Exercise Capacity and Progression From Prehypertension to Hypertension

Charles Faselis, Michael Doumas, John Peter Kokkinos, Demosthenes Panagiotakos, Raya Kheirbek, Helen M. Sheriff, Katherine Hare, Vasilios Papademetriou, Ross Fletcher, Peter Kokkinos

Abstract—Prehypertension is likely to progress to hypertension. The rate of progression is determined mostly by age and resting blood pressure but may also be attenuated by increased fitness. A graded exercise test was performed in 2303 men with prehypertension at the Veterans Affairs Medical Centers in Washington, DC. Four fitness categories were defined, based on peak metabolic equivalents (METs) achieved. We assessed the association between exercise capacity and rate of progression to hypertension (HTN). The median follow-up period was 7.8 years (mean (± SD) 9.2±6.1 years). The incidence rate of progression from prehypertension to hypertension was 34.4 per 1000 person-years. Exercise capacity was a strong and independent predictor of the rate of progression. Compared to the High-Fit individuals (>10.0 METs), the adjusted risk for developing HTN was 66% higher (hazard ratio, 1.66; 95% CI 1.2 to 2.2; \(P=0.001\)) for the Low-Fit and, similarly, 72% higher (hazard ratio, 1.72; 95% CI, 1.2 to 2.3; \(P=0.001\)) for the Least-Fit individuals, whereas it was only 36% for the Moderate-Fit (hazard ratio, 1.36; 95% CI, 0.99 to 1.80; \(P=0.056\)). Significant predictors for the progression to HTN were also age (19% per 10 years), resting systolic blood pressure (16% per 10 mm Hg), body mass index (15.3% per 5 U), and type 2 diabetes mellitus (2-fold). In conclusion, an inverse, S-shaped association was shown between exercise capacity and the rate of progression from prehypertension to hypertension in middle-aged and older male veterans. The protective effects of fitness were evident when exercise capacity exceeded 8.5 METs. These findings emphasize the importance of fitness in the prevention of hypertension. (Hypertension. 2012;60:00-00.)

Key Words: prehypertension ■ hypertension ■ exercise capacity ■ age

A plethora of evidence from observational studies strongly supports that cardiovascular (CV) risk increases progressively from blood pressure (BP) levels as low as 115/75 mm Hg and doubles for every 20/10-mm Hg increment of BP.\(^1\) Based on this, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) proposed that systolic blood pressure (SBP) levels of 120 to 139 mm Hg and/or diastolic blood pressure (DBP) levels of 80 to 89 mm Hg is defined as prehypertension.\(^2\) Evidence is now accumulated to support that prehypertension is associated with traditional CV risk factors, increased CV events, and target organ damage.\(^3\)–\(^6\) It is estimated that approximately 42 million men and 28 million women (37% of the adult US population) have prehypertension.\(^7\) Approximately 40% of these individuals will progress to hypertension within 2 years.\(^8\) The most prominent factors associated with the progression from prehypertension to hypertension are baseline BP and age.\(^8\)\(^9\) Studies based on physical activity questionnaires support that the fitness status of the individual may attenuate the progression to hypertension.\(^10\)–\(^12\) Similar findings are also reported in young adults (18 to 30 years) when fitness was assessed by a graded exercise test\(^13\); however, information on the association between an objectively assessed fitness status and the rate of progression from prehypertension to hypertension is limited. In addition, no studies addressed this association in older individuals. Since the lifetime risk for developing hypertension for middle-aged and elderly individuals is 90%, it is clinically significant to define factors that attenuate this rate.\(^14\) In this regard, increased exercise capacity or fitness may be such a factor.

