Beta-Blockade Mitigates Exercise Blood Pressure in Hypertensive Male Patients

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OBJECTIVES
The purpose of this study was to determine the antihypertensive agent(s) more likely to mitigate an exaggerated rise in exercise blood pressure (BP) in hypertensive patients.

BACKGROUND
An exaggerated rise in exercise BP is associated with increased cardiovascular risk. There are no recommendations for treating such response.

METHODS
Participants were hypertensive men (n = 2,318; age 60 ± 10 years), undergoing a routine exercise test at the Veterans Affairs Medical Center, Washington, DC. Antihypertensive therapy included angiotensin-converting enzyme inhibitors (n = 437), calcium-channel blockers (n = 223), diuretics (n = 226), and combinations (n = 1,442), beta-blockers alone (n = 201) or in combination with other antihypertensive agents (n = 467), and none (n = 208). Exercise BP, heart rate (HR) and rate-pressure product (RPP) at maximal and submaximal workloads were assessed.

RESULTS
After adjusting for covariates, patients treated with beta-blockers or beta-blocker–based therapy had significantly lower BP, HR, and RPP at 5 and 7 metabolic equivalents (METs) and peak exercise than those treated with any other antihypertensive agent or combination (p < 0.05). The likelihood of achieving an exercise systolic BP of ≥210 mm Hg was 68% lower (odds ratio = 0.32, 96% confidence interval 0.2 to 0.53) in the beta-blocker–based therapy versus other medications. African Americans exhibited higher BP and HR than Caucasians at all exercise workloads regardless of antihypertensive therapy and had over a 90% higher likelihood for an abnormal exercise BP response. This risk was attenuated by 35% with a beta-blocker–based therapy.

CONCLUSIONS
Significantly lower exercise BP, HR, and RPP levels are achieved with beta-blocker–based therapy than with other antihypertensive agents regardless of race. However, BP was better controlled in Caucasians than in African Americans regardless of antihypertensive therapy. (J Am Coll Cardiol 2006;47:794–8) © 2006 by the American College of Cardiology Foundation

An abnormal rise in systolic blood pressure (BP) during exercise is associated with left ventricular hypertrophy (LVH) (1,2), cardiovascular morbidity and mortality, or an exercise-induced acute cardiovascular event (3–6). At the very least, it often interferes with the completion of the exercise tolerance test (ETT) and prevents the accurate evaluation of potential or existing coronary heart disease (CHD).

The metabolic demand of many leisure and routine daily activities of middle-aged individuals is approximately 5 to 7 metabolic equivalents (METs) (7). Thus, it is reasonable to assume that the blood pressure (BP) response at workloads of 5 to 7 METs during a graded ETT reflects very closely the BP during daily activities (2). Relatively high BP levels may prevail in hypertensive patients engaging in routine daily activities, and this may influence cardiac structure and function. We and others have reported strong and significant associations among exercise BP at the intensities of 5 to 7 METs, BP during working hours, and left ventricular mass (8,9). An even greater concern is the BP response of hypertensive patients engaging in strenuous manual or recreational activities that require repetitive bursts of maximal or near maximal effort, such as snow-shoveling, basketball, tennis, etc. The repetitive BP peaks triggered during such activities may expose the hypertensive patient to a greater risk for an acute cardiovascular event.

Recommendations for treating an exaggerated BP response during exercise are not established and clinicians confronted with such response have no guidelines for medical therapy. We sought to determine the BP response during exercise in hypertensive male patients receiving various antihypertensive medications.

METHODS
Study population. During 1996 to 2005, a routine ETT was administered to 3,755 men at the Veterans Affairs Medical Center, Washington, DC. Of these, 2,318 (age 60 ± 10 years) were hypertensive and included in the study. Hypertension was defined by the clinical history in the patient’s medical record. Approximately 74% (n = 1,725) were African American, 24% (n = 545) Caucasian, and 2% (n = 48) Hispanic and other races. Owing to the small sample size,
Hispanics and other races were combined with Caucasians in all analyses. All subjects gave a written consent prior to ETT. About 47% (n = 1,087) of the patients were on antihypertensive monotherapy consisting of angiotensin-converting enzyme inhibitors (ACE-I) (n = 437), beta-blockers (n = 201), calcium-channel blockers (CCB) (n = 223), or diuretics (n = 226). In addition to monotherapy groups, we established the “beta-blocker–based therapy” and “Other Meds” groups. The beta-blocker–based therapy group (n = 668) included patients receiving a beta-blocker alone (n = 201) or in combination with any other antihypertensive agent (n = 467). The Other Meds group (n = 1,442) included patients receiving monotherapy (n = 886), or combination therapy (n = 556) of any antihypertensive agents that excluded beta-blockers. The remaining 208 (9%) were untreated.

