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Lifestyle Modification in Blood Pressure Study II (LIMBS): Study protocol of a randomized controlled trial assessing the efficacy of a 24 week structured yoga program versus lifestyle modification on blood pressure reduction ☆,☆☆,★

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ABSTRACT

Hypertension is a major public health issue affecting 68 million adults in the United States. Lifestyle modifications including complementary therapies such as the movement based mind body practice of yoga have become increasingly popular in the United States and have been considered as a potential alternative to medication in blood pressure reduction. We completed a pilot study in 2009 which showed meaningful decreases in 24-hour ambulatory blood pressure readings after a 12 week period of yoga participation. Based on data from our pilot study we are now completing The Lifestyle Modification and Blood Pressure Study (LIMBS II) which is a phase 2 randomized controlled trial designed to determine the effects of yoga therapy and enhanced lifestyle modification on lowering blood pressure in pre-hypertensive and stage 1 hypertensive subjects. Using 24-hour ambulatory blood pressure monitoring, LIMBS II aims to compare the effects on blood pressure reduction in subjects randomized for 24 weeks to one of the three following groups: yoga therapy versus blood pressure education program (sodium restriction and walking program) versus a combination program that involves components of both groups. LIMBS II will also examine the impact that changes in blood pressure have on cerebral blood flow. If successful, the LIMBS study will determine if yoga therapy combined with enhanced lifestyle modification will result in clinically meaningful decreases in blood pressure and thus can be implemented as an alternative to drug therapy for patients with prehypertension and stage 1 hypertension.

1. Introduction

Hypertension is a major public health issue affecting more than 70 million US adults and is a major risk factor in the development of stroke, cardiovascular (CV) and chronic kidney disease [1]. Patients with high normal blood pressure (BP)

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(Systolic BP of 130–139 mm Hg or Diastolic BP of 85–89 mm Hg) fall into the category of pre-hypertension [2] and are also at an increased risk for adverse CV events compared to normotensive controls [3]. Lifestyle modifications (LSM) have been recommended as first line approach for both prehypertensive and stage 1 hypertension patients [2]. LSM such as weight loss, dietary sodium reduction, limiting alcohol intake, aerobic exercise and adopting the DASH diet (a diet rich in fruits, vegetables, and low fat dairy products with a reduced content of saturated and total fat) have been shown to lower systolic BP in the range of 4–9 mm Hg [4,5]. Complementary and Alternative Medicine (CAM) modalities including mind-body therapies (MBT) have been used in managing modest elevations in BP [6]. Yoga has been shown to be one of the most popular CAM therapies with growing use particularly in older hypertensive patients [7–10].

Although yoga has been beneficial in treating a variety of medical conditions [11,12] limited data suggest a benefit of yoga on hypertension. There are now a number of published studies investigating the effects of various forms of yoga on hypertension [13–21] however there are only 6 randomized controlled trials (RCT) of any form of yoga for hypertension [13,17–21]. This includes our own previous study which demonstrated clinically meaningful reductions in 24-hour ambulatory BP readings with yoga [19].

It is not clear how the effects of MBTs on the brain result in changes in BP although there is evidence suggesting that there might be a specific relationship between frontal lobe activity and BP [22]. Previous work from our group and others has shown that the medial prefrontal cortex and anterior cingulate gyrus areas are activated during attention focusing tasks [23–25]. We have also observed increased regional cerebral blood flow (CBF) in the prefrontal cortex and anterior cingulate gyrus during several different types of meditation practices and yoga relaxation techniques [26]. Since yoga also involves physical activity, it is possible [40] that there will be an even greater enhanced effect on frontal lobe function via a combination of attention focusing and movement. One class of MRI perfusion techniques utilizes magnetically labeled arterial blood water as a noninvasive diffusible tracer for blood flow measurement. This approach has been termed arterial spin labeling (ASL), and can provide quantitative perfusion images in brain and other tissues.

The purpose of this study is to conduct a randomized clinical trial of yoga utilizing gold standard methodologies in the measurement of BP and neuroimaging techniques to rigorously evaluate the efficacy of a popularized form of yoga in subjects with prehypertension and stage 1 hypertension.

