examined, some important gaps in knowledge remain. First, there is a lack of research examining the relationship between lifetime smoking and EF. Second, further research is needed to clarify the nature of the relationship between moderate levels of physical activity and EF. Third, studies are needed to clarify the relationship between regular moderate alcohol consumption and EF. Fourth, since most studies on health behaviours and EF have been conducted in generally healthy noncardiac samples, this relationship should be explored in samples that have or are at risk for cardiovascular disease. Finally, since these variables often cooccur, research is needed to determine their independent effects. The primary goal of the current study was to examine the relationship between all four health behaviours and brachial artery reactivity, used as a proxy of EF, in a single sample. This allowed determination of whether each health behaviour had an impact on EF independent of the others and allowed evaluation of their relative impact on EF (Table 1).

Table 1: Summary table.

What is known about the topic	What this study adds
(i) Poor endothelial function is an early predictor of future cardiovascular events. (ii) Poor health behaviours, including smoking, sedentary behaviour, obesity, and excessive alcohol consumption, have individually been associated with endothelial dysfunction. (iii) These studies have generally compared "extreme" behaviours (e.g., marathon runners versus sedentary individuals).	(i) There are independent effects of current smoking habits, obesity and alcohol consumption on brachial artery reactivity. (ii) Whilst any improvement in a single health behaviour might have a positive influence on endothelial function, targeting multiple behaviours should yield greater benefits.

2. Methods

2.1. Participants. The study was a substudy of the Mechanisms and Outcomes of Silent Myocardial Ischemia (MOSMI) study, a longitudinal study of risk factors for silent ischemia and the impact of silent ischemia on cardiovascular outcome. A total of 904 consecutive patients referred for single-photon emission computed tomography (SPECT) exercise stress tests between July 2005 and December 2006 in the Nuclear Medicine Service of the Montreal Heart Institute were recruited. To be eligible for the MOSMI study, patients had to be undergoing SPECT exercise stress testing, be over 18 years old, and speak either English or French. Patients were excluded if they had experienced a cardiac event (e.g., myocardial infarction) in the last 4 weeks, if they had a more prominent medical condition than CVD (e.g., cancer, chronic obstructive pulmonary disease), or were pregnant or nursing. A subsample of 328 patients from the MOSMI study underwent EF testing. The selection of this group from the main cohort was done based on the random allocation to available testing time slots. There were no differences in age, sex, or CVD status between this subsample and those patients recruited for the MOSMI study but who were not included in final analysis. The MOSMI study was approved by the Human Ethics Committee of the Montreal Heart Institute and written informed consent was obtained from all participants.

2.2. Procedure. Patients presenting to the Nuclear Medicine Service of the Montreal Heart Institute on the day of their exercise stress test were approached to participate in the MOSMI study. Once consent was obtained, demographic and medical information, including health behaviours, was collected using a self-report questionnaire and waist circumference was measured. Patients then underwent standard treadmill exercise stress testing (Bruce protocol) followed by SPECT imaging. As per the SPECT protocol, all patients returned the following day to complete their rest scan. Prior to the rest scan patients underwent the forearm hyperaemic reactivity (FHR) test to measure brachial artery reactivity in response to hyperaemic challenge. All SPECT imaging was conducted according to standard procedure [52–54]. In general, patients were maintained on their usual medication, the only exception being that people were asked to withhold taking beta-blockers on the day of the exercise and rest SPECT studies.

2.3. Brachial Artery Reactivity Assessment. The FHR technique, implemented by a trained Nuclear Medicine technician, was used to assess brachial artery activity. FHR is considered a marker of EF [55, 56]. FHR measures alterations in the brachial artery endothelium following a hyperaemic challenge [57, 58]. The patient is seated with both arms extended over the top of a standard large field-of-view gamma camera with a low negative high resolution collimater (Scintronix, London, UK) facing upward, hands prone. To create the hyperaemic challenge, a blood pressure cuff (Adult First Responders, B&A Instruments, New York, New York) was placed on the right arm and inflated at 50 mmHg above systolic blood pressure for 5 minutes, after which it was released. Forty-five seconds after the cuff was deflated, 0.42 mCi/kg of the radioactive tracer Tc-99m-tetrofosmin (Myoview, Amersham Health, Princeton, NJ) was injected into the patient's arm via a small catheter positioned in the bend of the left arm. For the next 10 minutes, dynamic image acquisitions were realized using 128 $\times$ 128 matrices at a sampling rate one frame per second. From this, the ratio between the rate of blood flow into the right (the hyperaemic arm) and left (the control arm) arms, the relative uptake ratio (RUR), was calculated using custom-made software (Sygesa, Montreal, Canada). The higher one's RUR, the better the endothelial tissue is at responding to the hyperaemia, via the promotion of vasodilation. Thus, a higher RUR indicates better EF and a lower RUR indicates worse EF. More specifically, an RUR under 3.55 is considered to be indicative of endothelial dysfunction [58]. This technique has a high level of reproducibility with excellent intra- and interrater reliability [59].

2.4. Health Behaviours

2.4.1. Physical Activity. Leisure time physical activity was derived from a slightly adapted 12-month version of the Physical Activity Recall Interview [60]. Specifically, given the nature of activity patterns in Montreal, separate details were collected for winter-like and summer-like activities and then combined. Physical activity levels were calculated as average metabolic equivalents MET-hrs/week.

2.4.2. Smoking. Lifetime cigarette consumption was assessed using the standard calculation of pack/years (average number of packs smoked/day $\times$ number of years having smoked) [61]. Patients were also classified as current, ex-, and never smokers.

2.4.3. Obesity. As centrally distributed fat seems to be more significant in the aetiology of CVD [62], waist circumference was used as our measure of central adiposity. Prior to the EF test, the attending technician measured the participants' waist circumference at the mid-point between the super-illiac crest and the lower thoracic cavity.

2.4.4. Alcohol. Participants were asked to report their usual daily or weekly consumption of alcoholic beverages. Using this data, weekly units of alcohol consumed were estimated.

Table 2: Participant characteristics.

Variable	$M \pm$ SD or % (n)	Data missing (%)
Age (yrs)	59.7 ± 9.6	1%
Sex (% women)	25% (83)	0%
Endothelial dysfunction (RUR < 3.55)	44% (145)	0%
Average # drinks/week	13.4 ± 12.8	8%
Waist circumference (cm)	99.6 ± 12.0	3%
Leisure-time physical activity (MET-hrs/week)	7.2 ± 12.4	1%
Lifetime smoking (pack years)	15.7 ± 19.6	9%
Smoking status	Current: 11% (37) Previous: 57% (188) Never: 31% (102)	0%
Statin use	49% (157)	3%
Ace inhibitor use	26% (82)	3%
Cardiovascular disease	41% (133)	0%
Diabetes	16% (38)	0%
Hypercholesterolemia	62% (198)	2%
Hypertension	60% (196)	0%

2.5. Data Analysis. Our missing data analysis procedures used missing at random (MAR) assumptions, as per Rubin's rules [63]. We used the PROC MI method of multiple multivariate imputation in SAS. We independently analyzed 5 copies of the data, each with missing values imputed, and then used PROC MIANALYZE to average estimates of the variables to give a single mean estimate and adjusted standard errors according to Harrell's guidelines [64]. Details of the amount of missing data per variable are included in Table 2.

To examine the contributions of physical activity, smoking, obesity, and alcohol consumption to EF, a series of GLMs on the individual variables was also conducted, first for the individual health behaviours alone, second with the individual health behaviours and covariates, and third for all four behaviours together and the covariates. Since a nonlinear relationship was expected to exist between alcohol consumption and EF, participants were split into one of three groups in terms of their alcohol consumption. Group 1 consisted of heavy drinkers (defined as 22 or more drinks per week), group 2 consisted of abstainers, and group 3 consisted of moderate drinkers (1–21 drinks per week). The groups were defined as such since consuming 1–3 drinks per day has been associated with better EF than abstinence [51], while 4 or more drinks have been found to negatively impact EF acutely [50]. It was therefore expected that heavy drinkers would have the worst EF and moderate drinkers would have the best EF, creating a linear relationship between group number and EF. Age, sex, CVD status (CVD was defined as having a previous myocardial infarction, stroke, angioplasty, or coronary artery bypass graft), ace inhibitor use, statin use, hypertension, diabetes, and hypercholesterolemia were chosen as covariates *a priori*,

as all have been shown to have strong independent effects on EF [7, 65–71]. To examine potential interactions between the health behaviours an interaction term for each pair of continuous health behaviours was included one at a time in a GLM including the above-mentioned covariates.

To examine possible associations between the health behaviours and risk of having endothelial dysfunction, defined as an RUR under 3.55, two logistic regression analyses were conducted predicting endothelial dysfunction from all four health behaviours and the covariates together. For these analyses, waist circumference was split into tertiles: <92 cm, 92–108 cm, and >108 cm. Smoking was defined by smoking status (current/past/never). Alcohol consumption was split by the groups described above. Finally, physical activity was split into tertiles: 0, 0–9.7 and >9.7 MET-hrs/week.

3. Results

The characteristics of the 328 participants are presented in Table 2. The GLM analyses for individual health behaviours revealed that waist circumference (β (SEM) = −.03 (.01), $P <$ .0001) contributed significantly to EF. A trend for an effect of smoking on EF measured using pack-years ($F = 1.78$, $P =$ .075) was also found. However, physical activity (β (SEM) = −.01 (.01), $P =$ .528), smoking status (β (SEM) = −.22 (.15), $P =$ .131), and alcohol consumption (β (SEM) = .19 (.12), $P =$ .136) were not associated with EF as a continuous variable.

GLMs for the individual health behaviours with age, sex, CVD status, ace inhibitor use, statin use, hypertension, diabetes, and hypercholesterolemia as covariates were then conducted. These analyses revealed that waist circumference (β (SEM) = −.04 (.01), $P <$ .0001) contributed significantly to the variability in EF, while physical activity (β (SEM) = −.01 (.01), $P =$ .398), alcohol consumption (β (SEM) = −.17 (.13), $P =$ .167), and smoking measured according to pack-years (β (SEM) = −.01 (.01), $P =$ .203) or smoking status (β (SEM) = −.21 (.15), $P =$ .153) did not.

Results of a GLM with all covariates and health behaviours included revealed that waist circumference was a significant independent predictor of EF considered as a continuous variable (Table 3 and Figure 1). Neither alcohol consumption, physical activity, nor smoking, measured according to pack years were significantly related to EF (Table 3). Comparable results were found when lifetime smoking was replaced by current smoking status.

The results of the GLMs separately examining the interaction between each pair of health behaviours revealed no significant interaction effects.

A logistic regression analysis, including all covariates and health behaviours in the model revealed that in comparison to the lowest tertile of waist circumference (<92 cm), being in the second tertile (92–108 cm) was associated with a 90% increased risk of endothelial dysfunction (OR = 1.90, 95% CI = 1.01–3.59). Being in the third tertile for waist circumference (>108 cm), on the other hand, was associated with more than double the risk of endothelial dysfunction (OR = 2.39, 95% CI = 1.15–4.98). Alcohol consumption group was also a significant predictor of endothelial dysfunction such that being a nondrinker versus a moderate drinker was associated with nearly double the risk of endothelial dysfunction (OR = 1.99, 95% CI = 1.08–3.70), while the risk associated with being a heavy drinker did not differ from being a moderate drinker (OR = 1.57, 95% CI = 0.82–2.86). Being a past smoker versus a never smoker was associated with double the risk of endothelial dysfunction (OR = 2.00, 95% CI = 1.26–3.75), while the risk associated with being a current smoker did not reach significance (OR = 2.17, 95% CI = 0.88–4.84). Finally, the odds ratios for being in the first (OR = 0.82, 95% CI = 0.44–1.53) or second tertile (OR = 1.29, 95% CI = 0.70–2.35) in comparison with the third tertile for physical activity were not significant (Figure 2).

Table 3: Summary of multiple regression analysis for all health behaviours predicting brachial artery reactivity, controlling for age, sex, CVD status, ace inhibitor use, statin use, hypertension, diabetes, and hypercholesterolemia.

Variable	β	SE	t	P
Waist circumference	−0.03	0.01	−3.95	<.000
Physical activity	−0.01	0.01	−1.01	.313
Lifetime smoking	−0.00	0.01	−0.86	.392
Alcohol usage	0.14	0.12	−1.13	.258

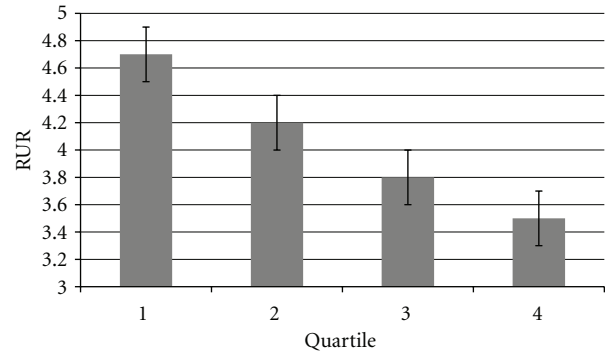

Figure 1: Mean relative uptake ratio (RUR) as a function of waist circumference split into quartiles, with standard error bars, adjusting for covariates, smoking, physical activity, and alcohol consumption.

4. Discussion

This study is the first attempt to assess the effects of waist circumference, physical activity, alcohol consumption, and smoking on EF in a single sample of cardiac patients. The GLM analyses revealed that waist circumference was negatively associated with continuous variations in EF and that there was a trend for a significant negative association between lifetime smoking and EF when they were each included in the model alone. However, when covariates were added to the model, this trend disappeared but the significant effect of waist circumference on EF remained. When all four health behaviours were included in the same model with the covariates, only waist circumference was significantly associated with EF considered as a continuous

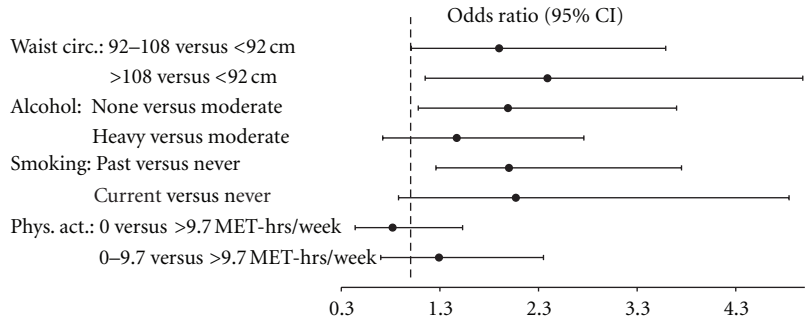

Figure 2: Forest plot of odds-ratios and 95% confidence intervals for the effect of each health behaviour on endothelial dysfunction adjusting for covariates and the other health behaviours.

variable. Additional logistic regression analyses, including all four health behaviours and covariates together, revealed that increased waist circumference also increased risk for clinical endothelial dysfunction. Surprisingly, abstinence from alcohol and past smoking predicted endothelial dysfunction, while heavy alcohol consumption and current smoking did not.

The current findings suggest that central adiposity is negatively associated with EF. Consistent with the current findings, several studies have found measures of central adiposity such as waist circumference and waist-hip ratio, to be predictors of cardiovascular outcomes in patients both with [72] and without [73–77] known CVD. Although the exact mechanism behind this obesity-induced increase in endothelial dysfunction is unclear, two candidate processes have been proposed: (1) via alternations in adipokine levels; and (2) via increases in free fatty acid levels. In brief, it would appear that increasing levels of obesity are associated with increases in adipokines that negatively influence the endothelium [78], and decreases in adipokines that exert positive effects on the endothelium [79]. For example, leptin, which is increased in obese patients, has been shown to increase the release of reactive oxygen species in human endothelial cells [78], thus diminishing the bioavailability of nitric oxide (NO), an important vasodilator and inhibitor of inflammation and platelet aggregation. Alternatively, adiponectin, which is downregulated in obese individuals [79], stimulates nitric oxide production, and promotes vasodilation [80]. Recent studies have also found increased levels of endothelial dysfunction when free fatty acids, which are abundant in patients with abdominal obesity [81], were administered exogenously [82, 83]. This alteration is thought to occur by free fatty acids decreasing endothelial nitric oxide synthase (eNOS) activity [82].

The findings regarding cigarette smoking and alcohol use are somewhat more complex. That is, GLM analyses indicate that these variables were not associated with continuous fluctuations of EF. However, the logistic regression analyses reveal that past (but not current) smoking and abstinence from alcohol (but not heavy consumption) both increased the risk of endothelial dysfunction. The fact that the odds ratios for current smoking did not reach significance may be partially due to small sample sizes since relatively few participants were current smokers. The finding that past smoking was associated with an increased risk of endothelial dysfunction suggests that smoking-induced endothelial damage is long lasting. This is consistent with previous research finding that the somewhat improved flow-mediated dilation of former smokers was not statistically greater than current smokers [6]. Smoking is thought to damage endothelial cells directly [84] and to increase oxidative stress, thereby decreasing nitric oxide availability [85]. Smoking also appears to reduce the immune system's ability to repair this endothelial damage by decreasing the number of circulating endothelial progenitor cells, which are mobilised in response to vascular injury [86]. Following smoking cessation, the number of circulating endothelial progenitor cells has been found to increase rapidly [87], suggesting that the EF of ex-smokers should begin improving soon after quitting. However, it is unknown to what extent the length of time of smoking or the length of time since quitting impacts current EF. It may therefore be the case that the ex-smokers in the current study had either smoked too long or had not been smoke-free long enough to exhibit fully recovered EF.

Our finding that heavy alcohol consumption is not associated with greater risk of endothelial dysfunction is inconsistent with previous research finding that heavy consumption has been found to induce endothelial cell apoptosis by increasing oxidative stress [88] and impairing nitric oxide production [89]. This finding may therefore be related to sample size, considering the relatively small number of heavy drinkers in the current study. However, that moderate alcohol consumption is associated with better EF than abstinence is consistent with previous findings [51]. It is believed that moderate alcohol consumption may improve EF by increasing NO levels [90] and decreasing homocysteine levels, which is an amino acid causing oxidative stress [91].

That physical activity was not found to be associated with EF is inconsistent with studies comparing sedentary individuals with athletes [9–11] but is consistent with the one study that has examined the relationship between moderate physical activity and EF in adults [30]. This finding suggests that physical activity may contribute little to EF among moderately active individuals at high risk for cardiovascular disease who likely engage in several poor health behaviours at once. Considering the average participant in this study does not meet the minimum requirements for physical activity set by the American College of Sports Medicine and the

American Heart Association [92], which is between 7.5 and 12.5 MET-hrs/week, greater levels of physical activity may be needed to see its effect on EF.

Of course, the results of the current study must be considered in light of some limitations. As with all cross-sectional studies, it is impossible to draw conclusions about the cause and effect relationship between the health behaviours assessed and EF. The current study also used retrospective self-report measures for physical activity, alcohol consumption, and smoking, which may be susceptible to recall bias. Drink type was also not taken into account for alcohol consumption, which is problematic given that wine has been found to have a unique beneficial effect on EF [47, 93]. Our failure to record patients' use of nicotine replacement therapy, known to affect EF [94], is also a limitation.

While the current study has its limitations, the fact that it examined the relationship between EF and smoking, obesity, physical activity, and alcohol consumption in the same statistical model is an important and unique strength. While other studies that have examined the effect of only one health behaviour on EF risk overestimating the portion of variance in EF explained by the behaviour, the present study should more accurately estimate the independent effect of each health behaviour on EF. This is particularly true since poor health behaviours tend to aggregate. It is also a strength that this study examined the effect of health behaviours on EF in a sample of patients at risk for cardiovascular disease since poor health behaviours would be expected to have the most important and imminent impact in this population. Other strengths of this study include its large sample size, the inclusion of several important covariates, and the quality of the health behaviour measures used. Finally, despite the relative novelty of the FHR technique, it has been shown to be highly reliable [59] and reproducible [58, 95].

In conclusion, the results of this study indicate that central adiposity and smoking are independently associated with worsening EF, while moderate alcohol consumption appears to have an independent positive effect on EF. Physical activity, on the other hand, does not seem to be associated with EF when controlling for other health behaviours and relevant covariates. These findings may imply that within a population exhibiting numerous risk factors for cardiovascular disease, weight reduction, smoking cessation, and moderate alcohol consumption should be emphasized and prioritized over increasing physical activity as interventions to improve patients' cardiovascular profiles. This prioritization may be particularly helpful given the difficulty with which individuals change just one health behaviour. Further work is needed to confirm the mechanisms by which central adiposity, smoking and alcohol consumption influence EF. Further research is also needed to examine the effect of health behaviours on EF over a longer period of time to examine how EF changes as a function of health behaviours over time. Future research should also aim to assess the extent to which the relationship between health behaviours and cardiovascular disease is explained by the impact of health behaviours on EF.

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Review Article

From Brain to Behavior: Hypertension's Modulation of Cognition and Affect

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Accumulating evidence from animal models and human studies of essential hypertension suggest that brain regulation of the vasculature is impacted by the disease. Human neuroimaging findings suggest that the brain may be an early target of the disease. This observation reinforces earlier research suggesting that psychological factors may be one of the many contributory factors to the initiation of the disease. Alternatively or in addition, initial blood pressure increases may impact cognitive and/or affective function. Evidence for an impact of blood pressure on the perception and experience of affect is reviewed vis-a-vis brain imaging findings suggesting that such involvement in hypertensive individuals is likely.

1. Introduction

Despite a long history of putative relationship between essential hypertension and psychological function, clear, particularly mechanistic, relationships remain elusive. Early work in humans postulated relationships between anger regulation and blood pressure [1] and work in animal models has long shown brain involvement in heightening blood pressure [2–4]. Recent animal investigations have reinforced this relationship and further implicated immune influences on blood pressure control [5]. The advent of brain imaging has been useful in specifying more clearly the neural involvement in hypertension and providing a possible bridge between behavioral and self-report information in humans and the mechanistic observations in animal models. The initial focus of the current paper is on neuroimaging results in humans. We argue that these findings suggest that the brain is an early target for hypertension. We then explore the implications for cognition and affect of these brain findings. Ideally, brain imaging can be used to further not only assessment of brain mechanisms but also complement psychological and neurophysiological investigations of the widely prevalent disease of essential hypertension.

2. Cross-Sectional Findings

Our work has led us to raise the possibility that essential hypertension early in its course alters brain function, see recent summary [6]. Initial studies compared normotensive individuals with hypertensive individuals without recent history of medication treatment [7, 8]. Based on prior work showing mild cognitive deficits in hypertensive individuals [9], we examined brain function using positron emission tomography while participants performed a working memory task; brain structure was assessed using magnetic resonance imaging. Similarities of performance and brain function were more striking than differences between the two groups, but a number of differences were evident. During memory performance, normotensive participants showed a greater regional cerebral blood flow (rCBF) response in the posterior parietal and thalamic brain areas, while hypertensive participants showed a greater extent of activation in the prefrontal cortex [10]. Relatedly, the activation of different areas of the brain during the memory task was more highly correlated in hypertensive relative to normotensive participants [8]. Other investigators have reported relatively decreased grey matter volume in certain brain areas among hypertensive relative to normotensive individuals [11, 12],

and we found differences as well [13]. Similarly, our results were consistent with prior reports of brain indices of aging. Namely, decreases in ventricular volumes in the brain as well as increases in prevalence of white matter hyperintensities were more evident in hypertensive individuals compared to similarly aged normotensive individuals, for example, [14]. Finally, blood pressure reactivity to laboratory challenges is known to prospectively relate to essential hypertension [15], and work of our colleague, Peter Gianaros, has shown consistent relationships between degree of activation in a number of limbic brain regions and degree of blood pressure response to challenges [16–19]. The results of our cross-sectional work clearly established that the human brain was impacted by hypertension. The presence of brain correlates of blood pressure responding in normotensive individuals suggested that blood pressure reactivity might be contributing to the later impact of hypertension on the brain. These results lead us to propose a vascular hypothesis suggesting that vascular responses as well as chronic cerebrovascular changes due to the disease had a subsequent impact on neural and thus neuropsychological (cognitive) function [7].

3. Longitudinal Findings

An intervention study based on our cerebrovascular hypothesis, however, led us to consider an alternative possibility that neural changes preceded or were concomitant with vascular changes induced by essential hypertension. Based on our vascular hypothesis, we treated previously unmedicated hypertensive patients for a year with an angiotensin converting enzyme (ACE) inhibitor or with *a beta* blocker. Prior work suggested that the ACE inhibitor would reverse vascular morphology changes associated with hypertension while the *beta* blocker would not, for example, [20, 21]. Remediation of the vascular morphology was then expected to enhance the capability of the hypertensive patients to vasodilate cortical vessels and hence more effectively adjust blood flow to active brain areas. In fact, despite excellent reductions in blood pressure by both medications, no differences between them or in pre- to postassessments occurred in resting or task-related cerebral blood flow [22]. Despite this failure of the test of our vascular hypothesis, some important observations were made. We had expected the lowering of blood pressure to reverse or stabilize brain indices that we had related to hypertension in our cross-sectional study. In fact, the degree of concomitant activation across brain areas increased and grey matter volume loss continued [23, 24]. Moreover, the degree of brain aging pretreatment and the robustness of the thalamic response to working memory pretreatment were predictive of the success of blood pressure lowering [22]. The state of the brain seemed to be a proxy for the severity of the essential hypertension. In short, a pathophysiological process underlying essential hypertension seemed to be continuing to influence the brain—peripheral pressure per se did not seem to be causing the brain changes that continued to be observed. Arguably, our intervention was only a year in the course of a long-lasting disease and alternative interpretations can be drawn. At present, we are attempting to support the hypothesis that brain changes are an early target of hypertension by examining whether brain signs of essential hypertension are present prior to or concurrently with the changes in blood pressure that lead to diagnosed essential hypertension.

4. Pathophysiology of Essential Hypertension

What are the implications of the possibility that essential hypertension is a disease that influences the brain early in its course? Furthermore, what factors might predispose individuals to essential hypertension and be so prevalent in our society that more than half of us over the age of sixty have essential hypertension? One implication is that factors influencing the brain rather directly, such as psychosocial factors, may be as important as biological and behavioral factors in contributing to the etiology of essential hypertension. This implication is hardly novel; it has been posited for many years, particularly within the psychosomatic medicine tradition. Few, however, believe that psychosocial factors are the sole cause of essential hypertension. The best concept of the causation of hypertension may still be the mosaic theory of Page [25, 26] that emphasizes the multiple factors known to influence the disease and the regulatory interactions between these factors. Essential hypertension is then expected to arise from not a single factor but rather numerous and likely different combinations of factors. Any particular combination of dysregulated processes may then overwhelm the complex, but redundant regulatory system that aims to maintain normal blood pressure. Approximately 30 years ago, Weiner [27] provided a comprehensive review of the psychobiology of hypertension with careful attention to extant work in humans and animal models. His approach echoed the mosaic theory, but evidence was updated and viewed from a psychosomatic perspective. The general conclusions from that review remain valid today. Essential hypertension appears to have multiple causes and may not even be a single disease. In addition, the factors inducing high blood pressure may not be the same as those maintaining the high blood pressure. The various etiological possibilities all involve a failure of regulatory function—within neural control of blood pressure, renal, and/or endocrine function.

Recent work has largely reinforced these conclusions [30–33]. Factors in the pathophysiology of hypertension noted by Page remain important and our knowledge of these individually are growing, for example, genetic, endocrine, and immune factors [5, 34–38]. Of note, greater attention to renal involvement in hypertension has been combined with greater knowledge of the interaction of renal and neural control [39–43].

We can examine the renin-angiotensin system more closely to illustrate the increasing importance of central regulation. The peripheral renin-angiotensin system has well-known influences on the kidney and vasculature, but maintenance of blood pressure also seems to involve renin-angiotensin present in the central nervous system. Angiotensin is present and appears active in the nucleus tractus solitarius and the dorsolateral ventral medulla—important blood

pressure regulatory areas [44]. Circulating angiotensin is also known to influence the brain via transmission through the circumventricular organ. Brain angiotensin influences neuroendocrine systems and, more surprisingly, influences learning and memory in animal models [45, 46]. Finally, angiotensin is responsive to stress and antagonists appear to both lessen stress responses and improve learning and memory in animal models [45, 46]. Thus, a disruption of the renin-angiotensin system would concurrently impact both brain and vascular function. This may account in part for interest in medication influencing brain angiotensin receptors that preserves brain function while reducing peripheral blood pressure as well as other medication [47].

5. Central Factors in Essential Hypertension

As part of the mosaic of disease factors, the involvement of neural control in affected regulatory systems suggests that the nervous system is contributory to the etiology and maintenance of some, if not all forms of, essential hypertension as well as it being a target of the disease. In reviewing the then-popular concept of "borderline hypertension," Weiner found stress to be a supportable factor influencing the pathophysiology of essential hypertension presumably through its impact on brain function. He found reasonably strong evidence for stressful experience moderating the development of hypertension in animal models, potential mediation by sympathetic nervous system dysfunction, and remediation of blood pressure with interventions on neural control. If anything since Weiner's review, psychological factors have been increasingly mentioned among initiating factors in concepts of hypertension unifying neural and renal factors in the disease, for example, [48, 49] The number of mechanisms which could be impacted by neural control has grown, but linking them to initiating factors is complex, particularly in humans. How the various influential factors become dysregulated and interact to create the natural history of regulatory failures that can lead to hypertension remains unknown. In short, as our knowledge of blood pressure regulation expands, the intertwining of neural, endocrine, and immune control becomes more evident as does the importance of central nervous system control. The robustness of these conclusions, however, should not be construed as resolving the primary question. We lack an empirically supported, general model of how blood pressure control is integrated such that essential hypertension occurs when a dysfunction occurs within one or, more likely, more contributory mechanisms.

Coordination by the brain does, however, seem critical to the operation of such a multifaceted control system. Regulatory failure due to any cause must influence normal brain function because the brain normally maintains normotensive levels of blood pressure. Brain counterregulation must fail, the brain itself may be affected, or the range of regulation possible must simply be exceeded so that the brain becomes permissive of heightened pressures. From this perspective, the brain must be an early target of essential hypertension. It remains arguable whether brain pathology is a primary initiating factor in essential hypertension. What psychological/behavioral factors might impact the brain and contribute to hypertension and be consistent with the present day pandemic level of essential hypertension? Diet/salt intake, physical inactivity, and stress seem likely candidates—factors readily related to demonstrated influences on hypertension (see, e.g., [50]).

For the remainder of our discussion we will focus on stress as an important factor that acts in concern with other biological and psychosocial factors. This focus is partially one of our personal interests, but one could argue that diet/salt and physical inactivity are themselves driven in part by coping with stress. In this context, it is important to point out that our discussion will proceed from accepting the global use of the term "stress" for purposes of the reviewing literature to a more specific examination of affective processing. In the future, it may be useful to assess separable influences of the environmental or psychological stressor, the individual's appraisal of such stressors, and their evaluation and use of particular coping strategies, see Lazarus [51, 52]. For example, the idea that overeating and physical inactivity are coping activities in response to stress is typically not well-supported empirically due to measurement difficulties as well as, typically, the investigators' greater interest in the maladaptive behavior itself and less with its exact source. Stress encompassing the constellation of involved stressors and processes provides a convenient proxy until we can analytically separate factors most critical for our dependent variable of interest, be it hypertension or dysphoria.