All demographic, medical, and medication information was obtained from patients’ computerized medical records just before ETT.

**Exercise assessments.** All patients underwent an ETT on the standard Bruce protocol (10). Patients were included in this study if they did not have a positive ETT based on the American College of Cardiology/American Health Association guidelines (11), impaired chronotropic response (12), history of an implanted pacemaker, use of digoxin, congenital valvular heart disease, pre-excitation syndrome, or left bundle branch block.

Peak exercise time was recorded in minutes. Peak workload was estimated as METs (10). Patients were encouraged to exercise until volitional fatigue in the absence of symptoms or other indicators of ischemia. For a more accurately estimated workload, the patients were not allowed to lean on the handrails.

Supine resting BP was assessed after 5 min of rest. Exercise BP was recorded at 2 min of each exercise stage, at peak exercise, and within 1, 3, and 5 min during recovery. Indirect arm-cuff sphygmomanometry was used for all BP assessments.

Additional parameters recorded were body weight, height, daily cigarette smoking habits as reported by the patient, total serum cholesterol and fasting blood glucose levels, and history of diabetes and other chronic diseases. Body mass index (BMI) was calculated as weight (kg) divided by height (m)².

**Statistical analysis.** Continuous variables are presented as mean ± standard deviation and categorical variables as absolute and relative frequencies (%). Associations between categorical variables were tested using Pearson chi-square test. Blood pressure comparisons between treatment groups were performed by the Student t test, Mann-Whitney test (for the skewed variable exercise duration), and one-way analysis of variance. The Bonferroni rule to correct for inflation in the type-I error was applied with multiple comparisons. Normality of the dependent variables was tested by the Kolmogorov-Smirnov test, and equality of variances between treatment groups was tested by the Levene test. Fixed effects general linear models were applied to evaluate differences on BP measurements between treatment groups, after controlling for various potential confounders. In particular, age, race, smoking, BMI, and resting BP were individually entered in the models and tested for their confounding effect on treatment groups. Additionally, the interactions between treatment groups and the aforementioned variables were tested. Finally, multiple logistic regression analysis was applied to evaluate the association between treatment groups on the likelihood of having abnormal systolic BP response (i.e., ≥210 mm Hg) during exercise, after controlling for various potential confounders as mentioned above. Deviance residuals were used to evaluate models’ goodness-of-fit. A p value of < 0.05 of two-sided tests was considered to be statistically significant. All statistical analyses were performed in SPSS software (version 12.0, SPSS Inc., Chicago, Illinois).

**RESULTS**

**Baseline characteristics.** Patient clinical characteristics by treatment group are presented in Table 1. Comparisons are made among the groups defined as “beta-blocker–based therapy,” “Other Meds,” and “Untreated.” Patients treated with beta-blocker–based therapy had lower resting heart rate (HR) compared with those treated with other antihypertensive medications. Age, BMI, exercise duration, and peak METs were similar between the two treated groups. Hypertensive untreated patients had significantly higher resting systolic and diastolic BP, higher HR, longer exercise duration, and higher peak MET level when compared with the other groups (Table 1).

Other clinical characteristics included 803 (35%) diabetic; 318 (14%) with total serum cholesterol of > 200 mg/dl, 1,035 (45%) obese (BMI > 29.9 kg/m²), 579 (25%) smokers, and 127 (6%) with family history of CHD. No significant associations were observed between treatment groups and the prevalence of high total cholesterol levels (p = 0.24), obesity (p = 0.87), and smoking habits (p = 0.32). However, African Americans and diabetics were more likely to be treated with ACE-I than other antihypertensive medications (p < 0.001).