2. Methods

2.1. Study design

The Lifestyle Modification in Blood Pressure Lowering Study II (LIMBS) is a randomized, non-blinded prospective controlled trial to assess the safety and efficacy of a 24 week structured yoga program (YP) vs. blood pressure education program (BPEP) vs. combined intervention (YP and BPEP). The study population consists of adults with prehypertension to stage 1 hypertension who are not taking any antihypertensive medications. This study is being performed at a single center using a parallel design. The main outcome is mean awake and 24 hour systolic and diastolic ambulatory BP. Based on the power analysis, the established recruitment goal is 120 subjects aiming for 102 completers (34 subjects per intervention). Eligibility is determined by 2 screening visits with a mean

Table 1
Inclusion/exclusion criteria.

Inclusion criteria
1). Subjects must be willing able to give written informed consent.
2). Age $\geq$ 18 years, but <75 years.
3). BP criteria: SBP of $\geq$130, but <160 mm Hg.
4). Willing to comply with all study-related procedures

Exclusion criteria
1) Subjects who are pregnant or post partum <3 months.
2) Subjects currently taking BP lowering medications or dietary supplements (magnesium, potassium, calcium >1200 mg/day, fish oils, ephedra, hawthorn, forskolin, etc).
3) Stage II hypertension (SBP > 160 mm Hg OR DBP ≥ 100 mm Hg)
4) Non-dominant arm circumference >50 cm.
5) BMI ≥ 40.0 kg/m^2. Subjects with BMI above 40 may be enrolled if PI deems subject physically able to perform all study exercises.
6) Practicing yoga >1×/month in the previous 6 months
7) Received/used experimental drug or device within 30 days prior to screening, or donated blood $\geq$1 pint within 8 weeks of screening
8) Diabetes mellitus
9) Established cardiovascular disease
10) Known arrhythmias or cardiac pacemakers
11) Current users (within 30 days) of any tobacco products
12) History of renal insufficiency (glomerular filtration rate < 60 ml/min)
13) Women consuming >7 alcoholic drinks/week; men consuming >14 drinks/week.
14) Known autonomic neuropathy
15) Known secondary cause of hypertension (renal artery stenosis, pheochromocytoma, coarctation of aorta, hyperaldosteronism).
16) Benzodiazepine, anti-psychotic drugs (3 month stable use of SSRIs are allowed), or steroid use.
17) Known severe musculoskeletal problems such as spinal stenosis that may limit participation in yoga.
18) Use of other MBT such as Qi Gong, Tai Chi, meditation.
19) Lack of internet access
20) Presence of non-removable metallic foreign object, surgically implanted electrical device, surgically placed metallic clip (aneurysm clip), ear implants, any history of metal implants in the eye

of 3 office BP readings at each screening in the range of SBP 130–160 mm Hg and DPB < 100 mm Hg. Screening, inpatient and follow-up visits take place at the clinical translational research center at the Hospital of the University of Pennsylvania. The yoga program is conducted offsite at Studio 34 (Studio 34 Yoga, LLC) in West Philadelphia.

2.2. Study participants

Eligible participants include adults aged 18–75 with a screening SBP of >130 mm Hg but < than 160 mm Hg. Subjects cannot be receiving any antihypertensive medications for 3 months prior to enrollment. Eligible subjects must be able to willingly consent to study participation and must be able to comply with the study requirements. Further inclusion and exclusion criteria are detailed in Table 1.

2.3. Study recruitment

The planned recruitment target is 120 subjects divided into cohorts consisting of 10–15 subjects. A diagram showing the details of recruitment is shown in Fig. 1. Cohorts begin at 12 week intervals, with 2 cohorts active simultaneously and a third cohort in the enrollment and recruitment stages. Subjects are recruited using IRB-approved newspaper and radio advertisements posted in the Philadelphia area and IRB-approved flyers distributed in the campus of the University of Pennsylvania. Additionally potentially eligible subjects are recruited from the hypertension and primary care practices at the Hospital of the University of Pennsylvania. All potential subjects are screened first by telephone to ensure that they meet inclusion and exclusion criteria. If they meet eligibility criteria, subjects then have 2 outpatient screening visits at the clinical translational research center (CTRC). The

