Systolic blood pressure during recovery from exercise is related to flow-mediated dilatation in patients with coronary artery disease

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ABSTRACT

Objective To assess the relationship between exercise-induced parameters obtained from the routine exercise stress testing (EST) and flow-mediated vasodilatation (FMD) as an index of endothelial function.

Design A retrospective study.

Setting Kurume University Medical Center, Kurume, Japan.

Patients All patients with stable coronary artery disease (CAD) who were admitted to Kurume University Medical Center.

Main outcome measure Results of EST and FMD.

Results We studied 66 patients (35 male/31 female) with CAD. All patients underwent symptom-limited EST and measurement of FMD. Exercise parameters included exercise-induced heart rate and systolic blood pressure (SBP). FMD did not differ between male and female groups. In univariate analysis, determinants of FMD included age and the change in SBP at 1 min after exercise. In Cox hazard model analysis, the change in SBP at 1 min after exercise ($p=0.011$) was an independent determinant of FMD. FMD in patients with abnormal SBP response group was significantly lower than that in normal SBP response group (4.2 ± 1.8 ns. $6.1\pm 2.6\%$, $p<0.05$).

Conclusions These findings suggest that SBP during recovery from exercise is associated with endothelial function in patients with CAD.

Several variables obtained from cardiopulmonary exercise testing have provided valuable diagnostic and prognostic information in patients with coronary artery disease (CAD). Of these, the abnormality of exercise-induced systolic blood pressure (SBP) response is a strong predictor of risk in patients with CAD.^{1–3} SBP response to exercise is complex and affected by several mechanisms—for example, the autonomic nervous system, smooth muscle and vascular endothelial function. Activity of the sympathetic nervous system increases from the onset of exercise to peak exercise as vagal activity weakens, but activity decreases rapidly when exercise stops and during recovery, in contrast with vagal reactivation. These factors affect the SBP response to exercise.

SBP is also regulated by vascular endothelial and smooth muscle function. Vascular smooth muscle relaxation is responsible for the increase in blood flow during exercise, and the vascular endothelium also contributes to adaptations to exercise in the arterial circulation by releasing the endothelium-dependent relaxing factor, nitric oxide. Impairment of endothelium-dependent vasodilatation has been

shown in patients with hypertension, dyslipidaemia, diabetes mellitus and heart failure.^{4–8} Therefore, it is thought that SBP during recovery from exercise might significantly correlate with endothelial function in CAD. Previous studies have shown a possible relationship between blood pressure response to maximal exercise and physiological mechanisms underlying arterial vasodilatation in well-trained healthy young subjects.⁹ However, little is known about the relation between exercise parameters during exercise stress testing (EST) and flow-mediated vasodilatation (FMD) in patients with CAD. Accordingly, this study investigated the relationship between exercise-induced hemodynamic parameters obtained from routine EST and FMD in patients with CAD.

PATIENTS AND METHODS

Study patients

The study population comprised 66 patients with stable CAD who were admitted to Kurume University Medical Center. Diagnostic criteria of CAD include typical history of chest pain, ischaemic ECG changes and/or coronary angiography. All patients had angiographically coronary stenosis. Of these, six had a previous myocardial infarction, and 60 patients had a history of angina pectoris with no evidence of previous infarction. No patients with chest pain syndrome were seen. Twenty patients had had percutaneous coronary intervention and four, coronary artery bypass graft surgery. Patients with atrioventricular block and pacemaker implantation inflammatory diseases, any other organ failure, orthopaedic or neuromuscular diseases were excluded from the study. All patients received conventional drug treatment— aspirin ($n=40$), calcium channel antagonists ($n=32$), HMG-CoA inhibitor ($n=33$), ACE inhibitors or angiotensin receptor blockers ($n=32$), insulin sensitising agent ($n=14$), isosorbide dinitrate ($n=13$) or sulfonylurea ($n=12$). Informed consent was obtained from all patients, and the study was approved by the human study committee of our institution.

Exercise stress test

All patients underwent symptom-limited EST. Treadmill exercise stress tests (ML4500, Fukuda Denshi, Tokyo) were performed using the Bruce (low level) or Sheffield protocol. The ECG and SBP (measured automatically) were recorded every minute before, during and after exercise. Criteria for stopping the exercise test included chest

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discomfort, life-threatening arrhythmias, ST-segment depression or elevation >0.2 mV, a fall in SBP from the preceding stage of >20 mm Hg or reaching the predicted target heart rate (HR) $((220 - \text{age}) \times 0.85)$. Exercise parameters included HR and SBP at rest, at peak exercise and 1, 2 or 3 min after exercise. All patients were divided into two groups: those with a normal or abnormal SBP response. The normal SBP response group had maximal SBP at peak exercise and normal SBP decay during exercise recovery. The abnormal SBP response group had an increase in SBP 1 min after exercise stopped compared with SBP at peak exercise.