**Exercise parameters.** The mean values of exercise parameters at 5 and 7 METs, (3 and 6 min of exercise on the
Bruce protocol) and peak exercise by treatment group are presented in Table 2. Unadjusted analysis revealed that patients in the beta-blocker–based therapy had significant lower BP and HR at 5 and 7 METs and peak exercise compared with untreated patients and those treated with other medications.

To account for possible confounding effects of the previous findings by differences in BMI, smoking, resting BP, and age, we adjusted for these potential confounders. Generalized linear models revealed that patients on beta-blocker–based therapy still had lower systolic BP at 5 METs (beta-coefficient ± standard error: 14.2 ± 1.2 mm Hg; p < 0.001), at 7 METs (15.5 ± 1.5 mm Hg; p < 0.001), and at peak of exercise (15.2 ± 1.3 mm Hg; p < 0.001), when compared with patients treated with other antihypertensive agents. Similarly, the exercise diastolic BP in these patients was lower at 5 METs (2.4 ± 0.2 mm Hg, p = 0.014), 7 METs (2.06 ± 1.2 mm Hg; p = 0.08), and peak of exercise workloads (1.9 ± 1.1 mm Hg; p = 0.007), as was HR at the same workloads (11.9 ± 1.2 beats/min [p < 0.001], 12.8 ± 1.5 beats/min [p = 0.001], and 17.1 ± 1.2 beats/min [p < 0.001], respectively). Subsequently, the rate-pressure product (RPP) at these workloads also was significantly lower (Table 2).

When we considered monotherapy, the findings were similar. More specifically, the systolic BP, HR, and RPP at 5 and 7 METs and at peak of exercise were significantly lower in patients treated with beta-blockers compared with those treated with CCBs, diuretics, or ACE-I (Table 3).

Intraracial comparisons revealed that both African Americans and Caucasians treated with beta-blocker–based therapy had lower BP, HR, and RPP at submaximal (5 and 7 METs) and maximal workloads than those on other medication (p < 0.001). There was no treatment-by-race interaction for exercise BP, HR, or RPP (p > 0.4).

Despite the lack of treatment-by-race interaction, we probed for racial differences. Inter-racial comparisons revealed that African Americans had consistently higher HR and BP than Caucasians regardless of antihypertensive regimen. More specifically, the resting BP of African Americans on beta-blocker–based therapy was about 7/4 (±2/1) mm Hg higher than that of Caucasians on the same therapy. Similarly, the BP at 5 and 7 METs and peak exercise was higher in African Americans by 11/6 (±2/1) mm Hg, 6/6 (±2/1) mm Hg, and 12/7 (±2/1) mm Hg, respectively (all p < 0.001). Age and BMI were similar. Comparisons regarding antihypertensive medications other than beta-blockers revealed similar findings. The BP of African Americans was higher than Caucasians by approximately 6/6 (±2/1) mm Hg, 9/6 (±2/1) mm Hg, and 7/6 (±2/1) mm Hg at 5 METs, 7 METs, and peak exercise, respectively. Resting BP and BMI were similar, but Caucasians

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### Table 1. Clinical Characteristics of the Patients by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Beta-Blocker–Based</th>
<th>Other Meds</th>
<th>Untreated</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>668</td>
<td>1,442</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61 ± 11</td>
<td>59 ± 10‡</td>
<td>59 ± 11‡</td>
<td>0.002</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.9 ± 5.8</td>
<td>29.8 ± 5.2</td>
<td>29.5 ± 5.2</td>
<td>0.69</td>
</tr>
<tr>
<td>Resting HR (beats/min)</td>
<td>66 ± 12</td>
<td>75 ± 14‡</td>
<td>73 ± 15‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting SBP (mm Hg)</td>
<td>129 ± 19</td>
<td>131 ± 19</td>
<td>142 ± 18‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting DBP (mm Hg)</td>
<td>80 ± 11</td>
<td>80 ± 11</td>
<td>88 ± 10‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>399 ± 148</td>
<td>418 ± 168‡</td>
<td>152 ± 176‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>METs (3.5 ml O₂/kg/min)</td>
<td>6.6 ± 2.1</td>
<td>7.0 ± 2.4†</td>
<td>7.5 ± 2.6†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The p values derived from analysis of variance for comparisons between beta-blockers vs. other medication or untreated groups.
†Bonferroni-corrected probability value <0.05 for the post-hoc comparisons between other antihypertensive agents or untreated groups vs. beta-blockers.
‡Bonferroni-corrected probability value <0.01 for the post-hoc comparisons between other antihypertensive agents or untreated groups vs. beta-blockers.

