

# Blood Pressure Response to Heart Rate During Exercise Test and Risk of Future Hypertension

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**Abstract**—Previous works have shown that exaggerated blood pressure response to exercise is a valid risk marker for future hypertension, yet the use of an exercise test as a means of early prediction of hypertension still requires methodological development and confirmation. The purpose of this study was to determine abnormal ranges of blood pressure responses in relation to heart rate increase during exercise and to examine the clinical utility of exercise blood pressure measurement in evaluating individual risk for developing hypertension. We examined exercise test data from a population-based sample of 1033 nonmedicated normotensive men (mean age,  $42.9 \pm 8.5$  years; range, 20 to 59 years). Percentile curves of systolic and diastolic blood pressure responses to relative heart rate increments during submaximal exercise were constructed using a third-order polynomial model with multiple regression analysis. Of the original study sample, a cohort of 726 subjects was followed for hypertensive outcome for an average period of 4.7 years. Progression to hypertension, defined as a blood pressure of  $\geq 140/90$  mm Hg or the initiation of antihypertensive therapy, was found in 114 subjects (15.4%). Kaplan-Meier survival estimates showed that the cumulative incidence of hypertension increased progressively with higher percentiles of systolic and diastolic blood pressure response (both,  $P < 0.01$ ). A Cox proportional survival analysis revealed a significantly increased risk for developing hypertension associated with exaggerated blood pressure response to exercise after multivariable adjustments for traditional risk factors (relative risk, 3.8; 95% confidence interval, 2.3 to 6.1). These results suggest that an exaggerated blood pressure response to heart rate during exercise is predictive of future hypertension independent of other important risk factors and lend further support to the concept that blood pressure measurement during exercise test is a valuable means of identifying normotensive individuals at high risk for developing hypertension. (*Hypertension*. 2002;39:761-766.)

**Key Words:** blood pressure ■ exercise ■ risk factors ■ epidemiology

Hypertension is recognized as a key risk factor for cardiovascular disease mortality and morbidity.<sup>1</sup> Emerging evidence that nonfatal and fatal cardiovascular diseases increase progressively with higher levels of blood pressure (BP)<sup>2,3</sup> makes early identification of persons at increased risk for developing hypertension a priority. It has been suggested that the development of hypertension is preceded by a prehypertensive state that may be manifested by abnormal cardiovascular reactivity to environmental and behavioral challenges, such as mental arithmetic tasks,<sup>4</sup> cold water immersion,<sup>5</sup> and both isometric and dynamic physical stress tests.<sup>6-14</sup> One of the most useful may be the exercise stress test, as it is now widely used in hospitals to detect coronary heart disease and in sports and occupational medicine to evaluate cardiorespiratory fitness. However, its reliability for identifying persons prone to develop hypertension and as a test for the prediction of hypertension onset is still being discussed. Previous studies addressing this issue have used different definitions for an exaggerated BP response to exercise, including some based solely on systolic BP

(SBP)<sup>7,11-14</sup> and others on SBP and diastolic BP (DBP) together.<sup>6,8-10</sup> Additionally, it has been indicated that the cut-off point separating normal from abnormal responses should be determined according to gender, age, and physical fitness,<sup>15</sup> which have all been shown to affect BP response independently and significantly.<sup>13</sup> However, without taking into consideration the impact of these factors, most studies have chosen to define exaggerated BP response only in terms of some designated BP level at maximal exertion and given submaximal workloads.<sup>7-9,11,14</sup> These methodological uncertainties may make it unclear whether the information gathered from exercise BP measurement is valuable for evaluating an individual's hypertensive risk profile. Thus, the validity of an exercise test for predicting future hypertension needs further methodological development and confirmation.

