Nondrug Interventions for Treatment of Hypertension

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The treatment of hypertension is no longer limited to the simple prescription of pharmaceuticals. For many patients, maximal medical therapy is insufficient to adequately treat refractory hypertension. In addition, some patients may prefer to explore therapies that do not involve drugs as an initial step. Utilizing our broadening understanding of the physiology of hypertension, new technology and interventions have been developed that allow for treatments that do not rely on medications. In addition, dietary supplements and modification, as well as herbal supplements, may be useful under the right circumstances. Lifestyle modification remains a necessary part of treatment for all patients with hypertension. This article will review the evidence behind some available nondrug interventions for the treatment of hypertension. *J Clin Hypertens (Greenwich).* 2011;13:829–835. ©2011 Wiley Periodicals, Inc.

The treatment of hypertension is no longer limited to the simple prescription of pharmaceuticals. For many patients, maximal medical therapy is insufficient to adequately treat refractory hypertension. In addition, some patients may prefer to explore therapies that do not involve drugs as an initial step. Utilizing our broadening understanding of the physiology of hypertension, new technology and interventions have been developed that allow for treatments that do not rely on medications. In addition, dietary supplements and modification, as well as herbal supplements, may be useful under the right circumstances. Of course, lifestyle modification remains a necessary part of treatment for all patients with hypertension. This article will review the evidence behind some available nondrug interventions for the treatment of hypertension.

LIFESTYLE MODIFICATION

Despite the abundance of pharmaceutical options for the treatment of hypertension, lifestyle modification remains an important approach in management. This is reflected by the inclusion of lifestyle and dietary modification in the approach recommended by the American Heart Association (AHA).[1] The benefit of exercise, salt restriction, the Dietary Approaches to Stop Hypertension (DASH) diet, and weight reduction has been well established. The DASH diet emphasizes fruits and vegetables and is high in fiber and low in fats. The DASH diet was found to lower systolic blood pressure (SBP) by 5.5 mm Hg in all patients. The effect was more pronounced in patients with hypertension, lowering the SBP by an average of 11.4 mm Hg.[2] Reducing salt intake in combination with the DASH diet appears to lower blood pressure (BP) further.[3] The addition of a regimented exercise routine and weight loss counseling reduced SBP by 3.7 mm Hg—the effect was more pronounced if added to the DASH diet.[4] Thus, the current AHA guidelines recommend the low-salt DASH diet in combination with an exercise and weight loss regimen universally for patients with hypertension.[1]

Limiting alcohol intake has also demonstrated improvement in BP control. Those who drink $\geq$3 glasses of alcohol per day have a higher incidence of hypertension.[5] The effect increases as the alcohol intake increases.[6] Reducing alcohol intake lowers BP.[7] Again, the effect appears to be related to the degree of reduction. It should be noted that a moderate alcohol intake appears to have a cardioprotective role, decreasing the incidence of myocardial infarction[8] and mortality.[9]

The relationship of smoking and hypertension is somewhat less clear. Cigarette smoking has an acute vasoconstrictive effect.[10] Those who smoke >15 cigarettes per day have a higher incidence of hypertension,[11] although there are conflicting data on whether smoking, in general, chronically raises BP.[12–14] Irrespective of the relationship of smoking with hypertension, all patients with hypertension should be counseled to quit smoking due to the excess cardiovascular risk associated with smoking.

DIETARY SUPPLEMENTS

Potassium

Diets low in potassium cause a rise in systemic BP. Conversely, it appears that potassium supplementation causes a decrease in SBP on an order of magnitude of 3 mm Hg to 12 mm Hg.[15–17] While the mechanism of this effect is not clear, it may be the result of a correction of a disturbance in norepinephrine-mediated vasoconstriction occurring in the setting of relative

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hypokalemia.[18] In addition, there is a demonstrated protective effect of potassium on the cardiovascular damage induced by salt-sensitive hypertension,[19] postulated to be due to antioxidant effects of potassium.[20] There is evidence that an increase in dietary potassium may carry similar benefit to supplementation.[16]

Calcium

Calcium supplementation causes a mild decrease in BP from vascular relaxation due to a paradoxical decrease in intracellular calcium. In one study, a 1500-mg daily dose of oral calcium caused a nonsignificant reduction of 1.7 mm Hg[21] in SBP. Benefits seen with calcium supplementation may be more pronounced in patients with a low baseline dietary intake of calcium.[22]

Vitamin D

Patients with hypertension are more likely than controls to have diminished levels of vitamin D.[23] Vitamin D supplementation causes a decrease in SBP of approximately 2.4 mm Hg, with no apparent effect on diastolic BP (DBP).[24] Low levels of vitamin D may stimulate smooth muscle proliferation and renin production, resulting in abnormal BP homeostasis.