DBP = diastolic blood pressure; HR = heart rate; MET = metabolic equivalent; SBP = systolic blood pressure.

### Table 2. Exercise Parameters of Patients on Combination Therapy

<table>
<thead>
<tr>
<th></th>
<th>Beta-Blocker–Based</th>
<th>Other Meds</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>668</td>
<td>1,442</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min) at 5 METs</td>
<td>103 ± 17</td>
<td>118 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mm Hg) at 5 METs</td>
<td>153 ± 28</td>
<td>167 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mm Hg) at 5 METs</td>
<td>85 ± 13</td>
<td>87 ± 13</td>
<td>0.1</td>
</tr>
<tr>
<td>HR (beats/min) at 7 METs</td>
<td>116 ± 17</td>
<td>130 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mm Hg) at 7 METs</td>
<td>166 ± 27</td>
<td>181 ± 28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mm Hg) at 7 METs</td>
<td>86 ± 16</td>
<td>87 ± 14</td>
<td>0.1</td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>127 ± 21</td>
<td>149 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak SBP (mm Hg)</td>
<td>177 ± 28</td>
<td>193 ± 28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak DBP (mm Hg)</td>
<td>89 ± 14</td>
<td>90 ± 15</td>
<td>0.1</td>
</tr>
<tr>
<td>RPP at 5 METs</td>
<td>15,929 ± 4,688</td>
<td>19,934 ± 4,804</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RPP at 7 METs</td>
<td>19,388 ± 5,118</td>
<td>24,098 ± 5,287</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RPP at peak exercise</td>
<td>22,800 ± 6,086</td>
<td>28,713 ± 5,632</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The p values derived from Student t test that evaluated differences between beta-blockers and other medication groups.

RPP = rate pressure product (HR · SBP); other abbreviations as in Table 1.
were slightly older (all p < 0.005). Similarly, findings were revealed for HR and rate-pressure product, at all exercise levels (all p < 0.001; data not presented).

Because exercise systolic BP of ≥210 mm Hg is considered significant for developing LVH (1), we categorized patients into those who achieved this BP level (n = 618) or did not achieve it (n = 1,700). After controlling for age, race, and resting BP levels, the likelihood of systolic BP of ≥210 mm Hg during exercise in those treated with beta-blockers in combination with other antihypertensive agents (beta-blocker–based) therapy was 68% lower (odds ratio [OR] = 0.32; 95% confidence interval [CI] 0.2 to 0.53) compared with those treated with combination therapy of other antihypertensive agents. When monotherapy was considered, the likelihood of exercise systolic BP of ≥210 mm Hg was 58% lower in those treated with beta-blockers compared with those treated with ACE-I (OR = 0.42; 95% CI 0.25 to 0.71), 74% lower compared with those treated with CCB (OR = 0.26; 95% CI 0.15 to 0.46), and 64% lower compared with those treated with diuretics (OR = 0.36; 95% CI 0.20 to 0.64).

When we stratified by race we observed that African Americans were at higher risk of having exercise systolic BP of ≥210 mm Hg compared with Caucasians (OR = 1.91; 95% CI 1.45 to 2.53) after adjusting for age, BMI, and resting BP. Additional multiadjusted analysis revealed that the use of beta-blockers in African Americans attenuated the effect of race on the likelihood of having an exaggerated exercise BP response by 35% (OR = 0.65; 95% CI 0.4 to 1.0).

