Original Paper

Improvements in Insulin Sensitivity and Muscle Blood Flow in Aerobic-Trained Overweight-Obese Hypertensive Patients Are Not Associated With Ambulatory Blood Pressure

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*To verify whether there are relationships between vascular and hormonal responses to aerobic training in hypertensive persons, sedentary hypertensive patients were randomized to an aerobic training or a callisthenic exercise group. The patients' 24-hour blood pressure, arterial compliance, forearm blood flow, and hormonal profile were evaluated at baseline and after 3-month training protocols. Mean maximal oxygen consumption (VO_2max) increased by 8% in the aerobic group (*P*<.001), while no change was observed in the control group. There was a decrease in insulin resistance (homeostatic model assessment of insulin resistance,* P*=.039) and plasma cortisol (*P*=.006) in the aerobic group only, that also demonstrated an increase in forearm blood flow (*P*<.001) after training. No relationship was observed between change in blood pressure or change in body mass and other parameters. Aerobic training can promote a decrease in cardiovascular risk in hypertensive adults by improving vascular function and insulin resistance, despite no changes in ambulatory blood pressure after a 3-month intervention.*
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Hypertension is an enormous public health challenge in both industrialized and developing countries, and it is the most important risk factor for cardiovascular (CV) diseases.[1] Physical exercise is recommended to help reduce blood pressure (BP) and lower the risk for developing CV disease.[2] A recent meta-analysis[3] of randomized controlled trials showed that in a hypertensive population, endurance training reduced resting systolic and diastolic BP by 6.9 mm Hg and 4.9 mm Hg, respectively, and ambulatory systolic BP and diastolic BP (4 studies, 5 groups) decreased by 3.4 mm Hg and 2.7 mm Hg, respectively. Despite this apparent reduction, changes in ambulatory systolic BP were nonsignificant in 3 groups, whereas reductions in diastolic BP were nonsignificant in 4 groups of these studies. These disparate results might be partially explained by methodologic differences, including small sample sizes and poor supervision of prescribed training intensity. Ambulatory BP (ABP) may be the more appropriate method of monitoring BP in exercise studies because, unlike office BP, it is not influenced by the "white coat effect" during treatment, placebo-induced hypotension, and regression to the mean phenomenon.[4]

Decreased activity of the autonomic nervous system,[5] lower plasma renin activity,[6] and reduction

in insulin resistance[7] are suggested mechanisms that underlie training-induced reductions in BP. Changes in plasma aldosterone[8] and cortisol[9] could also be involved in BP regulation during aerobic training. Neurohormonal and vascular adaptations are also potential mechanisms that could explain the BP-lowering effect of endurance training in hypertension; however, previous studies on endurance training in hypertension are inconsistent.

Therefore, the purpose of this randomized controlled study was to investigate the relationships between vascular and hormonal adaptations in nonmedicated essential hypertensive patients following a 3-month supervised aerobic training program, using ABP monitoring.

METHODS

Participants

This trial was carried out at the Hypertension Research Center of the Marília School of Medicine. The school's institutional ethics committee on human research approved the protocol and the procedures followed were in accordance with institutional guidelines. Patients with mild to moderate hypertension were included in the study. Exclusion criteria included diabetes mellitus and participation in regular exercise ($\geq$60 min/wk) during the previous semester. Antihypertensive patients were withdrawn at least 1 month before the initial screening when appropriate.

Sample size was estimated[10] to provide 90% power at α=0.05 (2-sided) in order to detect a 3-mm Hg difference (final−baseline) in BP, with a standard deviation of 3 mm Hg, presupposing a 20% loss to follow-up during the study. Using a 2:1 randomization design, at least 40 patients were required for the aerobic group and 20 patients were required for the control (CTL) group.

Experimental Design

After giving written informed consent, patients with high BP underwent an initial screening that included clinical examination, electrocardiogram and biochemistry tests. Initial ABP was used as a baseline BP and was used to avoid white coat hypertension. A progressive maximal treadmill exercise test was performed to exclude silent coronary heart disease and to assess maximal oxygen consumption (VO_2max). Plasma hormone measurements were obtained from fasting blood samples. Urinary metanephrines (as a surrogate of sympathoadrenal activity) and urinary sodium (UNa; as an indication of salt consumption) were assessed by 24-hour urine analysis. Vascular function was assessed through forearm blood flow (FBF) and arterial compliance measurements. Then, patients were randomized to the aerobic exercise training (AEX) or a postural exercise protocol, used as a CTL. After 3 months, the measurements were repeated. Patients were instructed to keep their usual dietary habits during the trial.

