ORIGINAL RESEARCH

Exercise Blood Pressure and the Risk for Future Hypertension Among Normotensive Middle-Aged Adults

Assaf Berger, MD; Ehud Grossman, MD; Moshe Katz, MD; Shaye Kivity, MD; Robert Klempfner, MD; Shlomo Segev, MD; Ilan Goldenberg, MD; Yehezkel Sidi, MD; Elad Maor, MD, PhD

***Background*—**The aim of the present study was to examine whether exercise blood pressure can be used to predict the development of hypertension in normotensive middle-aged adults.

***Methods and Results*—**We investigated 7082 normotensive subjects who were annually screened in a tertiary medical center and completed maximal treadmill exercise tests at each visit. After the initial 3 years, subjects were divided into approximate quartiles according to their average exercise systolic and diastolic blood pressure responses (≤158; 158 to 170; 170 to 183; ≥183 mm Hg for systolic blood pressure and ≤73; 73 to 77; 77 to 82; ≥82 mm Hg for diastolic blood pressure). Mean age of the study population was 48±9 years and 73% were men. Average baseline resting blood pressure was 120/77±12/7 mm Hg. During a follow-up of 5±3 years, 1036 (14.6%) subjects developed hypertension. The cumulative probability of new-onset hypertension at 5 years was significantly increased with increasing quartiles of exercise systolic blood pressure (5%, 9%, 17%, and 35%, respectively; $P<0.001$), with a similar association shown for diastolic blood pressure. After adjustment for baseline resting blood pressure and clinical parameters, each 5-mm Hg increments in exercise either systolic or diastolic blood pressures were independently associated with respective 11% ($P<0.001$) and 30% ($P<0.001$) increased risk for the development of hypertension.

***Conclusions*—**In normotensive middle-aged individuals, blood pressure response to exercise is associated with future development of hypertension. **(*J Am Heart Assoc*. 2015;4:e001710 doi:10.1161/JAHA.114.001710)**

Key Words: diastolic blood pressure • exercise • hypertension • systolic blood pressure

Essential hypertension is a prevalent disorder in the adult population and a well-known risk factor for the development of atherosclerosis and associated morbidity and mortality from cardiovascular diseases.[1] Due to its substantial burden, ample research has been taken to improve the detection of patients at risk for future hypertension, and several studies focused on the association with blood pressure (BP) response to exercise, with conflicting results. Certain studies found this phenomenon to be valid solely for the systolic BP (SBP) response and others for diastolic BP (DBP). Moreover, the majority of researchers defined exaggerated exercise responses as BP measured above strict cutoffs,[2–6] while there are limited data regarding a possible graded association between BP response to exercise and the risk for hypertension.

The present study was designed to evaluate, in a large cohort of normotensive middle-aged adults, whether elevated levels of systolic and diastolic BP during exercise predict the development of future hypertension.

Methods

Study Population

The study population has been described previously.[7] The Institute for Medical Screening of the Chaim Sheba Medical Center performs ≈9000 annual examinations. A computerized database established in the year 2000 was used as the source of data for the present study. All participants were asymptomatic subjects attending periodic health screening examinations as private individuals or as part of health-executive programs. Each annual examination includes a standard questionnaire regarding their demographic characteristics, medical history, lifestyle and health-related habits, as well as any unusual medical event since the previous encounter. The height and weight of all subjects are measured

From the Leviev Heart Center (A.B., M.K., R.K., I.G., E.M.), Departments of Internal Medicine D (E.G.) and C (S.K., Y.S.), Institute for Medical Screening (S.S.), and Pinchas Borenstein Talpiot Medical Leadership Program (E.M.), Chaim Sheba Medical Center, Ramat Gan, Israel; Sackler School of Medicine, Tel-Aviv University, Israel (E.G., S.K., R.K., I.G., Y.S.).

