

Design paper

Stop Hypertension with the Acupuncture Research Program (SHARP): clinical trial design and screening results

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Abstract

Hypertension is a major public health problem with serious medical and financial consequences. Barriers to successful conventional pharmacological treatment include side effects, out-of-pocket expenses, patient noncompliance and insufficient dosages. Acupuncture has been studied as an alternative therapy for controlling blood pressure (BP) but previous studies have serious methodological limitations. This paper describes the design of the Stop Hypertension with the Acupuncture Research Program (SHARP) trial, a pilot randomized clinical trial designed to gather preliminary data regarding the efficacy of traditional Chinese medicine (TCM)-based acupuncture for control of essential hypertension. The design of the SHARP trial balanced rigorous clinical trial methodology with principles of TCM. Eligible participants had systolic BP (SBP) 140–179 mm Hg and diastolic BP (DBP) 90–109 mm Hg in the absence of antihypertensive therapy. Following screening, participants were randomized to one of three groups: individualized, standardized or control acupuncture. Treatments were designed according to principles of TCM; nonspecific effects associated with the interventions were standardized across the randomized groups. For individualized acupuncture, points were tailored to each

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participant. Standardized acupuncture used a prespecified set of points. The invasive sham control acupuncture regimen was designed to be non-active. Each participant received a “prescription” for individualized acupuncture from an acupuncturist who was masked to treatment assignment, and was subsequently treated by an independent acupuncturist. Patients and those assessing BP were masked to treatment group. Acupuncture was delivered twice a week for 6 weeks. Follow-up visits were every 2 weeks to week 10 and then at months 4, 6, 9 and 12. The primary endpoint will be change in SBP from baseline to 10 weeks. DBP, BP trajectories over the 12-month follow-up and antihypertensive medication requirements will also be examined. Initial contact was documented for 1442 prospective participants from March 2001 to April 2002; 424 provided informed consent and 192 were ultimately randomized.

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1. Introduction

Hypertension is a condition with tremendous financial and public health impact. Although blood pressure (BP) can be controlled in most individuals, in practice, the majority of hypertensive individuals are unrecognized and/or inadequately treated with conventional pharmacologic therapies [1]. Acupuncture provides an alternative treatment approach with great potential advantages, but with little rigorous scientific evidence to support it. The Stop Hypertension with the Acupuncture Research Program (SHARP) trial is a pilot randomized clinical trial designed to gather preliminary data regarding the efficacy of acupuncture for treating hypertension without the use of pharmacologic therapy. This paper describes the design of SHARP and our experience with recruitment and screening for the trial.

1.1. Hypertension

Hypertension, defined as systolic blood pressure (SBP) of ≥ 140 mm Hg and/or diastolic blood pressure (DBP) of ≥ 90 mm Hg [2], affects an estimated 640 million persons worldwide [3], including approximately 50 million Americans [1,4]. The costs of inadequately controlled blood pressure can be measured financially and medically. Its financial impact in the United States is enormous—US\$47.2 billion in direct and indirect costs in 2002 [4]. Medically, the long-term consequences of untreated hypertension are among the most common and serious causes of morbidity and mortality in the United States, including myocardial infarction, stroke, congestive heart failure and renal failure.

Despite large-scale national efforts to identify, educate and treat individuals with hypertension, only 69% of hypertensive individuals are aware that they are hypertensive. Approximately half of all hypertensives take prescribed medications, but blood pressure is adequately controlled in only a quarter of the total [1,5]. Although the efficacy of lifestyle modifications and antihypertensive drugs for essential hypertension has been well established in clinical studies [6–8], treatment with conventional medical treatments may be limited by side effects, out-of-pocket costs, patient noncompliance with prescribed regimens, insufficient dosages of prescribed medications to achieve an adequate level of control, health-care provider neglect of hypertension, and the individual’s inability to make lasting and meaningful healthy lifestyle changes [2,9–14].

1.2. Acupuncture

Acupuncture has been a component of the Chinese health-care system for at least 2500 years and is widely practiced in the United States [15]. Acupuncture is based on the traditional Chinese medicine (TCM) concept that there are channels (or “meridians”) of energy flow (“qi”) within the body that help maintain the health of the individual and that disease and pain result from imbalances of qi. For any particular Western medically defined illness, there may be several different underlying patterns of disharmony from the TCM perspective. These patterns are diagnosed by symptoms and signs and by observing the patient’s overall affect (complexion and demeanor), tongue (color, shape, coating and texture) and radial pulse (speed, depth, rhythm, shape, quality and strength).

Acupuncture is seen as a way to access the energy channels and to restore balance by adding energy where it is deficient and releasing energy where it is obstructed. The practice of acupuncture encompasses several types of related techniques. All acupuncture involves stimulation of specific anatomic locations on the body (corporeal points) or on the ear (auricular points), most commonly by penetration of the skin with thin, solid metallic needles. Selection of corporeal points is based on knowledge of the “action and effects” of the points, as developed from ancient texts and over 2000 years of clinical experience. Modern TCM theory holds that there are also auricular points corresponding to particular organs, areas of the body or bodily systems. Accordingly, modern day acupuncture treatments often include both corporeal and auricular points.

Acupuncture needles are so thin that there is usually minimal discomfort when they penetrate the skin. The needles are advanced to varying tissue depths, depending on the location in the body, and a characteristic “de qi” feeling is elicited. The patient often describes de qi as a warmth, fullness, tingling or aching in the tissue, while the acupuncturist may sense the needle being grasped or tugged (“like a fish biting the hook”). De qi sensations have been correlated with the stimulation of A-delta fibers, followed by C-fibers and then by group 2 fibers [16–18]. Recent studies have quantified the mechanical grasping of needles and related it to deformation of subcutaneous connective tissue [19]. Such mechanically induced changes in connective tissue structure (caused by needle insertion and rotation) have been hypothesized as mechanisms by which acupuncture can affect a wide range of local and remote physiological processes [20]. It has been argued that in clinical trials in which there was questionable efficacy of acupuncture, the de qi sensation was not properly elicited and thus the failures may have been due to poor technique.

Possible mechanisms by which acupuncture reduces blood pressure in hypertensive patients include decreases in plasma renin, aldosterone and angiotensin II activity [21–24], increased excretion of sodium [25] and changes in plasma norepinephrine, serotonin and endorphin levels [26–28]. Enkephalins and β -endorphins mediate acupuncture’s effects to attenuate bradykinin-induced experimental hypertension in laboratory cats [29–31]. Some of these mechanisms are the same ones targeted by successful classes of pharmacological antihypertensive agents. As an example, angiotensin converting enzyme (ACE) inhibitors achieve their effect by inhibiting the activation of angiotensin I to its more active form. Chiu et al. [22] found lower angiotensin I levels in hypertensive patients who received acupuncture, compared with a control group of hypertensive patients who did not receive acupuncture.

A review of the literature reveals multiple published reports of the effectiveness of acupuncture on blood pressure and other hemodynamic parameters in humans [21–24,28,32–45]. There is a strong *prima facie* case for undertaking a more definitive study. The results of all studies to date, however, must be treated with caution because of serious methodological limitations: small sample sizes, lack of

randomization, inadequate or unspecified follow-up, poorly described treatment content, poorly characterized study subjects and rudimentary statistical analyses. The need exists for a rigorously designed and conducted randomized clinical trial in order to definitively evaluate the effectiveness of acupuncture for the management of hypertension.

One of the challenges in reaching definitive conclusions about the efficacy of acupuncture results from variability in acupuncture methodology, including the acupuncture points selected, duration of each treatment session, length of treatment course, intervals between treatments and form of needle stimulation (manual, thermal or electrical). Thus it is critically important that clinical trials involve reproducible standardized treatment protocols.

1.3. Potential acceptance by patients

In 1997, 41% of adults in the United States used alternative medical therapies (including acupuncture) [46], suggesting that these therapies are gaining acceptance with the general public. Surveys have demonstrated that the alternative treatments are often offered because of patient request and in the hopes of minimizing or avoiding unwanted side effects of conventional medicines [47].

2. Study organization

The SHARP trial was funded as a cooperative agreement by the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health. The New England Research Institutes (NERI) was the organizational center for the study. All clinical work was performed at the Massachusetts General Hospital (MGH). Trial activities at the MGH were divided between a Hypertension Center and an Acupuncture Center. Consultants from the New England School of Acupuncture and Wake Forest University collaborated on the design, monitoring and analysis of the trial. A data and safety monitoring board, appointed by NCCAM, provided independent monitoring of the study. See Appendix A for a complete list of investigators.