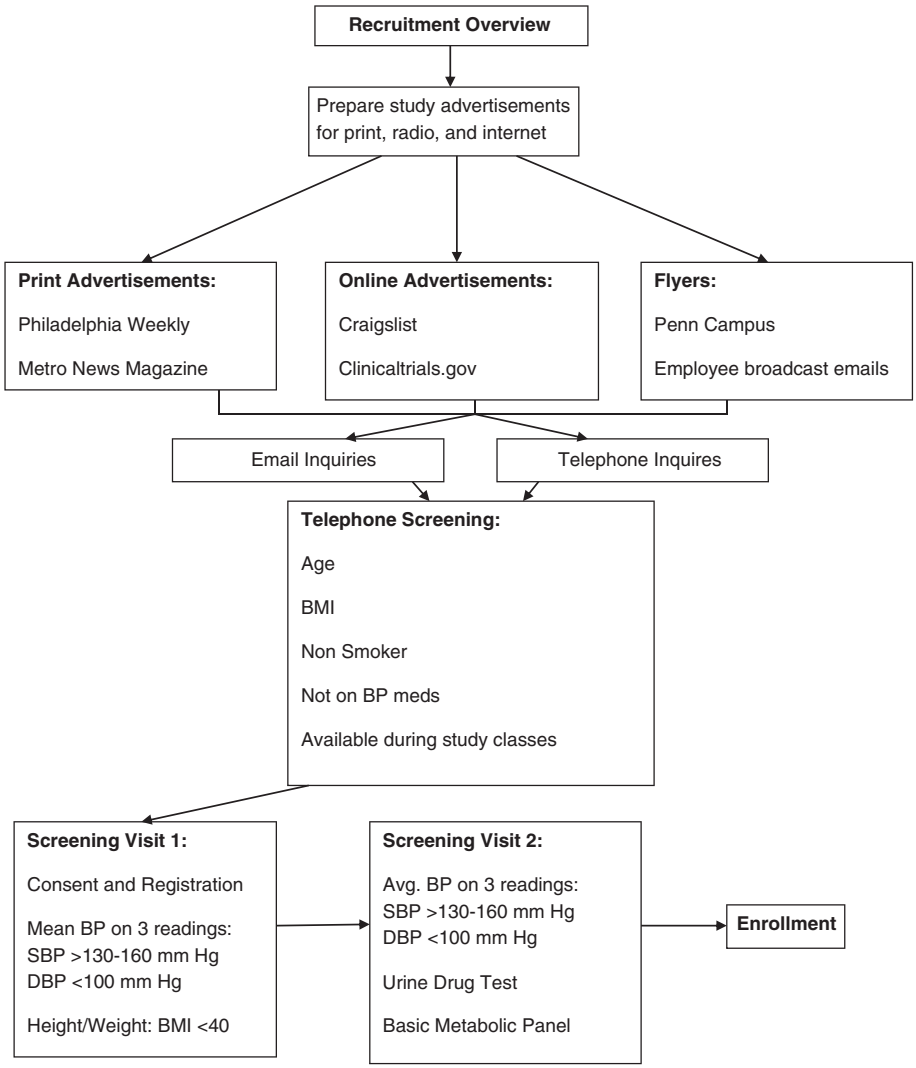

Fig. 1. Diagram of recruitment overview for the LIMBS study.

Table 2
Data collection overview.

Ambulatory blood pressure monitoring (ABPM)
• Subjects wear 24 hour ambulatory blood pressure monitor (Spacelabs Medical Inc.) during CTRC inpatient stay.
• BP recorded every 20 min during waking hours, every 30 min during sleep hours.
Fasting serum samples
• Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, creatinine levels
• Complete blood count including RBC, WBC, Hgb
• Peripheral blood mononuclear cells PBMC for telemorase activity analysis
• Asymmetric Dimethlyarginine (ADMA)
Urine samples
• Urine creatinine levels, microalbuminuria levels
• Total urine volume, 24 hour potassium and sodium levels
• Urinary isoprostane
Salivary swab
• Salivary cortisol levels
ECG
• To detect any abnormal heart rhythms indicative of past coronary complications

BP is recorded at 2 screening visits. At each visit the subject is seated in a semi-recumbent position for 5 min prior to the first BP reading. Three readings are taken at one minute intervals and a mean is derived from this set. An additional set of 3 readings may be taken if the first set yields an average SBP between 120 and 129 mm Hg.