Correspondence to: Assaf Berger, MD, Leviev Heart Institute, Sheba Medical Center, Tel Hashomer 52621, Israel. E-mail: assaf.berger@gmail.com

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at each visit, together with a physical examination, BP measurement, and laboratory blood tests that are analyzed at the center's lab. The Institutional Review Board of the Sheba Medical Center approved this study on the basis of strict maintenance of participants' anonymity during database analyses (approval number 8995-11-SMC). Data from subjects were recorded anonymously. No individual consent was obtained.

Inclusion and Exclusion Criteria

The complete database included 25 890 subjects. Inclusion criteria for the current study included at least 4 consecutive visits to the center with exercise BP documented (3 baseline visits and at least 1 additional visit to evaluate study outcome). Subjects were excluded if they had fewer than 4 visits (n=14 441); had a diagnosis of hypertension in any of the 3 baseline visits, were using antihypertensive medications, or had a history of cardiovascular disease, as defined by their primary care physicians (n=2508); had no 3 consecutive and complete exercise stress test (EST) documentations (n=452); or had longer than a 2-year gap between 2 consecutive visits (n=1407). The final study sample comprised 7082 individuals. Patients without a prior diagnosis of hypertension, who had BP readings ≥140 mm Hg for SBP and/or ≥90 for DBP during their baseline visits, were not excluded from the study. They were referred for further evaluation by their primary care physicians and newly diagnosed subjects were appropriately documented on the follow-up visits.

Resting and Exercise Blood Pressure Assessment

Over 3 years and at each annual examination, resting office SBP and DBP were measured, after 5 minutes of rest, in the left arm in the seated position by an examining nurse using a mercury column sphygmomanometer.

A maximal EST according to the Bruce protocol was performed under the supervision of, and interpreted by a board-certified cardiologist at each annual visit.[8] Participants were encouraged to reach their maximal age-specific target heart rate, and the test was terminated due to exhaustion or due to angina or other medical reasons. Using a standardized cuff sphygmomanometer, BP was recorded during the EST at the end of each 3-minute stage, at peak exercise, and during recovery (4 to 5 minutes after the exercise). For the purpose of this analysis, exercise SBP and DBP responses were defined according to their values at peak exercise. Measurements from the 3 baseline visits were used to calculate the average resting and exercise SBP and DBP. EST duration time was used to calculate metabolic equivalents based on well-characterized regression equations.[9]

Study Design

The study population was divided into 4 quartiles based on the average SBP and DBP responses during the first 3 exercise tests. The risk for developing new-onset hypertension in each quartile was compared to the lowest quartile. SBP quartiles cut-off values were as follows: ≤158, 158 to 170, 170 to 183, and ≥183 mm Hg. DBP quartiles cut-off values were as follows: ≤73, 73 to 77, 77 to 82, and ≥82 mm Hg. To further validate the consistency of the quartile analyses, both SBP and DBP exercise responses were also assessed as continuous measures.

For all participants, the following parameters from the initial baseline visit were also recorded: age, sex, body mass index, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), and fasting glucose levels. Estimated glomerular filtration rate (eGFR) was estimated according to the Modification of Diet in Renal Disease (MDRD) Study equation.[10] Smoking status was extracted from the survey questionnaire and for the purpose of the current analysis, subjects were divided into active smokers and none-active smokers. Similarly, patients were asked about their physical activity and were considered as either physically active or not. In addition, the use of lipid-lowering drugs was also taken into account.

Study End Point

At each annual visit, physicians update all clinical diagnoses in the computerized record of each patient. The primary outcome of the current study was the new onset of hypertension. Subjects were considered to have hypertension when, according to their primary care physicians, they had a diagnosis of hypertension or started using antihypertensive medications. Patients with 2 separate BP readings ≥140 mm Hg for SBP and/or ≥90 for DBP during a certain visit were referred for further evaluation by their primary care physician, with newly diagnosed and treated subjects appropriately documented on the follow-up visit.