3. Treatment groups, treatment comparisons and endpoints

Patients in SHARP were randomized to one of three acupuncture treatment groups: individualized (Ind), standardized (Std) or control (Ctl) (see Fig. 1). The protocols for all three groups are based on principles of TCM acupuncture, including the control regimen, which was designed to be inactive.

The control treatment involved needling of non-acupuncture points with minimal stimulation, an “invasive sham” acupuncture procedure [48]. To maintain blinding, patients were told in the consent form only that the control treatment used points “not used to treat hypertension.” The fact that the control points were not traditional acupuncture points was not mentioned and the terms “sham” and “placebo” were not used. This language was approved by institutional review boards from the NERI and the MGH (Partners Health Care System).

The two primary treatment comparisons will test the overall effect of acupuncture [(Std+Ind) versus Ctl] and specifically whether TCM-based acupuncture that has been individually tailored to the patient has an advantage over a standardized regimen that is also based on principles of TCM [Ind versus Std].

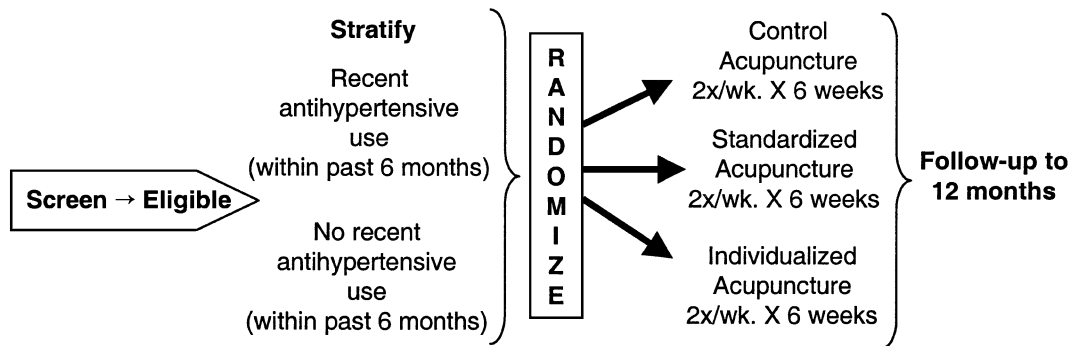


Fig. 1. Clinical trial schema.

Other treatment comparisons [Std versus Ctl, Ind versus Ctl] will be performed as secondary analyses. Treatment comparisons will be made for each of several endpoints:

- Change in SBP from baseline to 10 weeks (primary endpoint);
- Change in DBP from baseline to 10 weeks;
- Characterization of the trajectories of SBP and DBP over the entire 1-year period, including treatment group comparisons at time-points other than 10 weeks, an evaluation of how quickly any beneficial effect may begin, and how long the effect may last;
- Percentage of patients who initiate or resume conventional antihypertensives and the duration from randomization to initiation/resumption of conventional antihypertensives;
- Immediate effects (pre- versus post-acupuncture treatment) on SBP and DBP; and
- Acupuncture beliefs, masking assessment, adverse events and quality of life.

The choice of SBP rather than DBP for the primary endpoint is based on both medical and statistical arguments. Medically, SBP is more closely related to long-term cardiovascular outcomes than is DBP [49–51]. From the viewpoint of statistical efficiency, the measurement that has lower intraperson variability (higher within-person correlation) would be preferable. We estimated intraperson correlation of SBP and DBP measurements from the National Center for Health Statistics (NCHS) [52]. As part of the NCHS survey, blood pressure measurements were taken three times at a single medical exam. Age- and gender-stratified population standard deviations are reported by the NCHS for each measurement and for the average of the three measurements. Assuming the pairwise within-person correlations are equal within each stratum, these standard deviations can be used to estimate the correlations. Across age groups from 45 to 74 years, within-person correlations were higher for SBP (range 0.82–0.84) than for DBP (range 0.76–0.80), suggesting that SBP would result in a more efficient treatment comparison.

We also used data from the Pawtucket Heart Health Project [53]. In a repeated measures analysis of blood pressure measurements obtained over the course of several months, the estimated residual intraperson correlations for SBP and DBP were 0.74 and 0.67, respectively (H. Feldman, personal communication). These values are lower than the values from the NCHS, since they represent correlations between repeated measurements taken over a period of months rather than at a single sitting. However, as in the NCHS data, SBP has the higher correlation, suggesting that it would yield a more sensitive measure of treatment effect.

4. Screening and eligibility

Prospective study participants were identified through a combination of efforts including direct recruitment of patients receiving care at the Hypertension Center, brochures at the Hypertension Center and at other health clinics within and outside of the MGH, postings throughout the MGH, mass mailings, advertisements in newspapers and magazines, posters in the Boston subways and internet listings. In an effort to recruit participants through medical practitioners, an e-mail posting was sent to all physicians at the MGH and at several other major Boston-area hospitals, and presentations were made to health practitioners at several local medical facilities. Recruitment was also greatly enhanced by reports featuring the trial on local and national television news, in the Boston Globe and in other local newspapers.

The screening process involved at least three visits to the Hypertension Center over a period of weeks. For safety reasons, subjects were scheduled for blood pressure measurements during screening at intervals no greater than 14 days. Subjects could be found ineligible, or could drop out because they became uninterested in the study, at any time during screening. In particular, a stage 3 blood pressure reading at any time during screening ($SBP \geq 180$ and/or $DBP \geq 110$) excluded potential participants from entering the trial.

After a verbal introduction to the trial, prospective participants were asked several screening questions in interview format, including some eligibility criteria and minimal demographic information. This level of screening was typically done over the phone. All subsequent screening procedures took place in the Hypertension Center after providing written consent. Procedures differed depending on whether or not patients were on antihypertensive medications at the start of screening.

Following an initial blood pressure check, patients *on antihypertensive medications* were evaluated for the potential level of risk associated with stopping their medications in order to participate in the trial. This evaluation included a physical exam, clinical history, medication history, electrocardiogram (ECG) and assessment of liver function, electrolytes, fasting blood sugar, renal function, fasting lipid profile, urinalysis and a complete blood count.

Following these evaluations, patients were tapered off of antihypertensives with the goal of avoiding the risks associated with rebound hypertension. Medications were discontinued one at a time at weekly intervals in this order: diuretics, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, α adrenergic receptor antagonists, direct acting vasodilators, centrally acting agents and β adrenergic receptor blockers. Combination medications were discontinued one component at a time. Blood pressure was measured before discontinuing each successive medication (at least weekly). All medications except for β adrenergic receptor blockers and centrally acting agents were discontinued abruptly. β adrenergic receptor blockers and centrally acting agents were discontinued more gradually: 1/2 full dose for 3 consecutive days, 1/4 full dose for 3 consecutive days and 1/4 full dose every other day for two dosages. Two weeks after completion of tapering, the patient could begin the final “qualifying” sequence of blood pressure measurements (see below) and was required to repeat the ECG and laboratory tests for electrolytes, renal function, blood sugar, lipids and urinalysis. The liver function tests and complete blood count did not have to be repeated unless clinically indicated. Patients with laboratory values that were initially out of eligibility range but within range upon repeat testing were considered eligible.

Patients *not on antihypertensive medications* went through a similar screening process except they did not have to repeat the laboratory measurements or ECG. The physical exam, medical and medication

histories, lab measurements and ECG did not have to precede the qualifying sequence of blood pressure measurements.

A qualifying sequence of blood pressure measurements during screening was required for all patients. Minimum requirements consisted of three qualifying measurements satisfying $SBP \geq 140$ and < 180 mm Hg and $DBP \geq 90$ and < 110 mm Hg, and (1) at least 4 days elapsed between the first and second qualifiers, (2) no more than one nonqualifying blood pressure measurement between the first and second qualifiers, (3) at least 4 days elapsed between the second and third qualifiers, (4) no nonqualifying blood

Table 1
Eligibility criteria for the SHARP trial

Inclusion criteria

1. Patients with essential hypertension meeting blood pressure criteria outlined in the text. Briefly, this entails repeatable measurements of systolic blood pressure in the range 140 to 179 mm Hg and of diastolic blood pressure in the range 90–109 mm Hg in the absence of antihypertensive therapy.
2. Written informed consent.