Measurement of FMD

As recommended by the guidelines for ultrasound assessment of endothelial-dependent FMD of the brachial artery,¹⁰ the subjects abstained from smoking, alcohol and caffeine-containing drinks and foods for 4 h before the study and from vigorous exercise and EST on the day of the study. Measurements were undertaken in a warm, temperature-controlled room by the same operator at the same time of day. Endothelium-dependent vasodilatation was assessed by FMD of the brachial artery in the morning. Brachial artery diameter was measured by B-mode ultrasound imaging (UNEX EF 18G, UNEX Co, Aichi, Japan) with a 7.5 MHz linear artery transducer, and an ECG was recorded simultaneously. The right brachial artery was scanned in longitudinal sections 1–10 cm above the elbow after at least 5 min rest in a supine position, the skin surface was marked and the arm was kept in the same position during the study. After baseline measurement of the brachial artery diameter, FMD was determined by scans during reactive hyperaemia. A pneumatic cuff placed around the forearm was inflated to 50 mm Hg above systolic pressure and was deflated after 5 min. The brachial artery diameter was scanned and results recorded continuously from 30 s before, to 2 min after, cuff deflation to obtain a maximal diameter. After a 15 min rest, a second control scan of the diameter was recorded. The diameter of the artery was measured from one media–adventitia interface to the other at end-diastole, coincident with the R-wave on a continuously recorded ECG. The FMD was expressed as maximal percentage change in arterial diameter from the baseline diameter after the release of occlusion.

Statistical analysis

Values are presented as mean $\pm$ SD. Comparisons between groups were made by the unpaired *t* test and χ^2 test. Univariate analysis for determination of FMD was performed for 20 parameters (ie, age, sex, HR, SBP, HR and SBP response during exercise or recovery). A stepwise multiple linear regression analysis was performed for determinants of FMD, adjusted for age and sex. All statistical analyses were performed with the SPSS system. A *p* value of <0.05 was considered significant.

RESULTS

Clinical characteristics

Clinical characteristics of patients with a normal (50 patients) or abnormal (16 patients) SBP response during exercise testing are shown in table 1. The groups did not differ in age, sex, body mass index, the number of risk factors, the incidence of smoking and medication used.

Exercise parameters

Exercise parameters of patients with a normal or abnormal SBP response during exercise testing are shown in table 2. SBP at 1 min after exercise in the normal SBP response group was

Table 1 Clinical characteristics of study patients with normal and abnormal SBP response during exercise

Characteristics	Normal SBP response (n=50)	Abnormal SBP response (n=16)
Age (years), mean $\pm$ SD	68 $\pm$ 9	71 $\pm$ 8
Sex (male/female)	25/25	10/6
BMI (kg/m ²), mean $\pm$ SD	23.4 $\pm$ 3.1	22.4 $\pm$ 2.6
Risk factor (%)		
Hypertension	28 (56)	7 (44)
Dyslipidaemia	25 (50)	4 (25)
Diabetes mellitus	21 (42)	3 (19)
Smoking	6 (12)	3 (19)
Medication used (%)		
Antiplatelet agents	29 (58)	13 (81)
Calcium antagonists	23 (46)	7 (44)
Nitrates	19 (38)	9 (56)
ACIs and ARBs	20 (40)	10 (63)
Statins	23 (46)	8 (50)
β -Blockers	14 (28)	4 (25)
Diuretic agents	3 (6)	3 (19)

Results are shown as number (%) unless stated otherwise.

ARBs, angiotensin II receptor blockers; BMI, body mass index; SBP, systolic blood pressure.

significantly lower than that in the abnormal SBP response group. Moreover, the change in HR and SBP at 1 min after exercise, and the change in SBP at 2 and 3 min after exercise in the

Table 2 Exercise parameters in patients with normal and abnormal SBP response during exercise