Statistical Analyses

Continuous variables were compared across study groups using the 1-way ANOVA. For comparison of categorical data we used the χ^2 test. The probability of being free from hypertension by the different exercise BP groups was graphically displayed according to the method of Kaplan and Meier, with comparison of cumulative events across strata by the log-rank test. Multivariate Cox proportional hazards regression modeling was used to determine the hazard ratio (HR) for future hypertension of different exercise BP quartiles, compared to the lowest one as a reference. Censoring was defined as the last visit to the center or the first diagnosis of hypertension. All findings were further adjusted for potential covariates including age, sex, body mass index, low-density lipoprotein, high-density lipoprotein, fasting plasma glucose, estimated glomerular filtration rate levels, smoking status, physical activity, use of lipid-lowering drugs, and resting baseline SBP and DBP. Subjects with missing covariate data (N=360, 5%) were excluded from the multivariate model. An association was considered statistically significant for a 2-sided P<0.05. All analyses were performed with the SPSS 21.0 software (SPSS Inc, Chicago, IL).

Results

Subjects' Characteristics

The final study population comprised 7082 individuals, of whom 5189 (73%) were men. Mean age was 48±9 years. Resting BP were 120/77±14/9, 120/76±14/9, and 120/77±14/9 at the first, second, and third baseline visits, respectively. Baseline clinical and laboratory characteristics of study subjects by the systolic and diastolic exercise BP groups are presented in Table 1. Notably, subjects in the lower exercise BP response groups were younger, more likely to be women, had lower resting BP levels, lower body mass index, higher concentrations of high-density lipoprotein-C, and lower concentrations of total cholesterol, low-density lipoprotein-C, and triglycerides.

Blood Pressure Response During Exercise

The mean values and SD of exercise SBP and DBP were 167±17 and 76±6 mm Hg, respectively. Distributions of systolic and diastolic BP during exercise were close to normal, ranging from 100 to 243 mm Hg for SBP and from 50 to 112 mm Hg for DBP. The average intervisit variability between the 3 measurements of BP, as measured during peak exercise in each baseline visit, was <10%. Average coefficients of variation for peak exercise SBP and DBP were 8.01±5.4% and 7.43±5.5%, respectively. The results of EST by the different exercise SBP groups are presented in Table 2. Subjects in the highest exercise SBP group had a significantly shorter test duration, their resting and peak exercise heart rates were slower, and their recovery BP was higher as compared with the lower exercise SBP groups. Pre-exercise resting BP values in Table 2 represent BP measured at the initiation of EST, as opposed to office resting BP that was used in the multivariate analysis of this study and is presented in Table 1.

Table 1. Baseline Clinical Characteristics of the Study Population by Quartiles of Exercise SBP and DBP Responses

	Exercise SBP Quartiles, mm Hg					Exercise DBP Quartiles, mm Hg				
	≤158 (n=2063)	158 to 170 (n=1749)	170 to 183 (n=1974)	≥183 (n=1296)	P Value	≤73 (n=1470)	73 to 77 (n=2889)	77 to 82 (n=1728)	≥82 (n=995)	P Value
Age, y	46.6±9.2	47.8±9.6	48.5±9.5	50.8±9.2	<0.001	45.2±9.6	47.4±9.4	49.7±9.2	52.3±8.3	<0.001
Sex, % male	872 (42%)	1366 (78%)	1743 (88%)	1208 (93%)	<0.001	799 (54%)	2117 (73%)	1405 (81%)	868 (87%)	<0.001
BMI, kg/m^2	24.0±3.6	25.4±3.2	26.3±3.4	26.9±3.4	<0.001	23.8±3.1	25.2±3.2	26.3±3.6	27.3±3.7	<0.001
LDL, mg/dL	120±29	124±28	126±28	127±28	<0.001	118±29	124±29	127±28	127±28	<0.001
HDL, mg/dL	52±13	47±12	45±11	45±10	<0.001	51±13	48±12	46±12	45±11	<0.001
TC, mg/dL	192±34	195±34	197±34	198±34	<0.001	190±35	196±34	198±34	200±33	<0.001
eGFR, mL/min per 1.73 m^2	71.6±10.6	72.2±10.4	72.0±10.1	71.3±9.8	0.075	72.2±10.2	72.2±10.4	71.5±10.4	70.7±9.9	<0.001
Glucose, mg/dL	87±13	89±14	92±17	94±18	<0.001	86±13	89±14	92±17	95±19	<0.001
TG, mg/dL	109±59	126±67	137±75	139±70	<0.001	109±60	125±67	133±70	144±75	<0.001
Physically active, %	1276 (63%)	1110 (65%)	1341 (70%)	907 (72%)	<0.001	962 (67%)	1938 (69%)	1090 (65%)	644 (67%)	0.077
Current smoking, %	372 (18%)	302 (18%)	314 (16%)	209 (17%)	0.307	262 (18%)	526 (19%)	280 (17%)	129 (13%)	0.002
Lipid lowering drugs, %	23 (1.1%)	41 (2.3%)	35 (1.8%)	29 (2.2%)	0.021	16 (1.1%)	65 (2.2%)	32 (1.9%)	15 (1.5%)	0.046
Office resting SBP, mm Hg	112±10	119±9	124±10	129±11	<0.001	113±10	118±10	124±10	130±11	<0.001
Office resting DBP, mm Hg	72±6	77±8	78±6	81±6	<0.001	72±8	76±6	79±6	82±6	<0.001