Exclusion criteria

1. Secondary hypertension: e.g., renovascular disease, Cushing's disease, hyperaldosteronism.
 2. Uncontrolled diabetes mellitus: fasting blood glucose > 180 mg/dl.
 3. Other medical conditions that would preclude safe participation: e.g., endocrine disorders, thyroid disease, renal failure, anemia, hemorrhagic diathesis.
 4. Anticipating major surgery during the next 12 months.
 5. Unwilling to complete all study visits: anticipated absence of > 7 days during the first 4 weeks of acupuncture treatment; anticipated absence of > 14 days during the remainder of acupuncture unless the patient agrees to be scheduled for all 12 acupuncture treatments before their anticipated absence; only able to schedule acupuncture on consecutive days each week.
 6. Prior recent acupuncture: within the past 6 months.
 7. Unable or unwilling to taper off of all antihypertensive medications.
 8. Currently taking or probable need for treatment with the following medications during the next 12 months (chronic is defined as > 7 days continuous use): chronic bronchodilators, including inhalation therapy (bronchodilators on an as-needed basis were permitted); chronic sympathomimetic drugs (including weight reduction medications; sympathomimetic nasal sprays and oral decongestants were permitted); chronic aspirin therapy (except once-daily cardiovascular prophylaxis); nonsteroidal inflammatory drugs, including ibuprofen, naproxen, indomethacin; anticonvulsant medications; chronic dicyclomine hydrochloride; venlafaxine; immunosuppressive drugs or cytotoxic drugs within 12 months of enrollment; oral contraceptives containing estrogen (except postmenopausal hormone replacement); chronic oral corticosteroids (except topical, intraarticular, or inhaled corticosteroids or oral corticosteroids in short courses); anabolic steroids; bile acid-binding resins; chronic antipsychotic, tricyclic or tetracyclic antidepressant medications or lithium; monoamine oxidase inhibitors; bupropion hydrochloride; warfarin; ticlopidine; clopidogrel.
 9. Age: < 18 years.
 10. Pregnancy: pregnant within the past 4 months; currently pregnant; women of childbearing potential who were not using one of the following forms of birth control: abstinence, barrier methods or intrauterine device.
 11. Hemoglobin, platelet count or white blood count: clinically significant abnormalities.
 12. Serum potassium: outside the normal range.
 13. Alanine aminotransferase (SGPT): $> 1.5 \times$ upper limit of normal.
 14. Aspartate aminotransferase (SGOT): $> 1.5 \times$ upper limit of normal.
 15. Serum bilirubin: $> 1.3 \times$ upper limit of normal.
 16. Blood urea nitrogen or creatinine: clinically significant abnormalities.
 17. Protein on urine dipstick: $\geq 2+$.
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pressure measurements between the second and third qualifiers, and (5) no more than 31 days elapsed from the first to the third qualifier.

Additional assessments during screening included self-administered questionnaires to collect information on demographics, lifestyle, quality of life and acupuncture beliefs (described below). These questionnaires were completed after consent was obtained.

Eligibility criteria for the randomized trial are listed in [Table 1](#).

5. Randomization and stratification

Randomization took place at the time of the first acupuncture treatment via direct internet access to the NERI's randomization software, with a back-up system using sealed envelopes. As explained below, auricular acupuncture alternated between ears at consecutive treatment visits. To ensure that the three treatment groups were balanced with respect to which ear was treated first, the starting ear was chosen randomly at the time of randomization to acupuncture treatment group. Simultaneous randomization to the three acupuncture treatment groups and two starting ears was implemented by considering the six combinations as if they were six different treatment groups. A permuted block allocation scheme (block size 6) was used, stratified by history of antihypertensive medication history, with two strata: use versus no use of antihypertensives during the prior 6 months.

6. Acupuncture treatment

We wanted any effect of the TCM diagnostic procedure itself to be constant across the treatment groups. At the first treatment session, all patients were evaluated by a “diagnosing acupuncturist” who determined a TCM diagnosis and “prescribed” an individualized set of corporeal needling points and method of stimulation for each point. The diagnosing acupuncturists were masked to the patients' treatment group. The diagnosis and prescription were recorded on a data form and forwarded to the “treating acupuncturist,” who then followed the prescription *only* if the patient was in the individualized treatment group. Thus, two mutually exclusive sets of acupuncturists were used in the trial.

Diagnosing and treating acupuncturists were required to have a minimum of 3 years and 1 year postgraduate experience, respectively. In practice, participating diagnosing acupuncturists had 13–22 years experience, and all had received acupuncture training at colleges in the Peoples' Republic of China. Participating treating acupuncturists had 2–18 years experience. All study acupuncturists were licensed to practice in Massachusetts.

Training and certification for acupuncturists consisted of studying detailed training manuals and videotapes and attending an 8-h hands-on training session with a competency/certification exam. Continued adherence to specific protocol requirements was assured with periodic quality assurance assessments.

The diagnosing acupuncturist had access to the patient's blood pressure values and could use these data in making the prescription. The patient saw a diagnosing acupuncturist before the first treatment and for re-assessment of the TCM diagnosis and treatment prescription at the first treatment visit following

each scheduled blood pressure assessment, except not earlier than the fifth treatment. Re-assessment was allowed to mimic actual practice, where needling points might be modified in view of changing symptoms and blood pressure data.

Hypertension Center staff and diagnosing acupuncturists were masked to treatment assignment, treating acupuncturists and other Acupuncture Center staff were masked to blood pressure measurements, and patients were masked both to treatment and blood pressure values.

Measures taken to maintain masking in the Acupuncture Center included utilization of separate paper file folders (of different colors) for diagnosing and treating acupuncturists and kept in separate locked file cabinets. A copy of the diagnosis and prescription was kept in the diagnosing acupuncturist paper file so that the diagnosing acupuncturist would not see subsequent notes made by the treating acupuncturist. Blood pressure values from the Hypertension Center staff were kept in envelopes and stored in the diagnosing acupuncturist paper file so that the treating acupuncturist had no access to these data. Likewise, treatment assignment was stored only in the treating acupuncturist paper file. Participating acupuncturists were allowed to function only in one role during the study. Periodic quality assurance checks confirmed the maintenance of proper masking. Breaches of masking were reported on a standardized data collection form.

6.1. Development of acupuncture treatment protocols

All aspects of the acupuncture treatment protocols, including choice of TCM diagnostic categories and their criteria (signs and symptoms), active and sham acupuncture point choices, needling techniques and treatment schedules, were developed via consensus by the research team in consultation with a group of senior TCM acupuncturists and colleagues and in combination with reviews of the scientific literature and standard TCM textbooks.

6.2. Scheduling of acupuncture

The ideal treatment frequency and duration was twice a week for 6 weeks (total of 12 treatments), with 3 or 4 elapsed days between consecutive treatment sessions (e.g., every Monday and Thursday). The treatment period could extend to 8 weeks in order to complete as many of the sessions as possible if the ideal schedule could not be adhered to.

Patients who anticipated during screening only to be able to adhere to a schedule with consecutive day treatments each week (e.g., every Monday and Tuesday), and those who anticipated an absence of and >7 days during the first 4 weeks of acupuncture, were not eligible to enter the randomized study. Patients who anticipated an absence of and >14 days after the first 4 weeks until treatment was completed were also not eligible unless they agreed to complete the 12 treatments before their extended absence.

If a patient had to miss a week or more of acupuncture, it was considered preferable to give three treatment sessions in the weeks preceding and following the absence rather than to extend the total length of the treatment period. However, treatments on consecutive days or more than three treatment sessions in a week were prohibited.

Patients who were acutely ill on a scheduled acupuncture day were rescheduled. If there was a question about whether to cancel, the diagnosing acupuncturist was consulted. In the event of a cancellation, an adverse event report was filed to document the illness.

6.3. TCM diagnosis

Prior to the trial, five TCM diagnostic categories or patterns were identified that we thought would characterize the vast majority of patients with primary hypertension:

- Flare up of liver fire
- Liver yang rising with kidney yin deficiency
- Obstruction of phlegm and dampness
- Yin and yang deficiency
- Qi and blood deficiency leading to liver yang rising

See [Table 2](#) for signs and symptoms consistent with these TCM diagnostic categories. The diagnostician assigned a primary TCM diagnosis (and a secondary diagnosis, if appropriate). Not all signs and symptoms needed to be present for a particular diagnosis to be assigned.

The TCM diagnostician could modify the diagnosis and the recommended corporeal acupuncture points approximately every 2 weeks in view of changing symptoms and blood pressure data. Only the diagnostician was permitted to review the patient's blood pressure data. Blood pressure was not measured by the Acupuncture Center except in the event that the patient had an adverse event and the clinical management of the patient necessitated the immediate assessment of the patient's blood pressure.