Parameters	Normal SBP response (n=50)	Abnormal SBP response (n=16)
HR (bpm)		
Rest	75 $\pm$ 13	76 $\pm$ 11
Peak exercise	123 $\pm$ 23	121 $\pm$ 26
1 min after exercise	108 $\pm$ 23	113 $\pm$ 24
2 min after exercise	95 $\pm$ 19	94 $\pm$ 21
3 min after exercise	89 $\pm$ 17	85 $\pm$ 17
Δ HR	48 $\pm$ 21	45 $\pm$ 20
Δ HRP1	16 $\pm$ 13	8 $\pm$ 9*
Δ HRP2	29 $\pm$ 14	27 $\pm$ 11
Δ HRP3	35 $\pm$ 15	35 $\pm$ 13
Systolic blood pressure (mm Hg)		
Rest	132 $\pm$ 16	127 $\pm$ 19
Peak exercise	189 $\pm$ 27	179 $\pm$ 28
1 min after exercise	168 $\pm$ 29	189 $\pm$ 28*
2 min after exercise	158 $\pm$ 33	168 $\pm$ 20
3 min after exercise	147 $\pm$ 27	158 $\pm$ 22
Δ SBP	57 $\pm$ 24	51 $\pm$ 31
Δ SBPP1	21 $\pm$ 15	–11 $\pm$ 6#
Δ SBPP2	31 $\pm$ 25	11 $\pm$ 7**
Δ SBPP3	42 $\pm$ 24	21 $\pm$ 25**
METs	5.9 $\pm$ 1.4	5.5 $\pm$ 1.4

p* < 0.05, *p* < 0.005 and #*p* < 0.0001 as compared with the normal SBP response group.

Results are shown as mean $\pm$ SD.

HR, heart rate; Δ HR, HR at peak exercise–HR at rest; Δ HRP1, HR at peak exercise–HR at 1 min after exercise; Δ HRP2, HR at peak exercise–HR at 2 min after exercise; Δ HRP3, HR at peak exercise–HR at 3 min after exercise; SBP, systolic blood pressure; Δ SBP, SBP at peak exercise–SBP at rest; Δ SBPP1, SBP at peak exercise–SBP at 1 min after exercise; Δ SBPP2, SBP at peak exercise–SBP at 2 min after exercise; Δ SBPP3, SBP at peak exercise–SBP at 3 min after exercise; METs, metabolic equivalents.

normal SBP response group were significantly higher than those in the abnormal SBP response group. However, other exercise parameters did not differ between normal and abnormal SBP response groups.

Furthermore, no patients stopped EST owing to exercise-induced chest pain and/or ischaemic ST-segment changes.

Stepwise multiple linear regression analysis

In univariate analysis (table 3), determinants of FMD included age and the change in SBP at 1 min after exercise. In stepwise multiple linear regression analysis (table 4), the change in SBP at 1 min after exercise was an independent determinant of FMD in patients with CAD.

Flow-mediated vasodilatation

Mean FMD was $5.6 \pm 2.6\%$ in all patients. FMD in patients with an abnormal SBP response was significantly lower than that in normal SBP response group (figure 1). The FMD significantly correlated with the changes in SBP at 1 min after exercise ($r=0.32$, $p<0.01$) (figure 2).

DISCUSSION

Previous reports have shown a relation between exercise parameters during EST and FMD in healthy subjects.^{1 2 9} This is the first report demonstrating a significant relationship between FMD and the change in SBP at 1 min after exercise in patients with CAD.

During exercise, cardiac output is mainly diverted to the exercised skeletal muscles, while blood distribution is decreased in

Table 4 Stepwise multiple linear regression analysis

Variables	β	p Value
Δ SBPP1	0.37	0.011

β , standardised regression coefficients.

SBP, systolic blood pressure; Δ SBPP1, SBP at peak exercise–SBP at 1 min after exercise.

organs such as the kidney, liver and gastrointestinal tract. When exercise stops, sympathetic nerve activity rapidly decays, in contrast to vagal reactivation, and vascular resistance is decreased in the non-working muscle. The change in SBP at 1 min after exercise involves complex mechanisms such as the autonomic nervous system, smooth muscle and vascular endothelial function. A previous study¹¹ showed that sympathetic nerve activity is withdrawn and primarily vagal activity reactivated at 30 s after exercise, and at 2 min after exercise vagal reactivation is attenuated. As we assessed the SBP response at 1 min after exercise, it is possible that vagal activity might have affected the SBP response.

Smooth muscle and vascular endothelial function might also be related to the change in SBP at 1 min after exercise. In the previous study, since the vascular resistance was shown to increase in the non-exercised skeletal muscle of the forearm in patients with left ventricular dysfunction who underwent ergometric exercise,¹² arterial vasodilatation in the non-exercised skeletal muscle might be related to the change in SBP at 1 min after exercise. Many previous studies of patients with cardiovascular disease have shown that endothelium-dependent vasodilatation is impaired and that the recovery of SBP after exercise is attenuated.^{3–5 13 14} This is thought to be related to the impairment of nitric oxide release. Moreover, it has been shown that SBP increases during the recovery period after exercise in patients with severe CAD and chronic heart failure.^{13 14} In our study, severe exercise-induced myocardial ischaemia was not seen in the patients; however, significant differences in FMD were seen between the abnormal and normal SBP response groups.

