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
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, 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) documents (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. 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.

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. 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 $\chi^2$ 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 |
|-----------------------------|-----------------------------|
| Age, y                      | Sex, % male                 |
| ≤158 (n=2063)               | 158 to 170 (n=1749)         |
| 46.6±9.2                    | 170 to 183 (n=1974)         |
| 48.5±9.5                    | ≥183 (n=1296)               |
| 50.8±9.2                    | ≤73 (n=1470)                |
| 45.2±9.6                    | 73 to 77 (n=2889)           |
| 47.4±9.4                    | 77 to 82 (n=1726)           |
| 49.7±9.2                    | ≥82 (n=995)                 |
| 52.3±8.3                    | P Value                     |
| <0.001                      | ≤73 (n=1470)                |
| <0.001                      | 73 to 77 (n=2889)           |
| <0.001                      | 77 to 82 (n=1726)           |
| <0.001                      | ≥82 (n=995)                 |
| 0.001                       | 0.001                       |
| 0.001                       | 0.001                       |
| Glucose, mg/dL              | TG, mg/dL                   |
| 87±13                       | 109±59                      |
| 89±14                       | 126±67                      |
| 92±17                       | 137±75                      |
| 94±18                       | 139±70                      |
| 90±17                       | <0.001                      |
| 94±17                       | 962 (67%)                   |
| 92±17                       | 1938 (69%)                  |
| 95±19                       | 1090 (65%)                  |
| 92±17                       | 644 (67%)                   |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 94±18                       | 0.001                       |
| 90±17                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 0.001                       |
| 92±17                       | 0.001                       |
| 95±19                       | 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.
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).

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

| Exercise SBP Quartiles, mm Hg | Exercise DBP Quartiles, mm Hg | P Value | Duration of test, seconds | Rest HR, beats/min | Pre-exercise resting SBP, mm Hg | Pre-exercise resting DBP, mm Hg | Peak HR, beats/min | METs | HR recovery, beats/min | Recovery SBP, mm Hg | Recovery DBP, mm Hg | HRR, beats/min |
|------------------------------|-------------------------------|---------|-------------------------|-------------------|-------------------------------|-------------------------------|------------------|------|---------------------|-------------------|----------------|---------------|
| ≤158 (n=2063)                | ≤73 (n=1470)                  | <0.001  | 608±126                 | 77±11             | 122±10                        | 71±5                          | 166±11           | 10.9 | 90±13               | 112±15            | 68±8            | 90±14         |
| 158 to 170 (n=1749)          | 73 to 77 (n=2889)             | <0.001  | 651±139                 | 76±11             | 132±9                         | 75±5                          | 166±11           | 11.0 | 92±13               | 120±14            | 71±8            | 91±15         |
| 170 to 183 (n=1974)          | 77 to 82 (n=1728)             | <0.001  | 624±150                 | 75±11             | 138±10                        | 76±8                          | 166±11           | 11.2 | 91±13               | 123±14            | 73±10           | 90±15         |
| ≥183 (n=1296)                | ≥82 (n=995)                   | <0.001  | 600±164                 | 74±12             | 148±12                        | 78±5                          | 164±11           | 10.9 | 91±12               | 130±14            | 75±8            | 88±15         |

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.

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).
Exercise Blood Pressure and Risk of Future Hypertension  Berger et al

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).

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)

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, fasting plasma glucose, eGFR, lipid-lowering drugs use, physical activity, resting systolic and diastolic blood pressures.

†Adjusted for the above variables, including smoking status.

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. 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. 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.

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. 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.\textsuperscript{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.\textsuperscript{15} Moreover, we have recently shown in patients with high-normal BP that exaggerated BP response to exercise does not identify masked hypertension.\textsuperscript{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\textsuperscript{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.\textsuperscript{13} Another concern was the doubts raised regarding the accuracy of BP measurements during exercise and the reproducibility of these results.\textsuperscript{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.\textsuperscript{4} These authors later showed this gradual association in a larger cohort of men with a larger spectrum of normal resting BP.\textsuperscript{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.\textsuperscript{20} Moreover, subjects with exaggerated BP response had augmented rise of angiotensin 2 during exercise.\textsuperscript{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.\textsuperscript{22–24} However, formulating a standard algorithm to predict the development of hypertension and its associated disorders is of great importance.

**Sources of Funding**

The study was supported by a generous grant from the Shalvi Foundation for the support of medical research.

**Disclosures**

None.

**References**

1. Shrivastava SR, Shrivastava PS, Ramasamy J. The determinants and scope of public health interventions to tackle the global problem of hypertension. *Int J Prev Med*. 2014;5:807–812.
Exercise Blood Pressure and Risk of Future Hypertension  Berger et al

2. Farah R, Shurtleff-Swirski R, Nicola M. High blood pressure response to stress ergometry could predict future hypertension. *Eur J Intern Med*. 2009;20:366–368.