A second reason for our focus on stress is another finding from our treatment study that we briefly reviewed at the beginning of this paper. Examining individual differences in both the response to treatment of blood pressure and working memory performance, we observed a dorsomedial prefrontal area that was related to both [28]. The result suggested that activation in this area favored successful reduction in blood pressure levels but at the cost of poorer performance on working memory (in comparison to their pretreatment performance). As shown in Figure 1, in the same general brain area, we observed significant subareas in which significant regional cerebral blood flow activation posttreatment relative to pretreatment: (a) correlated with how well a participant had lowered blood pressure, (b) correlated negatively with the change in memory performance, and (c) correlated with both blood pressure lowering and memory performance—an area sharing these correlations. A thorough quantitative review of the literature [29] suggested that this virtually exact dorsomedial prefrontal area related to the contextual factors influencing emotion as well as to autonomic reactivity. Subsequent work (reviewed through http://www.neurosynth.org/) continues to support this functional relationship to affective responses to faces and scenes [53] and to autonomic nervous system responding [54, 55]. The latter paper is particularly relevant in that the dorsomedial prefrontal cortex showed an overlapping area that related to both autonomic responding (heart rate variability, blood pressure was not reported upon) as well as affective evaluation. Dorsomedial prefrontal cortex activation has

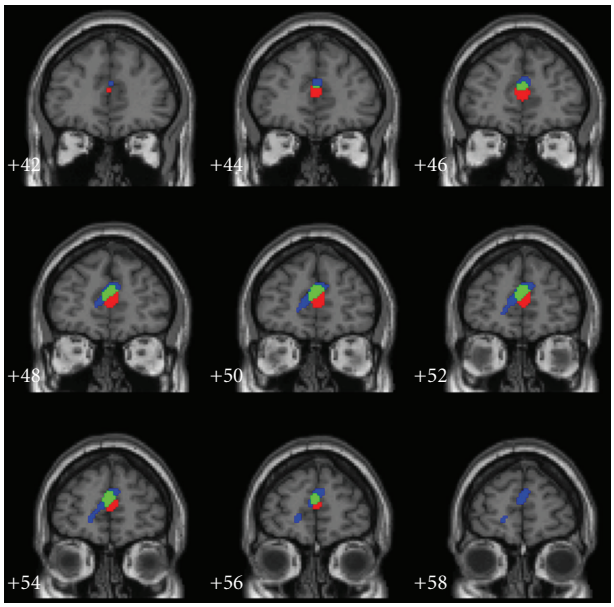

Figure 1: Dorsomedial prefrontal area in which greater regional cerebral blood flow post-treatment related to either better blood pressure decrease (red), poorer post-relative to pretreatment working memory performance (blue), or both (green). See details and relevant review [28, 29].

been related to empathetic responses with greater activation related to less tendency for personal distress [56]; a finding related to the modulation of dorsomedial prefrontal activation when anticipatory set was used to modulate affect [57]. Notably though, some work has shown the dorsomedial prefrontal cortex to be related to greater cortisol response to stress [58]; while other work again suggests activation of this area to be related to lower sensitivity to fear and disgust [59]. Overall, the literature seems consistent with an interpretation that at least portions of the dorsomedial prefrontal area organize affective and autonomic response to a challenge. If so, we then speculate that successful blood pressure regulation altered this organization in our treatment study. After treatment, a damping of the cognitive/affective response to challenge may have been instrumental in maintaining lower blood pressure. If this interpretation is correct, we could suspect that individual differences in the affective evaluation and response to situations might relate to the control of blood pressure and that these individual differences that might be expected to relate to individual differences in activation of dorsomedial prefrontal cortex.

An alternative to examining affective regulation would be examining cognitive function vis-a-vis hypertension. Indeed, our work was launched based on reviews showing that hypertensive individuals performed slightly more poorly than normotensive individuals on tests of executive attention and working memory [9, 60]. Cognitive function, however, remained stable throughout our treatment study. In addition, regional cerebral blood flow responses to a working memory task were unaffected by the successful treatment of blood pressure.

6. Stress and Hypertension

The notion that stress causes hypertension is popularly accepted, but the scientific basis for this is somewhat lacking. An initial issue is simply that stress refers to a host of conditions so that the statement that stress causes hypertension is simply impossibly vague. Scientific usage varies between stress defined as a response to a laboratory computer challenge or a daily hassle, to stress defined as the loss of a spouse or as a response to a continuing divorce proceeding. The popularity of the term likely stems from the sense that external events rather than one's own personality or misbehavior are inducing a negative psychological reaction. Being stressed is more socially acceptable than other alternatives for explaining negative psychological states. Stress, though, is certainly an interaction between the person and the environmental situation as so elegantly described by Lazarus [51, 52].

Reviews of stress and hypertension vary somewhat in how they use the stress concept, but generally are only minimally supportive of a relationship between stress, variously defined, and hypertension. Nykliček et al. [61] found that objective measures of stress were related to heightened blood pressure (though not all studies assessed essential hypertension per se). Objective measures in this paper included exposure to natural disasters, unsafe neighborhood conditions, noise exposure, and stressful occupation. In contrast they report minimal association when self reported stress was related to blood pressure. They make a reasonable case for a difference between studies examining hypertensive patients aware of their disorder relative to studies examining individuals unaware of their blood pressure status. Hypertensive patients were seen as tending to report a stressful background, possibly as an explanation to themselves of their condition. Unaware individuals with high blood pressure were observed to report low levels of stress and overall high psychological wellbeing. The reviewers suggest that contradictory findings relating hypertension to recalled stressful life events and occupational stress may be due in part to this dependence of stress reporting on awareness of hypertension. Another review examines an individual difference dimension that was developed specifically in relation to stress and hypertension in African Americans. As reviewed by Bennett et al. [62], John Henryism refers to a style of coping with stress—specifically, continuous active coping—that theoretically would positively correlate with blood pressure in groups faced with chronic stress and few resources, that is, lower class African Americans. Initial evidence supported this conceptualization, but the review notes results suggesting that the concept is not specific to African Americans and has been related to blood pressure in some studies regardless of social class or even more strongly in upper classes. John Henryism is interesting since that coping style contrasts markedly with the earlier descriptions of the hypertensive personality (see below). The concept may align more closely with work stress in the presence of little job control. Nonetheless, the review suggests that the relationship of John Henryism to blood pressure is now more obscure than when the concept was introduced. A more recent review [63] selected only studies

that were longitudinal or used case-control designs (reducing studies examined from 82 to 14, but still with over fifty-two thousand individuals included). Three studies examined the hypertensive aftermath of acute stressors, such as natural disasters, and no association was found between the acute stressors and blood pressure. This is in contrast to the prior review and suggests that the shorter term blood pressure increases after acute stress events may not be sustained, that is, essential hypertension may not be expressed after 3 years or more have passed since the acute event. When chronic stress was reviewed, the seven qualifying studies generally supported an association with better evidence for job stress. Affective response was examined and included reports of hopelessness and racial discrimination, that is, internalized responses assumed to result from a history of stressful events. Although mixed, the majority of these studies did show an association albeit not large between the affective response and hypertension. Overall, positive odds ratios from their reviews predominated, but the authors reserved judgment until better-designed studies with well-defined exposures and control for confounds were available. It is unfortunate that this review did not consider the hypertension awareness issue raised in the Nykliček review.

7. Cardiovascular Reactivity and Stress

One definition of stress of direct relevance to hypertension refers to the acute changes in blood pressure that occur in the laboratory in response to mental challenge tasks. Participants report that they find such tasks stressful, so the blood pressure responses to such tasks are then defined as a stress response. The mechanism of how such responses lead to essential hypertension is difficult to establish, although such responses do relate to the incidence of later hypertension [64], and, as noted above, brain mediation of such individual differences in responsivity seems established [16, 17, 65]. Reviews support the prospective relationship between heightened blood pressure response to such laboratory challenges and subsequent hypertension [15, 66]. This relationship has not been clearly shown to be mediated by psychological factors although there is a report of defensiveness contributing to the relationship between blood pressure reactivity to laboratory stress and subsequent high blood pressure [67]. The psychophysiological pathways between such acute pressure changes and the chronic disease state have been discussed by Krantz and Manuck [68]. As they note, the prospective correlation of acute blood pressure reactions and later hypertension might be seen as mechanistic if the laboratory reactivity generalized to either repetitive reactions in daily life or tonic increases during daytime or sleep hours [69, 70]. Strong evidence for such relationships has not been found, however, [64] although concepts of sustained reaction to acute events have been proposed to interact with other factors in the etiology of hypertension [71]. A promising, but not yet completely established, link would be between hypertension and delayed recovery of cardiovascular responses after an acute stressor as possibly related to continuing intrusive thoughts relevant to the stress, that is, rumination [72]. In short, stress defined as a cardiovascular reaction can be related to hypertension, but this defines stress in a circular fashion so our knowledge of psychological factors, more commonly thought to involve stress, is minimally advanced.

8. Pain and Hypertension

Although stress results in discomfort, the term is not usually applied to the acute reaction to a noxious stimulus, pain. Nonetheless, pain can be seen as a negative affect and pain has been well studied as a function of blood pressure. Pain perception is importantly related to blood pressure. France [73] reviewed the large body of evidence relating diminished pain sensitivity in animals and humans to high blood pressure. He also addressed the question of whether hypertension induces a reduction in pain sensitivity or if pain sensitivity changes precede the development of hypertension. Earlier, in a well-known paper, Dworkin et al. argued that acute blood pressure increases reduced pain and thus hypertension was acquired through instrumental learning reinforced by this reduction in pain sensitivity [74, 75]. Their model suggested that the baroreceptors in the carotid sinus and aortic arch responded to transiently increased pressure through transmission to the nucleus tractus solitarius, which then had a damping effect both on pain perception and blood pressure, see discussion of baroreceptor function in Berntson et al. [76]. The association of a reduction in pain contingent on an increase in blood pressure was the mechanism posited to lead to hypertension. This model has mixed empirical support and France [73] sought more general support for the hypothesis that pain hyposensitivity precedes the development of hypertension. This is supported by work in animal models of hypertension; at risk animals tested prior to the development of hypertension showing greater pain hyposensitivity relative to animals not at risk. Studies of humans at risk for hypertension due to family history and/or heightened resting blood pressure also have been observed to show a pain hyposensitivity. Finally, hypertension has been related to reduced pain reports during induction of baroreceptor reflexes. Based on this review, France [73] speculated that pathophysiology of the paraventricular area of the hypothalamus may be the mechanism for the reduced pain sensitivity. Functioning of this area is thought to act on pain through action of the baroreceptor reflex and its impact on enkephalins, through heightened opioid stimulation, or heightened activation of descending pathways inhibiting pain. Although exceptions exist, the opioid changes related to heightened blood pressure are the best known among these supposed pathways [77–79]. Recent work on visceral and somatic afferents, however, demonstrate surprisingly sustained effects on blood pressure of small fiber stimulation—effects mediated by long loop connections with the arcuate nucleus of the hypothalamus (known to regulate endogenous opioids) and with connections to neural areas known to exert sympathetic nervous system influences on blood pressure (i.e., rostral ventrolateral medulla) [80].

The relevance of this relationship between blood pressure and pain perception is increased by recent studies on both

brain imaging and the perception of emotion. Recent brain imaging studies have examined the "pain" of social exclusion and observed a striking overlap between brain regions responsive to this and to physical pain [81, 82]. Such findings support observations suggesting that blood pressure regulation may be more generally related to affect, for example, [83]. Relatedly, hints of an empirical relationship between underreporting of affect/wellbeing and the relative insensitivity to pain often observed among hypertensives were also found by Nyklíček et al. [84].

9. Personality and Hypertension

The examination of "affective response" as related to stress renders another review relevant; one relating hypertension to psychological factors closer to personality in most cases [85]. This review relates to the long history of cross-sectional studies claiming to reveal a "hypertensive personality" (see [27, 86, 87]), but chose to examine only prospective, longitudinal studies excluding the possibility of an influence of "hypertension awareness" and more reasonably raising the possibility that the psychological factor have a causative role. Fifteen qualifying studies were found. The majority of these examined negative affect (anger, hostility, defensiveness), but depression, neuroticism, and psychopathology were also represented. Among these studies, the majority was observed to show a relationship, but the strength of the overall relationship was low—corresponding to an r of.08. The Sparrenberger review [63] comments that some subsequent studies after the date of this review specifically examining depression have not observed a relationship.

10. Psychological Processes and Hypertension

Although physiological reactions, recovery, and pain sensitivity could mold personality and behavior, it seems more likely that some aspect of personality might lead to consistent interactions with the environment creating a risk for hypertension. Such a personality feature might relate directly to hypertensive risk or might act through cardiovascular reactivity. (To date, however, a personality mediator for blood pressure reactivity results has not been evident.) We assume that this aspect of personality might contribute to the present, but small relationships observed between stress broadly conceived (as in the reviews above) and high blood pressure. Based on our brain imaging results and the close relationship between stress and affect, in the remainder of the paper we will focus on current developments relating to the question of whether a particular aspect of affect perception and expression may be important in the etiology or early stage of essential hypertension.

As noted earlier, early psychosomatic theories propose a "hypertensive personality" that contributes to the development of hypertension [1, 86–89], with persons at risk for hypertension showing increased emotionality in everyday situations [86, 87]. Other work suggested a blunted perception of negative events that might be yet more specific than a personality type [90]. In the late 1970s Weiner [27] reviewed this literature as suggesting a relatively socially withdrawn personality that tended to be avoidant, but that could be hostile. Subsequent literature focused on the negative affect aspect. As noted above, a review of studies prospectively relating psychological factors to the development of hypertension did observe a small, but quantitatively supported relationship between measures of negative affect and hypertension development [85]. This relationship showed little specificity, however, as the measures showing predictivity included anger-in, trait anger, anger-out, anxiety, depression, anger-control, defensiveness, hopelessness, neuroticism, hostility and psychopathology.

11. Affectivity and Hypertension

There is a large body of literature connecting affect and hypertension [27, 91, 92]. The concept of a "hypertensive personality" origin of hypertension failed to achieve solid support and research moved toward the belief that hypertension and affective changes result from a common etiology related to affect. The literature continued to relate elevated blood pressure and essential hypertension with lower affect expression, more negative affectivity, and defensiveness (for a comprehensive review that goes beyond that possible here, see Jorgensen et al. 1996 [91]). Of note is a review by [92] explicitly examining whether high negative affect (anger ex-perience) combined with inhibited anger expression, that is, one version of the "hypertensive personality", was related to blood pressure. They failed to find this relationship but did show a small quantitative relationship between experience of negative affect and blood pressure—anger expression was not consistently related to blood pressure [92]. Of interest though, they note that the two scales most strongly relating negative affect/anger experience to blood pressure assess both these feelings as well as a reluctance to express such feelings.

The reluctance to express or even recognize affect has been examined separately as a correlate of blood pressure. Research on alexithymia, the inability to describe one's emotions, and hypertension has shown a positive relationship. A number of studies using shortened versions of the Toronto Alexithymia Scale (TAS) have found higher scores on the TAS-20 or TAS-26 to be correlated with higher blood pressures [93–96]. None of these studies have however been able to move beyond the observed relationship to an explanation of how hypertension leads to alexithymia or vice versa. Furthermore, there is some disagreement about the general relationship of alexithymia and hypertension [97, 98] as well as concern that only particular aspects of alexithymia may relate to heightened blood pressure [99]. Alexithymia may be considered to reflect an inability to verbalize one's own emotions, but it might also reflect a general impairment in the ability to recognize emotion. Lane et al. [100], for example, found that two alexithymia measures, the Toronto Alexithymia Scale and the Levels of Emotional Awareness, both correlate with the Perception of Affect test, which is designed to assess accuracy of verbal, non-verbal, and mixed (verbal and nonverbal) emotion recognition. This

relationship potentially links alexithymia to the literature on decreased emotion recognition in hypertensives.

Blunted perception of negative affect as well as blunted expression of affect once established has been suggested to help those unsuccessful at interpersonal conflict to avoid these situations resulting in a "profile of submissiveness, conflict avoidance, and low levels of anger experience and expression" [91]. A review by Jorgensen et al. focused on studies looking at measures of affect expression, negative affectivity, defensiveness (characterized by denial, repressive coping, and damping of affective function), or a combination of these in conjunction with measures of blood pressure [91]. The resulting meta-analysis of 83 studies found that individuals with higher blood pressure tended to have lower affect expression but higher negative affectivity and defensiveness than those with lower BP [91]. Additionally, awareness of hypertensive status was a significant predictor of study outcomes for both affect expression and negative affectivity [91]. Studies were not available to test whether awareness of hypertensive status influenced defensiveness. Of note, whether they were aware or unaware of their blood pressure levels, participants with high blood pressure were lower on affect expression than participants with lower blood pressure levels. Ultimately the analysis found defensiveness to be the most robust predictor of high blood pressure [91]. The authors speculated that defensiveness may be linked to the pain/opiod system: "(This association is) consistent with the involvement of central opioid-peptide mechanisms in the covariation of essential hypertension with defensiveness" [91, p. 311].

Affect might not be the central concept–an alternative perspective posits that hypertension induced changes in cognitive processing (resulting in deficits in perception, processing and recall of information) impairs affective responses to demanding interpersonal interactions [101]. Cognitive deficits have, however, proven to be relatively subtle and not present in low level processes such as perception, speed of processing, or even long-term memory [9, 60]. Mild deficits or blunted recognition and expression of emotion might, however, lead to a history of unsuccessful interpersonal interactions and through this to low self-efficacy and avoidance behavior [102, 103].

12. Affect and Pain

Other research has focused on affect as a mediator of pain perception in hypertension. An understanding that the perception of pain is not simply a physical response led researchers to explore the connection between hypoalgesia, affect, and hypertension. Fillingim and colleagues suggested that the effect of elevated blood pressure on pain is the result of reduced affective response rather than reduced pain sensitivity [104]. This relates to the surprising and reasonably consistent finding that negative events and symptoms are reported as lower among those with higher blood pressure, but only among those not diagnosed with hypertension [61, 84, 105]. This relationship does not seem to be necessarily related to negative affect/anxiety/defensiveness [105], but as noted above may be related to pain perception [105]. Associating possible underlying mechanisms, Wilkinson and France speculated that it is possible that changes in sensory, affective, and cognitive processing of noxious stimuli may influence hypoalgesia in hypertensives or those who are at risk for hypertension [106]. They looked at the activation of baroreflexes in conjunction with response to positive, negative and neutral affective stimuli. Though no connection was found between baroreflex stimulation and affective measures, an interaction between parental history of hypertension and mood showed reduced emotional valence ratings for both positive and negative images, but not for neutral images for subjects who had a positive parental hypertension history versus those whose parents did not have hypertension [106]. For ratings of arousal, those who have a positive parental history of hypertension reported less arousal to both positive and negative stimuli and higher arousal to neutral stimuli when compared to participants who had normotensive parents [106]. Although this study did not find support for the role of baroreflex stimulation in affective responding among individuals at risk for hypertension, the discovery of dampened emotional responses to both positive and negative stimuli in conjunction with similarly dampened autonomic and involuntary measures of response (i.e., skin conductance and EMG) for participants with a parental history of hypertension reinforce the belief that a common underlying mechanism contributes to the changes in affect, blood pressure, and other autonomic responses [106].

13. Positive Affect

It is important to keep in mind that affective response is multidimensional (e.g., valence positive-to-negative state and arousal high-to-low energy state) as a result, expansion of research into positive affectivity seemed the obvious next step. Pury et al. proposed that emotional responses of persons with high blood pressure to a broader range of stimuli (things other than stress and physical pain) can happen in 3 different ways: (1) lessened response to negative stimuli with no change in response to positive stimuli, (2) more positive responses to both positive and negative stimuli, or (3) "dampened emotional responses" to both positive and negative stimuli [107]. In their study Pury and colleagues took resting blood pressures of 65 normotensive young adults and then asked them to rate a series of photographs on valence and arousal [107]. Systolic BP was found to be associated with more neutral ratings for all of the photos, as well as for the positive photos and for the negative photos [107]. These findings show a dampened emotional response to visual stimuli for persons with a higher resting SBP causing Pury and colleagues to suggest that "prior research on the relationship between blood pressure and subjective ratings of negative stimuli (pain, psychosocial stress) may be reflecting a general tendency toward reduced responsiveness to emotionally provocative stimuli in general" [107, p. 585]. A more recent study by McCubbin et al. [108] found that zero order correlations show an inverse relationship between the Perception of Affect task scores and both systolic

Table 1: Diagrammatic illustration of integrated study of the natural history of hypertension.

Stage of Disease	Physiology	Affective	Cognitive
Normotensive/youth (genetic/familial risk)	All normal possible hyper-reactivity to lab stress, Mild elevation in SBP Opioid dysregulation	Anger? Reduced pain sensitivity	Subtle spatial attention, short term memory deficit
Borderline/Pre-hypertensive	BP >119/79 <140/90 with predominance of elevated DBP, sympathetic activation High cardiac output Baroreceptor adjustment; hyper reactivity to lab stress	Interpersonal difficulty Pain insensitivity Less awareness negative affect, positive affect?	
Early Hypertension (40–60yrs)	BP >140/90 High TPR Salt/diet sensitive Renin/angiotensin Aldosterone Sympathetic Structural/function brain changes Hyperreactivity	Above with transition to greater negative affect with inhibition of the expression of intense angry cognitive and emotive reactions	Mild deficits executive attention, working memory
Late Hypertension (60+ yrs)	Same BP or isolated systolic hypertension? maintenance of altered regulatory system	Continued high negative affect and expression of negative affect?; awareness of BP status may invert relationship	Deficits not as clear relative to age matched; Related to Alzheimer's Disease

and diastolic blood pressure in a predominantly African American sample. This finding further supports the theory of emotional dampening in persons with elevated blood pressure [108]. In summary the current literature seems to point at an evolving relationship between hypertension and affectivity. With those likely to develop hypertension exhibiting intense emotionality specifically in relation to the expression of anger and developing into blunted perception and expression of both positive and negative emotion [86, 87, 91, 107]. The evolution in the relationship between hypertension and affect further supports the idea for a common etiology, however there is much yet to be explored.

14. Concluding Remarks

Continued exploration into both positive and negative aspects of emotionality will be important in understanding the connection between hypertension and affectivity. Additionally, understanding this psychosomatic relationship requires careful concurrent assessment of both physiology and psychological function using valid and reliable measures. As Suls et al. [92] note, earlier work has been characterized by either careful psychological or physiological assessment but rarely by care in both areas. Prospective studies of the development of hypertension while monitoring affect and cognition will add much to the existing literature. As the relationship of blunted perception of affect (or of negative events) continues to be explored it should be useful to relate it to concepts of the development of hypertension. Weiner [27] reviewed work suggesting that normal blood pressure advanced to hypertension through a prehypertensive phase that could take different forms: initial increase in cardiac output, an increase in both heart rate or cardiac output, or an increase in peripheral vascular resistance. Although work has not refined these speculations greatly, the point is that the hypertension likely results from a variety of mechanisms and one of more of these may relate more strongly to the perceptual sensitivity characterizing some individuals that advance to hypertension. Table 1 is a rough table of what is somewhat known about physiology, affect, and cognition at different stages of hypertension. The table is incomplete, particularly in terms of the multiple physiological mechanisms suspected to impact hypertension. Brain indices are included but very little work has been done in this area. We have tried to develop the case that brain indices as well as self-report indices are pointing to a possible convergence that may enlighten us on how exactly affect, its perception, regulation, and expression may be related to the natural history of hypertension. As research goes forward, assessment of both continuous blood pressure as well as categorical measures relating to medical definitions of the disease should be included with attention to the issue of whether individuals are aware or unaware of their hypertensive status. The area would further benefit from the use of well-developed scales of affect that can be compared across studies as well as the use of any newly developed measures that capture hypotheses about the tantalizing relationship between affect and hypertension.

Notes. Progression of blood pressure with age derived from Franklin and Mitchell [109], early neuropsychological deficits [110, 111]. Physiological characterizations are incomplete; borderline/prehypertensive based on Köhler, Fricke, Ritz, & Scherbaum et al. [112]. Alzheimer relationship based on Wu et al. [113]. Dysregulation in multiple systems may independently lead to hypertension and the timing of such changes are largely unknown in humans. Evidence for this can be readily deduced from the variety of animal models that achieve hypertension via different routes [114].

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Review Article

Rumination as a Mediator of Chronic Stress Effects on Hypertension: A Causal Model

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Chronic stress has been linked to hypertension, but the underlying mechanisms remain poorly specified. We suggest that chronic stress poses a risk for hypertension through repeated occurrence of acute stressors (often stemming from the chronic stress context) that cause activation of stress-mediating physiological systems. Previous models have often focused on the magnitude of the acute physiological response as a risk factor; we attempt to extend this to address the issue of *duration of exposure*. Key to our model is the notion that these acute stressors can emerge not only in response to stressors present in the environment, but also to mental representations of those (or other) stressors. Consequently, although the experience of any given stressor may be brief, a stressor often results in a constellation of negative cognitions and emotions that form a mental representation of the stressor. Ruminating about this mental representation of the stressful event can cause autonomic activation similar to that observed in response to the original incident, and may occur and persist long after the event itself has ended. Thus, rumination helps explain how chronic stress causes repeated (acute) activation of one's stress-mediating physiological systems, the effects of which accumulate over time, resulting in hypertension risk.

1. Introduction

The question of why one person develops high blood pressure (BP) and another does not has long been controversial. For example, Freud in the 1930s hypothesized that keeping one's anger in will cause BP to rise. Theories of stress and disease came a bit later, and a multitude of experimental and field studies show that stress is indeed linked, both epidemiologically and causally, to physiological dysregulation and chronic illness. The model we present here builds on this research but attempts to take it a step further.

1.1. Stress as a Risk Factor for Hypertension. It is welldocumented that "stress" (broadly and variously defined) is a risk factor for hypertension (HTN) and other cardiovascular disease (CVD), including events and all-cause mortality [1–8]. The mechanisms that underlie this association, however, have not been as clearly specified. This is due, in part, to the ambiguity concerning the nature of "stress." The construct has been used and measured in many different ways, with little standardization across studies. Moreover, the notions of "chronic" and "acute" stress, and how they relate to one another, have not been clearly delineated, with little theoretical work targeted at identifying the respective domains of each. To the extent that we believe that stress—however it is defined—is indeed a risk factor for HTN, it is crucial that we identify the pathways through which it may lead to sustained elevated BP if we are to develop effective interventions to reduce stress, with the aim of reducing high BP and associated long term disease risk. In this paper, we will attempt to provide specifications concerning

the respective domains of acute and chronic stress and to present a model and review evidence that points to *rumination*—the cognitions and negative affect that stem from the experience of an acute stressor—as a key mechanism through which stress exerts its pejorative effects on autonomic functioning and the resting BP level. We then discuss implications for interventions and future research.

1.2. Acute Stress. In this paper, we operationalize acute stress as a situational factor. That is, a discrete event that stems from some aspect of one's immediate situation, and, for the most part, has an impact on the person only to the extent that (1) it is perceived, (2) the perception leads to negative cognitions and affect, and (3) that these cause perturbations in the various physiological stress-mediating systems (PSMSs) including autonomic, hypothalamic-pituitary-adrenal (HPA), and immune systems. By this definition, an acute stressor may also arise internally (i.e., a mental representation) and provoke continuing thoughts and emotions, and, concomitantly, their effects on the autonomic and other PSMSs. We have noted "for the most part" as some acute stressors will have effects independent of this mechanism. For example, a pin-prick may cause such perturbations, but via different, more direct, channels not involving cognition. In this paper, we focus on those acute stressors that exert their effects on the PSMSs via the ruminative (perception-negative cognition/affect) pathway. In research examining stress effects on BP, acute stressors have mostly been defined as standardized laboratory tasks such as mental arithmetic or the cold pressor. We and others have used an anger recall task, which we have shown is similarly effective in raising the BP and HR, decreasing heart rate variability (HRV), increasing cortisol, and other outcomes including impaired endothelial function [9–13].

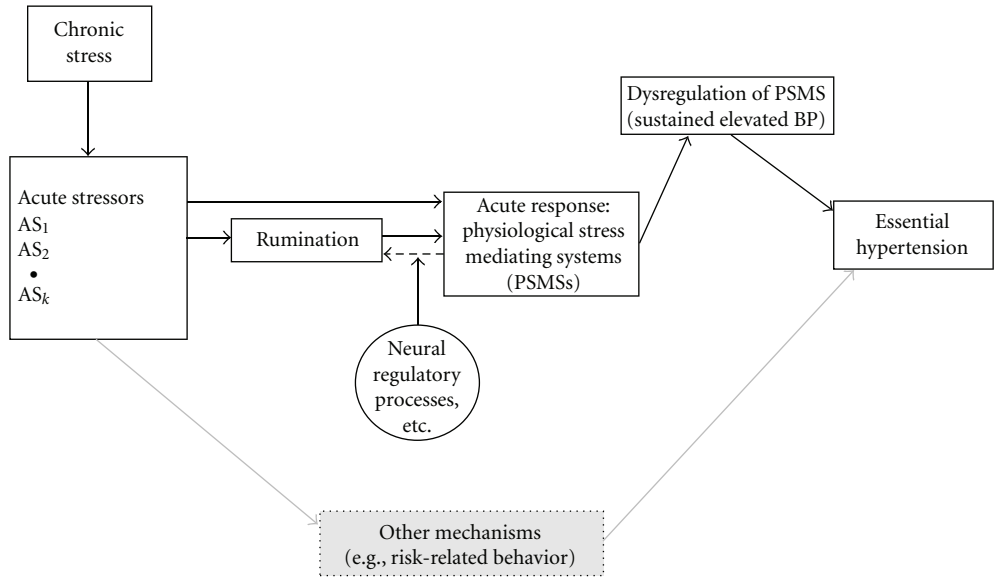
1.3. Chronic Stress. We do not currently have a fully useful definition and circumscribed domain for chronic stress; in the literature, it often appears to be a case of "we know it when we see it". Thus, caregiver status, low socioeconomic status (SES), an unpleasant low-paying job, and a stint in jail—all these seem like obvious sources of chronic stress. But what are the defining characteristics? Certainly, there is a sense that part of it is the "ongoingness" of the situation and part is the pervasiveness of the situation. Thus, one may find oneself continuously in the midst of the situation—being in prison is an extreme example, finding oneself further and further in debt with creditors calling at all hours is another. It is not necessarily the case, however, that even under such pervasive and ongoing conditions, one is continuously attending to the situation. Thus, the individual instances or moments that *do* invoke the situation and do provoke a reaction—the creditor's phone call, for example, or a worry episode regarding mounting dept—are intermittent, with a greater or lesser frequency depending on the nature of the chronic stressor. And we would regard the individual instances as examples of acute stressors, per the previous section, that arise from (are potentiated by) the chronically stressful context.

For the purposes of this paper, as with acute stress, we define chronic stress as a situational variable. In this instance, however, "situational" refers to a "background" that increases the likelihood that acute stressors—relating to the chronic stress situation—arise. (Acute stressors may also, of course, arise from sources not related to one's chronic stress). *Thus, we propose that chronic stress matters largely to the extent that it consists of a background situation that gives rise to acute stressors, with these acute stressors having an impact on the PSMSs.* It is important to note that this chronically stressful situation may affect one's BP via other pathways; thus, chronic stress has effects beyond "merely" being the source of acute stressors. For example, the parental caretaker may begin eating poorly and gain weight, and may increase salt intake, each of which will affect the BP via other pathways (i.e., health-related behaviors, in this instance, although these may arise in response to both the chronic stress background and the acute stressors that may arise).

So far, we have stated that acute stressors arise from environmental conditions, and often more frequently when the environmental conditions are characterized as chronically stressful. An individual exposed to such a situation will likely be exposed to "reminders" of the situation—such as the creditor's phone call—and may be apt to periodically recall the terrible conditions even without environmental cues. We suggest that there is functionally no differentiation between these "reminders" and the effects of the acute stressors, both produce acute stress, insofar as each leads to negative cognitions and affect and perturbations in the PSMSs. Posttraumatic stress disorder (PTSD) offers an example of this, albeit an extreme one. In some cases, a single event, even a brief one, may lead to persistent effects on cognition and affect. These effects can persist for decades as individuals with PTSD continue to deal with intrusive thoughts and emotions that recreate representations of the event (and associated stress and other physiological responses). In fact, evidence suggests that the frequency of these reexposures to the original event is strongly related to PTSD severity [14].

2. Rumination

A limitation of most acute stress models is that they do not take into account the *duration of exposure*. Rather, the focus is solely on the *magnitude* of the acute response. Thus, a person that exhibits a larger BP response to an acute stressor is presumed to be at greater risk for HTN than one who exhibits smaller responses. Stressor-related thoughts that may emerge over time as a result of (but temporally distal from) the acute stressor can also cause acute elevations in the PSMSs. Moreover, these physiological responses may persist as long as the recurring cognitions/emotions (e.g., anger or anxiety) persist. Relevant to this, Glynn and colleagues [15] have shown that recall of a laboratory stressor to which the subject had been exposed in a previous session produced BP responses comparable to those which occurred when the participant was exposed to the stressor itself. Thus, the cognitive and affective sequelae of the acute stressor may have as great an effect on the PSMSs as the original initiating event, long after that event has occurred (with the limits



Note: A number of moderators are not formally depicted in the model for ease of viewing (e.g., trait dimensions, coping resources and actions, distraction processes, etc.)

Figure 1: Schematic of the "chronic stress—rumination—HTN" model.

on the ruminative responses likely only constrained by the verisimilitude and intensity of the internal representation).

We thus broadly define rumination as *affect-laden cognitions that (1) result from exposure to an acute stressor (external in the environment or an internally generated representation); (2) in most individuals cause acute activation of relevant physiological stress-mediation systems; (3) "outlast" the original stimulus/acute stressor (i.e., the ruminative thoughts and accompanying negative affect—and their effect on physiological activation—persist even after the stressor itself is no longer present); (4) often reemerge—in some, over quite long periods of time; (5) typically do not lead to productive solutions, but rather resemble an "endless loop", that does not lead to insight or resolution of the issue.* We also note that, in addition to the term "rumination", there are many other related constructs. Some are often used interchangeably, such as perseverative cognitions, whereas others imply some differences. For example, distinct from rumination, which typically concerns *past* stressful events, one may experience anticipatory negative cognitions and affect concerning *future* events, which are often termed worry or anxiety; these states, too, can produce sustained effects on the PSMSs. It is as yet unclear whether these are distinctions that make a difference in terms of physiological consequences and/or HTN risk.

