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Stress Management Versus Lifestyle Modification on Systolic Hypertension and Medication Elimination: A Randomized Trial

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ABSTRACT

Isolated systolic hypertension is common in the elderly, but decreasing systolic blood pressure (SBP) without lowering diastolic blood pressure (DBP) remains a therapeutic challenge. Although stress management training, in particular eliciting the relaxation response, reduces essential hypertension its efficacy in treating isolated systolic hypertension has not been evaluated. We conducted a double-blind, randomized trial comparing 8 weeks of stress management, specifically relaxation response training (61 patients), versus lifestyle modification (control, 61 patients). Inclusion criteria were ≥55 years, SBP 140–159 mm Hg, DBP <90 mm Hg, and at least two antihypertensive medications. The primary outcome measure was change in SBP after 8 weeks. Patients who achieved SBP <140 mm Hg and ≥5 mm Hg reduction in SBP were eligible for 8 additional weeks of training with supervised medication elimination. SBP decreased 9.4 (standard deviation [SD] 11.4) and 8.8 (SD 13.0) mm Hg in relaxation response and control groups, respectively (both ps < 0.0001) without group difference ($p = 0.75$). DBP decreased 1.5 (SD 6.2) and 2.4 (SD 6.9) mm Hg ($p = 0.05$ and 0.01, respectively) without group difference ($p = 0.48$). Forty-four (44) in the relaxation response group and 36 in the control group were eligible for supervised antihypertensive medication elimination. After controlling for differences in characteristics at the start of medication elimination, patients in the relaxation response group were more likely to successfully eliminate an antihypertensive medication (odds ratio 4.3, 95% confidence interval 1.2–15.9, $p = 0.03$). Although both groups had similar reductions in SBP, significantly more participants in the relaxation response group eliminated an antihypertensive medication while maintaining adequate blood pressure control.

INTRODUCTION

The prevalence of hypertension in the elderly (aged 65 and over) increased from 44% in 1993–1995 to 55% in 2001–2003—an increase of 6 million elderly over this 11-year period.[1,2] Total annual medical expenditures attributed to hypertension (including co-morbidities) are estimated to range from $108–110 billion dollars.[3] Because systolic blood pressure (SBP) tends to increase while diastolic blood pressure (DBP) tends to decrease after age 60,[4] 65%–75%

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of elderly hypertensive patients have isolated systolic hypertension (SH). SH is defined as SBP greater than 140 mm Hg and DBP less than 90 mm Hg.[5] In this age group, the economic impact of SH is projected to affect 10 million Americans[6] and will continue to be a significant public health problem in the 21st century.[4]

In the elderly, SH is a more important risk factor for cardiovascular disease than elevated DBP or hyperlipidemia.[7] While numerous therapies treat hypertension, effectively reducing SBP in the elderly with SH remains a therapeutic challenge.[8,9] Many antihypertensive treatments cause side-effects such as dizziness, headache, fatigue, chest discomfort/cough, and sexual dysfunction, prompting some patients to discontinue therapy.[10,11] Since 40% of the elderly in the United States take five or more medications daily, they are also at greater risk for side-effects and drug–drug interactions.[12]

Safe and effective nonpharmacologic approaches to treat SH are of interest and public health importance.[9] Stress management techniques that elicit the relaxation response (RR)[13] are safe and effective for treating essential hypertension,[14–17] but have not been studied in an SH patient population. The RR is a coordinated physiologic response characterized by decreases in volumetric oxygen consumption ($\dot{V}O_2$),[13,18,19] heart and respiration rates,[13,18] responsivity to norepinephrine,[20] and elimination of carbon dioxide[18] and increases in exhaled nitric oxide.[19] It is considered the counterpart of the fight-or-flight response. The RR is not a technique. Rather it is elicited by scores of techniques that result in everyday thinking being suspended. This is often achieved by the repetition of a word, sound, prayer, phrase, or muscular activity and the disregard of routine thoughts when they occur through a return to the repetitions. Techniques that bring forth the RR have been practiced for millennia and include, in part, meditation, prayer, yoga, *t'ai chi, qigong*, the presuggestive stage of hypnosis, and autogenic training.[13,18,19] Since these effects are likely to be beneficial for the treatment of SH, we conducted a double-blind, randomized controlled trial to determine whether 8 weeks of training in eliciting the RR versus 8 weeks of lifestyle modification (control group) would reduce SBP in elderly patients with SH. The secondary objective of the trial was to determine whether the dose of one or more antihypertensive medications could safely be eliminated in patients who reduced their SBP.

MATERIALS AND METHODS

Study design

This 20-week randomized trial involved patients aged 55 and older with SH (Fig. 1).[9] The Committee for Clinical Investigations, Beth Israel Deaconess Medical Center (BIDMC), Boston, MA and the Institutional Review Board at the Massachusetts General Hospital (MGH), Boston, MA approved the study protocol and all amendments. The study was registered at clinicaltrials.gov (NCT00179543).

