Peak Systolic Blood Pressure in Exercise Testing is Associated With Scintigraphic Severity of Myocardial Ischemia in Patients With Exercise-Induced ST-Segment Depression

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Peak Systolic Blood Pressure in Exercise Testing is Associated With Scintigraphic Severity of Myocardial Ischemia in Patients With Exercise-Induced ST-Segment Depression

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Some electrocardiographic variables, including the degree of maximal ST-segment depression (STD), may not necessarily indicate the severity of exercise-induced myocardial ischemia. The present study examined whether maximal STD correlates with the severity and extent of exercise-induced myocardial ischemia, as assessed by thallium-201 (^{201}Tl) imaging, and which parameter of exercise testing reflects scintigraphic severity and extent in 270 patients who had a 1 mm or greater horizontal or down-sloping STD on exercise ^{201}Tl imaging. The scintigraphic severity and extent of exercise-induced ischemia was assessed and correlated with maximal STD, number of positive leads, workload, peak heart rate, peak systolic blood pressure (SBP), rate-pressure product, chest pain and the Duke treadmill score. Most of the scintigraphic markers of the severity and extent of ischemia had significant but weak correlation with all of those parameters. Multivariate analysis demonstrated that peak SBP and the Duke treadmill score (chest pain in only simple variables model) correlated independently with scintigraphic severity and extent of ischemia. Furthermore, most of the patients with a peak SBP of 200 mmHg or more had milder and less extensive ischemia. In patients with exercise-induced STD, the scintigraphic severity and extent of ischemia may be estimated by peak SBP and the Duke treadmill score. (*Jpn Circ J* 2000; **64:** 590–594)

Key Words: Exercise testing; Maximal ST-segment depression; Peak systolic blood pressure; ^{201}Tl perfusion imaging

In exercise testing, some electrocardiographic (ECG) and non-ECG variables, such as the degree of maximal ST segment depression (STD), the number of ECG leads exhibiting positivity, the presence of chest pain during exercise stress, the magnitude of workload, post-exercise systolic blood pressure (SBP) response and the Duke treadmill score, are presumed to be associated with the severity or the prognosis of ischemic heart disease (IHD).[1–8] Some cases, however, have a discrepancy between the degree of maximal STD and the reversible defect size on exercise perfusion scintigraphy,[9–11] which is a concern because some cardiologists tend to interpret marked STD during exercise testing as representing severe myocardial ischemia.[1,2,4,5] On the other hand, the absence of ischemic STD does not necessarily indicate the absence of exercise-induced ischemia.[12] Thus, the degree of STD on exercise testing may not indicate the severity of myocardial ischemia.

In the present study, we investigated whether maximal STD correlates with the severity and extent of exercise-induced myocardial ischemia, as assessed by thallium-201 (^{201}Tl) imaging, and which parameter of exercise testing reflects the scintigraphic severity and extent in patients with exercise-induced STD.

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Methods

Study Population

Two hundred and seventy patients (198 men, 72 women; mean age, 62±11 years) who had been referred to the Nuclear Cardiology Laboratory for evaluation of known or suspected coronary artery disease with exercise ^{201}Tl myocardial scintigraphy and who had satisfied the following conditions, comprised the study population: ≥1 mm horizontal or down-sloping STD 80 ms after the J point on exercise testing; no digitalis medication; and absence of left bundle branch block, Wolff-Parkinson-White syndrome and marked ST-T abnormality on resting ECG. Of the 270 patients, 116 (43%) patients had a previous myocardial infarction, 156 (58%) had angina pectoris, 4 (1.5%) had congestive heart failure, 7 (2.6%) had chronic renal failure, 73 (27%) had hyperlipidemia, 75 (28%) had hypertension, and 81 (30%) had diabetes mellitus. The medical regimens of the patients were as follows: nitrates 188 (70%) patients, Ca antagonists 187 (69%), nicorandils 86 (32%), β-adrenergic blockers 47 (17%), α-adrenergic blockers 4 (1.5%), angiotensin-converting enzyme inhibitors 19 (7%), and diuretics 19 (7%).