**DISCUSSION**

We retrospectively assessed the BP response during exercise in 2,318 hypertensive patients treated with various antihypertensive medications. We observed that the use of beta-blockers alone or in combination with other antihypertensive agents was associated with lower systolic and diastolic BP, HR, and RPP at the absolute submaximal workloads of 5 and 7 METs, as well as at peak exercise, compared with the use of ACE-I, CCB, and diuretics as monotherapy or in various combinations. The average systolic BP at 5 and 7 METs was lower by approximately 14 and 15 mm Hg, respectively, and by 16 mm Hg at peak exercise, when compared with patients treated with other antihypertensive agents. Moreover, beta-blockade–based therapy was associated with a lower likelihood of having an abnormal systolic BP response (systolic BP ≥210 mm Hg) during exercise, even after all adjustments for possible confounders were considered. These findings lead to the conclusion that the use of beta-blockers as monotherapy or in combination with other antihypertensive agents mitigates the BP response at maximal as well as absolute submaximal exercise workloads and could prevent an exaggerated BP response in hypertensive patients. We are not aware of any studies assessing the effects of antihypertensive therapy on exercise-induced hypertension, or studies comparing the effects of beta-blockers with other antihypertensive agents for the prevention of abnormal exercise-induced hypertension.

The lower BP and HR at absolute submaximal and maximal workloads suggest improved cardiac performance and hemodynamics and a consequent reduction in the work of the heart. This is further supported by the lower RPP observed in those on beta-blocker–based therapy. The clinical significance of these findings extends beyond the ETT. As previously mentioned, the metabolic demand of most routine daily and leisure time activities is about 5 to 7 METs (7). Therefore, it is reasonable to assume that the BP recorded at 5 to 7 METs during an exercise stress test represents the BP during routine daily activities.

Nevertheless, our findings suggest that beta-blockade, as monotherapy or in combination with other antihypertensive medications, may be a prudent approach to control the exaggerated BP response during exercise observed in some hypertensive patients. This is especially true for hypertensive patients engaging in vigorous physical activities, such as snow-shoveling, basketball, tennis, racquetball, etc., that
require repetitive bursts of effort to maximal or near maximal levels. For these individuals, beta-blockade–based therapy can protect against excessive and repetitive elevations in BP that may occur during such activities. However, a prospective study is necessary to confirm our findings and further address the clinical significance of our findings.

Our findings regarding African-American patients are of particular interest. The risk of having an abnormal BP response during exercise was over 90% higher in African-American patients compared with Caucasians. This risk was attenuated by 35% with a beta-blocker–based antihypertensive therapy.

Inter-racial comparisons revealed consistently higher BP and HR in African-American patients compared with Caucasians at any exercise workload. This was regardless of the antihypertensive therapy. This suggests that exercise BP in African-American hypertensive patients is more difficult to control than in Caucasians regardless of the antihypertensive regimen. Yet, beta-blockers are more effective in attenuating the risk of an abnormal exercise BP in African Americans than other antihypertensive medications. This is in accord with existing evidence of racial differences in response to different cardiovascular medications and the protection afforded by these agents (13). However, it is important to emphasize that we found no statistically significant racial differences on the effects of treatment on BP (no race-by-treatment interaction). Future prospective studies in sub-populations are needed to confirm our findings and help further delineate possible antihypertensive agent differences in the protection against cardiovascular morbidity and mortality events.

Study limitations. The present study is cross-sectional and therefore has limitations. Because of the design we cannot provide causal relationships but only state hypotheses to be evaluated in future randomized clinical trials. Smoking habits have been associated with high BP and low fitness levels. Although we adjusted for smoking, the use of self-reported information may confound our findings. The onset of hypertension, its severity, and the duration of antihypertensive therapy were not evaluated in our study owing to incomplete records. Finally, our findings are based on men only and therefore inferences to women are prohibited.

Conclusions. Our findings support that the use of beta-blockers as monotherapy or in combination with other antihypertensive agents mitigates the BP response at maximal and absolute submaximal exercise workloads and could prevent an exaggerated BP response in a considerable proportion of patients. Because the BP response to submaximal exercise workloads of 5 to 7 METs reflects the BP response during routine daily activities, beta-blockade–based therapy may be a prudent approach to control an excessive rise in BP during routine daily activities in hypertensive patients who exhibit an excessive BP response during exercise testing. Moreover, for patients engaging in vigorous activities such as snow-shoveling, basketball, tennis, racquetball, and so on, beta-blockade–based therapy can protect against excessive and repetitive elevations in BP which may occur during such activities. The need for a prospective study to further address the clinical significance of the current findings is necessary.

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REFERENCES


