Angiology
Volume 60 Number 2
April/May 2009 207-216

10.1177/0003319708316012
http://ang.sagepub.com

Sport Therapy for Hypertension: Why, How, and How Much?

Fabio Manfredini, MD, Anna M. Malagoni, MD, Simona Mandini, DSc, Benedetta Boari, MD, Michele Felisatti, DSc, Paolo Zamboni, MD, and Roberto Manfredini, MD

Exercise may prevent or reduce the effects of metabolic and cardiovascular diseases, including arterial hypertension. Both acute and chronic exercise, alone or combined with lifestyle modifications, decrease blood pressure and avoid or reduce the need for pharmacologic therapy in patients with hypertension. The hypotensive effect of exercise is observed in a large percentage of subjects, with differences due to age, sex, race, health conditions, parental history, and genetic factors. Exercise regulates autonomic nervous system activity, increases shear stress, improves nitric oxide production in endothelial cells and its bioavailability for vascular smooth muscle, up-regulates antioxidant enzymes. Endurance training is primarily effective, and resistance training can be combined with it. Low-to-moderate intensity training in sedentary patients with hypertension is necessary, and tailored programs make exercise safe and effective also in special populations. Supervised or home-based exercise programs allow a nonpharmacological reduction of hypertension and reduce risk factors, with possible beneficial effects on cardiovascular morbidity.

Keywords: life style; exercise; exercise therapy; physical training; hypertension; cardiovascular diseases

Exercise: Why?

Inactivity and Vascular Diseases

According to some authors, the human genome evolved within an environment of high physical activity.[1] Physical inactivity may, therefore, be responsible for a stress-induced or exercise-deficient phenotype[2] and various chronic disease conditions,[1] including hypertension. Exercise may reverse the adverse effects of inactivity,[3] improve physical capacity and quality of life,[4] and may represent a validated and recommended therapy in patients with atherosclerotic cardiovascular disease,[4] having a positive effect on cardiovascular longevity.[5] Exercise prevents or reduces the effects of metabolic, neurologic, and cardiovascular diseases, including arterial hypertension,[6] with protective action among subjects with hypertension.[5,7]

Lifestyle and Hypertension

High blood pressure (BP) is a common disease in all countries including the United States,[8] with elevated and increasing prevalence.[9] Blood pressure is associated with an increased incidence of all-cause and cardiovascular disease mortality,[10] independently of other risk factors.[9]

In individuals with hypertension, BP is normally counteracted by pharmacological therapy with high costs and sometimes with low efficacy and adverse effects.[8]

Lifestyle modifications are, therefore, recommended to avoid or reduce the pharmacological therapy in patients with hypertension or to maintain

From the Vascular Diseases Center (FM, AMM, SM, MF, PZ, RM), Center Biomedical Studies Applied to Sport (FM, RM), Department of Clinical and Experimental Medicine, Section of Clinica Medica (RM), University of Ferrara, Department of Rehabilitation Medicine (FM, RM), and Department of Internal Medicine (BB), S. Anna Hospital, Ferrara, Italy.

This study was supported by a scientific grant “Fondo di Ateneo per la Ricerca – FAR”, University of Ferrara, Ferrara, Italy.

Address correspondence to: Fabio Manfredini, MD, Vascular Diseases Center, C/o Centro Studi Biomedici applicati allo Sport-University of Ferrara, Via Gramicia 35, Ferrara 44100, Italy; e-mail: mdf@unife.it.

an acceptable BP profile in subjects at risk of developing hypertension or prehypertension[11-13]

Lifestyle modifications are effective alone or combined with pharmacological therapy.[14] Blood pressure reductions were observed following weight loss (5-20 mm Hg/10 kg), dietary modification as the dietary approaches to stop hypertension (DASH; 8-14 mm Hg), and increased physical activity (4-9 mm Hg). Dietary sodium reduction, low alcohol intake, and fish oil supplements can also be effective.[14,15]

Multiple lifestyle changes decreased the prevalence of hypertension in patients with prehypertension and in patients with stage 1 hypertension,[16] but the main behavioral interventions recommended to reduce BP are exercise and the DASH eating plan.[17] A low caloric version of this diet combined with a moderate-intensity exercise program under supervision decreased BP among overweight adults with hypertension on antihypertensive therapy.[18]

The reduction of BP following exercise was enhanced by a weight loss program in overweight patients at different stages of hypertension.[17,19-21] Diet and exercise, alone or combined, were equally effective in reducing the BP in subjects with normotensive and mild hypertension, with improvements similar to drug therapy in patients with higher baseline BP level.[8] In some patients, no additional improvement was derived by drug therapy.[22]

Effects of Acute and Chronic Exercise

Both acute and chronic exercises are effective in BP reduction.

Acute aerobic exercise (eg, 30 minutes at 50% VO_2max) improved stress-related BP response [23] and reduced ambulatory BP in patients with hypertension when performed before the stresses of daily living.[24] Acute exercise, alone or in combination with relaxation, decreased systolic BP (SBP) and diastolic BP (DBP) during mental stress.[25]

The acute hypotensive effect of exercise requires only 40% of maximal capacity[26] or 20 to 50 minutes of moderate aerobic exercise,[24,27] whereas even greater effect can be observed following higher exercise intensity.[28]

The duration of its effect following a single session of exercise was observed during the 24 hours in patients with hypertension, with a significant reduction for 5 hours.[24,26,29] The duration of the effect might be related to the exercise intensity and duration. Long-lasting reduction was observed in patients with hypertension following higher exercise intensity, with significant SBP and DBP reductions of 13/11 hours after the 75% sessions compared with 4/4 hours for both after 50% intensity.[28] The accumulation of sessions of physical activity in prehypertension showed a more prolonged effect on SBP and DBP than a single continuous session (11/10 hours vs 5/5 hours).[30]