We thus propose that it is largely the cumulative *duration of exposure* to this persistent representation of the acute stressor, with its attendant effects on, and eventual potential dysregulation of the stress-mediating physiological systems that contribute to sustained elevated BP and to HTN. That is, "actual" stressors are important, but that the ruminative representations (and their consequences) contribute more to observed PSMSs responses and to HTN risk. Figure 1 shows a schematic of a model that illustrates these predictions and pathways.

2.1. The Proposed Model. Figure 1 outlines the conceptual model. Chronic stress (a situational factor) sets the stage for and gives rise to the occurrence of acute stressor incidents that, depending on their nature, may lead directly to activation of the PSMSs (e.g., a pinprick) or may lead to ruminative thoughts and emotions that in turn may produce PSMSs responses. Coping resources are proposed as a moderator of the acute stressor—rumination link that in part determines whether the incident produces a ruminative response. Thus, many variables that have been implicated in stress effects are accounted for *before* they are perceived as stressful; and *rumination* is affected by the composite as a whole. For example, the perceived availability of social support operates before appraisal and thus, in some individuals, reduces the likelihood that the stimulus will activate ruminative thoughts and affect.

The thoughts and emotions that are evoked by the acute stressor affects the PSMSs, causing acute perturbations in the various systems. In those who tend to ruminate (more frequently and/or for longer duration), the effects on the PSMSs will be prolonged, and thus, *the individual is exposed to the effects of the stressor for a more sustained period of time*, which may lead to a resetting of homeostatic set points, including elevated resting BP. Herein, lies the critical role of *duration*, which many models of acute stress tend to ignore.

The dashed arrow shows a feedback mechanism such that the autonomic activation that results as a function of rumination itself becomes a stimulus that potentiates the negative emotions and cognitions; these in turn maintain

the autonomic activation, and so on. Why should this feedback loop ever stop? The person may fall asleep, or may become distracted—we view "distraction" as a potential moderator of this loop—leading to termination of the rumination and its effects on the PSMSs when a distractor of sufficient potency to "drive out" the ruminative thoughts and replace them with others is encountered. We also show a moderating effect of neural inhibition by the prefrontal cortex on the association between acute stress and rumination/worry. Finally, a number of other pathways known to exist, but not addressed as central to this paper, are depicted in greyscale (as rumination is not the only pathway by which stress may affect HTN). Specifically, addressing these additional pathways is, however, beyond the scope of this paper. Circles indicate that the variable is proposed as a moderator.

2.2. Old Wine in New Bottles? One issue is whether the proposed model represents a mere restatement of existing theoretical formulations or offers practical and/or theoretical advance. We are aware that many of the definitions and relationships among constructs herein have been proposed and discussed by others, many of whom developed theories that had a major impact on how stress was conceptualized. Thus, the models proposed by Selye [16] and by Lazarus and Folkman [17] are progenitors of the current proposed model. There are, as well, many other theories that address aspects of the questions at issue, and we have borrowed from some of these. The model as we present it, however, has been informed by recent advances in the psychophysiological, health, and social psychological literatures, and addresses issues not formerly considered. Moreover, this model is not intended to propose a general theory of stress; rather, the goal is to understand the factors that lead chronic stress to be a substantial risk factor for HTN, and the model we present focuses on this problem and the central role of rumination.

2.3. Unconscious Rumination. Although we have been discussing rumination as a largely active process, data from several lines of research suggest that individuals may be unaware of some portion—potentially a large portion—of their stress-related cognitions. Yet, even these "unconscious thoughts and feelings" can have an activating effect on the autonomic and other stress-mediating physiological systems. (We operationalize the term "unconscious" as indicating only that it occurs while one's attention is not or cannot be directed toward it, or is directed elsewhere, that is, out of awareness.) There is a rich body of research converging on the idea that "implicit emotion" plays a role in mental and psychosomatic disorders [18]. In the last two decades, developments in cognitive and social psychology have strongly indicated that a great deal of cognition occurs at the unconscious (or automatic) level [19, 20]. To date, several studies have shown that neurophysiological responses occur in response to threatening information that is shown subliminally, an accepted experimental model of "unconscious cognition" [18, 21]. More importantly for this paper, it has also been shown that such subliminal stimuli can increase BP [22–24].

Regarding chronic stress, we have found that (conscious) rumination was linked to cardiac activity in daily life, and this activity persisted for hours after the rumination itself had ended [25]. We and others [26–29] also found effects of daily stress and rumination on cardiovascular activity during subsequent sleeping at night, during which conscious rumination is presumably not possible. On the basis of these findings, some researchers [21, 30] have recently proposed that stress research may have missed an essential phenomenon by focusing solely on the conscious "tip of the iceberg" of stress-related thoughts and feelings. Unconscious rumination may be responsible for a considerable portion of cardiovascular activity in one's daily life. Pending development of appropriate measures—which remains a challenge—studying unconscious stress in the context of HTN and other stress-related somatic conditions may turn out to be a particularly fruitful pathway for future investigation.

2.4. Neurovisceral Moderators of Rumination. The perseverative cognitions that characterize rumination are thought to be under tonic inhibitory control by the prefrontal cortex [31, 32]. There are several conditions, including chronic stress or having an anxiety disorder, that lower prefrontal inhibition and thus render one more vulnerable to rumination as well as to prolonged and indiscriminate responses to environmental stimuli. Low prefrontal inhibition is characterized by low parasympathetic activation, which can be measured by low heart rate variability (HRV). (For a more detailed explanation, see [33, 34].) Low tonic levels of HRV might indicate a predisposition to "err on the side of caution" when confronted with threat. As such, an excitatory *positive feedback loop* is allowed to emerge, reflected in the psychological level in hypervigilance and rumination. As a consequence, the normally fine-tuned ability to adjust to changing environmental factors becomes a relatively rigid, inflexible response disposition, which is in fact a continuation of the default defense response in the absence of clear threat signals. This is reflected by a failure to recognize safe/neutral environmental signals and by responding to them as if they are threatening. In support of this idea, patients suffering from generalized anxiety disorder have been shown to have lower tonic levels of HRV, when compared to nonanxious controls [35]. Furthermore, people with low HRV have been shown to have an attentional bias for threatening information and interpret ambiguous situations more negatively [36].

In sum, we propose that low prefrontal inhibition, indexed by low HRV, predisposes people to respond with enhanced cognitive, affective, and physiological activity to stressors. This, in combination with the psychological vulnerability factors for rumination discussed above, can cause even neutral stimuli to trigger the stress response. As a consequence, the total time that people ruminate and worry about stressful events increases, thereby adding to the total duration of exposure to stress representations and their physiological effects in daily life.

2.5. Review of the Rumination Literature. The overarching prediction derived from the model is that an important mechanism underlying the observed relationship between

"chronic stress" and HTN is *rumination*, which typically stems from exposure to an acute stressor. *Thus, compared to individuals who show a lower tendency to regulate their angry and anxious and dysphoric thoughts using ruminative processes, high "trait" ruminators should be more likely to have more frequent, intense, and longer-lasting, ruminative thoughts and emotions as well as more (future) reoccurrences and occurrences that persist longer into the future.* In support of this prediction, rumination has been shown to increase engagement in depressed thinking [37, 38], is related to negative emotions, including anxiety [39, 40], anger [41–43], and depressed mood [43–45], and can prolong negative affect [42, 46]. Rumination appears to be a relatively stable characteristic, as test-retest is high for both anger [42] and depressed rumination scales [47, 48] (for periods ranging from one month to one year). Tendency to ruminate also predicts future occasions on which rumination is likely to occur. For example, ruminators were more likely to experience a depressive episode in the ensuing 18 months than nonruminators [47], with a similar result found by Nolen-Hoeksema [40]. Change in rumination levels predicted changes in depression over four months [48]. Furthermore, higher tendencies toward angry rumination were related to increases in experienced and expressed anger and to decreased satisfaction with life on future occasions [42].

2.5.1. High "Trait" Ruminators Should Also Be More Likely to Exhibit the Physiological Activation that Tends to Result from Such Thoughts. Increases in rumination have consistently been linked to higher blood pressure during recovery periods [49–54]. For example, compared with nonruminators, ruminators after an anger recall incident were more likely to brood about their anger thoughts during a recovery period in which they were not distracted [49]. Importantly, this tendency to ruminate translated-to-slower blood pressure recovery for these ruminators, demonstrating the ability for rumination to sustain high blood pressure. Other studies support this view as well; participants induced to recall a stressor they experienced in the lab (i.e., ruminate about the stressor) showed increases in blood pressure regardless of whether they ruminated about the stressor 30 minutes after it happened or one week later [50]. In other words, the mental representation of the stressor increased blood pressure regardless of temporal "distance" from the original event. Importantly, the relationship between rumination and blood pressure is not just in the moment. Compared to nonruminators, individuals who ruminate have higher resting [55, 56] and ambulatory blood pressures [56–58]. For example, Ottaviani and colleagues [58] had participants engaged in an anger recall interview, which successfully raised blood pressure. Next, half of the participants were assigned to a distraction condition where rumination was abolished, while the other half was not distracted and were allowed to continue ruminating about the anger inducing incident. Pertinently, not only did this nondistracted, ruminating group have elevated blood pressure during the recovery period immediately after the anger recall, but their blood pressure remained significantly elevated compared to their baseline levels when examining their mean ambulatory blood pressure readings taken over the ensuing 24 hours. Thus, there is evidence demonstrating the power of rumination to sustain elevated blood pressure not just over minutes, but hours and days.

2.5.2. High "Trait" Ruminators Should Tend to Exhibit Dysregulation of the Physiological Stress-Mediating Systems. Higher blood pressure tends to beget yet higher blood pressure over time [59]. In strictly biophysical terms, one mechanism by which the blood vessels in the body regulate blood flow is by constricting and expanding. As blood pressure increases, either more blood (i.e., higher cardiac output) enters the blood vessels or the blood enters the vessels with greater force (i.e., mean arterial pressure); either way, the blood vessels must expand and contract more to regulate blood flow. Over time, this process increases the thickness of the muscle around the vessels—the more often a person has higher blood pressure, the more the vessels work and the faster and thicker this layer grows. These thicker arterial walls are, however, more resistant to the force of blood flow, requiring the heart to work harder to pump enough blood hard enough for the vessels to properly regulate. With greater effort from the heart, blood pressure goes up, which further increases the muscles around the arteries.

This process explains how having sustained, untreated HTN in one's life is an independent predictor of cardiovascular morbidity [60]. High blood pressure can thus cause irreversible structural changes to the body. This process is conceptually similar to that of allostatic load [61], which can be described as a resetting of the physiological set points in an attempt to maintain homeostasis and thus function, but at a new set point (e.g., higher blood pressure). In the short-run, achieving allostasis is adaptive (e.g., the higher blood pressure allows the blood vessels to continue to regulate blood flow), but in the long term can have quite negative consequences [62]. Importantly, and supportive of the model presented here, the stressors that cause allostatic load are not major, impactful (but infrequent) stressors, but rather the cumulative effect of more frequent minor psychosocial stressors [63]. Key to this theory is that these frequent, more minor stressors have to produce sufficiently long response durations so as to lead to allostasis [64]. As discussed, the presence of an initial stressor does not automatically lead to the prolonged activation that causes the resetting of the body's set point or allostasis [65]. Rather, it is the presence and persistence of the cognitive representations (i.e., rumination, worry, and other perseverative cognitions) that can later reactivate/recreate a stressor in one's mind; this process and the resultant physiological changes are the circumstances that characterize and explain the chronic stress-HTN relationship.

3. Potential Factors Not Shown in the Model

We are attempting to describe a highly complex process and to understand why some are prone to ruminate and others are not, how attention—clearly a key determinant of the nature of one's conscious thoughts—as well as signal detection and hypervigilance for perceived threats and insults is implicated in the process. Finally, we note that classical

conditioning processes undoubtedly play a role, for example, a conditioned response to an eliciting stimulus may evoke the cognitive and affective response to past unconditioned aversive events. Consideration of these factors is beyond the scope of this paper, but will need to be addressed as our understanding of the processes increases.

3.1. A Brief Note Concerning Applications of the Model for Interventions to Reduce Stress and Thus Lower Risk for HTN and CVD. There are many avenues of approach to such interventions, in part because there are several pathways by which stress may cause HTN and heart disease. Thus, obvious targets are stress-related behaviors that may increase one's risk, such as smoking, weight gain, lack of exercise, increased salt intake, and interpersonal behaviors that may cause subsequent and ongoing stressful incidents, and so on. Interventions may, and do, target coping behaviors and skills. The model we propose suggests that an additional useful point of intervention may be the ruminative processes that can convert acutely stressful experiences into recurrent or chronic stress. For example, one approach would be the cognitive reframing of stress-related negative thoughts and affect as a means of undermining their power to evoke subsequent negative thoughts and affect, and thus reducing the duration of exposure to sustained activation of the PSMSs. Even here, several strategies suggest themselves. Cognitive behavior therapy [CBT] specifically targets such cognitions, and is a well-validated clinical technique. One large clinical trial—ENRICHD [66]—has indeed used CBT as an intervention to reduce CVD risk (in conjunction with a social support manipulation), but the results were largely negative. Rumination was not measured in that study, however, we would suspect that if the frequency and severity of the negative thoughts and cognitions were not reduced, such an intervention would be unlikely effective. Clinicians have developed interventions to train people to learn to forgive past perceived transgressions, and others have targeted one's ability to "let go" of anger. Although intriguing, their effects on rumination and on PSMSs activation have been the subject of only a handful of studies and thus data are sparse for these approaches [67]. We hope this model spurs additional intervention work that tests a range of intervention targets, potential mediators, and a wider range of outcomes. On a final note, we suggest that a combination of procedures, likely targeting behavior as well as cognition and affect, may have better results than either alone.

4. Summary and Conclusions

Defining "chronic stress" and understanding the pathways by which it may contribute to sustained elevated BP and eventual HTN is a large undertaking and certainly involves more than one mechanism. We have addressed one pathway, but others, including changes in risk-related behaviors and in the direct effects of chronic stress on HTN, are not addressed here, nor are physiological BP regulatory systems including the angiotensin system, short term regulatory systems including the baroreflex, or the role of endogenous opioids. To eventually form a comprehensive model of the development and maintenance of pathogenically high-sustained BP resting level, these pieces must be addressed as well. Our model attempts to make a more modest and circumscribed contribution, but we hope to integrate these potential mediators and moderators into the model in future studies.

We propose that acute BP and other changes in response to experiencing an acute stressor may be less important than the continuing PSMSs activation that often persists after the incident itself has long ended and may reoccur when the memory of the stressor is activated. Robert Sapolsky addressed this issue in his book *Why Zebras Do not Get Ulcers* [59], in which he noted in his evocative example that zebras do not have the capacity to recall the stress (the failed attack from the lion, e.g.,) that has beset them; therefore, they neither ruminate about the past nor worry about the future, and thus do not suffer the PSMSs consequences of engaging in such mental activity. And thus do not suffer ulcers or, presumably, HTN, at least not due to the pathway proposed in this paper. (The supposition here is that these acute events occur only intermittently for the beleaguered zebra; if they are occurring many times a day over long periods of time, the distinction between acute and chronic stress becomes blurred). It also may be worth speculating about the evolutionary underpinnings. For some time, evolution has been shaping and perfecting the "fight-or-flight" response system that is designed to engage under acute threat. Awareness, or consciousness, however, emerged only a short time ago in evolutionary terms, and it was not, according to our model, until this point that mammals—humans, at least, and perhaps some infrahumans—developed the capacity to self-reflect and, thus, to ruminate. Therefore, zebras do not develop ulcers, but humans do (as well as elevated BP and HTN risk).

It is widely accepted that chronic stress must be filtered in some manner by sensation and—more importantly—perceptual processes, thus leading to individual differences in response to environmental challenges or stressors. Similarly, the role of duration of exposure to the stress—or, as we suggest, to the contents of one's thoughts and emotions—*is*, we argue, the representation of the chronic stress in its purest form; it is, after all, those thoughts and emotions that largely affect the stress mediating physiology, which itself is a more proximal cause of HTN and CVD. Do the data support the model? As reviewed herein, parts of the model have been tested in different laboratories, often using different approaches, and the results seem to hang together to suggest that indeed, rumination is one important pathway by which the effects of chronic stress on the development of HTN are transmitted. Other portions of the model remain to be more systematically evaluated. Scores of studies, however, conducted across several laboratories, have turned their attention to the role of rumination and perseverative cognition, and we anticipate that many of the blanks will be filled in as research on this topic progresses. One important line of inquiry is to apply more intensive, within-person data capture approaches that can carefully document the temporal dynamics of these processes (such as the initial

occurrence and response to an acute stressor, and then its reoccurrence via ruminative processes and their associated responses; see [68]). Coupling ambulatory psychophysiology (e.g., BP) with ecological momentary assessment techniques is one well-validated approach that holds great promise in this regard [69].

We believe that the model we have proposed represents an advance in the manner in which we conceptualize stress and its effects on blood pressure and cardiovascular disease. Partly, this is because of the basis it provides to develop useful interventions as well as precise targets of those interventions. Researchers have been ruminating about the nature of stress for some time; we hope that this research will help turn these ruminations into productive ideas for further exploration.

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Research Article

Blood Pressure Reactivity to an Anger Provocation Interview Does Not Predict Incident Cardiovascular Disease Events: The Canadian Nova Scotia Health Survey (NSHS95) Prospective Population Study

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We examined the association between blood pressure (BP) reactivity to an anger provocation interview and 10-year incident CVD events in 1,470 adults from the population-based 1995 Nova Scotia Health Survey (NSHS95). In an unadjusted model, those in the highest decile of systolic BP reactivity were more than twice as likely to have an incident CVD event compared to those in the decile with no reactivity (HR = 2.33, 95% CI = 1.15 – 4.69, $P = 0.02$). However, after adjusting for age and sex, and then also for Framingham risk score, body mass index, and education, this relationship was attenuated and not statistically significant. Diastolic BP reactivity was not associated with CVD incidence in any model. Individual differences in BP reactivity to a laboratory-induced, structured anger provocation interview may not play a major role in clinical CVD endpoints.

1. Introduction

A longstanding hypothesis in the field of behavioral medicine holds that individuals who are prone to experiencing large increases in blood pressure (BP) during psychological stress are at increased risk for developing preclinical and clinical cardiovascular disease (CVD) states [1]. Indeed, evidence from prospective studies of the association of stress-associ–ated BP reactivity with preclinical disease, such as atherosclerosis or left ventricular hypertrophy, is fairly consistent [2]. A recent meta-analysis showed that greater cardiovascular responses (systolic or diastolic BP) to laboratory-based psychological stress tasks are associated with greater risk of incident hypertension and progression of carotid intima-media thickening [3]. Individual studies have likewise found that excessive BP responses to the threat of shock or to a cold pressor task predict 10-year elevated blood pressure among initially normotensive young men with a family history of hypertension [4]. Moreover, BP reactivity to psychological stress has been shown to predict incident hypertension at 4-year, 10-year, and 13-year follow-ups among 508 normotensive Finnish middle-aged men [5], 796 English male civil servants [6], and more than 4,100 multiethnic participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study [7], respectively. Elevated BP reactivity to stress has also been linked to carotid intima-media thickness in middle-aged Finnish men [8–10], progression of carotid atherosclerosis among non-medicated patients with existing atherosclerotic disease [11], and coronary artery calcification among a cohort of healthy young adults [12].

These preclinical disease states are notable health outcomes, but it is essential to consider whether BP reactivity to psychological stress ultimately predicts CVD events. Longitudinal studies of the association between BP reactivity

and clinical endpoints, which are scarce, have shown mixed results [2]. For example, the findings of one study that linked stress-related increases in diastolic BP to myocardial infarction or cardiac mortality [13] were not replicated in either of two subsequent studies [14, 15]. The interpretation of these equivocal results is complicated by methodological issues, such as differing assessments and definitions of BP reactivity, a lack of time-to-event data in some studies, failure to control for traditional CVD risk factors that may confound the BP reactivity-CVD association, and a reliance on the cold pressor task as a psychological stressor rather than on tasks that are analogues of real-world situations such as anger recall and structured interviews. Further, participants were typically not from epidemiologic samples, limiting the generalizability of the results to the general population.

In this study, we examined the association between BP reactivity to a structured anger provocation interview and 10-year incident CVD events in a population-based sample of 1.470 CVD-free individuals from Nova Scotia, Canada.

2. Materials and Methods

2.1. Participants. The 1995 Nova Scotia Health Survey (NSHS95) is a population-based survey implemented by Heart Health Nova Scotia and the Nova Scotia Department of Health to estimate the distributions of selected health indicators and preventive practices of Nova Scotians [16]. Participants were selected based on a probability sample designed by Statistics Canada, the national statistical agency and census bureau, and are representative of the Nova Scotian population in terms of age, sex, and geographic location. Study participants were non-institutionalized Nova Scotians, 18 years of age or older, and listed in the Medical Services Insurance registry, the government-sponsored universal health insurance plan. Pregnant women were excluded from the survey. The overall recruitment percentage (72%) is comparable to those reported in other large health surveys, with a final survey sample size of 3,227 participants. Propensity score analyses revealed no meaningful response biases [17]. Although demographic shifts have occurred in Nova Scotia, including a decreased rate of population growth, greater immigration than emigration, and an increasing median age, [18] we have no reason to suspect that these changes would alter the results of the analyses reported below.

We restricted our analysis to participants who had attended the clinic session and those without hospital discharge diagnoses of CVD during the 5 years before the baseline survey, as determined by International Classification of Diseases, Ninth Revision (ICD-9) [19] codes 410.X through 414.X (ischemic heart disease), 443.X (peripheral vascular disease), and 430.X through 435.X (cerebrovascular disease). Survey respondents were excluded because of refusal to permit linkage to medical outcomes ($n = 312$), preexisting CVD ($n = 451$), failure to attend the clinic visit ($n = 388$), failure to complete the Expanded Structured (anger provocation) Interview ($n = 391$), or lack of a resting BP or BP reactivity assessment ($n = 215$). Eight additional participants did not have data on diastolic BP reactivity, leaving 1,470 participants for the primary analysis of systolic BP reactivity (746 males, 724 females), and 1,462 participants for the secondary analysis of diastolic BP reactivity (743 males, 719 females). Participants who were excluded from our analyses had significantly higher levels of HDL cholesterol and were more likely to be female, a current smoker, and not have a high school education compared to those who were included.

2.2. Study Design. A group of 29 registered public health nurses were trained in standardized data collection and contacted potential survey participants by telephone from March through November 1995. Consenting participants were interviewed at home and then seen in clinic, approximately one week later, for measurement of height and weight and to provide a fasting blood sample. During the clinic assessment, participants completed a videotaped structured anger provocation interview that was subsequently reviewed and scored. Participants provided consent to store and use videotapes and to link future ischemic heart disease events with prior health care utilization. Additional study details are reported elsewhere [20, 21]. This study was approved by the Institutional Review Boards of Dalhousie University, Halifax, Nova Scotia, and Columbia University, New York, NY.

At baseline, each component of the Framingham risk score [22] was assessed, including sex, age, total and high-density lipoprotein (HDL) cholesterol levels, blood pressure, history of diabetes, and cigarette smoking. Total and HDL cholesterol levels were assayed from plasma samples by the Lipid Research Laboratory, University of Toronto, Toronto, Ontario [23]. Registered nurses used manual sphygmomanometers to measure resting systolic and diastolic BP. Two readings were obtained in the participant's home, two readings were obtained during the clinic visit (approximately 1 week later), and the average of these four readings was computed as a measure of resting systolic and diastolic BP. History of diabetes and completion of a high school education ("yes" versus "no") were ascertained by self-report. As per the Framingham risk score calculation [22], those who reported smoking currently or in the past year were categorized as smokers; all others were categorized as nonsmokers. Weight and height were measured twice, averaged, and used to calculate body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Hypertension was defined as current use of antihypertensive medication or resting systolic BP ≥ 140 or diastolic BP ≥ 90 (using the aforementioned measure of resting BP obtained during home and clinic visits).

The Expanded Structured Interview (ESI) is a 12-minute, interpersonally stressful interview designed to elicit anger and stress by asking participants about their characteristic responses to a variety of different situations (e.g., performing a task at work while under pressure, waiting in traffic, and playing a competitive game) [24]. The interview is based on the original Type A Structured Interview [25], with additional questions on anger expression and interpersonal stress at work. Recent analyses of the NSHS95 data document that a substantial majority (89.9%) of participants who completed the ESI was judged by trained observers as having displayed at least some hostility, either in the content of their responses or the tone of their speech [26]. Nurse interviewers

measured BP just prior to the ESI, at the midpoint of the interview, and at the end of the interview with a manual sphygmomanometer. Given that the ESI is designed to elicit maximal anger at its midpoint, the second of the three interview-based BP measures described above was selected as the measure of peak reactive BP. Systolic and diastolic BP reactivity were defined by subtracting resting BP from the second of the three interview-based BP assessments (i.e., a change score was computed).

Nurse interviewers were trained on how to properly conduct the ESI during a four-part training procedure: (1) an ESI workshop, (2) ESI practice, (3) feedback after reviewing the ESI practice tapes, and (4) feedback during the NSHS95 study. The ESI administration training workshop used methods that were similar to the training used by the CARDIA investigation, in which investigators were taught voice emphasis, question pacing, interview length, general question and probe content, and demeanor. After the training workshop, nurses completed 10 practice ESIs that were rated on five structured interview quality control measures (elaborations, empathy, length, presentation, and overlap). Written and oral feedback was provided to each ESI interviewer after the practice ESIs, and nurses began data collection only when their ESI interviewing skills were considered acceptable. During NSHS95 data collection, a random 5% of each nurse interviewer's ESIs were coded for the ESI quality control measures. Oral feedback about the quality control results was provided periodically throughout data collection to ensure that all interviewers maintained adequate ESI administration competence.

The main study outcome measure was the time-to-first-event defined as incident fatal or nonfatal CVD as determined by the ICD hospital discharge codes defined above and/or by death certificates. Events data were gathered from the provincial health care database through March 31, 2005, the 10-year period after the initial enrollment of subjects. Given that Nova Scotia provides universal health care insurance, and events occurring outside of Nova Scotia are reimbursed and captured, the accuracy of this measure of outcome assessment is high [27]. In the Canadian single-payer health system, physicians indicate underlying and contributing causes of death, which are subsequently recorded and submitted by nosologists as ICD codes upon death or discharge. A data quality committee from the Nova Scotia Department of Health meets with health records personnel to ensure accuracy, to conduct random chart reviews, and to adjudicate discrepancies in data entry. All deaths are reported to provincial offices and subsequently to the national census bureau (Statistics Canada), which applies a nationally consistent process of determining the underlying cause of death. Specifically, these data were converted to the ICD-9 codes by staff at Statistics Canada; and only those codes listed above (or the equivalent International Statistical Classification of Diseases, 10th revision (ICD-10) [28] codes) qualified as fatal CVD. Data were extracted by the Population Health Unit of Dalhousie University.

2.3. Statistical Analyses. Statistical analyses were performed using SPSS 18.0 [29]. When a limited number of items were missing for the Framingham risk score, we used a previously published regression-based approach to determine the best linear-predicted score based on the non-missing items [30–32]. For a given combination of missing items, scores were imputed only if the imputation equation predicting the total Framingham risk score from the non-missing items had an $R^2 \geq 75\%$; this condition was satisfied when data were available for at least five items from the Framingham risk score. The cohort was divided into deciles on the basis of the distribution of systolic BP reactivity (primary measure of reactivity) and diastolic BP reactivity (secondary measure of reactivity). Participants' baseline characteristics and their correlations with deciles of systolic and diastolic BP reactivity were examined using zero-order Pearson correlation coefficients for continuous variables and point-biserial correlation coefficients for binary variables.

For the analysis of the association between BP reactivity and incident CVD events, Cox proportional hazards regression analyses were used to calculate the unadjusted and adjusted hazard ratios and 95% confidence intervals (CI) of CVD associated with deciles of systolic BP reactivity, controlling for age and sex in one model and additionally controlling for Framingham risk score, BMI, and high school education in a second model. The fifth decile, which contained individuals with zero systolic BP reactivity, was selected as the referent group for the systolic BP reactivity analyses. The fourth decile, which contained individuals with zero diastolic BP reactivity, was selected as the referent group in the diastolic BP reactivity analyses. The chi-square statistic (χ^2) was used to test whether the risk of incident CVD events varied by decile of systolic BP reactivity. All analyses were repeated using diastolic BP reactivity as a secondary measure of BP reactivity.

Additional analyses considered BP reactivity as a continuous variable and also examined possible interactions of BP reactivity (top 3 deciles (30%) versus middle 4 deciles (40%) and bottom 3 deciles (30%) versus middle 4 deciles (40%)) with traditional CVD risk factors, including age (median split), sex, baseline hypertension status, quartile of Framingham risk score, being overweight or obese based on BMI, and resting BP. Finally, to determine the robustness of the primary analyses, we conducted three additional sensitivity analyses using alternate definitions of BP reactivity and resting BP. In the first, resting BP was included as a covariate in all models given that some researchers have recommended the use of residualized change as a measure of reactivity rather than absolute change [33]. In the second, BP reactivity was defined as the average of the second and third BP readings taken during the structured anger provocation interview relative to resting BP, as averaging may enhance the reliability of this measure of reactivity [34]. In the third, resting BP was defined as the average of clinic BP readings with the exclusion of the BP readings obtained at home. The results for all three sensitivity analyses were similar to the results obtained from the primary analyses. As such, we do not herein report further on these analyses, as the results do not alter the findings of the study.

Table 1: Baseline characteristics of 1,470 NSHS95 participants and their correlation with systolic and diastolic blood pressure reactivity to an anger provocation interview.

Characteristic	Total (N = 1,470)	Correlation* with deciles of systolic BP reactivity	Correlation* with deciles of diastolic BP reactivity
Mean age (SD), years	45.31 (17.9)	0.15‡	−0.01
Mean Framingham risk score (SD)	1.13 (9.25)	0.08†	−0.04
Mean BMI (SD), kg/m^2	27.03 (5.39)	−0.03	−0.05
Mean LDL cholesterol (SD), mmol/L	3.22 (0.90)	−0.002	−0.001
Mean HDL cholesterol (SD), mmol/ L	1.26 (0.34)	0.02	0.03
Mean total cholesterol (SD), mmol/ L	5.28 (1.08)	0.01	−0.02
Mean resting systolic BP (SD), mm Hg	124.39 (18.65)	−0.14‡	−0.09†
Mean resting diastolic BP (SD), mm Hg	77.02 (9.54)	−0.08†	−0.24‡
Female, n (%)	724 (49.3)	−0.01	−0.05
High school education, n (%)	1,054 (71.8)	0.01	0.01
Current smoker, n (%)	388 (26.4)	−0.09†	−0.03
Hypertension, n (%)	375 (25.5)	−0.07‡	−0.13‡
Diabetes mellitus, n (%)	56 (3.8)	−0.01	−0.02

Abbreviations: BP, blood pressure; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Associations of continuous variables with deciles of SBP and DBP reactivity are represented by zero-order Pearson correlation coefficients; associations of binary variables with deciles of reactivity are represented by point-biserial correlation coefficients. †$P < 0.01$; ‡$P < 0.001$.

3. Results and Discussion

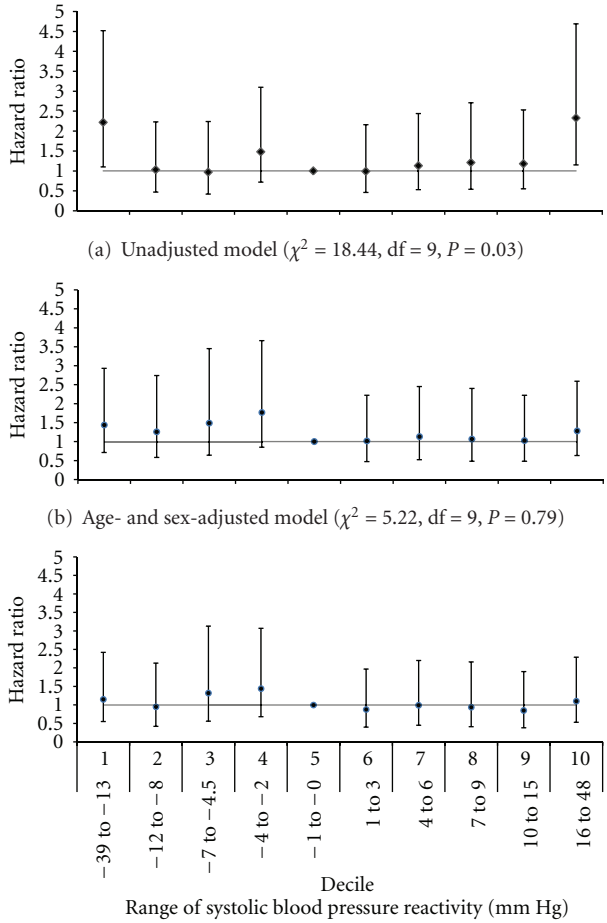
3.1. Results. Baseline characteristics of the 1,470 NSHS95 participants and their correlations with deciles of systolic and diastolic reactivity are reported in Table 1. The mean BP reactivity was 1.12 ± 11.04 mm Hg for systolic BP reactivity (range, −39–48 mm Hg) and 2.21 ± 7.36 mm Hg for diastolic BP reactivity (range, −22–27 mm Hg). Mean age and Framingham risk score were both positively correlated with deciles of systolic BP reactivity. Current smoking status, prevalence of hypertension, and mean resting systolic and diastolic BP were negatively correlated with deciles of systolic BP reactivity. Prevalence of hypertension and mean systolic and diastolic BP were also negatively correlated with deciles of diastolic BP reactivity.

