

Systolic Blood Pressure Response During Exercise Stress Testing: The Henry Ford Exercise Testing (FIT) Project

Wesley T. O'Neal, MD, MPH; Waqas T. Qureshi, MD, MS; Michael J. Blaha, MD, MPH; Steven J. Keteyian, PhD; Clinton A. Brawner, PhD; Mouaz H. Al-Mallah, MD, MSc

Background—The prognostic significance of modest elevations in exercise systolic blood pressure response has not been extensively examined.

Methods and Results—We examined the association between systolic blood pressure response and all-cause death and incident myocardial infarction (MI) in 44 089 (mean age 53 ± 13 years, 45% female, 26% black) patients who underwent exercise treadmill stress testing from the Henry Ford Exercise Testing (FIT) Project (1991–2010). Exercise systolic blood pressure response was examined as a categorical variable (>20 mm Hg: referent; 1 to 20 mm Hg, and ≤ 0 mm Hg) and per 1 SD decrease. Cox regression was used to compute hazard ratios (HR) and 95% CI for the association between systolic blood pressure response and all-cause death and incident MI. Over a median follow-up of 10 years, a total of 4782 (11%) deaths occurred and over 5.2 years, a total of 1188 (2.7%) MIs occurred. In a Cox regression analysis adjusted for demographics, physical fitness, and cardiovascular risk factors, an increased risk of death was observed with decreasing systolic blood pressure response (>20 mm Hg: HR=1.0, referent; 1 to 20 mm Hg: HR=1.13, 95% CI=1.05, 1.22; ≤ 0 mm Hg: HR=1.21, 95% CI=1.09, 1.34). A trend for increased MI risk was observed (>20 mm Hg: HR=1.0, referent; 1 to 20 mm Hg: HR=1.09, 95% CI=0.93, 1.27; ≤ 0 mm Hg: HR=1.19, 95% CI=0.95, 1.50). Decreases in systolic blood pressure response per 1 SD were associated with an increased risk for all-cause death (HR=1.08, 95% CI=1.05, 1.11) and incident MI (HR=1.09, 95% CI=1.03, 1.16).

Conclusions—Our results suggest that modest increases in exercise systolic blood pressure response are associated with adverse outcomes. (*J Am Heart Assoc.* 2015;4:e002050 doi: 10.1161/JAHA.115.002050)

Key Words: blood pressure • death • myocardial infarction • stress testing

Exercise stress testing is routinely used to identify individuals who potentially have obstructive coronary artery disease (CAD) and information regarding aerobic functional capacity also is obtained.¹ As a result of the

increase in cardiac output that occurs with exercise, systolic arterial blood pressure is expected to rise 20 mm Hg per metabolic equivalent of task.² Reductions in systolic blood pressure during exercise stress testing are associated with left ventricular systolic dysfunction and the presence of severe obstructive CAD.^{3,4}

Several studies have shown that a decline in systolic blood pressure below resting value (eg, exercise-induced hypotension) is associated with an increased risk of cardiovascular events.^{5–7} Additionally, an increased risk of cardiovascular mortality has been observed with low maximal systolic blood pressure responses in men and in patients with known hypertension and peripheral arterial disease.⁸ This led to the American Heart Association recommendation that decreases in systolic blood pressure >10 mm Hg below resting values are an absolute indication for exercise stress testing termination.¹ However, the aforementioned studies that led to this recommendation have been limited to specific subpopulations of predominately men.

Potentially, adverse outcomes are associated with even modest increases in exercise systolic blood pressure

From the Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC (W.T.O.); Section on Cardiovascular Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston Salem, NC (W.T.Q.); Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD (M.J.B.); Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI (S.J.K., C.A.B., M.H.A.-M.); Department of Internal Medicine, Wayne State University, Detroit, MI (M.H.A.-M.); Department of Cardiac Imaging, King Abdul Aziz Cardiac Center, Riyadh, Saudi Arabia (M.H.A.-M.).

