Association of blood pressure and heart rate response during exercise with cardiovascular events in the Heart and Soul Study

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Background **We sought to evaluate the association of blood pressure and heart rate response during exercise with myocardial infarction (MI), heart failure, stroke, transient ischemic attack (TIA) and death in ambulatory adults with coronary artery disease.**

Methods **A study population of 937 patients with stable coronary artery disease underwent treadmill exercise stress testing and was followed for 5 years. Participants were divided into quartiles based on peak SBP change, peak SBP and heart rate. We used multivariable Cox proportional hazards models to evaluate the association of change in SBP and heart rate with subsequent cardiovascular events.**

Results **The participants with SBP increases in the highest quartile had a decreased rate of hospitalization for heart failure [hazard ratio 0.38, 95% confidence interval (CI), 0.21–0.7; $P = 0.002$], MI (hazard ratio 0.3, 95% CI 0.15–0.58; $P = 0.0004$), stroke or TIA (hazard ratio 0.39, 95% CI 0.15–0.98; $P = 0.04$), and all cause mortality (hazard ratio 0.5, 95% CI 0.33–0.76; $P = 0.001$). After adjusting for age, history of MI and HTN, use of β blockers, statins and calcium channel blockers, resting heart rate, and SBP, participants with SBP change in the highest quartile remained at lowest risk of MI (hazard ratio 0.31, 95% CI 0.15–0.66, $P = 0.002$), hospitalization for heart failure (hazard ratio 0.46, 95% CI 0.22–0.97, $P = 0.04$) and death (hazard ratio 0.52, 95% CI 0.32–0.86, $P = 0.01$). This association was largely explained by greater exercise capacity in those with the highest SBP change. Change in heart rate had a similar association with cardiovascular events.**

Conclusion **In ambulatory patients with coronary artery disease, the group with the greatest blood pressure and heart rate increase had the lowest risk of MI, heart failure, stroke or TIA and death. These findings support the notion that a robust blood pressure response predicts favorable outcomes.** ***J Hypertens*** **28:2236–2242 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2010, **28**:2236–2242

Keywords: blood pressure, exercise, heart and soul study, outcome

Abbreviations: CHD, coronary heart disease; CI, confidence intervals; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MET, metabolic equivalents task; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack

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Received 28 November 2009 **Revised** 1 May 2010
Accepted 16 June 2010

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Introduction

Increased SBP measured either conventionally or with ambulatory methods predicts cardiovascular events [1,2]. The prognostic implications of the blood pressure response during exercise are less clear. Although older studies found that SBP increases during exercise were associated with adverse cardiovascular outcomes [3,4], more recent studies have suggested that SBP increases during exercise may be protective [5,6]. In a population of men with a history of myocardial infarction, Naughton *et al.* [5] reported that a maximal SBP of at least 140 mmHg during exercise was associated with decreased mortality. Likewise, in a study of 6213 patients referred for exercise stress testing, Gupta *et al.* [6] reported that higher maximal SBP response during exercise was associated with less mortality. Whether SBP change during exercise predicts cardiovascular events other than death has not previously been evaluated. In an ambulatory population of 908 patients with coronary heart disease, we sought to evaluate the association of blood pressure response to exercise with myocardial infarction, heart failure, stroke, transient ischemic attack, or death.

Methods

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with coronary disease. Methods and objectives have been described previously [7]. Briefly, we enrolled outpatients with documented Coronary Heart Disease (CHD) from two Veterans Affairs Medical Centers (San Francisco and Palo Alto, California), one university medical center (University of California, San Francisco, California, USA), and nine community health clinics in northern California. The presence of CHD was defined by having at least one of the following a history of MI, angiographic evidence of at least 50% stenosis in one or more major

0263-6352 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32833d455b

coronary vessels, prior evidence of exercise-induced ischemia by ECG or nuclear perfusion imaging, or a history of percutaneous or surgical coronary artery revascularization. Patients were excluded if they were unable to walk 1 block, had an acute coronary syndrome within the prior 6 months, or were planning to move from the local area within 3 years.