The time of day to exercise and the characteristics of subjects with hypertension (eg, dippers and nondippers) may be related to BP reduction following a single session of exercise.[31]

Greater BP reductions can be obtained with more prolonged training.[30] According to a meta-analysis of 36 controlled intervention studies, the average weighted net BP reduction following aerobic training was 5.3 and 4.8 mm Hg for SBP and DBP, respectively, with variations related to the baseline BP value and a gain in exercise capacity.[32] A subsequent meta-analysis involving 72 trials and 105 study groups reported a significant reduction in resting and daytime ambulatory BP of 3.0/2.4 mm Hg and 3.3/3.5 mm Hg, respectively, with higher reduction (−6.9/−4.9) in the patients with hypertension.[33]

The hypotensive effect of aerobic exercise training is observed in approximately 75% of people with essential hypertension,[34,35] with a nonresponder rate similar to pharmacological therapy.[35] Moderate aerobic exercise alone was not significantly effective in nonobese patients with mild hypertension and in sedentary, overweight or obese postmenopausal women.[36,37]

In general, a different effect in response to exercise training has been observed in relation to various aspects of the population under study.

Age has little or no influence on the changes in SBP,[38] even if middle-aged people with hypertension are thought to obtain greater benefits than young or older people.[29] In older adults with mild (grade I) hypertension, however, endurance exercise training can lower BP or potentiate the effects of antihypertensive medications.[39-41]

In young people, exercise, besides representing an effective health strategy for BP in high-risk adolescent girls,[42] lowered office BP in young subjects who were at stage I hypertension.[43,44]

In relation to sex, the attenuated response of BP to exercise training of women compared with men[38] has not been confirmed by other authors.[30] A meta-analysis including 21 studies representing 1029 subjects showed that aerobic exercise in women evokes a small reduction only in resting SBP, correlated with baseline values, initial body mass index, and resting heart rate.[45]

Positive effects following intermittent, moderate-intensity exercise were observed in postmenopausal women with hypertension.[42]

In terms of race, exercise training decreased BP in African-American patients and Black adults [46,47] and was more effective, especially on SBP reduction in patients with hypertension from Asia and Pacific island than in Caucasian patients.[29]

According to health conditions, more favorable changes in resting SBP and DBP were observed after training in patients with hypertension and postmyocardial infarction when compared with healthy subjects,[38,48] with an average BP reduction of −3/−3 mm Hg in patients with normotension, −6/−7 mm Hg in patients with borderline hypertension, and −10/−8 mm Hg in patients with hypertension,[32] and with postexercise reduction as a function of baseline values.[49]

Among unhealthy subjects, hyperadrenergic subjects with mild essential hypertension showed a good response after exercise,[50] and dippers significantly reduced the daytime SBP and DBP, whereas nondippers did not.[51] Overweight, normal-weight subjects,[52] and mild hypertensives with higher cardiac index and serum Na:K ratio[53] showed a BP reduction following aerobic exercise. In hemodialysis patients, an endurance exercise training program or stationary cycling during hemodialysis decreased both predialysis SBP and DBP with significant reductions in the antihypertensive medications.[54,55]

Positive reductions of BP were also observed following exercise training in patients with peripheral arteriopathy.[56]

A parental history of hypertension can be related to a different effect of exercise.

The antihypertensive effect of regular training can be maintained for 3 years.[57] After cessation of training, BP value returned to pretraining levels within a month,[41] persisted after 3 months in patients with hypertension[43] or increased in young normotensive women at risk for hypertension.[58]

Additional Effects on Hypotensive Action

Exercise training also shows favorable effects for other risk factors for coronary artery disease and atherosclerosis.[39] A recent meta-analysis showed improved body composition after training, with significant reductions of body weight (1.2 kg), waist circumference (2.8 cm), and percentage body fat (1.4%).[33] Body composition improvements, associated with BP reductions, explained 8% and 17% of the SBP and DBP reductions, respectively.[59]

Aerobic exercise reduced cardiovascular reactivity during stressful situations in mild hypertensives[60] and increased peak limb vascular conductance in older hypertensive subjects.[61]

Exercise also showed positive effects on left ventricular geometry in older people with hypertension. A regression of left ventricular hypertrophy, concentric remodeling, and reduced thickness of the interventricular septum were observed.[46,62,63]

Favorable effects on risk factors were also observed as improved lipid profile[33,64] and insulin resistance,[33,65] reduced factor VII and fibrinogen concentrations.[63]

Favorable or nonadverse effects on health-related quality of life and moods were reported in some patients[66-68] but not in mildly hypertensive volunteers following a 6-month walking program.[69]

Exercise: How?

The antihypertensive mechanism of exercise training is multifactorial,[70] mainly involving alterations in the sympathetic nervous system (SNS) and improvement of endothelial function.[33,35,70,71]

Autonomic Nervous System Activity

Cardiovascular diseases, including hypertension, are associated with an overactivity of the SNS.[72] Physical training regulates autonomic nervous system activity and induces modifications of the cardiovascular system function. A decreased SNS hyperactivity and hypertension in patients and a lowered sympathetic outflow and resting BP in normal individuals are observed.[6,71-73]

Following acute aerobic exercise, improvements in BP responses to stress were not related to variations of heart rate reactivity, but rather, regional vascular resistance, with significant increases in postexercise β1- and β2-receptors and lowered norepinephrine availability following a stress task.[22,74,75]

The effects of exercise training programs on the autonomic nervous system activity have been evaluated, and responsiveness and density of adrenergic and muscarinic receptors were evaluated without obtaining conclusive data, possibly due to methodological aspects.[71] The adenosine receptor was not found related to the training bradycardia.[76]