These findings suggest that exercise-induced nitric oxide release may differ between the two groups despite a similar

Table 3 Univariate analysis for determination of FMD

	B	p Value
Age	–0.292	0.017*
HR (bpm)		
Rest	0.072	0.566
Peak exercise	0.139	0.445
1 min after exercise	0.130	0.299
2 min after exercise	0.128	0.305
3 min after exercise	0.168	0.184
Δ HR	0.105	0.403
Δ HRP1	0.005	0.966
Δ HRP2	0.047	0.710
Δ HRP3	0.049	0.700
Systolic blood pressure (mm Hg)		
Rest	–0.232	0.061
Peak exercise	0.033	0.794
1 min after exercise	–0.173	0.164
2 min after exercise	–0.120	0.336
3 min after exercise	–0.056	0.658
Δ SBP	0.189	0.129
Δ SBPP1	0.318	0.009*
Δ SBPP2	0.187	0.132
Δ SBPP3	0.111	0.388
METs	0.019	0.881

* $p<0.05$.

FMD, flow-mediated vasodilatation; HR, heart rate; Δ HR, HR at peak exercise–HR at rest; Δ HRP1, HR at peak exercise–HR at 1 min after exercise; Δ HRP2, HR at peak exercise–HR at 2 min after exercise; Δ HRP3, HR at peak exercise–HR at 3 min after exercise; SBP, systolic blood pressure; Δ SBP, SBP at peak exercise–SBP at rest; Δ SBPP1, SBP at peak exercise–SBP at 1 min after exercise; Δ SBPP2, SBP at peak exercise–SBP at 2 min after exercise; Δ SBPP3, SBP at peak exercise–SBP at 3 min after exercise; METs, metabolic equivalents.

Figure 1 Flow-mediated vasodilatation (FMD) in patients with normal and abnormal systolic blood pressure (SBP) response. A significant difference in FMD was found between the two groups.

Figure 2 Relation between flow-mediated vasodilatation (FMD) and the changes in systolic blood pressure (SBP) at 1 min after exercise. A significant correlation was found between FMD and the changes in SBP at 1 min after exercise.

degree of exercise intensity and shear stress. Possibly, therefore, the change in SBP at 1 min after exercise and the SBP responses during exercise recovery closely reflect the endothelium-dependent vasodilatation. In a previous study,¹⁵ a raised SBP during recovery after exercise was predictive of hypertension. These findings may reflect dysfunction of endothelium-dependent vasodilatation.

The changes in HR at 1 min after exercise were significantly lower in the abnormal SBP response group than those in normal SBP response group. Although the mechanisms responsible for this difference in HR change are unclear, it is possible that oxygen debt in the group with an abnormal SBP response is greater than that in the group with a normal SBP response, because the double product of HR and SBP at peak exercise and exercise tolerance in the abnormal SBP response group were smaller than those in the normal SBP response group.

Limitations

Several possible limitations should be considered in this study. First, although 59/66 patients (89%) received drug treatment with a vasodilator or statin which might affect FMD, no significant difference in the number of drugs used was seen between the normal and abnormal SBP response groups. Moreover, the FMD obtained in our study was similar to that obtained for Japanese subjects aged ≥ 50 with coronary risk factors in the previous study.⁸ Thus, the effect of medication on FMD seems to be small. Second, study subjects comprised middle-aged patients with CAD. Hence, it is unknown whether our results can be generalised to older patients. Third, two different protocols—Bruce or Sheffield—were used. However, the SBP response did not differ between the two exercise protocols, which both involved multistage exercise with a treadmill and dynamic exercise. Finally, the patients with CAD enrolled in this study comprised patients with angina pectoris and previous infarction. Endothelial function may vary in this group and is unlikely to be uniform. Thus, further investigations are needed in a larger number of subjects and older patients.

Clinical implication

It is possible that SBP responses during exercise recovery represent a clinical marker of dynamic endothelial function during routine EST in patients with CAD. Therefore, these responses are clinically useful for consideration of choice of drugs and for assessing the clinical outcome of exercise rehabilitation.

In conclusion, this study suggests that SBP during recovery from exercise is closely related to FMD in patients with CAD.

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