Folate

Low dietary intake of folate has been associated with elevations in BP.[25] Women with an increased dietary or supplement-based intake of folate have been shown to have a lower incidence of hypertension.[26] Although prospective data are limited, a small study showed a 4-mm Hg drop in nocturnal SBP with high-dose folate supplementation.[27]

Coenzyme Q10

Coenzyme Q10, a mitochondrial enzyme involved in energy production and an antioxidant, may have a role in hypertension. Patients with hypertension tend to have lower levels of Coenzyme Q10.[28] Treatment with Coenzyme Q10 supplements was shown to reduce SBP by 16 mm Hg in a meta-analysis of randomized controlled trials.[29] The mechanism of action is not well established but may be related to its antioxidant effects.

Fish Oil

Numerous studies have shown a small but significant decrease in BP in patients taking high-dose fish oil supplements, with a 2- to 3-mm Hg decrease in SBP.[30–32] Various mechanisms have been postulated, including a resultant large-vessel dilatation after integration of fatty acids into membrane phospholipids.

Garlic

Garlic extract may decrease BP. Several studies have shown a 10- to 16-mm Hg decline in SBP in patients taking garlic extract.[33,34] However, study design and blinding may have been suboptimal,[35] so the efficacy of garlic remains at question.

Fruits and Vegetables

As mentioned previously, the DASH diet, which combines a relative increase in fruits and vegetables with a reduction in saturated and total fats, lowers BP. As part of the initial DASH trial, the group assigned to a fruit- and vegetable-rich diet alone showed a modest reduction in SBP of 2.8 mm Hg.[2] As mentioned previously, the greatest benefit was derived with a low-sodium, fruit- and vegetable-rich, and low-fat diet.[3]

Soy Protein

Some of the beneficial effects of a diet high in fruits and vegetables may be due to a relative decrease in the intake of animal protein. However, the addition of vegetable protein appears to have a beneficial effect on BP. The addition of soy protein has been studied, and a supplement of 40 g daily has been seen to cause a statistically significant decrease in SBP of 7.8 mm Hg.[36] While the mechanism is not well established, this may be due to high concentrations of the amino acid arginine, which is a nitric oxide precursor. Soy protein may also decrease plasma glucose concentration and decrease insulin resistance, which may be a risk factor for development of hypertension.

Flavonoids

Flavonoids are compounds found in high concentrations in tea, cocoa, wine, and grapes. These substances appear to have beneficial effects via nitric oxide–mediated vascular dilation.[37] Diets high in cocoa appear to lower SBP by 3 mm Hg to 5 mm Hg.[38,39] However, tea did not seem to show a benefit in pooled analysis.[38]

Vegetarian Diet

A vegetarian diet may result in lower BP although the mechanism is unclear. Patients randomized to a vegetarian diet demonstrated a reduction in SBP of 5 mm Hg.[40] Whether this effect is due to an increase in intake of substances present in the diet, an increase in dietary fiber, or a reduction in animal protein is not clear.

High-Fiber Diet

Numerous studies have evaluated diets high in fiber and fiber supplementation and their effects on BP. Several meta-analyses have shown a very mild 1-mm Hg to 2-mm Hg decrease in SBP in patients ingesting a high-fiber diet.[41,42] The benefit seems to be most pronounced in older patients and patients who are hypertensive at baseline.

HERBAL/ALTERNATIVE APPROACHES

Hawthorn

Hawthorn (*Crataegus laevigata*) is a tree, the extract from which has been used for reducing BP. Two studies showed a trend towards lower BP, which was not statistically significant.[43,44]

Coleus forskohlii

Coleus forskohlii, or forskolin, is an Indian plant that appears to have a vasodilatory and positive inotropic effect in animal models. While this extract has not been well evaluated in terms of effects on BP, it was effective in lowering cardiac filling pressures in patients with congestive heart failure.[45]

Mistletoe

Mistletoe, or viscum album, extracts have been used in traditional Chinese medicine to treat hypertension.[46] While no placebo-controlled trials have been performed, animal models have shown a reduction in BP with mistletoe extract.[47] Of note, mistletoe may be toxic at high concentrations.