6.4. Individualized acupuncture prescription - corporeal points

In order to avoid confounding by such issues as number of needling points and duration of treatment sessions, some restrictions were placed on the individualized acupuncture to try to match these features with the standardized and control groups.

The diagnosing acupuncturist could prescribe 8–12 corporeal acupuncture points, based upon the patient's primary and secondary TCM diagnoses. Most points chosen were selected from the "pool" of acupuncture points for the primary diagnostic category in [Table 3](#). See also [Fig. 2](#). The angle of insertion and depth of insertion for each point are specified in [Table 4](#). Terminology and abbreviations for corporeal acupuncture points follow Cheng [54].

All corporeal points not on the midline were prescribed bilaterally with each prescribed bilateral point counting as two points. For example, a prescription of 11 points might consist of 5 bilateral points and 1 point on the midline. The only exception was if the patient had a condition precluding needling on one side (e.g., a cast, amputated limb or other condition such as a hematoma, localized skin irritation, inflammation or infection). In these circumstances, bilateral points could be prescribed in a unilateral fashion rather than prohibited.

Diagnosing acupuncturists could select one or two acupuncture points from outside of the primary diagnostic category pool. If the patient had both a primary and secondary diagnosis, up to two needle locations could be chosen from the secondary diagnostic category pool. There was also the option of selecting one or two needle locations from outside of any of the pools. However, the total number of points could not exceed 12 with all but two coming from the primary pool. For patients with primary and secondary TCM diagnoses other than the 5 anticipated TCM diagnoses, 8–12 corporeal points could be selected from any of the 5 TCM diagnostic categories ([Table 3](#)). At most, 2 points could be from outside the pools but the total number of corporeal needles could not exceed 12.

Table 2
TCM signs and symptoms by diagnostic category

	Flare-up of liver fire	Liver yang rising with kidney yin deficiency	Obstruction of phlegm and dampness	Yin and yang deficiency	Qi and blood deficiency leading to liver yang rising
Pulse	wiry, fast	thin, wiry, fast	slippery and soggy	thin and deep	thin, choppy, slightly wiry in the liver position
Tongue	red, yellow coating, redder on the sides	red with no coating, peeled	greasy coating, swollen	red (yin xu), pale (yang xu)	pale, dry
Other primary symptoms	irritable, easily angered, frustrated, resentful, impatient, flushed face, thirsty, headaches, dizziness, bitter taste, tight neck and trapezius muscles	irritable, malar flush, dry mouth, insomnia, anxiety, night sweats, headache, dry eyes, sore and weak lower back, sore and weak knees, hot hands and feet	heavy head and/or body, muddled thinking, overweight, poor appetite, nausea, stuffy feeling in the chest and/or epigastrium, numbness in the limbs, heavy frontal headache	dizziness, shortness of breath, tinnitus, weak and sore lower back and knees, fatigued, flushed cheeks (yin), hot palms and soles (yin), aversion to cold (yang), pale face (yang), frequent nocturnal urination (yang), impotent (yang), leg edema (yang)	fatigued, sallow complexion, dizziness, insomnia and/or palpitations, blurred vision or dry eyes, no appetite, loose stools, scanty menses, amenorrhea or late periods
Secondary symptoms	constipation, dark urine, epistaxis	concentrated dark urine, dry stools, blurred vision, numbness and tremors of limbs, tinnitus			brittle nails, muscular weakness, muscle tension and twitching, floaters, dry skin and hair

Not all signs and symptoms need be present for a particular diagnostic category to be assigned.

Table 3
Pools of corporeal acupuncture needling points for each TCM diagnostic category

Flare-up of liver fire	Liver yang rising with kidney yin deficiency	Obstruction of phlegm and dampness	Yin and yang deficiency	Qi and blood deficiency leading to liver yang rising
GB 20	BL 18	BL 20	BL 23	BL 18
GB 21	BL 23	BL 64	CV 04	BL 20
GB 34	GB 20	CV 12	CV 06	BL 23
GB 43	GV 20	GB 20	GB 20	CV 04
GV 20	HT 07	GV 20	GV 04	CV 06
LI 04	KI 03	LI 04	GV 20	GB 20
LI 11	LI 04	LI 11	KI 03	GV 20
LR 02	LI 11	LR 03 ^a	LI 04	HT 07
LR 03 ^a	LR 03 ^a	PC 06	LI 11	KI 03
ST 36	SP 06	SP 06	LR 03 ^a	LI 04
ST 44	Yin Tang	ST 08	SP 06	LI 11
Tai Yang		ST 36	ST 36	LR 03 ^a
		ST 40		SP 06
				ST 36

Abbreviations of acupuncture points follow Cheng [54].

^a Option to needle toward KI 01.

Several acupuncture points felt to have little or no TCM basis in the treatment of hypertension were prohibited for safety or privacy reasons. (See Cheng [54] for point locations.) The following points were prohibited because of the small but potential risk of pneumothorax: BL 11–17, BL 41–50, GB 22–24, KI 21–27, LU 01–02, LR 14, PC 01, SP 16–21 and ST 12–18. Additional acupuncture points were prohibited because of the small but increased risk of injury to blood vessels, nerves or eyes; because of the sensitive nature of tissues around the mouth and lips; and to protect patient privacy by avoiding areas around the genitals: BL 01, BL 36, CV 01, GV 01, GV 15–16, GV 25, GV 27–28, LR 10–12, SP 12–13, ST 01–02, ST 09 and ST 30. Careful consideration was given to three additional points, BL 18–20, which were ultimately allowed. These points may be useful in treating individuals with hypertension but are located approximately 4 cm lateral to the posterior midline in the lower thoracic area and therefore present a theoretical risk of pneumothorax. Anatomically, the pleural space and lung in the area of these three points is usually over 4 cm deep and the depth of acupuncture needle insertion is less than 1 cm. Therefore, the risk of entering the pleural space is highly unlikely. However, treating acupuncturists were instructed to place the needles obliquely toward the spine and to exercise caution when needling these points.

In addition to point location, the diagnosing acupuncturist prescribed the method of stimulation (neutral or even, tonify or reinforce, disperse or reduce) for each point [54].

6.5. Individualized acupuncture prescription—auricular (ear) points

At each treatment session, the treating acupuncturist evaluated five auricular points (Liver, Heart, Shen Men, Jiang Ya Gou, Autonomic/Sympathetic; see Oleson [55], Huang [56] and Fig. 3) and determined the two that were most reactive, as indicated by heightened tenderness to applied pressure and/or increased skin conductance determined with a point detector (Pointer-Plus Locator/Stimulator,

