Abnormal Blood Pressure Response and Marked Ischemic ST-segment Depression as Predictors of Severe Coronary Artery Disease

MIGUEL E. SANMARCO, M.D., STEVEN PONTIUS, M.D., AND RONALD H. SELVESTER, M.D.

SUMMARY The usefulness of an abnormal blood pressure response and a marked ischemic ST-segment depression during exercise testing as predictors of severe coronary artery disease was assessed in 378 consecutive patients who had a maximal symptom-limited exercise test before coronary arteriography. An abnormal blood pressure response occurred in 90 patients. The sensitivity of this response for three-vessel or left main disease was 38.6%, the specificity 87.4% and the predictive value 70%. A marked ischemic ST-segment abnormality (MIST) appeared in 85 patients. The sensitivity of MIST for three-vessel or left main disease was 38.6%, the specificity 89.8% and the predictive value 74.1%. One hundred thirty-eight patients had either an abnormal blood pressure response or a marked ST-segment change. The sensitivity of either response for three-vessel or left main disease was 56.4%, the specificity 78.6%, and the predictive value 66.7%. Exercise duration and ejection fraction were not significantly different in patients with normal or abnormal blood pressure. We conclude that abnormal blood pressure and marked ischemic ST-segment depression during exercise testing are helpful in identifying a subset of patients with advanced coronary artery disease. The physiologic mechanism for these responses is probably exercise-induced ischemia.

EXERCISE TESTING is probably the most widely used method for identifying patients with probable coronary artery disease. Numerous parameters of stress testing may predict not only the presence of coronary artery disease, but also its functional significance and risk for the patient. The predictive value of ST-segment changes and its dependency on the type and degree of ST-segment abnormality have been reported. In addition to ST depression, the presence of exercise-induced ventricular arrhythmias, a change in the amplitude of the R wave and a fall in blood pressure below resting levels appear to be reliable predictors of severe coronary disease.

The significance of decreasing systolic blood pressure during exercise has been the subject of three recent reports. Thomson and Kelemen and more recently, Morris and co-workers have suggested that exercise-induced hypotension is highly specific for multiple-vessel coronary disease. However, Levites et

References
EXERCISE PREDICTORS OF SEVERE CAD/Sanmarco et al. 573

al. reported that exertional hypotension is not a reliable indicator of severe disease and is frequently seen in the absence of coronary artery disease, particularly in women. Therefore, it is difficult to draw conclusions regarding the usefulness of blood pressure abnormalities during exercise testing.

This retrospective study was undertaken to assess the significance of exertional hypotension and marked ischemic ST-segment depression during symptom-limited maximal stress testing and their relationship to the severity of coronary artery disease. We felt that these two parameters, alone or together, might be valuable in identifying a high-risk subgroup of the coronary disease population.

Materials and Methods

Patients

The study group included 378 consecutive patients who had cardiac catheterization and selective coronary arteriography within 1 month of completing a maximal treadmill exercise test. They were referred to USC-Rancho Los Amigos Hospital from 1973–1977 for diagnostic evaluation of known ischemic heart disease or presumed angina pectoris. Two hundred forty patients had had a previous myocardial infarction. Patients with clinical diagnoses of valvular heart disease, primary cardiomyopathy or bundle branch block and patients who had undergone cardiac surgery were excluded. There were 321 males and 57 females, ranging in age from 30–72 years (average 52 ± 9 years).

Exercise Testing

Each patient was exercised using the Bruce multistage treadmill protocol. Before the test, blood pressure and heart rate were taken with the patient supine, sitting and upright. Blood pressure and heart rate were then recorded at 1-minute intervals during exercise, immediately after exercise and every minute thereafter for 5–10 minutes. The ECG was continuously monitored and a recording was obtained at each 1-minute interval using four bipolar leads: X, Y, modified Lewis and V5. Patients exercised to a symptom-limited end point, such as severe angina pectoris, fatigue or shortness of breath. These end-point determinations were carefully assessed by the physical therapist and monitoring physician who performed the test.

Coronary Angiography

Right- and left-heart catheterizations were performed by the percutaneous femoral approach. Left ventricular cineangiography and selective coronary arteriography were recorded on 35-mm film at 60 frames/sec using a cesium iodide image intensifier system. Stenosis of coronary arteries was estimated as percent luminal narrowing; greater than 70% stenosis was considered hemodynamically significant. Left ventricular volumes and ejection fraction were calculated from the right anterior oblique ventriculogram using the area-length method of Dodge et al. 10

Definitions

An abnormal blood pressure response to exercise was defined as: 1) a failure of systolic blood pressure to rise at least 10 mm Hg after the first minute of exercise (flat blood pressure response) or 2) initial rise in blood pressure but subsequent fall by more than 20 mm Hg during exercise.

A marked ST-segment change was defined as a depression of 0.3 mV or more taken 80 msec after the J point with the ST segment flat or downsloping in any monitored lead.

The following formulas were used to calculate statistical definitions:

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \times 100
\]

\[
\text{Specificity} = \frac{TN}{TN + FP} \times 100
\]

\[
\text{Predictive value (+)} = \frac{TP}{TP + FP} \times 100
\]

\[
\text{Predictive value (−)} = \frac{TN}{TN + FN} \times 100
\]

\[
\text{Accuracy} = \frac{TP + TN}{All \ subjects} \times 100
\]

where TP = true positive, FN = false negative, TN = true negative and FP = false positive. Statistical significance was determined using the two-sample t test and chi-square analysis in two-by-two tables.