In an effort to enrich understanding in the emerging area of prehypertension, we assessed the prognostic value of peak exercise capacity (fitness status) on the progression to hypertension in middle-aged and older prehypertensive individuals referred for an exercise test for clinical reasons.
Methods

Study Design and Population
Between January 1986 and September 2009, a symptom-limited exercise tolerance test (ETT) was administered to more than 10,000 male veterans at the Veterans Affairs Medical Center, Washington, DC, to evaluate individuals with symptoms consistent with coronary heart disease and to exclude exercise-induced ischemia, as well as evaluate individuals before participation in exercise programs. Subjects were excluded from the study if they (1) had a history of an implanted pacemaker; (2) had a left bundle branch block that developed during the test; and (3) were unstable or required emergent intervention.15

Of the initial cohort, 2303 males were identified as prehypertensive and met the following criteria: (1) had resting systolic BP between 120 and 139 mm Hg and/or resting diastolic BP 80 to 89 mm Hg attained from their medical record on at least 2 different occasions in an outpatient clinic setting (BP measurements are routinely conducted in every patient visit at all Veterans Affairs Medical Centers); (2) were not receiving any antihypertensive or cardiac medication other than statins; (3) had no history of cardiovascular disease (CVD) or hypertension; and (4) successfully completed the exercise stress test. The cohort consisted of 1413 black individuals and 890 white individuals. All gave written consent for the study. The study was approved by the Internal Review Board of the institution. All demographic, clinical, and medication information was obtained from individuals’ computerized medical records just before the ETT. Each individual was also asked to verify the computerized information with regard to history of chronic disease, current medications, and cigarette smoking habits. Body weight and height were recorded before the test. Body mass index (BMI) was calculated as weight (kg) divided by height2 (m2). Demographic data are included in Table 1.

Electronic medical records were manually searched to identify the date a prehypertensive individual from the study cohort progressed to hypertension, as confirmed by a physician. As mentioned, BP measurements are routinely conducted and recorded in every patient visit at all Veterans Affairs Medical Centers. BP is assessed after at least 5 minutes of rest and while the individual is sitting. Indirect arm-cuff sphygmomanometry was used for all BP assessments. If the initial blood pressure reading was ≥140/90 mm Hg, BP assessment was repeated after an additional 10 to 15 minutes of rest. This procedure allows an accurate account of BP changes and the onset of hypertension for any patient.

Exercise Assessments
The exercise capacity was assessed by the standard Bruce protocol. Peak exercise time was recorded in minutes. Peak workload was estimated as metabolic equivalent (MET). One MET is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 mL per kg of body weight per minute.16 Exercise capacity (in METs) was estimated, based on exercise time via a commonly used equation for the Bruce protocol.17 Subjects were encouraged to exercise until volitional fatigue, in the absence of symptoms or other indicators of ischemia.18 The use of handrails during the exercise test was discouraged. Age-predicted peak exercise heart rate (HR) was determined, based on standardized methods.18

Supine resting HR and BP were assessed after 5 minutes of rest. Exercise BP was recorded at 2 minutes of each exercise stage, peak exercise, and during recovery. Indirect arm-cuff sphygmomanometry was used for all BP assessments. ST-segment depression was measured visually. ST depression ≥1.0 mm that was horizontal or down-sloping was considered to be suggestive of ischemia.

Determination of Fitness Categories
Four fitness categories were established, based on the MET level achieved. The MET cutoffs used were based on the peak MET level achieved by the entire cohort. Individuals with a peak MET level within the 30th percentile (≤6.5 MET) comprised the Least-Fit category (n=685). Those who achieved a MET level between the 31st to 60th percentile (6.6 to 8.5 MET) comprised the Low-Fit category (n=758). Subjects who achieved a MET level between the 61st and 90th percentile (8.6 to 10 MET) comprised the Moderate-Fit category (n=550), and those with a peak MET level above the 90th percentile (>10 MET), comprised the High-Fit category (n=310).

Statistical Analysis
Continuous variables are presented as mean ± standard deviation, while categorical variables are expressed as absolute and relative frequencies (%). Associations between categorical variables were tested using Pearson’s chi-square test. One-way analysis of variance was applied to determine age and BMI differences among the fitness categories.