Once eligibility criteria are met subjects are enrolled by the study coordinator and scheduled for their first inpatient visit at the CTRC. Eligible subjects have 3 overnight visits to the CTRC where they undergo 24 hour ambulatory blood pressure (ABP) monitoring at baseline, 12 weeks and 24 weeks after randomization. Blood, saliva and urine samples are collected for various assays including markers of oxidative stress and endothelial dysfunction as detailed in Table 2. The entire study duration is 28 weeks (24 weeks post-randomization) and includes a total of 2 screening visits, 3 evaluation visits, 2 functional MRI (fMRI) visits and a termination visit. A schematic of the visit timeline is shown in Fig. 2.

2.4. Randomization

After the completion of the baseline 24 hour ABP visit, subjects are assigned to either the yoga group, blood pressure education program (BPEP), or combined intervention using a simple (non-stratified), blocked randomization. Small blocks of six are used to avoid imbalances, and ensure that no group is off by more the three subjects per cohort. Using this system, the study statistician from the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania generates a list from which subjects are randomized in order of enrollment. At the time of discharge from the baseline 24 hour ABP stay, subjects are given a folder containing information about their group and any necessary documents or equipment they might need (pedometer for education and combo groups, yoga home practice DVD for yoga and combined intervention groups). Study classes begin within one to three weeks of randomization.

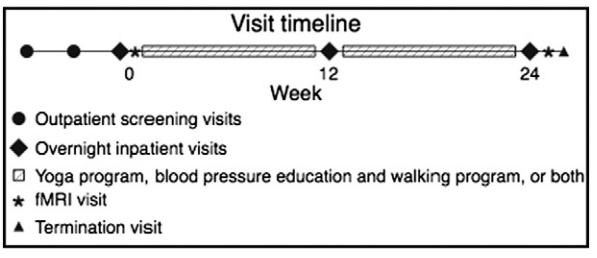

Fig. 2. Study visit timeline.

2.5. Primary outcomes

The Primary outcome of LIMBS II is to determine the effect of a structured 24-week yoga program on reducing mean awake and 24-hour ABP in adults with high normal to stage I hypertension. Additionally LIMBS aims to establish if the combined effects of a yoga program and a blood pressure education program are more effective at reducing 24-hour ABP than either group alone.

2.6. Secondary outcomes

Secondary outcomes include determining if the effects of yoga on changes in blood pressure are reflected in changes in cerebral blood flow as measured by ASL fMRI. Such changes may point to a neurophysiologic mechanism underlying the anticipated blood pressure responses. This is accomplished by performing ASL fMRI during resting and stimulated states and observing changes in regional CBF in the prefrontal cortex and cingulate gyrus before and after 24 weeks of yoga, BPEP or the combined intervention.

Additional Secondary outcomes surround the psychological and physiological impacts of yoga practice. LIMBS II is evaluating if participation in the yoga program or combined intervention will improve mood, reduce fatigue, and improve health related quality of life as compared to BPEP participation. Questionnaires are filled out by subjects at each CTRC inpatient visit. Research staff is available for questions to ensure that all questionnaires are appropriately completed with a minimum of missing items and collect questionnaires upon completion. The following measures are manually scored and entered into the database: [1] The Profile of Mood States (POMS), [2] Symptoms of Stress Inventory (SOSI), [3] Health Survey, [4] Cook Medley Anger and Hostility Scale, [5] Treatment Preference, [6] Expectancy Scale, [7] The Perceived Competence Scale, [8] Paffenbarger Physical Activity scale, and [9] Beck Depression Inventory.

2.7. Intervention

The yoga program (YP) intervention consists of 3 components: semi-private structured classes; self-practice, and community structured classes. Subjects start with bi-weekly yoga classes, gradually adding a self-practice, and eventually working subjects into regularly, structured, community classes. All classes are taught by one of Studio 34's certified Forrest Yoga (FY) instructors. FY (http://www.forrestyoga.com) is a form of Hatha yoga. The 90 minute class sequence is outlined in Table 3. YP subjects begin with

Table 3
Forest yoga 90 minute class sequence.