In patients with mild hypertension after exercise training, a decrease in frequency-modulated sympathetic activity and an increase in vagal modulation of heart rate were observed.[77]

Following endurance training, a meta-analysis involving 72 trials showed a reduction of plasma norepinephrine by 29%,[33] whereas other studies showed a reduction of only urinary and platelet norepinephrine[78] or an increase in serum taurine, which is possibly responsible for the reduction in plasma norepinephrine levels.[79] Total plasma catecholamines were also found reduced after a training programme in patients with mild hypertension, but changes in SBP significantly correlated with the changes in plasma renin activity.[66]

A marked reduction in resting sympathetic nerve activity was also observed following endurance training by direct recording by microneurography of postganglionic muscle sympathetic nerve activity from the peroneal nerve.[80] The action of exercise through the impact of elevated blood volume on low-pressure baroreceptors was also hypothesized.[81]

Physical exercise not only induces peripheral modifications but may also alter neurochemistry and neuronal function, may increase neurogenesis in selected brain regions and improve plasticity within neural networks regulating SNS activity, may lower sympathoexcitation by reduced activation of neurons within cardiovascular regions of the brain.[72,82]

Endothelium and Exercise

The endothelium is both a target and a mediator of arterial hypertension,[83] and the exercise-induced reduction of BP is mediated by improved endothelial function.[40] Exercise training influences the responsiveness of vascular smooth muscle, and some of its effects are associated with the properties of nitric oxide to regulate vascular tone, to induce vasodilatation, and to inhibit excitation–contraction coupling. Nitric oxide production in endothelial cells and its bioavailability for vascular smooth muscle are increased by hormones and autacoids, drugs, and physical stimuli.[84-87] Exercise increases blood flow and shear stress,[71,88] up-regulates the level of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymes, including vitamins and flavonoids, and reduces the levels of pro-oxidant enzymes.[89-94] These factors increase nitric oxide availability in the vascular smooth muscle and endothelium-dependent vasodilatation.[95-98]

Regular aerobic exercise can also positively influence the levels of endothelin-1. This vasoconstrictor agent, contributing to the endothelial dysfunction, is linked to the etiology of various pathologies, including hypertension.[83,99,100]

Genotype, Exercise, and Hypertension

In hypertension, genetic factors can play a role in endothelial dysfunction and in response to exercise.[83,101]

Aerobic exercise in adolescence, high-intensity aerobic exercise throughout life, and low DBP in adulthood were associated with factors partly sharing the same genes. Genetic factors explained 35% and 39% of the variance in DBP and SBP, respectively.[102]

The trainability of SBP in families with hypertension seems partly determined by genetic factors, whereas DBP trainability is more related to environmental effects.[103] Angiotensin-converting enzyme (ACE) gene I/D polymorphism was found associated with the response to mild exercise therapy in essential hypertensives.[104] The possibility that apolipoprotein E, ACE, and lipoprotein lipase genotypes might identify hypertensive responders to exercise training in terms of improved BP, lipoprotein lipids, and cardiovascular disease risk has been discussed.[105]

A polymorphism of nitric oxide synthase 3 was significantly associated with the prevalence of systolic hypertension only in the patients with the lowest physical activity level,[106] whereas older hypertensives with the ACE II genotype showed greatest improvement in insulin action following a 6-month aerobic exercise program (AEX).[107] In addition, exercise reduces genetic predisposition to increased systemic arterial stiffness.[108]

Exercise training positively influenced the expression of some genes related with cardiovascular regulation, including BP, in sedentary animals, either active or trained.[109]

Exercise: How Much?

Type of Exercise

In a meta-analysis of randomized controlled trials, aerobic exercise training (walking, jogging, stationary bicycling, or any combination of these activities) produced a small but clinically significant effect.[110] Endurance training is considered effective in lowering the resting BP in patients with mild to severe hypertension [39,52,67,77,111,112] with an average reduction of 10.5/7.6 mm Hg for SBP and DBP, respectively.[113]

Resistance training was also studied. A slight SBP reduction during recovery following a single session of resistance exercise was observed in women with normotensive and borderline hypertension.[114] Resistance exercise programs were found to reduce resting SBP and DBP of approximately 2% and 4%, with an average decrease of 3 mm Hg and without differences between conventional or circuit resistance training protocols.[111,115,116]

Resistance training is not recommended as the only form of exercise for patients with hypertension[113] and is considered as a complement to AEXs in the prevention, treatment, and control of hypertension.[10,117] In addition, despite the well-known benefits derived from an increased muscle mass, safety and effectiveness of resistance training in some populations with cardiovascular disease or low aerobic fitness needs careful evaluation.[116]

According to some authors, power training in appropriately configured programs was also considered useful for patients with hypertension.[118]

Similarly, isometric exercise, generally contraindicated in patients with hypertension, has been considered effective in normotensive individuals and in older adults with hypertension when performed as isometric handgrip training.[119-121]

Different types of exercise may be also used to reduce BP. Promising or favorable results in terms of BP reduction were shown following swimming programs[122] or disciplines alternative to conventional exercise as Qigong or T'ai Chi programs.[123-125]

Intensity, Volume, and Exercise Prescription

The effect of exercise on BP has been observed after energy expenditures requiring a low percentage of the maximal capacity.[26] In general, the intensity of exercise recommended was from moderate to mild (lactic threshold or 50% maximum oxygen uptake).[70] Low-intensity exercise training was equal or more effective than moderate-intensity training in reducing resting BP and BP responses to stress and in obtaining patient compliance.[29,126-128] A similar antihypertensive effect, primarily diurnal or nocturnal, was observed following low-intensity or moderate-intensity training in sedentary patients with mild to moderate hypertension.[129] A DBP reduction was observed in patients with claudication walking at a selected speed, lower than the usual pace.[56]