Correspondence to: Mouaz H. Al-Mallah, MD, MSc, Cardiac Imaging, King Abdul-Aziz Cardiac Center, King Abdul-Aziz Medical City (Riyadh), National Guard Health Affairs, Department Mail Code: 1413, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. E-mail: mouaz74@gmail.com

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response, and this population merits closer evaluation for the presence of coronary heart disease. Such a finding would have important implications for populations that have not been extensively studied as data from diverse racial populations of men and women are lacking. Therefore, the purpose of this study was to examine the prognostic implications of decreased systolic blood pressure response during exercise treadmill stress testing using data from the Henry Ford Exercise Testing (FIT) Project, a racially diverse registry of men and women aimed to elucidate the association between cardiorespiratory fitness and outcomes.

Methods

Study Population

Details of the design, procedures, and methods used in FIT have been previously described.⁹ Briefly, the project population consists of 69 885 consecutive patients who underwent physician-referred exercise treadmill stress testing in the Henry Ford Health System, including affiliated hospitals and ambulatory care centers throughout the metropolitan area of Detroit, Michigan between 1991 and 2009. Data regarding treadmill testing, medical history, and medications were collected by laboratory staff at the time of testing. Follow-up data were collected from electronic medical records and administrative databases. The FIT Project was approved by the Henry Ford Health System institutional review board.

In this analysis, we examined the association between exercise systolic blood pressure response (peak systolic blood pressure—resting systolic blood pressure) and all-cause death and incident myocardial infarction (MI). We excluded

patients with missing baseline characteristics, medication data, and/or follow-up data ($n=1668$). Additionally, participants with prior CAD (prior MI, coronary angioplasty, coronary artery bypass grafting surgery, or coronary angiography with evidence of obstructive CAD) ($n=9946$) and severe valve disease ($n=423$) were excluded. The focus of this analysis was largely on decreased systolic blood pressure response, and participants with exaggerated systolic blood pressure rise (male: peak systolic ≥ 210 mm Hg; female: ≥ 190 mm Hg) were excluded ($n=13 759$).^{1,10} The final sample included 44 089 (mean age 53 ± 13 years, 45% female, 26% black) patients.

Exercise Stress Testing

Exercise treadmill stress testing was conducted using the Bruce protocol.¹¹ Patients <18 years old at the time of testing or those who underwent pharmacological stress testing, modified Bruce, and other non-Bruce protocol tests were excluded from the database. Antihypertensive medications were held prior to stress testing. Resting heart rate was measured from the resting ECG and blood pressure was manually measured prior to each stress test with each participant in the seated position. Heart rate was measured continuously during testing and blood pressure values were measured every 3 minutes. Peak heart rate and blood pressure were the highest recorded values for each participant. Target heart rate was calculated as 85% of the age-predicted maximal heart rate determined by the formula $220 - \text{age}$. Failure to achieve this heart rate was referred to as chronotropic incompetence. Initial treadmill speed was set at 2.7 km/h and increased to 4.0, 5.4, 6.7, 8.0, and 8.8 km/h on minutes 3, 6, 9, 12, and 15, respectively. Exercise workload was expressed in metabolic equivalents of task. We examined the association between exercise systolic blood pressure response as a categorical variable (>20 mm Hg: referent; 1 to 20 mm Hg, and ≤ 0 mm Hg) and as a continuous variable per 1 SD decrease in the systolic blood pressure response. Exercise-induced hypotension was defined as systolic blood pressure responses ≤ 0 mm Hg and values were grouped 1 to 20 mm Hg based on the graphical dose-response relationship between systolic blood pressure response and all-cause death and MI using restricted cubic spline models with knots incorporated at the 5th, 50th, and 95th percentiles.¹²