Aerobic Training Program. Aerobic training was offered Monday through Friday in 1-hour sessions (5-minute stretching warm-up, 50-minute jogging on an electronic treadmill, 5-minute cool-down) at an exercise intensity corresponding to 50% to 70% VO_2max. In every exercise session, laboratory staff supervised the exercise. The intensity was monitored using a Polar A3 heart rate monitor (Polar Electro Oy, Kempele, Finland).

CTL Exercise Protocol. The exercise protocol for the CTL group was performed in 1-hour sessions, 3 times per week. The exercises consisted of several types of isometric calisthenics with special attention to posture and breathing techniques. No isotonic exercises were included.

Outcome Measures

Ambulatory BP. ABP was obtained prior to randomization and again in the first week after the end of the intervention. ABP was always obtained during a workday, and at least 24 hours after the last exercise session. BP measurements were obtained with an automatic oscillometric SpaceLabs model 90207 device[11] (SpaceLabs, Inc, Issaquah, WA) at 20-minute intervals, beginning at 9 AM and continuing for 24 hours. A tracing was considered adequate if at least 90% of measurements were acceptable.[12] Means of 24-hour systolic and diastolic BPs were used for statistical purposes.

VO_2max. VO_2max was determined by indirect calorimetry (SensorMedics Vmax 229 system; SensorMedics Co, Yorba Linda, CA) during a treadmill stress test using a modified Naughton protocol.[13] After 2 minutes of rest in the standing position, all patients performed the exercise until symptoms (fatigue or dyspnea) made them unable to continue. During the test, heart rate and rhythm were registered by electrocardiography with 12 derivations. Additionally, systolic and diastolic BPs were measured using the auscultatory method, and subjective perception of exertion was obtained from each patient using the Borg Scale at the end of each stage of the test protocol. Interruption of the test was accepted if the patient reached one of the

criteria: (1) a respiratory quotient (RQ) $\geq$1.1; (2) a heart rate >90% of the predicted maximum for age; or (3) a plateau in VO_2 before an increment in the exertion, where RQ was the relationship between the carbon dioxide production (VCO_2) and the volume of oxygen consumed (VO_2). VO_2max was calculated as the average value during the last 30 seconds of test.

Blood Collection and Analysis. Prior to the blood draws, patients fasted for 12 hours and refrained from exercise for 48 hours. All of the samples were collected from the antecubital vein with the patient in a semisupine position. Blood samples were collected in 10-mL tubes containing anticoagulant and chelating agent, separated by centrifugation, frozen and stored until analyzed. Insulin was measured using a chemiluminescence technique. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used as an insulin resistance index.[14] C-peptide and aldosterone were measured via radioimmunoassay. Time-resolved immunofluorimetry was used to assess cortisol. Plasma renin was measured by an immunoradiometry technique. Urinary metanephrines were measured using enzyme immunoassay.

FBF. FBF was measured using a mercury-filled Silastic strain-gauge plethysmograph. With the patient in the supine position, a strain gauge was attached to the upper part of the left arm and connected to a plethysmography device. A wrist cuff was inflated to 50 mm Hg above the systolic BP to exclude the hand circulation from confounding the measurements. Occlusion of the distal circulation was performed 1 minute before each measurement and throughout the measurement of FBF. The upper arm congesting cuff was inflated to 40 mm Hg for 7 seconds in each 15-second cycle to occlude venous outflow from the arm using a rapid cuff inflator. The FBF output signal was transmitted to a computer and registered and analyzed using NIVP3 software (Hokanson, Inc, Bellevue, WA). FBF was expressed as mL per minute per 100 mL of forearm tissue volume. Four plethysmographic measurements were averaged for analysis of FBF.[15,16]

Arterial Compliance. Large artery, or capacitive (C1), and small artery reflective, or oscillatory (C2), compliance was derived from radial artery waveforms, obtained using a calibrated tonometer (model CR-2000; Hypertension Diagnostics Inc, Eagan, MN).[17] All C1 and C2 compliance measures were obtained between 8 AM and 11 AM in a quiet laboratory. The patient's arm was supported by an angulated "wrist stabilizer," ensuring a constant wrist position. The tonometer was housed inside a holding and positioning device that wrapped around the supported arm, completely stabilizing the arm in position after the tonometer was applied. The waveforms were then calibrated to the systolic and diastolic cuff pressure values of an integrated oscillometric device (cuff placed on the contralateral arm with respect to the tonometer). A computer-based third-order, 4-element modified Windkessel model of the circulation was used to match the diastolic pressure decay of the waveforms and to quantify changes in arterial waveform morphology.[18] The values of C1 and C2 were considered the weighted averages of the values obtained on individual waveforms during a 30-second recording period.