In the present study, we examined exercise test data from a population-based sample of middle-aged normotensive men to determine abnormal ranges of BP response during exercise in relation to heart rate (HR) increase, and we evaluated the clinical utility of exercise BP measurement as a means of

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**TABLE 1. Clinical Characteristics in 1033 Study Sample**

Variables	
Age, y	42.9±8.5
Body mass index, kg/m <sup>2</sup>	23.1±2.7
Systolic blood pressure, mm Hg	126.2±8.5
Diastolic blood pressure, mm Hg	77.6±6.4
Heart rate, bpm	65.2±9.7
Total cholesterol, mmol/L	5.12±0.87
HDL cholesterol, mmol/L	1.36±0.34
LDL cholesterol, mmol/L	3.05±0.77
Triglyceride, mmol/L	1.42±0.57
Fasting blood glucose, mmol/L	5.26±0.41
Alcohol consumption, g/wk	134.5±97.6
Current smoker, %	50.3
Parental history of hypertension, %	31.4

Values are expressed as mean±SD or percentage.

identifying any increased risk for developing hypertension after adjustment for traditional important risk factors.

## Methods

### Study Population

A total of 2483 men participated in biannual medical examinations conducted at our laboratory from 1992 to 1995. Of these, 1514 participants underwent a bicycle ergometric test. Subjects were excluded if they (1) had a history of cardiovascular or renal diseases or diabetes; (2) had electrocardiographic evidence of coronary heart disease or cardiac arrhythmia; (3) were hypertensive, as defined by currently using any antihypertensive medication or having an average resting BP of  $\geq 140/90$  mm Hg taken on 3 separate visits; (4) were  $<20$  years or  $>59$  years of age; or (5) had incomplete exercise BP measurement data. Consequently, 1033 subjects free from cardiovascular disease and with normal ECG results were eligible for this study. Based on their exercise test results, BP and HR responses to exercise were evaluated. Clinical characteristics of the study sample are shown in Table 1.

After the exercise test at baseline, the subjects were followed for hypertensive outcome until 1999. Of these, 47 had missing data on covariates at baseline, 84 did not participate in the biannual follow-up examinations, and 139 had incomplete BP information. Additionally, 37 subjects were eliminated from further analysis because they began to engage in regular sports activities after educational programs about lifestyle modification. It is well known that a subject's risk of developing hypertension may be decreased by a program of aerobic exercise.<sup>2</sup> Therefore, the follow-up study was based on 726 subjects who had complete exercise test data, as well as covariates at baseline and hypertensive status on follow-up. The average length of follow-up was 4.7 years (range, 3.6 to 6.9 years). The subjects received standardized medical examinations consisting of anthropometric, physiological, and blood biochemical measurements. They also completed a questionnaire about personal and parental medical histories, medication used, and habits of daily living, including smoking, alcohol consumption, and physical activity. Written informed consent, including clearance for use of the examination data, was obtained after an explanation of the study aims and procedures was given.

### Resting Blood Pressure Measurement

Resting BP was measured 3 times in the seated position by well-trained physicians using a mercury sphygmomanometer. The average of the 3 readings was used for the representative examination value. The measurement was performed under controlled con-

ditions in a quiet room and using the same protocol at both the baseline and follow-up examinations.

### Ergometer Exercise Testing

A graded symptom-limited maximum exercise test was performed on an electronically braked bicycle ergometer (Fukuda Denshi, ML-1400). Workload was progressively increased using a linear-slope method at a rate of 12.5 W/min until the subjects complained of exhaustion. Throughout the test, ECG lead V<sub>3</sub> and HR were monitored continuously, and BP was recorded every minute noninvasively with an automated sphygmomanometer (Nippon Colin, STBP-780B). The device was an auscultatory unit using R-wave gating in the identification of Korotkoff sounds.<sup>16</sup>

### Hypertensive Status at Follow-Up

During the follow-up period, the hypertensive outcome of the subjects was ascertained based on answers to the questionnaire regarding medical histories and BP measurements conducted at the biannual medical examination. A subject was considered hypertensive if (1) his resting BP was  $\geq 140/90$  mm Hg and did not decrease again into the normotensive range or (2) he began to receive antihypertensive medications during the follow-up period.