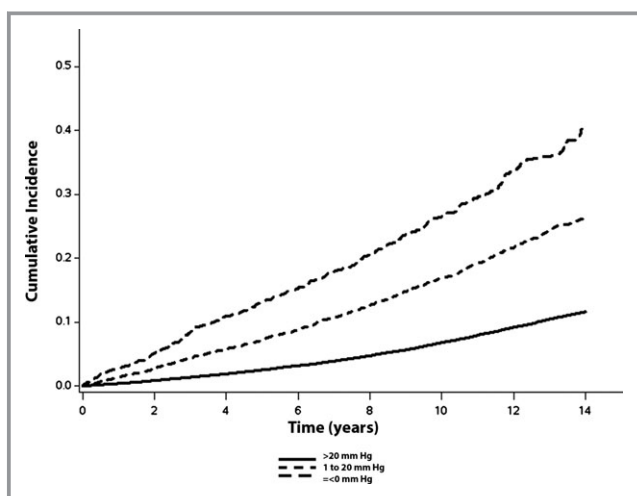


Figure 1. Cumulative incidence of all-cause death by systolic blood pressure response. Cumulative incidence curves are statistically different (log-rank $P<0.0001$).

Patient Characteristics

Demographics, body mass index, prior history of cardiovascular disease, and smoking status were obtained at the time of treadmill testing. Diabetes mellitus was defined as a prior diagnosis of diabetes, the use of hypoglycemic medications

Table 1. Baseline Characteristics (N=44 089)

Characteristics	Systolic Blood Pressure Response			P Value*
	≤0 mm Hg (n=1413)	1 to 20 mm Hg (n=5548)	>20 mm Hg (n=37 128)	
Age (mean±SD), y	63±14	58±14	52±12	<0.001
Black race, %	371 (26)	1546 (28)	9508 (26)	0.002
Male, %	639 (45)	2268 (41)	21 131 (57)	<0.0001
Smoker, %	591 (42)	2239 (40)	15 405 (41)	0.26
Obesity, %	310 (22)	1301 (23)	8030 (22)	0.009
Diabetes, %	387 (27)	1165 (21)	5809 (16)	<0.001
Hypertension, %	1165 (82)	3939 (71)	20 305 (55)	<0.001
Hyperlipidemia, %	1191 (84)	4540 (82)	29 836 (80)	<0.001
Aspirin, %	343 (24)	1188 (21)	5989 (16)	<0.001
Antihypertensive medications, %	966 (68)	3076 (55)	13 494 (36)	<0.001
Lipid-lowering therapies, %	403 (29)	1368 (25)	7066 (19)	<0.001
METs achieved, mean±SD	6.3±3.2	7.7±3.0	9.8±2.8	<0.001
Chronotropic incompetence, %	31 199 (84)	3451 (62)	681 (48)	<0.001

METs indicates metabolic equivalents of task.

*Statistical significance for categorical data tested using the χ^2 method and continuous data using the Wilcoxon rank-sum procedure.

including insulin, or a database-verified diagnosis of diabetes. Hypertension was defined as a prior diagnosis of hypertension, use of antihypertensive medications, or a database-verified diagnosis of hypertension. The blood pressure at the time of the test was not used to diagnose hypertension. Dyslipidemia was defined by prior diagnosis of any major lipid abnormality, the use of lipid-lowering medications, or a database-verified diagnosis of hypercholesterolemia or dyslipidemia.

All-Cause Death

The National Death Index was used to obtain death dates for patients through April 2013. Linkage with the National Death Index was based on a multiple-criteria deterministic matching algorithm, which included each patient's social security number, first name, last name, and date of birth. Complete matching occurred in >99.5% of patients in the FIT database.

Incident MI

We included incident fatal and nonfatal MI cases. Events were ascertained through linkage with administrative claim files from services delivered. These files included appropriate International Classification of Disease Codes. Complete follow-up for MI events was available through May 2010.

