Paradoxical Systolic Blood Pressure Increase after Graded Exercise Predicts Severe Coronary Artery Disease

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Abstract

Background: Although exercise treadmill testing (ETT) is a well-accepted examination for patients with suspected coronary artery disease (CAD), there is paucity of information regarding clear-cut predictors of severe CAD. This study aims to investigate whether paradoxical systolic blood pressure (SBP) increase after ETT can help predict severe CAD. We also test the clinical utility of constructing a prediction model through multivariate regression models.

Methods: SBP at 3-min of recovery equal to or higher than SBP at 1-min of recovery after ETT is defined as paradoxical SBP increase. Angiographic severe CAD is defined as left main disease, triple- or two-vessel disease with involvement of the proximal left anterior descending artery. This prospective study followed up 672 patients who underwent their first angiography within 90 days after positive ETT were evaluated.

Results: The sensitivity and specificity of paradoxical SBP increase in predicting severe CAD was 58.4% and 78.6%, respectively. After controlling related cardiovascular factors, including peak metabolic equivalents, paradoxical SBP increase was an independent predictor, with an OR (95% CI) of 3.52 (2.28~5.43) for severe CAD. A clinical model to estimate severe CAD was derived from the baseline exercise measurements and characteristics. By using the simple points system, we could determine that patients with a score greater than 5 have 50% risk, whereas those with 9 points even have 94% risk of severe CAD.

Conclusions: These findings indicate the benefit of applying paradoxical SBP increase as an important predictor of severe CAD and the usefulness of constructing a prediction model in clinical practice.

Keywords: paradoxical SBP increase, exercise treadmill test, severe coronary artery disease

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INTRODUCTION

Severe coronary artery disease (CAD) confers a high risk of catastrophic complications in cardiac patients if under-diagnosed or if treatment is delayed. Using parameters from exercise treadmill tests (ETT) to identify patients at high risk of severe CAD has been encouraged, but satisfactory indicators have rarely been identified in the past three decades.[1-6] Exercise-induced electrocardiogram ST-segment changes are commonly used to detect CAD, but such changes also occur in patients with diabetes, left ventricular hypertrophy, or pre-excitation electrocardiogram even without epicardial coronary artery stenosis. Moreover, the relatively low sensitivity and specificity have forced investigators to search for new methods that may increase diagnostic accuracy.[5-7]

Amon et al. proposed the ratio of post-exercise systolic blood pressure measurements (SBP) at ETT as a highly sensitive and specific index for diagnosing CAD.[8] Previous studies have also reported that a blunted decline in SBP followed by elevated SBP after exercise are associated with increased risk of CAD.[6,9] However, Acanfora et al. have reported that abnormal post-exercise SBP response is less useful as a predictor than ST-segment changes because of its lower sensitivity.[10] Thus, the diagnostic value of post-exercise SBP response remains controversial.

Our previous study has confirmed that paradoxical SBP increase during recovery after graded exercise, defined as SBP at 3 min of recovery equal to or greater than SBP at 1 min of recovery is an important predictor of cardiovascular mortality.[11] However, the association of post-exercise paradoxical SBP increase and CAD severity has not yet been well established. Therefore, this study aimed to investigate the diagnostic value of paradoxical SBP increase after ETT as a valid predictor of severe CAD. In our previous studies, we have clearly demonstrated that predicting cardiovascular outcomes through multivariate regression models might be more practical and powerful than just using one important risk factor.[12] Therefore, in this prospective study, we try to construct a prediction model and test its feasibility by considering paradoxical SBP and other significant predictors for the relative risk of severe CAD.

MATERIALS AND METHODS

Study Subjects

This study was a prospective follow-up study on 13,397 patients who underwent symptom-limited treadmill testing at National Taiwan University Hospital from January 2000 to June 2002, whereby 3,221 patients with positive treadmill testing results using the standard ST criteria were evaluated. Patients younger than 20 years old and those with pre-excitation syndrome or left bundle branch block on resting electrocardiogram were excluded. Patients who had received coronary angiography and/or percutaneous coronary intervention before the examination were also excluded in order to clarify the diagnostic value.[4]

Clinical disease history, cardiovascular risk factors, and medications were obtained from detailed chart review. A final group of 672 patients who underwent their first angiography within 90 days of exercise testing were enrolled for analysis. The local institution committee approved the study protocol.