Table. Demographic and Clinical Characteristics in the Entire Cohort and According to Exercise Capacity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Entire Cohort</th>
<th>Least-Fit (≤6.5 MET)</th>
<th>Low-Fit (6.6–8.5 MET)</th>
<th>Moderate Fit (8.6–10 MET)</th>
<th>High-Fit (&gt;10 MET)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2303</td>
<td>685</td>
<td>758</td>
<td>550</td>
<td>310</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>54±12</td>
<td>62±11*</td>
<td>55±10*</td>
<td>49±10*</td>
<td>45±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.2±4.8</td>
<td>27.3±5.2*</td>
<td>27.6±5.0*</td>
<td>27.4±4.4*</td>
<td>26.0±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting HR (beats/min)</td>
<td>71±13</td>
<td>74±13*</td>
<td>72±13*</td>
<td>69±12*</td>
<td>65±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting SBP (mm Hg)</td>
<td>124±9</td>
<td>126±9*</td>
<td>123±9*</td>
<td>122±9</td>
<td>122±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting DBP (mm Hg)</td>
<td>79±7</td>
<td>79±8</td>
<td>80±7</td>
<td>80±6</td>
<td>79±6</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>33.7</td>
<td>34.9*</td>
<td>36.8*</td>
<td>30.9</td>
<td>28.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10.7</td>
<td>15.6*</td>
<td>11.7*</td>
<td>6.7*</td>
<td>3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>18.3</td>
<td>17.8</td>
<td>19.7</td>
<td>18.5</td>
<td>15.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>4.8</td>
<td>3.6</td>
<td>5.8</td>
<td>5.5</td>
<td>3.9</td>
<td>0.31</td>
</tr>
</tbody>
</table>

†Overall differences for the 4 fitness categories.

MET indicates metabolic equivalent; y, years; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; O2, oxygen. *Different from the High-Fit category (Bonferroni adjusted P values<0.05).
categories. The assumption of equality of variances between treatment groups was tested by the Levene’s test, and normality was tested using P-P plots. Interaction between races and the progression to hypertension was also tested. Post hoc procedures were used to discern differences between fitness categories, and the Bonferroni rule to correct for the inflation in type-I error was applied.

Cox proportional hazard models were used to determine the variables that were independently and significantly associated with progression from prehypertension to hypertension (categorical, yes versus no), and to calculate the corresponding hazard ratios (HR) and 95% confidence intervals (CI). The hazard for progression from prehypertension to hypertension was calculated for each fitness category, with the High-Fit category (individuals with an exercise capacity >10 METs) as the reference group. The models were adjusted for age in years, BMI, resting systolic blood pressure, diabetes, and smoking. Furthermore, trend analysis and $\chi^2$ tests, testing various equations (linear, parabolic, cubic), were applied to describe the dose-response relationship between fit categories and the estimated HRs.

$\bullet$ Results

During a median 7.8-year follow-up period (mean (± SD) of 9.2±6.1 years), 728 of 2303 (31.6%) individuals developed hypertension. The incidence rate of progression for the entire cohort was 34.4 per 1000 person-years of observation. There was no interaction between race-by-fitness categories ($P=0.79$) or race-by-peak METs achieved ($P=0.38$), and, therefore, the data were not stratified by race.

$\bullet$ Demographic and Clinical Characteristics

Participant characteristics and exercise data for the entire cohort and for each fitness category are presented in Table. Age was lower when moving from the Least-Fit to the Highest-Fit category ($P<0.001$). BMI and resting systolic blood pressure were different when comparing the Least-Fit to High-Fit ($P<0.001$ for both variables). Significant differences were also noted among all groups regarding the prevalence of smoking ($P=0.01$) and diabetes ($P<0.001$). Thus, age, BMI, resting systolic blood pressure, diabetes, and smoking were used as covariates when probing for differences in the progression rate to hypertension among the 4 fitness categories.