3. Singh JP, Larson MG, Manolio TA, O’Donnell CJ, Lauer M, Evans JC, Levy D. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham Heart Study. *Circulation*. 1999;99:1831–1836.

4. Miyai N, Arita M, Morikita Y, Nakagawa H, Nishio T, Takeda S. Exercise BP response in subjects with high-normal BP: exaggerated blood pressure response to exercise and risk of future hypertension in subjects with high-normal blood pressure. *J Am Coll Cardiol*. 2000;36:1626–1631.

5. Manolio TA, Burke GL, Savage PJ, Sidney S, Gardin JM, Oberman A. Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the CARDIA study. *Am J Hypertens*. 1994;7:234–241.

6. Matthews CE, Pate RR, Jackson KL, Ward DS, Macera CA, Kohl HW, Blair SN. Exercise blood pressure response and 5-year risk of elevated blood pressure. *J Clin Epidemiol*. 1998;51:29–35.

7. Maor E, Kopel E, Sidi Y, Goldenberg I, Seglev S, Kivity S. Effect of mildly attenuated heart rate response during treadmill exercise testing on cardiovascular outcome in healthy men and women. *Am J Cardiol*. 2013;112:1373–1378.

8. Pescatello LS. *ACSM’s Guidelines for Exercise Testing and Prescription/ American College of Sports Medicine*. 9th ed. Philadelphia: Wolters Kluwer/ Lippincott Williams & Wilkins Health; 2014.

9. Pollock ML, Bohannon RL, Cooper KH, Ayres JJ, Ward A, White SR, Linnerud AG. A comparative analysis of four protocols for maximal treadmill stress testing. *Am J Cardiol*. 1976;92:39–46.

10. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis*. 2014;63:820–834.

11. Sharabi Y, Ben-Cnaan R, Hanin A, Bartovitch G, Grossman E. The significance of hypertensive response to exercise as a predictor of hypertension and cardiovascular disease. *J Hum Hypertens*. 2001;15:353–356.

12. Schultz MG, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked blood pressure response is “unnecessary” by low-intensity exercise blood pressure. *Blood Press*. 2011;20:284–289.

13. Lima SG, Albuquerque MFP, Oliveira JR, Ayres CFJ, Cunha JEG, Oliveira DF, Lemos RR, Souza MBR, Silva OB et al. Exaggerated blood pressure response during the exercise treadmill test as a risk factor for hypertension. *Braz J Med Biol Res*. 2013;46:368–374.

14. Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham Heart Study. *Ann Intern Med*. 1992;116:203–210.

15. Nakashima M, Miura K, Kido T, Saeki K, Tamura N, Matsui S, Morikawa Y, Nishio M, Nakanishi Y, Nakagawa H. Exercise blood pressure in young adults as a predictor of future blood pressure: a 12-year follow-up of medical school graduates. *J Hum Hypertens*. 2004;18:815–821.

16. Grossman A, Cohen N, Shemesh J, Koren-Morag N, Leibowitz A, Grossman E. Exaggerated blood pressure response to exercise is not associated with masked hypertension in patients with high normal blood pressure levels. *J Clin Hypertens (Greenwich)*. 2014;16:277–282.

17. Holmqvist L, Mortensen L, Kancos C, Ljungman C, Mehlig K, Manhem K. Exercise blood pressure and the risk of future hypertension. *J Hum Hypertens*. 2012;26:691–695.

18. Sharabi Y, Almer Z, Hanin A, Messerli FH, Ben-Cnaan R, Grossman E. Reproducibility of exaggerated blood pressure response to exercise in healthy patients. *Am Heart J*. 2001;141:1014–1017.

19. Miyai N, Arita M, Miyashita K, Morikita I, Shiroya S, Tashio I. Blood pressure response to heart rate during exercise test and risk of future hypertension. *Hypertension*. 2002;39:761–766.

20. Thanassouli G, Lyass A, Benjamin EJ, Larson MG, Vita JA, Levy D, Hamburg NM, Widlansky ME, O’Donnell CJ, Mitchell GF, Vasan RS. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham Heart Study. *Circulation*. 2012;125:2836–2843.

21. Shim CY, Ha J-W, Park S, Choi E-Y, Choi D, Rim S-J, Chung N. Exaggerated blood pressure response to exercise is associated with augmented rise of angiotensin II during exercise. *J Am Coll Cardiol*. 2008;52:287–292.

22. Lewis GD, Gona P, Larson MG, Plehn JF, Benjamin EJ, O’Donnell CJ, Levy D, Vasan RS, Wang TJ. Exercise blood pressure response and the risk of incident cardiovascular disease (from the Framingham Heart Study). *Am J Cardiol*. 2008;101:1614–1620.

23. Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. *Am J Hypertens*. 2013;26:357–366.

24. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galarisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schneider RE, Sirnes PA, Sleight P, Vignamia M, Waeber B, Zannad F. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.