Forrest Yoga — 90 minute class sequence

I. **Breath work** (**pranayama**): **5–7 min**
II. **Warm up poses**: **25 min**
  a. Seated poses — ie. side bends, forward bends (ex. Janu Sirsasaana), twists (ex. Ardha Matsyendrasana), hip (ex. Baddha Konasana, Agnistambhasana) and shoulder openers
III. **Abdominals**: **2–3 min**
  a. Bridge (Setu Bandha Sarvangasana) with or without variations, Dolphin or Turbo Dog with or without variations (Adho Mukha Svanasana variations)
  b. Inversions and Wall Work (ex. Adho Mukha Vrksasana)
IV. **Hot poses**: **40 min**
  a. Sun salutations, B series with standing poses, or standing pose series (ex. Virabhadrasana I, Virabhadrasana II, Utthita Trikonasana)
  b. Backbends — only incorporated if class focus is on backbends (ex. Ustrasana, Dhanurasanam, Natarajasana, Urdhva Dhanurasana)
  c. Apex poses (most challenging poses for the class level)
V. **Cool/warm down**: **5–7 min**
  a. Warm down poses: ie. abdominals, deep twists
  b. Cool down poses: ie. forward bends (ex. Janu Sirsasaana, Paschimottanasana), side bends, straddle (ex. Upavistha Konasana, Prasarita Padottanasana), splits (Hanumanasana)
VI. **Deep relaxation** (**Savasana**): **5–7 min**

two classes per week. This is enough yoga practice to impact the students, while minimally intruding in their daily life. During the first three months, YP subjects gradually begin a self-practice, which helps YP subjects to learn to be self-sufficient and to be more responsible for their health. The self-practice begins bi-monthly and increases to weekly over the initial 3 months. After 12 weeks of semi-private classes, YP subjects are required to participate in regular FY community classes. Semi-private classes are structured classes, "restricted" to members of a single cohort and are 90 minutes long. YP subjects are required to attend 2 semi-private classes each week, during the first 12 weeks of the program. Each class follows a set sequence of poses and the intensity of the poses is gradually increased over the first half of the program. The same series of 12 unique classes is used for every cohort. The semi-private class format allows YP subjects to become familiar with the other members of their class and allows for a more comfortable and enjoyable introductory experience of yoga. This format also allows for smaller classes where we can provide high-quality attention and instruction tailored to the YP subjects. Each week the class sequence will build upon the information provided on the prior week, providing YP subjects with a deep understanding of the practice. Community classes are the regular FY classes offered at Studio 34 and are open to anyone in the community. YP subjects are required to attend 2 community classes per week during months 4–6 of the program, in addition to doing one self-practice per week. These are 90 minute classes and sequenced with the same standardized FY sequence specifications and taught by the same FY instructors as the semi-private classes. Integrating YP subjects into community classes allows us to examine the YP effects in real-world conditions, and aims to help YP subjects to develop a yoga practice that is maintainable beyond the duration of this study.

At the beginning of the YP, subjects are provided with Ana Forrest's "Strength and Spirit" DVD, which contains a 90 minute-long class taught by Ana Forrest. YP subjects are required to do the DVD class, in their home, twice during the first month, three times during the second month and weekly during the third month. During months 4–6, YP subjects are required to complete one home practice DVD session per week or to attend two additional community classes at the yoga studio. All YP participants are asked to record their home practices so as to monitor progress and encourage accountability. The self-practice is optional for the combined intervention subjects.

Subjects who are not randomized into the YP group are randomized to the Blood Pressure Education Program (BPEP) or to the combined intervention program (COMBO). The BPEP program consists of small group health education classes and a walking program. Every other week subjects attend a nutritional lecture taught by a study dietitian. On alternate weeks the BPEP subjects attend motivational talks about a variety of topics including weight loss, walking programs, and healthy lifestyle choices or they are given educational DVDs or literature to read on the weeks that they are not attending a BPEP class. In total the BPEP program includes 12 BPEP classes and 12 motivational experiences. Additionally, BPEP subjects are expected to walk 6 days a week gradually increasing to 180 min of walking per week or 10,000 steps per day. BPEP subjects are provided with a pedometer upon randomization to increase compliance and track progress. The BPEP classes provide a community atmosphere that mirrors what is felt by YP subjects attending community classes.

COMBO subjects are required to attend two yoga classes per week in addition to the bi-weekly BPEP nutrition lecture and participate in the walking program. Home practices and motivational sessions are optional for COMBO subjects.

2.8. Data collection

All study subject information is organized into individual subject binders and stored securely in a location only accessible to research personnel. Upon completion, a subject's information is uploaded electronically to a Microsoft Access Database file and double keyed to ensure accuracy. Study subject information is collected using IRB approved source documents specific to each study visit. Upon enrolling, each subject is assigned an identification number which is used to track information throughout the study. Subject binders contain copies of all consents, screening materials, and study visit source documents in addition to any logs or memos pertinent to the subject. Additional binders are kept to house original consent forms and screening logs, and adverse event logs. Screen fails are either destroyed or stored for future participation depending on the wishes of the subject.