Definitions of cardiovascular risk factors and mortality

Hypertension was defined as SBP $\geq$140 mmHg or diastolic BP $\geq$90 mmHg, or the use of at least one class of anti-hypertensive agents. Non-insulin-dependent diabetes mellitus (DM) was defined as fasting blood glucose $\geq$26 mg/dL and/or the use of insulin or at least one oral hypoglycemic agent. Patients with cholesterol levels $\geq$200 mg/dL, low-density lipoprotein cholesterol levels $\geq$130 mg/dL, or on lipid-lowering agents, were defined as having hyperlipidemia. Body mass index was calculated

as body weight in kg over body height in meters, squared. Smoking habit was obtained from a detailed review of chart records. Mortality data were obtained by matching all study subjects with mortality certificate data (2007 edition) from the Department of Health, Executive Yuan, Republic of China (Taiwan). All-cause mortality and cardiovascular mortality were defined according to codes in the International Classification of Diseases, Ninth Revision. Mortality data of codes 390 to 459 were coded as CVD in the analyses.

Exercise treadmill testing (ETT)

The ETT methods used followed our previous study.[4,11] Briefly, electrocardiograms were recorded using an exercise system (CASE Marquette 16, Marquette Electronics Inc., Milwaukee, Wisconsin). The modified Bruce protocol was used for symptom-limited treadmill testing. Heart rate, BP, and 12-lead electrocardiogram with shift of ST-segment were recorded during the pre-exercise standing period, and at 60 seconds before the end of each stage, at peak exercise and at 1, 3 and 5 minutes of recovery. The total exercise time was also recorded.

Target heart rate was defined as 85% of maximal achievable heart rate [220 beats per minute minus age in years]. The Tango exercise BP monitor (SunTech Medical, NC, USA) automatically measured and displayed the patient's systolic and diastolic BP along with heart rate. The levels of ST-segment 60 milli-seconds after the J point were measured in each lead using a computer-assisted system. Ischemic or positive ST-segment change was defined as 1 mm or more of horizontal or down-sloping ST-segment depression and 2 mm or more of up-sloping ST-segment depression.

Paradoxical SBP increase, a phenomenon of abnormal post-exercise SBP change, was defined as SBP at 3 min / SBP at 1 min of the recovery phase (SBP recovery 3/1 ratio) $\geq$14,11. Peak metabolic equivalents (METs) were calculated by means of commonly applied functions for predicting oxygen uptake for treadmill work (metabolic equivalent = 1.11 + 0.016 × exercise time in seconds).[13]

Coronary angiography

Digital coronary angiograms were recorded in three orthogonal projections. The minimal lumen diameter and nearby proximal normal segment were measured for every coronary artery. An expert cardiologist who was blind to the hemodynamic data from exercise testing visually estimated coronary artery narrowing and expressed it as percent lumen diameter stenosis. Quantitative measurements of coronary artery dimension were also made using a computer-based edge enhancement technique (DCI System; Philips, Best, The Netherlands) to assist the assessments, as previously described.[14]

The diagnosis of CAD was made from evidence of any localized coronary artery stenosis or diffuse coronary artery narrowing, which was defined as >50% diameter stenosis in one or more of the following coronary arteries: left main coronary artery, left anterior descending artery (LAD), left circumflex, right coronary artery, or major branches of these arteries. Severe CAD was defined as left main disease, triple- or two-vessel disease with involvement of the proximal LAD. Mild CAD was defined as CAD that was not categorized as severe CAD.

Statistical analyses

Demographic and cardiovascular risk factors of the study subjects were compared between CAD and non-CAD groups. Cross-group data were compared using Student's unpaired *t* test for continuous data and Chi-square test for categorical data to test the significance level.

The sensitivity and specificity of using paradoxical SBP increase as a predictor for CAD and severe CAD were estimated. Chi-square test was applied to evaluate the trend effects of cardio-vascular risk factors among differently graded severities of angiographic CAD. SBP response during ETT at different exercise stages

was plotted against angiographic severity: non-CAD, mild CAD and severe CAD. The strength of the association between CAD or severe CAD and exercise time, maximal achievable heart rate, paradoxical SBP increase and other potential risk factors (including age, gender, hypertension, hyperlipidemia, DM, and smoking) was expressed in terms of odds ratios (OR) with 95% confidence intervals (95% CI) using multivariate logistic regression analysis. The person-year method was used to calculate incidence rates of all-cause and CVD mortalities, and survival curves were estimated according to SBP response after ETT using the Kaplan-Meier procedure. All analyses were performed using Version 8.2 of the SAS statistical package, and a p value <0.05 was considered statistically significant.