A progressive decrease in BP with increased exercise intensity was reported.[43,130,131] A meta-analysis of randomized controlled trials showed the lack of additional effect on BP reduction training at an intensity above 70% VO_2 max for more than 3 sessions per week.[111]

A volume of exercise a little above sedentary levels (61-90 min/wk) is necessary to reduce BP,[132] even if training from 3 to 5 times per week during 30 to 60 minutes per session was effective in reducing BP.[133]

Durations as short as 20 minutes were accompanied by BP reduction[48] and interval exercise (eg, four 10-minutes sessions of brisk walking) were as effective as 40 minutes of continuous brisk walking per day.[134] No relationship between exercise frequency per week and BP decrease was observed.[132]

The exercise prescription recommended for treating hypertension requires endurance training supplemented by resistance exercise on most, preferably all, days of the week. Exercise should be performed at moderate intensity for a minimum of 30 minutes of continuous or accumulated physical activity per day.[10] The above described prescription requires individualization, especially in terms of intensity and duration over a training period.[114,135] Exercise programs, especially for some populations, might require a preliminary medical evaluation or exercise tolerance assessment to be safe, effective, and able to meet the patient's necessities and capabilities.[4,14,119,136]

Exercise programs for patients can be home-based or under supervision, with different positive aspects.[137] For patients with hypertension, supervised programmes that reduce risks[4] were followed by positive results[138] and were more effective than recommended exercise alone.[139] Blood pressure reductions, however, were observed following unsupervised home-based programs.[140,141]

Conclusions

Physical activity, alone or combined with other lifestyle interventions, represents an effective non-pharmacological tool,[6,35,142,143] providing multiple additional benefits beyond BP reduction.[35,48] Exercise can be considered as a cornerstone therapy for the prevention, treatment, and control of hypertension;[10,33] it requires motivation by both patient and physician.[12] There may never be one pill to replace all the health benefits of exercise.[144]

References

1. Booth FW, Gordon SE, Carlson CJ, et al. Waging war on modern chronic diseases: primary prevention through exercise biology. *J Appl Physiol.* 2000;88:774-787.
2. Tsatsoulis A, Fountoulakis S. The protective role of exercise on stress system dysregulation and comorbidities. *Ann N Y Acad Sci*. 2006;1083:196-213.
3. Arakawa K. Hypertension and exercise. *Clin Exp Hypertens*. 1993;15:1171-1179.
4. Casillas JM, Gremeaux V, Damak S, et al. Exercise training for patients with cardiovascular disease. *Ann Readapt Med Phys*. 2007;50:386-418.
5. Fang J, Wylie-Rosett J, Alderman MH. Exercise and cardiovascular outcomes by hypertensive status: NHANES I epidemiological follow-up study, 1971-1992. *Am J Hypertens*. 2005;18:751-758.
6. Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. *FASEB J*. 2000;14:1685-1696.
7. Engstrom G, Hedblad B, Janzon L. Hypertensive men who exercise regularly have lower rate of cardiovascular mortality. *J Hypertens*. 1999;17:737-742.
8. Bacon SL, Sherwood A, Hinderliter A, et al. Effects of exercise, diet and weight loss on high blood pressure. *Sports Med*. 2004;34:307-316.
9. Centers for Disease Control and Prevention (CDC). Prevalence of actions to control high blood pressure—20 states, 2005. *MMWR Morb Mortal Wkly Rep*. 2007;56:420-423.
10. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine. American College of Sports Medicine Position Stand. Exercise and hypertension. *Med Sci Sports Exerc*. 2004;36:533-553.
11. Penco M, Petroni R, Pastori F, et al. Should sports activity be encouraged or contraindicated in hypertensive subjects? *J Cardiovasc Med (Hagerstown)*. 2006;7:288-295.
12. Tejada T, Fornoni A, Lenz O, et al. Nonpharmacologic therapy for hypertension: does it really work? *Curr Cardiol Rep*. 2006;8:418-424.
13. Gran B. Non-pharmacological methods reduce drug use in the treatment of hypertension. A two-year trial in general practice. *Scand J Prim Health Care*. 1991;9:121-128.
14. Franco V, Oparil S, Oscar A, et al. Hypertensive therapy: part II. *Circulation*. 2004;109:3081-3088.
15. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens*. 2006;24:215-233.
16. McGuire HL, Svetkey LP, Harsha DW, et al. Comprehensive lifestyle modification and blood pressure control: a review of the PREMIER trial. *J Clin Hypertens (Greenwich)*. 2004;6:383-390.
17. Miller ER III, Erlinger TP, Young DR, et al. Results of the diet, exercise, and weight loss intervention trial (DEW-IT). *Hypertension*. 2002;40:612-618.
18. Gordon NF, Scott CB, Levine BD. Comparison of single versus multiple lifestyle interventions: are the antihypertensive effects of exercise training and diet-induced weight loss additive? *Am J Cardiol*. 1997;79:763-767.
19. Blumenthal JA, Sherwood A, Gullette EC, et al. Exercise and weight loss reduce blood pressure in men and woman with mild hypertension: effect on cardiovascular, metabolic and hemodynamic functioning. *Arch Intern Med*. 2000;160:1947-1958.
20. Dengel DR, Hagberg JM, Pratley RE, et al. Improvements in blood pressure, glucose metabolism, and lipoprotein lipids after aerobic exercise plus weight loss in obese, hypertensive middle-aged men. *Metabolism*. 1998;47:1075-1082.
21. Anderssen S. Holme I, Urdal P, et al. Diet and exercise intervention have favourable effects on blood pressure in mild hypertensives: the Oslo Diet and Exercise Study (ODES). *Blood Press*. 1995;4:343-349.
22. Kelemen MH, Effron MB, Valenti SA, et al. Exercise training combined with antihypertensive drug therapy. Effects on lipids, blood pressure and left ventricular mass. *JAMA*. 1990;263:2766-2771.
23. Hamer M, Taylor A, Steptoe A. The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. *Bio Psychol*. 2006;71:183-190.
24. Brownley KA, West SG, Hinderliter AL, et al. Acute aerobic exercise reduces ambulatory blood pressure in borderline hypertensive men and women. *Am J Hypertens*. 1996;9:200-206.
25. Santaella DF, Araujo EA, Ortega KC, et al. Aftereffects of exercise and relaxation on blood pressure. *Clin J Sport Med*. 2006;16:341-347.
26. Thompson PD, Crouse SF, Goodpaster B, et al. The acute versus the chronic response to exercise. *Med Sci Sport Exerc*. 2001;33(suppl 6):438-445.
27. Wallace JP, Bogle PG, King BA, et al. The magnitude and duration of ambulatory blood pressure reduction following acute exercise. *J Hum Hypertens*. 1999;13:361-366.
28. Quinn TJ. Twenty-four hour, ambulatory blood pressure responses following acute exercise: impact of exercise intensity. *J Hum Hypertens*. 2000;14:547-553.
29. Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension: an update. *Sports Med*. 2000;30:193-206.
30. Park S, Rink LD, Wallace JP. Accumulation of physical activity leads to the greater blood pressure reduction than a single continuous session, in prehypertension. *J Hypertens*. 2006;24:1761-1770.
31. Park S, Jastremski CA, Wallace JP. Time of day for exercise on blood pressure reduction in dipping and nondipping hypertension. *J Hum Hypertens*. 2005;19:597-605.