Statistical Analysis

Categorical variables were reported as frequency and percentage, while continuous variables were reported as mean±SD. Statistical significance for categorical variables was tested using the χ^2 method and the Wilcoxon rank-sum procedure for continuous variables. Follow-up time was defined as the date of exercise stress testing until the outcome of interest, death, loss to follow-up, or end of study period. Kaplan–Meier estimates were used to compute cumulative incidence curves for all-cause death and incident MI by systolic blood pressure response, and the differences

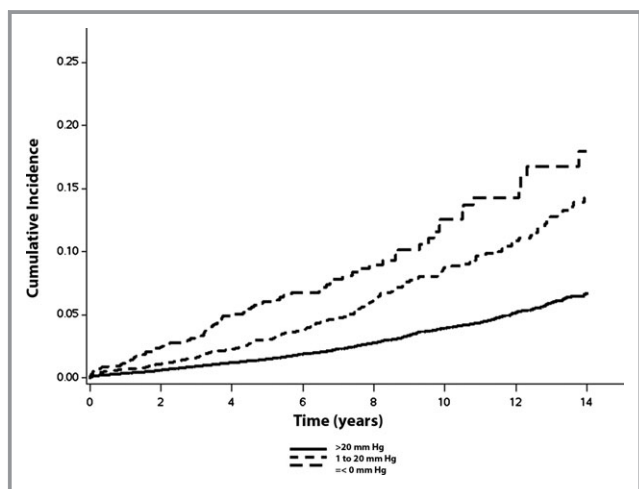


Figure 2. Cumulative incidence of myocardial infarction by systolic blood pressure response. Cumulative incidence curves are statistically different (log-rank $P<0.0001$).

Table 2. Risk of All-Cause Death

	Events/No. at Risk	Model 1* HR (95% CI)	P Value	Model 2† HR (95% CI)	P Value	Interaction‡ P Value
Systolic blood pressure response						
>20 mm Hg	3283/37 128	1.0	—	1.0	—	
1 to 20 mm Hg	1050/5548	1.64 (1.53, 1.76)	<0.001	1.13 (1.05, 1.22)	<0.001	—
≤0 mm Hg	449/1413	2.07 (1.87, 2.29)	<0.001	1.21 (1.09, 1.34)	<0.001	—
Per 1 SD decrease	4782/44 089	1.31 (1.27, 1.34)	<0.001	1.08 (1.05, 1.11)	<0.001	—
Age[§]						
<52 y	909/22 317	1.61 (1.51, 1.71)	<0.001	1.17 (1.10, 1.26)	<0.001	0.009
≥52 y	3873/21 772	1.47 (1.43, 1.51)	<0.001	1.11 (1.08, 1.15)	<0.001	
Sex[§]						
Female	1705/20 051	1.30 (1.24, 1.36)	<0.001	1.09 (1.04, 1.15)	<0.001	0.15
Male	3077/24 038	1.31 (1.27, 1.35)	<0.001	1.07 (1.04, 1.11)	<0.001	
Race[§]						
Nonwhite	1685/14 967	1.29 (1.23, 1.35)	<0.001	1.03 (0.98, 1.08)	0.25	0.056
White	3097/29 122	1.31 (1.26, 1.35)	<0.001	1.10 (1.06, 1.14)	<0.001	

HR indicates hazard ratio; METs, metabolic equivalents of task.

*Adjusted for age, sex, and race.

†Adjusted for Model 1 covariates plus smoking, hypertension, diabetes, obesity, hyperlipidemia, antihypertensive medication use, lipid-lowering medication use, aspirin, METs, and chronotropic incompetence.

‡Interactions tested using Model 2.

§All HRs presented are for the systolic blood pressure response per 1 SD decrease and were computed without the interaction term in the model.

||Dichotomized at the median age for study participants.

in estimates were compared using the log-rank procedure. Cox regression was used to compute hazard ratios and 95% CI) for the association between systolic blood pressure response and all-cause death and MI, separately. Multivariable models were constructed as follows: Model 1 adjusted for age, sex, and race; Model 2 adjusted for Model 1 covariates plus smoking, hypertension, diabetes, obesity, hyperlipidemia, antihypertensive medication use, lipid-lowering medication use, aspirin, metabolic equivalents of task, and chronotropic incompetence. We tested for interactions between our main effect variable and age (stratified by median age), sex, and race (whites versus nonwhites) using Model 2. The proportional hazards assumption was not violated in our analysis. Statistical significance was defined as $P < 0.05$ for the main effect model and tests for interaction. SAS[®] version 9.3 (Cary, NC) was used for all analyses.