Exercise Testing

All patients underwent symptom-limited exercise testing in the fasting state using a bicycle ergometer (Lode B.V., Groningen Inc, The Netherlands) linked to a monitor system (CASE 15, Marquette Electronics Inc, USA). Patients pedaled the bicycle ergometer, starting with 50 W for 2

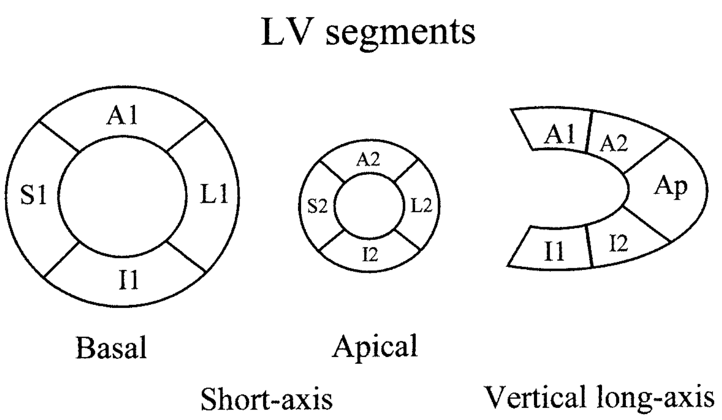

Fig 1. Nine regions of interest on 2 reconstructed short-axis slices and one vertical long-axis slice. A1, S1, I1 and L1 = basal anterior, septal, inferior, lateral segments; A2, S2, I2 and L2 = apical anterior, septal, inferior, lateral segments; Ap, apical segment; LV, left ventricular.

min, with an increment of 25 W for each 2-min stage. All tests were performed in the mid morning. Cardiac medications were withheld on the morning of the day of exercise testing. The ECG was continuously monitored; a standard 12-lead ECG and blood pressure were recorded in the supine and bicycle sitting positions and at every minute during exercise and recovery. Indications for stopping the exercise test were uncomfortable dyspnea or angina, serious arrhythmia, progressive reduction of SBP and leg fatigue. One minute before the anticipated end of exercise, 74 MBq of ^{201}Tl (Nihon Mediphysics Inc, Japan) was injected intravenously and flushed with saline, and the patient was encouraged to exercise for an additional minute. The patient recovered in the supine position for a maximum of 5 min and then underwent scintigraphic imaging.

The exercise test was considered positive when the ECG revealed more than 1 mm horizontal or down-sloping STD 80 ms after the J point, compared with the rest ECG just before exercise. The raw data were examined for consistency, requiring 3 consecutive beats with similar findings. The maximal STD and number of leads exhibiting the criteria of positivity were noted. Chest pain was noted according to the numerical treadmill angina index by Mark et al;[7,8] that is, 0 for no angina, 1 for nonlimiting angina, and 2 for exercise-limiting angina. All exercise tracings were analyzed independently by 2 examiners who were blinded to the clinical data and who resolved differences by consensus. We also calculated the Duke treadmill score[7,8] as follows: duration of exercise in minutes converted to Bruce treadmill protocol – (5 × the maximal STD during or after exercise, in millimeters) – (4 × the treadmill angina index).

We evaluated the following variables: (1) 2 ECG variables (ie, maximal STD and the number of leads exhibiting positivity); (2) 5 non-ECG variables of exercise (ie, the workload that patients attained, peak heart rate, peak SBP, peak rate–pressure product and chest pain during exercise); and (3) the complex index (ie, the Duke treadmill score).