Statistical Analysis

Data were analyzed on an intention-to-treat basis with participants lost to follow-up excluded from the analysis. The use of parametric tests require data to satisfy two assumptions: (1) the data within each group must be distributed normally (K-S normality test), and (2) variances between groups must be homogeneous (*F* test). A 1-way analysis of variance with repeated measures (time) was used to analyze weight, oxygen consumption, BP, and vascular variables when examining for program effects. Significant main effects were followed-up with Bonferroni post hoc analyses to locate specific differences over time. Nonparametric tests were used to analyze hormone changes and respective correlations (Mann–Whitney *U*-test, Wilcoxon Signed test, Spearman Correlation test). The statistical analysis was performed using STATVIEW version 5.0 (SAS Institute, Inc, Cary, NC). Values were expressed as mean (95% confidence interval [CI]) and were considered significant at $P \leq .05$.

RESULTS

Fifty-five patients (30 women and 25 men; mean age, 49 [47–52] years) in the AEX group and 24 patients (18 women and 6 men; mean age, 53 [50–56] years) in the CTL group completed the study. Originally, 62 individuals (34 women and 28 men) entered the study in the AEX group and 28 individuals (21 women and 7 men) in the CTL group, but 7 individuals in the AEX group and 4 in the CTL group discontinued participation due to noncompliance with the protocol.

There were 15 (27%) and 6 (25%) untreated hypertensive patients in the AEX and CTL groups,

Table I. Baseline Biochemical Values of AEX and CTL Groups

Variables	AEX (n=55)	CTL (n=24)	*P* Value
Creatinine, μmol/L	81.7 (76.4–87.0)	70.0 (64.3–75.6)	.012
Uric acid, μmol/L	326.8 (302.5–351.2)	239.9 (186.0–293.8)	.003
Total cholesterol, mmol/L	5.9 (5.5–6.2)	6.0 (5.6–6.5)	ns
HDL-C, mmol/L	1.2 (1.1–1.3)	1.4 (1.2–1.5)	.027
Triglycerides, mmol/L	2.1 (1.7–2.5)	1.9 (1.5–2.2)	ns
LDL-C, mmol/L	3.7 (3.4–4.0)	3.8 (3.3–4.2)	ns
Glucose, mmol/L	5.4 (5.2–5.5)	5.4 (5.1–5.6)	ns

Abbreviations: AEX, aerobic exercise training group; CTL, control group; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ns, not significant. Values are expressed as mean (95% confidence interval). *P* for comparisons between pre-training and post-training values.

respectively. Mean times of antihypertensive drug withdrawal before the baseline ABP measurement were 6.9 (5.6–8.2) weeks for the AEX group and 6.4 (5.1–7.8) weeks for the CTL group (*P*=not significant).

On average, exercise protocols were performed for 15 weeks. Participants attended 90% of the sessions and the mean time in the target zone was 45 minutes per session.

AEX and CTL groups differed at baseline for weight (*P*=.031), C-peptide (*P*=.023), FBF (*P*=.033), creatinine (*P*=.012), uric acid (*P*=.003), and high-density lipoprotein cholesterol (*P*=.027). Baseline group characteristics and training effects are summarized in Table I and Table II.

Body Mass and Diet

At the end of the study, a slight but significant decrease in body mass index (BMI) was observed in both groups. This change over time (Δ) might imply that study participants voluntarily reduced caloric ingestion during the protocol, assuming that the CTL group did not expend more calories during the study. The magnitude of the BMI change did not differ between groups between baseline and follow-up (*F* value=1.23, *P*=.27). Urinary sodium did not vary in either group, suggesting that study participants maintained stable sodium ingestion during the study (ΔAEX=3 mEq/L, *P*=.41 and ΔCTL= 11 mEq/L, *P*=.57).