32. Fagard RH. Prescription and results of physical activity. *J Cardiovasc Pharmacol*. 1995;25 (suppl 1):20-27.
33. Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. *Eur J Cardiovasc Prev Rehabil*. 2007;14:12-17.
34. Hagberg JM, Brown MD. Does exercise training play a role in the treatment of essential hypertension? *J Cardiovasc Risk*. 1995;2:296-302.
35. Volker K. Physical activity, hypertension and cardiac and circulatory system. *Med Clin (Munich)*. 2006;101 (suppl 1):61-65.
36. Blumenthal JA, Siegel WC, Appelbaum M. Failure of exercise to reduce blood pressure in patients with mild hypertension. Results of a randomized controlled trial. *JAMA*. 1991;266:2098-2104.
37. Church TS, Earnest CP, Skinner JS, et al. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese post-menopausal women with elevated blood pressure: a randomized controlled trial. *JAMA*. 2007;297:2081-2091.
38. Wilmore JH. Dose-response: variation with age, sex, and health status. *Med Sci Sports Exerc*. 2001;33(suppl 6):622-634.
39. Ehsani AA. Exercise in patients with hypertension. *Am J Geriatr Cardiol*. 2001;10:253-273.
40. Westhoff TH, Franke N, Schmidt S, et al. Too old to benefit from sports? The cardiovascular effects of exercise training in elderly subjects treated for isolated systolic hypertension. *Kidney Blood Press Res*. 2007;30:240-247.
41. Motoyama M, Sunami Y, Kinoshita F, et al. Blood pressure lowering effect of low intensity aerobic training in elderly hypertensive patients. *Med Sci Sports Exerc*. 1998;30:818-823.
42. Ewart CK, Young DR, Hagberg JM. Effects of school-based aerobic exercise on blood pressure in adolescent girls at risk for hypertension. *Am J Public Health*. 1998;88:949-951.
43. Vriz O, Mos L, Frigo G, et al. Harvest study investigator: effects of physical exercise on clinic and 24-hour ambulatory blood pressure in young subjects with mild hypertension. *J Sports Med Phys Fitness*. 2002;42:83-88.
44. Palatini P, Graniero GR, Mormino P, et al. Relation between physical training and ambulatory blood pressure in stage I hypertensive subjects. Results of the HARVEST trial. Hypertension and ambulatory recording Venetia study. *Circulation*. 1994;90:2870-2876.
45. Kelley GA, Kelley KS. Aerobic exercise and resting blood pressure in women: a meta-analytic review of controlled clinical trials. *J Womens Health Gend Based Med*. 1999;8:787-803.
46. Kokkinos PF, Narayan P, Colleran JA, et al. Effects of regular exercise on blood pressure and left ventricular hypertrophy in african-american men with severe hypertension. *N Engl J Med*. 1995;333:1462-1467.
47. Melby CL, Goldflies DG, Hyner GC. Blood pressure and anthropometric differences in regularly exercising and nonexercising black adults. *Clin Exp Hypertens A*. 1991;13:1233-1248.
48. Lesniak KT, Dubbert PM. Exercise and hypertension. *Curr Opin Cardiol*. 2001;16:356-359.
49. Pescatello LS, Kulikowich JM. The aftereffects of dynamic exercise on ambulatory blood pressure. *Med Sci Sports Exerc*. 2001;33:1855-1861.
50. Duncan JJ, Farr JE, Upton SJ, et al. The effects of aerobic exercise on plasma catecholamines and blood pressure in patients with mild essential hypertension. *JAMA*. 1985;254:2609-2613.
51. Nami R, Mondillo S, Agricola E, et al. Aerobic exercise training fails to reduce blood pressure in nondipper-type hypertension. *Am J Hypertens*. 2002;13:593-600.
52. Whelton SP, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2002;136: 493-503.
53. Kinoshita A, Urata H, Tanabe Y, et al. What types of hypertensives respond better to mild exercise therapy? *J Hypertens*. 1988;6(suppl 6):631-633.
54. Hagberg JM, Goldberg AP, Ehsani AA, et al. Exercise training improves hypertension in hemodialysis patients. *Am J Nephrol*. 1983;3:209-212.
55. Miller BW, Cress CL, Johnson ME, et al. Exercise during hemodialysis decreases the use of antihypertensive medications. *Am J Kidney Dis*. 2002;39:828-833.
56. Manfredini F, Conconi F, Malagoni AM, et al. Training guided by pain threshold speed: effects of a home-based program on claudication. *Int Angiol*. 2004;23:379-387.
57. Ketelhut RG, Franz IW, Scholze J. Regular exercise as an effective approach in antihypertensive therapy. *Med Sci Sports Exerc*. 2004;36:4-8.
58. Buckworth J, Convertina VA, Cureton KJ, et al. Increased finger arterial blood pressure after exercise detraining in women with parental hypertension: autonomic tasks. *Acta Physiol Scand*. 1997;160:29-41.
59. Stewart KG, Bacher AC, Turner KL, et al. Effect of exercise on blood pressure in older persons: a randomized controlled trial. *Arch Intern Med*. 2005;165:756-762.
60. Perkins KA, Dubbert PM, Martin JE, et al. Cardiovascular reactivity to psychological stress in aerobically trained versus untrained mild hypertensives and normotensives. *Health Psychol*. 1986;5:407-421.
61. Tanaka H, Reiling MJ, Seals DR. Regular walking increases peak limb vasodilatory capacity of older hypertensive humans: implications for arterial structure. *J Hypertens*. 1998;16:423-428.
62. Turner MJ, Spina RJ, Kohrt WM, et al. Effect of endurance exercise training on left ventricular size and remodelling in older adults with hypertension. *J Gerontol A Biol Sci Med Sci*. 2000;55:M245-251.
63. Zanettini R, Bettega D, Agostoni O, et al. Exercise training in mild hypertension: effects on blood pressure, left ventricular mass and coagulation factor VII and fibrinogen. *Cardiology*. 1997;88:468-473.

