ABNORMAL POSTEXERCISE SYSTOLIC BLOOD PRESSURE RESPONSE IS A GOOD INDICATOR OF IMPAIRED LEFT VENTRICULAR FILLING DURING SUPINE CYCLE ERGOMETER EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE

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To determine whether the postexercise systolic blood pressure (SBP) response is a useful marker of left ventricular filling abnormalities, supine leg exercise testing was conducted in 14 control subjects and 70 patients with coronary artery disease (CAD). An abnormal postexercise SBP response (the ratio of SBP after 3 min of recovery to the peak exercise SBP) was defined as 0.85 or more, which represented the cutoff point with the highest sensitivity and specificity for prediction of pulmonary artery wedge pressure (PAWP) of at least 20 mmHg at peak exercise in CAD patients. There was a significant difference between the SBP ratios of the two groups (Control, 0.72±0.05; CAD, 0.86±0.13; p<0.01). There was no significant difference between the PAWP of the two groups at rest, but the PAWP at peak exercise was significantly higher in the CAD group (20.2±8.9 mmHg) than in the control group (11.5±4.0 mmHg)(p<0.01). PAWP at peak exercise was ≥20 mmHg in 35 (50%) of the 70 CAD subjects. The SBP ratio was significantly correlated with PAWP at peak exercise (r=0.67, p<0.01) in the CAD group, but not in the control group. An SBP ratio of ≥0.85 showed a sensitivity of 80% and a specificity of 80% for predicting a peak exercise PAWP of ≥20 mmHg in CAD patients. After the administration of a calcium channel blocker, the SBP ratio showed a sensitivity of 80% and a specificity of 95% in the CAD group (n=25), and was significantly correlated with the PAWP at peak exercise (n=25, r=0.69, p<0.01). These observations indicate that the SBP ratio is a good indicator of exercise-induced impairment of left ventricular filling dynamics during supine leg exercise.

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Key words:
- SBP ratio
- Coronary artery disease
- Supine leg exercise
- Left ventricular filling

STUDIES1-3 have shown that the ratio of the early recovery systolic blood pressure (SBP) to the peak exercise SBP (SBP ratio) in patients with significant coronary artery
Fig. 1. Relative cumulative frequency (proportion of total frequency) of SBP ratios in patients with CAD, from highest to lowest values in the group with PAWP < 20 mmHg at peak exercise, and from lowest to highest values in the group with PAWP ≥ 20 mmHg at peak exercise.

disease (CAD) is higher than that in normal individuals, which suggests that the SBP ratio is useful for identifying patients with CAD.

The pulmonary artery wedge pressure (PAWP) reflects the left ventricular end-diastolic pressure (LVEDP), a clinically useful index of left ventricular filling dynamics, even during exercise. There is a margin of safety of approximately 20 mmHg in the development of pulmonary edema. LVEDP above 20 mmHg during supine exercise is usually defined as abnormal. Although PAWP measurements are clinically useful, the method is invasive.

We conducted this investigation to determine whether the SBP ratio would be a useful marker of exercise-induced impairment of left ventricular filling based on measurements of PAWP in patients with CAD. In addition, we investigated the relationship between the SBP ratio and PAWP at peak exercise after the administration of a calcium channel blocker.

METHODS AND MATERIALS

Study Population
We retrospectively studied 84 consecutive subjects with suspected CAD without prior myocardial infarction who were referred to Nagoya University Hospital for cardiac catheterization. Of those, 14 were age-matched control subjects with normal coronary arteries on coronary angiography (control group; 12 men and 2 women; mean age 55 years, range 38 to 67). The remaining 70 patients (62 men and 8 women; mean age 56 years, range 38 to 71) had angiographic evidence of 75% or greater stenosis in one or more major coronary arteries. Thirty-four patients had 1-vessel disease, 16 had 2-vessel disease, and 20 had 3-vessel disease. Patients with abnormal Q waves on a standard 12-lead electrocardiogram, congenital or valvular heart disease, cardiomyopathy, or intraventricular conduction disturbances were excluded from the study. The study was approved by the appropriate institutional review committees, and each patient gave
informed consent.

**Hemodynamic Studies**

PAWP was measured by a triple lumen thermistor Swan-Ganz catheter positioned in the pulmonary artery percutaneously through the left axillary vein. The brachial artery was cannulated with a Teflon catheter to directly measure arterial pressure. PAWP and arterial pressure were measured by a Siemens pressure transducer (746) from a zero reference level 5 cm below the angle of Louis.