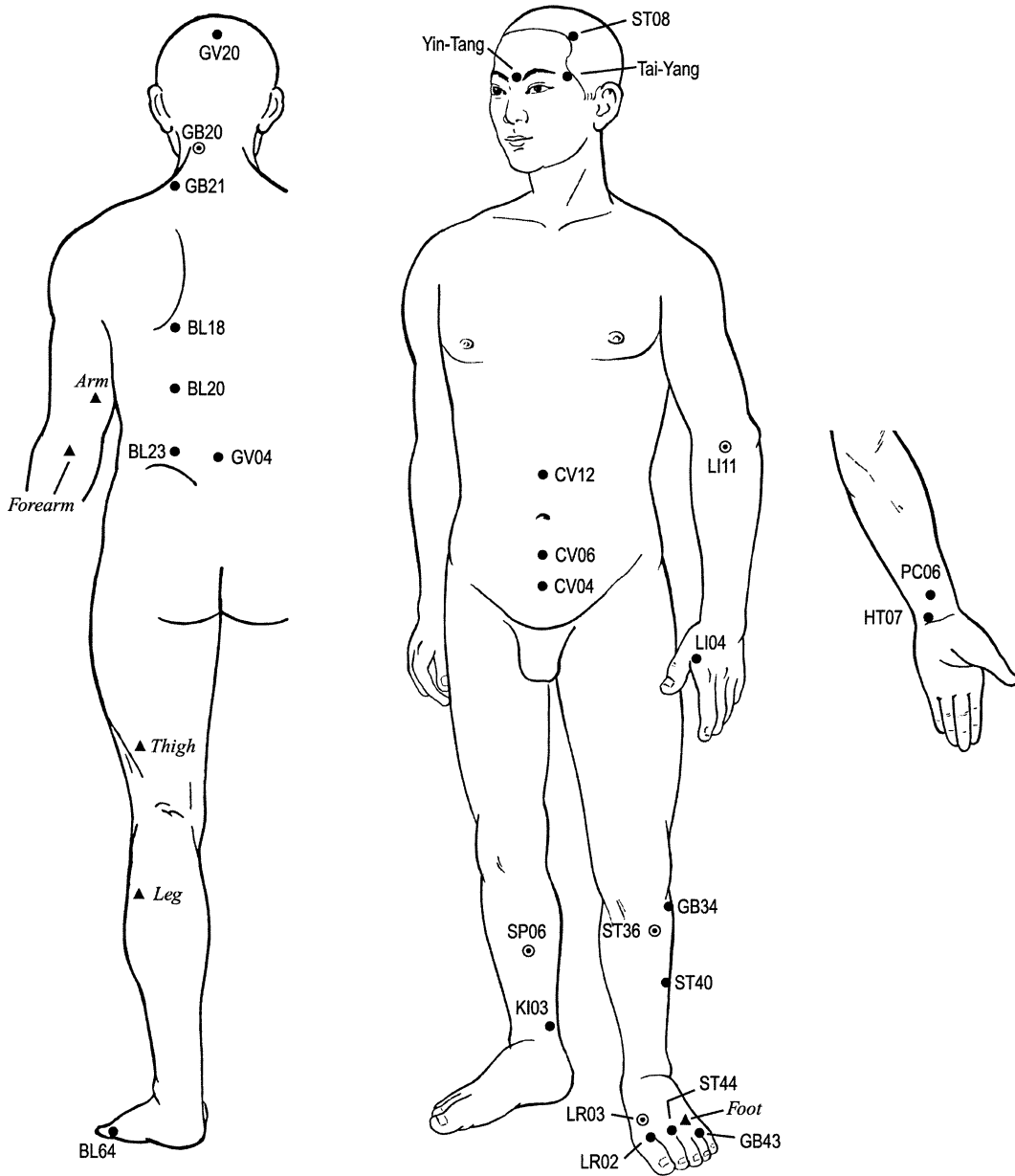


Fig. 2. Locations of corporeal acupuncture points. All points not on the midline were needed bilaterally, although only one side is shown in the figure. Control points are indicated by filled triangles, ▲, and are labeled in italics (5 bilateral locations, 10 needles total). Standardized points are indicated by bull's eyes, ⊙ (5 bilateral locations, 10 needles total). Patients in the individualized treatment group were needed in 8–12 locations selected primarily from among the individualized (filled circles, ●) and/or standardized (bull's eyes, ⊙) points, with some limited option for using other points (see text). See Cheng [54] and Table 5 for precise descriptions of anatomic locations.

Table 4

Individualized and standardized treatment group corporeal point specifications; abbreviations of acupuncture points follow Cheng [54]

Point	Name	Angle of insertion	Depth ^a (in.)
BL 18	Ganshu	oblique	0.5–0.7
BL 20	Pishu	oblique	0.5–0.7
BL 23	Shenshu	perpendicular	1.0–1.5
BL 64	Jinggu	perpendicular	0.3–0.5
CV 04	Guanyuan	perpendicular	0.8–1.2
CV 06	Qihai	perpendicular	0.8–1.2
CV 12	Zhongwan	perpendicular	0.5–1.2
GB 20 ^b	Fengchi ^b	toward tip of nose	0.5–0.8
GB 21	Jianjing	perpendicular	0.3–0.5
GB 34	Yangling–quan	perpendicular	0.8–1.2
GB 43	Xiashi	perpendicular	0.3–0.5
GV 04	Mingmen	perpendicular	0.5–1.0
GV 20	Baihui	subcutaneous	0.3–0.5
HT 07	Shenmen	perpendicular	0.3–0.5
KI 03	Taishi	perpendicular	0.3–0.5
LI 04	Hegu	perpendicular	0.5–1.0
LI 11 ^b	Quchi ^b	perpendicular	1.0–1.5
LR 02	Xingjian	oblique	0.3–0.5
LR 03 ^b	Taichong ^b	perpendicular or toward KI 01 ^c	0.3–0.5
PC 06	Neiguan	perpendicular	0.5–0.8
SP 06 ^b	Sanyinjiao ^b	perpendicular	0.5–1.0
ST 08	Touwei	subcutaneous	0.5–1.0
ST 36 ^b	Zusanli ^b	perpendicular	0.5–1.2
ST 40	Fenglong	perpendicular	0.5–1.0
ST 44	Neiting	perpendicular	0.3–0.5
	Tai Yang ^d	perpendicular	0.3–0.5
	Yin Tang ^d	subcutaneous	0.3–0.5

^a The needle selection should be long enough to reach the depth of the point. Guidelines for needle diameter and for length of needle are as follows:

Carbo					
Diameter (mm)	0.30	0.25	0.22	0.20	0.18
Length (mm)	40, 50	40, 50	25, 40, 50	15, 25, 40	13, 25
Length (in.)	1.6, 2.0	1.6, 2.0	1.0, 1.6, 2.0	0.6, 1.0, 1.6	0.5, 1.0
Seirin					
Diameter (mm)	0.30	0.25	0.20	0.18	0.16
Length (mm)	40, 50	40, 50	15, 30, 40	30, 40	15, 30
Length (in.)	1.6, 2.0	1.6, 2.0	0.6, 1.2, 1.6	1.2, 1.6	0.6, 1.2

^b Standardized acupuncture treatment group.

^c For LR 03, the TCM diagnostician had the option of prescribing either a perpendicular insertion or insertion toward KI 01. If the patient was in the standardized treatment group, a perpendicular insertion was used regardless of the acupuncture prescription.

^d Tai Yang and Yin Tang are not ordinarily referred to by a numbered abbreviation.

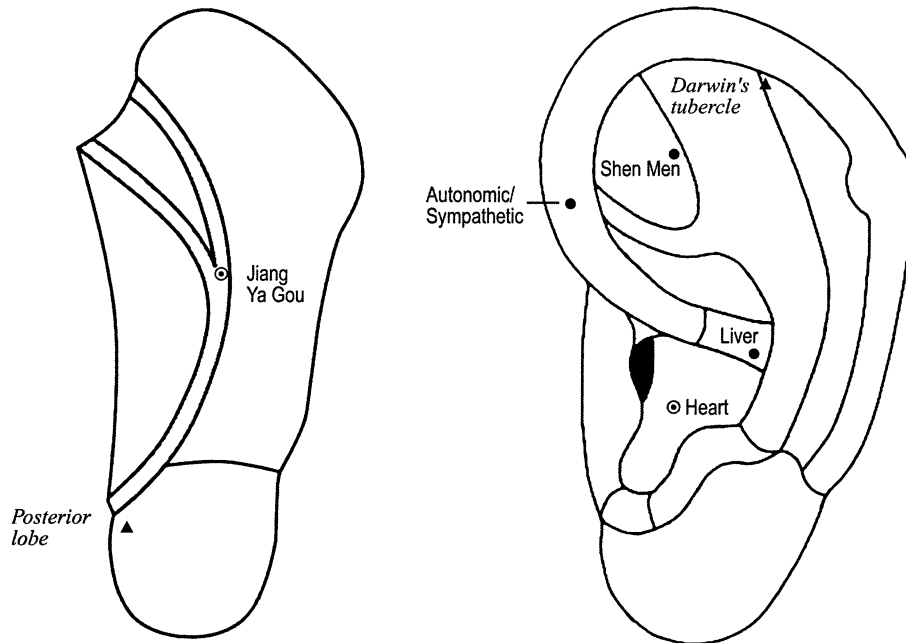


Fig. 3. Locations of auricular acupuncture points. One ear was needled during each treatment, alternating ears at consecutive visits. Control points are indicated by filled triangles, ▲, and are labeled in italics (two needles). Standardized points are indicated by bull's eyes, ⊙ (two needles). Patients in the individualized treatment group were needled in two locations selected from among the individualized (filled circles, ●) and/or standardized (bull's eyes, ⊙) points. See Oleson [55], Huang [56] and Table 5 for precise descriptions of anatomic locations.

Mayfair Medical, Hong Kong). We are not aware of reliability or validity studies of this instrument. However, it is in widespread use among practitioners of auricular acupuncture. The two most active points constituted the “prescription” for individualized auricular acupuncture.