Additionally, subjects are required to keep a log on the LIMBS study website (http://limbs.cohenhtn.com/). Upon enrollment, each subject is assigned a user name and password to access the LIMBS site. Subjects are required to log in weekly and record their semi-private/community classes and their self-practice (YP), or walking data (BPEP/COMBO). Subjects are also required to report a bi-weekly BP reading and weight. The LIMBS website is designed to encourage subject compliance and serves only as a secondary data source. Class attendance is

directly reported by instructors to the study coordinator each week.

2.9. Statistics

2.9.1. Sample size

All sample size calculations were done and verified using nQuery Version 4 (Dataxiom Software Inc.). They are conservative in that they do not take advantage of the additional power of the repeated measures analysis under the random effects ANOVA model, but instead assume an ITT analysis at the 24 week time point based on an ANOVA model without the additional power by adding baseline and 12 week data. Accordingly, our best estimate is that we will need at least 34 completers per group or 102 total completed subjects to answer our primary aim that YP will reduce mean 24 hour DBP by at least 4 mm Hg compared to the BPEP group. We expect a dropout rate of 15%, thus we would need 40 subjects per group or 120 total randomized subjects for this study.

2.9.2. Randomization

For this trial we are using simple (non-stratified), blocked randomization. We use small blocks of 6 to avoid imbalances (group size will never be off by more than 3 subjects). The scheme was developed before the start of the trial by the biostatistician, and codes are placed in 1 sealed envelope, one for each of the 3 groups. Once a cohort is fully eligible and ready to start, the biostatistician opens the envelope and makes the assignments known to the study coordinator.

2.9.3. Statistical analysis

All intermediate computations, statistical analyses, and graphical presentations will be produced using SAS V9. Data quality will be assessed by descriptive summaries and graphical methods to examine sample distribution of the key variables. This will be done both for our demographic variables and outcome variables of interest. Based on our experience in our prior study, we anticipate that the population distribution of the outcome variables for Primary and Secondary outcomes is normal. We will evaluate the balance between groups achieved by randomization, baseline values of all variables will be compared between the YP, BPEP and combined intervention. Group differences for continuous characteristics will be compared between groups using the one way ANOVA for independent samples. Proportions will be compared between groups using the chi-square test, or Fischer's exact tests when expected cell counts are less than 5.

The Primary outcome will be the change in mean 24 hour DBP. This endpoint will be derived from ABPM. Mean SBP and DBP will be calculated for each patient as (week 24–baseline). Differences in the mean change between the YP, BPEP and combined intervention will be compared using the time–group interactions under the random effect repeated measures ANOVA model in SAS PROC MIXED. An analogous test of group differences in mean change since baseline at 12 weeks will also be provided by the random effects repeated measures ANOVA model.

The Secondary outcome change in regional cerebral blood flow will be assessed between 24 weeks and baseline. This will be defined as week 24–baseline. In order to initiate the evaluation of fMRI data, all images will initially be converted into a format compatible with SPM2 software (Wellcome Department of Cognitive Neurology, London, UK). Images will be analyzed using a voxel based analysis. We will test whether the fMRI data before and after yoga training are different in specific regions, particularly the prefrontal cortex and cingulate gyrus. The pre and post-program baseline scans will be compared as well as the pre and post program meditation scans. Statistically significant differences between sets of data will be assessed at each voxel with a threshold of $P < 0.001$. To correct for correlated multiple comparisons, clusters of voxels which survive this threshold are assessed further using the theory of random Gaussian fields, which calculates the significance of clusters based on their peak height and spatial extent. The statistical threshold for correction of multiple comparisons is $P < 0.05$. The locations of the cluster peaks can be linked to anatomical labels. Further, covariates, such as age, can be included in the analysis as either confounds, or as covariates of interest, and correlations with brain activity mapped. SPM also allows for a comparison of perfusion data to various neuropsychological and clinical data. A linear regression model will be applied initially between the perfusion data and scores on cognitive function tests and will also be applied through the SPM2 software. Correlations will be considered significant for a $P < 0.05$ after correction for multiple comparisons.