VO_2max and ABP

There was a mean 8% increase in the VO_2max of the AEX group at the end of the aerobic training, but no change was seen in the CTL group. The two protocols had a significantly different effect on VO_2max (*F* value=12.36, *P*=.0008). No significant changes in ABP occurred after the 3-month period in either group (Table I). Stratification of groups by initial renin or metanephrine tertiles did not distinguish BP responses to training. There was no correlation between ABP and plasma hormone changes at the end of the exercise protocols.

Hormones

Plasma renin, aldosterone, C-peptide, and urinary metanephrine did not significantly vary in either group during the study. There was no significant difference between groups for changes in the aldosterone/renin ratio during the study. There was a mean decrease in the AEX group of 0.34 and a mean decrease in the CTL group of 0.41 (*P*=.831). In the AEX group, cortisol and HOMA-IR significantly decreased by 15% and 25%, respectively, whereas no changes were observed in the CTL group. There were no correlations between BMI and ΔHOMA-IR or between HOMA-IR and Δcortisol (Spearman rank correlation).

Arterial Compliance and FBF

Arterial elasticity indices did not significantly change in either group. FBF increased by 32% in the AEX group, while it did not significantly change in the CTL group. A significant interaction effect between FBF variation and exercise protocol was observed (*F* value=4.1, *P*=.047). There was no correlation between ΔFBF and ΔHOMA-IR (Spearman rank correlation).

DISCUSSION

The main finding of this study was that vascular and ABP changes were not associated with the hormonal response after 3 months of an aerobic training program in a hypertensive population. The moderate aerobic training did not change ABP and arterial compliance, but the training did reduce

Table II. Ambulatory Blood Pressure, Hormone Level, and Vascular Function Responses to AEX and CTL Protocols

	AEX (N=55)			CTL (N=24)		
Variables	Pre	Post	*P* Value	Pre	Post	*P* Value
BMI, kg/m^2	30.0 (28.8–31.2)	29.5 (28.3–30.7)	<.001	29.6 (27.8–31.5)	29.3 (27.3–31.3)	.044
VO_2max, mL/kg/min	24.8 (23.0–26.5)	26.7 (24.9–28.6)	<.001	23.4 (21.2–25.7)	23.2 (20.1–26.3)	.368
24-hour SBP, mm Hg	141.1 (138.0–144.3)	141.1 (138.2–144.1)	.999	140.9 (136.9–144.9)	140.8 (136.2–145.4)	.935
24-hour DBP, mm Hg	90.0 (87.6–92.4)	89.5 (86.8–92.3)	.481	88.3 (84.8–91.9)	88.3 (84.0–92.5)	.941
Daytime SBP, mm Hg	145.3 (142.1–148.5)	145.0 (142.0–148.0)	.770	144.0 (139.8–148.3)	144.0 (139.2–148.9)	.999
Daytime DBP, mm Hg	93.7 (91.2–96.2)	93.0 (90.0–96.0)	.330	91.6 (87.9–95.3)	91.2 (86.7–95.7)	.688
Nighttime SBP, mm Hg	130.8 (127.4–134.1)	130.4 (127.1–133.7)	.745	132.8 (128.6–137.0)	131.5 (126.6–136.3)	.485
Nighttime DBP, mm Hg	80.3 (77.8–82.9)	79.9 (77.2–82.6)	.610	81.0 (77.5–84.5)	80.1 (75.8–84.4)	.613
Dipping, %	12.2 (10.3–14.1)	11.9 (10.4–13.5)	.760	9.4 (7.3–11.7)	9.5 (6.9–12.1)	.978
Renin, pmol/L	0.24 (0.18–0.30)	0.29 (0.22–0.36)	.159	0.21 (0.17–0.25)	0.32 (0.17–0.46)	.151
Aldosterone, pmol/L	0.28 (0.23–0.33)	0.26 (0.21–0.31)	.049	0.29 (0.26–0.33)	0.29 (0.24–0.34)	.939
Cortisol, nmol/L	335 (229–371)	283 (253–313)	.006	322 (259–386)	335 (282–388)	.714
C-peptide, pmol/L	0.95 (0.80–1.09)	0.86 (0.75–0.97)	.081	0.69 (0.58–079)	0.64 (0.53–076)	.493
HOMA-IR, μU/mL × mmol/L	2.7 (1.7–3.7)	2.0 (1.6–2.5)	.036	1.6 (1.2–1.9)	2.0 (1.4–2.6)	.253
Urinary metanephrines, nmol/L	1731 (1400–2062)	1704 (1497–1910)	.959	1693 (1247–2139)	1644 (1215–2073)	.995
C1, mL/mm Hg × 10	15.5 (14.2–16.9)	15.3 (14.0–16.7)	.938	14.2 (12.0–16.4)	16.0 (12.5–19.6)	.104
C2, mL/mm Hg × 100	4.5 (3.7–5.2)	4.8 (4.0–5.6)	.367	4.1 (3.4–4.9)	3.7 (3.2–4.3)	.330
FBF, mL/dL/min	4.0 (3.6–4.4)	5.4 (4.9–5.9)	.001	4.7 (4.2–5.2)	5.0 (4.4–5.6)	.444