6.6. Acupuncture needling

Patients were given an opportunity to ask the acupuncturists questions related to the placement of needles only. Discussion about the patient's blood pressure, treatment group, or the location of points was prohibited. All study acupuncture occurred in private treatment rooms. The patients removed their outer clothing including shoes and stockings. A clean sheet was provided to cover the patient and supportive rolls or pillows were used for patient comfort. The skin was cleaned with an alcohol wipe over the needling locations before the acupuncture needle was inserted. During the first acupuncture visit, the acupuncturist demonstrated the point locator on his/her own hand before using it on the patient's ear.

Two types of needles were used, needles with and without guide tubes (Seirin Kasei, Shimizu, Japan; Carbo, Suzhou, China). The choice was left up to the treating acupuncturist. All needles were sterile, disposable (one time use only), and made of surgical-grade stainless steel. Sizes utilized are shown in Table 4 (footnote a).

Patients in all three treatment groups received auricular acupuncture in two locations at every treatment session. Auricular acupuncture was unilateral at each visit, with the side alternating between

left and right ears at consecutive treatment visits. The starting ear was chosen randomly. If it was not possible to alternate ears (for example in the case of local inflammation or other irritation), the same ear was used as during the previous treatment visit.

6.6.1. *Individualized acupuncture*

The individualized acupuncture group received corporeal acupuncture treatment according to the prescription (locations and methods of stimulation) made by the diagnosing acupuncturist. If the prescription included only anterior corporeal points, the patient was needled in the supine position. Needles were retained for 30 min and stimulated according to the prescription at the time of initial insertion, and again at 10 and 20 min. If both anterior and posterior points were prescribed, anterior points were needled first (supine position) and retained for 20 min with the prescribed needle stimulation at the time of initial insertion and at 10 min. The needles were then removed and the patient placed in the prone position. The posterior points were then needled and retained for 10 min, with the prescribed needle stimulation at the time of insertion. See [Table 4](#) and [Fig. 2](#) for specific information regarding needle depth, angle of needle insertion and point locations. Auricular acupuncture locations were determined by the treating acupuncturist as described above. Auricular acupuncture needles were inserted prior to corporeal needles. All auricular points were needled unilaterally using 15 mm long, 0.20 mm diameter needles that were inserted without stimulation, perpendicular to the skin to a depth of 1–2 mm or deep enough to be engaged securely in subcutaneous tissue and retained without stimulation during the 30-min treatment period (see [Fig. 3](#)).

6.6.2. *Standardized acupuncture*

Standardized corporeal acupuncture consisted of 5 bilateral corporeal points (total of 10 points), needled in the supine position using a neutral method of stimulation (obtaining “de qi” without any further stimulation). At 10, 20 and 30 min, the acupuncturist touched each corporeal needle but did not stimulate the needles. The acupuncture points were LI 11, ST 36, GB 20, LR 03 and SP 06. See [Table 4](#) and [Fig. 2](#) for specific information regarding angle of needle insertion, depth and location of points.

Two auricular needles, Heart and Jiang Ya Gou, were inserted prior to corporeal needling, without stimulation and retained for 30 min (see [Fig. 3](#)).

6.6.3. *Control acupuncture*

Patients randomized to the control acupuncture group had 5 corporeal locations needled bilaterally (total of 10 points) and 2 auricular locations needled unilaterally at each visit. See [Table 5](#), [Figs. 2 and 3](#) for anatomic descriptions of the locations. Our main objectives in designing the control treatment were to choose non-acupuncture points we thought to be the least reactive while maintaining masking as best as possible. The following criteria guided our choices of control points:

- not be considered active according to TCM theory,
- in the same vicinity of the standardized and most commonly used individualized points,
- distant from points thought to have an effect on the cardiovascular and sympathetic nervous system,
- points on the extremities should include locations above the elbow and knee (considered to be less reactive than points below elbows and knees according to TCM qi circulation theory),
- should be needled very shallowly with no stimulation whatsoever, and
- the numbers of points should match the standardized group.

Table 5
Control treatment group point specifications^a

Point	Patient position	Anatomic landmark	Point location	Relationship to meridians
Leg	supine	head of the fibula	approximately 4 in. down the leg from the head of the fibula, then half the distance from the BL to GB channel on the posterolateral leg toward the belly of the m. gastrocnemius	between BL and GB meridians
Foot	supine	3rd and 4th metatarsals	approximately 1.0–1.5 in. above the 3rd and 4th web space between the 3rd and 4th metatarsals	near GB 41 between GB and ST meridians
Thigh	prone ^b	popliteal fossa	approximately 4 in. above the popliteal fossa, then half the distance from the BL to the GB channel on the posterolateral thigh	between BL and GB meridians
Arm	prone ^b	olecranon and medial epicondyle of the humerus	approximately 4 in. above the olecranon process and half way toward the medial epicondyle	between SI and TH meridians
Forearm	prone ^b	medial epicondyle of the humerus	extensor surface of the forearm midway between TH 9 and SI 8	between SI and TH meridians
Ear	N/A ^c	Darwin's tubercle	superior and medial to Darwin's tubercle, at the most superior portion of the scaphoid fossa, between the helix and the antihelix	in the auricular area for finger points
Ear	N/A ^c	posterior ear lobe	on the posterior earlobe, in the most superior and medial portion of the lobe; bounded superiorly by the most inferior portion of the posterior groove	no named points in this area

^a Corporeal control locations were needled bilaterally using a 25- or 30-mm long, 0.20-mm diameter needle, inserted perpendicular to the skin without stimulation. Corporeal needles were inserted to a depth sufficient to hold the needle perpendicular (approximately 6 mm). Supine points were touched by the acupuncturist at 10 min and withdrawn at 20 min. Prone points were touched at 30 min, just before withdrawal. All auricular control locations were needled unilaterally using 15-mm long, 0.20-mm diameter needles that were inserted without stimulation, perpendicular to the skin to a depth of 1–2 mm, or deep enough to be engaged securely in subcutaneous tissue. Auricular needles were retained without stimulation during the 30-min treatment period.

^b With arms flexed, palms down.

^c Not applicable (auricular needles should be in place during both supine and prone positions).

In all corporeal locations, needles were inserted perpendicular to the skin without stimulation. Supine corporeal points were touched by the acupuncturist at 10 min and withdrawn at 20 min. The patient was then turned over to lie prone and the remainder of the corporeal needles inserted. After an additional 10 min (30 min total time), the needles were touched and removed without stimulation. Auricular acupuncture needles were inserted prior to corporeal needling, without stimulation and were retained without stimulation during the 30-min treatment period.

7. Blood pressure measurement

In order to reduce “white coat hypertension,” study nurses certified by the NERI took nearly all of the study blood pressure measurements [57]. Study physicians were allowed to take blood pressures for

clinical purposes, such as when monitoring a patient tapering or resuming antihypertensive medication, but were discouraged from taking other study measurements.

Patients were asked to bare their right arms for the blood pressure measurement. If the sleeve was tight, the patient was asked to remove his or her shirt or pull the arm out of the sleeve. A gown was made available if the patient felt more comfortable using one. Pulse and blood pressure measurements were made after the patient had been seated quietly, with back supported and feet flat on the floor, in an erect but comfortable posture for at least 5 min. The patient remained seated in this fashion until all replicate blood pressure measurements were completed, waiting at least 2 min between replicate measurements.

Study measurements were made using numbered Baumanometer wall-mounted mercury sphygmomanometers (W.A. Baum and Co., Copiague, NY) that were certified annually. Once a patient completed screening, study nurses did not discuss measurements with the patient or the acupuncture staff. At each study visit, the official blood pressure measurements were completed before other measures, i.e., physical exam and completion of self-administered questionnaires. Patients who ate, smoked, ingested caffeine or exercised during the hour prior to a blood pressure measurement were asked to return after an hour had passed.

Standardized procedures were used to determine the midpoint of the upper arm, measure arm circumference at this midpoint, determine blood pressure cuff size, apply the cuff, determine peak inflation level and measure blood pressure [2]. Ordinarily, three replicate blood pressure measurements were taken at each visit, the first replicate reading dropped, and the blood pressure for that visit calculated as the average of the second and third readings. If the second and third systolic or second and third diastolic pressures differed by 6 mm Hg or more, two additional measures were taken, for a total of five, and the second through fifth measurements averaged.

Blood pressure measurement procedures were observed periodically by NERI staff, and analyses of final digit preferences for each study nurse were performed periodically throughout the trial in order to monitor compliance with the measurement protocol.