Categorization Point Predicting Model

In addition, the predictive power of paradoxical SBP increase after exercise with regard to angiographic severe CAD was explored by adding the most powerful confounding factor, METs, into the multivariate logistic regression analysis. We used the multivariate logistic regression model to establish a parsimonious model for predicting risk of severe coronary artery disease. We constructed the categorization point model according to the clinically related covariates using the methods suggested by Sullivan and colleagues.[15] Briefly, first, we categorized each continuous variable into meaningful groups and assigned point values according to the coefficients from the multivariate logistic model, after which we summed up the total points by adding an assigned point to each variable for each individual. Second, we determined the probability (P) of severe coronary artery disease after coronary angiography by the following formula: Risk = $1-S_0(t)\exp(\Sigma\beta X-\Sigma\beta X)$, where $S_0(t)$ is the risk of severe CAD within 90 days after TXT study at the mean values of the risk factor, β's are the multivariate logistic regression coefficients, X's are the individual's values on the variables, and X-bar is the means or proportions of the variables. Finally we plotted the diagram curves for severe CAD according to different summations of risk scores.

RESULTS

Baseline characteristics by paradoxical SBP increase status

The baseline characteristics of the study subjects are shown in Table 1. All patients had a positive treadmill test. Based on post-exercise SBP changes, 208 patients were assigned to the paradoxical SBP increase group while 464 patients were in the ordinary SBP response group. Patients with paradoxical SBP increase tended to be older males with lower METs and less exercise time. They also had higher baseline SBP although the diastolic BP was insignificant in the two groups.

In addition, there were higher prevalences of diabetes, hypertension, and hyperlipidemia in patients with paradoxical SBP increase. The percentages of CAD and severe CAD were much higher in the paradoxical SBP increase group than in the ordinary SBP response group.

Table 2 shows the validity of paradoxical SBP increase as a predictor for angiographic diagnosis of CAD and severe CAD. The sensitivity of paradoxical SBP increase for predicting CAD and severe CAD was 44.4% (158/356) and 58.4% (101/173), respectively, and the corresponding specificity for CAD and severe CAD was 84.2% (266/316) and 78.6% (392/494), respectively.

SBP response during ETT and the angiographic documented CAD severity

Figure 1 shows the plot of systolic blood pressure response at rest, peak exercise, and 1 min, 3 min, and 5 min of recovery after graded exercise based on the assessment of coronary angiographic severity, stratified by non-CAD, mild CAD, and severe CAD groups. Patients with severe CAD were characterized with less SBP increase at peak exercise and delayed SBP decline at 3 min of recovery, defined as paradoxical SBP increase after ETT. There was no significant

Table 1. Baseline characteristics by paradoxical systolic blood pressure (SBP) increase status

Characteristics	Paradoxical SBP increase group n = 208	Ordinary SBP response group n = 464	P value
Age, years	59.3 ± 10.1	57.0±9.7	0.0040
Male, %	73.6	67.2	0.1011
Diabetes Mellitus, %	28.9	17.9	0.0013
Hyperlipidemia, %	49.0	41.2	0.0570
Smoking Habit, %	42.3	36.2	0.1322
Body Mass Index, Kg/m^2	25.5 ± 3.3	25.4 ± 3.3	0.5609
Hypertension, %	78.4	67.6	0.0047
Systolic BP, mmHg	145.6 ± 20.9	138.0 ± 20.4	<.0001
Diastolic BP, mmHg	85.3 ± 10.5	84.0 ± 10.6	0.1428
Systolic BP ratio after exercise	1.1 ± 0.1	0.9 ± 0.1	<.0001
Beta-blocker use, %	92.3	93.4	0.4893
Maximal heart rate, beat/min	160.3 ± 11.3	163.1 ± 9.7	0.0021
Max heart rate achievable, %	84.5 ± 11.3	90.1 ± 9.3	<.0001
Peak metabolic equivalents (METs)	6.4 ± 1.9	7.4 ± 1.7	<.0001
Exercise time, sec	331.1 ± 117.5	395.5 ± 103.0	<.0001
Coronary artery disease, %	76.0	42.7	<.0001
Severe coronary artery disease, %	48.6	15.5	<.0001
BP drop at peak exercise, %	13.9	9.7	0.1042
Typical angina at exercise termination, %	5.77	1.29	0.0028

Table 2. Measures of sensitivity and specificity related to paradoxical SBP increase as a predictor of coronary artery disease (CAD) or severe CAD

Paradoxical SBP Increase	**CAD**		
	Present	Absent	Total
Positive	158	50	208
Negative	198	266	464
Total	356	316	672
Paradoxical SBP Increase	**Severe CAD**		
	Present	Absent	Total
Positive	101	107	208
Negative	72	392	464
Total	173	499	672