Thallium Imaging

Early single-photon emission computed tomography (SPECT) was performed 5–10 min after exercise, and late SPECT was performed 3–4 h after early SPECT. In 150 patients (55.6%), 34 MBq of ^{201}Tl was re-injected intravenously immediately after early SPECT imaging.[13]

The SPECT images were acquired using a 3-headed SPECT system (PRISM3000, Picker International, Inc, OH, USA) equipped with low-energy, general purpose, parallel-hole collimators and interfaced with a computer system (Odyssey, Picker International, Inc). Twenty projection images over 120° per head were acquired in a 64×64 matrix for 20 s per projection. No attenuation or scatter correction was used. Transverse slices were reconstructed by a filtered backprojection algorithm after pre-processing of the projection images with a Butterworth low-pass filter. Vertical long-axis, short-axis and horizontal long-axis tomograms were reconstructed from the transverse slices. The defect score of ^{201}Tl imaging was visually determined for each of the total 9 myocardial segments (basal anterior, basal septal, basal inferior, basal lateral, apical anterior, apical septal, apical inferior, apical lateral walls and apex; Fig 1) according to a 4-point scoring system: 0 = normal, 1 = mildly reduced, 2 = moderately reduced and 3 = markedly reduced.[14,15] A summed difference score (SDS) was defined as the sum of the differences between the early and late scores of each of the 9 segments. Extent was defined as the percentage of segments of which the difference between the early and the late defect scores was positive; for example, an extent of 33.3% means that 3 of the total 9 segments have a reversible defect.

Coronary Angiography and Left Ventriculography

Some patients underwent coronary angiography and left ventriculography. The number-of-vessel disease was defined as the number of main coronary arteries with more than 75% luminal diameter narrowing. Left main trunk disease was defined as a left main trunk with more than 50% luminal diameter narrowing. The left ventriculography ejection fraction was calculated by the centerline method.

Data Analysis

All measures were expressed as mean ± SD. Comparisons of continuous data between 2 groups were made using Student's t test. Correlation between 2 variables was examined by nonparametric linear regression analysis. Multivariate linear regression analysis was used to examine which variables among the ECG and non-ECG indexes were independently related to the severity and extent of the scintigraphic indexes. We analyzed 2 models; one included only simple variables (ie, maximal STD, the number of leads exhibiting positivity, the workload that patients attained, peak heart rate, peak SBP and chest pain during exercise) and the other included the number of leads exhibiting positivity, peak SBP and the Duke treadmill score. Statistical significance was defined as $p<0.05$. We also analyzed the data in patients with the SDS ≥1 (ischemic group), as well as the data in patients with and without a previous myocardial infarction and in patients without resting STD (resting STD <1 mm).

Results

An SDS ≥1 was observed in 211 (ischemic group) of the total 270 patients.

Correlation of Exercise Variables With Scintigraphic Variables (Tables 1,2)

In the total group, the degree of maximal STD, the number of leads exhibiting positivity and chest pain correlated positively with the SDS and the extent. The workload that the patients attained, peak heart rate, peak SBP, peak rate-pressure product and the Duke treadmill score all correlated negatively with SDS and the extent. However, these correlation coefficients were low even if they had significant correlation.

In the ischemic group, the degree of maximal STD and chest pain also correlated positively with SDS and the extent. The number of leads exhibiting positivity correlated positively only with SDS. The workload that the patients attained, peak SBP, peak rate-pressure product and the Duke treadmill score negatively correlated with SDS and the extent. However, these correlation coefficients were low even if they had significant correlation.

In patients without a previous myocardial infarction (n=154), the degree of maximal STD, peak SBP, chest pain and the Duke treadmill score correlated with SDS and the extent. The correlation coefficients of SDS with the degree of maximal STD, peak SBP, chest pain and the Duke treadmill score were 0.331 ($p<0.001$), –0.234 ($p<0.01$), 0.355 ($p<0.001$) and –0.447 ($p<0.001$), respectively. The correlation coefficients of the extent with the degree of maximal STD, peak SBP, chest pain and the Duke treadmill score were 0.291 ($p<0.001$), –0.209 ($p<0.01$), 0.295 ($p<0.001$) and –0.389 ($p<0.001$), respectively.