8. Antihypertensive medications

Patients with blood pressures ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic at the week 10 study visit or later were started on antihypertensive medication, ordinarily an ACE inhibitor or angiotensin receptor blocker. However, the therapy could be individualized by the study physician based on the subject's prior medication history, blood pressure response and concomitant medical problems. Antihypertensive medications were initiated immediately if the blood pressure of any randomized study subject measured ≥ 180 mm Hg systolic or ≥ 110 mm Hg diastolic. In addition, antihypertensives were initiated in the first 10 weeks following randomization if an adverse event developed that would be ameliorated by blood pressure reduction, or if two consecutive blood pressure measurements (at least 7 days apart) of $SBP \geq 170$ or $DBP \geq 105$ were detected, starting at the week 4 visit or later. Patients were seen at intervals of no greater than 2 weeks until their blood pressure fell to below 140 mm Hg systolic and 90 mm Hg diastolic. With these safeguards in place, we felt that it was ethical to withhold medications for up to 3 months (including screening) with a blood pressure above 140/90 mm Hg.

9. Adverse events

The incidence of adverse effects of acupuncture in multiple studies is low [58,59]. We monitored patients for adverse events of any kind, including possible effects of acupuncture, of remaining off of antihypertensive medications and of taking antihypertensives (for those who went back on medication). Any other unexpected medical event was also recorded. Patients were asked whether they had developed an adverse event or side effect of treatment each time their blood pressure was measured. The relationship of the adverse event to acupuncture therapy and/or antihypertensive therapy was assessed by the study physician and nurses. Serious adverse events were defined and reported according to policies of the Human Research Committees of the NERI, the MGH and the NCCAM.

10. Acupuncture beliefs

Patients' beliefs or expectations regarding the efficacy of a medical intervention can influence their treatment response [60–63]. We employed a self-administered instrument based on the “treatment credibility scale” of Borkovec and Nau [64] to assess beliefs and expectations regarding the efficacy of acupuncture for treating hypertension. Various versions of this instrument have been employed in acupuncture studies [65]. Vincent [66] found one version to have good internal consistency and test–retest reliability. The three questions employed in SHARP were: (1) How confident are you that acupuncture can control your blood pressure?; (2) How confident would you be in recommending acupuncture treatments to a friend with high blood pressure?; and (3) Does treating high blood pressure with acupuncture make sense to you? Responses were assessed using a five-point Likert scale. The instrument was administered during screening, at the week 2 visit and at the week 10 visit.

11. Assessment of masking

The success of patient masking was assessed with a self-administered instrument. Patients were asked to indicate which treatment group they thought they were randomized to, by circling one of four choices: the three treatment groups and “don't know.” If they indicated one of the three treatment groups, a second question asked how confident they were of their answer (on a 5-point Likert scale) and a list of 10 yes/no questions addressed which factors their assessment was based on. Representative factors included change (or lack of) in blood pressure and in overall well being, sensations during acupuncture, changes in use of medication, location of acupuncture points and “just guessing.” The instrument was administered at the months 4 and 12 visits, i.e., after the primary endpoint was assessed.

12. Functional health status

Functional health status was measured in SHARP participants using the SF-36, a validated self-report questionnaire that has been in wide use for more than a decade [67]. The SF-36 focuses on eight dimensions of health. Previous studies have shown that hypertensive patients score lower on the SF-36

than do normotensive patients [68–70]. In addition to general health, domains most consistently affected are those related to physical symptoms. A linear relationship has been observed between the use of antihypertensive medications and functional health status [68]. SHARP participants were asked to complete the SF-36 during screening and at the week 10 and month 12 visits.

13. Schedule of measurement

Table 6 shows the schedule of acupuncture treatments and study assessments during the randomized trial. Scheduling of acupuncture is described above. Blood pressure was measured every 2 weeks until the week 10 visit, then at months 4, 6, 9 and 12. More frequent blood pressure measurements were made as clinically indicated. Comprehensive patient evaluations were performed at the week 10 and month 12 visits.

The target dates for all visits were measured from the first day of acupuncture. Visit windows were established around the target dates for each visit. For visits through week 10, each window extended from 6 days prior to 7 days after the target date. For later visits, each window extended from 1 month prior to 1 month after the target date.

14. Statistical considerations

A minimum sample size of 180 randomized patients was established on an ad hoc basis for this pilot study. Although not designed to evaluate efficacy definitively, it is useful to project the magnitude of treatment effects that this and larger sample sizes would be able to detect with high probability.

Table 6
Schedule of treatment and study assessments

	Screening	Week								Month				
		1	2	3	4	5	6	8	10	4	6	9	12 ^a	
Acupuncture treatment ^b		X	X	X	X	X	X							
Blood pressure	X		X ^c		X		X ^c	X	X	X	X	X	X	X
Acupuncture beliefs	X		X						X					
Lifestyle	X								X					X
Quality of life	X								X					X
Masking assessment										X				X
Physical exam	X								X					X
Clinical/medication history	X								X					X
Laboratory values ^d	X								X		X			X
Electrocardiogram	X								X					X

^a If the patient dropped out of the study prior to month 12, the month 12 assessments were to be completed at the time of dropout.

^b Ideally, twice per week for 6 weeks. However, if this could not be adhered to, treatment could extend to 8 weeks in order to complete as many as possible of 12 acupuncture treatments.

^c At weeks 2 and 6: both a standard (pre-acupuncture) and post-acupuncture blood pressure were measured.

^d Laboratory assessment included complete blood count, urinalysis, creatinine, blood urea nitrogen, electrolytes, fasting blood sugar and lipid profiles.

With three treatment groups, there are two degrees of freedom for treatment comparisons. Denoting Ctl=control, Std=standardized and Ind=individualized, the following two orthogonal contrasts were prespecified as being of primary importance:

- Ctl versus (Std+Ind): control versus active (standardized and individualized combined),
- Std versus Ind: standardized versus individualized.

The power calculations are based on the change in blood pressure from baseline to week 10. An estimate of the standard deviation of the change in blood pressure is required to perform the calculations. We used baseline and 3-month blood pressure measurements from over 4000 patients in the Medical Research Council (MRC) hypertension trial for older patients [71] to provide these estimates (S. Pocock, personal communication). After removing the treatment effects and adjusting for baseline values by analysis of covariance, the patient-to-patient standard deviations of change in SBP and DBP were 16.6 and 9.8 mm Hg, respectively. Table 7 shows the expected differences in blood pressure change that would be detected with 85% power, using an analysis adjusted for baseline value and a two-sided $\alpha=0.05$ test.

Table 7 illustrates that the pilot trial will only have high statistical power if there are fairly large treatment effects, for example if the expected SBP reduction with active acupuncture is 8.53 mm Hg greater than with control acupuncture. A total sample size of 900 would provide good power if this treatment difference is 3.82 mm Hg.

The primary efficacy analysis will compare treatment groups with respect to blood pressure change from baseline to 10 weeks. All randomized patients with available outcome data will be included in this analysis and patients will be classified according to their original treatment assignment, according to the intention-to-treat principle [72]. The simplest comparison is with a two-sample t test. We expect the distribution of change scores to be approximately normally distributed. However, nonparametric analysis will be used to check robustness of the conclusions. Further analyses, adjusting for baseline covariates (including baseline blood pressure) will use analysis of covariance.

Table 7
Treatment group difference (δ , mm Hg) detectable with 85% power

	Total sample size				
	180	360	540	720	900
<i>Systolic blood pressure</i>					
Ctl versus (Std+Ind)	8.53	6.03	4.93	4.27	3.81
Std versus Ind	9.98	6.97	5.69	4.93	4.41
<i>Diastolic blood pressure</i>					
Ctl versus (Std+Ind)	5.04	3.56	2.91	2.52	2.25
Std versus Ind	5.87	4.11	3.36	2.91	2.60

Ctl=control, Std=standardized, Ind=individualized. We assumed standard deviations for systolic blood pressure and diastolic blood pressure, adjusted for baseline value, of 16.6 and 9.8 mm Hg, respectively, and loss of 15% of endpoint data due to patient dropout and loss to follow-up. For example, with 180 patients, and assuming 15% missing data (153 evaluable patients), if patients receiving TCM-based acupuncture (Std+Ind) have an expected 8.53 mm Hg greater decline in systolic blood pressure than patients receiving control acupuncture, there will be an 85% chance of declaring this treatment contrast significant using a two-sided $\alpha=0.05$ test.

In addition to exploratory and graphical methods, mixed effects models [73] will be used to model the trajectory of blood pressure over time. These models can include nonlinear trajectories, interaction terms between time and treatment to allow different trajectories for the different treatment groups, baseline covariates to adjust for patient characteristics and time-varying covariates, for example to model the effects of introducing conventional medications. The goal is to describe the blood pressure trajectory over time while adjusting appropriately for fixed and time-varying covariates and for intrasubject correlation.