### Data Analyses

We evaluated the individual relationships of SBP and DBP response with HR increments from data obtained during submaximal exercise at workloads of 50, 75, and 100 W. In this analysis, HR was expressed relatively as a percentage of maximal HR reserve (HRR) to allow evaluation at the same metabolic workload in individuals with varying levels of resting and maximal HR, which were related to gender, age, and physical fitness. HRR was calculated according to the following formula:  $HRR = [(HR \text{ at } 50, 75, \text{ and } 100 \text{ W of exercise} - \text{resting HR}) / (\text{gender-specific age-predicted maximum HR} - \text{resting HR})] \times 100$ . Thereafter, the 10th, 25th, 50th, 75th, and 90th percentile values of SBP and DBP were calculated for HRR in each increment of 5% by a nonparametric method. Percentile curves of SBP and DBP response by HRR were constructed by fitting a third-order polynomial model to the regression equations of SBP and DBP with a percentage increase in HRR using multiple regression analysis. An exaggerated BP response to exercise was determined by plotting an individual subject's measured SBP and DBP at a 100-W workload on the BP response percentile curves by HRR. A subject was considered to have an exaggerated BP response if his SBP or DBP was at or above the pressure on each of the 90th percentile curves.

Associations between BP response to exercise and future development of hypertension were evaluated by estimation with Kaplan-Meier survival curves. In this analysis, SBP and DBP responses to exercise were arbitrarily divided into subcategories based on each of the quartile values that were derived from the BP response percentile curves by HRR. A Cox proportional hazard survival model was used to estimate the strength and independence of BP response to exercise in determining the risk of future hypertension. Relative risk with the corresponding 95% confidence interval were estimated in the model and used to quantify the hypertensive risks. Exercise SBP and DBP responses were assessed separately by means of unadjusted, age-adjusted, and clinical covariate-adjusted analyses. The clinical covariates were entry age, body mass index, physical working capacity (as cardiorespiratory performance capacity), resting SBP and DBP, fasting blood glucose, total cholesterol, HDL cholesterol, triglycerides, alcohol consumption, physical activity, and parental history of hypertension. Additionally, a secondary multivariate Cox analysis was performed to identify independent factors significantly associated with hypertensive outcome from a normotensive state. The following recognized major risk factors for hypertension were entered into the stepwise Cox model as independent variables: exaggerated BP response to exercise, high-normal resting BP, entry age, body mass index, physical working capacity, fasting blood glucose, atherogenic index, alcohol consumption, and parental history of hypertension. The reference levels for high-normal resting BP

**TABLE 2. Systolic and Diastolic Blood Pressure and Heart Rate at Rest and During Exercise Test by Age Group**

Variables, Age, y	Ergometric Work					
	Rest	25W	50W	75W	100W	125W
SBP, mm Hg						
20–29	125.9±8.4	136.2±10.6	138.8±11.7	146.4±12.6	162.7±13.9	180.5±15.2
30–39	126.6±8.0	136.6±9.8	139.4±10.3	147.5±10.7	164.4±12.6	182.6±14.4
40–49	125.5±9.4	135.2±12.7	138.9±12.4	148.4±13.0	167.0±14.2*	186.7±17.1*
50–59	126.7±8.7	136.3±11.9	140.9±12.2	151.3±14.2*	170.9±16.4†	193.7±18.3†
DBP, mm Hg						
20–29	76.7±8.1	75.9±7.9	74.8±8.3	74.9±8.7	76.4±9.1	79.1±10.7
30–39	77.3±6.8	77.4±7.6	76.2±6.8	76.8±7.5	79.4±7.4	82.4±9.3*
40–49	77.9±7.2	77.3±7.9	76.5±7.8	77.8±8.7	81.8±9.0*	85.3±9.8*
50–59	78.3±7.7	78.2±8.1	77.5±8.0*	79.5±7.7*	83.9±8.5†	88.6±10.4†
HR, bpm						
20–29	74.6±9.7	90.9±8.7	102.1±8.2	112.6±8.7	126.4±9.5	142.5±10.3
30–39	71.3±10.8	85.5±10.1*	96.9±9.8*	108.5±8.7*	121.1±9.1†	136.1±9.8†
40–49	67.1±8.8*	82.0±8.7†	92.1±7.8†	102.9±8.0†	116.0±8.1†	131.1±8.9†
50–59	65.8±8.6†	80.5±7.6†	90.0±7.4†	101.8±7.8†	115.4±8.4†	131.7±9.9†