CAD: Sensitivity: 158/356 = 44.4%, Specificity: 266/316 = 84.2%, Positive prediction value = 158/208 = 76.0%, Negative prediction value = 262/464 = 57.3%
Severe CAD: Sensitivity: 101/173 = 58.4%, Specificity: 392/499 = 78.6%, Positive prediction value = 101/208 = 48.6%, Negative prediction value = 392/464 = 84.5%

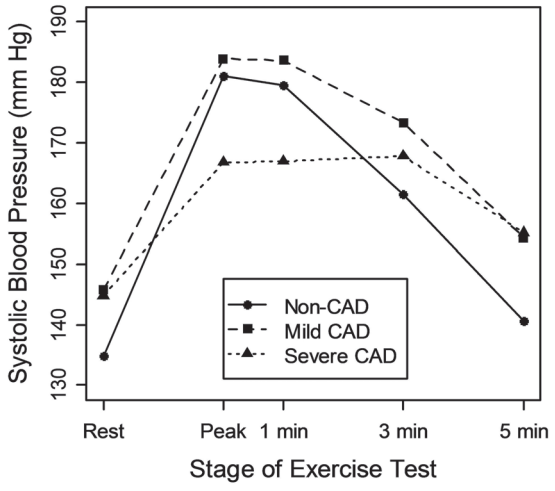

Figure 1. Systolic blood pressure response at rest, peak exercise, and at 1 min, 3 min, and 5 min of recovery during exercise treadmill test, according to CAD severity by coronary angiography: non-CAD, mild CAD, and severe CAD, respectively.

difference in SBP response between the non-CAD and mild CAD groups.

High-risk predictors for angiographic CAD or severe CAD

When severe CAD is treated as outcome measure, paradoxical SBP increase and male gender were shown to be even more powerful predictors with an OR of 3.52 (95% CI: 2.28~5.43) and 8.03 (95% CI: 4.27~15.09), respectively. There was also a significant decrease in the risk of CAD for every one minute increase of exercise time [OR = 0.78 (95% CI: 0.71~0.85)] and for every one MET increase [OR = 0.77 (95% CI: 0.70~0.84)]. Following the multivariate logistic regression model, we adjusted all the confounding factors for CAD. We were able to estimate the correlation coefficients and relative risk of severe CAD after controlling related cardiovascular risk factors. Gender, hyperlipidemia and diabetes were regarded as significant predictors for severe CAD, consistent with previous studies. Paradoxical SBP had the strongest association with severe CAD in addition to male gender [OR = 3.95 (95% CI: 2.58~6.05)] (Table 3). Furthermore, the increase of METs was the most powerful protective predictor for severe CAD after controlling for risk factors [OR = 0.71 (95% CI: 0.62~0.83].

All-cause and cardiovascular mortality

Table 4 shows higher all-cause mortality, but not cardiovascular mortality, in the paradoxical SBP increase group, compared to the ordinary SBP response group. With regard to the patient characteristics, when stratified under all-cause mortality, there was significantly less exercise time, lower METs, and higher prevalence of CAD and severe CAD in the paradoxical SBP increase group, compared to the ordinary SBP response group. However, when stratified under cardiovascular mortality, there was only a significantly higher prevalence of severe CAD in the paradoxical SBP increase group.

Figure 2 shows Kaplan-Meier survival curves for an average 6.2-year all-cause (A)

Table 3. Multivariate logistic regression for predictors of severe CAD

Characteristics	Univariate	Model 1	Model 2	Model 3	Model 4
Age ≥60 years	2.24(1.58~3.19)‡	1.18(0.76~1.83)	1.18(0.76~1.83)	1.42(0.89~2.27)	1.43(0.90~2.29)
Male gender	4.30(2.63~7.03)‡	8.03(4.38~14.72)‡	8.06(4.39~14.79)‡	7.18(3.86~13.34)‡	7.24(3.9~13.47)‡
Hypertension	1.56(1.04~2.34)*	0.84(0.48~1.46)	0.85(0.49~1.47)	0.85(0.48~1.51)	0.86(0.48~1.53)
Hyperlipidemia	2.17(1.53~3.09)‡	2.3(1.54~3.44)‡	2.31(1.55~3.45)‡	2.22(1.46~3.37)‡	2.24(1.48~3.40)‡
Diabetes mellitus	2.88(1.95~4.26)‡	1.94(1.22~3.09)†	1.95(1.23~3.11)‡	1.97(1.21~3.21)†	2.00(1.23~3.25)†
Smoking habit	1.74(1.22~2.47)‡	0.91(0.59~1.41)	0.92(0.60~1.41)	0.93(0.60~1.46)	0.93(0.60~1.46)
Beta-blocker use	0.84(0.43~1.65)	0.67(0.30~1.48)	0.67(0.30~1.47)	0.74(0.33~1.69)	0.75(0.33~1.70)
METs	0.71(0.64~0.79)‡	0.65(0.57~0.75)‡	0.65(0.56~0.75)‡	0.72(0.62~0.83)‡	0.71(0.62~0.83)‡
Rest SBP, mmHg	1.01(1.01~1.02)‡	1.00(0.99~1.02)	1.00(0.99~1.02)	1.00(0.99~1.01)	1.00(0.99~1.01)
Rest DBP, mmHg	1.01(1.00~1.03)	1.01(0.99~1.04)	1.01(0.99~1.04)	1.02(0.99~1.04)	1.02(0.99~1.04)
HRR < 12 beat/min	1.74(1.15~2.63)†	—	0.93(0.57~1.52)	—	0.84(0.51~1.41)
Paradoxical SBP increase	5.14(3.55~7.44)‡	—	—	3.92(2.56~5.99)‡	3.95(2.58~6.05)‡