A total of 161 nonfatal and 10 fatal incident CVD events occurred during the 10 years of follow-up for the 1,470 participants included in these analyses. In the unadjusted Cox proportional hazards regression model, systolic BP reactivity significantly predicted risk of incident CVD (χ^2 = 18.44, df = 9, P = 0.03) (Figure 1). Specifically, those in the lowest and highest deciles of systolic BP reactivity were, respectively, 2.2 (95% confidence interval (CI) = 1.10–4.53, P = 0.03) and 2.3 (95% CI = 1.15–4.69, P = 0.02) times as likely to develop incident CVD relative to those in the decile with no systolic BP reactivity. However, systolic BP reactivity no longer significantly predicted incident CVD events when age and sex were added to the model (χ^2 = 5.22, df = 9, P = 0.79) and it remained nonsignificant with further adjustment for Framingham risk score, BMI, and education level (χ^2 = 4.33, df = 9, P = 0.89). Results were similar when systolic BP reactivity was treated as a continuous rather than a categorical variable (data not shown). Diastolic reactivity did not predict incident CVD events in unadjusted (χ^2 = 10.37, df = 9, P = 0.32), age- and sex-adjusted (χ^2 = 9.55, df = 9, P = 0.39), or fully adjusted (χ^2 = 8.90, df = 9, P = 0.45) Cox regression models (Figure 2).

We next considered whether exaggerated BP reactivity interacted with age, sex, hypertension status, being obese or overweight based on BMI, quartiles of Framingham risk score, or resting BP in the prediction of incident CVD. Neither systolic nor diastolic BP reactivity significantly interacted with any of these variables in the prediction of incident CVD (all P's for interaction terms > 0.16).

3.2. Discussion. We evaluated whether BP reactivity to a structured anger provocation interview predicted incident CVD disease events in a prospective population-based study. In an unadjusted model, systolic BP reactivity to anger provocation significantly predicted risk of incident CVD such that those in the lowest and highest deciles of systolic BP reactivity were more than twice as likely to develop incident CVD compared to those in the decile with no reactivity. However, systolic BP reactivity, at any decile level, did not predict incident CVD events above and beyond traditional CVD risk factors, including age, sex, Framingham risk score, BMI, and completion of a high school education. Further, diastolic BP reactivity, at any decile level, did not predict CVD in unadjusted and adjusted models. These results are supported by a strong study design, including a large, population-based sample that was randomly selected, careful capture of CVD events at 10-year follow-up using hospital records, and the use of a psychological stressor that individuals will most likely experience in the natural environment. In addition, important potential confounders were considered, and analysis of possible interactions of BP reactivity with traditional CVD risk factors was conducted to elucidate whether certain subgroups were at risk.

Research examining the relation between BP reactivity to a psychologically stressful interview and either preclinical

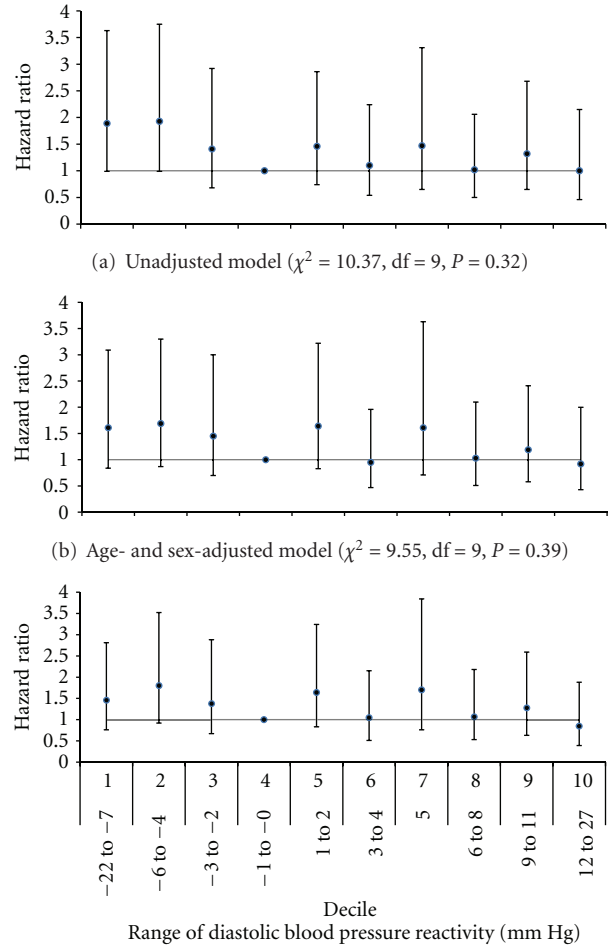


(a) Unadjusted model (χ^2 = 18.44, df = 9, P = 0.03)

(b) Age- and sex-adjusted model (χ^2 = 5.22, df = 9, P = 0.79)

(c) Fully-adjusted model (χ^2 = 4.33, df = 9, P = 0.89)

Figure 1: Hazard ratio with 95% confidence intervals of incident cardiovascular disease events by decile of systolic blood pressure reactivity in (a) an unadjusted model, (b) age- and sex-adjusted model, and (c) model additionally adjusted for body mass index, Framingham risk score, and high school education.



(a) Unadjusted model (χ^2 = 10.37, df = 9, P = 0.32)

(b) Age- and sex-adjusted model (χ^2 = 9.55, df = 9, P = 0.39)

(c) Fully-adjusted model (χ^2 = 8.90, df = 9, P = 0.45)

Figure 2: Hazard ratio with 95% confidence intervals of incident cardiovascular disease events by decile of diastolic blood pressure reactivity in (a) an unadjusted model, (b) age- and sex-adjusted model, and (c) model additionally adjusted for body mass index, Framingham risk score, and high school education.

or clinical CVD outcomes is limited. The single study that examined whether BP reactivity to a Type A structured interview predicts CVD events did not find a significant association in a small sample of participants with pre-existing CVD [35]. More recent evidence suggests that BP reactivity to being interviewed about a recent, stressful interpersonal situation predicts future BP [36]. Although this finding suggests that increased BP reactivity to a psychologically stressful interview may be associated with hypertension onset, there is little evidence that it is associated with clinically evident CVD.

A few additional studies have examined prospective associations of BP reactivity to other psychological stressors of questionable ecological validity with CVD events. For example, one study reported a positive association of systolic BP reactivity with incident stroke [37] and another reported an association of diastolic BP reactivity with both myocardial infarction and total CVD [38]. However, the former study was limited to middle-aged men and the stressor was anticipation of an exercise test while the latter study enrolled only patients with hypertension, defined BP reactivity as the difference between nurse and physician assessments (a variant of the white-coat effect), and did not include any other type of psychological stressor. Other studies that have reported significant associations of BP reactivity with CVD events [39, 40] have been limited to patients with preexisting CVD, included relatively small samples of fewer than 100 participants, have not controlled for age, sex, and other traditional CVD risk factors, and/or have relied on cognitive tasks such as mental arithmetic and the Stroop test that likely have less ecological validity than the anger provocation interview used in the current study.

Additional prospective studies of the possible cardiovascular effects of BP reactivity have defined reactivity in response to the cold pressor task, with some of these showing that reactivity does predict incident CVD events [13] and others failing to replicate this finding [14, 15]. Given the use of the cold pressor task in these studies, however, their

comparability to the current study is unknown. We elicited BP reactivity to a psychological stressor that is a laboratory analogue of a real-world situation rather than relying on a mixed physical/psychological stressor such as the cold pressor task. Although few, if any, studies have tested whether BP reactivity to anger provocation is a more valid method of eliciting reactivity than the use of a cold pressor task, people are more likely to experience anger in their daily lives than they are to hold their hands in near-freezing water for several minutes. In addition, the cold pressor task risks producing primarily reflex hemodynamic changes [3]. As such, our study findings likely have greater lab-to-field generalizability, with respect to psychological stress, than those of studies that have used the cold pressor task.

Although systolic BP reactivity predicted 10-year incident CVD events in an unadjusted Cox proportional hazards regression model in the current study, this finding was no longer significant after simple adjustment for age and sex. In addition, age was significantly correlated with deciles of systolic BP reactivity in bivariate analyses, suggesting that age is an important confounder of the relation between stress-related systolic BP reactivity and incident CVD events. Indeed, previous studies have demonstrated significant associations of age with systolic BP reactivity [41–44], lending support to the idea that age confounds the association of systolic BP reactivity with incident CVD events. Moreover, although some studies have suggested that the predictive validity of BP reactivity may differ for men and women [3], the association between BP reactivity and incident CVD in the current study was not modified by gender as well as other important characteristics such as age, hypertension status, resting BP, Framingham risk score, or being overweight or obese.

There are several possible limitations to our study. First, our primary measure of BP reactivity was defined in relation to a single BP reading during the structured anger provocation interview. Previous studies have shown that the aggregation of cardiovascular responses across multiple time points and multiple stressful situations improves the reliability and generalizability of such measures [34]. Although we replicated our null finding using a measure of reactivity based on the average of the second and third interview-based BP readings, the reliability of our reactivity measure would have been increased even further if we had additional measures of BP during the ESI. Second, although some studies suggest that cardiac reactivity to an anger provocation interview in the laboratory is associated with reactivity in real life [45], such evidence is limited [46]. Indeed, the manual ascertainment of blood pressure in the middle of the anger provocation interview may not be comparable to typical experiences elicited in the natural environment. Third, this study did not include ascertainment of incident hypertension diagnosis or other preclinical disease endpoints as outcomes. Although future studies could examine whether reactivity to anger provocation is associated with hypertension and other preclinical outcomes, additional studies such as these may not be needed if BP reactivity does not ultimately lead to incident CVD events. Finally, the mean age of our sample was relatively young. Although we found that age of the participant at baseline did not interact with the relation between BP reactivity and incident CVD events, it is unclear whether our results can be extended to a population of elderly participants without initial CVD.

4. Conclusion

Neither systolic nor diastolic BP reactivity to anger provocation significantly predicted incident CVD events independent of traditional CVD risk factors, including age, sex, Framingham risk score, BMI, and education in a population-based study. These results suggest that BP reactivity to a laboratory-induced structured anger provocation interview does not play a major role in the development of CVD.

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Research Article

Decreased Cognitive/CNS Function in Young Adults at Risk for Hypertension: Effects of Sleep Deprivation

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Hypertension has been linked to impaired cognitive/CNS function, and some of these changes may precede development of frank essential hypertension. The stress and fatigue of sleep deprivation may exacerbate these cognitive changes in young adults at risk. We hypothesize that individuals at risk for hypertension will show significant declines in cognitive function during a night of sleep deprivation. Fifty-one young adults were recruited for 28-hour total sleep deprivation studies. Hypertension risk was assessed by mildly elevated resting blood pressure and by family history of hypertension. A series of cognitive memory tasks was given at four test sessions across the sleep deprivation period. Although initially comparable in cognitive performance, persons at risk showed larger declines across the night for several indices of working memory, including code substitution, category, and order recall. These results suggest that cognitive/CNS changes may parallel or precede blood pressure dysregulation in the early stages of hypertension development. The role of CNS changes in the etiology of essential hypertension is discussed.

1. Introduction

Hypertensive patients have impaired cognitive and CNS function, and some of these changes may precede development of frank essential hypertension. Subtle cognitive changes in younger persons at risk for hypertension may become more readily apparent during the systemic stress of sleep deprivation. We hypothesize that young adults at risk for hypertension will show significant declines in cognitive function during a night of sleep deprivation.

Cognitive decline in older persons with advanced hypertension is especially well documented and likely represents, at least in part, the damaging effects of sustained high blood pressure on CNS microvasculature, and, hence, brain function [1–5]. For example, hypertension is associated with increased likelihood of dementia in older adults [6–9]. Some of the cognitive decline in older hypertensive patients can be reversed by pharmacological, dietary, and weight loss approaches to blood pressure reduction [10], indicating that chronic high blood pressure can have a damaging effect, either directly or indirectly, on brain function.

However, some cognitive changes may precede the development of frank clinical hypertension, suggesting a more complex association between the CNS and blood pressure in the development of essential hypertension. For example, decreased cognitive/CNS function has been recently found in middle aged and younger hypertensives [11, 12], young people with mildly elevated blood pressure [13], and in normotensives with a positive family history of hypertension [14, 15]. These findings suggest that relatively minor preclinical changes in blood pressure are associated with subtle changes in brain function. Therefore, CNS changes may parallel, precede, and/or contribute to blood pressure elevations, especially in young persons whose cerebral vasculature has not been exposed to the deleterious effects of significant and sustained blood pressure elevations. Thus, the study of cognitive changes in early stages of hypertension development may provide insight into the possible neurogenic precursors and/or etiologic mechanisms of essential hypertension. Interestingly, the systemic stress and fatigue of sleep deprivation may exacerbate both cognitive and circulatory changes in young adults at risk for development of hypertension.

For example, sleep deprivation has been shown to disrupt executive attention, working memory and other higher cognitive functions [16]. Moreover, neural systems that underlie executive function are especially vulnerable to the effects of sleep deprivation in some individuals [17]. Young adults at risk for hypertension development later in life show a spectrum of neural, endocrine and circulatory changes during stress [18–20], possibly including the systemic stress of sleep deprivation. For example, some of studies from our sleep laboratory recently showed that a night of sleep deprivation increased blood pressure in young adults with a positive family history of hypertension versus negative family history controls [21]. The present study, part of that larger series of sleep deprivation studies, focuses on the effect of sleep deprivation on cognitive function in persons at risk for hypertension. We hypothesize that persons at risk for hypertension will show declines in higher cognitive performance during sleep deprivation.

2. Materials and Methods

2.1. Participants. Participants were fifty-one volunteers (28 males and 23 females) with an average age of 22.9 years. Young adult study participants were recruited from campus and the surrounding community with ages ranging from 19–32 years old. This sample included graduate and undergraduate students, university employees, and community citizens. Average body weight was 148 ± 25.7 lbs., and average body mass index was 22.6 ± 3.26. The participants completed questionnaires about personal and family medical history, sleep habits, and alcohol and tobacco use. Only persons reporting a regular diurnal sleep/wake cycle were selected for participation. The final study population was a healthy, normal sample without sleep disorders or significant cardiovascular, neurological, endocrine, or psychiatric disease. All subjects refrained from use of caffeine and tobacco and exercise throughout the study period. Informed consent was obtained from each subject before participation. All procedures were approved by the Clemson University Institutional Review Board.

2.2. Procedures. The present investigation is part of a larger series of studies of sleep deprivation and sustained operations. Procedures have been described in detail by Pilcher and coworkers [22]. Participants were recruited through posted flyers detailing the two-day sleep deprivation study. After screening, volunteers met with researchers three days before the study to discuss the consent form, study procedures, and instructions in completing the study. The participants were instructed to sleep for eight hours each night for the three days prior to the sleep deprivation study. Participants were also instructed not to drink alcohol the day before the study and were told not to consume any caffeine or substances high in sugar (e.g., candy bar) the morning of the study. Participants were given an Actiwatch (Mini Mitter Company Inc., Bend, OR, USA) that they wore for the three days prior to the study. Actiwatches were worn on the nondominant arm to record wrist movement indices of normal sleep/wake patterns.

Participants also received a sleep log to provide information on sleep habits prior to the onset of the study. These sleep logs were to be completed each morning of the three days prior to the study. The sleep logs included questions inquiring about sleep quality, time going to bed, time getting out of bed, and napping throughout the day. Analysis of Actiwatch data confirmed accuracy of sleep logs to verify adherence to instructions. Participants reported at 9:30 AM on Day 1 and were transported to the residential sleep laboratory. Food and noncaffeinated beverages were provided throughout the study.

The participants completed a series of tasks and questionnaires and were given scheduled breaks and meals throughout the study period. Training on the cognitive tasks was completed in two periods on Day 1. Four testing sessions were scheduled at approximately 8:30 PM, 1:00 AM, 5:30 AM, and 10:00 AM across the sleep deprivation period. The study ended on Day 2 when participants were transported back to their residences and instructed to sleep before operating heavy equipment or driving.

2.3. Measures

2.3.1. Sleep and Health. Questionnaires were administered to obtain information on typical sleep patterns and individual and familial medical history for each participant. The Pittsburgh Sleep Quality Index (PSQI) was used to assess recent sleep quality. Its reliability and validity has been verified by Buysse and coworkers [23].

2.3.2. Blood Pressure. Resting blood pressure (BP) was measured upon arrival and departure at approximately 11 PM each day and at approximately 8:30 PM, 1:00 AM, 5:30 AM, and 10:00 AM over the study period. Electronic blood pressure measurements were taken using GE Dinamap Pro100 machines (Medical Solutions, Minneapolis, MN.). Dinamap performance was verified on a regular basis for zero offset, integral offset, and gain using a mercury manometer. All devices performed within manufacturer tolerances. Research assistants were trained on theory and application of blood pressure determination using both auscultatory and oscillometric techniques, including use of appropriate cuff sizes and other American Heart Association guidelines for blood pressure determination [24]. At each blood pressure determination, participants sat quietly in a comfortable armchair for five minutes prior to taking five BP readings at one-minute intervals. The last three readings were averaged to create a single, stable resting BP index at each time period.

2.3.3. Memory Tasks. The participants also completed five subtests from the Automated Neuropsychological Assessment Metrics (ANAM). This measure is a battery of cognitive tests developed by the Office of Military Performance Assessment (OMPAT; Washington, DC). The ANAM tests have strong correlations with traditional measures of neuropsychological functioning, high test-retest reliability (typically = 0.80, 0.95 range), high differential stability, and a large database of studies providing construct validity [25]. The measure includes five different tasks, all of which were used

for the purposes of this study. The tasks were given in the following order for each administration (testing and training): Code Substitution Learning (CDS), Code Substitution Immediate Memory Recall (CDI), Sternberg Memory Recall (ST6), Continuous Performance Test (CPT), and Code Substitution Delayed Memory Recall (CDD). Participants were given the battery 5 times during the training sessions to control for learning effects and then once during each of the 4 testing sessions. ANAM tasks took approximately 12–14 minutes to complete. Apart from the fixed order required by ANAM components, task order was fixed within subjects, but counterbalance between subjects.

2.3.4. Code Substitution Learning (CDS). Participants were presented with a set of symbols (δ, ¥, æ, ◄, ╢, ↕, Ω, √, ≡) that corresponded to a number, 1–9. With the key on the screen for reference, they were given a symbol and number and asked to respond if the pair correctly matched the given key. Participants were given 72 trials during each administration of the task. Each stimulus was displayed for 4000 milliseconds, and the time allowed for response was 4200 milliseconds before the next stimulus was displayed.

2.3.5. Code Substitution Immediate Recall (CDI). Participants were asked to recall the previous key of numbers and symbols that was given during the Code Substitution Practice task. They were presented with a symbol and number pair and indicated if the stimulus matched the previously memorized key. Participants were given 18 trials during each administration of the task. Each stimulus was displayed for 4000 milliseconds, and the time allowed for response was 4200 milliseconds before the next stimulus was displayed.

2.3.6. Code Substitution Delayed Recall (CDD). After completing two additional tasks (see ST6 and CPT below), participants were asked to recall the memorized key given during the Code Substitution Practice task after approximately 10 minutes had elapsed since it was presented. The participants were given 36 trials in the CDD. Each stimulus was displayed for 4000 milliseconds, and the time allowed for response was 4200 milliseconds before the next stimulus was displayed.

2.3.7. Sternberg Memory Recall (ST6). Participants were given a set of 6 letters to memorize. They could review the letters until pressing the space bar to continue the task. Single "probe" letters were then flashed on the screen. The participants then indicated if the stimulus was part of the memory set. The probe was displayed on the screen for 1400 ms. The maximum time to respond to each presented stimulus was 1500 milliseconds.

2.3.8. Category Recall and Order Recall. Participants completed a Category Recall (CatRecall) task presented on a computer to test memory. The CatRecall memory task was developed using E-prime at the University of Maryland's Center for Advanced Study of Language and derived from previously formed category memory tasks [19]. At the beginning of the task, the participant was presented with 6 different categories containing 8 examples within each category, for example, animal: cat, bird, dog, horse, lion, mouse, snake and wolf. Subjects were allowed to study the words and categories for an unlimited amount of time before continuing.

Participants were presented with a "memory list," which was a series of six words, one from each category. Each word in the memory list was displayed on the computer screen for 400 milliseconds. Participants were then presented with a probe category such as "music" from the 6 available category names. The probe category was displayed for 3000 ms. Participants were then asked to identify which word from the memory list was originally included in the category presented.

The order recall task presented participants with a memory list of 6 words, one at a time. Participants were asked to remember the 6 words in order, and when presented with a cue word from the memory list, to correctly choose the word from the memory list that followed the cue word.

2.3.9. Continuous Performance Test (CPT). Participants were presented single-digit numbers (1–9) one at a time. Once a second number appeared, they indicated whether that number was the same as the previously presented number (a 1-back task). Participants were presented with 179 numbers resulting in 178 trials. This task was divided into two sections: with feedback (1 minute) and without feedback (4 minutes). The probe was displayed on the screen for 1000 ms, and participants were given a maximum of 1500 milliseconds to respond.

2.3.10. Classifications of Subjects by Risk for Hypertension. Risk for subsequent development of hypertension was determined in two different ways, by resting blood pressure levels and by reported parental history of hypertension. Classification of risk by resting blood pressure levels was based on criteria outlined in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) [26]. Briefly, subjects rested in a seated position while blood pressure determinations were made on two different days at approximately the same time each day. Classifications were based on the average of two readings each day. Participants were classified as normal if they had no blood pressure above 120 mmHg systolic and 80 mmHg diastolic on both days of measurement. Participants were classified as prehypertensive if they had blood pressure between 120–139 systolic or 80–89 diastolic on both days of measurement. No participants were classified above the prehypertensive range. Risk associated with moderately elevated pressures in young adults has been shown by several studies. For example, the level of pressure in young adults has been shown to predict both the level of pressure and incidence of essential hypertension in later life [27, 28]. Moreover, a recent meta-analysis showed that persons with SBP 130–139 or DBP 85–89 have up to 55% increased risk of stroke [29].

Participants were classified with a positive family history of hypertension if one or both biological parents were identified as having been diagnosed with essential hypertension

Table 1: Means (± standard errors) for systolic and diastolic blood pressure and cognitive performance accuracy across a night of sleep deprivation with sustained cognitive work. All cognitive performance data are in percent correct.

	8:30 PM	1:00 AM	5:30 AM	10:00 AM
Systolic blood pressure (mmHg)	113.0 (1.64)	112.6 (1.78)	111.5 (1.72)	112.0 (1.57)
Diastolic blood pressure (mmHg)	66.3 (1.13)	67.2 (1.03)	66.6 (1.22)	66.5 (1.00)
Category recall	74.2 (2.05)	75.1 (2.42)	69.9 (2.58)	72.2 (2.41)
Code substitution learning	96.6 (.40)	94.9 (.66)	91.4 (.87)	92.7 (.90)
Code substitution immediate recall	93.3 (1.16)	88.5 (2.18)	83.2 (2.73)	86.9 (1.92)
Code substitution delayed recall	91.5 (1.53)	85.0 (2.37)	80.2 (2.18)	81.0 (2.31)
Sternberg memory recall	96.7 (.50)	91.6 (1.20)	90.1 (1.87)	86.7 (1.99)
Continuous performance test	90.2 (1.15)	83.9 (2.35)	76.6 (2.32)	75.3 (2.56)

by a physician. Participants with no reported parental hypertension were classified as negative family history. Validity of self-reported parental hypertension has been consistently demonstrated through direct contact with parents and parents' physicians [30–32].

2.4. Data Analyses. All BP data were entered into Microsoft Excel and imported into SPSS (IBM, Armonk, NY, USA) for statistical analyses. Cognitive performance measures were initially analyzed in a $2 \times 2 \times 4$ (Risk × Sex × Time) design using the SPSS General Linear Model with Time as the within subjects variable, Risk and Sex as between subjects variables, and multivariate F tests for main effects and interactions with Time. One set of Risk analyses were conducted using JNC-7 grouping of blood pressure (prehypertensive versus normotensive). Additional analyses were conducted using family history of hypertension (positive versus negative family history) as an alternate Risk variable. Post hoc simple main effects were assessed using Fisher's LSD.

3. Results

Means and standard errors for blood pressures and cognitive performance of all participants at the four test sessions are shown in Table 1. Repeated measures ANOVAs on cognitive performance generally showed significant sleep deprivation-induced declines in performance for all subjects across testing periods. For example, when collapsed across risk status, significant declines across time were observed for code substitution simultaneous ($F(3, 41) = 7.71$, $P < .001$), code substitution immediate ($F(3, 41) = 8.903$, $P < .001$), code substitution delayed ($F(3, 41) = 21.876$, $P < .001$), and continuous performance ($F(3, 41) = 11.955$, $P < .001$).

3.1. Effects of Sleep Deprivation on Blood Pressures in High- and Low-Risk Groups. Using the JNC-7 criteria for classification of blood pressure, 19.6% of participants (10 of 51) were classified as prehypertensive. Average age was 21.9 years for the prehypertensive group and 23.0 years for the normal group. Using family history of hypertension as an index of risk, 23.5% of participants (12 of 51) reported a positive family history of essential hypertension in at least one biological parent. Average age was 23.0 years for the positive family history group and 22.7 years for the negative family history group. There were no significant group differences in age, weight, body mass index, or distribution of sex among risk groups ($P > .05$). Only 3.9% of participants (2 of 51) had both a prehypertensive classification and a positive family history of hypertension.

Results for blood pressures across time and by risk groups have been reported elsewhere [16]. Briefly, the prehypertensive groups showed significantly higher resting systolic (multivariate $F(1, 46) = 20.839$, $P < .001$, $\eta^2 = .312$) and diastolic [multivariate $F(1, 48) = 4.638$, $P = .036$, $\eta^2 = .088$] blood pressure across all time periods. Using family history of hypertension for risk categorization, there were no significant initial baseline differences in blood pressure between high- and low-risk groups, however the Family History X Time interaction for diastolic blood pressure was significant [multivariate $F(3, 46) = 4.574$, $P = .007$, $\eta^2 = .230$], indicating that diastolic blood pressure for the two family history groups significantly diverged across the night of sleep deprivation, with slight decreases across the night in subjects with negative family history and concomitant increases in subjects with positive family history of hypertension.

3.2. Effects of Sleep Deprivation on Cognitive Performance in Persons at Risk for Hypertension. Repeated measures ANOVAs show significantly greater declines in cognitive performance of prehypertensives versus normotensives over the period of sleep deprivation. For example, Figure 1 shows the significant Risk Group × Time interaction for immediate code substitution memory performance [$F(3, 41) = 4.073$, $P = .013$, $\eta^2 = .230$]. Unlike normotensives, prehypertensives showed a large decline in memory performance at the 5:00 AM test ($P = .03$), but their performance accuracy recovered by the subsequent 10:00 AM test. Figure 2 shows the significant Risk Group × Time interaction for delayed code substitution memory performance [$F(3, 41) = 4.359$, $P = .009$, $\eta^2 = .242$]. Relative to normotensives, prehypertensives showed a large decline in memory at the 5:00 AM test ($P = .009$) that remained through the subsequent 10:00 AM test ($P = .017$). A similar Risk Group × Time interaction was observed for category recall [$F(3, 45) = 3.288$, $P = .029$, $\eta^2 = .180$]. In this case, the performance decline in prehypertensives did not emerge until the 10:00 AM test ($P = .046$). For the Sternberg memory task, a significant Risk Group × Time × Sex interaction achieved statistical significance [$F(3, 41) = 3.248$, $P = .031$, $\eta^2 = .192$], indicating a decline in

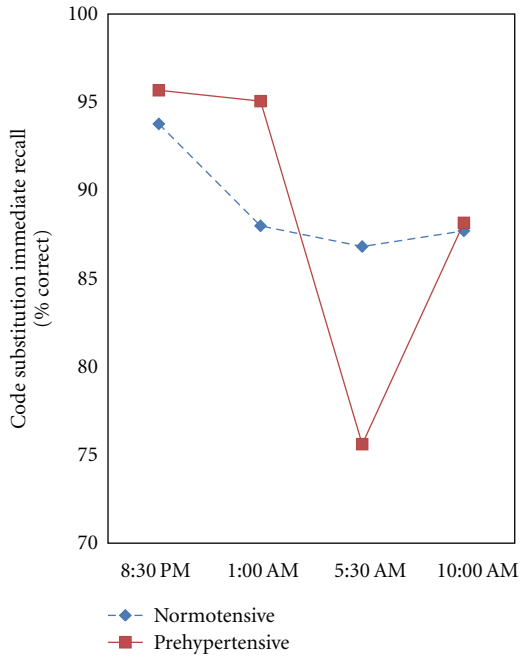

Figure 1: The effect of sleep deprivation on immediate code substitution recall (% correct) in persons classified by JNC-7 criteria of prehypertensive or normotensive. The time by Risk Group interaction was significant [multivariate $F(3, 41) = 4.073$, $P = .013$, $\eta^2 = .230$]. Fisher's LSD indicates a significant drop in performance at 5:30 AM, in prehypertensives ($P = .03$).

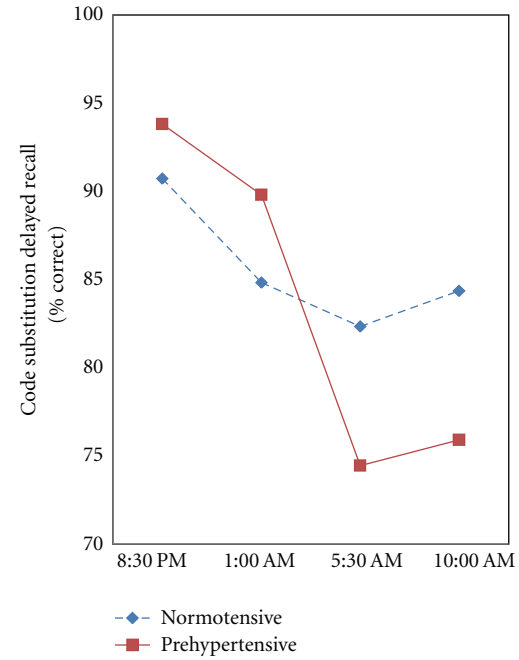

Figure 2: The effect of sleep deprivation on delayed code substitution recall (% correct) in persons classified by JNC-7 criteria of prehypertensive or normotensive. The time by Risk Group interaction was significant [multivariate $F(3, 41) = 4.359$, $P = .009$, $\eta^2 = .242$]. Fisher's LSD indicates a significant drop in performance at 5:30 AM ($P = .009$) and 10:00 AM ($P = .017$) in prehypertensives.

performance at the 10:00 AM testing in prehypertensive women.

Using family history as the risk variable, a significant Risk Group × Time interaction was observed for order recall [$F(3, 21) = 4.061$, $P = .020$, $\eta^2 = .367$]. In this case, persons with a positive family history showed a decline in order recall performance at 1:00 AM and 5:00 AM, with a relative recovery by the 10:00 AM testing. The effect of family history of hypertension over time is shown in Figure 3. No other Risk Group × Time interactions achieved statistical significance.

3.3. Relationship between Sleep-Deprivation-Induced Changes in Cognitive Function and Blood Pressures across the Night. Throughout the night of sleep deprivation, blood pressure was determined prior to each cognitive testing session. Therefore, we also examined the correlations between sleep-deprivation-induced changes in blood pressure and cognitive function across the night. While most correlations were not statistically significant, we did observe a pattern of significant positive correlations (2-tailed probabilities) between blood pressure and corresponding cognitive function, especially at the 1:00 AM test session. For example, at the 1:00 AM test session, SBP was positively correlated with performance on simultaneous code substitution ($r(49) = .526$, $P < .001$), Sternberg memory task ($r(49) = .335$, $P = .023$) and the continuous performance task ($r(49) = .435$, $P = .003$). Similarly, DBP was significantly correlated with performance on simultaneous code substitution ($r(49) = .394$, $P = .007$) and the Sternberg memory task ($r(49) = .412$, $P = .004$) at the 1:00 AM test session.