Patients were recruited from hospital clinics (MGH and BIDMC) and by brochures, newspaper advertisements, and Internet postings. Potentially eligible individuals were screened for the study if they were at least 55 years of age,

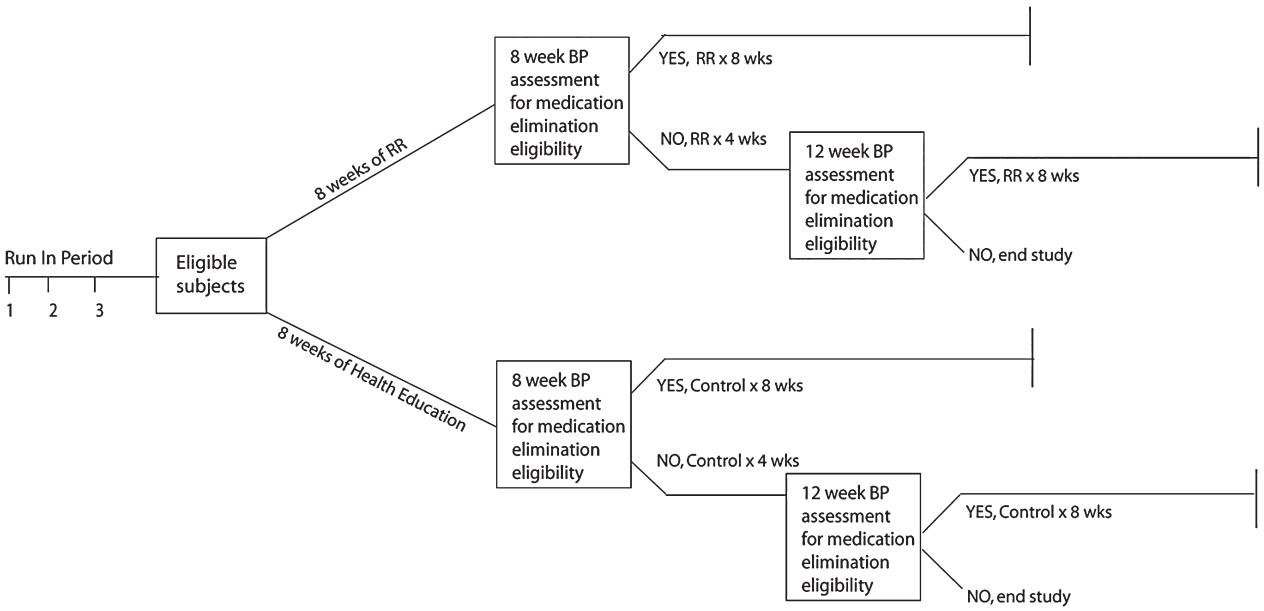

FIG. 1. Flow chart depicting subject participation. The phases of the study are presented. RR, relaxation response; SBP, systolic blood pressure.

had a SBP of 140–159 mm Hg, a DBP <90 mm Hg, while on two antihypertensive medications. They were ineligible if the dose of any antihypertensive medication had been changed within the 4 weeks prior to screening; if they had a major medical illness in the previous 6 months (heart, kidney or liver disease, stroke, cancer, endocrinopathy, or psychiatric illness); if they had an abnormal laboratory test; if they currently smoked; or if they previously practiced any mind/body techniques. The potentially eligible individuals started a "run-in" period of three consecutive weekly visits to establish the presence of SH and verify whether antihypertensive medications had been changed. Participants were seated for 5 minutes and blood pressure was measured using a certified, manual, wall-mounted mercury sphygmomanometer (W.A. Baum and Co., Copiague, NY) with an appropriately sized arm cuff; the first and fifth Korotkoff sounds denoted SBP and DBP, respectively.[21] During each of these run-in visits, the study nurse (BB) obtained at least three blood pressure measurements while the patient remained seated, waiting at least 2 minutes between measurements. If the SBP or DBP varied by more than 8 mm Hg, additional measurements were taken until the values were within this range. The average of the closest three measurements was used to determine final eligibility for the study, and the average blood pressure obtained during the final run-in visit was used as the baseline value. The same study nurse (BB) made all of the blood pressure measurements and used a questionnaire to assess the presence/absence of adverse events during all blood pressure assessment visits.

A randomization list, without stratification, using an allocation ratio of 1:1 and permuted blocks of 2 and 4 patients per block, was generated by Dr. Patricia Hibberd prior to study enrollment. Only therapists providing the RR or lifestyle modification training accessed this list. Eligible patients were randomized to either group after successful completion of the run-in period.

After 8 weeks of training, patients returned for blood pressure measurements using the same procedures as described above. The study nurse (BB) measuring blood pressure was blinded to the study treatment. The 8-week outcome for blood pressure was the average of the closest three blood pressure measurements. This blood pressure was used to determine eligibility for the medication elimination protocol (Fig. 1). Participants were eligible to participate in the supervised medication elimination protocol if their SBP was <140 mm Hg, DBP was <90 mm Hg, there had been a reduction of ≥5 mm Hg from baseline SBP, and there had been no change in their antihypertensive regimen during the 8 weeks. Those who did not meet criteria at week 8 were eligible to continue their assigned treatment and were reevaluated using the same criteria at week 12.

Patients who were eligible for medication elimination had the dose of one antihypertensive medication reduced by half (or a clinically appropriate amount) by the blinded study physician (RMZ) and had their blood pressure checked after 4 weeks. If the SBP remained <140 mm Hg and DBP remained <90 mm Hg, then the medication dose was again reduced by a clinically appropriate amount or eliminated. If the SBP increased above 140 mm Hg or DBP above 90 mm Hg, the original dosage was resumed. The final three blood pressure measurements were taken 8 weeks after each participant started the medication elimination protocol. The average of these three measurements was considered the final blood pressure value. Patients were classified as successfully eliminating one antihypertensive medication if their SBP did not exceed 140 mm Hg after eliminating at least one medication.

The trial was double blinded; patients were informed that two different "stress management" training programs were being compared. All personnel measuring blood pressure and prescribing medication changes were also blinded to group assignment. Therapists providing training in the RR or lifestyle modification were not involved in assessment of study outcomes.