p values: *<0.05, †<0.01, ‡<0.005; SBP, systolic blood pressure; METs, Peak metabolic equivalents; HRR, Heart rate recovery = HR at peak exercise – HR at 1 minute of recovery phase.

Table 4. Characteristics of subjects with all-cause and cardiovascular mortality by paradoxical systolic blood pressure (SBP) increase status

	All-cause mortality			Cardiovascular mortality		
	Paradoxical SBP increase group	Ordinary SBP response group	P value	Paradoxical SBP increase group	Ordinary SBP response group	P value
Characteristics	n = 22 (10.58%)	n = 29 (6.25%)		n = 7 (3.37%)	n = 9 (1.94%)	
Age, years	63.95±11.97	65±9.25	0.7263	57.14±10.76	63.33±14.02	0.3507
Male, %	59.09	65.52	0.6383	57.14	66.67	1.0000
Diabetes Mellitus	63.64	41.38	0.1153	71.43	22.22	0.1262
Hyperlipidemia	45.45	31.03	0.2915	57.14	33.33	0.6145
Smoking Habit	31.82	44.83	0.3460	14.29	44.44	0.3077
Body Mass Index, Kg/m2	25.34±4.14	24.64±2.95	0.5482	25.34±3.29	24.62±2.01	0.6638
Hypertension	81.82	82.76	1.0000	71.43	77.78	1.0000
Systolic BP, mmHg	150.59±25.38	151.28±21.86	0.9181	144.86±34.49	148.89±22.65	0.7818
Diastolic BP, mmHg	87.18±13.27	84.28±12.23	0.4217	85.14±15.90	85.00±17.15	0.9866
Beta-blocker use, %	90.91	100.00	0.1812	85.71	100.00	0.4375
Maximal heart rate	127.41±20.23	132.34±21.72	0.4120	128.00±21.69	133.11±20.78	0.6393
Peak metabolic equivalents	5.00±1.40	6.22±1.63	0.0072	5.30±1.10	6.38±1.56	0.1416
Exercise time, sec	243.18±87.66	319.31±101.59	0.0071	261.86±68.47	329.56±97.56	0.1419
Coronary artery disease, %	95.45	55.17	0.0014	100.00	66.67	0.2125
Severe coronary artery disease, %	68.18	10.34	<.0001	71.43	11.11	0.0350