Values are expressed as mean±SD. Numbers of subjects in each age group are 214, 264, 312, and 243 for 20, 30, 40, and 50 years, respectively.

\* $P<0.05$ ; † $P<0.01$  vs 20 years.

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were pressures of <130/85 mm Hg. The null hypothesis was rejected at  $P<0.05$  as the level of significance. Data analysis was performed using the SPSS statistical package 10.0 for Windows (SPSS Software).

## Results

### Blood Pressure Response During Exercise

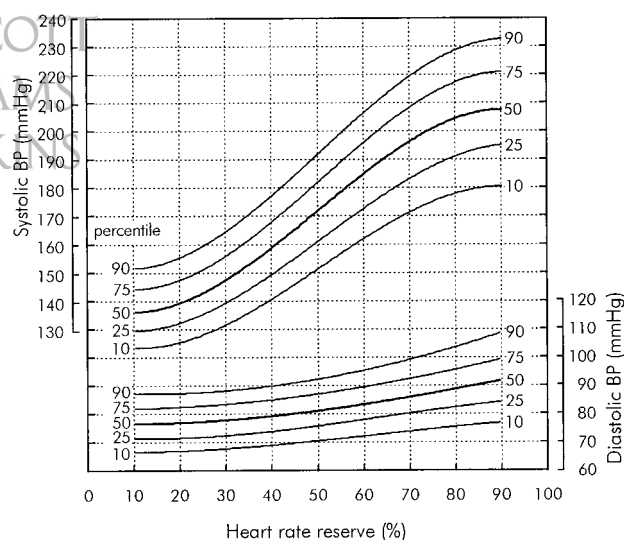
The values of mean±SD of SBP, DBP, and HR of the study sample measured while sitting at rest and during submaximal exercise at ergometric workloads of 25, 50, 75, 100, and 125 W by 10-year age groups are shown in Table 2. A comparison of subjects in different age groups demonstrated that older subjects had greater SBP and DBP increases during exercise

despite no apparent significant differences while the subjects were at rest. Associations of exercise SBP and DBP with other physiological and blood biochemical variables after adjustment for the effect of resting SBP and DBP are shown in Table 3. All variables, except body mass index and HDL cholesterol, were significantly correlated with exercise SBP and DBP. The highest correlation coefficient was found in the percent increase in HRR for exercise SBP ( $r=0.53$ ,  $P<0.01$ ) and DBP ( $r=0.50$ ,  $P<0.01$ ). Percentile curves (10th, 25th,

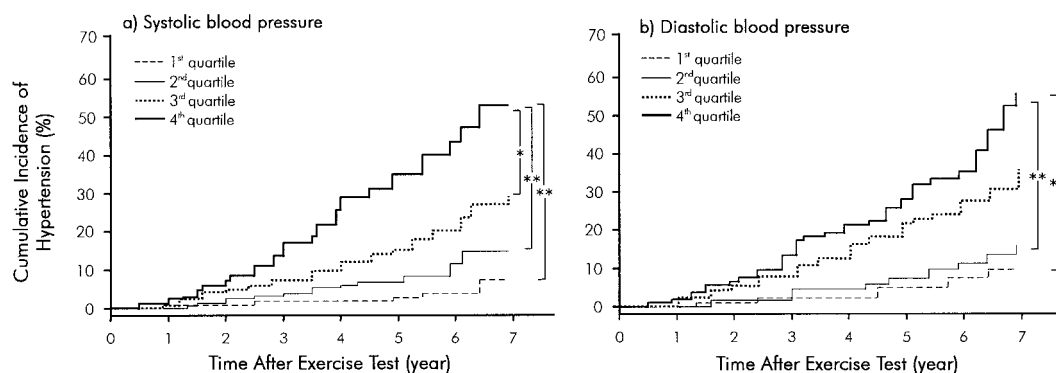
**TABLE 3. Association Between Exercise SBP and DBP and Clinical and Exercise Testing Parameters After Adjustment for Resting BP**