Study intervention and compliance

To ensure equivalent time and attention, all patients attended 60-minute individual training sessions for 8 consecutive weeks according to a standard research protocol [19] and listened to a 20-minute audiotape at home every day. As a measure of compliance, patients recorded the amount of time spent listening to audiotapes in a daily diary, and these diaries were reviewed with their therapist each week.

Relaxation response group

At each weekly RR session, trainers provided 15 minutes of instruction in approaches that elicit the relaxation response—diaphragmatic breathing, guided body scan, repetition of a self-chosen word, and mindfulness meditation. Participants were led through a scripted 20-minute guided relaxation response elicitation, and in the remaining 25 minutes they received health information about cardiac risk factors, stress and hypertension, and mind/body approaches for coping with stress. Patients in the RR group were asked to listen to the same 20-minute relaxation response audiotape daily.

Lifestyle modification control group

At each weekly control session, participants received 60 minutes of written and verbal information about the stress response and its impact on health, identification of cardiac risk factors, role of stress in hypertension, and specific guidelines and recommendations for sodium restriction, weight reduction, and improving diet and exercise habits.[5] Throughout the course of the trial, patients in the control group were asked to listen to a series of different 20-minute lifestyle modification audiotapes daily.

Statistical analysis

Based on other similar studies evaluating the effect of mind–body interventions on SBP reduction and taking into account the possible dropouts, we used a moderate effect size of 0.55 for determining the study sample size. With a sample of 61 patients per group, we had 85% power to detect a moderate effect size of 0.55 using a two-sample *t*-test with two-sided type I error of 0.05.

Baseline characteristics of the two groups were compared using two-sided *t*-tests for continuous variables and χ^2 or Fisher Exact tests for categorical variables. Metabolic syndrome, one of the baseline characteristics, was determined using the International Diabetes Federation definition with the exception that obesity was defined as body mass index $\geq$30 kg/m^2.[22] Similarly, we compared the characteristics of the eligible patients in the two groups at their time of entry into the supervised medication elimination protocol. The primary outcome was change in SBP from baseline to 8 weeks in the two treatment groups, and this was compared using a two-group *t*-test. This primary comparison was assessed using intent-to-treat (ITT) principles. As in a comparable trial,[23] missing data were imputed using the last-observation-carried-forward (LOCF) method. Results were reported

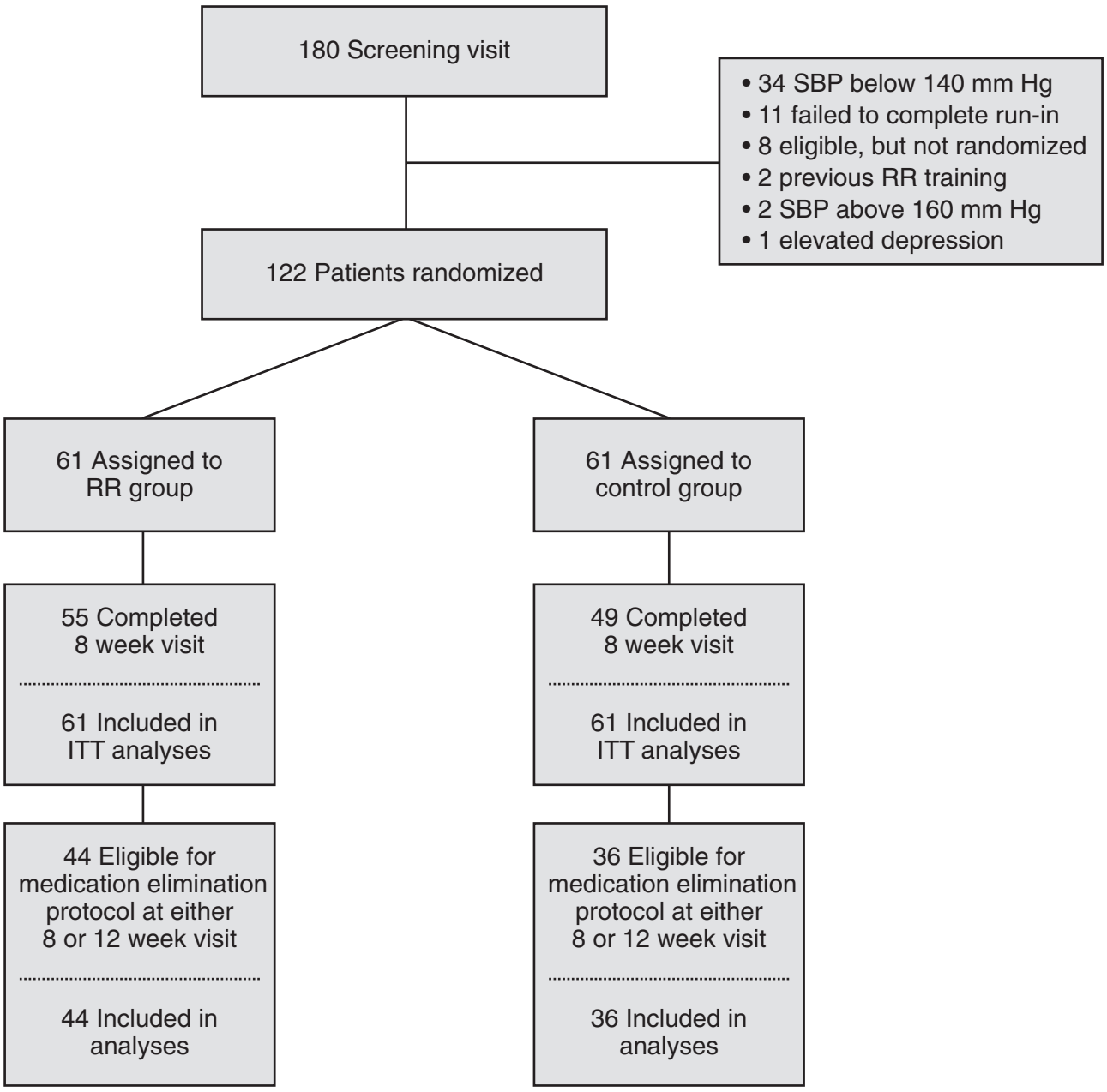

FIG. 2. Flow of participants through the study.