2.10. Safety

Lifestyle modification is initially indicated for a period of 6 months for patients with uncomplicated prehypertension and stage 1 hypertension. The principal investigator has final determination whether participants meet criteria and can safely be enrolled in the study. If a potential participant is on medication, this can be judged on a case-by-case basis by the principal investigator. Generally subjects would NOT meet criteria for participation but if a potential participant has mild, well controlled hypertension on a low dose of monotherapy it is feasible that they could be enrolled in the study if BP remains within an acceptable range for 3 months after medication is discontinued. The potential subject would only be eligible for enrollment after a 3-month medication-free period. Most potential participants however who are already on medication would not meet medical criteria to withhold therapy. During the study if subjects develop worsening hypertension despite the intervention (SBP $>$ 180 mm Hg; DBP $>$ 110 mm Hg) they are withdrawn from the study and referred to their primary care physicians to initiate antihypertensive medication. If SBP $>$ 180 mm Hg or DBP $>$ 110 mm Hg and subject is symptomatic the subject is referred to the emergency room or their primary care physician for further evaluation.

3. Results

The study is ongoing and will be completed by January 2014 and results are expected to be available shortly thereafter.

4. Discussion

Although yoga has been beneficial in treating a variety of medical conditions (arthritis [11,12], gait disorder [27], depression [28], diabetes [29] and metabolic syndrome) the data regarding the effects of yoga on lowering blood pressure are limited. Although there are a number of published studies investigating the effects of various forms of yoga on hypertension [13–21], most of these studies are uncontrolled case reports or small cohort studies conducted in India with significant methodological limitations [14–16,30]. There are only 6 randomized controlled trials (RCT) of any form of yoga for hypertension [13,17–21]. This includes our own previous study completed at the University of Pennsylvania in which subjects with prehypertension to stage 1 hypertension were randomized to a structured Iyengar Yoga (IY) Program or enhanced LSM. This study showed clinically meaningful reductions in 24-hour ambulatory BP readings in the IY group at 12 weeks [19]. The most recent publication from India was a cross-over randomized controlled trial of an earlier RCT of non-pharmacological interventions in hypertension. Subjects were prehypertensive adults who were randomly allotted to a group that they had not been in in the previous trial [21]. They were assigned to one of 4 groups for 8 weeks: control group, brisk walking 50–60 min, 3–4 days a week, sodium restriction to at least half of their previous intake or yoga for 30–45 min per day, 5 days per week. All 3 groups aside from the control group showed reduction in BP but physical exercise showed a greater reduction in BP in the range of 5/6 mm Hg whereas sodium reduction and yoga showed a less impressive decline in BP in the range of 2.5/2.0 mm Hg [20]. Another study involved 101 subjects with features of the metabolic syndrome who were randomized to standard medical therapy or yoga and a form of transcendental meditation. SBP was reduced significantly by 16 mm Hg in the treatment group [31]. Another prior study was an 8 week pranayama and asana yoga program conducted in 27 untreated hypertensive patients and 27 controls living in Thailand [13]. The experimental group significantly reduced SBP by 25 mm Hg at 8 weeks compared to 2 mm Hg increase in the control group. DBP significantly decreased by 18 mm Hg in the experimental group compared to an increase of 2 mm Hg in the control group. In India, 33 hypertensive adults were randomly assigned to 3 groups (yoga, medications only, or no therapy) and were followed for 11 weeks [17]. Yoga was performed at home for 6 h per week and included a combination of asanas, pranayamas and mantras. At the end of the study, SBP was reduced by an impressive 33 mm Hg compared to 4 mm Hg in the control group and 24 mm Hg in the poorly described drug therapy group. The differences were significant compared to both control and drug treatment. In an older randomized controlled trial from England, 43 patients with known hypertension, most of whom were already medically treated, were randomized to yoga plus biofeedback or usual care [18]. Treatment reduced SBP by 26 mm Hg vs. 9 mm Hg in the control. This study however used a mixed intervention which included biofeedback in addition to yoga, and did not include any movement.

A general critique of the published yoga and BP research includes the fact that most studies were not randomized, had inadequately described yoga or control programs, did not collect information on other lifestyle confounders (e.g. adoption of vegetarian diet, reduction in alcohol intake) and did not use standardized, reliable outcome measures. There is also the very real possibility of publication bias in which negative yoga trials have not been published.