Rauwolfia

Rauwolfia is a genus of evergreen trees and shrubs found mainly in tropical regions. This extract was previously widely used in the 1950s and does have a hypotensive effect.[48] Rauwolfia can have pronounced side effects, including restlessness, insomnia, dyspnea, and weight gain.

Acupuncture

Acupuncture has been proposed for treatment of hypertension. Studies have been mixed and quite heterogeneous in terms of population and methods. While there is no conclusive evidence that acupuncture lowers BP, several studies have shown a lower BP with acupuncture vs placebo in patients also prescribed antihypertensive medications.[49,50]

Meditation

As with acupuncture, studies regarding meditation's effects on BP have been fairly heterogeneous. In a meta-analysis, transcendental meditation appeared to lower SBP by 4.7 mm Hg.[51] Other techniques that may show benefit include Zen Buddhist meditation and Qi Gong.[52]

Supplements That May Increase BP

In the evaluation of a patient with hypertension, it is important to identify factors that may exacerbate hypertension. Several herbal remedies may cause an increase in BP, including St John's wort, ephedra/ma huang, yohimbine, and licorice.[53,54] St John's wort may also interfere with the metabolism of other medications, including calcium channel blockers.

DEVICES

Numerous devices have been developed to provide an alternative or supplemental approach to treating hypertension. Several devices involve an invasive approach, while others use technology that requires the patient to participate in various exercises.

Implantable Baroreflex Stimulator: Rheos

The Rheos device (CVRx Inc, Minneapolis, MN) is an implantable system that consists of leads implanted around the carotid sinus which connect to a generator. The device uses the baroreflex pathways in the carotid sinus. Typically, a rise in SBP or blood volume causes vascular stretch.[55] This is detected by baroreflex receptors in the carotid sinus and elsewhere that signal the nucleus tractus solitarius in the medulla, via the glossopharyngeal and vagus nerves. This, in turn, causes inhibition of central sympathetic nuclei and activation of parasympathetic nuclei. The physiologic result is a decrease in vascular tone, heart rate, and cardiac contractility. There are also renal effects, with a resulting diuresis and decreased renin excretion.[56] These effects lead to a fall in BP.

The Rheos system delivers electrical impulses to the carotid sinus baroreceptors, stimulating them and mimicking a high pressure/volume state. The baroreflex cascade is initiated, resulting in a decrease in vascular tone and a drop in BP. The device is implanted under general anesthesia, with the leads tunneled subcutaneously into the space surrounding the carotid sinus. After implantation, the device-stimulation parameters can be adjusted. The device has been evaluated in patients with resistant hypertension. In an early efficacy study of 10 patients, there was a reduction in SBP of 22 mm Hg and DBP of 18 mm Hg.[57] The implantation of the system was well tolerated with no adverse events related to the device. The mean surgical time of implantation was 198 minutes.[58] These results were reproduced in a European sampling of 45 patients, with some having a sustained reduction in BP after 2 years.[59] Recently, the Rheos Pivotal Trial[60] demonstrated that 54% of patients with the device had a $\geq$10-mm Hg reduction in SBP at 6 months and 88% had a sustained response at 12 months. In addition, there were significantly decreased short- and long-term adverse events in patients with the system. A total of 81% of patients were found to be "responders" to the Rheos system, with an average SBP decrease in these patients of 44 mm Hg at 12 months. Patients with the device also demonstrated a decline in left ventricular hypertrophy at 1 year. The system was generally well tolerated, although some short-term surgical complications were noted. These included a 4.4% rate of permanent nerve injury, a 4.8% rate of transient nerve injury, and a 4.4% rate of general surgical complications, of which 86% completely resolved. A second-generation system with a miniaturized carotid sinus lead may decrease the rate of adverse surgical outcomes.