However, in patients with a previous myocardial infarction (n=116), the degree of maximal STD, peak SBP, chest pain and the Duke treadmill score correlated with SDS and the extent. The correlation coefficients of SDS with the degree of maximal STD, peak SBP, chest pain and the Duke treadmill score were 0.284 ($p<0.01$), –0.345 ($p<0.001$), 0.439 ($p<0.001$) and –0.439 ($p<0.001$), respectively. The correlation coefficients of the extent with the degree of maximal STD, peak SBP, chest pain and the Duke treadmill score were 0.259 ($p<0.01$), –0.373 ($p<0.001$), 0.415 ($p<0.001$) and –0.415 ($p<0.001$), respectively.

In patients without resting STD (n=240), the degree of maximal STD, positive leads, peak heart rate, peak SBP, peak rate–pressure product, chest pain and the Duke treadmill score correlated with SDS and the extent (Table 3).

Exercise Variables for Estimation of the Degree of Ischemia

Multivariate linear regression analysis showed that only peak SBP ($p=0.002$) and chest pain ($p<0.001$) independently correlated with severe ischemia (ie, the SDS) in the total group, whereas maximal STD was not an independent variable ($p=0.33$). Exercise variables that independently correlated with extensive ischemia (ie, extent) were peak SBP ($p<0.001$) and chest pain ($p<0.001$), whereas maximal STD was not an independent variable ($p=0.41$). When the Duke treadmill score was added into multivariate regression analysis, the analysis showed that only peak SBP and the Duke treadmill score independently correlated with severe and extensive ischemia in the total group ($p<0.001$ for all 4 combinations).

In the ischemic group, only peak SBP independently correlated with SDS and the extent ($p<0.001$, $p<0.001$, respectively). Maximal STD and chest pain did not independently correlate with SDS and the extent ($p=0.33$ and $p=0.59$, respectively, for maximal STD; and $p=0.38$ and $p=0.10$, respectively, for chest pain). Even when the Duke treadmill score was included, multivariate linear regression analysis showed that only peak SBP correlated with SDS ($p<0.001$) and the extent ($p<0.001$), and that the Duke treadmill score did not independently correlated with SDS ($p=0.086$) or the extent ($p=0.431$).

Peak SBP as a Marker of Severe and Extensive Ischemia

The relationship of peak SBP with SDS and the extent in the total group were depicted in Fig 2. As the range of SDS and of the extent were from 0 to 14 and from 0 to 88.8%,

Table 1 Correlation Coefficients of Exercise Variables With Scintigraphic Variables in the Total Group (n=270)

	SDS	*Extent*
Degree of maximal STD	*0.358‡*	*0.328‡*
Positive leads	*0.220‡*	*0.201†*
Workload	*–0.239‡*	*–0.218‡*
Peak heart rate	*–0.242‡*	*–0.227‡*
Peak SBP	*–0.363‡*	*–0.356‡*
Peak rate–pressure product	*–0.372‡*	*–0.361‡*
Chest pain	*0.406‡*	*0.373‡*
Duke treadmill score	*–0.485‡*	*–0.446‡*

SBP, systolic blood pressure; STD, ST-segment depression; SDS, summed difference score. †p<0.01, ‡p<0.001.

Table 2 Correlation Coefficients of Exercise Variables With Scintigraphic Variables in the Ischemic Group (n=211)

	SDS	*Extent*
Degree of maximal STD	*0.211†*	*0.163**
Positive leads	*0.157†*	*0.124*
Workload	*–0.236†*	*–0.202†*
Peak heart rate	*–0.120*	*–0.095*
Peak SBP	*–0.386‡*	*–0.377‡*
Peak rate–pressure product	*–0.313‡*	*–0.296‡*
Chest pain	*0.295‡*	*0.244‡*
Duke treadmill score	*–0.331‡*	*–0.266‡*

*SBP, systolic blood pressure; STD, ST-segment depression; SDS, summed difference score. *p<0.05, †p<0.01, ‡p<0.001.*

Table 3 Correlation Coefficients of Exercise Variables With Scintigraphic Variables in Patients Without Resting STD (n=240)

	SDS	*Extent*
Degree of maximal STD	*0.354‡*	*0.322‡*
Positive leads	*0.208†*	*0.182†*
Workload	*–0.269‡*	*–0.243‡*
Peak heart rate	*–0.279‡*	*–0.265‡*
Peak SBP	*–0.496‡*	*–0.383‡*
Peak rate–pressure product	*–0.414‡*	*–0.401‡*
Chest pain	*0.411‡*	*0.376‡*
Duke treadmill score	*–0.493‡*	*–0.451‡*

SBP, systolic blood pressure; STD, ST-segment depression; SDS, summed difference score. †p<0.01, ‡p<0.001.