A total of 1024 participants were enrolled in the study between September 2000 and December 2002. All participants completed a day-long baseline study appointment that included a comprehensive medical history questionnaire and an exercise stress test. Of the 1024 participants, 87 were unable to complete the exercise treadmill stress test for mechanical reasons, leaving 937 participants for this analysis. Of these 937 participants, 496 (53%) had a history of MI, 504 (54%) had a history of revascularization, and 228 (24%) had a history of CHD based on prior evidence of exercise-induced ischemia or an abnormal coronary angiogram. Because exercise-induced hypotension is a known predictor of cardiovascular events [8,9], 29 participants with a hypotensive blood pressure response during exercise were excluded, leaving 908 participants for the final analysis. The hypotensive response was defined as resting blood pressure higher than peak systolic blood during exercise. The protocol was approved by the appropriate institutional review boards and all participants provided written informed consent.

Participants were instructed to fast for at least 4 h, except for taking their usual medications. All patients took their last dose of their medication on the morning of the treadmill (approximately 3 to 4 h prior to the treadmill). Resting blood pressure and heart rate were measured manually with a standard sphygmomanometer after at least 5 min in the supine position. We performed a symptom-limited, graded exercise treadmill test according to Standard Bruce protocol. To achieve maximal heart rate, participants who were unable to continue the Standard Bruce protocol were switched to lower settings on the treadmill and encouraged to exercise for as long as possible. Blood pressure was measured manually at 3 min intervals throughout the treadmill test, using the same arm and cuff that was used for the resting blood pressure.

Our primary outcome was change in SBP. Blood pressure monitoring continued at 3 min intervals into recovery until the heart rate and blood pressure were within baseline limits. Peak SBP was defined as the highest SBP recorded during exercise. Change in SBP was defined as peak minus resting SBP. Percentage change was defined as [(peak minus resting)/(peak)] SBP. Peak heart rate was defined as the highest heart rate during exercise and change in heart rate was defined as peak minus resting heart rate. Continuous, 12-lead electrocardiographic monitoring was performed throughout the testing and exercise capacity was calculated as the total metabolic equivalents tasks (METs) achieved.

Cardiovascular events

The outcome variables were subsequent hospitalization for heart failure, myocardial infarction, stroke or transient ischemic attack, and all cause mortality. We conducted annual telephone follow-up interviews with participants (or their proxy) to ask about death or hospitalizations. For any identified event, two independent and blinded adjudicators reviewed medical records, ECGs, death certificates, and coroner's reports. If both adjudicators agreed on the outcome classification, their classification was binding. If there was disagreement in the classification, they conferred, reconsidered their classification, and, if necessary, requested consultation from a third adjudicator.

Heart failure was defined as hospitalization for a clinical syndrome involving at least two of the following paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, and cardiomegaly or pulmonary edema on chest radiography. These signs and symptoms must have represented a clear change from the usual clinical status [10]. Nonfatal myocardial infarction was defined using standard criteria [11]. Stroke was defined as a new neurological deficit not known to be secondary to brain trauma, tumor, infection, or other cause. Transient ischemic attack was defined as a focal neurological deficit (in the absence of head trauma) lasting more than 30 s and no longer than 24 h, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 min and with subsequent complete resolution. Deaths were determined by death certificates and coroner's reports. Deaths were considered due to heart disease if they resulted from a documented acute myocardial infarction, sudden death, severe cardiac dysrhythmia, or if they occurred during hospitalization for congestive heart failure or revascularization.

Other variables

Age, sex, ethnicity, medical history, and smoking status were determined by questionnaire. We measured weight and height and calculated BMI (calculated as weight in kilograms divided by height in meters squared). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (San Mateo, California, USA). All participants underwent resting echocardiography using an Acuson Sequoia ultrasound System (Mountain View, California, USA). Fasting venous blood samples were drawn for measurement of high-density lipoprotein and triglyceride levels; low-density lipoprotein levels were calculated. We obtained standard two-dimensional views and performed planimetry with a computerized digitization system to determine left ventricular ejection fraction. We categorized participants as having diastolic dysfunction if their ratio of peak early-to-late mitral inflow diastolic filling velocity was more than 0.75 and the velocity time integral in their pulmonary vein was

greater during diastole than during systole. Left ventricular end systolic volume index was calculated as left ventricular end systolic volume divided by body surface area.