Renal Sympathetic Denervation: Symplicity Catheter

There is a suggestion that hypertension in chronic kidney disease may be driven by sympathetic overactivity originating from renal afferent pathways.[61–63] The central mechanism appears to stem from a reflex mechanism to preserve renal perfusion in a chronic ischemic state.[64]

The Symplicity catheter (Ardien, Inc, Mountain View, CA) system is designed to ablate these sympathetic renal pathways. It is inserted percutaneously

through the femoral artery and into the renal arteries and radiofrequency pulses are delivered at several points throughout the renal arteries. The overactive sympathetic pathways are disrupted, resulting in a decrease in the inappropriately elevated sympathetic tone and a decrease in BP. Initial trials have been favorable. In a proof of concept study enrolling 50 patients with refractory hypertension, SBP was reduced by 14 mm Hg after 1 month and 27 mm Hg at 1 year.[65] Further follow-up and pooled data demonstrated a 2-year SBP reduction of 32 mm Hg.[66] In the randomized Symplicity HTN-2 trial, 100 patients with resistant hypertension underwent renal sympathetic denervation or were assigned to the control group.[67] Patients who received the ablation had a reduction in SBP by 32 mm Hg after 6 months, compared with a control group where there was no change in BP. In these studies, there were few procedural-based complications, with one patient in the pilot study having the procedure aborted due to a renal artery dissection that resolved without complication or intervention and one patient having progression of a previously existing atherosclerotic plaque. Longer-term studies are currently ongoing to confirm the safety and efficacy of this technique.

Paced Breathing: RESPeRATE

As discussed earlier, techniques such as meditation have been shown to decrease BP. Slowed respiratory rates appear to have a beneficial effect on BP.[68–70] As respiratory rates slow, lung inflation increases. This then increases activation of stretch receptors in the lungs, which feed back to the central nervous system, and leads to vasodilation.

The RESPeRATE device (InterCure, Inc, New York, NY) uses biofeedback to progressively slow breathing. The system utilizes a controller unit, a respiration sensor, and headphones. Musical tones are played based on the patient's respirations, and the patient is instructed to follow the tones to adjust their breathing pattern. The device is used for 15 minutes daily. By progressively prolonging the expiratory phase, the patient's breathing cycle is slowed. The device decreased the SBP by 15 mm Hg at 2 months, compared with 11.3 in the placebo (music relaxation) group.[71] The response appeared to persist beyond the period where the device was in use.[71,72] Subsequent studies showed a more modest, but significant, 5-mm Hg decrease in SBP.[73]

Isometric Handgrip Exercises: Zona Plus

Isometric exercise is defined as exercise performed without muscle shortening or joint angle change. This type of exercise has been shown to decrease BP when performed in the arms, legs, or hands.[74–77] Previously, exercise was thought to increase BP due to a pressor response. Isometric exercise, however, does not increase heart rate (suggesting that there is no sympathetic effect)[75] and, in fact, increases vagal tone and improves autonomic function.[77,78] Isometric exercise also decreases oxygen radicals[79] and enhances endothelial-mediated vasodilation,[80] perhaps accounting for some of the BP benefits.

The Zona Plus (Zona Health, Boise, ID) is a dynamometer that is held in either hand. It initially prompts the user to squeeze as hard as possible. It uses this to calculate the maximal voluntary contraction and provides feedback to the user to a goal of 30% of this number. The device prompts the user to perform 42-minute sets of squeezing, with 1-minute rest in between. In pooled data, this device showed a decrease

TABLE. Summary of Nondrug Interventions for Treatment of Hypertension

Intervention	Treatment Effect	Type of Evidence Available
Lifestyle modification		
DASH diet	↓ SBP 5.5 mm Hg (↓ SBP 11.4 mm Hg in hypertensive patients)	R, O
Low-salt DASH diet	↓ SBP 7.1 mm Hg (↓ SBP 11.5 mm Hg in hypertensive patients)	R, O
Dietary supplements		
Potassium	↓ SBP 3–12 mm Hg	R, B, P, M
Calcium	↓ SBP 1.4–1.7 mm Hg	R, B, P, M
Vitamin D	↓ SBP 1.9–3.6 mm Hg[a]	R, B, P, M
Folate	↓ SBP 4 mm Hg	R, B, P, C
Coenzyme Q10	↓ SBP 16 mm Hg	R, B, P, M
Fish oil	↓ SBP 2–3 mm Hg	R, B, P, M
Garlic	↓ SBP 10–16 mm Hg[b]	R, P, M
Fruits and vegetables	↓ SBP 2.8 mm Hg	R, O
Soy protein	↓ SBP 7.8 mm Hg	R, B, P
Flavonoids	↓ SBP 3–5 mm Hg	R, P, M
Vegetarian diet	↓ SBP 5 mm Hg	R, O
High-fiber diet	↓ SBP 1–2 mm Hg	R, B, P, M
Herbal/alternative approaches		
Hawthorn	↓ SBP 3.6 mm Hg[a]	R, B, P
Coleus forskohlii	↓ Cardiac filling pressures	Comp
Mistletoe	↓ BP in rats	Comp, A
Rauwolfia	↓ SBP and DBP	Comp
Acupuncture	↓ SBP 5 mm Hg[a]	R, B, P, M
Meditation	↓ SBP 4.7 mm Hg	R, B, P, M
Devices/interventions		
Rheos implantable baroreflex stimulator	↓ SBP 22 mm Hg, >10 mm Hg reduction in SBP in 54% of patients[c]	R, B, P
Symplicity renal sympathetic denervation	↓ SBP 32 mm Hg[c]	R, O
RESPeRATE Paced Breathing	↓ SBP 5–15 mm Hg	R, O
Zona Plus isometric handgrip exercises	↓ SBP 5.7 mm Hg	R, O, M