Abbreviations: AEX, aerobic exercise training; BMI, body mass index; C1, large artery elasticity index; C2, small artery elasticity index; CTL, control; DBP, diastolic blood pressure; FBF, forearm blood flow; HOMA-IR, homeostatic model assessment of insulin resistance; VO_2max, maximal oxygen consumption. Values are expressed as mean (95% confidence interval). *P* for comparisons between pre-training and post-training values.

adrenocortical tone and insulin resistance, while increasing muscle blood flow.

Our results conflict with those of previous randomized controlled trials with comparable sample sizes. In the trial of Cooper and colleagues[19] with 47 nonmedicated hypertensive participants (mean age, 46 years; mean baseline BMI=26.6 kg/m^2), the intervention was very short (6 weeks), physical activity was poorly described, fitness gain was not reported, and ABP and patient weight did not significantly change over the course of the program. In a study by Blumenthal and colleagues,[20] 39 untreated hypertensives (mean age, 44 years; mean baseline BMI=27.2 kg/m^2) underwent a 4-month supervised aerobic training intervention. These participants did not demonstrate a significant reduction in ABP or weight, despite a fitness gain of 16%. In another study by Blumenthal and colleagues,[21] 54 nonmedicated hypertensives (mean age, 47 years; mean baseline BMI=32.8 kg/m^2) participated in a supervised aerobic training program for 6 months. These participants demonstrated mild but significant reductions in ABP and weight in addition to a fitness gain of 12%. In our study, there was a median increase in fitness level by 12%, the mean baseline BMI was 30.0 kg/m^2, and the mean weight loss was 1.4 kg (95% CI, 2.2–0.7). This occurred despite no reduction in ABP.

ABP response to aerobic training might be correlated to protocol duration, but may not be influenced by weight change or fitness gain. A possible explanation for the substantial variability in training-induced BP response might be the influence of genetic polymorphisms on the exercise effect in persons with hypertension.[22,23,24] In the present study, neither baseline hormone levels nor the magnitude of hormone after training predicted ABP changes. To our knowledge, there are no randomized controlled trials that verify the relationship between ABP and hormonal changes after exercise training in persons with hypertension. Office BP studies have disparate results regarding a possible association between BP and hormonal profile during exercise training.[25–28]

The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study data showed large interindividual variability in cortisol levels in response to exercise training.[9] Few studies have investigated plasma cortisol response to exercise training in hypertension. No significant change in plasma cortisol was observed after 10 weeks of supervised moderate exercise in 19 mild hypertensive adults.[6] Compared with the present study, this trial was shorter, the exercise training was unsupervised, and participants were younger.

Insulin resistance in essential hypertension is characterized by impaired insulin stimulation of blood flow in skeletal muscle.[29] Exercise training can increase insulin sensitivity in hypertension,[30] and this effect is not related to changes in hemodynamics.[31] Because C-peptide level did not significantly change at the end of the aerobic program in our study, the amelioration in insulin resistance was likely due to greater peripheral tissue sensitivity to insulin action on glucose uptake. The improvement in muscle blood flow observed in the present study was not correlated with the decrease in insulin resistance, supporting the idea that the effect of aerobic exercise on carbohydrate metabolism is mainly mediated by cellular mechanisms.[32]

Trials that reported effects of aerobic exercise programs on plasma renin activity in hypertensive patients had conflicting results.[6,27] The study of Hagberg and colleagues[27] showed similar reductions in plasma renin activity of active and control after 9 months of training. These results are contrary to other reports,[26,33] including the present one, that used similar training programs in hypertensive adults. Our results contradict the previously held ideas that baseline plasma renin activity affects the response of BP and renin activity with training.