64. Tsai JC, Chang WY, Kao CC, et al. Beneficial effect on blood pressure and lipid profile by programmed exercise training in Taiwanese patients with mild hypertension. *Clin Exp Hypertens*. 2002;24:315-324.
65. Rinder MR, Spina RJ, Peterson LR, et al. Comparison of effects of exercise and diuretic on left ventricular geometry, mass, and insulin resistance in older hypertensive adults. *Am J Physiol Regul Integr Comp Physiol*. 2004;287:R360-368.
66. Dubbert PM, Martin JE, Cushman WC, et al. Endurance exercise in mild hypertension: effects on blood pressure and associated metabolic and quality of life variables. *J Hum Hypertens*. 1994;8:265-272.
67. Tsai JC, Yang HY, Wang WH, et al. The beneficial effect of regular endurance exercise training on blood pressure and quality of life in patient with hypertension. *Clin Exp Hypertens*. 2004;26:255-265.
68. Danzer E, Gallert K, Friedrich A, et al. Result of an intensive training program for hypertension at the institute for preventive medicine. *Dtsch Med Wochenschr*. 2000;125:1385-1389.
69. Stanton JM, Arroll B. The effect of moderate exercise on mood in mildly hypertensive volunteers: a randomized controlled trial. *J Psychosom Res*. 1996;40:637-642.
70. Arakawa K. Exercise, a measure to lower blood pressure and reduce other risks. *Clin Exp Hypertens*. 1999;21:797-803.
71. Zanesco A, Antunes E. Effects of exercise training on the cardiovascular system: pharmacological approaches. *Pharmacol Ther*. 2007;114:307-317.
72. Mueller PJ. Exercise training and sympathetic nervous system activity: evidence for physical activity dependent neural plasticity. *Clin Exp Pharmacol Physiol*. 2007;34:377-384.
73. Krieger EM, Brum PC, Negrao CE. Role of arterial baroreceptor function on cardiovascular adjustments to acute and chronic dynamic exercise. *Biol Res*. 1998;31:273-279.
74. Halliwill JR. Mechanisms and clinical implications of post-exercise hypotension in humans. *Exerc Sport Sci Rev*. 2001;29:65-70.
75. Brownley KA, Hinderliter AL, West SG, et al. Sympathoadrenergic mechanisms in reduced hemodynamic stress responses after exercise. *Med Sci Sports Exerc*. 2003;35:978-986.
76. Priviero F, De Nucci G, Antunes E, et al. Chronotropic response to adenosine receptor stimulation in rat right atria after run training. *Clin Exp Pharmacol Physiol*. 2004;31:741-743.
77. Izdebska E, Cybulska I, Izdebskir J, et al. Effects of moderate physical training on blood pressure variability and hemodynamic pattern in mildly hypertensive subjects. *J Physiol Pharmacol*. 2004;55:713-724.
78. Jo Y, Arita M, Baba A, et al. Blood pressure and sympathetic activity following responses to aerobic exercise in patients with essential hypertension. *Clin Exp Hypertens A*. 1989;11 (suppl 1):415-417.
79. Tanabe Y, Urata H, Kiyonaga A, et al. Changes in serum concentration of taurine and other amino acids in clinical antihypertensive exercise therapy. *Clin Exp Hypertens A*. 1989;11:149-165.
80. Grassi G, Serravalle G, Calhoun D, et al. Physical exercise in essential hypertension. *Chest*. 1992;101 (suppl 5):312-314.
81. O'Sullivan SE, Bell C. The effects of exercise and training on human cardiovascular reflex control. *J Autom Nerv Syst*. 2000;81:16-24.
82. Beatty JA, Kramer JM, Plowey ED, et al. Physical exercise decreases neuronal activity in the posterior hypothalamic area of spontaneously hypertensive rats. *J Appl Physiol*. 2005;98:572-578.
83. Spieker LE, Noll G, Ruschitzka FT, et al. Working under pressure: the vascular endothelium in arterial hypertension. *J Hum Hypertens*. 2000;14:617-630.
84. Vanhoutte PM, Fournet-Bourguignon MP, Vilaine JP. Dysfunction of the nitric oxide pathway during coronary endothelium regeneration [discussion]. *Bull Acad Natl Med*. 2002;186:1525-1541.
85. Giles TD. Aspects of nitric oxide in health and disease: a focus on hypertension and cardiovascular disease. *J Clin Hypertens (Greenwich)*. 2006;8(12)(suppl 4):2-16.
86. Bowles DK, Woodman CR, Laughlin MH. Coronary smooth muscle and endothelial adaptations to exercise training. *Exerc Sport Sci Rev*. 2000;28:57-62.
87. Laughlin MH, Welshons WV, Sturek M, et al. Gender, exercise training, and eNOS expression in porcine skeletal muscle arteries. *J Appl Physiol*. 2003;95:250-264.
88. Rudic RD, Shesely EG, Maeda N, et al. Direct evidence for the importance of endothelium-derived nitric oxide in vascular remodelling. *J Clin Invest*. 1998;101:731-736.
89. Droge W. Free radicals in the physiological control of cell function. *Physiol Rev*. 2002;82:47-95.
90. Linke A, Adams V, Schulze PC, et al. Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle. *Circulation*. 2005;111:1763-1770.
91. Francisco Javier O, Manuel R, Manuel RR. Regular physical activity increases glutathione peroxidase activity in adolescents with down syndrome. *Clin J Sport Med*. 2006;16:355-356.
92. Fukai T, Siegfried MR, Ushio-Fukai M, et al. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *J Clin Invest*. 2000;105:1631-1639.
93. Rush JW, Turk JR, Laughlin MH. Exercise training regulates SOD-1 and oxidative stress in porcine aortic endothelium. *Am J Physiol Heart Circ Physiol*. 2003;284:H1378-1387.
94. Chang SP, Chen YH, Chang WC, et al. Increase of antioxidation by exercise in the liver of obese zucker rats. *Clin Exp Pharmacol Physiol*. 2004;31:506-511.