Variables	Exercise SBP	Exercise DBP
Age, y	0.25†	0.18†
Body mass index, kg/m <sup>2</sup>	−0.06	−0.07
Total cholesterol, mmol/L	0.12†	0.11*
HDL cholesterol, mmol/L	−0.08	−0.04
LDL cholesterol, mmol/L	0.15†	0.09*
Triglyceride, mmol/L	0.12*	0.14†
Fasting blood glucose, mmol/L	0.13†	0.17†
PWC, watt	−0.49†	−0.44†
Exercise HR, bpm	0.44†	0.42†
Exercise HRR, %	0.53†	0.50†

Values are partial correlation coefficients after adjusting for resting SBP and DBP. Exercise SBP, DBP, HR, and HRR indicate SBP, DBP, HR, and maximal HR reserve during exercise at the workload of 100W; PWC, physical working capacity at 75% of HR max. \* $P<0.05$ ; † $P<0.01$ .



**Figure 1.** Percentile curves of SBP and DBP responses by HRR during ergometric tests in normotensive men. The curves were constructed by fitting a third-order polynomial model to the regression equations of SBP and DBP with HRR during submaximal workloads of 50, 75, and 100 W.



**Figure 2.** Cumulative incidence of hypertension in normotensive men as a function of the quartiles of SBP and DBP response to exercise derived from BP response curves by HRR. \* $P < 0.05$ , \*\* $P < 0.01$

50th, 75th, and 90th) of SBP and DBP responses by HRR are illustrated in Figure 1.

### Follow-Up Analysis

Over the 3427 person-years of follow-up, 114 subjects (15.7%) progressed to hypertension. The survival curves demonstrated dose-response associations of the development of hypertension with exercise SBP and DBP responses in quartiles on the BP response curves by HRR, with a significantly higher propensity to develop hypertension being observed in those with the highest quartile of exercise SBP and DBP response (Figure 2). Unadjusted Cox models revealed that exaggerated SBP and DBP responses to exercise were significantly associated with future hypertension. After adjustment for age, the risk for developing hypertension was increased for both pressures. Further adjustment for potential confounders did not effectively alter the association, with those subjects who exhibited exaggerated BP response at a nearly 3- to 4-fold greater risk for developing hypertension compared with those with normal BP response (Table 4).

A secondary stepwise Cox analysis found the following independent variables to be significantly associated with the incidence of hypertension; exaggerated BP response ( $P < 0.001$ ), resting high-normal BP ( $P < 0.001$ ), entry age ( $P = 0.008$ ), and body mass index ( $P = 0.023$ ). An exaggerated BP response had a stronger association with hypertensive outcome compared with that of a resting high-normal BP and other selected variables ( $R = 0.21$ ) (Table 5).

### Discussion

The primary objective of this study was to evaluate the clinical significance of abnormal pressor reactivity to physical exertion, which is considered an early marker of future hypertension. We have found that an exaggerated BP response to HR increase during ergometric exercise was associated with a 3- to 4-fold greater risk for developing hypertension, after controlling for traditional risk factors. Therefore, this approach lends further support to the concept that exercise BP measurement is a valuable means for the identification of an increased risk of future hypertension in apparently healthy normotensive adults.