Reports on changes in sympathetic activity after exercise training in hypertensive patients are conflicting.[6,27,34] The heterogeneity of the sympathetic response to exercise training could partially account for the variability of the BP response to exercise.[5] The hypothesis that post-training changes in BP and sympathetic tone in hypertensive patients depend on the baseline sympathetic tone was not confirmed in our study. Plasma hormone levels are not consistently modified by aerobic training. The changes in plasma hormone levels could not account for variations in BP. Additionally, stratification of patients according to hormonal profile failed to predict BP response to exercise training. Therefore, phenotypic characteristics may not be sufficient to distinguish "responders" from "nonresponders."

Longitudinal studies that investigated effects of regular exercise on arterial compliance are conflicting with regard to the relationship with BP.[35–38] Central arterial compliance increased to levels similar to those of endurance-trained men, independent of changes in body mass, BP, or VO_2max, after 3 months of moderate training in 20 middle-aged or older sedentary healthy men.[35] Four weeks of moderate exercise training induced a significant increase in arterial compliance in 13 healthy young men,

and this change was linearly related to a significant increase of 12% in VO_2max.[36] On the other hand, in older isolated systolic hypertensive patients, systemic arterial compliance did not significantly change at the end of an endurance training program, despite a significant VO_2max increase of 13% after 8 weeks.[37] A recent randomized controlled trial[38] investigated the effects of exercise training on BP and arterial compliance in 51 older mild hypertensive adults. After 6 months, there was a significant increase in VO_2max (16%), a decrease in discrete diastolic BP, improvement in body composition, and no significant change in arterial compliance. Collectively, these results suggest that hypertension blunts the beneficial effects of regular exercise on arterial distensibility, possibly by accelerating age-related structural arterial modifications that render large arteries less susceptible to the effects of exercise training.

The response of basal blood flow to exercise training in hypertensive patients may depend on the specifics of the exercise protocol. Neither brisk walking[39] nor aerobic training with an intensity of 70% VO_2max changed basal FBF.[40] Nevertheless, results of the present study corroborate with others,[40] indicating that training at an intensity corresponding to 50% VO_2max can provoke an increase in FBF, suggesting that mild exercise can be effective in ameliorating muscle blood flow.

CONCLUSIONS

Metabolic and vascular benefits of a short aerobic exercise program are not associated with ABP in individuals with essential hypertension. While mild to moderate aerobic training may impact public health, the clinical significance of this training as an isolated treatment for hypertension is still not clear. More randomized controlled trials with adequate sample size and longer duration are needed to further elucidate the effects of regular exercise on 24-hour BP profiles and vascular function in hypertensive patients. The stratification of patients with hypertension according to genetic profiles might clarify some obscure aspects of the effects of exercise training on BP in essential hypertension.

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REFERENCES

1 Whelton PK. Epidemiology and the prevention of hypertension. *J Clin Hypertens*. 2004;6:636–642.
2 Mancia G, De Backer G, Dominiczak A, et al. A 2007 guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). *Eur Heart J*. 2007;28:1462–1536.
3 Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension*. 2005;46: 667–675.
4 Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: a meta-analysis. *J Hypertens*. 2004;22:435–445.
5 Brown MD, Dengel DR, Hogikyan RV, et al. Sympathetic activity and the heterogenous blood pressure response to exercise training in hypertensives. *J Appl Physiol*. 2002;92: 1434–1442.
6 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.
7 Pescatello LS, Blanchard BE, Van Heest JL, et al. The metabolic syndrome and the immediate antihypertensive effects of aerobic exercise: a randomized control design. *BMC Cardiovasc Disord*. 2008;8:12.
8 Jones JM, Dowling TC, Park J-J, et al. Differential aerobic exercise-induced changes in plasma aldosterone between African Americans and Caucasians. *Exp Physiol*. 2007;92:871–879.
9 Feitosa MF, Rice T, Rosmond R, et al. A genetic study of cortisol measured before and after endurance training: the HERITAGE Family Study. *Metabolism*. 2002;51:360–365.
10 Rosner B. *Fundamentals of Biostatistics*, 5th edn. Pacific Grove, CA: Duxbury Press; 2000.
11 O'Brien E, Mee F, Atkins N, et al. Accuracy of the SpaceLabs 90207 determined by the British Hypertension Society protocol. *J Hypertens*. 1991;9:573–574.
12 O'Brien E, Asmar R, Beilin L, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens*. 2003;21:821–848.
13 Kleber FX, Waurick P, Winterhalter M. CPET in heart failure. *Eur Heart J*. 2004;6(suppl D):D1–D4.
14 Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
15 Rhéaume C, Waib PH, Lacourcière Y, et al. Effects of angiotensin antagonism with tasosartan on regional and systemic haemodynamics in hypertensive patients. *J Hypertens*. 1998;16(Pt 2):2085–2089.
16 Higashi Y, Sasaki S, Nakagawa K, et al. A noninvasive measurement of reactive hyperemia that can be used to assess resistance artery endothelial function in humans. *Am J Cardiol*. 2001;87:121–125.
17 Cohn JN, Finkelstein S, McVeigh G, et al. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension*. 1995;26:503–508.
18 Zimlichman R, Shargorodsky M, Boaz M, et al. Determination of arterial compliance using blood pressure waveform analysis with the CR-2000 system. *Am J Hypertens*. 2005;18:65–71.
19 Cooper AR, Moore LAR, McKenna J, et al. What is the magnitude of blood pressure response to a programme of moderate intensity exercise? Randomized controlled trial among sedentary adults with unmedicated hypertension *Br J Gen Pract*. 2000;50:958–962.