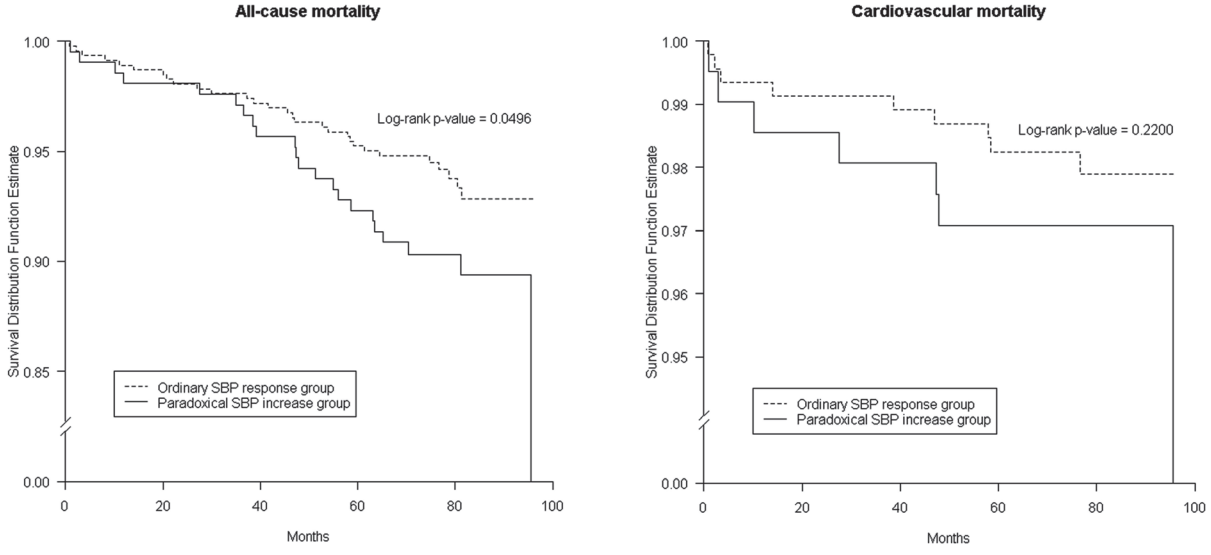

Figure 2. Kaplan-Meier survival curves for all-cause and cardiovascular mortalities in the study population, stratified by 2 categories according to SBP response after exercise treadmill test.

and cardiovascular mortality (B) in the 2 groups of patients. Compared with patients from the ordinary SBP response group, there was a significant decrease in all-cause survival in patients from the paradoxical SBP increase group (p value = 0.0496). However, there was no significant difference in cardiovascular mortality between these two groups, which might be due to the short term of follow-up duration, and the fact that there were few patients with cardiovascular mortality.

Estimated coefficients and predicting scores of severe CAD

We further calculated the estimated Coefficients and Relative Risk (95% CI) for the clinical predictors derived from the above multivariate logistic regression models for severe CAD. The clinical predictors included gender, hyperlipidemia, diabetes, METs and paradoxical SBP increase. Their estimated coefficients, standard errors, relative risks and 95% confidence intervals are shown in Table 5. We then developed a simple point system for the clinical model to estimate severe CAD derived from the baseline exercise measurements and characteristics (Table 6): gender (3 points), hyperlipidemia (1 point), diabetes (1 point), METs (-3~2 points) and paradoxical SBP increase (2 points). This approach allowed manual estimation of risk of severe CAD for each individual as shown in Figure 3. By using the simple points system, we determined that patients with score over 5 have 50% risk whereas those with 9 points even have 94% risk of severe CAD. The diagram for relative risk is shown in Figure 3.

DISCUSSION

This is the first study to identify paradoxical SBP increase after standard symptom-limited ETT as a clear-cut predictor of severe CAD, after controlling other confounding factors including METs. Patients with positive ETT by ischemic ST criteria and hemodynamic changes of paradoxical SBP increase after graded exercise are at increased risk of severe CAD with an OR of 3.52. This study reconfirmed the in-depth study by McHam et al. which proposed the novel, clinical application of post-exercise SBP ratio at 3 min / 1 min as a predictor of CAD severity.[6] We further determined that the paradoxical SBP increase might be a better cut-off point for the angiographic diagnosis of severe CAD. The significant delay in decline of SBP at 3 minutes among patients with severe CAD that is shown in Figure 1 also supports the choice of using paradoxical SBP increase as the favored predictor of severe CAD. This relatively easy diagnosis, coupled with appropriate sensitivity and high specificity of diagnostic accuracy make the application of this novel index (paradoxical SBP increase) by clinical cardiologists feasible. This is

Table 5. Estimated Coefficients and Relative Risk (95% CI), and significance levels from the multivariate logistic regression for severe coronary artery disease

Characteristics	Coefficients	OR	95% C.I.		*p* value
Intercept	-1.1624				
Gender	1.9851	7.280	4.125	12.848	<.0001
Hyperlipidemia	0.7981	2.221	1.471	3.355	0.0001
Diabetes mellitus	0.6673	1.949	1.215	3.127	0.0057
METs	-0.3624	0.696	0.613	0.79	<.0001
Paradoxical SBP increase	1.3408	3.822	2.522	5.793	<.0001

Table 6. The simple points system according to the prediction models, and the total points and absolute risk function in the study participants

Risk factor	Categories	Reference	β	Points
Gender	**Female**	0	1.9851	0
	Male	1		3
Hyperlipidemia	**No**	0	0.7981	0
	Yes	1		1
Diabetes mellitus	**No**	0	0.6673	0
	Yes	1		1
METs	2-3	2.5	-0.3624	2
	3-5	4		1
	5-6	5.5		0
	6-8	7		-1
	8-10	9		-2
	≥10	11		-3
Paradoxical SBP increase	**No**	0	1.3408	0
	Yes	1		2