It has been hypothesized that exercise-induced stress could unmask a latent tendency toward hypertension.<sup>12</sup> Accord-

ingly, an exaggerated BP response to exercise in normotensive subjects has been thoroughly examined in relation to the risk of future hypertension.<sup>9-14</sup> Most previous studies addressing this issue have focused solely on SBP<sup>7,11-14</sup> rather than on SBP and DBP together.<sup>6,8-10</sup> Because physical exertion leads to an increase in cardiac output, a rise in SBP is a natural consequence of dynamic exercise. In contrast, DBP remains unchanged or shows only a slight increase as a consequence of metabolic vasodilatation of the peripheral vessels.<sup>17</sup> However, some researchers<sup>11,17,18</sup> have observed a significant rise in DBP even in normotensive subjects, suggesting an increased resting peripheral vascular resistance<sup>11,19</sup> and impaired capacity for exercise-induced vasodilation.<sup>20,21</sup> This hemodynamic pattern can be explained by a hyperreactivity of the sympathetic nerves and an increased vascular response to adrenergic stimulation or by a thickening of the arteriolar wall that alters its ability to respond to vasoconstrictor stimuli.<sup>18</sup> Among subjects with such vascular characteristics, higher cardiac output not only raises SBP but also causes marked DBP elevations such as those occurring in established hypertension. Therefore, both DBP and SBP appear to be important criteria for determining abnormal cardiovascular reactivity to physical stress. Additionally, the definitions of exaggerated BP response at maximal levels of exertion<sup>8,9,11,13</sup> may be problematic. During ergometric exercise, manual or automated sphygmomanometry is commonly used to measure BP because it is a noninvasive, relatively inexpensive, and simple procedure. There is general agreement that indirect measurements yield SBP readings that do not differ significantly from direct intravascular measurements.<sup>22</sup> Conversely, statistically significant differences appear in indirect DBP readings measured especially during maximal exercise<sup>16,22,23</sup> because maximal ergometric work requires isometric muscle contractions, which produce a marked increase in total peripheral resistance.<sup>11,17,18</sup> However, it has been demonstrated that direct and indirect measurements of DBP satisfactorily correlate below the workload of mild or moderate exercise.<sup>17,18,22,23</sup> Furthermore, several studies have shown that endurance-trained persons are more likely to exhibit significantly higher SBP increases during maximal exercise than untrained persons, despite their reduced risk for developing hypertension.<sup>24,25</sup> These findings lead to the idea that an exaggerated BP response to exercise



**TABLE 4. Unadjusted, Age-Adjusted, and Multiple Adjusted Associations Between Exaggerated SBP and DBP Response to Exercise and Risk of Hypertension**

Variables	Unadjusted RR (95% CI)	Age-Adjusted RR (95% CI)	Multiple Adjusted RR (95% CI)
Ex-SBPR	6.24 (4.01–9.54)	6.62 (5.27–10.03)	3.70 (2.18–5.69)
Ex-DBPR	4.75 (2.94–7.38)	4.91 (3.04–7.64)	2.89 (1.88–4.44)

Ex-SBPR indicates exaggerated SBP response; Ex-DBPR, exaggerated DBP response. Multiple adjusted RR is the RR adjusted for entry age, body mass index, resting SBP and DBP, total cholesterol, triglyceride, fasting blood glucose, physical working capacity, alcohol consumption, physical activity, and parental history of hypertension.

should be determined based on SBP and DBP together from data obtained during relatively low submaximal exercise workload. This level of exercise has the additional benefit of requiring minimum cooperation from the subjects, and it limits the influence of exercise duration and physical conditioning.

Although previous studies have defined exaggerated BP response only in terms of a designated BP level, it has been indicated that the cut-off point separating normal from abnormal pressor reactivity should be determined according to gender, age, and physical fitness.<sup>15</sup> This means that some adjustments are required for the differences in a subject's metabolic stress level at a workload for which an exaggerated BP response is determined. In this study, the highest correlation between SBP and DBP during submaximal exercise was observed in HR increases to workload, which was expressed relatively as the percentage of HRR. Monitoring HR response during exercise is commonly accepted to play an important role in the assessment of exercise intensity because it linearly responds to workload and is closely associated with oxygen uptake.<sup>26</sup> However, despite the usefulness of assessment by HR response, individual differences in resting HR and maximal HR should be considered.<sup>27</sup> Previous studies have shown that the relative HR, as defined by the percentage of HR range from resting to maximal, can compensate for the individual differences and provide more accurate estimates of exercise intensity in both athletes and nonathletes.<sup>27,28</sup> Therefore, we have evaluated exercise SBP and DBP response based on the relative HR increase to workload. This approach can allow a comparison of individuals with varying levels of conditioning that are related to gender, age, and physical fitness and may thus contribute to