20 Blumenthal JA, Siegel WC, Appelbaum M. Failure of exercise to reduce blood pressure in patients with mild hypertension. *JAMA*. 1991;266:2098–2104.

21 Blumenthal JA, Sherwood A, Gullette ECD, et al. Exercise and weight loss reduce blood pressure in men and women with mild hypertension. Effects on cardiovascular, metabolic, and hemodynamic functioning. *Arch Intern Med*. 2000;160:1947–1958.

22 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.

23 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.

24 Franks PW, Bhattacharyya S, Luan J, et al. Association between physical activity and blood pressure is modified by variants in the G-protein coupled receptor 10. *Hypertension*. 2004;43:224–228.

25 Miura S, Tashiro E, Sakai T, et al. Urinary kallikrein activity is increased during the first few weeks of exercise training in essential hypertension. *J Hypertens*. 1994;12:815–823.

26 Tashiro E, Miura S, Koga M, et al. Crossover comparison between the depressor effects of low and high work-rate exercise in mild hypertension. *Clin Exp Pharmacol Physiol*. 1993;20:689–696.

27 Hagberg JM, Montain SJ, Martin WH III, et al. Effect of exercise training in 60- to 69-year-old persons with essential hypertension. *Am J Cardiol*. 1989;64:348–353.

28 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.

29 Laine H, Knuuti MJ, Ruotsalainen U, et al. Preserved relative dispersion but blunted stimulation of mean flow, absolute dispersion, and blood volume by insulin in skeletal muscle of patients with essential hypertension. *Circulation*. 1998;97:2146–2153.

30 Bursztyn M, Ben-Ishay D, Shochina M, et al. Disparate effects of exercise training on glucose tolerance and insulin levels and on ambulatory blood pressure in hypertensive patients. *J Hypertens*. 1993;11:1121–1125.

31 Rhéaume C, Waib PH, Lacourcière Y, et al. Effects of mild exercise on insulin sensitivity in hypertensive subjects. *Hypertension*. 2002;39:989–995.

32 Gautier J-F, Mauvais-Jarvis F. Activité physique et insulinosensibilité. *Diabetes Metab (Paris)*. 2001;27:255–260.

33 Matsusaki M, Ikeda M, Tashiro E, et al. Influence of workload on the antihypertensive effect of exercise. *Clin Exp Pharmacol Physiol*. 1992;19:471–479.

34 Kohno K, Matsuoka H, Takenaka K, et al. Renal depressor mechanisms of physical training in patients with essential hypertension. *Am J Hypertens*. 1997;10:859–868.

35 Tanaka H, Dinenno FA, Monahan KD, et al. Aging, habitual exercise, and dynamic arterial compliance. *Circulation*. 2000;102:1270–1275.

36 Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. *Am J Physiol*. 1994;266:H693–H701.

37 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.

38 Stewart KJ, 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.

39 Higashi Y, Sasaki S, Sasaki N, et al. Daily aerobic exercise improves reactive hyperemia in patients with essential hypertension. *Hypertension*. 1999;33:591–597.

40 Kouamé N, Nadeau A, Lacourcière Y, et al. Effects of different training intensities on the cardiopulmonary baroreflex control of forearm vascular resistance in hypertensive subjects. *Hypertension*. 1995;25:391–398.