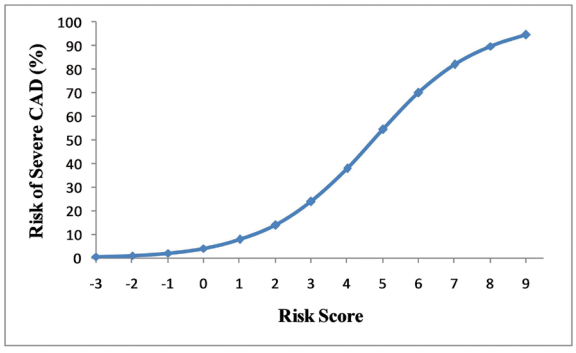

Figure 3. A prediction diagram curve for the percentages of severe CAD according to different risk scores.

further supported by evidence from average 6.2-year Kaplan-Meir survival analysis of all-cause mortality in this study, and from our previous study as an independent predictor of CV mortality in 10-year follow-up.[11]

Our study also demonstrated the clinical utility and feasibility of using a multivariate logistic model to derive a prediction model for severe CAD, which can provide an acceptable and easier prediction model by taking into account other significant cardiovascular risk factors. For example, if total points were 7, the estimated risk of severe CAD was around 82%. This is the first prospective study to show the practical application of combining simple clinical and demographic data with the individual's response to grade exercise in order to develop a predictive scoring system for severe CAD. Our clinical model was simple to implement, and included 6 covariates which were obtained from routine history taking and exercise screening. By using the system, we could identify those with higher risk for severe CAD confidently and refer the patients for a more aggressive approach, such as directly for coronary angiography. Whether the application of this predictive scoring system in clinical practice results in a decrease in CV events or even mortality will need to be determined by further,

larger randomized study.

Other studies have suggested using the 3-minute post-exercise SBP ratio (SBPR, calculated by dividing the SBP three minutes into recovery phase of ETT by the SBP at peak exercise) to express the rate of decline in post-exercise SBP.[16,17] These studies have found that the SBPR values were associated with the presence and severity of CAD, documented by coronary angiography and thallium-201 scintigraphy.[9,16-18] However, these studies have been limited by either inadequate sample size or insufficient analysis of all possible confounding risk factors. The use of the 3-minute post-exercise SBPR as an index is not practical in clinical application. By contrast, the rationale behind using the paradoxical SBP increase after graded exercise as the index for the prediction of severe CAD is evidenced by Table 1 and Figure 1, indicating a simple index of "SBP recovery 3/1 ratio $\geq$1". In addition to its acceptable sensitivity and specificity, another convincing aspect is the evidently abnormal physiological response that not only shows no decline, but in fact an increase in 3-min SBP compared to 1-min SBP of the recovery phase.

It has been shown that METs derived from exercise time are one of the most powerful predictors of CAD severity and cardio-vascular events.[19] The univariate analysis in this study also documents a strong correlation between CAD and METs. By incorporating this important factor into the multivariate logistic regression, this study has proven that paradoxical SBP increase remains significantly associated with CAD and severe CAD. This is one of the key advantages where this study differs from previous studies. The term "paradoxical SBP increase" is used instead of "three-minute SBP recovery" because peak-exercise SBP is hard to record correctly and in a timely manner. In contrast, SBP at 1 minute in recovery is measured in a more steady condition. With the cut-point ratio at one, physicians can interpret this important risk factor easily, even before the end of the exercise treadmill test. As such, patients with the highest risk can be distinguished more easily after an ETT examination and prompt decision-making can take place.

The diagnostic sensitivity of paradoxical SBP increase for CAD in this study is only 44.4%, even though the specificity is 84.2%. Nonetheless, the corresponding sensitivity and specificity for severe CAD is acceptable and may be a promising indicator for identifying these patients. Among patients with positive ETT who received their first coronary angiography as shown in this study, 58.4% were considered severe CAD if their hemodynamic response showed paradoxical SBP increase during recovery after graded exercise. The high specificity (78.6%) of this test further adds to its validity as an independent predictor for angiographic severe CAD.