Continuous values are expressed as mean±SD. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2. Results of Exercise Stress Test According to Exercise SBP and DBP Groups

	Exercise SBP Quartiles, mm Hg					Exercise DBP Quartiles, mm Hg				
	≤158 (n=2063)	158 to 170 (n=1749)	170 to 183 (n=1974)	≥183 (n=1296)	*P* Value	≤73 (n=1470)	73 to 77 (n=2889)	77 to 82 (n=1728)	≥82 (n=995)	*P* Value
Duration of test, seconds	608±126	651±139	624±150	600±164	<0.001	651±143	648±144	624±141	591±148	<0.001
Rest HR, beats/min	77±11	76±11	75±11	74±12	<0.001	74±11	75±11	77±11	77±17	<0.001
Pre-exercise resting SBP, mm Hg	122±10	132±9	138±10	148±12	<0.001	126±13	133±13	136±12	144±13	<0.001
Pre-exercise resting DBP, mm Hg	71±5	75±5	76±8	78±5	<0.001	70±5	74±4	77±4	81±10	<0.001
Peak HR, beats/min	166±11	166±11	165±11	163±10	<0.001	168±11	166±11	164±11	161±10	<0.001
METs	10.9±2.3	11.0±2.5	11.2±2.7	10.9±2.8	0.002	11.6±2.5	11.2±2.5	10.6±2.4	10.0±2.5	<0.001
HR recovery, beats/min	90±13	92±13	91±13	91±12	<0.001	90±12	91±13	91±14	91±13	0.083
Recovery SBP, mm Hg	112±15	120±14	123±14	130±14	<0.001	114±15	119±14	123±15	129±16	<0.001
Recovery DBP, mm Hg	69±8	71±8	73±10	75±8	<0.001	67±7	71±8	74±9	77±11	<0.001
HRR, beats/min	90±14	91±15	90±15	88±15	0.001	94±14	91±15	87±15	84±14	<0.001

Values are expressed as mean±SD. DBP indicates diastolic blood pressure; HR, heart rate; HRR, heart rate reserve; METs, metabolic equivalents; SBP, systolic blood pressure.

Hypertension During Follow-up

Of the 7082 subjects who attended the baseline annual examinations and underwent treadmill testing, 1036 (14.6%) developed new-onset hypertension during 5±3 years of follow-up. The average number of follow-up visits was 5.5±3 per subject. Kaplan–Meier survival analysis showed that the cumulative probability of new-onset hypertension at 5 years was highest among subjects in the top SBP quartile, intermediate among those in the second and third exercise SBP quartiles, and lowest among subjects in the lowest quartile (35%, 17%, 9%, and 5%, respectively; *P*<0.001 for the overall difference during follow-up; Figure 1). Similarly, Kaplan–Meier survival analysis showed a direct correlation between increasing DBP quartiles and the cumulative probability for the development of new-onset hypertension during 5 years of follow-up (3%, 10%, 18%, and 40%, respectively; *P*<0.001 for the overall difference during follow-up; Figure 2).