**Bicycle Ergometer Exercise Testing**

 Except for sublingual nitroglycerin given to relieve chest pain, all drugs were withdrawn at least 3 days before the study. Symptom-limited supine bicycle ergometer tests were performed in all subjects8,9. Subjects began exercising at a workload of 25W, which was increased by 25W every 3 min. They continued exercising until typical chest pain or severe fatigue occurred. During exercise testing, electrocardiographic (modified 12 leads and Frank X, Y, and Z leads) and systemic hemodynamic measurements were obtained continuously. The SBP was measured directly during each minute of exercise testing.

**Definition of abnormal postexercise SBP response**

The SBP ratio was derived by dividing SBP values obtained 3 min after exercise by the peak values. Fig. 1 shows the relative cumulative frequency of SBP ratios in groups with and without PAWP values of ≥20 mmHg at peak exercise in the CAD patients. The cutoff point with the highest sensitivity and specificity for predicting a peak exercise PAWP of ≥20 mmHg was 0.85. An SBP ratio ≥0.85 was considered abnormal.

**Administration of calcium channel blockers**

To determine whether the SBP ratio would be a useful marker of left ventricular filling dynamics after improvement of acute myocardial ischemia by antianginal drugs, we administered a single dose of nilvadipine (6 mg) or nisoldipine (10 mg) to 25 patients with CAD after the control exercise test. Exercise testing using the same method, duration, and workload as in the control study was performed 1.5 h after drug administration.

**Angiography**

Left heart catheterization was performed using standard techniques. Left ventriculography was performed in the right and left anterior oblique projections. Left ventricular ejection fraction was determined by the area-length method10. Coronary arteriograms, obtained in multiple projections, were analyzed by two angiographers who were unaware of the results of exercise testing. Significant coronary stenosis disease was defined as 75% or greater stenosis in any of the three major coronary arteries.

**Calculations**

The baseline from which the observed ECG changes were measured was a line which joined two consecutive P-Q junctions. The magnitude of the ST segment depression was measured using a magnifying glass (×7 magnification power) calibrated in tenths of a millimeter. Test results were reviewed independently by a second observer, and differences were resolved by joint study of the record. The use of a calibrated magnifying glass substantially increased interobserver agreement. Each exercise test was interpreted without knowledge of the results. The ECG criteria for a positive test in any lead were a horizontal or downsloping ST segment depression of ≥1 mm 0.08 sec after the J point in at least three consecutive complexes. The extent of ST change was expressed as the maximal value of ischemic ST segment depression in any of the 15 leads recorded.

**Statistical Analysis**

Results are expressed as the mean±SD. For statistical analysis, paired and non-paired t-tests, chi-square analyses, linear regression analysis, and the sign test11 were performed when appropriate. The level of significance was set at p<0.05. We evaluated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the SBP recovery ratio for detecting patients with a peak exercise PAWP of ≥20 mmHg. The following definitions were used: sensitivity=(true positive)/(true positive+true negative)×100; specificity=
TABLE I CLINICAL CHARACTERISTICS AND EXERCISE RESPONSE

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=14)</th>
<th>CAD group (n=70)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55±8</td>
<td>56±8</td>
<td>NS</td>
</tr>
<tr>
<td>Men/Women</td>
<td>12/2</td>
<td>62/8</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>4</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>152±23</td>
<td>156±24</td>
<td>NS</td>
</tr>
<tr>
<td>Normal resting ECG</td>
<td>9</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise time</td>
<td>565±109</td>
<td>451±170</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>76±6</td>
<td>72±10</td>
<td>NS</td>
</tr>
</tbody>
</table>

(CAD, coronary artery disease; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; NS, not significant.)

TABLE II COMPARISON OF SYSTOLIC BLOOD PRESSURE (SBP) AND SBP RATIO BETWEEN CONTROL SUBJECTS AND PATIENTS WITH CAD

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
<th>Rest</th>
<th>Peak</th>
<th>Recovery at 3 min</th>
<th>SBP ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>152±23</td>
<td>212±34</td>
<td>152±28</td>
<td>0.72±0.05</td>
</tr>
<tr>
<td>CAD</td>
<td>156±24</td>
<td>190±33</td>
<td>162±28</td>
<td>0.86±0.13</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>NS</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

(true negative)/(true negative + false positive) × 100; positive predictive value = (true positive)/(true positive + false positive) × 100; negative predictive value = (true negative)/(true negative + false negative); and accuracy = (true positive + true negative)/(all subjects) × 100.