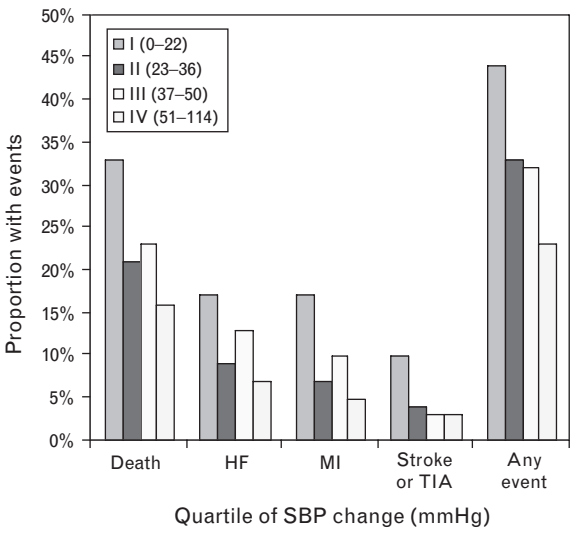
Statistical analysis

Participants were divided into quartiles of change in SBP increase. Differences in baseline characteristics across the quartiles were compared by analysis of variance and the chi-squared test for continuous and categorical variables respectively. We used Cox proportional hazards models to evaluate the association of change in SBP and heart rate with subsequent hospitalization for heart failure, myocardial infarction, stroke or transient ischemic attack, and all cause mortality. The proportional hazards assumption of all models was confirmed. For these analyses, we report hazard ratios (hazard ratios) with 95% confidence intervals (CIs). All analyses were performed using SAS version 9.1 statistical software (SAS Institute Inc, Cary, North Carolina, USA).

Results

The 908 participants with SBP increases during exercise were divided into quartiles based on their blood pressure response to exercise (Table 1). Compared with participants who had SBP increases in the lowest quartile, those with increases in the highest quartile were younger, less likely to have a history of hypertension or myocardial infarction, and were less likely to be using diuretics, β blockers or calcium blockers. Participants who had SBP increases in the highest quartile also had lower resting SBP and higher exercise capacity than those in the lowest quartile. There was no significant difference in history of heart failure, stroke, diabetes, or revascularization or in systolic or diastolic function across the quartiles.

Fig. 1



Proportion with events by quartile of SBP change during exercise (all *P* values <0.05).

Greater increases in SBP and heart rate were associated with fewer subsequent cardiovascular events (Fig. 1, Table 2). In unadjusted models, each standard deviation (SD = 20 mmHg) increase in SBP change was associated with a 31% decreased rate of myocardial infarction, a 28% decreased rate of heart failure, a 40% decreased rate of stroke or transient ischemic attack, and a 20% reduction

Table 1 Characteristics of 908 study participants based on peak SBP change during exercise (peak exercise − resting SBP)

Variable Range of SBP change	Quartile I *N* = 240 0–22 mmHg	Quartile II *N* = 232 23–36 mmHg	Quartile III *N* = 232 37–50 mmHg	Quartile IV *N* = 204 51–114 mmHg	*P* value
Age	70±10	67 ± 11	66 ± 10	63 ± 10	<0.0001
Male	204 (85)	190 (82)	194 (84)	170 (83)	0.84
White	145 (60)	132 (57)	146 (63)	129 (63)	0.46
BMI (kg/m^2)	28.3 ± 5.5	28.0 ± 5.0	28.9 ± 4.7	28.5 ± 5.3	0.32
Medical history					
Hypertension	185 (77)	176 (76)	150 (65)	121 (60)	<0.0001
Myocardial infarction	143 (60)	124 (54)	119 (52)	92 (46)	0.03
Heart failure	47 (20)	42 (18)	30 (13)	30 (15)	0.21
Stroke	35 (15)	38 (16)	30 (13)	19 (9)	0.16
Diabetes	68 (28)	49 (21)	63 (27)	45 (22)	0.19
Revascularization	143 (60)	142 (61)	147 (63)	118 (58)	0.68
Medications					
Diuretics	86 (36)	71 (31)	54 (23)	48 (24)	0.006
β blockers	169 (70)	133 (57)	128 (55)	96 (47)	<0.0001
Statin	161 (67)	148 (64)	158 (68)	122 (60)	0.26
ARB/ACE	128 (53)	120 (52)	117 (50)	92 (45)	0.35
Ca channel blocker	75 (31)	64 (28)	47 (20)	30 (15)	0.0002
Current smoking	45 (19)	55 (24)	41 (18)	39 (19)	0.36
LDL cholesterol (mg/dl)	101.7 ± 32.6	107.6 ± 37.2	102.4 ± 31.1	104.5 ± 32.1	0.23
Diastolic dysfunction	37 (17)	24 (12)	24 (12)	21 (12)	0.25
LV ejection fraction	61.7 ± 9.9	61.0 ± 9.8	62.2 ± 9.3	62.9 ± 9.1	0.21
End systolic volume index	22.9 ± 18.4	21.3 ± 12.1	20.9 ± 17.0	19.6 ± 12.2	0.17
Resting heart rate	66.4 ± 11.5	67.3 ± 12.1	68.9 ± 11.9	68.1 ± 12.2	0.11
Systolic blood pressure	138.5 ± 20.0	131.8 ± 17.1	129.6 ± 15.6	123.6 ± 16.4	<0.0001
Exercise capacity (METS)	5.7 ± 2.5	7.0 ± 2.9	7.9 ± 3.0	9.2 ± 3.8	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LDL, low-density lipoprotein; LV left ventricular.