Abbreviations: ↓ decreased; A, animal model; B, blinded; C, cross-sectional; Comp, comparative; DASH, Dietary Approaches to Stop Hypertension; O, open-label; P, placebo-controlled; M, meta-analysis; R, randomized; SBP, systolic blood pressure.
[a]Nonsignificant. [b]Study design/blinding issues are present.
[c]Refractory hypertension.

in SBP of 5.7 mm Hg in patients exercising 3 days per week for 8 weeks.[81]

AREAS OF UNCERTAINTY

Much of the evidence for these therapies comes from small studies with end points that typically include only BP. Clinical outcomes such as stroke or myocardial infarction have not been evaluated, although lower BP correlates with improved clinical outcomes.[82,83] While many of the device therapies have been evaluated in addition to currently recommended pharmacologic therapy, the efficacy of adding dietary, herbal, or alternative therapies is not well established. While combinations of antihypertensive drugs from different classes is a recommended approach that results in an additive benefit, it is not clear whether combinations of herbal or dietary supplements will also be additive. Safety profiles of the herbal supplements have not been rigorously established. Formulations can be variable and they are not regulated by the United States Food and Drug Administration. Many of the studies evaluating the supplements referenced here are small and data are often derived from pooled analysis. In particular, studies to date evaluating garlic as well as many of the alternative approaches have significant limitations in study design. The Table summarizes the available evidence. Ideally, randomized, placebo-controlled trials are needed to confirm the efficacy of many of the herbal or dietary supplements on the treatment of hypertension. The invasive device-based therapies are currently being evaluated for use in refractory hypertension. Should they prove efficacious and safe their use as a first-line therapy may come into play. Longer-term clinical trials of the invasive therapies are ongoing and will further delineate their safety profiles.

CONCLUSIONS

The first-line approach to hypertension refractory to lifestyle modification remains pharmacologic therapy in combination with the low-salt DASH diet.[84] However, a wide variety of alternative therapies are available for treatment of hypertension, whether using them to improve BP control to complement medications, as a first-line approach in combination with lifestyle modification to treat mild hypertension, or in combination with maximal drug therapy for refractory hypertension. These therapies may be of particular use in patients who are reluctant to take medications or are in search of methods to reduce their BP further in combination with pharmacologic therapy. Device- or intervention-based approaches are proving to be safe and effective and may offer the advantage of a one-time treatment that has lasting benefit.