A potential problem that may be induced by the introduction of conventional medical treatment is the possibility that the effects of treatment on blood pressure could mask an effect of acupuncture. For example, if the standardized and individualized acupuncture treatments truly do control blood pressure better than the control acupuncture treatment, but more patients in the control group go on conventional therapy, which itself lowers blood pressure, we could observe no difference between the groups. One approach is to carry the last measurement taken before conventional therapy forward to subsequent visits. Another approach to be explored is outlined by White et al. [74]. Briefly, an assumption is made that, if patients on conventional treatments were not treated, their blood pressures would be above the group median. The median is then used as a measure of location (rather than the more conventional measure, the mean) and analyzed with statistical methods, which are invariant to the shape of the distribution above the median, for example quantile regression [75].

The number of patients who start antihypertensive medications over time will be tabulated. Particular attention will focus on the percentage of patients who meet protocol criteria for resuming antihypertensive medications before or at the week 10 visit. In addition, time-to-event methods will be used to describe the percentage who start medications over time.

Exploratory subgroup analyses will include treatment comparisons within subgroups formed from baseline characteristics such as TCM diagnostic group, antihypertensive medication history and gender.

15. Screening experience

Screening began in March 2001 and ended in July 2002. Initial contact was documented for 1442 prospective participants of which 995 (69%) underwent the formal screening interview, 424 (29%) gave informed consent and 192 (13%) were ultimately randomized.

Prospective participants were asked how they heard about the study. A recruitment source was obtained for 87%. Among these, the reported sources were print media (35%; mostly advertisements and an article in the local press), mailings (28%; mostly from a postcard mass-mailing campaign), television news reports about the study (14%), medical practitioner (11%; 8% from the SHARP Hypertension Center physician's practice and 3% from other practices), posted advertisements and flyers (6%), word of mouth (6%) and other sources (4%). These percentages add to and >100% because 4% reported more than one source.

Of the 1442 potential participants contacted, 1018 (71%) were excluded during initial screening (29% self-reported a trial exclusion criterion, 37% uninterested, 5% closed out without additional screening when recruitment goals were completed) and 424 (29%) provided written informed consent (14% subsequently excluded based on trial eligibility criteria, 2% withdrew for lack of interest, 13% randomized). Among all those uninterested in the trial, 33% either gave no specific reason, did not return phone calls, or did not show up for in-person screening visits. The most common other exclusion

reasons were the time commitment for trial participation (26%) and not wanting to discontinue antihypertensive medications (22%).

We investigated whether particular recruitment sources were associated with different screening outcomes. Patients of the Hypertension Center physician were the most likely to be randomized (32%). Television news reports also had a high yield (26% randomized). The lowest yields were among respondents to mass mailings (8%) and print media (11%). Respondents were least likely to exclude themselves due to the time commitment if they heard about the study from a medical practitioner and most likely to exclude themselves for this reason if they heard about the study from television or mass mailings. Other exclusion reasons were fairly constant across the different recruitment sources.

Among patients who provided informed consent, those on antihypertensive medications at the start of screening required an average of 4.7 screening visits to the Hypertension Center over a median of 32 days. Patients not on antihypertensive medications completed screening faster (average 3.0 visits over a median of 15 days).

16. Discussion

As patient interest in and use of complementary and alternative medicine (CAM) increases, the need to demonstrate efficacy and safety of these practices also increases. Inadequate research thus far is due in part to “a lack of adequate or accepted research methodology” [76]. A particular challenge in this realm is achieving the proper balance between rigorous scientific evaluation of a treatment and adherence to the essence and fundamental principles underlying the CAM treatment. This notion of balance was a priority in the design of the SHARP trial. The methodology utilized research principles and methods typically used to evaluate allopathic treatments (e.g., randomization, blinding, standardization of the acupuncture “experience” across the three treatment groups and use of a control group) aiming to ensure ample control and scientifically meaningful results. At the same time, attention was devoted to upholding fundamental principles of TCM (e.g., TCM diagnoses and diagnosing acupuncturists’ discretion in prescribing points and methods of stimulation for individualized treatment). We hope that our methodology can be adapted for use in other trials.

It has been difficult to extrapolate clinical generalizations from previously published case reports and series because there has been inconsistency in terms of number and location of points treated, needling techniques used, and duration and frequency of treatments [77]. Indeed, this is a limitation that plagues most of acupuncture research. The SHARP study explores two commonly used techniques, individualized therapy and standardized therapy, both based on the principles of TCM. The protocol was developed with the collaboration of acupuncture clinicians and theorists and allows for individualized clinical decision making within some constraints, while still allowing for valid comparisons between groups.

In the United States, the general standard of acupuncture practice is to treat patients twice weekly during the early phases of treatment. Needle insertion time generally ranges from 15 to 30 min. For treating hypertension, the research team decided (based on published hypertension studies and input from a team of experienced acupuncturists in the Boston area) that the 30-min sessions twice weekly for 6 weeks would be a reasonable time, frequency and length to observe any potential therapeutic benefits.

This schedule would also minimize the demands placed on the subjects' schedules, thereby facilitating recruitment.

The protocol required the involvement of two separate types of acupuncturists, diagnosing acupuncturists (masked to treatment arm) and treating acupuncturists (masked to blood pressure responses). Obviously, two acupuncturists working in these separate roles would not ordinarily be used in clinical practice, but were needed to maintain the masking constraints of this controlled trial. Although several procedures had to be developed to protect the "separateness" of the two groups of acupuncturists, the logistics proved to be quite manageable and the process was not objectionable to study patients.

We used an invasive sham control treatment that involved needling of non-acupuncture points with minimal stimulation. Other invasive sham interventions include needling of acupuncture points that are not expected to affect the clinical problem at hand and needling relevant acupuncture points but at shallower depths and/or with limited stimulation [48,65,78]. Others have argued that control conditions in acupuncture trials should not involve penetration of the skin, referred to as non- or minimally invasive sham acupuncture [48]. Special retractable needles have been developed for research purposes with the goal of delivering a control while keeping the patient blinded [79,80]. Other approaches have included pressing with a fingernail [81] or toothpick [82,83] and tapping with the rigid plastic "guide tube" that is often used to facilitate insertion of acupuncture needles [84].

We felt that using less invasive or noninvasive control conditions could introduce confounding into the design. For example, if skin penetration alone is efficacious and our control treatment did not involve penetration, we would not be able to distinguish the effect of penetration from any effect of TCM-based acupuncture. Therefore, our choice of an invasive sham acupuncture control is a relatively conservative one. It includes the nonspecific physiological effects associated with actual penetration of the skin, with its attendant psychological reactions, but uses anatomical locations that are not active according to TCM principles. We are limited in our ability to study nonspecific effects and other psychosocial components associated with "placebo" effects [63]. Rigorous investigation of the placebo response would have required a more complex trial design with multiple control groups.

We also did not think that a conventional pharmacologic therapy control group would have addressed the aims of our study. If acupuncture has an effect relative to the sham control, it might then be appropriate to compare acupuncture with medication in a subsequent trial.

Recruitment and screening for the trial proved to be a challenge. Although many potential participants were very motivated, the time commitment and the requirement of discontinuing medications were deterrents for some. The time commitment was more of a barrier for those who heard about the study from television news reports or mass mailings. It was less of an issue for patients referred by a medical practitioner, but the vast majority of these patients were already a part of the MGH "system" and this familiarity with the study site may have been influential. In addition to acting as a deterrent to recruitment, the requirement that participants be off of antihypertensive medications at the start of the randomized trial also made screening considerably more difficult. A fifth of potential participants who dropped out of screening for lack of interest did so because they did not want to discontinue medications. Among those who consented for full screening, the median time to screen patients on medications was twice as long, and required 57% more screening visits, than for those not on medications.

In summary, this report describes a carefully planned pilot randomized clinical trial evaluating TCM-based acupuncture for the control of hypertension. One of our aims in designing the SHARP trial was to address methodologic flaws in previous trials. We present an approach necessitating the close and coordinated efforts of a multidisciplinary team. We also document details of the acupuncture treatments and controls, with rationales, so that the results can be interpreted and replicated. The adherence to strict methodological techniques and the maintenance of traditional acupuncture precepts are combined to provide a model for future evaluations of complementary and alternative therapies.

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Appendix A. Study organization

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