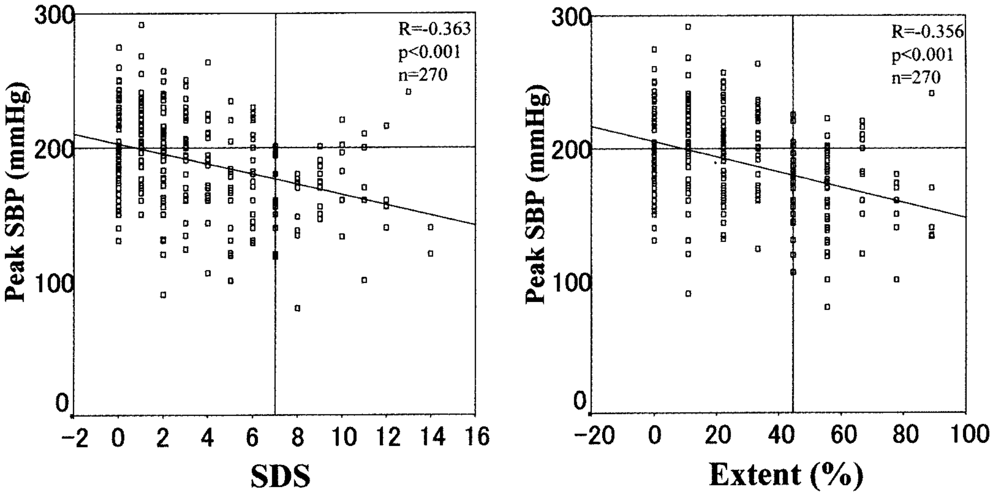

Fig 2. (Left) Relationship between peak systolic blood pressure (SBP) and the summed difference score (SDS) in the total group. (Right) Relationship between peak SBP and extent in the total group.

Table 4 Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Ischemic Severity and Extent by Peak Systolic Blood Pressure <200 mmHg

	Total group		*Ischemic group*	
	Severe ischemia	*Extensive ischemia*	*Severe ischemia*	*Extensive ischemia*
Sensitivity	82.0% (41/ 50)	80.2% (65/ 81)	82.0% (41/ 50)	80.2% (65/ 81)
Specificity	49.1% (108/220)	53.4% (101/189)	47.8% (77/161)	53.8% (70/130)
Positive predictive value	26.8% (41/153)	42.5% (65/153)	32.8% (41/125)	52.0% (65/125)
Negative predictive value	92.3% (108/117)	86.3% (101/117)	89.5% (77/ 86)	81.4% (70/ 86)

Table 5 Difference of Coronary Angiographic Findings Between Patients With Peak SBP <200 mmHg and Those With Peak SBP ≥200 mmHg

	Peak SBP <200 mmHg (n=115)	*Peak SBP ≥200 mmHg (n=72)*	*p value*
Vessel disease			
0	8 (7%)	22 (30.6%)	
1	26 (22.6%)	24 (33.3%)	
2	43 (37.4%)	16 (22.2%)	
3	38 (33.3%)	10 (13.9%)	
Average	2.0±0.9	1.2±1.0	<0.0001
LMT	10 (8.7%)	2 (2.8%)	0.120
LVEF	54±21%	59±28%	0.424

SBP, systolic blood pressure; LMT, left main trunk disease; LVEF, ejection fraction in left ventriculography.

respectively, we used medians (score 7 and 44.4%, respectively) as the discriminating points of scintigraphic severe ischemia and extensive ischemia. That is, scintigraphic severe and extensive ischemia were defined as SDS ≥7 and extent ≥44.4%, respectively. As shown in Fig 2, most patients with scintigraphically severe and extensive ischemia did not have a SBP of more than 200 mmHg. Both the sensitivity and negative predictive value of a peak SBP less than 200 mmHg for scintigraphically severe and extensive ischemia were high for the total group, as well as for the ischemic group (Table 4). In other words, the patients with peak SBP of 200 mmHg or more are likely to have milder and less extensive ischemia.