Results

Baseline characteristics stratified by systolic blood pressure response are shown in Figure 1. Differences in baseline characteristics across systolic blood pressure responses were observed for all characteristics with the exception of smoking (Table 1).

Over a median follow-up of 10 years (interquartile range=7.3, 13.8 years), a total of 4782 (11%) deaths occurred (incidence rate per 1000 person-years=10.2, 95% CI=9.9, 10.5). The incidence rate (per 1000 person-years) of all-cause death increased with decreases in systolic blood pressure response (>20 mm Hg: 8.1, 95% CI=7.9, 8.4; 1 to 20 mm Hg: 19.7, 95% CI=18.5, 20.9; ≤0 mm Hg: 33.8, 95% CI=30.8, 37.0). The cumulative incidence for all-cause death by systolic blood pressure response is shown in Figure 1 (log-rank $P < 0.0001$).

Over a median follow-up of 5.2 years (interquartile range=2.7, 8.1 years), a total of 1188 (2.7%) MIs occurred (incidence rate per 1000 person-years=4.6, 95% CI; 4.3, 4.8). The incidence rate (per 1000 person-years) of MI increased with decreases in systolic blood pressure response (>20 mm Hg: 3.9, 95% CI=3.6, 4.1; 1 to 20 mm Hg: 8.0, 95% CI=7.0, 9.1; ≤0 mm Hg: 12.5, 95% CI=10.2, 15.4). The cumulative incidence of MI by systolic blood pressure response is shown in Figure 2 (log-rank $P < 0.0001$).

An increased risk of all-cause death was observed for participants with decreasing systolic blood pressure response (Table 2). Subgroup analyses are shown for blood pressure response as a continuous variable by age, sex, and race (Table 2). A differential association was observed when the analysis was stratified by age, with participants <52 years

Table 3. Risk of Myocardial Infarction

	Events/No. at Risk	Model 1* HR (95% CI)	P Value	Model 2† HR (95% CI)	P Value	Interaction‡ P Value
Systolic blood pressure response						
>20 mm Hg	867/37 128	1.0	—	1.0	—	—
1 to 20 mm Hg	232/5548	1.54 (1.32, 1.78)	<0.001	1.09 (0.93, 1.27)	0.28	—
≤0 mm Hg	89/1413	1.93 (1.54, 2.41)	<0.001	1.19 (0.95, 1.50)	0.14	—
Per 1 SD decrease	1188/44 089	1.30 (1.23, 1.37)	<0.001	1.09 (1.03, 1.16)	0.003	—
Age§ 						
<52 y	308/22 317	1.44 (1.29, 1.61)	<0.001	1.11 (0.99, 1.25)	0.081	0.71
≥52 y	880/21 772	1.41 (1.33, 1.50)	<0.001	1.13 (1.05, 1.20)	<0.001	
Sex 						
Female	399/20 051	1.31 (1.18, 1.44)	<0.001	1.10 (0.99, 1.22)	0.078	0.60
Male	789/24 038	1.29 (1.21, 1.38)	<0.001	1.09 (1.02, 1.17)	0.016	
Race 						
Nonwhite	518/14 967	1.26 (1.17, 1.38)	<0.001	1.02 (0.94, 1.12)	0.62	0.29
White	670/29 122	1.32 (1.23, 1.42)	<0.001	1.14 (1.06, 1.23)	<0.001	

HR indicates hazard ratio; METs, metabolic equivalents of task.

*Adjusted for age, sex, and race.

†Adjusted for Model 1 covariates plus smoking, hypertension, diabetes, obesity, hyperlipidemia, antihypertensive medication use, lipid-lowering medication use, aspirin, METs, and chronotropic incompetence.

‡Interactions tested using Model 2.

§Dichotomized at the median age for study participants.

||All HRs presented are for the systolic blood pressure response per 1 SD decrease and were computed without the interaction term in the model.

(median age) having a stronger association with all-cause death compared with persons ≥52 years (Table 2).