McHam et al reported that 3-minute post-exercise SBPR has a high specificity of 81%, and a low sensitivity of 38% for detection of severe CAD, respectively.[6] This indicates that the theoretical use of Youden's index to estimate the best cut-off point of 3-minute post-exercise SBPR to predict severe CAD is not practical in clinical use. Thus, we chose paradoxical SBP increase as the presumed best cut-off point of 3-minute post-exercise SBPR in this study. Acanfora et al. also stated that SBP recovery ratios did not appear better than ST segment depression for diagnosing CAD on account of the low sensitivity and lack of reproducibility.[10] By contrast, the current study was confined to patients with a positive ETT, which greatly promoted the sensitivity of paradoxical SBP increase for CAD. The sensitivity and specificity of paradoxical SBP increase for severe CAD were then acceptable for this specific group. Moreover, it was demonstrated that males and those with paradoxical SBP increase had higher risks for angiographic CAD, with OR of 4.55 and 2.98, respectively, after controlling other covariates. Their effects were even more significant for severe CAD, with OR of 8.03 (95% CI: 4.27~15.09) and 3.52 (95% CI: 2.28~5.43), respectively. Male gender is a well-documented

risk factor for CAD.[20] It may be concluded that for male patients with a positive ETT test, the presence of paradoxical SBP increase is a very important factor for further management and may suggest the need for more invasive intervention.

Left ventricular dysfunction develops during maximal exercise[21] and a rapid amelioration of left ventricular asynergy after cessation of exercise[22] has been put forward as the possible mechanism of abnormal SBP response after maximal exercise. In CAD patients, mechanisms of abnormal SBP response after exercise have been studied using pulmonary artery catheterization.[9,21] Miyahara et al. have shown that increased pulmonary capillary wedge pressure and decreased cardiac index develop during exercise once abnormal 3-min SBP response post-exercise is observed in patients with CAD.[19] In addition, a paradoxical increase in stroke volume and systemic vascular resistance with exaggerated sympathetic activity is also observed after exercise.[9] Thus, the absence of the physiological response of increased cardiac output or stroke volume during peak exercise (or 1-min SBP after graded exercise) in patients with paradoxical SBP increase could be attributed to severely defective myocardial perfusion as a result of critical coronary obstruction, disturbing the normal blood pressure response. These studies support the hypothesis that mechanisms of paradoxical SBP increase in the recovery phase may be due to recovery from transient myocardial ischemia during and immediately after maximal exercise testing.

Systemic vascular resistance index decreases during exercise, but rebounds to a higher level during recovery in the abnormal SBP response group. This may be explained by an exaggerated sympathetic nervous activity. Sympathetic over-activation and the associated sympatho-vagal imbalance may be the mechanism involved in paradoxical SBP increase after graded exercise. The significant predictors of severe CAD identified in this study such as diabetes, hyperlipidemia, shorter exercise time or lower METs, and inadequate HR achievable also corroborate our study. An important implication of this study is the urgency to convince cardiologists to consider the clinical utility of using the relatively non-invasive ETT (without exposure to radiation) for the detection of high-risk patients, focusing on severe CAD, but not only on CAD in clinical practice. There is increasing evidence to support the use of current widely-promoted, non-invasive imaging studies, such as cardiac computed tomography angiography or coronary calcification in the detection of coronary atherosclerosis and stenosis.[23,24] These new technologies challenge the clinical use of traditional ETT in the practice of cardiologists, however, there is an inevitable risk of exposure to radiation and contrast medium while receiving computed tomography coronary angiography.[23-25] Despite low doses of radiation exposure, a long-term, large-scale follow-up study revealed a non-negligible lifetime attributable risk for cancer,[23] and for contrast medium related nephropathy or hypersensitivity.[23,24] Thus, the findings of this study may provide new insights with regard to the evaluation of high-risk patients for severe CAD by traditional and non-invasive ETT, which take into account both ischemic ST-segment changes and further simple calculations of the post-exercise hemodynamic BP response of each patient.

Limitations

There are some limitations to this study. First, it is known that blood pressure measured by indirect arm-cuff sphygmomanometer may be somewhat inaccurate during exercise. However, a previous study has confirmed that SBP measurements obtained during exercise by cuff sphygmomanometer may be comparable to those obtained by an invasive method.[20] Therefore, SBP measured by automated BP measurement devices (Tango exercise BP monitor) used by well-trained personnel are acceptably accurate. Second, this study included only patients with positive ETT reports and those undergoing cardiac catheterization within 90 days after the test.

Therefore, "post-referral bias" may have been introduced, since the physician did not persuade the patients to receive coronary angiogram according to their hemodynamic response, based on current evidence and recommendation. Finally, because the evaluation was derived retrospectively, further prospective studies are warranted.

Conclusions

Paradoxical SBP increase after exercise and male gender are the two most important risk factors for severe CAD among patients with positive ETT test. These findings indicate the benefit of assessing post-exercise SBP changes as an important predictor in clinical practice aside from the routine standard criteria of ischemic ST-segment changes. While the decision for further coronary angiography for patients with a positive ETT test may be disputable due to the relatively low specificity, more aggressive examinations and intervention may be reasonable recommendations for patients with paradoxical SBP increase after exercise.

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