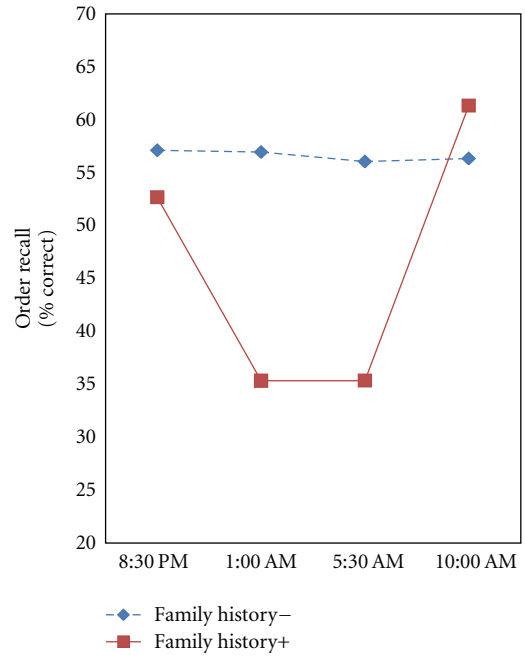

Figure 3: The effect of sleep deprivation on the order recall task (% correct) in persons classified as positive or negative family history of hypertension. The time by Risk Group interaction was significant [multivariate $F(3, 21) = 4.061$, $P = .020$, $\eta^2 = .367$].

4. Discussion

Sleep deprivation has been shown to impair functioning of the distributed thalamoprefrontal cortical networks subserving attention and higher order cognitive processes [16, 17]. Consistent with these and other studies of sleep deprivation, measures of higher cognitive performance declined over time across all participants, regardless of risk status [22, 33]. However, our results show significantly greater cognitive declines in otherwise healthy young adults at risk for hypertension. No consistent differences between high- and low-risk groups in cognitive function were seen at the earlier times of testing, but the cognitive decline in high risk groups emerged most consistently at the 5:30 AM and 10:00 AM tests, after significant sleep deprivation. This suggests that subtle cognitive differences between high- and low-risk groups became apparent only after significant sleep deprivation had occurred. Persons at risk did not show exaggerated cognitive declines in relatively simple tasks, even after significant sleep deprivation. However, high-risk groups showed larger performance decrements across time in tasks requiring significant sustained attention and working memory. For example, there were no interactions of risk groups across time on code substitution learning with simultaneous display, but significant declines were seen for code substitution in both immediate and delayed recall tasks. Interestingly, memory performance of prehypertensives degraded on the more difficult delayed recall task by the 5:30 AM testing and remained low through the final 10:30 AM test session. In contrast, performance on the easier immediate recall task declined in prehypertensives at the 5:30 AM tests, but showed recovery at the 10:00 AM testing. This pattern likely reflects the partial recovery of alertness and cortical arousal associated with the rise in circadian rhythms entrained by sunrise in the light/dark cycle [34]. Prehypertensives also showed greater declines in performance over time in the category recall task. In addition, the decline in Sternberg recall performance in prehypertensives was confined primarily to women. Because of the small sample size in this group, this result should be interpreted with caution until confirmatory evidence is available.

Interestingly, we also observed a decline in order recall performance in persons with a positive family history of hypertension. Because there were no initial differences in resting blood pressure between positive and negative family history groups, this finding suggests that even mild elevations in resting pressure are not necessary for expression of the association between risk for hypertension and cognitive performance decline. This suggests that CNS changes may occur before significant blood pressure dysregulation.

4.1. Sleep Deprivation, Blood Pressure Control, and Cognition. Sleep deprivation and/or disruption can influence the sympathetic nervous system and blood pressure acutely [21] and via chronic sleep loss [34, 35]. However in the present study, scores on the Pittsburgh Sleep Quality Index global scale showed no group differences in chronic sleep quality, regardless of risk categorization (all Ps $> .1$). Thus, it is unlikely that the differential effects of acute sleep deprivation on these risk groups resulted from lower chronic sleep quality in high-risk groups.

Interestingly, sleep-deprivation-induced changes in acute blood pressure and cognition across the night showed a trend for positive correlations, especially at the 1:00 AM testing. This suggests that individuals with the worst cognitive performance at this time of night also showed signs of decreased arousal as indexed by lower acute blood pressure at the time of testing. This may reflect the relationship between cortical and autonomic arousal and is consistent with reports of decreases in blood pressure and attentiveness with increasing fatigue [36].

Overall, the cognitive decline in persons with mild elevations in resting blood pressure (JNC-7 prehypertensive) is consistent with results of Ditto et al. [14], Thyrum et al. [15], and others [13]. To our knowledge, this is the first study to report cognitive declines in persons with a positive family history of hypertension, without concomitant elevations in chronic resting blood pressure. The effect of family history was observed only for the order recall task, and additional research is needed to confirm the role of family history without associated elevations in resting blood pressure. Nevertheless, the present results clearly indicate that the systemic stress and fatigue of sleep deprivation exposes occult cognitive/CNS changes in otherwise healthy young adults at risk for hypertension development later in life.

4.2. Brain Function and Blood Pressure Control Mechanisms. Changes in cognitive function in younger persons without a history of significant and sustained high blood pressure may provide insight into the early etiological mechanisms in the developmental pathophysiology of hypertension. It is possible that even modest, subclinical resting blood pressure elevations could directly engender subtle CNS functional damage [14]. However, our finding of cognitive decline in a group of young adults with familial hypertension raises the possibility that functional CNS changes may be occurring in persons at risk before the development of mild elevations in chronic resting blood pressure. Nevertheless, persons with familial hypertension have increased blood pressure [18] and HPA reactivity to psychological stress [20], so it is possible that these periodic stress-associated blood pressure elevations may influence CNS function, even in the absence of modest elevations in chronic resting blood pressure. Additionally, stress can impair working memory in association with systemic cortisol release [37]. The precise role of glucocorticoids and other stress hormones in the observed cognitive declines in groups at risk remains to be determined. Additional research is needed to further explore the potential effect of acute, stress-induced elevations in blood pressure and stress hormones on brain function.

Notwithstanding the above, there are other possible links between blood pressure and CNS function in otherwise healthy young adults at risk. For example, CNS changes could be involved intimately with the progressive blood pressure dysregulation that eventuates in frank essential hypertension later in life. Several pathways could influence this process. Firstly, changes in CNS function and blood pressure control could be related indirectly with each other, but correlated

with a heretofore unknown, underlying mechanism affecting both through distinct, but noninteractive pathways. Secondly, and even more intriguingly, CNS changes could contribute directly to dysfunction of autonomic and neuroendocrine systems involved in regulation of blood pressure. Under the latter scenario, changes in higher CNS function could cascade distally via central control of sympathoadrenomedullary, hypothalamic pituitary adrenocortical (HPA), and perhaps other neuroendocrine axes [38, 39] to provoke the blood pressure dysregulation observed in the early stages of hypertension development.

In support of this notion, an accumulating body of evidence points to a broad spectrum of subtle CNS changes in otherwise healthy persons with either mildly elevated blood pressure or normal resting blood pressure with other risk factors such as a positive history of hypertension. For example, prior work in our lab has shown abnormalities in opioidergic inhibition of both the HPA and the sympathoadrenomedullary axes in persons at risk for hypertension [19], suggesting alteration in brain mechanisms, either at or proximal to the paraventricular hypothalamus. Moreover, a large literature shows that hypertensive humans and animals as well as persons at risk for hypertension show reduced responsivity to pain [40, 41]. Recent findings suggest that changes in affective pain sensitivity may reflect a more generalized emotional dampening [42, 43] and may result in impaired perception of affective environmental cues [44]. This raises the possibility that subtle changes in brain function and performance may actually contribute to the autonomic dysregulation of blood pressure in persons at risk. For example, it is likely that modest changes in appraisal of threatening stimuli and/or memory function could directly contribute to increased psychological and/or psychosocial distress, with its consequent autonomic disturbance and blood pressure dysregulation. A dampening in threat appraisal could reduce motivation and directly contribute to reduced performance on complex tasks, including the cognitive learning and memory tasks.

The notion of CNS changes preceding blood pressure dysregulation is consistent with a recent report of reduced cry response to painful vitamin K injections in newborn infants with hypertensive grandparents [45]. Therefore, genetic and/or maternal stress hormone-based changes in fetal nervous system development [46, 47] could provoke subtle alterations in brain function, blood pressure control, and programming for adult disease. Thus, the notion of preexisting changes in CNS function in persons at risk for hypertension provides explanation for a large body of data and suggests a novel new possibility for CNS origins of blood pressure dysregulation in the developmental etiology of essential hypertension.

4.3. Methodological Limitations. Several limitations should be considered in interpretation of the present results. First, the 28-hour sleep deprivation methodology requires significant costs, as well as intensive time burden on participants. Thus, modest samples sizes are typical of studies where sleep deprivation is experimentally manipulated. Although a larger sample size would have been preferable, the present study nevertheless produced several significant results in line with hypothesized outcomes. This suggests that the current sample size has sufficient statistical power to expose reliable links between brain function and hypertension risk. Moreover, the experimental manipulation of sleep deprivation in the current study avoids the many potential covariates that confound correlational epidemiological studies of chronic sleep loss. Nevertheless, risk group differences in aerobic fitness or other related variables may have affected these results, despite similarities in body weight and BMI. Interestingly, only two subjects were classified as both prehypertensive and positive family history. This finding could reflect the relatively young age of the present sample. For example, the categorization by family history in our sample could favor a later developing blood pressure rise. An older study sample might show more persons with a family history of hypertension in the prehypertensive blood pressure range. Regardless of methodological limitations, the present results suggest that healthy young adults at risk for hypertension show decreased memory performance during a single night of sleep deprivation.

4.4. Conclusions. The overall findings of this study indicate that young adults at risk for hypertension show decreases in higher cognitive function during sleep deprivation. The sleep deprivation-induced cognitive declines in persons at enhanced risk are significantly greater than those seen in their low-risk counterparts. These risk-related cognitive declines are seen primarily in tasks that require sustained attention and working memory and emerge only after significant sleep deprivation. These results suggest that some cognitive effects in hypertensive patients may reflect CNS changes that occur prior to development of significant and sustained high blood pressure. Taken together with other findings, these results suggest that CNS changes may parallel, precede, or even contribute to blood pressure dysregulation in the early stages of the development of hypertension. Better understanding of the potential CNS origins of essential hypertension could lead to new strategies for treatment and prevention of this costly and widespread disease.

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Review Article

Sodium Consumption: An Individual's Choice?

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Excess intake of dietary salt is estimated to be one of the leading risks to health worldwide. Major national and international health organizations, along with many governments around the world, have called for reductions in the consumption of dietary salt. This paper discusses behavioural and population interventions as mechanisms to reduce dietary salt. In developed countries, salt added during food processing is the dominant source of salt and largely outside of the direct control of individuals. Population-based interventions have the potential to improve health and to be cost saving for these countries. In developing economies, where salt added in cooking and at the table is the dominant source, interventions based on education and behaviour change have been estimated to be highly cost effective. Regardless, countries with either developed or developing economies can benefit from the integration of both population and behavioural change interventions.

1. Introduction

Cardiovascular diseases are the leading cause of death worldwide [1]. In 2008, an estimated 17.3 million people died from cardiovascular disease [1]. Of those deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million due to stroke [1]. A disproportionate amount of those deaths, over 80%, take place in low- and middle-income countries and occur at similar rates among men and women [1]. Not surprisingly, elevated blood pressure levels are a major cause of these diseases and are found at higher rates among low- and middle-income countries [1]. The relationship between blood pressure levels and risk of developing cardiovascular disease is strong and well supported [2]. In 2008, approximately one billion adults worldwide had uncontrolled hypertension (defined as systolic blood pressure $\geq$140 mm Hg systolic and/or diastolic blood pressure $\geq$90 mm Hg) [1]. Given the increasing prevalence of hypertension worldwide and the associated risk for developing cardiovascular disease, public health interventions aimed at reducing blood pressure are crucial.

Many national and international agencies have acknowledged the role of lifestyle and diet, in particular sodium intake, on blood pressure levels. Diets high in salt are now recognized as one of the leading risks to cardiovascular health in the world as they increase blood pressure in both children and adults [3]. Furthermore, a recent meta-analysis of randomized trials has demonstrated that modest reductions in dietary sodium intake are associated with significant reductions in blood pressure in both normotensives and hypertensives and a 20% reduction in cardiovascular events [4, 5]. A reduction in salt intake of 6 g/day lowered blood pressure by 7/4 mm Hg diastolic in hypertensives and 4/2 mm Hg in normotensives [4]. This relationship has been empirically supported and is sufficiently strong to warrant recommendations for public health interventions aimed at substantially reducing dietary sodium intake. Furthermore, sodium reduction is noted as one of the most cost effective and most easily implemented strategies to improve population health [5–13]. Reducing dietary salt is recommended by the World Health Organization and many national governmental and nongovernmental health organizations. Some agencies, however, do not promote a reduction in dietary sodium, namely, nongovernmental or commercial organizations such as the Salt Institute, as they are sponsored by either the food or salt industries [9, 11, 14–17]. Regardless, it is apparent that

the risks associated with an increase in salt consumption, chiefly those related to an increase in blood pressure, are linear [3, 18]. Most health economic models input relatively small changes in blood pressure that occur in those with normal and high blood pressure as estimated by short-term modest reductions in dietary sodium [7, 8, 19]. Some models also include the gastric cancers that are positively associated with, and probably caused by, high-salt intake [13]. Typically, the health economic models do not include the potential impact of longer term irreversible increases in blood pressure, age-related increases in blood pressure, the epigenetic phenomena, whereby exposure to excess salt in utero may increase blood pressure in offspring, or that sodium may increase vascular and cardiac disease in the absence of changes in blood pressure [7, 8, 12, 19–21]. The burden of disease studies also do not account for diseases that have a pathophysiological basis and close association with high sodium diets (i.e., increased severity and frequency of asthma attacks [22], increased calcium containing kidney stones [23], osteoporosis [23], or obesity related to the consumption of calorie containing beverages caused by sodium-induced thirst [24]). Hence the burden of disease associated with excess dietary salt is not only high, but may also be underestimated [20].

The objective of this commentary is to review current sodium consumption worldwide, discuss cost-effective strategies to reduce dietary sodium, as well as briefly review the role of behavioural and policy-based environmental interventions in reducing dietary sodium on a population-based scale.

2. Salt Consumption

Humans evolved on diets consisting of natural plant and animal foods containing small amounts of sodium, typically less than 2 g/day [25, 26]. Today, nearly all populations consume far greater quantities of salt than those provided in natural, unprocessed food diets. The World Health Organization currently recommends a daily consumption of less than 5 grams of salt [9], although some agencies recommend that no more than 1500 mg of sodium should be consumed per day [27–29], calculated as 2/3 tsp of table salt. In most populations, sodium intake is 5.7 g or more/day after age 5, with many populations consuming and average of over 10 g/day [30–32]. Furthermore, within high sodium consumption countries, only a small proportion of individuals consume the recommended levels of salt. For example, in Canada, a country with average salt consumption of 8.5 gm/day, 85% of men and 60% of women aged 9 to 70 consume over the upper recommended limit for salt and the vast majority (>90%) are above the level recommended for individuals to consume [33, 34].

Excess sodium intake results in adverse effects beyond those of increasing blood pressure. For example, one study found that in a population of overweight adults, a daily intake of sodium greater than 2300 mg/day was associated with a 61% increase in coronary heart disease mortality, an 89% increase in stroke mortality, and a 39% increase in all-cause mortality over a 19-year period [35]. Along with the other sodium-related illnesses discussed above (i.e., gastric cancers, kidney stones, etc.), it is clear that the economic costs associated with such illnesses can be substantial.

3. Cost Effectiveness of Interventions to Reduce Dietary Salt

In countries with developed economies, salt added during the processing of foods accounts for the vast majority of dietary salt (75–80%) [36]. An additional 10% of dietary salt is accounted for by salt that is naturally occurring in foods, while the rest is accounted for by salt added at the table or during cooking [36]. In low- to-middle income countries where populations may have limited access to processed foods, salt added at home, in cooking, or at the table, accounts for the majority of dietary salt [14]. Reducing dietary salt is estimated to save substantial health care costs [7, 10, 16, 30, 37–41]. For example, reducing dietary salt by 3 g/day in the United States is estimated to save 194,000 to 392,000 quality adjusted life years and reduce health care costs $10 to $24 billion US dollars a year [7]. In Canada, reducing salt consumption to recommended levels is estimated to reduce the prevalence of hypertension by 30% and to save up to $430 million dollars per year just in direct hypertension management costs alone [38]. In lower-income countries, programs aimed at reducing consumption of dietary salt through an intervention largely based on education are estimated to cost little (less than $0.40 USD per person per year), reduce premature deaths by close to 14 million in 10 years, and to be slightly more cost effective than strategies to reduce tobacco use (both highly advocated interventions) [8, 40].

4. Awareness and Barriers to Change

Although there is a general lack of awareness of salt as a health issue in many countries, some countries with established salt reduction programs show increasing awareness [41]. For example, in Canada, 80% of people diagnosed with hypertension are attempting to reduce dietary sodium [42]. In addition, many food companies have developed low-salt options to their product lines for people to choose, with some companies reducing salt additives in their full product line [43]. In developed economies, there are substantial barriers to free choice in those who chose to eat less salt [16, 44]. In most countries, nutritional information is not readily available. It is often the case that nutritional information is available only on the company's website, by asking for and reviewing a binder on site, or only readily available after purchase. Even in the United States and Canada, countries with mandatory labelling of packaged foods, the labels are often difficult to interpret. Also serving sizes may be variable and not comparable between products. In an unpublished study, we found that in a sample of over 100 people with diabetes who had received training on how to read a food label, not one could accurately answer how much of a processed food they could eat in a day when presented with the food label. In other countries, food labelling on packaged foods may not be mandatory and labelled foods may not be available.

In remote regions and areas where populations vulnerable to the development of elevated blood pressure reside, low-salt alternative choices are typically not available. Furthermore, these populations may not have the health literacy with which to make informed choices. Food processors and manufacturers often use pervasive marketing techniques to create consumer demand for high-salt foods, which undermine efforts of public health and individual education interventions that attempt to reduce sodium intake. Moreover, these marketing techniques are often directed towards children by making consumption of such foods seem "fun" [45].

Perhaps the greatest barrier to choosing and maintaining a low-sodium diet is that high-salt foods are ubiquitous and hence difficult for those who choose low-salt diets [16, 46]. In Canada, high-salt diets are by and large perceived as unhealthy by the general population [47]. However, it is often the case that the same people who recognize that Canadians in general consume too much salt, believe that their personal consumption of dietary sodium is within the recommended amount [47]. This suggests that even a relatively affluent, well-educated population may have difficulty identifying and avoiding high-salt foods even if they perceive it is a health issue and have chosen to follow a low-salt diet. Some of the challenges of individual choice in selecting low salt diets is perhaps best illustrated by clinical trials where highly motivated patients are carefully and repeatedly trained how to select low-salt foods but generally can only sustain small reductions in salt intake long term [44, 48].

5. Population Interventions to Reduce Dietary Salt

Population-based approaches to reducing dietary salt may be effective in developed economies and have shown promising results for reducing blood pressure. In the late 1950s, the Japanese Government implemented a campaign to reduce salt intake given the high stroke mortality rates. Ten years later, salt intake was reduced from an average of 13.5 to 12.1 g/day overall, and from 18 to 14 g/day in the northern regions [49]. The reduction resulted in a decrease in average blood pressure and an 80% reduction in stroke mortality [49]. In the 1970s, Finland's government began a public education campaign and enforced regulations on food processing companies through a warning label on high-salt foods in order to reduce salt consumption across the country [50, 51]. More than 30 years later, the overall sodium intake in Finland has decreased more than 40%, with a subsequent decrease in mean diastolic blood pressure of greater than 10 mm Hg and an 80% decline in the mortality rate from heart disease and stroke [52]. Similar results were also seen on smaller scales in the DASH (Dietary Approached to Stop Hypertension) trial conducted in the USA [3, 53]. This trial assessed three levels of dietary sodium intake on two diets (American diet versus DASH diet) and demonstrated that reducing sodium in either diet resulted in lower blood pressure [3, 12, 53].

More recently in the United Kingdom, reductions in the amount of salt added to foods, in conjunction with a social marketing campaign, have been associated with reduction in population salt intake [14]. In developing economies widespread replacement of salt with a partial salt replacement (sodium, potassium magnesium combination) holds great promise [54, 55]. For example, a recent double-blind randomized controlled trial conducted in rural northern China found that replacing household salt with a reduced-sodium, high-potassium salt substitute for 1 year reduced systolic blood pressure by 5.4 mm Hg [55]. This low cost change in diet has shown promising outcomes for blood pressure reduction with little to no burden on the consumer.

6. Individual- and Population-Based Approaches

Clearly both a mix of population approaches and behavioural approaches targeting individuals are required to reduce sodium intake to within recommended levels [10, 11, 15, 16, 33, 56]. Similar methods have been successfully employed in reducing tobacco use [57]. With respect to individually targeted efforts, for example, a variety of behavioural interventions, including brief physician smoking cessation counselling, was found to meaningfully increase smoking quit rates [58]. However, it has become increasingly clear that education targeted towards individuals may be necessary, but not sufficient, to motivate long-term health behaviour change [59, 60]. Behavioural medicine researchers have begun testing and implementing more sophisticated models of behaviour change. For example, Motivational Interviewing, a directive patient-centred counselling approach focused on exploring and resolving ambivalence, which emerged as an effective therapeutic approach within the addictions field [61], has recently shown promise for other complex behaviour change problems such as weight loss in overweight and obese patients [62] and adherence to antihypertensive medication [63]. In contrast with recommendations for behaviour change delivered through education and advice giving, Motivational Interviewing differs in that motivation for change is elicited from individuals, rather than imparted by a health-care provider [64].

The mix of behavioural interventions and population interventions depends on the specific circumstances of both the individual and the population. In countries with developed economies, population-based approaches, and a reduction of salt additives to food, supplemented by public education campaigns, need to be the primary means of intervention to ensure that the healthy option that is low in salt is the easiest option—a basic caveat of public health interventions. A universal reduction in salt additives during the manufacturing process has a strong potential to reduce health disparities in vulnerable populations while improving overall population health. Behavioural interventions may be most important to ensure the population and especially policy makers understand and are supportive of the need to reduce dietary salt. However, for specific individuals with strong motivation or at a greater personal risk from consuming a diet high in sodium, intensive behavioural interventions may be efficacious. Notably sole reliance on the individual behavioural approach is likely to have a smaller impact on a population basis, to be expensive, and to increase health disparity.

In developing economies, where the majority of sodium intake comes from salt added at the table and in cooking, behavioural interventions are more likely to be effective in reducing overall intake than population-based means [8, 32]. In this case, the individual needs to understand the consequences of excess sodium intake and change their behaviors (i.e., eating habits) to reduce sodium intake. Nevertheless, even in this setting, population interventions may still play an important role. Partial replacement of table salt (sodium chloride) with various mineral salts (mixtures of sodium, potassium, and/or magnesium and calcium) has been shown to be highly effective to reduce overall sodium consumption and also reduce blood pressure [55, 65]. Efforts to reduce dietary salt are also likely to reduce dietary iodine, therefore monitoring dietary iodine adequacy and revising the iodine content of salt is essential to maintain population health in most settings, including developed countries [66]. Population interventions that ensure widespread replacement of salt with a partial salt substitute that contains iodine may be the dominant strategy to reduce sodium intake on a large-scale basis in combination with behaviour change interventions.

7. Conclusion

Given the promising outcomes observed in recent randomized controlled trials and population-based interventions, reducing dietary sodium intake to modest levels (approximately 5 g/day) worldwide would result in a major improvement in overall health and reduce the costs associated with diseases connected to excess sodium intake. However, it is apparent that relying solely on interventions that target individual behaviour is not the ideal approach for reducing sodium consumption. While it may contribute to behaviour change among highly motivated individuals and increase the acceptability of population-based interventions, the latter approach seems better suited for this particular health behaviour.

Conflict of Interests

The authors declare that they have no financial or commercial conflict of interests to disclose.

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Research Article

State Anxiety Is Associated with Cardiovascular Reactivity in Young, Healthy African Americans

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Although several studies have shown that enhanced cardiovascular reactivity can predict hypertension development in African Americans, these findings have not been consistent among all studies examining reactivity and hypertension susceptibility. This inconsistency may be explained by the influence of anxiety (state and trait) on the blood pressure response to stress. Therefore, this study sought to determine whether anxiety is associated with blood pressure response to cold pressor (CP) and anger recall (AR) stress tests in young healthy African Americans. Modeling using state and trait anxiety revealed that state anxiety predicts systolic (SBP) and diastolic blood pressure DBP response to CP and AR ($P \leq 0.02$). Interestingly, state anxiety predicted heart rate changes only to CP ($P < 0.01$; $P = 0.3$ for AR). Although trait anxiety was associated with SBP response to AR and not CP, it was not a significant predictor of reactivity in our models. We conclude that anxiety levels may contribute to the variable blood pressure response to acute stressors and, therefore, should be assessed when performing cardiovascular reactivity measures.

1. Introduction

Although enhanced cardiovascular reactivity is generally associated with future development of hypertension and other cardiovascular events [1–5], there are studies that have failed to show any relationship between reactivity to stress and future elevation of blood pressure [1, 6–12]. The reason for these inconsistent findings is unclear. Emerging evidence suggest that some stress tests may be better predictors of future cardiovascular events than other stressors [4, 5, 10]. For example, blood pressure response to arithmetic and star tracing stress tests predicted high blood pressure while reactivity to cold pressor stress test did not [13, 14]. Furthermore, metanalysis of studies that assessed mental stress tests and hypertension development revealed variable success of mental tests in predicting hypertension. Among the different types of mental stressors, cognitive mental stressors were more consistent in predicting hypertension compared to emotion evoking, interview, and public speaking stressors [10]. The inconsistencies in prediction do not appear to be explained by differences in the type (mental, physical, or psychophysical) of stress tests for there is inconsistent predictability even among the types of stressors.

Another possible explanation for the inconsistencies in reactivity prediction of adverse cardiovascular outcomes is the interaction of psychosocial factors with cardiovascular responses to acute laboratory stressors. Anxiety is one such psychosocial factor that may determine reactivity responses. Metanalysis of over 700 studies revealed that chronic (trait) anxiety is associated with decreased cardiovascular reactivity [15]. In contrast, a study of young European population revealed that acute (state) anxiety was associated with significantly increased reactivity to cold pressor test but not mental stress test [16]. These observations, when taken together, suggest that individuals may be inaccurately identified as hyperresponsive if anxiety is not considered as a confounder in the reactivity response to acute laboratory stress tests. Consequently, inaccurate assessment of increased reactivity

due to the interaction of anxiety with acute stressors may explain the inconsistent reports of increased risk of hypertension with increased reactivity.

This study sought to investigate whether (1) anxiety determined the blood pressure response to stress tests and (2) anxiety differentially influenced blood pressure response to anger recall and cold pressor stress tests in African Americans. We chose to study African Americans for several reasons: (1) this group is characterized as hyperresponsive to stress [7, 17–20], (2) several reports have failed to find increased reactivity in this population [4, 8, 21–23], and (3) psychosocial factors, including anxiety, are significantly associated with blood pressure in this population [24–29]. We report that state (in the moment) anxiety was significantly associated with blood pressure response to both stressors (anger recall and cold pressor stress tests) in this population. These results support the idea that identification of hyperresponders to acute stress tests among African Americans must take into account anxiety levels before determining whether an individual has increased reactivity to acute stress and/or that anxiety may play an important role along with reactivity response in hypertension development. However, our results do not support the idea that anxiety differentially impacts reactivity response to psychological, psychophysical, and physical stressors.

2. Methods

2.1. Participants and Procedures. A sample of 179 (116 males, 63 females) participants of African descent were recruited to the study. All study procedures and materials were approved by and in compliance with the North Carolina Central University institutional review board. Eligibility criteria for entry were (1) be 18 to 65 years old (2) being a student or employee at North Carolina Central University or living in the surrounding regions of Durham, Orange and Wake counties, (3) having no diagnosed cardiovascular disease (self-reported), and (4) not taking any hypertensive medication. These regions of Durham, Orange, and Wake counties make up the North Carolina Triangle region that is in the stroke belt (e.g., a geographic region with a higher occurrence of stroke) [30]. Of these 179, only 50 are reported in the current report; these were selected based on the type of mental stress used. The 50 participants reported here met the following criteria: (1) completed both the trait anxiety scale and the state anxiety scale, and (2) were between the ages of 18 and 40 years old. Study participants were scheduled at either 9 am or 1 pm for the three-hour study protocol. After receiving informed consent, trained staff measured blood pressure by sphygmomanometer method with a GE Dinamap Pro 100 automatic model and a cuff size appropriate for the body size. Each participant was allowed five minutes to sit quietly before taking the first resting parameters. The Dinamap was set to assess systolic blood pressure (SBP) and diastolic blood pressure (DBP) at one-minute intervals for the resting measurements as well as during the two acute stressor tasks. State anxiety survey was administered prior to baseline blood pressure measurements. Following resting blood pressure and heart rate measurements, participants were administered the cold pressor test, consisting of submersion of the hand in ice cold water for three minutes followed by a five-minute recovery period. A psychological stressor, anger recall, was given only after blood pressures and heart rate returned to baseline resting values. Anger recall stress consisted of 5 minutes of contemplating an event that evoked anger, 5-minute discussion about the event, and 5-minute recovery period. Trait anxiety survey was administered following the completion of the anger recall stressor. Cardiovascular reactivity was calculated as the difference between the average baseline prestressor blood pressure and the average change in blood pressure over the 5-minute stress period.

The study protocol consisted of state anxiety assessment, resting BP measurement, second resting BP measurement, cold pressor stressor, third resting BP measurement, anger recall stressor, trait anxiety assessment, recording medical history, body mass index measurement, and completing a demographics questionnaire.

2.2. Psychosocial Anxiety Measure. Anxiety was assessed using the state-trait anxiety inventory [31]. State anxiety is defined as an acute response to a threatening or challenging situation, while trait anxiety is defined as a stable and enduring tendency to be anxious. Each subscale is a 20-item self-report inventory. Each item is rated on a four-point scale (1 = almost never, 4 = almost always). Items from each subscale are summed to create a total state anxiety score and a total Trait Anxiety score. Higher scores on the state anxiety subscale indicate greater anxiety at the present time; higher scores on the trait anxiety subscale indicate greater anxiety, in general. The state anxiety subscale has an alpha coefficient of .87, and the trait anxiety has an alpha coefficient of .88, indicating good (since .80 or greater) internal consistency in this sample.

3. Statistics

Data analysis was performed using SAS 9.1.3 for Windows [32]. Scoring of the psychosocial scales Spielberger State Trait Anxiety Inventory utilized scoring protocols documented in prior research as indicated above and were confirmed with factor analysis. Cronbach's alpha values were confirmed as reported above. Mean, standard deviation, standard error, median, and quartile calculations provide data reductions for SBP, DBP, and other clinical measures with multiple measurements. Regression models, goodness of fit, multivariate parameter estimates, and confidence intervals were evaluated for each stressors impact on SBP, and DBP. Two participants did not complete the cold pressor stressor; thus, the sample size is 48 for the cold pressor cardiovascular reactivity and 50 for the anger recall cardiovascular reactivity.

4. Results

Table 1 shows the baseline characteristics of the study sample. The African American study samples are relatively young

Table 1: Participants traditional cardiovascular risk factors.

	Total *N*	Mean (SD) Median (Q1, Q3)
Age	50	23.6 (6.7) 21 (19, 25)
SBP	50	114.3 (11.9) 112.6 (105.9, 123.6)
DBP	50	69.9 (7.4) 68.9 (64.3, 72.7)
MAP	50	87.2 (7.2) 86.0 (63.0, 75.8)
HR	50	70.3 (9.8) 69.4 (63.0, 75.8)
HOMA	21	2.1 (2.0) 2.0 (0, 2.0)
Glucose	30	83.4 (14.5) 83.5 (79.0, 92.0)
Insulin	21	10.9 (8.5) 9.2 (5.1, 14.4)
BMI	50	28.1 (7.1) 26.2 (23.0, 33.2)
Waist	40	81.1 (16.2) 77.6 (71.4, 89.0)
Cholesterol	30	169.1 (36.1) 170.5 (146, 195)
HDL	30	54.5 (15.3) 53.5 (42, 65)
LDL	30	99.3 (36.0) 97.5 (69, 123)
Triglycerides	30	76.5 (30.5) 65.5 (54, 94)

(median age of twenty-one years) with normal BMI (median BMI was 26.2 kg/m^2; normal BMI is 25–30 kg/m^2) and waist circumference normal values of less than 102 for males and 88 cm for females [33–35]. This group also had normal cholesterol (less than 200 mg/dL), triglycerides (less than 150 mg/dL), glucose (less than 126 mg/dL), and insulin (<10 mIU) levels. This group was normotensive with median systolic (SBP) and diastolic (DBP) blood pressures of 114 and 70 mmHg, respectively.

A summary of the cardiovascular reactivity responses to AR and CP is shown in Table 2. Cardiovascular reactivity was defined as the change in cardiovascular parameters (SBP, DBP, mean arterial pressure (MAP), and heart rate (HR)) following the induction of a stress stimulus compared to baseline cardiovascular parameters. Both the CP stressor and the AR stressor produced significant rises in SBP, DBP, and HR. All of the values returned to baseline during the recovery period except for SBP during the CP recovery period. Repeated measures ANOVA and the multiple comparison test, Student-Newman-Keuls test, verified that the two stressor tasks (CP and AR) produced statistically significant increases ($P < 0.0001$) in the cardiovascular parameters in comparison to the resting measurements. The results suggest that both tasks induced stress-related cardiovascular activity.