Although not significant, a trend was observed for increased MI risk when systolic blood pressure response was examined as a categorical variable (Table 3). However, an increased risk of MI was observed for the continuous variable per 1 SD decrease in systolic blood pressure response (Table 3). Subgroup analyses are shown in Table 3 for systolic blood pressure response as a continuous variable by age, sex, and race.

The graphical representations of the associations between systolic blood pressure response and risk of all-cause death and MI are shown in Figures 3 and 4, respectively. As shown, the risk of all-cause death and MI was observed to increase with decreasing systolic blood pressure responses. The risk was highest for those with responses lower than resting values.

Discussion

In this analysis from the FIT Project, we have shown that an increased risk of adverse outcomes (eg, death and MI) exists in individuals who have lower systolic blood pressure responses during exercise stress testing, and the risk for

these outcomes is highest among those with exercise-induced hypotension. A differential association was observed between systolic blood pressure response and all-cause death by age, with the association being stronger for younger compared with older patients.

Several studies have examined the association between decreased systolic blood pressure response during exercise stress testing and cardiovascular outcomes. An examination of 2036 patients referred to the Long Beach Veterans Medical Center showed that exercise-induced hypotension in those with prior coronary heart disease is associated with an increased risk of cardiac events.⁵ Similar results were observed in a prospective study of 588 males from the same Veterans Affairs Medical Center undergoing exercise stress testing.⁶ Exercise-induced hypotension also has been shown to predict long-term mortality and major adverse cerebrovascular and cardiac events in patients referred for treadmill testing to evaluate for the presence of peripheral arterial disease.⁷ Additionally, decreased exercise systolic blood pressure response (systolic blood pressure response ≤44 mm Hg) was shown to be associated with an increased risk of cardiovascular mortality.⁸ In contrast, 2 studies of male patients from 2 university-affiliated Veterans Affairs Medical Centers who underwent standard exercise treadmill testing failed to show an association with exercise-induced