both with imputed data and without imputed data (completers only). We also estimated the statistical significance of the change in SBP over the 8 weeks within each group using a paired *t*-test.

We used a Pearson χ^2 test to compare the proportion of patients in each group who successfully eliminated at least one antihypertensive medication. We then estimated the odds ratio (OR) of successful medication elimination for the relaxation response versus control groups controlling for differences in characteristics at the start of the medication elimination protocol and SBP decrease using a logistic regression model. Missing data were imputed as failed to successfully eliminate at least one antihypertensive medication for the ITT analysis. Data were also analyzed for completers only as a sensitivity analysis. The Statistical Analysis System (SAS) version 9.1 (SAS, Cary, NC) was used for analyses.

RESULTS

Participants

The first patient was randomized in August 2001 and the last participant completed the study in May 2005. Of 180 individuals screened, 58 were excluded—36 did not meet the eligibility criteria for SBP, 11 failed to complete the run-in, 8 declined to participate after completing the run-in period, 2 had prior experience with mind/body approaches, and 1 person had moderate depression on the Beck Depression Inventory (Fig. 2). The remaining 122, randomly assigned to the RR or control group (61 per group), had similar baseline SBP (146.2 versus 145.3 mm Hg) and DBP (77.3 versus 77.6 mm Hg). Other characteristics were well matched in the two groups, except the RR patients were taking more antihypertensive medications, were nearly 5.5 kg heavier than the control group, had higher serum creatinine, and a higher proportion met criteria for metabolic syndrome (Table 1).

SBP and DBP after 8 weeks

Eighteen patients did not complete the 8-week visit (6 in the RR group and 12 in the control group). Completers (n = 104) and noncompleters (n = 18) had similar baseline characteristics including SBP (146.8 versus 145.6 mm Hg, $p = 0.34$), DBP (79.7 versus 77.1 mm Hg, $p = 0.17$). Based on the ITT analysis with LOCF for these 18 patients, the decrease in SBP at 8 weeks was 9.4 (standard deviation [SD] 11.4) and 8.8 (SD 13.0) mm Hg for RR and control, respectively (both $p < 0.0001$) and no group difference ($p = 0.75$; Fig. 3). Similarly, patients in both RR and control groups had modest changes in DBP between baseline and 8 weeks (−1.5 [SD 6.2] and −2.4 [SD 6.9] mm Hg, $p = 0.05$

Table 1. Baseline Characteristics of 122 Randomized Participants

Characteristics	*RR group (N = 61)*	*Control group (N = 61)*
Age, y	66.6 ± 6.9	67.0 ± 7.6
Female, *n* (%)	30 (49)	37 (61)
Race *n* (%)		
White	55 (90)	51 (84)
African-American	4 (7)	6 (10)
Other	2 (3)	4 (6)
Blood pressure at baseline, mm Hg		
Systolic	146.3 ± 5.5	145.3 ± 4.7
Diastolic	77.3 ± 7.1	77.6 ± 7.8
No. of blood pressure medications at baseline* *n* (%)		
2	29 (48)	43 (70)
2+	32 (52)	18 (30)
Blood pressure at baseline, *n* (%)		
β-Blocker	36 (59)	31 (51)
Angiotensin-converting-enzyme inhibitor	31 (51)	26 (43)
Diuretics	41 (67)	33 (54)
Calcium channel blockers	27 (44)	22 (36)
Angiotensin II receptor antagonist	17 (28)	23 (38)
Other	7 (12)	10 (16)
Statins, *n* (%)	18 (30)	12 (20)
Metabolic syndrome**, *n* (%)	33 (54)	17 (28)
Weight, kg	82.4 ± 18.3	77.1 ± 18.3
Creatinine* mg/dL	1.05 ± 0.31	0.96 ± 0.20

Values are mean ± standard deviation or no. (%) of subjects, *$p < 0.05$; **$p < 0.01$.
RR, relaxation response.