Table 2: Cardiovascular reactivity responses to cold pressor and anger recall.

	Cold pressor[a] Mean (SD) Median(Q1, Q3) *N*	Anger recall[a] Mean (SD) Median(Q1, Q3) *N*
ΔSBP	17.0 (9.9) 16.3 (11.3, 23.5) 48	9.9 (8.8) 10.1 (3.4, 14.6) 50
ΔDBP	12.5 (7.8) 12.0 (7.1, 18.3) 48	6.4 (5.4) 5.8 (2.9, 10.6) 50
ΔMAP	12.2 (7.7) 11.1 (6.2, 17.4) 48	6.5 (5.2) 5.8 (2.9, 9.9) 50
ΔHR	6.7 (7.1) 6.5 (2.1, 9.9) 48	4.7 (5.8) 4.7 (0.8, 8.2) 50

[a] All values were significantly different from baseline ($P < 0.0001$).

We examined Pearson's correlations of state anxiety, trait anxiety, age, BMI, and resting cardiovascular measures with the cardiovascular reactivity parameters. Trait anxiety had a statistically significant, positive correlation with state anxiety ($n = 50$; Pearson's $r = 0.47$; $P < 0.001$, two-tailed Pearson's correlation). State anxiety had statistically significant, positive correlations with CP reactivity response for SBP (average change; $n = 48$; Pearson's $r = 0.37$; $P = 0.01$), DBP (average change; $n = 48$; Pearson's $r = 0.40$; $P = 0.005$). Similarly, state anxiety was highly correlated with the AR reactivity response for SBP ($n = 50$; Pearson's $r = 0.34$; $P = 0.015$) and DBP ($n = 50$; Pearson's $r = 0.35$; $P = 0.013$). State anxiety exhibited differential effects on HR response to CP and AR. Specifically, state anxiety was significantly associated with HR change to CP (average change; $n = 48$; Pearson's $r = 0.37$; $P = 0.009$) but was not related to HR changes to AR ($n = 50$; Pearson's $r = 0.14$; $P = 0.30$).

Trait anxiety also had a differential association with reactivity to CP versus AR. Trait anxiety had a nonsignificant correlation with SBP ($n = 48$; Pearson's $r = 0.23$; $P = 0.12$) but a positive, significant correlation for DBP ($n = 48$; Pearson's $r = 0.34$; $P = 0.02$) reactivity response to CP. As for AR, trait anxiety was positively and significantly correlated with SBP ($n = 50$; Pearson's $r = 0.35$; $P = 0.012$) but was not significantly correlated with DBP ($n = 50$; Pearson's $r = 0.23$; $P = 0.11$).

Age, BMI, and resting cardiovascular measures had nonsignificant correlations with both CP reactivity and AR reactivity as measured by SBP, DBP, and HR changes. Resting SBP was only associated with MAP changes with CP and AR

Table 3: Parsimonious linear regression models for cardiovascular reactivity to cold pressor test.

	R^2	df	F	P	Variables	β	t	P
ΔSBP	0.14	1,46	7.35	0.009	State anxiety	8.72	2.71	0.009
ΔDBP	0.16	1,46	8.63	0.005	State anxiety	7.36	2.94	0.005
ΔMAP	0.15	1,46	7.94	0.007	State anxiety	7.00	2.82	0.007
ΔHR	0.14	1,46	7.48	0.009	State anxiety	6.28	2.73	0.009

The models explained 14% of the variance for SBP, 16% for DBP, 15% for MAP, and 14% for HR.

Table 4: Parsimonious linear regression models for cardiovascular reactivity to anger recall.

	R^2	df	F	P	Variables	β	t	P
ΔSBP	0.12	1,49	6.39	0.015	State anxiety	7.33	2.53	0.015
ΔDBP	0.12	1,49	6.69	0.013	State anxiety	4.59	2.59	0.013
ΔMAP	0.20	1,49	11.67	0.001	State anxiety	5.60	3.42	0.001
ΔHR	0.02	1,49	1.08	0.303	State anxiety	2.02	1.04	0.303

The models explained 12% of the variance for SBP, 12% for DBP, 20% for MAP, and 2% for HR.

stress tests (Pearson's $r = 0.33$; $P < 0.02$ and $r = 0.38$; $P < 0.01$, resp.).

The following variables were evaluated in the stepwise procedure: state anxiety, trait anxiety, resting cardiovascular measures, body mass index, and age. The variable selection results of the stepwise algorithm suggested the use of state anxiety for a parsimonious model of both cold pressor cardiovascular reactivity as well as anger recall cardiovascular reactivity.

Our next step was to evaluate regression models to predict cardiovascular reactivity with state anxiety as the independent variable. The model for predicting the CP increase in SBP (see Table 3) had an r^2 of 0.14 and state anxiety as a significant parameter ($P = 0.009$). State anxiety was also a significant independent variable ($P = 0.005$) in the model of the CP change in DBP ($r^2 = 0.16$). Similar results were found with the model for predicting the change in cardiovascular reactivity for the AR stressor as shown in Table 4. State anxiety was a significant parameter for the change in SBP ($P = 0.015$, $r^2 = 0.12$) and DBP ($P = 0.013$, $r^2 = 0.12$).

Each model was scrutinized to verify adherence to the assumptions of regression modeling (linear relationship between independent variables and dependent variables, homoscedasticity of the errors, and errors are independent and normally distributed). Plots of residuals of each model against the predicted values were checked. Shapiro-Wilke statistics did not reject the null hypothesis of normal distribution of the residuals.

5. Discussion

This study investigated whether anxiety differentially affects cardiovascular reactivity to cold pressor and anger recall stress tests in a sample of young, healthy, community dwelling African American adults, a population prone to develop cardiovascular disease. Importantly, we show that the state (at the moment) anxiety was significantly associated SBP and DBP responses to both cold pressor and anger recall laboratory stress tests in this population. In contrast to blood pressure, state anxiety differentially predicted HR response to CP but not AR. On the other hand, chronic (trait) anxiety was not a significant predictor of reactivity in our statistical models. We interpret these results to mean that the state of anxiety at the time of the stressor must be considered when assessing cardiovascular reactivity to laboratory stress tests. Failure to consider state anxiety as a confounder of reactivity responses may lead to misidentifying some individuals as hyperresponders when compared to others. Misidentification of individuals may contribute in part to the inconsistent findings of increased reactivity in African Americans and to the inconsistent prediction of hypertension in those with increased vascular reactivity. Alternatively, these results can be interpreted to mean that the interaction of state anxiety and cardiovascular reactivity may be important determinants of hypertension development in African Americans.

Anxiety, chronic anxiety in particular, has been linked to the development of disease [36]. Contrary to what would be expected, chronic anxiety has been shown to be negatively associated with cardiovascular reactivity [15]. Although chronic anxiety and cardiovascular reactivity associations have been studied, few studies have investigated the role of state anxiety in determining blood pressure response to stress. State anxiety is important in predicting the DBP "white coat" response and is effective in predicting ambulatory evening systolic blood pressure in young black males [24]. Studies that have investigated the effect of state anxiety on reactivity did not include African Americans [16, 37]. Our study provides evidence that young healthy African Americans who are anxious prior to the stress tests are likely to have higher blood pressure responses to the stress. Thus, variability in hyperresponsiveness response to laboratory stress tests in African Americans may be due in part to a failure to consider state anxiety as a confounder.

Although many studies have shown that enhanced cardiovascular reactivity predicts hypertension development and other cardiovascular events [1–5], there are several studies that failed to show any relationship between reactivity to stress and hypertension development [1, 6–12]. The reason

for the variable predictive response to laboratory stress tests is unclear. The inconsistency may be a consequence of the type of stressors used [4, 5, 38, 39] and the interaction of psychosocial factors with blood pressure response to the stressor [40–42]. Psychological stress tests may be better than cold pressor stress tests at predicting future cardiovascular events [4, 5, 22, 43, 44]. This differential effect of stressor type and hypertension development may be a consequence of differential psychosocial factor interaction with stressors. In a study of a European population, psychosocial factors appear to have a greater impact on reactivity to cold pressor than reactivity to mental stress [16]. Our study compares the impact of anxiety on reactivity to cold pressor and anger recall in African Americans. Anxiety was significantly associated with blood pressure response to both stressors in this population.

Another explanation for the inconsistent findings of increased risk of hypertension development with increased reactivity is the interaction of psychosocial factors with cardiovascular reactivity to promote hypertension development. For example, studies show that hostility, depression, and anger contribute to increased reactivity [40, 45, 46]. Psychosocial factors also are associated with increased incidence of cardiovascular events [47–50] as well as the development of cardiovascular disease [51, 52]. We show that the psychosocial factor, anxiety, can influence the reactivity response to acute stress. However, because the study design was cross-sectional, it could not be determined whether state anxiety interaction with cardiovascular response to acute stress predicts hypertension development.

This study shows that the current state of anxiety was significantly associated with blood pressure response to laboratory stress tests. Consequently, anxiety levels should be assessed when using acute laboratory stress tests for identification of those with increased cardiovascular reactivity. Further studies are needed to determine whether reactivity normalized to anxiety increases the accuracy in identifying hyperresponders and, subsequently, predicting future hypertension development.

6. Limitations

The small sample size is a major limitation of this study. These findings need to be validated in a larger cross sectional population of African Americans. Additionally, our study design did not allow us to determine whether the impact of anxiety on blood pressure response to acute stressor is unique to anxiety or whether other psychosocial factors similarly influence blood pressure response to acute stress in our cohort. Another limitation of the study is that adrenergic system activation was not measured; consequently, it could not be determined if the two stressors differentially activated the beta or alpha-adrenergic receptor pathways. This information would be helpful in future longitudinal studies that will address how activation of the alpha and beta adrenergic receptors pathways ultimately leads to hypertension development and the attending cardiovascular disease. A longitudinal study design will also help to address the question of whether inclusion of anxiety enhances the ability of increased reactivity to predict future elevations of blood pressure.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Clinical Study

Psychosocial Determinants of Health Behaviour Change in an E-Counseling Intervention for Hypertension

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We evaluated the influence of psychological stress and depression on motivation to adhere to recommended guidelines for exercise and diet. This study was conducted within a larger e-counseling trial. Subjects diagnosed with hypertension ($n = 387$, age = 44–74 years, 59% female) completed assessments at baseline and within 2 weeks after a 4-month intervention period. Outcomes included mean level of readiness to change diet and exercise and symptoms of depression and stress. Per protocol analysis defined e-counseling support as follows: ≥8 e-mails = therapeutic dose, 1–7 e-mails = subtherapeutic dose, and 0 e-mails = Controls. Baseline adjusted symptoms of depression and stress were inversely correlated with improvement in exercise (partial $R = -.14$, $P = .01$, and partial $R = -.17$, $P = .01$, resp.) but not diet or e-counseling. Subjects who received a therapeutic dose of e-counseling demonstrated greater readiness for diet adherence versus Controls ($P = .02$). Similarly, subjects receiving a therapeutic level of e-counseling demonstrated significantly greater readiness for exercise adherence versus Controls ($P = .04$). In sum, e-counseling is associated with improved motivation to adhere to exercise and diet among patients with hypertension, independent of symptoms of psychological stress and depression.

1. Introduction

Health behaviour change for diet and exercise in combination with drug therapy is critical for the treatment of hypertension [1]. Meta-analysis indicates that counseling initiatives to increase patient motivation to change health behaviour can significantly improve outcomes across a wide array of behaviours, including exercise and diet [2, 3]. However, it is not established whether novel programs of motivational counseling, which are delivered via the internet, are sufficient to improve patient readiness to adhere to exercise and diet, among persons diagnosed with hypertension. It is also unknown whether the potential efficacy of this e-counseling initiative is compromised significantly by symptoms of psychological stress and depression, which are well known to inhibit motivation to change health behaviours [4, 5].

The I-START trial (Internet-based Strategic Transdisciplinary Approach to Risk Reduction and Treatment) was an e-counseling intervention that used goal setting features from motivational interviewing [6] to improve adherence to health behaviour change in patients diagnosed with hypertension. The purpose of the present substudy was to evaluate whether e-counseling significantly increased motivation to change exercise and diet behaviour in patients enrolled in I-START, as defined by the Transtheoretical model of stages of readiness for change [7, 8]. In addition, this study investigated whether behaviour change following e-counseling in I-START was significantly associated with presenting symptoms of psychological stress and depression.

2. Methods

2.1. Subjects. Subjects were recruited by self-referral through an e-based program of the Heart and Stroke Foundation of Canada (HSF): My Blood Pressure Action Plan (BPAP); http://www.heartandstroke.ca/hs_Risk.asp?media=bp_hsfhomepage.

2.2. Inclusion/Exclusion Criteria. Enrollment included 387 subjects between the ages of 45–74 years in this study. All subjects were diagnosed with stage I or II hypertension (140–159/90–99 mmHg or 160–180/100–110 mmHg, resp.) as confirmed by their family physician. Subjects receiving antihypertensive pharmacotherapy were required to have had an unchanged treatment regimen for a minimum of 4 months. Participation of these subjects was also contingent on confirmation by their physician that there was no current plan to alter their medical treatment. Subjects were not living in an institution and they were competent in English or French. All subjects provided consent to consult with their family physician to confirm medications and diagnosis.

Subjects were excluded from the study if they self-reported having a current diagnosis of cardiovascular disease or major psychopathology (e.g., bipolar mood disorder), or a history of alcohol or substance abuse in the last year, or if they had an anxiety disorder due to panic, phobias, obsession-compulsion, or traumatic stress.

2.3. Materials. Readiness to change health behaviour was assessed using a health promotion lifestyle profile (HPLP) [9]. This profile provided a global index of adherence according to Health Canada Guidelines for exercise, diet, and smoke-free living as defined by the self-reported stage of readiness to change the following behaviours: daily dietary intake of vegetables and fruits, dietary restriction of fat and sodium, daily physical activity and weekly planned exercise, as well as smoke-free living. The HPLP measured stage of readiness to change on a 4-point continuous scale (Table 1) in which 1 corresponded to the Precontemplation stage, 2 corresponded to the Contemplation stage, 3 corresponded to the Preparation stage, and 4 corresponded to the Action/Maintenance stage. The HPLP is inversely associated with body weight, Body Mass Index, waist circumference, and changes in weight over time [9].

Symptoms of depression were assessed using the Beck Depression Inventory-II (BDI-II), which is a 21-item self-administered inventory designed to measure cognitive-affective and somatic-behavioural symptoms of depression present in the last two weeks [10].

Psychological stress was measured using the Perceived Stress Scale (PSS), which is a self-administered scale that assesses the degree to which situations in one's life during the last month are appraised as stressful [11].

2.4. Procedure. Participants were first given a baseline assessment in which anthropometric data, stage of readiness to change health behaviours, depression, and psychological stress were evaluated. Following assessment, participants were randomized into two conditions: the 4-month e-Counseling condition, using the HSF web-based program entitled "Blood Pressure Action Plan" (BPAP) [12] and a Waitlist Control condition. Subjects in the e-Counseling group identified their priority for behaviour change from a list of recommended lifestyle changes for blood pressure control. They self-rated their motivation to initiate/maintain change for this behaviour, and the e-counseling system provided them with programmed feedback on "change goals" that were based on principles from motivational interviewing [6] and were tailored to each individual's level of readiness for health behaviour change. They were sent weekly e-mails during the first month, biweekly e-mails during the second month, and monthly e-mails during months 3 and 4. Controls received an e-health newsletter from the HSF that contained general information and advice for cardiovascular health and healthy living. The Post-Intervention assessment included the full assessment protocol that was administered at Baseline, and it was scheduled within 2 weeks following completion of the 4-month intervention.

Table 1: Stage of readiness to change health behaviour.

Scale Number	Stage of Change	Definition
(1)	Precontemplation	Having little or no intention of changing behaviour in the next 6 months.
(2)	Contemplation	Beginning to acknowledge that they have a problem, and thinking seriously about solving it; intention to change within 6 months.
(3)	Preparation	Making plans about how they will change their behaviour within the next month.
(4)	Action/Maintenance	Making overt changes in their behaviour and surroundings in the last 6 months and/or maintaining behaviour change, often with relapses; can last from 6 months to about 5 years.

Note. Definition of Stage of Change is based on Prochaska's Stages of Change Model [8].

All subjects provided informed consent prior to participating in the study, and the study was approved by the Research Ethics Board of all participating institutions.

2.5. Statistical Analysis. For the purpose of this substudy of our clinical trial, the results are presented according to a per protocol analysis that includes 3 groups: e-counseling subjects who received ≥8 e-mails (therapeutic dose); e-counseling subjects who received 1 to 7 e-mails (subtherapeutic dose); and subjects who received 0 e-mails (control condition).

Descriptive analyses and analysis of variance or chi-square analyses were used to describe sample characteristics between the three groups. Analysis of covariance was used to evaluate the effectiveness of e-counseling in improving levels of readiness to change exercise and diet behaviour, as well as levels of depression, and stress, adjusted for baseline readiness to change exercise and diet, baseline depression and stress, sex, age, and antidepressant-anxiolytic medications. Paired t-tests were used to examine the main effect of change in psychological distress over time. Bonferroni post hoc tests (adjusted for two post hoc comparisons) were used to compare both e-Counseling groups with the Control group. Zero-order and partial correlations were used to examine

Table 2: Baseline characteristics of subjects.

Characteristics	M ± SE or N (%)			
	0 e-mails ($n = 227$)	1–7 e-mails ($n = 63$)	≥8 e-mails ($n = 97$)	P value
Age (years)	56.7 ± 0.5	57.0 ± 0.9	55.6 ± 0.7	0.40
Sex: Female (%)	120 (52.9)	39 (61.9)	70 (72.2)	0.005
Household income:				
< $60k	80 (35.2)	16 (25.4)	32 (33.0)	0.63
$60 k–$99,999	81 (35.7)	24 (38.1)	37 (38.1)	
≥ $100 k	66 (29.2)	23 (36.5)	28 (28.9)	
Body mass index (kg/m^2)				
<25	41 (18.1)	11 (17.5)	18 (18.6)	0.85
25–29.9	88 (38.8)	29 (46.0)	41 (42.3)	
≥30	98 (43.2)	23 (36.5)	38 (39.2)	
Waist circumference				
$F > 88$ cm, $M > 102$ cm	143 (63.0)	36 (57.1)	60 (61.9)	0.70
Cardiovascular risk factors				
Total cholesterol mmol/L	5.3 ± 0.1	5.1 ± 0.1	5.4 ± 0.1	0.23
Diabetes	16 (7.0)	5 (7.9)	2 (2.1)	0.17
Smoking	8 (3.5)	3 (4.8)	6 (6.3)	0.55
Framingham 10-yr absolute risk	9.5 ± 0.4	8.8 ± 0.7	9.1 ± 0.6	0.65
Psychological distress				
Depression	7.4 ± 0.5	7.9 ± 1.0	8.8 ± 0.8	0.37
Stress	14.5 ± 0.4	14.5 ± 0.8	15.6 ± 0.7	0.94
Readiness to change				
Exercise	3.6 ± 0.04	3.3 ± 0.1	3.5 ± 0.1	0.06
Diet	3.5 ± 0.04	3.5 ± 0.1	3.5 ± 0.1	0.84

the association between psychological variables and readiness for health behaviour change. Partial correlations were adjusted for baseline stress and depression, as well as baseline exercise and diet.

3. Results

Initially, 10, 658 individuals who resided within the recruitment areas for the present study completed the self-assessment program on the website for HSF. From this sample, 782 individuals completed the telephone screening for this investigation. The present study sample enrolled 387 subjects who met the eligibility criteria and who provided written consent to participate in the study.

3.1. Baseline Characteristics of Sample. Table 2 presents the background characteristics of the sample measured at baseline, grouped according to our per protocol analysis of therapeutic e-counseling (≥8 e-mails), subtherapeutic e-counseling (1–7 e-mails), and the control condition (0 e-mails). There were no significant differences between groups in age, income tertile, education, Framingham ten-year absolute risk score, CVD risk factors, stress, depression, readiness to change exercise, and readiness to change diet. There was a significant group difference in sex, in which there was a greater percentage of female subjects in the therapeutic e-counseling groups ($\chi^2 = 10.7$, $P = 0.005$).

3.2. Health Behaviour Change and Psychological Distress. Table 3 displays the zero-order correlations between baseline levels of psychological distress and readiness for health behaviour change. Partial correlations are also presented for baseline-adjusted scores for stress and depression and self-reported exercise and diet at the Post-Intervention assessment. At baseline, stress and depression were inversely associated with readiness to change exercise ($P = 0.001$ and $P = 0.002$, resp.) and readiness to change diet ($P = 0.04$ and $P = 0.05$, resp.). There was also a significant inverse association between baseline adjusted stress and depression with exercise at Post-Intervention ($P = 0.01$ and $P = 0.01$, resp.), but not for diet.

3.3. Psychological Distress, E-mail Support, and Health Behaviour Change. Table 4 displays the mean values for readiness to change exercise and diet behaviour at the Post-Intervention assessment. There was a significant difference among the group means for both readiness to change exercise and diet behaviour ($F = 5.55$, $P = 0.02$, partial $\eta^2 = .02$ and $F = 5.07$, $P = 0.03$, partial $\eta^2 = .02$, resp.). Post hoc comparisons demonstrated that the mean for readiness to change exercise and the mean for readiness to change diet in the therapeutic e-counseling group was significantly greater than the mean for Controls.

There were no significant group differences in mean levels of stress ($P = 0.96$) or depression ($P = 0.35$) at

Table 3: Correlations of psychological distress and readiness for change.

		r	P value
Correlates of baseline exercise	Depression	−0.17	0.002
	Stress	−0.18	0.001
Correlates of baseline diet	Depression	−0.11	0.05
	Stress	−0.11	0.04
Correlates of Post-Intervention exercise*	Depression	−0.14	0.01
	Stress	−0.17	0.01
Correlates of Post-Intervention diet*	Depression	−0.08	0.15
	Stress	−0.05	0.37

* Partial correlations adjusted for baseline exercise, diet, depression, and stress.

Table 4: Readiness for change Post-Intervention.

	M ± SE or N (%)		
	0 e-mails ($n = 227$)	1–7 e-mails ($n = 63$)	≥8 e-mails ($n = 97$)
Exercise* after intervention	3.51 ± 0.04	3.62 ± 0.08	3.68 ± 0.07†
Diet* after intervention	3.60 ± 0.03	3.54 ± 0.06	3.73 ± 0.05‡

* Adjusted for baseline readiness to change exercise/diet, sex, age, antidepressant-anxiolytic medications, baseline depression, and stress.
Bonferroni post hoc comparison to 0 E-mail group: †$P = 0.04$, ‡$P = 0.02$.

Post-Intervention, after adjusting for baseline stress and depression, as well as antidepressant-anxiolytic medications. Nevertheless, we observed a main effect for change in means for stress and depression across baseline and Post-Intervention assessments, independent of our intervention: depression, 7.9 ± 0.04 and 6.1 ± 0.04, $P < .001$; stress, 14.8 ± 0.03 and 13.6 ± 0.03, $P < .001$.

4. Discussion

The results of this study demonstrate that e-counseling is significantly associated with therapeutic improvements in lifestyle change. A reduction in symptoms of depression and stress was significantly associated with an increase in readiness to change exercise. Interestingly, readiness to change diet was not associated with change in levels of depression and stress which suggested that this relationship may be mediated by situational factors outside the scope of this analysis. To our knowledge, this is the first study to show that e-counseling with features of motivational interviewing [6] is significantly associated with improved readiness to change exercise and diet behaviour among patients with hypertension, independent of symptoms of psychological distress.

4.1. Psychological Distress and Health Behaviour Change. Baseline stress and depression were inversely associated with baseline levels of readiness to change exercise and diet. This is consistent with previous reports that psychological distress is a barrier to health behaviour change which in turn can impede blood pressure control [1]. It is noteworthy that our findings partially corroborate this theory. Change in stress and depression over the 4-month intervention period was inversely associated with exercise at Post-Intervention. On the other hand, we failed to observe an association between Post-Intervention assessment of diet and corresponding levels of psychological stress and depression. We additionally failed to observe a direct effect of e-counseling on these symptoms of psychological distress. Nevertheless, we did observe a main effect of change in these symptoms across baseline and Post-Intervention assessments, independent of the intervention. Given that stress reduction is commonly recommended for patients with hypertension who also present with elevated psychological distress, it is a priority for future trials to establish whether the combination of e-counseling for lifestyle and stress reduction can evoke a direct or indirect therapeutic effect on blood pressure control.

It is important to note that the current findings do not clarify the causal relationship between psychological distress and motivation to change exercise and diet. It is possible that as subjects were enrolled in this study their symptoms of stress and depression decreased, which in turn facilitated an increase in motivation to adhere to health behaviours. Alternatively, increased adherence to health behaviours may have facilitated a reduction in symptoms of stress and depression. Indeed, the relationship between psychological distress and health behaviour is likely bidirectional in nature [13].

This study did not find a significant relationship between psychological distress and readiness to change diet at the Post-Intervention assessment, suggesting a more complex relationship between these variables. As others have suggested [14], dietary behaviour is determined by biological, anthropological, economic, psychological, and sociocultural factors. It may be advisable for future e-counseling initiatives for hypertension to monitor social determinants of adherence to diet since these may be important therapeutic targets for intervention.

4.2. Limitations. The findings of this study may be limited to subjects who have relatively low levels of psychological distress and increased motivation to pursue self-help information for improving heart health. Subjects enrolled in the present study had initially logged onto the BPAP program of the Heart and Stroke Foundation website. In addition, measures of readiness to change are self-report and may have been influenced by socially desirable responding. Nevertheless, we have presented preliminary evidence supporting the criterion validity of the self-reported readiness to change exercise and diet. We reported that these measures of readiness were inversely associated with body weight, Body Mass Index, waist circumference, and changes in weight over time [9].

5. Conclusion

A novel finding of the present study is that e-counseling is associated with improved motivation to adhere to exercise and diet among patients with hypertension, independent of symptoms of psychological stress and depression. Given that we observed an inverse relationship between psychological distress and self-reported exercise following the intervention, a priority for future research is to determine whether e-counseling for lifestyle and stress reduction offer a therapeutic advantage for blood pressure control.

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Research Article

Differential Impact of Stress Reduction Programs upon Ambulatory Blood Pressure among African American Adolescents: Influences of Endothelin-1 Gene and Chronic Stress Exposure

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Stress-activated gene × environment interactions may contribute to individual variability in blood pressure reductions from behavioral interventions. We investigated effects of endothelin-1 (ET-1) LYS198ASN SNP and discriminatory stress exposure upon impact of 12-week behavioral interventions upon ambulatory BP (ABP) among 162 prehypertensive African American adolescents. Following genotyping, completion of questionnaire battery, and 24-hour ABP monitoring, participants were randomized to health education control (HEC), life skills training (LST), or breathing awareness meditation (BAM). Postintervention ABP was obtained. Significant three-way interactions on ABP changes indicated that among ET-1 SNP carriers, the only group to show reductions was BAM from low chronic stress environments. Among ET-1 SNP noncarriers, under low chronic stress exposure, all approaches worked, especially BAM. Among high stress exposure noncarriers, only BAM resulted in reductions. If these preliminary findings are replicated via ancillary analyses of archival databases and then via efficacy trials, selection of behavioral prescriptions for prehypertensives will be edging closer to being guided by individual's underlying genetic and environmental factors incorporating the healthcare model of personalized preventive medicine.

1. Introduction

Essential hypertension (EH) is a major risk factor for cardiovascular disease (CVD), and EH incidence among youth is increasing [1]. African Americans (AAs) experience a higher prevalence, earlier onset, and greater severity of EH-related complications than other ethnic groups [2]. From late childhood onward, AAs display increased levels of resting and ambulatory blood pressure (ABP) compared to other ethnic groups [3–5]. BP levels are monotonically associated with future CVD morbidity and mortality [6]. Stage I prehypertensive adults (i.e., SBP/DBP 121–129/81–84 mmHg) have a 40% increased risk and adults with stage II prehypertension (i.e., SBP/DBP 130–139/85–89 mmHg) are twice as likely to develop CVD compared to those with optimal BP (<120/<80 mmHg) [6–8]. BP percentile ranking tracks from late childhood into adulthood [9–11] placing AA adolescents with BP between the 50th and 95th percentiles for age and sex at an increased risk of future EH and CVD development [9].

EH, like other multifactorial chronic diseases, results from a complex interplay between an individual's genetic underpinnings, lifestyle behaviors, psychosocial factors, and exposures to various environmental toxins. Over time, this dynamic interplay eventuates in adverse structural and functional changes in biological organ systems culminating in disease manifestation [12, 13]. Among the myriad of environmental toxins, psychosocial stress such as repeated

exposures to unfair treatment and discrimination associated with socioeconomic status (SES) inequality and race have been implicated as contributing to EH, especially among AAs [14, 15].

Few pediatric studies have addressed impact of unfair treatment and discrimination upon BP. Clark and Gochett [14] found perceived racism to be positively associated with increased resting SBP among AA youth who reported a strong intolerance to racist attitudes. Matthews and colleagues observed unfair treatment to be associated with increased daytime ABP and night/day ABP ratios in adolescents [16], especially among AA adolescents living in lower SES neighborhoods [17].

AAs' BP control abnormalities are frequently associated with increased vasoconstrictive tone [18–20]. Studies involving normotensive youth and young adults have shown that higher levels of resting BP and exaggerated BP responses to physical and behavioral stressors between AAs and European Americans (EAs) are often due to higher levels and/or greater increases in vasoconstrictive tone [21–24]. Associations between psychosocial stress-related factors and autonomic nervous system (ANS) dysregulation indicate that excessive endothelial activation also plays a contributory role [25]. The endothelial and vascular smooth muscle cells produce endothelin-1 (ET-1), a potent vasoconstrictor, and endothelium-derived relaxing factor (EDRF; a potent vasodilator). Imbalances between circulating concentrations, and/or receptor sensitivity may lead to exacerbations of vasoconstrictive mediated BP control compounding the contributions of ANS dysregulation. Among hypertensive adults and normotensive adolescents and adults, AAs have exhibited higher plasma ET-1 levels compared to EAs [23, 26–28]. Among normotensive adolescents and young adults, AAs have shown greater behavioral stress induced plasma ET-1 increases compared to EAs [23, 26]. A recent study by Cooper et al. found that among AA adults, greater self-reported discrimination exposure was associated with higher ET-1 levels, regardless of SES [29].

The ET-1 gene is localized on chromosome 6, spans 5.5 kb, and contains 5 exons and 4 introns. It has been identified as a candidate gene for EH and CVD [30]. A G-to-T transversion predicting a Lysine-Asparagine change at amino acid 198 (Lys198Asn) single-nucleotide polymorphism (SNP) has been associated with increased BP levels from adolescence to middle age in Japanese EAs and AAs [31–33]. The Lys198Asn SNP has also been associated with exaggerated BP reactivity to laboratory stressors, particularly within the context of background stress-related factors. For example, in a previous study, T allele carriers from lower SES backgrounds exhibited the greatest BP increases to a video game challenge compared to all other subgroups [26]. Rabineau et al. [34] found vasoconstrictive reactivity to behavioral stress was the highest among T-allele carriers with poor anger management skills. These latter sets of findings along with other recent studies [35–37] lend support to the gene × environment model of stress-induced EH [38, 39]. That is, individuals with genetic susceptibility for EH, who are exposed to frequent environmental stress and/or other stress-related potentiating factors (e.g., ineffective coping skills), will be most likely to exhibit the greatest BP stress reactivity and to eventually develop EH and CVD.

Behavioral stress reduction interventions (e.g., meditation, cognitive behavioral coping skills, etc.) implemented to improve BP control and other CVD risk factors have primarily involved adults and quality of research designs and results have been mixed [40–42]. Rainforth et al. [42] reviewed 107 stress reduction BP control studies and conducted a meta-analysis involving 20 studies that were classified as well-designed randomized control trials (RCTs). All but two of the studies involved prehypertensive and hypertensive adults. Collectively, Transcendental Meditation (TM) was the only treatment found to significantly reduce resting and/or 24 hour BP.

Far fewer RCTs have been conducted involving youth, but findings are promising. Black et al. [43] reviewed 16 pediatric sitting-meditation RCTs, including breathing awareness meditation (BAM). Median effect sizes ranged from 0.16 to 0.29 for physiologic outcomes including resting and ambulatory BP, heart rate, and total peripheral resistance [43]. In a recent study, BAM showed significantly greater reductions in ambulatory SBP and sodium excretion compared to cognitive behavioral skills training (LST) and health education control (HEC) among a group of AA prehypertensive teenagers [44]. Increased SNS activation and increased endothelial system activity (i.e., increased ET-1 levels) have both been shown to increase sodium appetite [45, 46]. The reduced sodium excretion may be indicative of reductions in sodium appetite as a result of improvements in ANS regulation and/or ET-1 activity.