Differences in Coronary Angiographic Findings and Ejection Fraction in Left Ventriculography

Table 5 shows the difference in coronary angiographic findings between patients with a peak SBP less than 200 mmHg and those with peak SBP of 200 mmHg or more. Patients with the former had more extensive coronary artery lesions than those with the latter SBP. However, the 2 groups had the same ejection fraction.

Discussion

The present study has shown that the degree of maximal STD on exercise testing does correlate with the scintigraphic severity and extent of myocardial ischemia in patients with exercise-induced STD, but that the correlation is weak. Among the ECG and non-ECG variables, multivariate analysis demonstrated that the peak SBP and the Duke treadmill score (or chest pain, when simple variables were analyzed) independently correlated with scintigraphically severe ischemia, but that the degree of maximal STD did not.

Previous studies suggested that some ECG and non-ECG variables were associated with the presence of severe IHD,[1-6] and one of them was the degree of maximal STD.[1,2,4,5] The current study showed significant correlation between the degree of maximal STD and severe IHD, but the correlation coefficient was low. Bogaty et al showed that the correlation of the degree of maximal STD with the extent of the perfusion abnormality on scintigraphy was significant but weak.[9] They also showed that the degree of maximal STD could not differentiate the number of diseased vessels. Taylor et al could not demonstrate a significant difference in ^{201}Tl redistribution defects between patients who exhibited STD <2 mm and those who exhibited STD ≥2 mm.[10] Those studies, as well as the present study, thus indicate that severe and extensive ischemia can not be detected by the degree of maximal STD.

Of the ECG and non-ECG variables used in the present study, peak SBP and chest pain during exercise showed a weak but significant correlation with scintigraphic perfusion measures of the severity and the extent of ischemia. Chaitman et al showed that one of the exercise variables associated with a significantly increased risk in the non-cardiac perioperative period was an inability to increase or actually decrease SBP with progressive exercise.[16] They did not define the level of blood pressure at which severe ischemia was suspected. Lauer et al reported that those with exercise hypertension (defined as ≥210 mmHg in men and ≥190 mmHg in women) had a lower likelihood of angiographically severe disease and a lower mortality rate.[17,18] As the discriminating level of peak SBP between severe and mild ischemia, we adopted 200 mmHg, which corresponds to their average of 210 mmHg in men and 190 mmHg in women,[17,18] and is easier to remember. To our knowledge, this is the first report to show that patients with exercise hypertension have milder and less extensive ischemia even if they have STD of more than 1 mm. Briefly, patients who can attain a SBP of more than 200 mmHg are unlikely to have scintigraphically severe and/or extensive ischemia even if they have STD of more than 1 mm.

The Duke treadmill score has been the most well-validated means of interpreting exercise testing,[1,2] but it has been devised by analyzing many variables other than peak SBP.[7,8] From our results, peak SBP is another independent means of interpreting exercise testing. Further studies are required to devise a new exercise testing index combining the Duke treadmill score and peak SBP in order to evaluate the severity and prognosis of IHD more accurately.

Conclusions

The concordance of maximal STD with scintigraphically severe and extensive ischemia is generally poor. Only peak SBP, in addition to the Duke treadmill score (or chest pain, when the only simple variables are analyzed), can estimate the scintigraphic severity and extent of ischemia. Patients who can increase the SBP to more than 200 mmHg during exercise are unlikely to have severe and/or extensive ischemia. To evaluate the severity of ischemia and the prognosis of IHD more accurately, it is desirable to use peak SBP in addition to the Duke treadmill score.

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