References

1. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2006;47:296–308.
2. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336:1117–1124.
3. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med*. 2001;344:3–10.
4. Group WGotPCR. Effects of comprehensive lifestyle modification on blood pressure control. *JAMA*. 2003;289:2083–2093.
5. Klatsky AL, Friedman GD, Siegelaub AB, Gérard MJ. Alcohol consumption and blood pressure. *N Engl J Med*. 1977;296:1194–1200.
6. Fuchs FD, Chambless LE, Whelton PK, et al. Alcohol consumption and the incidence of hypertension: the atherosclerosis risk in communities study. *Hypertension*. 2001;37:1242–1250.
7. Xin X, He J, Frontini MG, et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2001;38:1112–1117.
8. Beulens JWJ, Rimm EB, Ascherio A, et al. Alcohol consumption and risk for coronary heart disease among men with hypertension. *Ann Intern Med*. 2007;146:10–19.
9. Malinski MK, Sesso HD, Lopez-Jimenez F, et al. Alcohol consumption and cardiovascular disease mortality in hypertensive men. *Arch Intern Med*. 2004;164:623–628.
10. Najem B, Houssiere A, Pathak A, et al. Acute cardiovascular and sympathetic effects of nicotine replacement therapy. *Hypertension*. 2006;47:1162–1167.
11. Bowman TS, Gaziano JM, Buring JE, Sesso HD. A prospective study of cigarette smoking and risk of incident hypertension in women. *J Am Coll Cardiol*. 2007;50:2085–2092.
12. Mikkelsen KL, Wiinberg N, Hoegholm A, et al. Smoking related to 24-h ambulatory blood pressure and heart rate. *Am J Hypertens*. 1997;10:483–491.
13. Green MS, Jucha E, Luz Y. Blood pressure in smokers and nonsmokers: epidemiologic findings. *Am Heart J*. 1986;111:932–940.
14. Primatesta P, Falaschetti E, Gupta S, et al. Association between smoking and blood pressure: evidence from the health survey for England. *Hypertension*. 2001;37:187–193.
15. Dickinson HO, Nicolson DJ, Campbell F, et al. Potassium supplementation for the management of primary hypertension in adults. *Cochrane Database Syst Rev*. 2006;3:CD004641.
16. He FJ, Markandu ND, Coltart R, et al. Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. *Hypertension*. 2005;45:571–574.
17. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA*. 1997;277:1624–1632.
18. Bianchetti MG, Weidmann P, Beretta-Piccoli C, Ferrier C. Potassium and norepinephrine- or angiotensin-mediated pressor control in prehypertension. *Kidney Int*. 1987;31:956–963.
19. Wu G, Tian H, Han K, et al. Potassium magnesium supplementation for four weeks improves small distal artery compliance and reduces blood pressure in patients with essential hypertension. *Clin Exp Hypertens*. 2006;28:489–497.
20. Ando K, Matsui H, Fujita M, Fujita T. Protective effect of dietary potassium against cardiovascular damage in salt-sensitive hypertension: possible role of its antioxidant action. *Curr Vasc Pharmacol*. 2010;8:59–63.
21. Pikilidou MI, Befani CD, Sarafidis PA, et al. Oral calcium supplementation ambulatory blood pressure and relation to changes in intracellular ions and sodium-hydrogen exchange. *Am J Hypertens*. 2009;22:1263–1269.
22. Reid IR, Ames R, Mason B, et al. Effects of calcium supplementation on lipids, blood pressure, and body composition in healthy older men: a randomized controlled trial. *Am J Clin Nutr*. 2010; 91:131–139.
23. Kim DH, Sabour S, Sagar UN, et al. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol*. 2008;102: 1540–1544.
24. Wu SH, Ho SC, Zhong L. Effects of vitamin D supplementation on blood pressure. *South Med J*. 2010;103:729–737.
25. Ng X, Boyd L, Dufficy L, et al. Folate nutritional genetics and risk for hypertension in an elderly population sample. *J Nutrigenet Nutrigenomics*. 2009;2:1–8.
26. Forman JP, Rimm EB, Stampfer MJ, Curhan GC. Folate intake and the risk of incident hypertension among US women. *JAMA*. 2005; 293:320–329.
27. Cagnacci A, Cannoletta M, Volpe A. High-dose short-term folate administration modifies ambulatory blood pressure in postmenopausal women. A placebo-controlled study. *Eur J Clin Nutr*. 2009; 63:1266–1268.
28. Yamagami T, Shibata N, Folkers K. Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension. *Res Commun Chem Pathol Pharmacol*. 1975;11:273–288.