RESULTS

Clinical characteristics and responses to exercise

As shown in Table I, there were no significant differences between groups in age, gender, history of hypertension, SBP values at rest, normal resting ECG, or left ventricular ejection fraction. Exercise time was significantly shorter in the group with CAD than in controls. The exercise end-point was severe fatigue in all controls, but was typical chest pain in 52, and severe fatigue in 18 subjects in the CAD group. Exercise-induced ischemic ST depression was noted in 54 subjects in the CAD group. None of the subjects had a left ventricular ejection fraction below 50%.

SBP and SBP ratio

The differences between the SBP levels during exercise testing and the SBP ratios in the control and CAD groups are shown in Table II. At rest, there was no significant difference between the SBP's of the control and CAD groups. At peak exercise, the SBP in the CAD group was significantly higher than that in controls (p<0.01). However, after 3 min of recovery, the difference in SBP between the two groups disappeared. The SBP ratio in patients with CAD was significantly higher than that in the control group. Changes in SBP levels obtained from two representative subjects from each group are shown in Fig. 2.

PAWP response to exercise

Changes in PAWP during exercise are shown in Fig.3. In the control group, PAWP increased significantly, from 6.7±2.4 mmHg at rest to 11.5±4.0 mmHg at peak exercise (p<0.01). In the CAD group, the PAWP at rest (6.3±3.6 mmHg) did not differ from that in controls, but PAWP at peak exercise (20.2±8.9 mmHg) was significantly higher than that in controls (p<0.01). None
of the patients showed a large V wave in the PAWP (defined as exceeding the A wave pressure by >10 mmHg) during peak exercise.

Evaluation of PAWP by SBP ratio

There was no significant correlation between SBP ratio and PAWP at peak exercise in controls. However, the SBP ratio was significantly correlated with PAWP at peak exercise in the CAD group (r=0.67, p<0.01) (Fig. 4). The usefulness of an SBP ratio ≥0.85 to identify subjects with PAWP ≥20 mmHg at peak exercise is shown in Fig. 5. None of the subjects in the control group had an SBP ratio ≥0.85 and a peak exercise PAWP ≥20 mmHg. On the other hand, among the 70 CAD patients, the SBP ratio was ≥0.85 in 35 (50%) patients and PAWP was ≥20 mmHg in 35 (50%) patients. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of an SBP ratio of ≥0.85 for predicting a peak exercise PAWP ≥20 mmHg were each 80% in patients with CAD.

Effects of calcium channel blockers on the relationship between SBP ratio and PAWP

Changes in exercise responses after the administration of a calcium channel blocker are shown in Table III. The administration of a calcium channel blocker significantly decreased the SBP ratio from the baseline value (p<0.01). The number of patients with an SBP ratio ≥0.85 at peak exercise also decreased significantly (p<0.01). The SBP ratio was significantly correlated with PAWP at peak exercise (r=0.69, p<0.001) after the administration of a calcium channel blocker (Fig. 6). After drug administration, an SBP ratio of ≥0.85 showed a sensitivity of 80%, a specificity of 95%, a positive predictive value of 80%, a negative predictive value of 95%, and an accuracy of 95% for predicting a peak exercise PAWP ≥20 mmHg.

DISCUSSION

Evaluation of an increase in PAWP by SBP ratio

Because the severity of exercise-induced impairment of left ventricular filling varies in patients with CAD, it would be useful to have a noninvasive method for evaluating left ventricular filling during dynamic exercise testing. When we evaluated the SBP ratio based on exercise-induced changes in PAWP, we found that: 1) the SBP ratio was significantly higher in CAD patients than in controls; 2) the increment in PAWP was significantly greater in CAD patients than in controls; 3) PAWP was ≥20 mmHg at peak exercise in one half of the CAD patients, but in only a small number of controls; 4) the SBP ratio showed a significant positive correlation with PAWP at peak exercise in patients with CAD, but not in controls; and 5) the ability of an SBP ratio of ≥0.85 to identify CAD patients with a PAWP of ≥20 mmHg at peak exercise was good. Carroll et al. previously found that late diastolic filling was restricted in patients with exercise-

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Fig. 3. Changes in pulmonary artery wedge pressure (PAWP) during supine exercise. There was no significant difference in PAWP at rest between the control group and the patients with CAD. However, exercise produced a significant difference in PAWP between the two groups.