Consistent with the univariate findings, multivariate Cox proportional hazards regression modeling showed that increasing BP quartiles were independently associated with a statistically significant increased risk for the development of new-onset hypertension during follow-up (Table 3). After excluding subjects with missing covariate data, the multivariate analysis was based on a group of 6722 subjects. Compared with subjects in the lowest exercise SBP quartile, those in the highest quartile experienced a pronounced 2.58-fold (*P*<0.001) increased risk for future hypertension (Table 3). Similarly, subjects in the highest exercise DBP quartile had the highest risk for future hypertension with a 3.60-fold increased risk (*P*<0.001). The independent association between exercise BP response and the risk for future hypertension was also shown when exercise SBP and DBP were assessed as continuous measures. This analysis showed that each 5-mm Hg increment in exercise SBP response was independently associated with a statistically significant 11% (*P*<0.001) increased risk for the development of hypertension. Similarly, each 5-mm Hg increase in exercise DBP response was associated with a 30% (*P*<0.001) increased risk for future hypertension (Table 3).

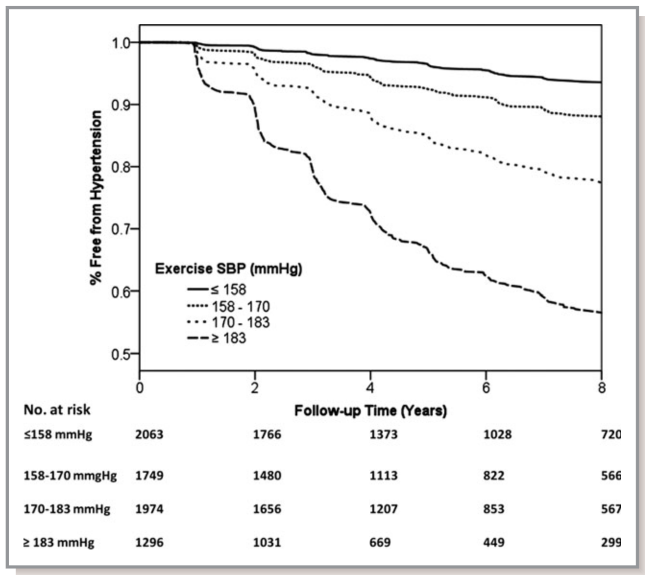

Figure 1. Kaplan–Meier survival curves showing the cumulative probability of hypertension-free survival according to exercise systolic blood pressure (SBP) quartiles (log rank *P*<0.001).

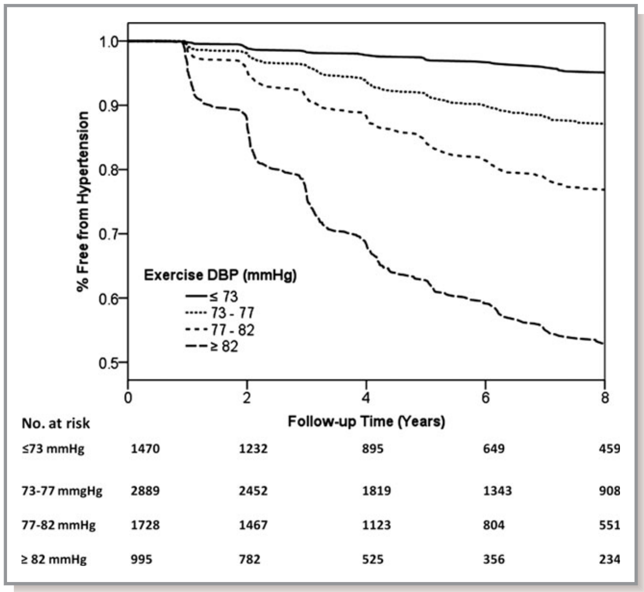

Figure 2. Kaplan–Meier survival curves showing the cumulative probability of hypertension-free survival according to exercise diastolic blood pressure (DBP) quartiles (log rank $P<0.001$).