a decrease in the misclassification of abnormal BP reactivity and more clearly identify its association with the risk of future hypertension.

The results of our stepwise multivariate model showed a significant and independent risk for developing hypertension in a specific group with high-normal resting BP. This finding clearly confirms claims in previous studies that the preeminence of baseline resting BP itself is strongly associated with future hypertension. However, the model also found a stronger association between exercise BP response and subsequent hypertension than with resting BP. Our results are supported by some studies,<sup>6,8,9,11</sup> whereas several others have suggested that the predictive value of BP measured during exercise for future hypertension is lower than that measured at rest.<sup>7,10,14</sup> Hence, which pressure is more informative and valuable as an early marker of hypertension still remains to be elucidated. The inconsistency may have arisen from differences in methodology, characteristics of the study population, and clinical covariates considered in the analysis. However, the finding that an individual relative risk for developing hypertension in normotensive adults with slightly elevated resting BP is greatly increased if they exhibit an exaggerated BP response to exercise indicates that the measurement of exercise BP can provide some additional, important information concerning the risk for developing hypertension that cannot be estimated by resting BP alone. Additionally, measurements of resting BP often show spuriously elevated values because of anxiety, which decreases the reproducibility of the results and their usefulness for predicting future hypertension. It has been indicated that better test-retest reliability can be achieved by BP assessment during an exercise test.<sup>29,30</sup> Thus, information provided by this relatively simple assessment could be more

**TABLE 5. Stepwise Proportional Hazards Analysis of Risk Factors for Developing Hypertension From Normal Blood Pressure**

Variables	$\beta$	SE	P value	R	RR (95% CI)
Exaggerated BP Response, mm Hg	1.573	0.200	<.001	0.209	3.82 (2.26–6.13)
Resting High-normal BP, mm Hg	1.427	0.239	<.001	0.157	3.17 (1.61–5.66)
Age, y	0.046	0.014	.008	0.082	1.05 (1.02–1.07)
Body mass index, kg/m <sup>2</sup>	0.075	0.033	.024	0.048	1.08 (1.01–1.15)

$\beta$  indicates partial regression coefficient; SE, standard error of the  $\beta$  coefficient; R, partial correlation coefficient. Variables considered in the model are exaggerated BP response, resting high-normal BP, entry age, body mass index, atherogenic index, fasting blood glucose, physical working capacity, alcohol consumption, and parental history of hypertension. Atherogenic index=(total cholesterol–high-density lipoprotein cholesterol)/high-density lipoprotein cholesterol. The referent category for high-normal resting BP is pressure of less than 130/85 mm Hg.

useful than that obtained by the repeated, standardized, and careful measurement of resting BP.

In conclusion, to reduce the impact of subsequent cardiovascular complications, the early identification of a subgroup that is more likely to develop hypertension is a critical concern. Our results showed that the individual relative risk of hypertension in normotensive subjects was greatly increased if they exhibited an exaggerated BP response to exercise. This finding confirms the additional and incremental contribution of BP response to exercise above resting BP in predicting subsequent hypertension. Although routine mass exercise testing is not recommended to identify future hypertensive individuals, it is possible to obtain exercise test results as these tests are now widely utilized to evaluate cardiorespiratory performance capacity in sports and occupational medicine as well as to detect coronary heart disease in hospital or office settings. The data may provide important information about a hypertensive risk profile in a population of apparently healthy normotensive adults.

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