Table 2 Number (proportion) of participants with any cardiovascular events (myocardial infarction, heart failure, stroke/transient ischemic attack or death) by quartile of change in SBP and heart rate during exercise

Variable	Quartile I	Quartile II	Quartile III	Quartile IV	*P* value
Change in SBP (mmHg)	0–22 mmHg	23–36 mmHg	37–50 mmHg	51–114 mmHg	
	106 (44)	76 (33)	74 (32)	47 (23)	<0.0001
Percentage change in SBP	0.00–16.36	16.39–27.42	27.43–40.00	40.30–101.79	
	96 (42%)	82 (36%)	70 (31%)	55 (24%)	0.0005
Peak SBP	104–152	153–168	170–182	184–265	
	94 (41%)	89 (37%)	59 (28%)	61 (27%)	0.002
Change in heart rate (beats/min)	0–46	47–63	64–78	79–136	
	116 (49%)	87 (38%)	59 (27%)	41 (19%)	<0.0001
Percentage change in heart rate	0–66.67	67.19–92.73	93.10–119.74	120.00–274.42	
	111 (48%)	84 (38%)	60 (27%)	48 (21%)	<0.0001
Peak heart rate	65–114	115–131	132–147	148–203	
	103 (46%)	87 (37%)	65 (30%)	48 (21%)	<0.0001

Table 3 Systolic blood pressure change (entered per SD increase) as a predictor of cardiovascular events

	Myocardial infarction		Heart failure		Stroke or TIA		All cause mortality		Any event	
Model	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Unadjusted	0.69 (0.56–0.86)	0.001	0.72 (0.59–0.88)	0.001	0.60 (0.43–0.85)	0.004	0.80 (0.69–0.92)	0.002	0.77 (0.69–0.87)	<0.0001
Model 1	0.72 (0.58–0.91)	0.005	0.81 (0.66–0.99)	0.04	0.64 (0.45–0.91)	0.01	0.88 (0.76–1.01)	0.07	0.85 (0.75–0.95)	0.006
Model 2	0.76 (0.61–0.96)	0.02	0.82 (0.66–1.01)	0.06	0.62 (0.43–0.89)	0.01	0.89 (0.77–1.03)	0.12	0.86 (0.76–0.97)	0.01
Model 3	0.77 (0.61–0.97)	0.03	0.82 (0.66–1.01)	0.07	0.65 (0.45–0.94)	0.02	0.88 (0.76–1.02)	0.09	0.86 (0.76–0.97)	0.02
Model 4	0.76 (0.60–0.97)	0.03	0.80 (0.64–1.00)	0.04	0.65 (0.44–0.95)	0.03	0.84 (0.72–0.98)	0.03	0.84 (0.74–0.96)	0.008
Model 5	0.87 (0.68–1.11)	0.26	1.00 (0.80–1.25)	0.98	0.65 (0.43–0.98)	0.04	1.00 (0.86–1.17)	0.99	0.97 (0.85–1.11)	0.69

CI, confidence interval; TIA, transient ischemic attack. Model 1: Adjusted for age; Model 2: Adjusted for age, history of myocardial infarction, and history of hypertension; Model 3: Adjusted for above plus use of beta blocker, statin, calcium channel blocker; Model 4: Adjusted for above plus resting heart rate and resting SBP; Model 5: Adjusted for above plus exercise capacity (METS).

in all cause mortality (Table 3). After adjustment for age, history of myocardial infarction and hypertension, use of β blockers, statins and calcium blockers, resting heart rate and resting blood pressure, each SD increase in SBP remained significantly associated with all of these events (Table 3). However, greater exercise capacity appeared largely responsible for the predictive effects of increased SBP on cardiovascular events, with the exception of a stroke, which remained associated with blood pressure response even after adjustment for exercise capacity.