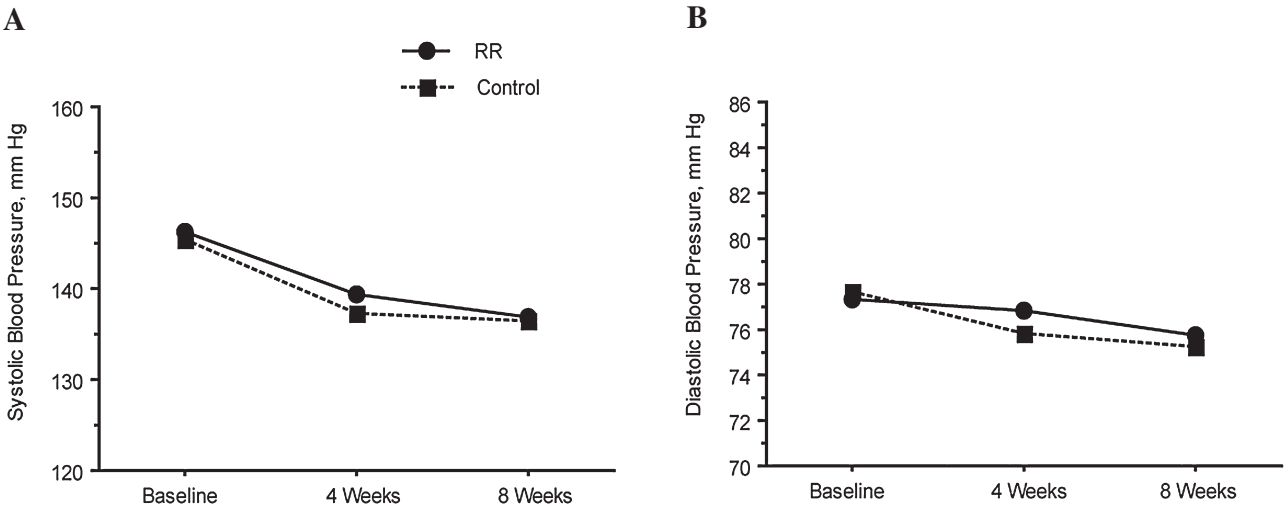

FIG. 3. The effect of relaxation response (RR) on systolic and diastolic blood pressure. The mean systolic (**A**) and diastolic (**B**) blood pressures are shown for the RR and lifestyle modification control groups at baseline, 4-week, and 8-week visits.

and 0.01, respectively) with no group difference ($p = 0.48$). The sensitivity analysis using patients who completed the protocol achieved almost identical results: change in SBP was −10.2 (SD 11.6) and −9.4 (SD 13.9) and change in DBP was −1.6 (SD 6.5) and −2.6 (SD 7.3) in the RR and control groups, respectively.

Both RR and control groups had minimal weight loss over the 8-week intervention averaging 0.65 (SD 3.50) and 0.33 (SD 2.07) kg, respectively. Weight loss was not correlated with 8-week reductions in SBP or DBP (both $p > 0.05$).

Antihypertensive medication elimination

Sixty-six percent (66%) ((44+36)/122) of all study patients were eligible for medication elimination protocol based on whether their 8-week or 12-week SBP was below 140 mm Hg and had decreased by at least 5 mm Hg from baseline. Specifically, 44 participants in the RR group (34 after 8 weeks and 10 after 12 weeks) and 36 participants in the control group (33 at 8-week visit and 3 at 12-week visit) were eligible for supervised antihypertensive medication elimination. Characteristics were well balanced between the two groups except that a higher proportion of RR patients had metabolic syndrome, higher serum creatinine, and were taking more antihypertensive medications (Table 2).

Based on the ITT analysis, 14 (32%) in the RR group versus 5 (14%) in the control group were able to maintain their SBP ≤140 mm Hg while one or more antihypertensive medications was eliminated. After controlling for the differences in characteristics at the start of the medication elimination

Table 2. Characteristics of 80 Participants in Medication Elimination Protocol

Characteristics	*RR group (N = 44)*	*Control group (N = 36)*
Age, y	65.9 ± 7.0	67.1 ± 7.7
Female, *n* (%)	21 (48)	22 (61)
No. of blood pressure medications at baseline* *n* (%)		
2 medications	22 (50)	29 (81)
2+ medications	22 (50)	7 (19)
Blood pressure at baseline, mm Hg		
Systolic	145.6 ± 5.2	144.5 ± 3.6
Diastolic	77.6 ± 7.1	77.7 ± 8.1
Statins, *n* (%)	15 (34)	9 (25)
Metabolic syndrome**, *n* (%)	27 (61)	11 (31)
Creatinine* mg/dL	1.03 ± 0.28	0.93 ± 0.17
Blood pressure change from baseline to start of medication elimination protocol, mm Hg		
Systolic	−16.7 ± 7.9	−16.7 ± 7.4
Diastolic	−4.2 ± 6.2	−5.2 ± 6.0

Values are mean ± standard deviation or no. (%) of subjects, *$p < 0.05$; **$p < 0.01$.
RR, relaxation response.

protocol (number of antihypertensive medications at the start of the protocol, presence of metabolic syndrome, and serum creatinine), and reduction in SBP from baseline, patients in the RR group were more likely to successfully eliminate one or more antihypertensive medications (OR 4.3, 95% confidence interval [CI] 1.2–15.9, $p = 0.03$). The results of the sensitivity analysis in the 60 completers in the medication elimination protocol achieved similar conclusions (OR 3.8, 95% CI 0.95–14.9; $p = 0.06$). Figure 4 identifies the antihypertensive medications eliminated by medication class and group.

Compliance. The daily average that the RR group listened to their assigned audiotapes was 924 seconds (15.4 minutes, SD 7.6) and 852 seconds (14.2 minutes, SD 8.9) for the control group with no group difference ($p = 0.42$).

Adverse events. Two (2) serious adverse events occurred during the entire study (diagnosis of lung cancer and chest tightness/dizziness), both in the control group and both considered unlikely to be related to participation in the study. Eighteen (18) patients in the RR group and 14 in the control group had minor adverse events (mostly respiratory infections and pain), all but an episode of back pain in a RR group patient were considered unlikely related to the study.