95. Graham DA, Rush JW. Exercise training improves aortic endothelium-dependent vasorelaxation and determinants of nitric oxide bioavailability in spontaneously hypertensive rats. *J Appl Physiol*. 2004;96:2088-2096.
96. Dimmeler S, Fleming I, Fisslthaler B, et al. Activation of nitric oxide synthase in endothelial cells by AKT-dependent phosphorylation. *Nature*. 1999;399:601-605.
97. Davis ME, Cai H, Drummond GR, et al. Shear stress regulates endothelial nitric oxide synthase expression through c-SRC by divergent signaling pathways. *Circ Res*. 2001;89:1073-1080.
98. Davis ME, Cai H, McCann L, et al. Role of c-SRC in regulation of endothelial nitric oxide synthase expression during exercise training. *Am J Physiol Heart Circ Physiol*. 2003;284:H1449-1453.
99. Kirkby NS, Hadoke PW, Bagnall AJ, et al. The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? [published online ahead of print October 29, 2007]. *Br J Pharmacol*. doi:10.1038/sj.bjp.0707516.
100. Van Guilder GP, Westby CM, Greiner JJ, et al. Endothelin-1 vasoconstrictor tone increases with age in healthy men but can be reduced by regular aerobic exercise. *Hypertension*. 2007;50:403-409.
101. Zhang B, Sakai T, Noda K, et al. Multivariate analysis of the prognostic determinants of the depressor response of exercise therapy in patients with essential hypertension. *Circ J*. 2003;67:579-584.
102. Hernelahti M, Levalahti E, Simonen RL, et al. Relative roles of heredity and physical activity in adolescence and adulthood on blood pressure. *J Appl Physiol*. 2004;97:1046-1052.
103. Rice T, An P, Gagnon J, et al. Heritability of HR and BP response to exercise training in the HERITAGE family study. *Med Sci Sports Exerc*. 2002;34:972-979.
104. Zhang B, Sakai T, Miura S, et al. Association of angiotensin-converting-enzyme gene polymorphism with the depressor response to mild exercise therapy in patients with mild to moderate essential hypertension. *Clin Genet*. 2002;62:328-333.
105. Hagberg JM, Ferrell RE, Dengel DR, et al. Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. *Hypertension*. 1999;34:18-23.
106. Kimura T, Yokoyama T, Matsumura Y, et al. NOS3 genotype-dependent correlation between blood pressure and physical activity. *Hypertension*. 2003;41:355-360.
107. Dengel DR, Brown MD, Ferrell RE, et al. Exercise induced changes in insulin action are associated with ACE gene polymorphisms in older adults. *Physiol Genomics*. 2002;11:73-80.
108. Greenfield JR, Samaras K, Campbell LV, et al. Physical activity reduces genetic susceptibility to increased central systolic pressure augmentation: a study of female twins. *J Am Coll Cardiol*. 2003;42:264-270.
109. Schweitzer NB, Alessio HM, Hagerman AE, et al. Access to exercise and its relation to cardiovascular health and gene expression in laboratory animals. *Life Sci*. 2005;77:2246-2261.
110. Halbert JA, Silagy CA, Finucane P, et al. The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer. *J Hum Hypertens*. 1997;11:641-649.
111. Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2000;35:838-843.
112. Pinto A, Di Raimondo D, Tuttolomondo A, et al. Twenty-four hour ambulatory blood pressure monitoring to evaluate effects on blood pressure of physical activity in hypertensive patients. *Clin J Sport Med*. 2006;16:238-243.
113. Kokkinos PF, Narayan P, Papademetriou V. Exercise as hypertension therapy. *Cardiol Clin*. 2001;19:507-516.
114. Fisher MM. The effect of resistance exercise on recovery blood pressure in normotensive and borderline hypertensive women. *J Strength Cond Res*. 2001;15:210-216.
115. Braith RW, Stewart KJ. Resistance exercise training: its role in the prevention of cardiovascular disease. *Circulation*. 2006;113:2642-2650.
116. Cornelissen VA, Fagard RH. Effects of resistance training on resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens*. 2005;23:251-259.
117. Pollock ML, Franklin BA, Balady GJ, et al. AHA Science Advisory: resistance exercise in individuals with and without cardiovascular disease: benefits, rationale safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation*. 2000;101:828-833.
118. Weisser B, Richter H, Siewers M. Power training for patients with arterial hypertension. *MMW Fortschr Med*. 2006;148:33-34.
119. Franklin BA, Gordon S, Timmis GC. Exercise prescription for hypertensive patients. *Ann Med*. 1991;23:279-287.
120. Taylor AC, McCartney N, Kamath MV, et al. Isometric training lowers resting blood pressure and modulates autonomic control. *Med Sci Sports Exerc*. 2003;35:251-256.
121. McGowan CL, 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.
122. Tanaka H, Bassett DR Jr, Howley ET, et al. Swimming training lowers the resting blood pressure in individuals with hypertension. *J Hypertens*. 1997;15:651-657.
123. Lee MS, Pittler MH, Guo R, et al. Qigong for hypertension: a systematic review of randomized clinical trials. *J Hypertens*. 2007;25:1525-1532.