Single BP measurements during peak exercise at the first, second, or third baseline visits were also independently associated with future hypertension. For example, while using the same adjustment models, each 5-mm Hg increment in exercise SBP and DBP during the first baseline visit was associated with respective 5% ($P<0.001$) and 10% ($P<0.001$) increased risk for future hypertension (data not shown). In addition, our results were similar for both men and women, as verified using interaction analysis (data not shown).

Table 3. Multivariate Adjusted HR for New-Onset Hypertension by Different Quartiles of Exercise SBP and DBP Responses

Outcomes	Hazard Ratio, 95% CI	*P* Value
Exercise SBP*		
Low: 2nd quartile (158 to 170 mm Hg) vs lowest quartile	1.25 (0.96 to 1.63)	0.101
Middle: 3rd quartile (170 to 183 mm Hg) vs lowest quartile	1.78 (1.38 to 2.28)	<0.001
High: 4th quartile (≥183 mm Hg) vs lowest quartile	2.58 (1.99 to 3.34)	<0.001
Each exercise SBP category increase	1.40 (1.30 to 1.51)	<0.001
Continuous model: 5-mm Hg rise	1.11 (1.08 to 1.13)	<0.001
Exercise DBP†		
Low: 2nd quartile (73 to 77 mm Hg) vs lowest quartile	1.89 (1.37 to 2.62)	<0.001
Middle: 3rd quartile (77 to 82 mm Hg) vs lowest quartile	2.33 (1.69 to 3.22)	<0.001
High: 4th quartile (≥82 mm Hg) vs lowest quartile	3.60 (2.59 to 4.99)	<0.001
Each exercise DBP category increase	1.43 (1.33 to 1.54)	<0.001
Continuous model: 5-mm Hg rise	1.30 (1.24 to 1.37)	<0.001

Final analysis was based on 6722 subjects, after excluding participants with missing covariate data. Lowest quartiles of SBP and DBP: <158 mm Hg and DBP <73 mm Hg, respectively. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; SBP, systolic blood pressure.
*Adjusted for age, sex, BMI, LDL, HDL, fasting plasma glucose, eGFR, lipid-lowering drugs use, physical activity, resting systolic and diastolic blood pressures.
†Adjusted for the above variables, including smoking status.

Discussion

The main finding of the current study is that among normotensive subjects, assessment of SBP and DBP response during exercise can be used to improve risk stratification with respect to future development of chronic hypertension, independently of baseline clinical factors and resting BP measurements. Furthermore, we have shown that the association between exercise BP response and the risk for future hypertension is graded, with even small increments in exercise BP response resulting in a corresponding risk increase.

Prior studies have shown conflicting results regarding the association between SBP and DBP response to exercise and the risk of hypertension. A study comprising 2310 normotensive subjects showed that exaggerated DBP response to exercise (defined as age-adjusted DBP greater than the 95th percentile during the second stage of exercise) was associated with a 4-fold increase in the risk for future hypertension in men and a 2-fold increase in women, respectively. However, exaggerated SBP response to exercise (similarly defined) showed only a weak association with future hypertension. In a subgroup analysis of subjects from the same study with high-normal BP, both increased SBP and DBP during exercise were good predictors of hypertension.[3] An additional study that followed healthy subjects for 5 to 8 years showed that exaggerated SBP and DBP responses can increase the risk for future hypertension by 7.6- and 5.7-folds, respectively.[11] A practical significance to these findings came with the report that exaggerated SBP response to low-intensity exercise can help identify patients with untreated masked hypertension.[12]