$\bullet$ Predictors of Progression to Hypertension

Cox proportional hazard analysis revealed that exercise capacity (HR, 0.93; CI, 0.89 to 0.98; $P=0.005$); age (HR, 1.018; CI, 1.01 to 1.02; $P<0.001$); BMI (HR, 1.029; CI, 1.01 to 1.04; $P<0.001$); baseline SBP (HR, 1.015; CI, 1.008 to 1.020; $P<0.001$) and history of diabetes mellitus (HR, 2.00; CI, 1.70 to 2.50; $P<0.001$) were independent predictors of the rate of progression from prehypertension to hypertension. The rate of progression to hypertension according to the type of prehypertension defined by SBP, DBP, or both was also assessed. In this regard, the rate of progression was significantly higher for those with prehypertension defined by both SBP and DBP when compared to those with isolated systolic prehypertension (40.7% versus 32.3%, respectively; $P=0.002$) and isolated diastolic prehypertension (40.7% versus 24.3%; $P<0.001$). The rate was also higher for individuals with isolated systolic prehypertension compared with those with isolated diastolic prehypertension (32.3% versus 24.3%, respectively; $P<0.001$).

$\bullet$ Risk of Progression to Hypertension Across Fitness Categories

Cox regression analyses across fitness categories are presented in Figure 1 and 2. Individuals in the High-Fit category (peak exercise capacity >10 METS) were compared with those who achieved 8.6 to 10 METS (Moderate-Fit); 6.6 to 8.5 METS (Low-Fit); and ≤6.5 METS (Least-Fit). The relative
risk for developing hypertension was progressively higher as exercise capacity decreased. More specifically, the rate was 1.36 (CI, 0.99 to 1.80; \( P = 0.056 \)) for the Moderate-Fit; 1.66 (CI, 1.2 to 2.2; \( P = 0.001 \)) for the Low-Fit; and 1.72 (CI, 1.2 to 2.3; \( P = 0.001 \)) for the Least-Fit individuals. Trend analysis revealed an S-shaped association between fit categories and risk for hypertension; suggesting that Least-Fit and Low-Fit categories exhibited similar increase in the risk as compared with the High-Fit category.

**Discussion**

In this study, we evaluated the association between exercise capacity and the rate of progression from prehypertension to hypertension in middle-aged and older male veterans. The presented findings support an increase in the rate of progression to hypertension with decreased exercise capacity. The most pronounced and very similar increase in risk occurred in the 2 lowest-fit categories (66% and 72% higher risk, respectively), suggesting an S-shaped association between fitness and rate of progression to hypertension. Although the Low-Fit category did not achieve statistical significance (\( P = 0.056 \)), it is important to note that individuals in this fitness category had a 36% higher risk for developing hypertension compared with those in the High-Fit category. In general, these findings support an earlier report in young adults\(^{13} \) and provide additional information for a population with several risk factors more prone to developing hypertension. Furthermore, it emphasizes that even relatively moderate fitness levels offer protection against the development of hypertension.

Additional factors that contribute to an increased rate of progression to hypertension were age, BMI, SBP, and diabetes. The risk increased by 19.5% for every 10 years of age, 16% for every 10-mm Hg incremental increase in resting systolic BP, and 15% for every 5 U of incremental increase in BMI. The risk for individuals with type 2 diabetes was doubled. It is also clinically significant to note that the rate of progression to hypertension was higher in individuals with isolated systolic prehypertension when compared with isolated diastolic prehypertension and even higher for those whose prehypertension was defined by both SBP and DBP. Therefore, healthcare providers should adopt a more aggressive approach regarding fitness and other lifestyle modifications for such individuals.