DISCUSSION

In this randomized trial, we found that 8 weeks of stress management training (via elicitation of the RR) and lifestyle modification resulted in SBP reduction of more than 9 mm Hg in elderly patients with SH. This result has clinical impact since reduction in SBP of 5 mm Hg reduces mortality by 7%[5] and risk of stroke by 30%.[7] Our observed SBP reduction was larger than exhibited in two previous studies of stress management or RR on essential hypertension in middle-aged patients,[14,17] but equivalent to published study of older essential hypertensives.[16] Our results are comparable to the 11.8 mm Hg reduction in SBP reported in a substudy of SH patients provided with the 8-week Dietary Approaches to Stop Hypertension (DASH) diet.[24] To our knowledge, the present study and the DASH trial[24] are the only nonpharmacologic interventions that consistently and significantly reduce SBP in "hard-to-treat" elderly adults with SH. We recognize that our study patients had a mean age of 67 years (versus 72 and 70 years in two recent studies of elderly patients with SH,[25,26] but since 36 subjects (30%) were aged 70–79 and 5 (4%) were aged over 80, our results are likely generalizable to these "hard-to-treat" elderly with SH. Both groups reduced their SBP by a similar and larger amount than we had anticipated. We realize that we had insufficient statistical power to detect a difference in the observed reductions in SBP, between treatment groups, but we did not calculate "*post-hoc*" power, because the observed differences between groups would not be clinically significant. However, it is noteworthy that about two thirds of the study subjects responded to nonpharmacologic therapy.

An important but secondary result occurred in the 80 (66%) participants who reduced their SBP to ≤140 mm Hg and by at least 5 mm Hg from baseline, which enabled them to participate in the supervised medication elimination protocol. A higher proportion of patients were able to successfully eliminate at least one antihypertensive medication in the RR group than in the control group; medication elimination was safe in both groups. Potential implications of this

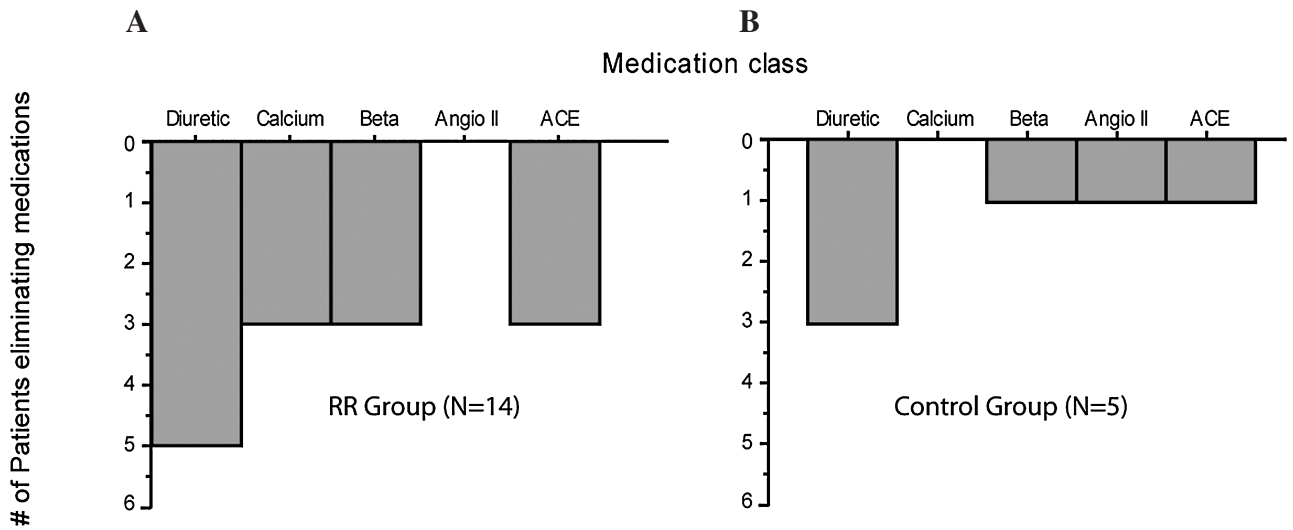

FIG. 4. Outcome of medication elimination protocol. The number of participants in the relaxation response (RR) group (**A**) and control group (**B**) able to eliminate specific classes of antihypertensive medications. Calcium, calcium-channel blocker Beta, β-blocker; Angio II, angiotensin II receptor antagonist; ACE, angiotensin-converting-enzyme inhibitor. Note: 1 subject in the control group was able to eliminate both an ACE inhibitor and a diuretic.

result include improved control of SH, decreased costs of treatment of SH, fewer side-effects, and increased patient adherence to antihypertensive therapy. There was imbalance between treatment groups in the number of antihypertensive medications that subjects were taking at baseline, raising the concern that it might have been easier for patients on three medications to eliminate one medication than those on two medications. We attempted to control for this imbalance using logistic regression when we compared the likelihood of medication elimination between the two study groups. Importantly, there was no evidence that number of medications independently predicted ability to eliminate antihypertensive medications.

A major strength of our study is that it utilized a double-blind design in which the assessment of outcomes and dose modifications were made by a nurse and physician, respectively, each blinded to group assignment. We were concerned about the possibility that the study physician and nurse measuring and evaluating the systolic blood pressure might have been unblinded to treatment assignment, so in addition to the above, we also counseled subjects to avoid discussion of their treatment with these personnel. We also conducted site visits to evaluate whether subjects were informing the study nurse and physician about their treatment assignment, and this did not occur. Furthermore, subjects were blind to the study hypothesis and were not explicitly aware of their treatment assignment in relation to the chance that it might reduce SBP. To reduce bias in analysis, the study blind was only broken after the final data set was cleaned and frozen for analysis. This rigor adds credibility to the result that patients in the RR significantly reduced their SBP and were more likely to successfully eliminate antihypertensive medications. The results in our control group are also in line with other interventions, lending weight to the validity of the conclusions.