29. Rosenfeldt FL, Haas SJ, Krum H, et al. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. *J Hum Hypertens*. 2007;21:297–306.
30. Cicero AF, Derosa G, Di Gregori V, et al. Omega 3 polyunsaturated fatty acids supplementation and blood pressure levels in hypertriglyceridemic patients with untreated normal-high blood pressure and with or without metabolic syndrome: a retrospective study. *Clin Exp Hypertens*. 2010;32:137–144.
31. Mori TA, Burke V, Puddey I, et al. The effects of [omega]3 fatty acids and coenzyme Q10 on blood pressure and heart rate in chronic kidney disease: a randomized controlled trial. *J Hypertens*. 2009;27:1863–1872.
32. Geleijnse JM, Giltay EJ, Grobbee DE, et al. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens*. 2002;20:1493–1499.
33. Ried K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. *Maturitas*. 2010;67:144–150.
34. Reinhart KM, Coleman CI, Teevan C, et al. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Ann Pharmacother*. 2008;42:1766–1771.
35. Simons S, Wollersheim H, Thien T. A systematic review on the influence of trial quality on the effect of garlic on blood pressure. *Neth J Med*. 2009;67:212–219.
36. He J, Gu D, Wu X, et al. Effect of soybean protein on blood pressure: a randomized, controlled trial. *Ann Intern Med*. 2005; 143:1–9.
37. Fraga CG, Litterio MC, Prince PD, et al. Cocoa flavanols: effects on vascular nitric oxide and blood pressure. *J Clin Biochem Nutr*. 2011;48:63–67.
38. Taubert D, Roesen R, Schomig E. Effect of cocoa and tea intake on blood pressure: a meta-analysis. *Arch Intern Med*. 2007;167:626–634.
39. Ried K, Sullivan T, Fakler P, et al. Does chocolate reduce blood pressure? A meta-analysis. *BMC Med*. 2010;8:39.
40. Margetts BM, Beilin LJ, Vandongen R, Armstrong BK. Vegetarian diet in mild hypertension: a randomised controlled trial. *Br Med J (Clin Res Ed)*. 1986;293:1468–1471.
41. Streppel MT, Arends LR, van't Veer P, et al. Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. *Arch Intern Med*. 2005;165:150–156.
42. Whelton SP, Hyre AD, Pedersen B, et al. Effect of dietary fiber intake on blood pressure: a meta-analysis of randomized, controlled clinical trials. *J Hypertens*. 2005;23:475–481.
43. Walker AF, Marakis G, Morris AP, Robinson PA. Promising hypotensive effect of hawthorn extract: a randomized double-blind pilot study of mild, essential hypertension. *Phytother Res*. 2002; 16:48–54.
44. Walker AF, Marakis G, Simpson E, et al. Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomised controlled trial. *Br J Gen Pract*. 2006;56:437–443.
45. Baumann G, Felix S, Sattelberger U, Klein G. Cardiovascular effects of forskolin (HL 362) in patients with idiopathic congestive cardiomyopathy – a comparative study with dobutamine and sodium nitroprusside. *J Cardiovasc Pharmacol*. 1990; 16:93–100.
46. Ye F, Du GZ, Cui AQ, Lu XT. Study on the mechanism of compound mistletoe fluid extract in relieving hypertension. *J Tradit Chin Med*. 2009;29:291–295.
47. Radenkovic M, Ivetic V, Popovic M, et al. Effects of mistletoe (Viscum album L., Loranthaceae) extracts on arterial blood pressure in rats treated with atropine sulfate and hexocycline. *Clin Exp Hypertens*. 2009;31:11–19.
48. Mc GM, Segel N. The Rauwolfia alkaloids in the treatment of hypertension. *Br Heart J*. 1955;17:391–396.
49. Lee H, Kim SY, Park J, et al. Acupuncture for lowering blood pressure: systematic review and meta-analysis. *Am J Hypertens*. 2009;22:122–128.
50. Kim LW, Zhu J. Acupuncture for essential hypertension. *Altern Ther Health Med*. 2010;16:18–29.
51. Anderson JW, Liu C, Kryscio RJ. Blood pressure response to transcendental meditation: a meta-analysis. *Am J Hypertens*. 2008;21: 310–316.
52. Ospina MB, Bond K, Karkhaneh M, et al. Meditation practices for health: state of the research. *Evid Rep Technol Assess (Full Rep)*. 2007;155:1–263.
53. Mansoor GA. Herbs and alternative therapies in the hypertension clinic. *Am J Hypertens*. 2001;14:971–975.
54. Zullino D, Borgeat F. Hypertension induced by St. John's Wort – a case report. *Pharmacopsychiatry*. 2003;36:32.
55. Chapleau MA. Arterial baroreflexes. In: Izzo J, Sica DA, Black HR, eds. *Hypertension Primer*. 4th ed. London, UK: Lippincott Williams & Wilkins; 2008:120–123.