Exercise capacity and fitness status are associated inversely with mortality risk in relatively healthy individuals\(^ {19} \) and those with comorbidities including type 2 diabetes mellitus,\(^ {20} \) hypertension\(^ {21} \) and prehypertension.\(^ {22} \) The current findings support that a moderate increase in exercise capacity may attenuate the progression from prehypertension to hypertension. This fitness status is likely to be attained by most middle-aged and older individuals by moderate intensity physical activities (ie, brisk walk), 20 to 40 minutes per session, most days of the week.\(^ {23,24} \) The significantly high likelihood of progression to hypertension (90%) for middle-aged and older individuals with prehypertension bestows great clinical and public health significance to this finding.

An argument can be made that the outcomes of our findings may be influenced by the lifestyle of veterans that may differ substantially from other cohorts. Therefore, our findings may not have wide application. Although we cannot account on the degree of lifestyle similarities between cohorts, it is unlikely that the socioeconomic factors of our cohort would be more favorable than others; however, an important consideration is the equal access to care independent of a patient’s financial status provided by the Veterans Health Administration.\(^ {25} \) This permits epidemiological evaluations while minimizing the influence of disparities in medical care.\(^ {26} \) Moreover, the existence of electronic health records within the VA Healthcare System, which enable detailed observation of prior history and alterations in health status, minimizes the potential impact of confounding factors on our findings.

Another consideration is that substantial differences may exist in the fitness status of our cohort compared with cohorts.

**Figure 2.** Event-free distribution rate curves, representing the risk of progression from prehypertension to hypertension, according to fitness categories. Rates were adjusted for age, body mass index, resting systolic blood pressure, diabetes mellitus, and smoking.
comprised mostly by nonveterans. Because veterans are required to maintain a higher degree of fitness status during military service, decline in fitness may occur later in life. In this regard, our findings on the impact of fitness regarding the rate of progression from prehypertension to hypertension are underestimated.

Limitations
The current observational study is retrospective and, therefore, has several limitations and cannot provide causal relationship. First, only Veteran males were included, limiting the generalization of our findings to women. Second, no information regarding the dietary and physical activity habits and socioeconomic or health changes of our cohort during the follow-up period was available. Finally, direct evidence to support that brisk walking can lower the rate of progression from prehypertension to hypertension cannot be provided. All the aforementioned parameters were taken into account for the interpretation of the results, and the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement was followed.

Conclusions
An increase in the rate of progression to hypertension with decreased exercise capacity among middle-aged and older prehypertensive men was evident. The most pronounced and very similar increase in risk occurred in the 2 lowest-fit categories, suggesting an S-shaped association. These health benefits are evident at moderate levels of fitness, attainable by a brisk walk of 20 to 40 minutes most days of the week, by most middle-aged and older individuals. Fitness attenuates the risk for developing hypertension, regardless of age, BMI, and other traditional risk factors.

Perspectives
Our findings have a significant clinical and public health impact for the following reason. First, the attenuation of the rate of progression to hypertension is achieved at a fitness level represented by an exercise capacity >8.5 METs. This level of fitness is likely attainable by a brisk walk of 20 to 40 minutes most days of the week, by most middle-aged and older individuals. Since walking requires virtually no instruction, has a relatively low cost, carries a low risk of injury, and can be easily implemented to large populations, it may constitute an effective intervention to mitigate the progression to hypertension.

Disclosures
None.

References

Novelty and Significance

What Is New?

- Moderate improvements in fitness status attenuates the rate of progression from prehypertension to hypertension.

What Is Relevant?

- The fitness status necessary to attenuate the risk for developing hypertension is relatively moderate and achievable by daily brisk walks. This can have a significant impact on public health care.

Summary

Our findings are unique because they support that moderate levels of physical activity, such as a brisk walk of 20–40 minutes per day, most days of the week, can slow down the rate of progression from prehypertension to hypertension. Since walking requires virtually no instructions, has low risk of injury, is relatively inexpensive, and can be implemented in large populations of all ages, it represents an attractive approach for lowering the risk of developing hypertension. Since 40% of the 70 million individuals in the United States with prehypertension will develop hypertension within 2 years, our findings can have a significant impact on public health care and quality of life.
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