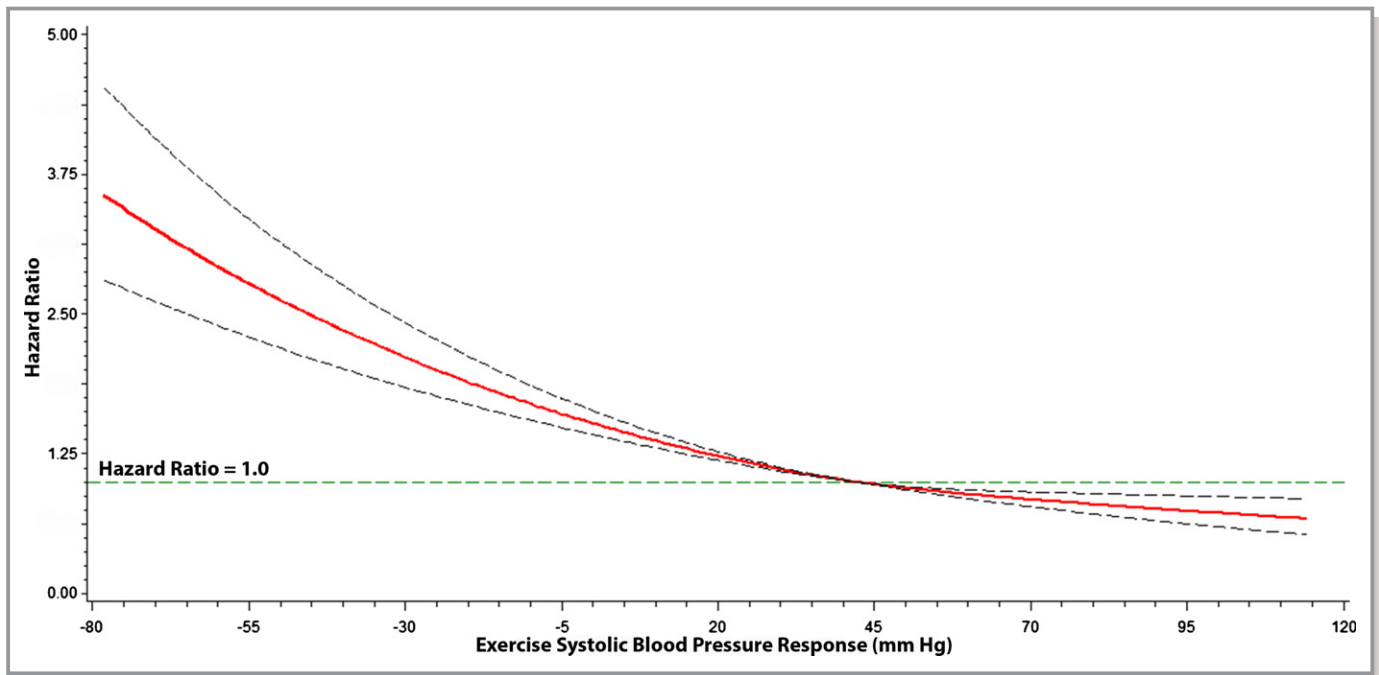


Figure 3. Risk of all-cause death across systolic blood pressure response. Each hazard ratio was computed with the median difference between peak and resting systolic blood pressure value of 42 mm Hg as the reference and was adjusted for age, sex, race, smoking, hypertension, diabetes, obesity, hyperlipidemia, antihypertensive medication use, lipid-lowering medication use, aspirin, METs, and chronotropic incompetence. Dotted lines represent the 95% CI. MET indicates metabolic equivalent of task.

hypotension and cardiovascular events when excluding patients with known cardiovascular disease.^{13,14} The aforementioned studies largely focused on male populations with

limited racial diversity, thus decreasing the generalizability to other populations. Our data confirm in a much larger cohort that decreases in exercise systolic blood pressure response,