Fig. 4. Correlation between SBP ratio and pulmonary artery wedge pressure (PAWP) at peak exercise in the CAD group. The SBP ratio was significantly correlated with the PAWP.

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Fig.5. Usefulness of an SBP ratio $\geq 0.85$ to identify subjects with PAWP $\geq 20$ mmHg at peak exercise. Open circles: control subjects with PAWP $<20$ mmHg at peak exercise; open squares: CAD patients with PAWP $<20$ mmHg at peak exercise; closed squares: CAD patients with PAWP $\geq 20$ mmHg at peak exercise.

induced ischemia, which is similar to our finding in a previous study.13 These findings indicate that the SBP ratio is a useful index of severe, exercise-induced impairment of left ventricular filling in patients with CAD. Moreover, even after anti-anginal drugs were administered to improve acute myocardial ischemia, a significant correlation between the SBP ratio and the PAWP at peak exercise was maintained and the ability of the SBP ratio to diagnose patients with a markedly elevated PAWP remained good. These observations suggest that the SBP ratio is applicable in the clinical setting. The doses of nilvadipine (6 mg) and nisoldipine (10 mg) used appear to be appropriate for a single-dose study.9,14

An excessive elevation of LVEDP has been believed to be due to either reduced left ventricular diastolic distensibility with higher diastolic pressure at any left ventricular volume15–17 or to severe impairment of contractility.18–20 Recently, decreased myocardial distensibility has been shown to contribute significantly to the increase in left ventricular diastolic pressure during angina pectoris.21,22 Whatever mechanism may be involved, LVEDP is a suitable indicator of left ventricular filling; an excessive increment in this variable after exercise is believed to indicate left ventricular dysfunction as a result of a larger volume of ischemic myocardium in patients with CAD.7,23,24 None of the patients in the present study showed mitral regurgitation on left ventriculography or large V waves on the PAWP curve, defined as exceeding the A wave pressure by $>10$ mmHg, at rest or during exercise. According to Haskell and French,9

<table>
<thead>
<tr>
<th>TABLE III</th>
<th>EXERCISE RESPONSES BEFORE AND AFTER THE ADMINISTRATION OF A CALCIUM CHANNEL BLOCKER IN 25 PATIENTS WITH CORONARY ARTERY DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control test</td>
<td>Ca channel blocker</td>
</tr>
<tr>
<td>Abnormal SBP response</td>
<td>14</td>
</tr>
<tr>
<td>SBP ratio</td>
<td>0.89±0.13</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>157±23</td>
</tr>
<tr>
<td>Peak</td>
<td>194±36</td>
</tr>
<tr>
<td>Recovery at 3 min</td>
<td>170±27</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>6.4±3.1</td>
</tr>
<tr>
<td>Peak</td>
<td>23.2±10.0</td>
</tr>
<tr>
<td>Ischemic ST depression (mV)</td>
<td>0.20±0.11</td>
</tr>
<tr>
<td>Exercise-induced angina</td>
<td>25</td>
</tr>
</tbody>
</table>

PAWP, pulmonary artery wedge pressure.
PAWP can be used to estimate left ventricular end-diastolic pressure despite the presence of mitral regurgitation if the V wave is small. Therefore, the left ventricular end-diastolic pressure measurements during supine leg exercise testing in our study appear to be accurate and reliable.

We previously reported that an abnormal postexercise SBP response during supine exercise testing in patients with CAD is related to the extent of left ventricular functional impairment associated with the severe myocardial ischemia induced by exercise, and to the peripheral vasomotor tone during the early phase of recovery. We also compared the blood pressure measurements obtained by cuff sphygmomanometer during supine exercise testing with such data obtained by the invasive method, and confirmed the accuracy of the cuff method. Moreover, the SBP ratio has a good reproducibility. These findings suggest that an abnormal postexercise SBP response is a useful marker of the presence of severe impairment of left ventricular filling induced by exercise in the clinical setting.

LIMITATIONS OF THIS STUDY

There may be some limitations to our study. First, although supine exercise was performed, the upright treadmill exercise test may be employed more frequently in countries such as Japan and the USA. Therefore, further investigation using treadmill exercise is indicated. Second, we cannot exclude the possibility that the anxiety of the patients due to exercise testing using an invasive technique may have influenced the SBP.

Clinical Implications

In the present study, we found that the SBP ratio served as a useful index of severe impairment of left ventricular filling dynamics during supine leg exercise testing. The SBP ratio may be useful in evaluating the severity of impaired left ventricular filling during exercise in patients with CAD.

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