56. Lohmeier TE, Hildebrandt DA, Warren S, et al. Recent insights into the interactions between the baroreflex and the kidneys in hypertension. *Am J Physiol Regul Integr Comp Physiol*. 2005;288:R828–R836.
57. Bisognano J, Sloand J, Papademetriou V, et al. An implantable carotid sinus baroreflex activating system for drug-resistant hypertension: interim chronic efficacy results from the multi-center rheos feasibility trial. *Circulation*. 2006;114:II_575-a-, Abstract 2751.
58. Illig KA, Levy M, Sanchez L, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. *J Vasc Surg*. 2006;44:1213–1218.
59. Scheffers IJ, Kroon AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol*. 2010;56:1254–1258.
60. Bisognano JD, Sica D, Nadim M, et al. *Results from the Rheos Pivotal Trial: baroreflex activation therapy sustainably lowers blood pressure in patients with resistant hypertension*. New Orleans, LA: American College of Cardiology Scientific Sessions; 2011.
61. Augustyniak RA, Tuncel M, Zhang W, et al. Sympathetic overactivity as a cause of hypertension in chronic renal failure. *J Hypertens*. 2002;20:3–9.
62. DiBona GF. Sympathetic nervous system and the kidney in hypertension. *Curr Opin Nephrol Hypertens*. 2002;11:197–200.
63. Mancia G, Grassi G, Giannattasio C, Seravalle G. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension*. 1999;34:724–728.
64. Siddiqi L, Joles JA, Grassi G, Blankestijn PJ. Is kidney ischemia the central mechanism in parallel activation of the renin and sympathetic system? *J Hypertens*. 2009;27:1341–1349.
65. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275–1281.
66. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension*. 2011;57:911–917.
67. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*. 2010;376: 1903–1909.
68. Pitzalis MV, Mastropasqua F, Massari F, et al. Effect of respiratory rate on the relationships between RR interval and systolic blood pressure fluctuations: a frequency-dependent phenomenon. *Cardiovasc Res*. 1998;38:332–339.
69. Novak V, Novak P, de Champlain J, Nadeau R. Altered cardiorespiratory transfer in hypertension. *Hypertension*. 1994;23:104–113.
70. Cooke WH, Cox JF, Diedrich AM, et al. Controlled breathing protocols probe human autonomic cardiovascular rhythms. *Am J Physiol*. 1998;274:H709–H718.
71. Schein MH, Gavish B, Herz M, et al. Treating hypertension with a device that slows and regularises breathing: a randomised, double-blind controlled study. *J Hum Hypertens*. 2001;15:271–278.
72. Rosenthal T, Alter A, Peleg E, Gavish B. Device-guided breathing exercises reduce blood pressure: ambulatory and home measurements. *Am J Hypertens*. 2001;14:74–76.
73. Meles E, Giannattasio C, Failla M, et al. Nonpharmacologic treatment of hypertension by respiratory exercise in the home setting. *Am J Hypertens*. 2004;17:370–374.
74. Howden R, Lightfoot J, Brown S, Swaine I. The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. *Exp Physiol*. 2002;87:507–515.
75. Ray CA, Carrasco DI. Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. *Am J Physiol Heart Circ Physiol*. 2000;279:H245–H249.
76. Wiley RL, Dunn CL, Cox RH, et al. Isometric exercise training lowers resting blood pressure. *Med Sci Sports Exerc*. 1992;24:749–754.
77. Taylor AC, McCartney N, Kamath MV, Wiley RL. Isometric training lowers resting blood pressure and modulates autonomic control. *Med Sci Sports Exerc*. 2003;35:251–256.
78. Millar PJ, MacDonald MJ, Bray SR, McCartney N. Isometric handgrip exercise improves acute neurocardiac regulation. *Eur J Appl Physiol*. 2009;107:509–515.
79. Peters PG, Alessio HM, Hagerman AE, et al. Short-term isometric exercise reduces systolic blood pressure in hypertensive adults:

possible role of reactive oxygen species. *Int J Cardiol*. 2006;110: 199–205.
80. McGowan C, Visocchi A, Faulkner M, et al. Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. *Eur J Appl Physiol*. 2007;99:227–234.
81. Millar PJ, Bray SR, McGowan CL, et al. Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis. *Blood Press Monit*. 2007;12:307–314.
82. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765–774.
83. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827–838.
84. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.