The effects of yoga on lowering blood pressure in these prior studies have mostly been modest however data from the Framingham Heart Study showed that a 2 mm Hg reduction in DBP could reduce the risk of stroke or transient ischemic attack by 14% [32] while a 10 mm Hg reduction in SBP, seen with prescription drugs and in some meditation studies [33], is associated with a 30% relative reduction in risk of stroke [34]. Thus smaller reductions in BP (5 mm Hg in SBP or 2 mm Hg in DBP) achievable through diet, some dietary supplements and mind body therapies can be expected to significantly reduce CVD morbidity. We believe, based on our pilot data, that there is a genuine need for a rigorously conducted randomized clinical trial of yoga assessing the effects of lowering BP in patients with prehypertension and stage 1 hypertension. Even if the effects of yoga on hypertension are modest this can still provide substantial CV protection for this group of patients with mild to moderate hypertension and may afford patients the opportunity to engage in yoga instead of committing to lifelong antihypertensive medication.

Conducting any lifestyle or behavioral modification research can be challenging as it is often difficult to ensure compliance with the interventions used and there is often a higher dropout rate in these studies than with conventional drug studies. In our power calculation we assumed a dropout rate of 15% which is probably too conservative and will likely be closer to 20%. To compensate for this unexpected drop out rate we do intend to recruit a larger sample size to ensure we have at least 34 completers in each cohort.

There is a substantial literature as to the potential neurophysiological correlates of mind body therapies (MBT) and there is evidence suggesting that there might be a specific relationship between frontal lobe activity and BP [22] although the mechanism underlying this is not clear. We have shown in previous work from our group a model for the neurophysiological changes associated with meditation [23]. This model is based, in part, on studies that have correlated brain function with specific behaviors and experiences, including that of meditation. In our model, meditation is considered to be an attention-focusing task. Studies have generally shown that the medial prefrontal cortex and anterior cingulate gyrus areas are activated during attention focusing tasks [24,25]. In SPECT studies by our group, we observed increased regional cerebral blood flow (CBF), which is closely coupled to neural activity and metabolism, in the prefrontal cortex and anterior cingulate gyrus during several different types of meditation practices. These practices included Iyengar Yoga, meditation, Tibetan Buddhist meditation, Transcendental meditation and Centering Prayer [35–37]. A study utilizing functional magnetic resonance imaging (fMRI) of subjects performing a similar yoga relaxation technique designed to bring about “relaxation response”, demonstrated increased CBF in the frontal and limbic regions [26]. Since yoga also involves physical activity, it is possible that there will be an even enhanced effect on frontal lobe function via a combination of attention focusing and movement. Several methods are now available

for measuring cerebral perfusion and related hemodynamic parameters using MRI. One class of MRI perfusion techniques utilizes magnetically labeled arterial blood water as a noninvasive diffusible tracer for blood flow measurement. This approach has been termed arterial spin labeling (ASL), and can provide quantitative perfusion images in brain and other tissues. The purpose of this study will also be to evaluate changes in CBF before and after the yoga training program. In order to do this, we will make use of ASL-based functional magnetic resonance imaging (fMRI). As compared to blood oxygenation dependent (BOLD) fMRI, ASL fMRI provides greater sensitivity to gradual changes in regional brain function that may occur over time [38,39]. The goal of the proposed study is to use ASL fMRI to evaluate changes in resting and stimulated CBF in the prefrontal cortex and cingulate gyri before and after 24 weeks of yoga, LSM or the combined intervention. We expect that fMRI will show changes in CBF in prefrontal cortex and cingulate gyri in response to yoga therapy.

5. Conclusion

Pre-hypertension and hypertension are growing public health concerns which are closely linked to CV disease. While drug therapy is indicated for patients with persistent hypertension, national guidelines highlight the benefit of non-pharmacological approaches to managing both prehypertension and stage I uncomplicated hypertension [2]. Effective and safe CAM therapies such as yoga encourage patient self-reliance and establish healthier lifestyles, have few side-effects, and do not pose problems of drug–supplement interactions typical of many biologically based therapies. This study utilizes gold standard methodologies in the measurement of BP and neuroimaging techniques to rigorously evaluate the efficacy of a popularized form of Hatha yoga in this population and explore possible mechanisms of action. This is also the first randomized controlled trial to evaluate combining yoga with a diet and exercise program.

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