We hypothesize that the larger than expected reduction of SBP in both treatment groups might have been due to the support provided to study subjects, possibly through improved compliance with study regimens. The similar magnitude in reduction in SBP in both groups may be the effect of the intervention, the fact that participants spent identical amounts of time with study staff, and the prescribed time spent listening to study audiotapes. Since all patients were informed that the study was comparing two different stress management programs, the two groups likely had similar expectations for improvement. At the end of the study, participants were asked whether they thought that they had been assigned to the active experimental or control group; 50% in the RR group correctly identified that they were in the experimental group, whereas 62% in the control group correctly identified that they were in the control group ($p = 0.43$). The mechanisms by which the reduction in SBP occurred are likely to be different in the two groups. Since the lifestyle modification control group received considerable information on blood pressure–reducing recommendations of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VII (e.g., sodium and weight reduction, increased exercise, and enhanced nutrition), changes in SBP were presumably due, at least in part, to modifications in diet and exercise.[5] Hypertensive patients have endothelial dysfunction and low plasma levels of nitric oxide (NO) metabolites.[27] Since RR elicitation is associated with increased NO in healthy subjects,[19] we hypothesize that in the current study RR elicitation may have increased endothelial NO production resulting in vascular dilatation[28] and reduced SBP. Furthermore, since four of the five classes of antihypertensive drugs (except diuretics) increase NO availability,[29] this could explain how RR group participants were more successful than controls in eliminating antihypertensive medications. It is possible that NO increases resulting from relaxation response elicitation might substitute for NO production stimulated by antihypertensive medications. Despite much theoretical support for the role of NO in treatment of hypertension,[28,29] there are no studies evaluating the therapeutic role of endogenous NO in older adults with SH.

Despite promising results, our study has several limitations. First, participants were on different combinations of antihypertensive medications, with differential effects on the ability to reduce or eliminate blood pressure medication. It was not possible to standardize the particular antihypertensive medication to be withdrawn as that depended on the initial dosage and side-effects. Future investigations of this approach to BP reduction and diminishing dependence on drug therapy might address the question of whether the RR takes the place of any particular class of antihypertensive therapy. For example, are agents that have central nervous system–dependent mechanisms of activity (i.e., β-adrenergic-blocking drugs, or clonidine) more easily replaced by RR-responsive patients, or are peripheral-acting drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers) that may have a vasodilator effect mediated by nitric oxide more likely to be replaced by a technique working through a NO-mediated mechanism? As expected, since decisions about medication elimination were conducted in a blinded fashion, there was no difference in the types of medications targeted for medication reduction. Second, we recognize that the dose–response effect on SBP is not the same for all medications, even for those in the same class. However, there was no evidence of systematic bias in those patients targeted for elimination in this blinded trial. Third, our trial may not have been long enough to establish the durability of the RR training in lowering SBP and eliminating antihypertensive drug therapy. Future studies should include monitoring for a longer period of time. Fourth, there was no monitoring of lifestyle modifications that may explain changes in SBP or ability to eliminate antihypertensive medications in both groups. However, weight loss was minimal across both groups and was not correlated with 8-week blood pressure

reductions. Fifth, the authors recognize that the sample size was limited and had insufficient power to evaluate other potential predictors of responsiveness to the RR intervention. Sixth, since this trial did not include a "no-treatment" control group, it was not possible to determine whether the approximately 9 mm Hg SBP reduction would have occurred regardless of treatment assignment. It was not intended to evaluate nontherapy or neglect of the BP elevation in these patients. The patients had systolic BP elevations above acceptable levels, they were older, and thus at risk for atherothrombotic vascular events. Ethically, nontherapy was not an acceptable treatment alternative. Finally, this study was not specifically designed to address whether the treatments enabled subjects to eliminate antihypertensive medications, because that was not the primary outcome of the study. The authors recognize that the subjects who participated in the medication elimination portion of the study could be a biased subset.

Pharmacologic studies of stage 1 SH indicate that patients treated with placebo have reductions ranging from 2.0[30] to 3.4[31] mm Hg in SBP over 8 weeks. Studies of aerobic exercise versus normal sedentary activity report a modest (~4 mm Hg) reduction in SBP,[32] and in the DASH trial[24] of conventional versus fruit/vegetable diets, patients achieved an average of 0.6 mm Hg and 3.8 mm Hg reduction in DBP and SBP reduction, respectively. Thus, the reduction in SBP achieved by both groups in this trial was greater than that reported in studies of usual care (or placebo) and other therapeutic approaches to SH. The final limitation of the study was the observed difference between groups in three baseline characteristics. Strict procedures were followed during the randomization process and on review of the quality control procedures, no errors were found, nor were there any errors in consecutive assignment of study subjects. The authors conclude that baseline differences were due to chance.

In summary, 8 weeks of RR training and lifestyle modification reduced SBP by ~9 mm Hg in elderly patients with SH, but patients receiving RR training were more likely to eliminate at least one antihypertensive medication. Additional studies are needed to evaluate whether medication elimination can be safely sustained through practice of the RR and whether this approach results in decreases in morbidity and mortality in the elderly with SH.