In contrast to the above evidence, supporting the possible use of exaggerated BP response to exercise tests in predicting future hypertension, there have been few reports that cast doubts regarding their validity and clinical usefulness. For instance, no association was found between exaggerated BP response during treadmill tests and the development of hypertension in 3.5 years of follow-up.[13] Another study showed that the apparent relation between exercise SBP response and left ventricular mass is confounded by age, resting SBP, and body mass, questioning the relevance of positive echocardiographic findings reported in other studies.[14] In a 12-year follow-up of young Japanese adults, exaggerated SBP response during exercise was not associated with hypertension among women. The association was positive in men, but SBP during exercise was a weaker predictor for future hypertension than that measured immediately after exercise.[15] Moreover, we have recently shown in patients with high-normal BP that exaggerated BP response to exercise does not identify masked hypertension.[16]

Several explanations have been proposed for the inconsistent results. First, there are no uniform criteria for the definition of exaggerated BP responses to exercise. For instance, certain studies focused on SBP rather than DBP responses, others defined different cutoffs based on absolute values or percentiles of BP levels, and some took into account the work or heart rate achieved during the test. Moreover, there has been great variability in terms of the exercise tests used. Some used the standard treadmill tests, while others used bicycles[17] and more importantly, BP responses were measured at different stages of these tests. In addition, the great range of observation periods used by different studies has significantly influenced their various results.[13] Another concern was the doubts raised regarding the accuracy of BP measurements during exercise and the reproducibility of these results.[18]

Our study has several strengths that assisted in answering the abovementioned difficulties, and thus supported prior data regarding the association between the entities: First, our large number of subjects allowed stratification of the risk for hypertension by the levels of BP responses to exercise, while adjusting for multiple factors, including resting BP levels and habitual physical activity. Moreover, by using the average of 3 consecutive exercise BP measurements, we overcame doubts regarding the reproducibility of BP measurements during exercise. In addition, the exercise test we studied was the standard treadmill test according to the Bruce protocol, making the results applicable worldwide. In addition, we have a very precise follow-up of our large cohort of subjects and therefore were able to identify all new cases of newly diagnosed hypertension.

Unlike most other studies that evaluated the association between exaggerated BP response to exercise and the development of hypertension, we graded the risk for hypertension according to the level of BP response in exercise. Only few reports discussed the possibility of grading the risk for hypertension according to the level of BP response in exercise. Some researchers managed to do so by showing that in subjects with high-normal resting BP taking bicycle exercise tests, those in the upper quartiles of BP response corrected for heart rate had a higher incidence of hypertension, comparing to those in the lower ones.[4] These authors later showed this gradual association in a larger cohort of men with a larger spectrum of normal resting BP.[19] Our results are thus unique by showing a significant and gradual association in a wide spectrum of normotensive individuals and in a larger cohort of both men and women.

The biological basis for these findings has been linked to endothelial dysfunction and increased arterial wall stiffness, resulting in increased BP during exercise and the development of future hypertension.[20] Moreover, subjects with exaggerated BP response had augmented rise of angiotensin 2 during exercise.[21]

An important limitation to the generalization of our results has to do with the study population, which was based on subjects enrolled in our annual medical survey, signifying that most came from a high socioeconomic status. Moreover, as our data regarding the physical activity of the participants in the survey was based on yes\no questions, we could not clearly quantify the influence of this important variable on the results. In addition, though accurate in measuring BP response to exercise, our protocol of 3 consecutive exercise tests might be difficult to implement in the general population for routine use.

Perspectives

Our results further support the association between BP responses during exercise and the development of future hypertension. In addition, they reveal a gradually increasing risk for hypertension by the level of BP measured during exercise, after adjusting for multiple factors. These findings signify that increased BP response during exercise is either a predictor for future hypertension or a condition in the spectrum between normotension and hypertension. Positive test results may help target individuals at risk for hypertension and encourage them to make changes in daily life in advance. The link between exaggerated BP response to exercise and the development of cardiovascular diseases is still controversial.[22–24] However, formulating a standard algorithm to predict the development of hypertension and its associated disorders is of great importance.

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Disclosures

None.

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