Compared with the 240 participants who had SBP increases in the lowest quartile, the 204 participants with SBP increases in the highest quartile had a 70% decreased rate of myocardial infarction, a 62% decreased rate of hospitalization for heart failure, a 61% decreased rate of stroke or transient ischemic attack, and a 50% reduction in all cause mortality (Table 4). After adjusting for age, history of myocardial infarction, history of hypertension, use of β blockers, statins and calcium channel blockers, resting heart rate and resting blood pressure, participants with SBP increases in the highest quartile remained at lower risk of MI (hazard ratio 0.31, 95% CI 0.15–0.66, $P = 0.002$), hospitalization for heart failure (hazard ratio 0.46, 95% CI 0.22–0.97, $P = 0.04$) and death (hazard ratio 0.52, 95% CI 0.32–0.86, $P = 0.01$). However, greater exercise capacity appeared largely responsible for the predictive effects of increased SBP change on other events, with the exception of myocardial infarction which remained strongly associated with blood pressure response, even after adjustment for exercise capacity (Table 4).

We also divided the sample separately into quartiles based on their peak SBP and heart rate during exercise (Table 5). Compared with participants with peak SBP and peak heart rate in the lowest quartile, those in the highest quartile had

Table 4 Association of increased SBP change (quartile IV vs. I) as a predictor of cardiovascular events

	Myocardial infarction		Heart failure		Stroke or TIA		All cause mortality		Any event	
Model	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Unadjusted	0.30 (0.15–0.58)	0.0004	0.38 (0.21–0.70)	0.002	0.39 (0.15–0.98)	0.04	0.50 (0.33–0.76)	0.001	0.49 (0.35–0.70)	<0.0001
Model 1	0.28 (0.14–0.56)	0.0003	0.48 (0.26–0.91)	0.02	0.46 (0.18–1.22)	0.12	0.60 (0.39–0.93)	0.02	0.57 (0.40–0.82)	0.003
Model 2	0.34 (0.16–0.68)	0.003	0.47 (0.24–0.93)	0.03	0.36 (0.13–1.05)	0.06	0.66 (0.42–1.03)	0.07	0.60 (0.41–0.88)	0.009
Model 3	0.32 (0.10–0.67)	0.002	0.47 (0.24–0.95)	0.04	0.38 (0.13–1.12)	0.08	0.59 (0.37–0.93)	0.02	0.58 (0.39–0.86)	0.007
Model 4	0.31 (0.15–0.66)	0.002	0.46 (0.22–0.97)	0.04	0.38 (0.12–1.17)	0.09	0.52 (0.32–0.86)	0.01	0.55 (0.36–0.84)	0.005
Model 5	0.43 (0.20–0.95)	0.04	0.96 (0.46–2.00)	0.91	0.38 (0.11–1.29)	0.12	0.83 (0.50–1.38)	0.47	0.81 (0.53–1.24)	0.33

CI, confidence interval; TIA, transient ischemic attack. Model 1: Adjusted for age; Model 2: Adjusted for age, history of myocardial infarction, and history of hypertension; Model 3: Adjusted for above plus use of β blocker, statin, calcium channel blocker; Model 4: Adjusted for above plus resting heart rate and resting SBP; Model 5: Adjusted for above plus exercise capacity (METS).