The above review indicates that among stress reduction RCTs, meditation is consistently associated with significant BP reductions. However, even among the meditation RCTs showing significant BP reductions, noticeable inter-individual differences have been observed both across and within studies [41–44, 47]. For example, in Rainforth et al.'s [42] meta-analysis, the 95% confidence interval for resting SBP change from 6 TM studies was (−2.3 to −7.6 mmHg), with net changes between TM and health education ranging from −1.1 to −10.7 mmHg. Recently, in a group of college students, Nidich et al. [48] found TM to provide an average change of −2.0 mmHg for resting SBP. A subgroup identified as high-risk for EH (i.e., family history of EH) showed a reduction of −5.0 mmHg.

The variability within and across RCTs using meditation interventions with comparable study samples and adherence rates may partially be due to combined influences of heterogeneity in genetic susceptibility for physiological responsivity to stress and propensity for exposure to stressful events. In genetics, penetrance represents the percentage of cases carrying a gene or allele among those displaying the phenotype of interest; expressivity represents variations or magnitude in a phenotype expression. Phenotypes can vary in penetrance and expressivity by a number of factors including exposure to environmental factors, allelic variation, and complex gene by environment interactions [49]. A growing literature is indicating that higher genetic penetrance and/or expressivity may adversely impact the degree of benefit obtained from behavioral as well as pharmacologic programs aimed at

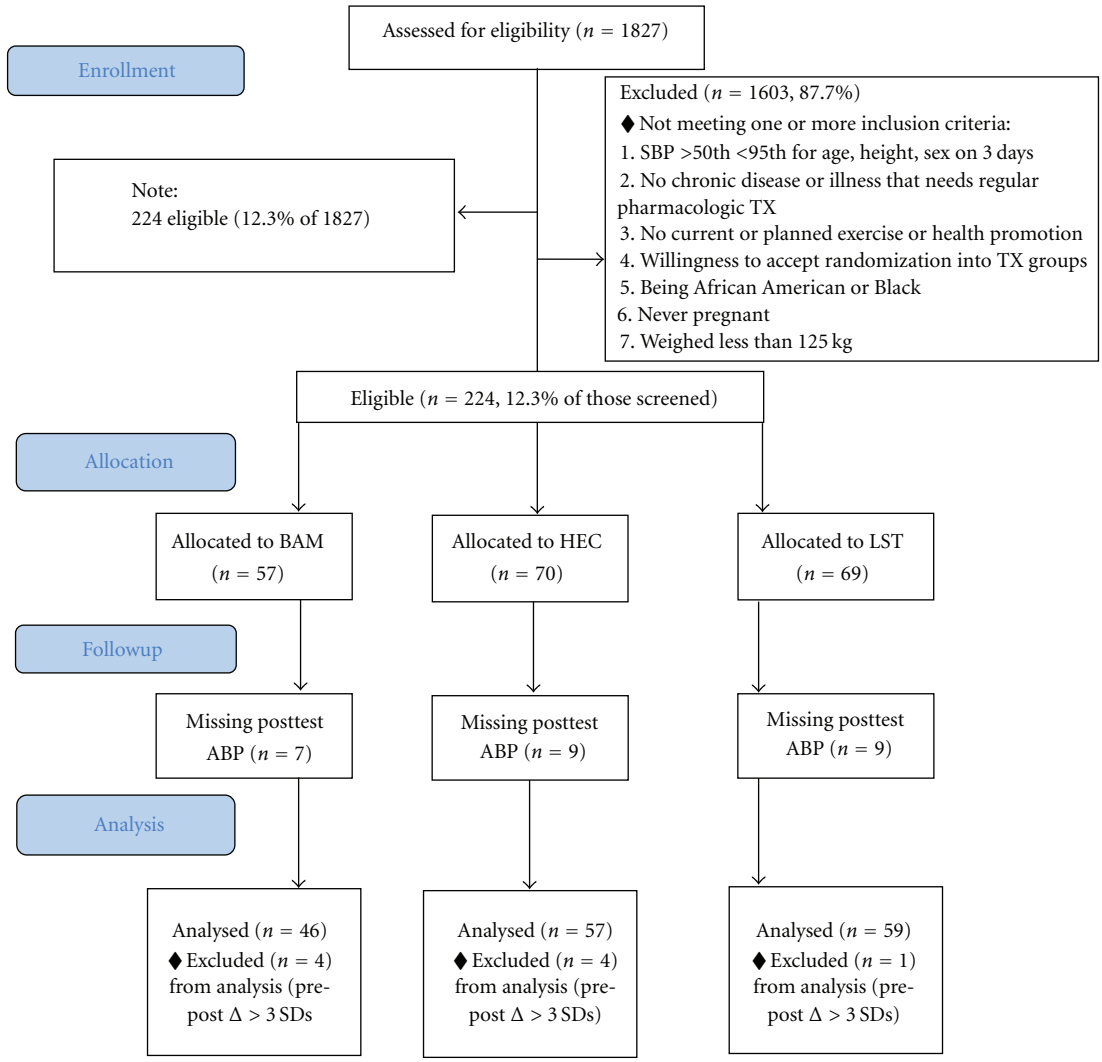


Figure 1: Consort diagram of participant distribution.

improving relevant phenotypes. For example, among smokers who participated in cognitive behavioral interventions plus pharmacologic smoking cessation therapies, the carriers of nicotine metabolizing genetic variants, particularly those from high tobacco smoke exposure-laden environments, exhibited lower cessation rates and earlier relapse compared to noncarriers [50]. Similarly, ancillary analyses of the highly successful Diabetes Prevention Program which involved at-risk adults from obese laden environments receiving placebo, metformin, and lifestyle interventions revealed carriers of the TCF7L2 genetic variant associated with diabetes, had significantly higher incidence of diabetes acquisition during the study than noncarriers irrespective of the treatment they received [51].

The purpose of this preliminary study was to evaluate the potential modulating influences of genetic variability in the ET-1 SNP and differential discrimination-based stress exposure upon changes in ambulatory BP after 12-week exposure to BAM, LST, and HEC among prehypertensive AA adolescents. We hypothesize that ET-1 carriers will be less likely to respond to any stress reduction treatment given the purported propensity of a greater genetic predisposition to ANS/ET-1 imbalances related to BP control. Following, we expect ET-1 carriers who report high levels of discrimination will have the most difficulty reducing ambulatory BP compared to other subgroups due to the combination of having higher genetic penetrance for an ANS/ET1 imbalance related to BP control, combined with increased likelihood of expressivity of the ANS/ET1 imbalance as a result of high levels of chronic stress exposure. Among the treatment groups, we hypothesized that BAM would have greater beneficial impact upon ambulatory BP reduction compared to LST and HEC.

2. Methods

2.1. Subjects. As shown in Figure 1, a total of 1827 students who would be participating in a semester-long ninth grade health education class were screened over a five-year period

to determine eligibility for participation in the study. Eligibility criteria included having (1) resting SBP between 50th and 95th percentile for age, height and sex [52] on three consecutive occasions at school, (2) no history of congenital heart defect, diabetes, sickle cell anemia, asthma, or any chronic illness or health problem that requires regular pharmacological treatment, (3) no current or planned engagement in a formal exercise, health promotion, or organized sports program outside of regular school physical education courses, (4) willingness to accept randomization by school into treatment groups, (5) being "African American" or "Black", based on parental report, (6) never pregnant at any point in the study, and (7) weighing less than 125 kg. The Institutional Review Boards of the Georgia Health Sciences University and the Medical University of South Carolina approved the study.

From the 224 eligible participants, genotyping was not conducted on 30 students. Thirty-two were omitted due to either missing postevaluation ambulatory BP ($n = 23$), or having extreme changes ($n = 9$) in postintervention 24-hour SBP (≥ 3 SDs compared to the entire sample; 15 mmHg in either direction).

The distribution of the remaining 162 subjects by treatment group was: BAM ($n = 46$, 16 males), LST ($n = 59$, 24 males), and HEC ($n = 57$, 20 males). There was no differential loss of subjects by treatment group ($X^2 = 3.65$, $df = 2$, $P = .72$) and no significant differences between omitted subjects ($n = 62$) and the remaining 162 on anthropometric variables and ambulatory BP levels at baseline (all P's $> .10$).

2.2. Procedures

2.2.1. BP Screening. Three consecutive days of school screenings were conducted. Height was measured by stadiometer and weight by a Detecto CN20 scale (Cardinal Scale Manufacturing Co., Webb City, Mo, USA). Seated SBP was recorded using Dinamap 1846SX monitors (Critikon, Inc., Tampa, Fla, USA) at minutes 5, 7, and 9 of a 10-minute rest period. The first measurement each day was discarded and the other two measurements were averaged.

2.2.2. Genotyping. Genomic DNA was extracted from buccal cells using QiaAmp DNA Blood Mini Kits (Qiagen). Extracted DNA was stored at -80°C until analyzed. The ET-1 Lyn198Asn genotype was detected by polymerase chain reaction (PCR) followed by direct sequence analysis [31].

2.2.3. Ambulatory Blood Pressure Evaluation. Before and following the intervention, ambulatory SBP and DBP were recorded for 24 hours. Measurements were recorded every 30 minutes during school, every 20 minutes during self-reported after school waking hours, and every 30 minutes during self-reported sleep hours using Spacelabs 90207 monitors (SpaceLabs, Inc., Issaquah, Wash, USA). This monitor has been previously validated, and ambulatory BP has been found to be a better predictor of EH than casual BP [53]. Acceptability of ambulatory readings was based on previously established criteria including pulse pressure >20 mmHg, DBP $\geq$ 45 mmHg but <100 mmHg, SBP > 70 mmHg but <180 mmHg, HR > 39 bpm but <180 bpm [47, 54, 55]. Hourly averages were obtained by averaging all readings for each clock hour across: daytime (8 a.m. to 10 p.m.), nighttime (12 a.m. to 6 a.m.), and 24-hour periods. As in previous studies, to be included in analyses, hourly averages for SBP and DBP required a minimal of 50% of total possible evaluations for the respective time period [47, 54, 55]. The percentage of ambulatory evaluations across groups for the pre/postinterventions were 78%|80%. The percentage of ambulatory evaluations by group for the pre/postinterventions were similar: BAM 78%|81%, LST 78%|79%, and HEC 79%|80%.

2.2.4. Discrimination Assessment. The 9-item everyday discrimination scale (EDS) was used to assess exposure to discrimination [56, 57]. Frequency of encounters was assessed using a 6-point response format (almost every day, at least once a week, a few times a month, a few times a year, less than once a year, and never). The EDS was administered via paper and pencil during pre- and postintervention evaluations as part of a battery of psychosocial questionnaires. The EDS has good internal consistency $\alpha = .88$ [58], and unidimensional factor structure [56]. Cronbach's α was.84 in the current sample of preintervention data. To investigate influence of everyday discrimination, a median split was conducted on preintervention EDS scores creating low and high EDS groups. Participants whose score fell on the median were included in the high EDS group (49% low EDS, 51% high EDS). The EDS was chosen as a measure of chronic stress due to its use in several recent pediatric BP association [16, 17, 56] and adult ET-1 association studies [29]. In addition, the relevance of item content was pertinent to our sample of adolescent AAs (e.g., and "in your day-to-day life, how often have you felt threatened or harassed or felt treated with less respect than other people").

2.2.5. Interventions. The 12-week intervention was conducted at two high schools during subjects' regular health education classes. Students taking these classes do not take physical education during that semester. Health education teachers implemented the training and were supervised by program instructors. Qualitative assessments of the teachers' program implementations were conducted weekly with three Likert scale items (0–4 scale), which assessed thoroughness, class attentiveness, and enthusiasm. Average instructors ratings across the 12-week intervention were 3.34 ± 0.26 for thoroughness, 3.28 ± 0.32 for class attentiveness, and 3.31 ± 0.27 for enthusiasm. There were no significant differences for instructor ratings across the treatment groups (all P's $> .06$).

2.3. Health Education Control (HEC). Weekly health education lessons consisted of 50-minute sessions on CV health-related lifestyle behaviors based upon National Heart, Lung and Blood Institute guidelines for youth and included brochures, handouts, videotapes, discussions, and recommendations for increasing physical activity (e.g., walking, sports, etc.), establishing and maintaining prudent diet (e.g.,

Table 1: Baseline anthropometric characteristics.

Characteristic	BAM ($n = 46$)	LST ($n = 59$)	HEC ($n = 57$)
Age (years)	15.0 ± 0.6	15.0 ± 0.7	15.2 ± 0.8
Sex (male/female)	16/30	27/32	25/32
Weight (kg)	66.3 ± 15.8	70.8 ± 17.3	66.8 ± 16.5
Height (cm)	163.4 ± 8.3	167.5 ± 8.6	163.6 ± 7.9
BMI (kg/m^2)	24.8 ± 5.3	25.1 ± 5.0	24.9 ± 5.9
LYS198ASN (TT/TG|GG)	14|32	25|34	23|34
EDS (high/low)	22/24	29/30	30/27
24-hour SBP	119.3 ± 6.1	119.8 ± 6.5	121.8 ± 6.8
Daytime SBP	124.0 ± 6.4	123.7 ± 6.5	126.2 ± 7.5
Nighttime SBP	109.1 ± 6.6	110.6 ± 8.7	111.16 ± 8.1
24-hour DBP	68.6 ± 5.6	68.0 ± 5.5	69.3 ± 6.2
Daytime DBP	73.4 ± 5.9	72.5 ± 5.5	73.9 ± 6.6
Nighttime DBP	57.9 ± 6.1	57.9 ± 6.7	58.7 ± 5.7

reducing fat intake). HEC is a basic health education course and is considered a "usual practice" control group in this study.

2.3.1. Life Skills Training (LST). Weekly 50-minute sessions using selected components of the LST program involved group discussions, passive and active modeling, behavioral rehearsal, feedback, reinforcement, and behavioral homework assignments. The selected program components provided training in problem-solving skills, reflective listening, conflict resolution, and anger management to enhance social skills, assertiveness, and personal and social competence [59]. No relaxation or stress reduction techniques were given to the LST or HEC groups.

2.3.2. Breathing Awareness Meditation (BAM). BAM is exercise one of the Mindfulness-Based Stress Reduction Program [60]. Practice involves focusing upon the moment, sustaining attention on the breathing process and passively observing thoughts. The individual sits upright in a comfortable position with eyes closed and focuses on diaphragm movements while breathing in a slow, deep, relaxed manner. Ten-minute sessions were conducted during health education class and at home each weekday. On weekends, subjects were instructed to practice 10-minute sessions twice daily. Self-reported BAM home practice adherence was 86.6 ± 7.4 percent. There were no significant differences between treatment groups on in-school attendance ($F[2,\ 160] = 2.36, P = .10$), HEC 81%, BAM 79%, and LST 88%.

2.4. Data Analysis. Change in values of daytime, nighttime, and 24-hour SBP, and DBP were compared using a series of 2 (ET- 1 genotype) by 3 (treatment group) by 2 (EDS group) analyses of variance of change scores (post-minus preintervention values) that covaried the respective preintervention values (ANCOVAs). ANOVA analyses were initially conducted on preintervention anthropometric and ambulatory BP values. In addition, changes in smoking (i.e., average cigarettes per week) and exercise (i.e., days/week engaged in sweat inducing physical activities) from the youth risk behavior surveillance system [61], and body mass index covarying preintervention values were examined among subgroups. There were no significant preintervention differences or pre- to post-changes found among the groups (all P's $> .10$).

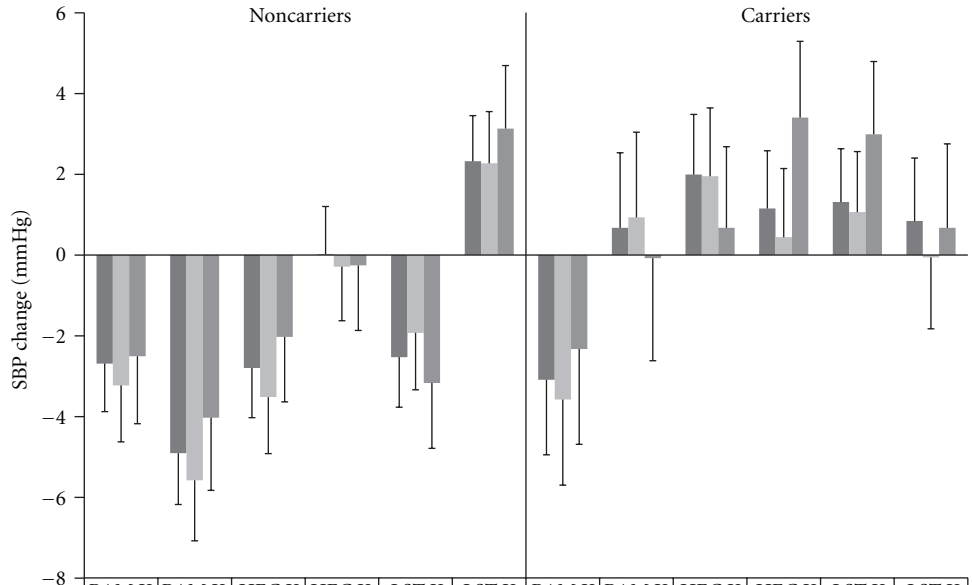
To further examine three-way interactions, two-way interactions and simple main effects across each level of a third variable were calculated using the same preintervention covariates. The third variable was chosen on the basis of the largest F-ratio from the two variables that only had two levels (i.e., ET-1 genotype or EDS group). Adjusted F-values (F_{adj}) were calculated using the mean square for the analyses of interest divided by the mean square error term taken from the original model. All subsequent comparisons following the initial three-way ANCOVA were examined using Bonferroni adjusted alpha levels.

The series of analyses was originally completed with general linear modeling using EDS as a continuous variable which, as anticipated, revealed similar patterns of significant results and conclusions [62]. Given the complex interpretations of the multiple interactions that differentiate across groups, the previously described ANCOVA models using dichotomized median split EDS values are presented.

3. Results

Preintervention anthropometric and ambulatory data are shown in Table 1. There were no significant differences between the treatment groups, ET-1 genotype, EDS, or treatment group by ET-1 genotype by EDS interactions on any of these parameters (all P's $> .10$).

3.1. Genotyping. Genotype frequencies included 100 participants homozygous for the G allele, 52 heterozygous G and T allele carriers, and 10 homozygous for the T allele. Frequencies were in Hardy-Weinberg equilibrium ($X^2 = .87, df = 1, P = .35$) [63]. Due to the small number of homozygous T allele carriers, participants classified either as heterozygous or homozygous for the T alleles were classified



	BAM X low (17)	BAM X high (15)	HEC X low (16)	HEC X high (18)	LST X low (16)	LST X high (19)	BAM X low (07)	BAM X high (07)	HEC X low (11)	HEC X high (12)	LST X low (10)	LST X high (14)
24-hour	−2.69	−4.91	−2.80	0.02	−2.53	2.32	−3.09	0.67	1.99	1.15	1.31	0.84
Daytime	−3.23	−5.58	−3.52	−0.29	−1.93	2.27	−3.58	0.93	1.95	0.44	1.06	−0.06
Nighttime	−2.51	−4.03	−2.03	−0.26	−3.17	3.13	−2.33	−0.08	0.67	3.40	2.99	0.67

Figure 2: Change in ambulatory SBP as a function of everyday discrimination, ET-1 SNP carrier status, and treatment group. Note: BAM: breathing awareness meditation, HEC: health education control, LST: life skills training. Low: bottom 50th percentile for everyday discrimination; High: top 50th percentile for everyday discrimination. Values in parentheses indicate *n* for that subgroup.

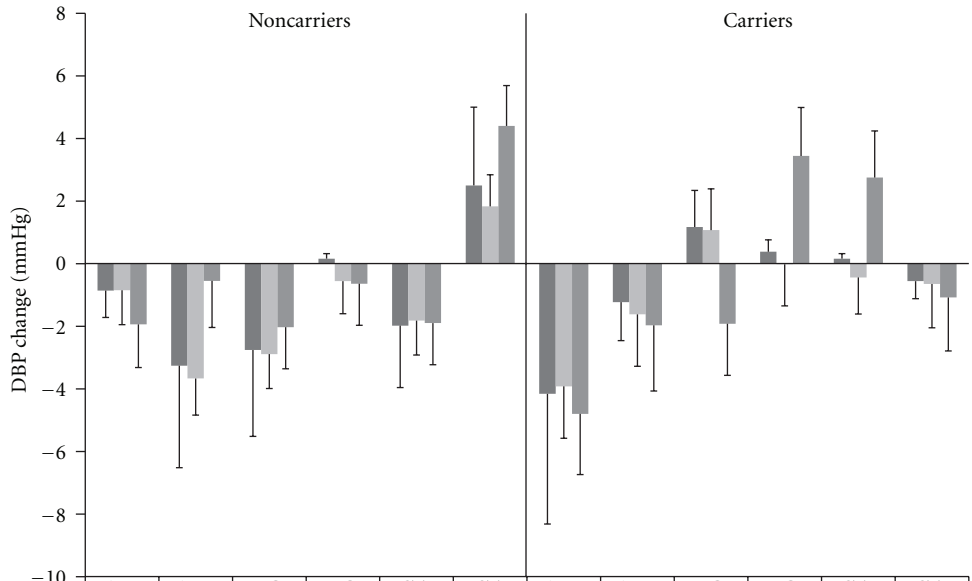
as "carriers" (38%), and homozygous G allele carriers were classified as "noncarriers" (62%).

3.2. Everyday Discrimination. A two-way (carrier status) x treatment group ANOVA was conducted on the EDS pretest scores and verified no significant baseline differences due to carrier status, treatment group, or the interaction between carrier status and genotype (all P's $> .24$). A X^2 analyses was used to examine the median split by treatment group dispersion rate and was not significant ($P = .88$). Finally, EDS change scores were examined to determine if any treatment group resulted in significant changes to EDS during the duration of the study. No significant changes in EDS scores by treatment group, ET-1 T allele carrier status, or their interactions were found (all P's $> .29$). Correlations between pre- and postintervention EDS scores were significant ($r = .59$, $P < .001$) and indicate that these scores were stable throughout the study.

3.3. Ambulatory Systolic Blood Pressure

3.3.1. 24-Hour SBP. The omnibus ANCOVA revealed significant main effects for ET-1 genotype ($F[1, 149] = 7.57$, $P < .01$) and treatment group ($F[2, 136] = 4.73$, $P = .01$) which were subsumed within an ET-1 genotype x treatment group x EDS group interaction ($F[2, 149] = 4.14$, $P = .02$). Results of the three-way interaction are depicted in Figure 2. Subsequent analyses examined the two-way interactions and simple effects for ET-1 carriers and noncarriers separately. No significant interactions or simple main effects for ET-1 carriers were found. Among ET-1 noncarriers, a significant simple main effect for treatment group ($F_{adj}[2, 149] = 4.46$, $P < .05$) was subsumed within an EDS x treatment group interaction ($F_{adj}[2, 149] = 4.46$, $P < .05$). Further simple effects analyses of treatment effects were separately conducted across the low and high EDS groups. There was no treatment effect among the ET-1 noncarriers who reported low EDS with groups showing comparable 24-hour SBP changes (range = −2.5 to −2.8 mmHg). There was a significant treatment group effect among those from high EDS backgrounds ($F_{adj}[2, 149] = 8.26$, $P < .05$). Post hoc analyses revealed that those who received BAM showed greater decline than LST recipients (−4.9 versus +2.4 mmHg, $P < .05$).

3.3.2. Daytime SBP. Significant main effects for ET-1 genotype ($F[2, 146] = 5.38$, $P = .02$) and treatment group ($F[2, 146] = 3.90$, $P = .02$) were subsumed within a three-way interaction involving the EDS group ($F[2, 146] = 4.00$, $P = .02$). The pattern of the three-way interaction was similar to that observed for 24-hour SBP (see Figure 2). Subsequent analyses revealed no significant interactions or simple main effects for ET-1 carriers. Among ET-1 noncarriers, a simple main effect for treatment group was found ($F_{adj}[2, 146] = 5.32$, $P < .05$). Post hoc examination revealed BAM participants showed greater reductions compared to LST (−4.4 versus +.19 mmHg, $P < .05$).



	BAM X low (17)	BAM X high (15)	HEC X low (16)	HEC X high (18)	LST X low (16)	LST X high (19)	BAM X low (07)	BAM X high (07)	HEC X low (11)	HEC X high (12)	LST X low (10)	LST X high (14)
24-hour	−0.86	−3.26	−2.76	0.16	−1.98	2.50	−4.16	−1.23	1.17	0.38	0.16	−0.56
Daytime	−0.85	−3.67	−2.89	−0.56	−1.82	1.83	−3.92	−1.62	1.07	−0.02	−0.44	−0.65
Nighttime	−1.94	−0.55	−2.03	−0.64	−1.90	4.40	−4.80	−1.97	−1.92	3.44	2.75	−1.08

Figure 3: Change in ambulatory DBP as a function of everyday discrimination, ET-1 SNP carrier status, and treatment group. Note. BAM: breathing awareness meditation, HEC: health education control, LST: life skills training. Low: bottom 50th percentile for everyday discrimination; High: top 50th percentile for everyday discrimination. Values in parentheses indicate n for that subgroup.

Although not statistically significant, the subgroup of ET-1 SNP noncarriers who reported high EDS and received BAM exhibited the greatest reduction across all subgroups (−5.6 versus range of −3.5 to +2.3 mmHg). The only subgroup among ET-1 SNP carriers to show a reduction was those with low EDS that received BAM (−3.6 versus range of −.06 to +1.95 mmHg).

3.3.3. Nighttime SBP. A significant main effect for ET-1 genotype ($F[1, 130] = 4.68$, $P = .03$) and a trend for treatment group ($F[2, 130] = 3.01$, $P = .06$) were subsumed within a three-way interaction involving the EDS group ($F[2, 130] = 3.01$, $P = .05$). The pattern was similar to 24-hour and daytime SBP and is shown in Figure 2. Subsequent analyses revealed no significant interactions or simple main effects for the high EDS group. Among the low EDS group, a significant main effect for ET-1 carrier status was found ($F_{adj}[2, 130] = 4.13$, $P < .05$; noncarriers = −1.7 versus carriers = +1.8 mmHg).

3.4. Ambulatory Diastolic Blood Pressure

3.4.1. 24-Hour DBP. A significant treatment group main effect ($F[2, 149] = 4.58$, $P = .01$) was subsumed within a significant three-way interaction ($F[2, 149] = 5.38$, $P = .01$). Figure 3 displays the results of the three-way interaction. Subsequent analyses revealed no significant interactions or simple main effects for ET-1 carriers. Among ET-1 noncarriers a significant two-way interaction between EDS and treatment group ($F_{adj}[2, 149] = 6.56$, $P < .05$) and a significant simple main effect among noncarriers ($F_{adj}[2, 149] = 4.28$, $P < .05$) were found. Further examination of treatment group effects among ET-1 noncarriers who reported low EDS was not significant and all treatment groups showed similar reductions in 24-hour DBP. Examination of treatment group among the ET-1 noncarriers who reported high EDS was significant ($F_{adj}[2, 149] = 8.38$, $P < .05$). Post hoc analyses revealed that participants who reported high EDS and received BAM were significantly different from those who received LST (−3.4 versus +2.5 mmHg, $P < .05$). The pattern of results is similar to the patterns found across SBP for ET-1 noncarriers; however, magnitude of change was less for DBP compared to SBP. For ET-1 carriers, more subgroups showed a reduction for DBP than SBP. However, those who received BAM displayed the best results and low EDS individuals showed better reduction than those high in EDS (−4.16 versus−1.23 mmHg). Interestingly, ET-1 carriers who received BAM and reported low EDS had the best improvement compared to other subgroups including noncarriers (−4.16 mmHg compared to range of −3.26 to +2.50 mmHg).

3.4.2. Daytime DBP. A significant treatment group effect ($F[2, 146] = 3.26$, $P = .04$) was subsumed within a three-way interaction ($F[2, 146] = 3.52$, $P = .03$) which is displayed in Figure 3. Subsequent analyses showed no significant interactions or simple main effects for ET-1 carriers. Among ET-1 noncarriers, a significant two-way interaction between EDS and treatment group emerged

($F_{adj}[2, 146] = 4.77$, $P < .05$). Subsequent analyses showed no significant effects of treatment group among the low EDS subgroup. A treatment group effect was significant among the high EDS subgroup ($F_{adj}[2, 146] = 6.07$, $P < .05$) and post hoc analyses revealed that the BAM subgroup was significantly different from the LST subgroup (−3.6 versus +1.8 mmHg, $P < .05$).

3.4.3. Nighttime DBP. A significant treatment group effect ($F[2, 130] = 3.91$, $P = .02$) was subsumed within a two-way interaction involving ET-1 genotype and treatment group ($F[2, 130] = 3.33$, $P = .04$). When conducted separately, no significant interactions or simple main effects for ET-1 noncarriers were found. Among ET-1 carriers, there was a significant treatment group effect ($F_{adj}[2, 130] = 4.45$, $P < .05$) and post hoc analyses revealed that participants who received BAM were significantly different from those who received LST (−3.6 versus +.74 mmHg, $P < .05$). Although a significant three-way interaction was not observed for nighttime DBP, for comparison purposes, the pattern of changes across ET-1 genotype, treatment group, and EDS group are displayed in Figure 3.

4. Discussion

In this preliminary study, we hypothesized that individuals who were ET-1 SNP carriers would have greater difficulty in responding to any of our intervention treatments for improving ambulatory BP. In the following, we also expected ET-1 SNP carriers who reported high levels of discrimination to be the most difficult to show ambulatory BP reductions. Finally, we hypothesized that BAM would have greater beneficial impact upon ambulatory BP reduction compared to LST and HEC. Our hypotheses were partially supported. BAM participants exhibited greater reductions in 24-hour, daytime and nighttime SBP and DBP compared to the LST and HEC groups. The modulating influences of ET-1 SNP status and EDS were similar across all three ambulatory indices for SBP and DBP. Among ET-1 SNP carriers, the only subgroup to show a consistent reduction in SBP and DBP was BAM recipients who also reported low EDS. In many cases, the other subgroups showed relatively little reduction or even increases in BP. Among ET-1 SNP noncarriers, all three treatments were helpful in reducing BP among those who reported low EDS. Only BAM was beneficial in reducing BP among those who reported high EDS.

The ET-1 Lys198Asn SNP has been shown to play a significant role in vasoconstrictive mediated BP control in normotensive and hypertensive youth and adults [23, 24, 31, 34, 36]. Our findings provide further indirect support for the significant role of the ET-1 SNP in BP control among AAs. For all ambulatory SBP indices, ET-1 carrier status was a significant main effect showing fewer improvements compared to noncarriers. As noted above, BAM was the only treatment approach to have success in reducing SBP among ET-1 SNP carriers and only if they reported low EDS. It appears that among AAs, behavioral stress BP reduction programs such as BAM and LST may have difficulty in countering the combination of increased genetic propensity for stress-activated ANS imbalance/ET-1 activation and high frequency of environmental stress exposure [23, 24, 26, 34].

The cognitive skills-based program (LST) only benefitted ET-1 noncarriers and only if they reported low EDS. Participants who reported high EDS displayed a slight increase in ambulatory SBP. Acquisition of the LST skills (e.g., reflective listening, assertiveness without aggressiveness, etc.) may require the entire 12 weeks. Perhaps implementation of these newly learned skills in interpersonal conflict prone environments initially results in augmented vigilance and sympathetic/endothelial system activation, rather than reductions of such. The slight increase in ambulatory SBP among LST subjects who reported high EDS supports this rationale. Future studies would benefit from the utilization of repeated ambulatory BP and biomarker monitoring evaluations (e.g., total peripheral resistance, cardiac output, and nocturnal dipping), along with concomitant self monitoring of stressful encounters, affective states, coping responses, rumination, and using technological advances in cell phone capabilities.

Although provocative, these results should be interpreted cautiously. This was an exploratory ancillary analysis of an RCT, and subgroup cell sizes were relatively small. We examined potential confounding influences of sex, BMI, physical activity, and smoking and did not detect significant subgroup differences at preintervention or in response to the interventions. The issue of relatively small sample sizes within the three-way interactions can best be addressed by replication with larger sample sizes. One approach to consider would be to capitalize upon archival BP reduction RCTs that involved stress reduction programs and if not available, we would aquire DNA samples from the participants. We speculate that BP control improvements among BAM participants may have been partially a result of improved ANS balance/ET-1 activity. Several previous findings showed that BAM also reduced overnight sodium excretion purportedly through a reduction in sodium appetite. However, decreased sodium appetite is a correlate and not an adequate surrogate measure of ANS/ET-1 activity. The dynamic interplay between biological systems related to BP control warrants inclusion of biological measures of multiple systems and investigation of the interactions among pathways including the endothelial, ANS, renin-angiotensin and aldosterone, and HPA axis [25, 38].