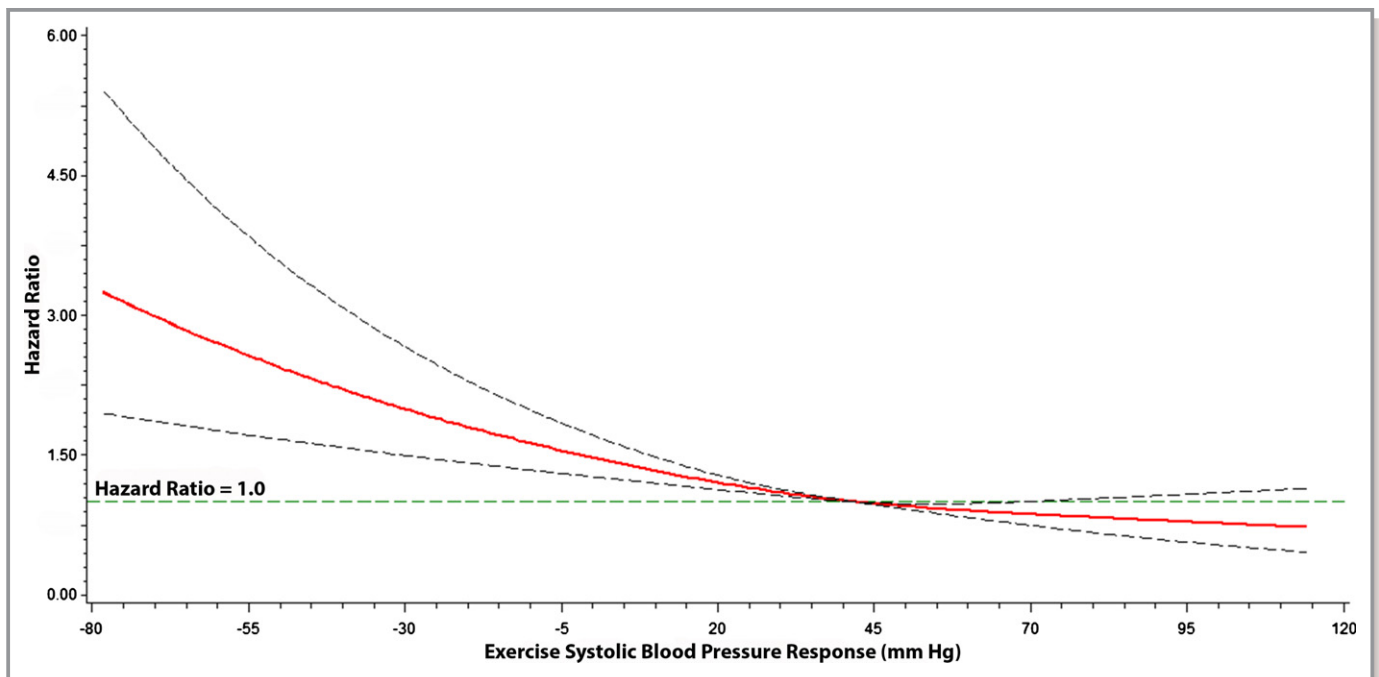


Figure 4. Risk of myocardial infarction across systolic blood pressure response. Each hazard ratio was computed with the median difference between peak and resting systolic blood pressure value of 42 mm Hg as the reference and was adjusted for age, sex, race, smoking, hypertension, diabetes, obesity, hyperlipidemia, antihypertensive medication use, lipid-lowering medication use, aspirin, METs, and chronotropic incompetence. Dotted lines represent the 95% CI. MET indicates metabolic equivalent of task.

including exercise-induced hypotension, are associated with an increased risk of all-cause death and incident MI in both men and women from diverse racial backgrounds.

Several mechanisms have been proposed to explain the increased risk of adverse cardiovascular outcomes in those with decreased systolic blood pressure response during exercise stress testing. During exercise, systolic arterial blood pressure is expected to rise 20 mm Hg per metabolic equivalents of task as a result of increases in cardiac output.² However, when exercise systolic blood pressure decreases below resting values, this often signifies underlying cardiac pathology. Patients with exercise-induced hypotension have been shown to have an increased risk of left ventricular systolic dysfunction and obstructive CAD, thus predisposing to a higher risk of cardiac events.^{3,4} Abnormalities in the autonomic nervous system that occur during exercise stress testing are also possibly detected in persons with decreased systolic blood pressure responses. Autonomic imbalance has been linked to the development of heart failure, and similar disturbances possibly occur in those with decreased exercise systolic blood pressure response.¹⁵ Although several explanations exist, further research is needed to determine the underlying mechanisms associated with the increased risk of adverse events in those with decreased systolic blood pressure response during exercise stress testing.

Currently, the American Heart Association recommends that persons with drops in systolic blood pressure >10 mm Hg below resting values terminate exercise stress testing.¹ These recommendations have been based on studies from male populations with limited generalizability to females and minority populations.^{5–8} Our results suggest that the risk for adverse outcomes occurs with modest elevations in systolic blood pressure, and this risk is not limited to decreases in systolic blood pressure below resting values. Additionally, our results were similar between men and women and also between whites and nonwhites. In aggregate, our results suggest that even those with presumably “normal” exercise blood pressure responses (eg, increases by 1 to 20 mm Hg) merit closer evaluation for underlying coronary heart disease, and this suggestion is not limited to males or specific subpopulations. Therefore, a closer examination of current recommendations regarding exercise stress testing termination and exercise systolic blood pressure response is needed.

The current study should be interpreted in the context of several limitations. We examined the association between exercise systolic blood pressure response and all-cause death and MI. All-cause death was ascertained by linkage with the National Death Index, and we were unable to determine the specific cause of death for each patient. Additionally, incident MI was ascertained using data that were specific to the Henry Ford Health System, and any cases that occurred in other

health systems possibly were missed. Furthermore, we included several covariates in our multivariable models that likely influenced mortality and the development of MI. However, we acknowledge that residual confounding remains a possibility.

In conclusion, using data from the FIT registry, we have shown that even modest elevations in systolic blood pressure during exercise stress testing are associated with an increased risk of all-cause death and MI. Further research is needed to determine the pathophysiologic link between this abnormal response during exercise and the adverse outcomes examined. Potentially, this population merits closer evaluation for the presence of obstructive CAD.

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Disclosures

None.

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