Table 5 Association of changes in SBP and heart rate with cardiovascular events

Model	Increase in SBP Quartile IV vs. I		% change in SBP Quartile IV vs. I		Peak SBP Quartile IV vs. I		Increase in heart rate Quartile IV vs. I		% change in heart rate Quartile IV vs. I		Peak heart rate Quartile IV vs. I	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Unadjusted	0.49 (0.35–0.70)	<0.0001	0.55 (0.39–0.76)	0.0004	0.66 (0.48–0.91)	0.01	0.30 (0.21–0.43)	<0.0001	0.35 (0.25–0.49)	<0.0001	1.41 (0.29–0.58)	<0.0001
Model 1	0.57 (0.40–0.82)	0.003	0.68 (0.48–0.96)	0.03	0.73 (0.52–1.01)	0.06	0.36 (0.25–0.52)	<0.0001	0.37 (0.27–0.52)	<0.0001	0.52 (0.37–0.75)	0.0004
Model 2	0.60 (0.41–0.88)	0.009	0.74 (0.51–1.07)	0.11	0.71 (0.50–1.00)	0.05	0.36 (0.25–0.52)	<0.0001	0.37 (0.26–0.52)	<0.0001	0.55 (0.38–0.80)	0.002
Model 3	0.58 (0.39–0.86)	0.007	0.77 (0.53–1.13)	0.19	0.71 (0.50–1.02)	0.06	0.36 (0.25–0.53)	<0.0001	0.37 (0.26–0.53)	<0.0001	0.52 (0.35–0.79)	0.002
Model 4	0.55 (0.36–0.84)	0.005	0.70 (0.45–1.09)	0.11	0.63 (0.40–0.99)	0.05	0.38 (0.26–0.57)	<0.0001	0.40 (0.26–0.61)	<0.0001	0.46 (0.30–0.72)	0.0006
Model 5	0.81 (0.53–1.24)	0.33	0.95 (0.61–1.49)	0.82	1.01 (0.63–1.62)	0.98	0.62 (0.38–0.99)	0.05	0.63 (0.38–1.05)	0.07	0.75 (0.45–1.25)	0.27

CI, confidence interval. Model 1: Adjusted for age; Model 2: Adjusted for age, history of myocardial infarction, and history of hypertension; Model 3: Adjusted for above plus use of β blocker, statin, calcium channel blocker; Model 4: Adjusted for above plus resting heart rate and resting SBP. Model 5: Adjusted for above plus exercise capacity (METS).

significantly fewer cardiovascular events. After adjusting for age, history of myocardial infarction, history of hypertension, use of β blockers, statins and calcium channel blockers, resting heart rate and resting blood pressure, participants with peak SBP and heart rate in the highest quartile remained at lower risk of cardiovascular events. Again, this association appeared to be explained by greater exercise capacity in those with the highest blood pressure and heart rate responses.

Discussion

The clinical significance of blood pressure increase with exercise has been evaluated in several different populations with conflicting results. In this study, we evaluated the association of blood pressure response to exercise with myocardial infarction, heart failure, stroke, transient ischemic attack and death in ambulatory adults with coronary artery disease. Those with the greatest blood pressure and heart rate increase had the lowest risk of subsequent MI, heart failure, stroke or TIA and death. Conversely, those with more modest blood pressure or heart rate increases had substantially poorer outcomes. Greater exercise capacity was in large part responsible for the predictive effect of blood pressure and heart rate increase on cardiovascular events, with the possible exception of MI and stroke.

Some studies have demonstrated that increased blood pressure response to exercise is associated with increased mortality [3,4]. In a study of 4907 middle-aged men with no history of heart disease, Filipovsky *et al.* [3] suggested that the magnitude of the increase in SBP with exercise might represent a risk factor for death from cardiovascular and noncardiovascular causes, independently of resting blood pressure. In a study of 1999 healthy men, Mundal *et al.* [4] showed that patients who increased their SBP to 200 mmHg or greater during a bicycle ergometer exercise test had a greater than two-fold increase in the risk of cardiovascular mortality within 16 years compared with the men who did not increase their SBP to a similar extent. This difference persisted after adjustment for a range of classical cardiovascular risk factors.

More recent studies have suggested that SBP increases during exercise may be protective [5,6]. In 2000, Naughton *el al.* [5], studied the relation of maximal SBP with exercise to physical conditioning and mortality in 641 men with prior myocardial infarction. This study compared 123 men with maximal exercise SBP of 140 mmHg or less with 518 men whose maximal exercise SBP were 140 mmHg or greater. The group with the smaller blood pressure increase had a significantly higher mortality rate over 3 years ($P < 0.003$) compared with men with higher levels of maximum SBP. In their study, the association of low maximum exercise SBP with mortality persisted at low (<6 METs) as well as high (≥6 METs) levels of exercise capacity. In another study of 6145 consecutive patients who underwent

symptom-limited exercise stress test (EST), Gupta *et al.* [6] found that an increment in SBP of 44 mmHg or greater during EST was associated with a 23% improvement in survival over a mean follow-up of more than 6 years. They concluded that SBP response to maximal EST adds prognostic information to CV mortality independent of age and exercise capacity.