As noted earlier, retrospective post hoc analyses of meditation based BP RCTs involving prehypertensives and hypertensives (especially those involving AAs) may lend some support to whether the relationships found in this study translate to others. Finding similar patterns of ambulatory BP changes among ET-1 SNP status and other indices of chronic stress exposure would augment support for BAM as a viable approach for inclusion in nonpharmacologic programs aimed at the prevention of EH and CVD among certain subgroups of individuals (e.g., ET-1 SNP noncarriers, and carriers from low stress environments). The ease of BAM administration allows it to be practiced in virtual any setting (i.e., public schools, churches, recreation centers, and homes) adding to its utility to become part of multifaceted

dissemination efforts to help decrease CVD morbidity and mortality [64].

Unfortunately, our study found none of the behavioral stress reduction programs were beneficial among ET-1 SNP carriers who reported high EDS exposure. If our results are replicated, exploration of alternative behavioral and/or pharmacologic approaches that target endothelial function is warranted. Part of the study inclusion requirements was no current or planned engagement in a formal exercise, health promotion, or organized sports programs outside of regular school physical education courses, and the measures we used for physical activity were not differently influenced by the subgroups. However, behavioral interventions that are directed specifically at enhancing high-intensity physical activity may be beneficial. Aerobic exercise training has been shown to inhibit vasoconstrictive (e.g., endothelin-1) and promote vasodilatory (i.e., nitric oxide) mechanisms related to BP control providing evidence as a potentially effective therapeutic strategy [65–67]. Specific to the ET-1 LYS198ASN SNP, Rankinen et al. [67] found a two fold higher risk of hypertension among low aerobically fit carriers, whereas, aerobically fit carriers' hypertension risk was comparable to noncarriers. Additional research is needed to determine if physical activity can specifically benefit AA ET-1 carriers who report high levels of background stress.

For some individuals, a gene x environment personalized behavioral intervention approach may not improve BP control to desired levels. If this occurs, pharmacogenomics-based primary prevention interventions should be considered. Several large-scale pharmacologic RCTs have proven beneficial in reducing onset of EH in prehypertensive adults [68, 69]. Among ET-1 SNP carriers, an endothelin type A receptor antagonist may help foster vasodilation-mediated BP control. In a recent study, Weber et al. found Darusentan, a selective endothelin type A antagonist, to control treatment resistant hypertension [70].

5. Conclusions

In summary, the findings provide preliminary evidence of some of the underlying contributors that may have moderated BP reductions but were not examined in previous meditation RCTs. "One-size fits all" approaches to primary and secondary preventive health-care are being replaced with strategies described as preventive, predictive, personalized, and participatory [71]. Increasingly, behavioral and pharmacologic interventions are being tailored on the basis of individual's underlying genetic propensities and environmental factors (e.g., attitudes, stress exposure, etc.). Personalized medicine is in its infancy, but eventually, via empirical scrutiny, more efficacious best practice prevention and treatment approaches will evolve. The end result will help reduce the incidence of chronic diseases and improve the quality and longevity of life among those with these diseases.

Abbreviations

AA: African American
ABP: Ambulatory blood pressure
BAM: Breathing awareness meditation
BP: Blood pressure
CVD: Cardiovascular disease
DBP: Diastolic blood pressure
EDS: Everyday discrimination scale
EH: Essential hypertension
ET-1: Endothelin one
HEC: Health education control
LST: Life skills training
PCR: Polymerase chain reaction
SBP: Systolic blood pressure
SNP: Single nucleotide polymorphism
ANS: Autonomic nervous system.

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Research Article

Depressive Symptoms and 24-Hour Ambulatory Blood Pressure in Africans: The SABPA Study

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Disturbances in circadian rhythm might play a central role in the neurobiology of depression. We examined the association between depressive symptoms and 24-hour ambulatory BP in a sample of 405 (197 black and 208 Caucasian) urbanized African teachers aged 25 to 60 yrs (mean 44.6 ± 9.6 yrs). Depressive symptoms were assessed using the self-administered 9-item Patient Health Questionnaire (PHQ-9). After adjusting for age, sex, and ethnicity, participants with severe depressive symptoms (PHQ-9 ≥ 15) had higher odds of hypertension defined from ambulatory BP and/or use of antihypertensive medication (odds ratio = 2.19, 95% CI, 1.00–4.90) in comparison to participants with no symptoms. Compared to Caucasians with no depressive symptoms, those with severe symptoms had blunted nocturnal systolic BP drop of 4.7 mmHg (95% CI, −0.5 to 10.0, $P = 0.07$). In summary, depressive symptoms were associated with the circadian BP profile in black and Caucasian Africans.

1. Introduction

Studies examining the association between common mood disorder, such as depression and risk of hypertension, have produced mixed findings. Several studies have reported positive associations between depression and risk of incident hypertension [1–4] whereas others have observed null findings [5, 6], or attributed the effects to hypertension labeling [7]. There is even some evidence to suggest lower blood pressure (BP) in participants with depressive symptoms [8, 9]. In the Whitehall II study of British civil servants that examined longitudinal trajectories, the risk of hypertension increased with repeated experience of depressive episodes over time and became evident in later adulthood [10]. Thus, the association between depression and hypertension is complex.

One limitation of this body of work is the reliance on clinic BP readings taken on one occasion. In a recent study of older participants that underwent 24-hour ambulatory BP recordings, those reporting depressive symptoms demonstrated a blunted nocturnal systolic BP fall and were more likely to be nondippers, defined as having nocturnal systolic BP fall of less than 10% [11]. There is increasing recognition that disturbances in circadian rhythm play a central role in the neurobiology of depression, even recognizing its importance as a novel pharmacological target in treating the disorder [12]. Depression is associated with alterations in hormone and catecholamine circadian rhythms [13], which may be the result of poorly regulated neurotransmitter feedback control systems that become erratic when chronically stressed. Melatonin, for example, is an endogenous antihypertensive molecule released by the pineal gland that

plays a role in the biological regulation of circadian rhythms and has been associated with depression. In addition, nocturnal melatonin secretion is impaired among nondipper hypertensive patients [14].

Further studies are required to examine the association between depressive symptoms and the circadian BP profile, which might help to further clarify the equivocal nature of existing literature. The aim of this study was therefore to examine the association between depressive symptoms and circadian BP profiles using 24-hour ambulatory monitoring. The study was conducted in a sample of black and Caucasian Africans who were recruited as part of the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study—presently the only study in sub-Saharan Africa focusing on the contribution of psychosocial risk factors to cardiovascular health. Thus, a further aim was to assess potential ethnic differences in the association between depression and BP.

2. Methods

2.1. Participants and Procedures. Participants were recruited as part of the SABPA study conducted between February 2008 and May 2009. The study sample comprised urbanized African teachers working for the Dr. Kenneth Kaunda Education district in the North West Province, South Africa. The reason for this selection was to obtain a homogenous sample from a similar socioeconomic class. All eligible participants between the ages of 25 and 60 years were invited to participate. Exclusion criteria were an oral temperature above 37°C, psychotropic substance dependence or abuse, blood donors, and individuals vaccinated in the past 3 months. Participants were fully informed about the objectives and procedures of the study prior to their recruitment. Assistance was available for any participant who requested conveyance of information in their home language. All participants signed an informed consent form and the study was approved by The Ethics Review Board of the North-West University (Potchefstroom Campus). Participants were transported at 1630 hours to the Metabolic Unit Research Facility of the North-West University and familiarized with the protocol and completed a battery of psychosocial questionnaires. After receiving a standardized dinner participants were encouraged to go to bed at around 2200 hours and were woken at 0545 hours the following morning to undergo a battery of clinical assessments.

2.2. Depressive Symptoms. Depressive symptoms were assessed using the self-administered 9-item Patient Health Questionnaire (PHQ-9), which has been extensively validated in various clinical patient groups and different ethnic populations including sub-Saharan Africans [15, 16]. In the present study the PHQ-9 displayed good reliability (Cronbach's alpha = 0.81). The PHQ-9 measures the frequency of depressive symptoms corresponding to the 9 key symptoms of depression used by the *Diagnostic and Statistical Manual of Mental Disorder Fourth Edition* (DSM-IV) criteria to diagnosed major depressive episode. Participants indicated the frequency of experiencing symptoms during the prior two weeks, ranging from "not at all" (scored as zero), "several days" (one point), "more than half the days" (two points), "nearly every day" (three points), thus giving possible scores of 0–27. We used previously described PHQ-9 cut points (15) to derive three categories; no depressive symptoms (score <5), mild-moderate symptoms (score of 5–14), and severe symptoms (score of 15 and above).

2.3. Blood Pressure Measures. Semirecumbent clinic BP was measured twice using a mercury Sphygmomanometer with a 5-minute rest between each reading. Participants underwent 24-h ambulatory BP monitoring during the working day prior to the clinic visit. At ~0800 hours, participants were attached with an ambulatory BP monitor (Meditech CE120 CardioTens; Meditech, Budapest, Hungary) on the nondominant arm at their workplace. The apparatus was programmed to measure BP at 30 min intervals during the day (0800–2200 hours) and every hour during nighttime (2200–0600 hours). On average, the cuff successfully inflated 72.6% of the time across all participants. Participants were asked to continue with normal daily activities and record any abnormalities such as headache, nausea, and feeling stressed on their ambulatory diary cards. The data was analyzed using the CardioVisions 1.15 Personal Edition software (Meditech). Hypertension was defined as mean 24-hour BP >125/80 mmHg [17], and nondippers were defined as participants having nocturnal systolic BP fall of less than 10% of their average daytime BP [18].

2.4. Covariates. Sodium fluoride, plasma, and serum samples from fasting blood were stored at −80°C for the analysis of biochemical risk markers. Fasting sodium fluoride (glucose) and serum samples for total and high-density lipoprotein (HDL) cholesterol, gamma glutamyl transferase, and high-sensitivity C-reactive protein (CRP) were analyzed using two sequential multiple analyzers (Konelab 20i; Thermo Scientific, Vantaa, Finland; Unicel DXC 800—Beckman and Coulter, Germany). The intra- and intercoefficients of variation for all assays was below 10%.

2.5. Statistical Analyses. Differences in the characteristics of participants in relation to depressive symptoms were analysed using ANOVA tests to examine continuous variables and chi-square tests to examine categorical variables. All CRP values were log transformed to normalize the distribution. General linear models were used to examine differences in BP between depressive symptoms categories. Logistic regression was used to examine the associations of depressive symptoms with hypertension and nondipper status. Hypertension was defined from BP readings and/or use of antihypertensive medication. The models were adjusted for covariates, including age, sex, ethnicity, CRP, body mass index, total/HDL cholesterol, and glucose. These covariates were selected on an *a priori* basis, as depressive behavior is accompanied by perturbations in glucose and lipid metabolism, inflammatory, and neural serotonergic system function, all of

Table 1: Characteristics of the study sample ($N = 405$).

Variable	No depressive symptoms		Mild- moderate depressive symptoms		Severe depressive symptoms	
	Black ($n = 42$)	Caucasian ($n = 101$)	Black ($n = 120$)	Caucasian ($n = 95$)	Black ($n = 35$)	Caucasian ($n = 12$)
Age (yrs)	43.8 ± 7.3	46.3 ± 10.8	44.7 ± 8.3	43.8 ± 10.7	43.3 ± 7.8	43.3 ± 11.3
Sex (% men)	66.7	58.4	58.8	45.7	34.3*	33.3*
Body mass index (kg·m^2)	27.7 ± 6.6	27.2 ± 5.4	30.7 ± 7.2	27.7 ± 6.5	31.2 ± 7.1*	29.8 ± 6.7
Total/HDL cholesterol ratio	4.41 ± 1.85	5.21 ± 1.63	4.34 ± 1.58	4.71 ± 1.58	5.08 ± 3.31	5.41 ± 1.69
C-reactive protein (mg/L)†	3.95 (54.3)	1.10 (14.1)	5.05 (53.6)	1.90 (26.3)	5.33 (32.5)	2.90 (25.7)*
Glucose (mmol/L)	5.59 ± 2.23	5.80 ± 0.97	5.59 ± 1.64	5.55 ± 0.62	5.92 ± 3.01	5.53 ± 0.50
Antihypertensive medication usage (%)	21.5	8.9	22.5	8.4	14.3	8.3

*$P < 0.05$ for trend across depressive symptom groups compared within own ethnicity; values displayed as mean ± SD unless stated (†non-normally distributed values displayed as median and range).

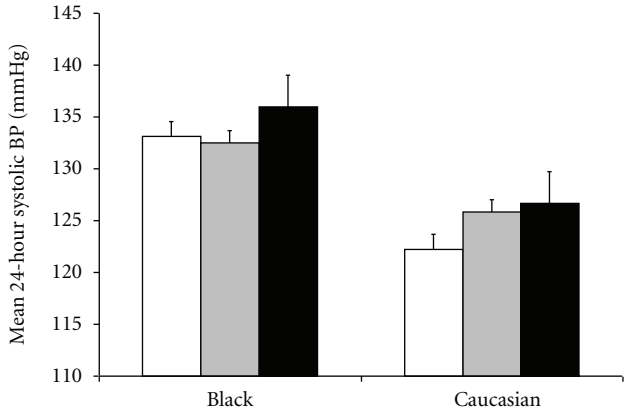

Figure 1: Association between depressive symptoms and mean 24-hour ambulatory systolic blood pressure in black and Caucasian Africans. White, grey, and black bars represent none, mild-moderate, and severe depressive symptoms, respectively. Values for blood pressure are mean ± SEM, adjusted for age, sex, and antihypertensive medication.

Table 2: The association between depressive symptoms and hypertension defined from 24 hr ambulatory blood pressure readings. ($N = 405$).

Depressive symptoms	Cases/N	Model 1 OR (95% CI)	Model 2 OR (95% CI)
None	80/143	Reference	Reference
Mild-moderate	142/215	1.91 (1.15–3.18)	1.79 (1.02–3.13)
Severe	32/47	2.19 (1.00–4.90)	1.86 (0.76–4.57)

‡defined as mean 24 hr BP ≥ 125/80 mmHg and/or use of antihypertensive medication.
Model 1; adjustment for age, sex, ethnicity.
Model 2; adjustment for age, sex, ethnicity, + C-reactive protein, body mass index, total/HDL cholesterol, glucose.

which are associated with exacerbated hypertension [19]. We fitted interaction terms in order to assess potential ethnic differences in the association between depression and BP. All analyses were conducted using SPSS version 14.

3. Results

The sample comprised 197 black (aged 44.2 ± 8.0 yrs) and 208 Caucasians (aged 45.0 ± 10.8 yrs). Severe depressive symptoms were reported in 11.6% of the sample. Black participants were more likely to report any depressive symptoms compared with Caucasians (age- and sex-adjusted odds ratio = 3.72, 95% CI, 2.35–5.89). Depressive symptoms were associated with several risk factors including higher body mass index and elevated CRP (see Table 1). In addition, black ethnicity was strongly related to other risk factors, including elevated CRP, BMI, and BP.

Hypertension was prevalent in 62.1% of the sample when using the 24-hour ambulatory BP criteria. There was a strong correlation between clinic and ambulatory systolic BP ($r = 0.74$, $P < 0.001$). Black participants recorded higher 24-hour systolic BP (age-, sex-, medication-adjusted $\beta = 7.8$, 95% CI, 5.0–10.6 mmHg) compared to Caucasians. There was an association between depressive symptoms and 24-hour ambulatory BP (see Figure 1). For example, compared to participants with no depressive symptoms, those with severe symptoms had marginally increased 24-hour systolic BP of 4.2 mmHg (95% CI, −0.5 to 8.9, $P = 0.08$) after adjustment for age, sex, ethnicity, and antihypertensive medication. Depressive symptoms were associated with a twofold risk of hypertension defined from 24-hour ambulatory BP monitoring (Table 2), although when hypertension was defined from clinic BP readings (≥140/90 mmHg) there was no associations with depression (odds ratio of hypertension for severe depressive symptoms = 1.36, 95% CI, 0.63–2.96). The associations of depressive symptoms and 24-hour hypertension were slightly attenuated after further adjustments for other risk factors including body mass index, CRP, total/HDL cholesterol, and glucose. We found no evidence for any statistically significant ethnic differences in the association between depression and BP. The removal of four participants who reported use of antidepressant medication did not alter any of the results.

Fifty-nine participants (14.5%) recorded experiencing stress on their diary cards during the ambulatory monitoring

Table 3: The association between depressive symptoms and nondipper status.

Depressive symptoms	Cases/N	Model 1 OR (95% CI)	Model 2 OR (95% CI)
None	45/143	Reference	Reference
Mild-moderate	75/215	1.04 (0.65–1.67)	1.01 (0.62–1.63)
Severe	23/47	1.74 (0.85–3.58)	1.74 (0.83–3.63)

Model 1; adjustment for age, sex, ethnicity, antihypertensive medication.
Model 2; adjustment for age, sex, ethnicity, antihypertensive medication + C-reactive protein, BMI, total/HDL cholesterol, glucose.

day, and those participants had elevated 24-hour systolic BP compared with nonstressed (age-, sex-, ethnicity-adjusted $\beta = 5.5$, 95% CI, 1.7 to 9.3 mmHg, $P = 0.004$). Participants reporting severe depressive symptoms were more likely to report feeling stressed (age-, sex-, ethnicity-adjusted odds ratio = 2.96, 95% CI, 1.16–7.50). When we added stress as a covariate, the difference in 24-hour systolic BP between participants reporting none and severe depressive symptoms was no longer evident ($\beta = 3.3$, 95% CI, −1.4 to 8.0 mmHg, $P = 0.16$), which suggests stress might partly explain the link between depression and the circadian BP profile.

We further examined the association between depressive symptoms and nocturnal BP decline (Table 3 and Figure 2). A nocturnal systolic BP fall of less than 10% (nondipper) was observed in 31.4% of the sample, and black participants were more likely to be nondippers compared with Caucasians (age-, sex-, medication-adjusted odds ratio = 1.62, 95% CI, 1.04–2.51). There was a weak association between depressive symptoms and nocturnal BP decline that was particularly evident in Caucasians. For example, compared to Caucasians with no depressive symptoms, those with severe symptoms had blunted nocturnal systolic BP drop of 4.7 mmHg (95% CI, −0.5 to 10.0, $P = 0.07$) after adjustment for age, sex, and antihypertensive medication (Figure 2). In the whole sample there was evidence of elevated risk of nondipping in participants with severe depressive symptoms although this did not reach statistical significance (Table 3), nor was there any significant interaction by ethnicity.

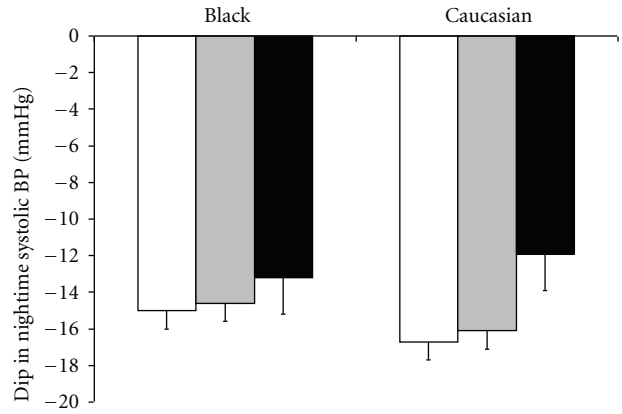

Figure 2: Association between depressive symptoms and change in ambulatory systolic blood pressure between daytime and night in black and Caucasian Africans. White, grey, and black bars represent none, mild-moderate, and severe depressive symptoms, respectively. Values for blood pressure are mean ± SEM, adjusted for age, sex, and antihypertensive medication.

4. Discussion

This is presently the only study in sub-Saharan Africa to examine the association between depressive symptoms and risk of hypertension. Black Africans are known to have elevated BP compared with Caucasians [20], and this was confirmed in the present study. Black participants from the present study also demonstrated a higher prevalence of depressive symptoms. Despite this, the association between depressive symptoms and BP remained independent of ethnicity and there was no evidence for any significant ethnic differences in the association between depression and BP.

Previous studies in this area have been limited by only taking clinic BP readings, but in the present study we also collected data from 24-hour ambulatory BP monitoring. Our main findings show an association between depressive symptoms and 24-hour ambulatory BP. To our knowledge, only one other study examining depression has employed ambulatory BP monitoring [11]. They found an association between depressive symptoms and blunted nocturnal systolic BP fall. Our findings are partly consistent with those results although we did not find strong evidence for an association between depression and risk of nondipping, which might be explained by the older age of participants from the previous study. Several large epidemiological cohort studies have found evidence for an association between depression and elevated risk of incident hypertension at followup [1–3, 10]. However, in other studies depressive disorder was associated with lower systolic BP [8, 9], although use of tricyclic antidepressants was associated with greater risk of hypertension [5, 8]. These inconsistencies might therefore be partially explained by inadequate assessments of BP, antidepressant medication, different measures of symptoms and diagnostic criteria for depression, or other confounding factors.

The associations between depressive symptoms and 24-hour BP were attenuated after further adjustments for other risk factors including body mass index, CRP, cholesterol, and glucose. However, given that these factors might act as intermediate mechanisms on the causal pathway from depression to hypertension, our models may have been overadjusted. For example, depressive symptoms were associated with body mass index and CRP, both of which have been implicated in hypertension risk [21, 22]. Indeed, these mechanisms have also been linked with the association between depression and coronary heart disease [23–25].

From our results we might speculate that daily stress partly explains the link between depression and the circadian BP profile. Participants with severe depressive symptoms were more likely to report feeling stressed on the ambulatory BP monitoring day, which corroborates with observations that depressed individuals are more likely to report events as stressful and to complain and endorse somatic symptoms.

Heightened BP reactivity to laboratory-induced stressors has been prospectively associated with a greater risk of hypertension [26], thus if elicited repeatedly in a person's life these responses might be clinically relevant. Moreover, there is also overlapping biology between the neurohormonal control of BP and the subsequent downstream effects of psychological stress, one in particular being the gaseous transmitter and neuroregulator, nitric oxide [27]. Indeed, naturalistic studies have shown profound effects of acute stressors on BP. For example, the World Trade Centre terrorist attacks in New York on 11th September 2001 produced a substantial and sustained increase in the BP of participants from the local community [28]. There was also a 20% increase in systolic BP following a moderate intensity earth quake that struck central Italy, which was followed by a long lasting period of enhanced BP variability and blunted nocturnal BP fall [29]. Work stress has also been associated with elevated 24-hour ambulatory BP [30] although the findings from prospective cohort studies in relation to work stress and hypertension risk have been generally inconsistent [31–36].

The strengths of this study include the unique sample of participants from sub-Saharan Africa, a well-validated measure of depressive symptoms, and the use of 24-hour ambulatory BP assessments. A limitation is the cross-sectional design, thus we cannot infer causality, identify potential mediators, nor determine the direction of the observed relationship between depression and hypertension. In addition, we did not assess history of major depression and recurrent symptoms, which might be important given the link between persistent depressive symptoms and cardiovascular risk [37]. In summary, we found an association between depressive symptoms and 24-hour ambulatory BP in black and Caucasian Africans. The equivocal nature of the existing work in this area might be explained by reliance on clinic BP readings and failure to capture the circadian BP profile.

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Author's Contributions

M. Hamer had full access to the data and takes responsibility for the integrity of the data and accuracy of the data analyses. M. Hamer performed statistical analyses. L. Malan is the principle investigator and led the study. All authors contributed to the concept and design of study, drafting, and critical revision of the paper.

Conflict of Interests

The authors declare that there is no conflict of interest.

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Research Article

Self-Monitoring of Blood Pressure in Hypertension: A UK Primary Care Survey

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This study aimed to determine the prevalence of Self-Monitoring Blood Pressure amongst people with hypertension using a cross-sectional survey. Of the 955 who replied (53%), 293 (31%) reported that they self-monitored blood pressure. Nearly 60% (198/331) self-monitored at least monthly. Diabetic patients monitoring their blood glucose were five times more likely than those not monitoring to monitor their blood pressure. Self-monitoring is less common in the UK than internationally, but is practiced by enough people to warrant greater integration into clinical practice.

1. Introduction

Monitoring of blood pressure (BP) is a key aspect of the diagnosis and management of hypertension [1]. Self-monitoring of BP by patients at home is one strategy by which hypertensive patients can participate in their own health care and leads to small but significant reductions in blood pressure [2]. National surveys of adults in the UK show that blood pressure control has gradually improved since the 1990s; however, many patients remain uncontrolled and amongst those at the highest risk, such as those with other comorbid conditions, the situation is worse [3]. Novel interventions are therefore needed if optimum blood pressure control is to be achieved, and self-monitoring appears to be a useful option.

International surveys have found that over 70% of people with hypertension self-monitor blood pressure [4–7]. Available data from the UK suggest much lower uptake in both specialist clinics [8, 9] and the general population [10]. Limited data are available regarding self-monitoring in primary care hypertensive patients.

This study aimed to determine the prevalence of self-monitoring of BP in primary care hypertensive patients and to highlight the characteristics of those that self-monitor blood pressure.

2. Methods

A questionnaire was sent to 1815 patients with hypertension registered with four general practices in the West Midlands, UK between November 2008 and April 2009, to determine the prevalence and patterns of use of self-monitoring of blood pressure. Self-monitoring was defined in the questionnaire and information sheet as "taking your own measurements of blood pressure outside your usual visit to your GP practice, usually within the home." Participating practices were chosen to represent a range of ethnic diversity and affluence of the patient population using the Index of Multiple Deprivation, an estimate of the socioeconomic deprivation of the practice population [11] linked to the practice postcode. Participants were adult patients (18+) identified by Read (morbidity) code with or without a Read code of Diabetes (Type 1 and 2). Patients were requested to return the blank questionnaire if they did not want to participate. A second questionnaire was mailed to nonrespondents approximately two weeks later.

Analyses were undertaken using SPSS (version 15, http://www.spss.com). The results presented are descriptive, reported as percentages and odds ratios with 95% confidence

Table 1: Characteristics of people self-monitoring and not self-monitoring blood pressure.

Demographics	Self-monitor n[a] (% of total number)	Do not self-monitor n (% of total number)	Chi-square (P)
Total number	293 (31)	662 (69)	—
Male	137 (50)	284 (47)	0.76 (0.382); NS
Female	135 (49)	318 (53)	
Age range (years)			
18–60	116 (40)	201 (31)	7.13 (0.008)
61 and over	177 (60)	453 (70)	
Ethnic origin			
White	223 (77)	554 (86)	10.98 (0.001)
Other	65 (23)	89 (14)	
Employed*	109 (38)	154 (24)	19.45 (0.001)
Retired/ unemployed	179 (62)	493 (76)	
Antihypertensive medication[a]	261 (90)	579 (88)	0.50 (0.479); NS
Diabetes+	75 (25)	155 (23)	0.53 (0.467); NS

[a]Numbers may not add up to total because of missing values.
*Part time or full time employment.
+Coded as having diabetes by GP clinical system.

intervals. Demographic characteristics including age, gender, ethnicity, and current status of employment were collected. Some descriptive categories were collapsed for the analysis.

It was assumed that approximately 20% of hypertensive individuals would be self-monitoring BP (twice that seen in a recent UK population survey [10]). To estimate the true prevalence of home self-monitoring with 95% confidence and 5% precision, returned surveys from at least 246 patients were needed. A larger sample drawn from four practices was chosen to increase generalisability and account for non-responders.

3. Results

Of the 1815 questionnaires mailed, 1062 were returned giving a return rate of 59%. Of these, 107 (10%) were returned blank and excluded from analysis, 955 were returned and analysable, giving an overall response rate of 53%. Of these 421/874 (48%) were male, and the age range was 21 to 81+. Of the 931 respondents reporting ethnicity, 81% were white, 6% Asian or Asian British, 7% Black British, 3% were Chinese and 3% were Mixed or other not stated. In view of the small numbers of nonwhite ethnicities, these have been collapsed into one group for the rest of the analysis.

293 reported currently self-monitoring blood pressure (crude prevalence 30.7%, 95% CI 27.8–33.7%). A quarter of respondents (230, 24.1%) had concurrent diabetes, of whom 155 (67.4%) monitored blood glucose and 75 (32.6%) monitored blood pressure. There was no difference in the prevalence of self-monitoring of blood pressure in people with or without diabetes (odds ratio = 1.13, 95% CI 0.82 to 1.55). Amongst the 230 people with diabetes, 156 (68%) monitored blood glucose. This group was 5 times more likely to monitor their blood pressure compared to those that do not monitor their blood glucose (odds ratio = 5.30, 95% CI 2.46 to 11.39).

Table 2: Self-blood-pressure monitoring frequency reported by self-monitoring respondents (n = 305).

	Overall N (% of total number)
More than once per day	9 (3)
Once per day	33 (11)
Twice a week	31 (10)
Once per week	54 (18)
Once per month	71 (23)
Not on a regular basis	107 (35)

Characteristics of those measuring their own BP are shown in Table 1. Younger people (aged between 18 to 60) were 1.5 times more likely to measure their own blood pressure than older people (over 60) (odds ratio 1.48, 95% CI 1.11 to 1.97). The odds of ratio for self-monitoring blood pressure was 1.81 (95% CI 1.27 to 2.59) for nonwhite ethnic group compared to the white ethnic group. Those in employment were also twice as likely to monitor their BP than those not employed (OR = 1.95, 95% CI 1.45–2.63).

Most people who self-monitored used an automated electronic BP device (247/293, 84.3%; CI 95% 73.5–94.3) with a small percentage (29/293, 9.9%) indicating they monitored using a manual machine. At least 65% reported monitoring at least once per month, most commonly once or twice a week (85/198 43%). Self-reported frequencies are shown in Table 2. Of those respondents currently not self-monitoring, nearly 60% (384/662 58%) reported they would consider self-monitoring in the future.

4. Discussion

This survey has found that approximately 30% of primary care patients with hypertension self-monitored blood pressure whether or not they had diabetes. People who self-monitored were more likely to be younger (18–60), in

employment (full time or part time), and from minority ethnic backgrounds (Asian, Black, or other ethnic groups) than those who did not self-monitor. People with diabetes who self-monitored blood glucose were more likely to also self-monitor blood pressure.

These findings, in common with those of a local community study [10] support findings from international studies that those with hypertension self-monitor blood pressure more commonly than normotensive populations [4, 6]. The current study suggests that people in primary care self-monitor less frequently than those attending specialist clinics [9], and that despite recent increased marketing of self-monitoring equipment, the UK has some way to go before such monitoring achieves the prominence currently seen internationally [5–7]. One small Scottish study reports that 31% of people with hypertension own a monitor which is similar to our results [12]. Assuming our figures are representative, then over 2 million people with hypertension may be currently self-monitoring in the UK.

In our study the frequency of monitoring for many respondents was low (42% monitoring more than monthly). This may reflect uncertainty of the appropriate frequency of monitoring; in the UK, National guidelines do not specify regimes for self-monitoring of blood pressure other than for diagnosis [13]. Patients and practitioners need better information on which to base self-monitoring regimes.

The high uptake of self-monitoring in ethnic minority groups could perhaps reflect an increased awareness of the risks of cardiovascular disease amongst this group or by their GPs who may have recommended self-monitoring [14]. An alternative explanation is confounding by age. Our results show that those respondents from minority ethnic groups were younger compared to the white population (as is the case in the population in general) [15] and as self-monitoring was more common in younger people then this may be the explanation.

The response rate for this study was not as high as hoped and responders may have differed from the rest of the population. However, the proportion of males in the sample (48%, 95% CI 44.9% to 51.5%) was similar to the 2001 census of West Midlands (49%) although the proportion of the people from a White ethnic background (84%, 95% CI 80.9% to 85.7%) was lower than the corresponding 2001 census figure (89%).

The results of this short survey identify a group of individuals with hypertension who currently self-monitor blood pressure with or without GP recommendation. Whilst this could reflect a healthy self-empowered population where hypertensive patients are taking more responsibility for their own health, previous research also suggests that patients may not be reporting this data to their GP or health professional and also monitoring under minimal or no supervision [7, 16]. This could therefore represent a lost opportunity which could be exploited by GPs being aware of the fact that a significant proportion of their hypertensive patients are self-monitoring.

Self-monitoring is practiced by an appreciable minority in UK primary care. In accordance with the findings from our study, people diagnosed as hypertensive could be potentially three times more likely to self-monitor than the general population. General Practitioners should be aware that around a third of their patients with hypertension could be monitoring their own blood pressure and of the opportunities that this could bring to daily management.

Ethical Approval

A favourable ethical opinion was gained from South Staffordshire Research Ethics Committee on 5th October 2007, ref. 07/H1206/61 and the relevant Trusts gave R&D approval.

Competing Interests

The authors declare that there is no conflict of interests.

Authors' Contribution

S. Baral-Grant and R. McManus had the original idea and gained the funding. S. Baral-Grant and M. Haque performed the analysis. R. McManus, S. Greenfield and A. Nouwen supervise SBG's PhD for which this study forms a part. S. Baral-Grant wrote the first draft. All authors commented on subsequent drafts and have approved the final version. R. McManus will act as guarantor.

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