124. Cheung BM, Lo JL, Fong DY, et al. Randomized controlled trial of qigong in the treatment of mild exercise hypertension. *J Hum Hypertens*. 2005;19:697-704.
125. Young DR, Appel LJ, Jee S, et al. The effect of aerobic exercise and T'ai chi on blood pressure in older people: result of a randomized trial. *J Am Geriatr Soc*. 1999;47:277-284.
126. Moreira WD, Fuchs FD, Ribeiro JP, et al. The effect of two aerobic training intensities on ambulatory blood pressure in hypertensive patients: results of a randomized trial. *J Clin Epidemiol*. 1999;52:637-642.
127. Rogers MW, Probst MM, Gruber JJ, et al. Differential effects of exercise training intensity on blood pressure and cardiovascular responses to stress in borderline hypertensive humans. *J Hypertens*. 1996;14:1369-1375.
128. Matsusaki M, Ikeda M, Tashiro E, et al. Influence of workload on the antihypertensive effects of exercise. *Clin Exp Pharmacol Physiol*. 1992;19:471-479.
129. Marceau M, Kouame M, Lacourciere Y, et al. Effects of different training intensities on 24-hour blood pressure in hypertensive subjects. *Circulation*. 1993;88: 2803-2811.
130. Reaven PD, Burrett-Connor E, Edelstein S. Relation between leisure-time physical activity and blood pressure in older women. *Circulation*. 1991;83:559-565.
131. Cooper AR, Moore LA, McKenna J, et al. What is the magnitude of blood pressure response to a program of moderate intensity exercise? Randomised controlled trial among sedentary adults with unmedicated hypertension. *Br J Gen Pract*. 2000;50:958-962.
132. Ishikawa-Tanaka K, Ohta T, Tanaka H. How much exercise is required to reduce blood pressure in essential hypertensives: a dose-response study. *Am J Hypertens*. 2003;16:629-633.
133. Fagard RH. Exercise characteristics and blood pressure response to dynamic physical training [discussion]. *Med Sci Sports Exerc*. 2001;33 (suppl 6):484-492; S493-494.
134. Elley R, Bagrie R, Arroll B. Do snacks of exercise lower blood pressure? A randomized crossover trial. *N Z Med J*. 2006;119:U1196.
135. Schwarz S, Halle M. Blood pressure lowering through physical training—what can be achieved? *MMW Fortschr Med*. 2006;148:29-32.
136. Hamer M. The anti-hypertensive effects of exercise: integrating acute and chronic mechanisms. *Sports Med*. 2006;36:109-116.
137. Ashworth NL, Chad KE, Harrison EL, et al. Home versus center based physical activity programs in older adults. *Cochrane Database Syst Rev*. 2005;1:CD004017.
138. Nho H, Tanaka K, Kim HS, et al. Exercise training in female patients with a family history of hypertension. *Eur J Appl Physiol Occup Physiol*. 1998;78:1-6.
139. Bonet J, Coll R, Rocha E, et al. Supervised versus recommended physical exercise in hypertensive women. Is its recommendation enough? *Blood Press*. 2003;12: 139-144.
140. Nunes AP, Rios AC, Cunha GA, et al. The effects of nonsupervised exercise program, via internet, on blood pressure and body composition in normotensive and prehypertensive individuals. *Arq Bras Cardiol*. 2006;86:289-296.
141. Kolbe-Alexander TL, Lambert EV, Charlton KE. Effectiveness of a community based low intensity exercise program for older adults. *J Nutr Health Aging*. 2006;10:21-29.
142. Higashi Y, Yoshizumi M. Exercise and endothelial function: role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. *Pharmacol Ther*. 2004;102:87-96.
143. Marsh SA, Coombes JS. Exercise and endothelial cell. *Int J Cardiol*. 2005;99:165-169.
144. Williams RS, Kraus WE. Exercise and health: can biotechnology confer similar benefits? *PLoS Med*. 2005;2:e68.