Our study adds to this literature by demonstrating that increased SBP and heart rate change with exercise not only predicts decreased mortality, but also decreases in other adverse cardiovascular events, including myocardial infarction, heart failure, and stroke or TIA. Participants with the highest blood pressure and heart rate response were more physically active and achieved higher METS during exercise test. After adjusting for greater exercise capacity, increased blood pressure and heart rate changes were no longer predictive of cardiovascular outcomes, suggesting that better exercise capacity is largely responsible for this association. However, even after adjusting for exercise capacity, each SD increase in SBP change was associated with a 35% reduced risk of stroke, and patients with SBP change in the highest quartile had a 57% reduced risk of MI compared with those whose blood pressure change was in the lowest quartile.

Mechanistically, the predictive association of increased exercise blood pressure with reductions in subsequent MI and stroke has several possible explanations. Increased maximal blood pressure necessarily reflects increased maximal myocardial performance as measured by left ventricular power [12]. This in turn depends upon adequate blood supply to myocardial segments at peak exercise. Exercise response is also dependent upon autonomic regulation, which may play a critical role in cardiovascular prognosis. Active coronary vasomotor tone is important for maintaining subendocardial blood flow during exercise. Regulation of coronary vascular resistance represents a balance between the myriad of vasodilator and vasoconstrictor signals exerted by neurohormonal influences, the endothelium, and metabolic signals arising from the myocardium [13]. Finally, exaggerated blood pressure responses to exercise may, in part, reflect higher baseline levels of systemic vasodilatation through both nitric oxide-dependent and independent mechanisms [14]. It appears likely that a combination of these factors may be responsible for our findings.

Of note, participants with exercise-induced hypotension were excluded from our study because exercise-induced hypotension is a significant predictor of CV events [8,9]. Dubach *et al.* [9], showed that exercise-induced hypotension, as defined by a drop in SBP during exercise below the standing preexercise value, indicated a significantly increased risk for cardiac events (3.2-fold, $P < 0.005$). Morris *et al.* [8] showed that a drop in SBP below the resting value during exercise was the strongest predictor of cardiovascular death in a study of 588 men who had been referred for cardiac catheterization after exercise test.

Our study has several strengths, including careful measurement of cardiovascular disease severity and potential confounding variables, as well as detailed ascertainment of cardiovascular events. Nevertheless, a number of limitations must be borne in mind when interpreting our results. The median change in SBP was low (37 mmHg), and there were very few patients with a truly exaggerated blood pressure response to exercise. In addition, the use of antihypertensive medications in this cohort may complicate the interpretation of blood pressure increases with exercise. Although exercise stress testing and noninvasive SBP measurements reflect real-life practice, a potential limitation is the use of indirect arm-cuff sphygmomanometry for SBP measurements when individuals are on a treadmill [15]. Future studies might consider ambulatory blood pressure monitoring (ABPM) for gathering hemodynamic data in an active subject. It is well established that ABPM measurements correlate more closely to surrogates of cerebrovascular and cardiovascular disease than traditional isolated manual blood pressure data points [16]. A comparison of exercise and ABPM in this population might provide a fruitful opportunity for further studies. Finally, the majority of our study participants were Caucasian men, and therefore our results may not be generalizable to women or other demographic groups.

In conclusion, in ambulatory patients with coronary artery disease, individuals with the highest blood pressure and heart rate response to exercise exhibited the lowest risk of MI, heart failure, stroke or TIA and death. The association of SBP and heart rate increase with decreased cardiovascular events was largely explained by greater exercise capacity. However, increased SBP during exercise remained associated with a decreased risk of MI even after adjustment for age, resting blood pressure, and exercise capacity. These findings support the notion that a robust blood pressure and heart response to exercise is a marker of favorable outcome.

Acknowledgements

There are no conflicts of interest.

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