CONCLUSIONS

The prevalence of hypertension worldwide is substantial and is increasing markedly, in concert with the aging population. Recent estimates suggest that 1 billion persons are hypertensive and that this number will grow to 1.5 billion by the year 2025.[33] Yet, only 30% of patients with hypertension are controlled using current modest targets as a measure of success.[34] If blood pressure targets are reduced, as they currently are for diabetic patients, for the entire population, the number of patients classified as hypertensive will soar beyond current estimates and the percentage of patients whose blood pressure is adequately controlled will drop significantly. The solution to this dilemma is not more widespread prescription of antihypertensive pharmacologic therapy. The treatment of prehypertension is feasible, but expensive and likely to elicit side-effect/adverse events in many patients.[35] A side-effect-free treatment strategy such as the RR offers an as yet untapped opportunity to meet these goals. If our findings in SH can be extended to other patient populations, the benefits in preventing vascular events as well as the cost savings in decreased drug dependence are incalculable.

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REFERENCES

1. NHANES III Data Files. Online document at: www.cdc.gov/nchs/about/major/nhanes/nh3data.htm Accessed August 10, 2007.
2. NHANES 2003-2004. Online document at: www.cdc.gov/nchs/about/major/nhanes/nhanes2003-2004/nhanes03_04.htm Accessed August 10, 2007.
3. Hodgson TA, Cai L. Medical care expenditures for hypertension, its complications, and its comorbidities. Med Care 2001; 39:599–615.
4. Franklin SS, Gustin WT, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. Circulation 1997;96:308–315.
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. JAMA 2003;289:2560–2572.
6. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305–313.
7. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of outcome trials. Lancet 2000;355:865–872.
8. Nuesch R, Schroeder K, Dieterle T, et al. Relation between insufficient response to antihypertensive treatment and poor

compliance with treatment: A prospective case-control study. BMJ 2001;323:142–146.
9. Franklin SS, Jacobs MJ, Wong ND, et al. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: Analysis based on National Health and Nutrition Examination Survey (NHANES) III. Hypertension 2001;37:869–974.
10. Ross SD, Akhras KS, Zhang S, et al. Discontinuation of antihypertensive drugs due to adverse events: A systematic review and meta-analysis. Pharmacotherapy 2001;21:940–953.
11. Chen K, Chiou CF, Plauschinat CA, et al. Patient satisfaction with antihypertensive therapy. J Hum Hypertens 2005;19:793–799.
12. Gurwitz JH. Polypharmacy: A new paradigm for quality drug therapy in the elderly? Arch Intern Med 2004;164:1957–1959.
13. Beary JF, Benson H. A simple psychophysiologic technique which elicits the hypometabolic changes of the relaxation response. Psychosom Med 1974;36:115–120.
14. Benson H, Rosner BA, Marzetta BR, et al. Decreased blood-pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response. Lancet 1974;1: 289–291.
15. Leserman J, Stuart E, Mamish M, et al. Nonpharmacologic intervention for hypertension: Long term follow up. J Cardiopulmonary Rehabil 1989;9:316–324.
16. Schneider RH, Staggers F, Alexander CN, et al. A randomised controlled trial of stress reduction for hypertension in older African Americans. Hypertension 1995;26:820–827.
17. Schneider RH, Alexander CN, Staggers F, et al. A randomized controlled trial of stress reduction in African Americans treated for hypertension for over one year. Am J Hypertens 2005;18:88–98.
18. Wallace RK, Benson H, Wilson AF. A wakeful hypometabolic physiologic state. Am J Physiol 1971;221:795–799.
19. Dusek JA, Chang BH, Zaki J, et al. Association between oxygen consumption and nitric oxide production during the relaxation response. Med Sci Monit 2006;12:CR1–CR10.
20. Hoffman JW, Benson H, Arns PA, et al. Reduced sympathetic nervous system responsivity associated with the relaxation response. Science 1982;215:190–192.
21. Kalish LA, Buczynski B, Connell P, et al. Stop Hypertension with the Acupuncture Research Program (SHARP): Clinical trial design and screening results. Control Clin Trials 2004;25: 76–103.
22. Shaw LJ, Berman DS, Hendel RC, et al. Cardiovascular disease risk stratification with stress single-photon emission computed tomography technetium-99m tetrofosmin imaging in patients with the metabolic syndrome and diabetes mellitus. Am J Cardiol 2006;97:1538–1544.
23. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. JAMA 2003; 289:2083–2093.
24. Moore TJ, Conlin PR, Ard J, et al. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. Hypertension 2001;38:155–158.
25. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255–3264.
26. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension: The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997;350:757–764.
27. Forte P, Copland M, Smith LM, et al. Basal nitric oxide synthesis in essential hypertension. Lancet 1997;349:837–842.
28. Vita JA. Nitric oxide-dependent vasodilation in human subjects. Methods Enzymol 2002;359:186–200.
29. Napoli C, Ignarro LJ. Nitric oxide-releasing drugs. Annu Rev Pharmacol Toxicol 2003;43:97–123.
30. Black HR, Elliott WJ, Weber MA, et al. One-year study of felodipine or placebo for stage 1 isolated systolic hypertension. Hypertension 2001;38:1118–1123.
31. Grimm RH Jr., Black H, Rowen R, et al. Amlodipine versus chlorthalidone versus placebo in the treatment of stage I isolated systolic hypertension. Am J Hypertens 2002;15:31–36.
32. Ferrier KE, Waddell TK, Gatzka CD, et al. Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. Hypertension 2001;38:222–226.
33. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: Analysis of worldwide data. Lancet 2005; 365:217–223.
34. Prevalence of actions to control high blood pressure—20 states, 2005. MMWR Morb Mortal Wkly Rep 2007;56:420–423.
35. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 2006;354:1685–1697.

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