Results

Abnormal Blood Pressure

Of 378 patients reviewed, 90 (24%) had abnormal blood pressure responses during exercise: 65 had a blood pressure drop and 25 had a flat blood pressure response. The average drop in blood pressure was 33.7 mm Hg (range 20–70 mm Hg); in eight patients the systolic blood pressure fell below resting levels. The average time on the treadmill at which the blood pressure dropped was 5.6 ± 2.2 minutes. There were 80 males and 10 females and the average age was 53 ± 10 years (mean ± sd).

Table 1 shows the relationship of abnormal blood pressure response to severity of coronary artery disease. Of the 90 patients, 63 had three-vessel disease or left main stenosis (predictive value 70%). The sensitivity of an abnormal blood pressure response for disease of this severity was 39% and the specificity 87%. Only 4.6% of patients with normal coronary
TABLE 1. Relationship of Abnormal Blood Pressure and Marked Ischemic ST Changes to Severity of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Number of vessels with &gt; 70% stenosis</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>LM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>65</td>
<td>68</td>
<td>82</td>
<td>134</td>
<td>29</td>
<td>378</td>
</tr>
<tr>
<td>Abnormal BP only</td>
<td>3</td>
<td>7</td>
<td>14</td>
<td>21</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td>MIST only</td>
<td>1</td>
<td>4</td>
<td>14</td>
<td>22</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td>Abnormal BP and MIST</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>12</td>
<td>30</td>
<td>67</td>
<td>25</td>
<td>138</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; LM = left main stenosis; MIST = marked ischemic ST depression.

arteries, 11.7% with one-vessel disease and 19.5% with two-vessel disease had abnormal blood pressure responses (fig. 1).

The relationship between abnormal blood pressure response and resting ventricular function is shown in table 2. Although the ejection fraction tended to be lower in patients with an abnormal blood pressure response, the difference was not statistically significant. As defined in the Methods section, abnormal blood pressure included patients whose blood pressure did not rise or whose blood pressure fell. There was no significant difference in ejection fraction between these two groups (fig. 2).

The duration of exercise in patients with and without abnormal blood pressure response (grouped according to the number of vessels involved) is shown in table 3. Average exercise duration was appreciably higher in patients without significant coronary obstruction or one-vessel disease; the lowest duration was found in patients with left main stenosis. Within each subset, however, there was no significant difference in exercise duration between the normal and abnormal blood pressure groups.

Thirty-seven patients showed their blood pressure fall before stage III of the Bruce protocol; 27 of these had three-vessel or left main disease (predictive value 73%). The sensitivity and specificity of this finding were 16.7 and 95.4%, respectively. Forty-five patients experienced angina pectoris either before or during the blood pressure drop; 35 of them had three-vessel or left main disease (predictive value 77.8%). The sensitivity of this combination of findings was 21.5% and the specificity was 95.4%.

Of the 90 patients with an abnormal blood pressure response, 78 (87%) had ST depression of 0.1 mV or more; in 37 patients (41%) the ST depression was ≥0.3 mV. Twelve patients (13%) had no significant ST depression; three of them had normal coronary arteries, two had one-vessel, two had two-vessel and five had three-vessel disease.

Influence of Antihypertensive Medications

Seventy-seven patients (20% of the total population) were receiving propranolol or other antihypertensive medications (most often α-methyldopa) at the time of exercise testing; 19 of these (24.7%) had an abnormal blood pressure response. Of the 301 patients not taking blood pressure medications, 71 (23.6%) had an abnormal response. The prevalence, therefore, of exercise-induced blood pressure abnormalities was almost identical in both groups (chi square 0.04, p = NS). Furthermore, the exclusion of these 77 patients from the statistical analysis did not significantly change the sensitivity, specificity or predictive value of exercise-induced blood pressure abnormalities.

Marked ST-segment Depression

Of 378 patients studied, 85 (22%) had marked ischemic ST-segment depression of 0.3 mV or more; 37 of these also had an abnormal blood pressure response. There were 81 men and four women. The average age was 52 ± 8 years (mean ± SD).

The relationship of marked ST-segment abnormalities and severity of coronary artery disease is shown in table 1. Of the 85 patients with marked ST abnormalities, 63 had three-vessel or left main disease (predictive value 74.1%). A marked ischemic response...
of this degree, however, was not common in patients with three-vessel or left main disease; the sensitivity was 38.6% and the specificity was 89.8%. Marked ischemic ST depression was noted in only 1.5% of patients with normal coronary arteries, 7% with one-vessel disease and 19% with two-vessel disease (fig. 1).

Resting ejection fraction and duration of exercise were not significantly different in patients with or without markedly ischemic ST changes (tables 4 and 5).

One hundred thirty-eight of 378 patients had either an abnormal blood pressure or marked ST-segment change; 92 of these patients had three-vessel disease or left main stenosis (predictive value 66.7%). The sensitivity of either response for three-vessel or left main disease was 56.4% and the specificity 78.6%. Of the 215 patients with lesser degrees of coronary involvement, only 46 (21%) manifested either abnormality; 30 had two-vessel disease, 12 had one-vessel disease and four had normal coronary arteries. Table 6 summarizes the usefulness of an abnormal blood pressure response or a marked ST-segment change in predict-
ing three-vessel or left main disease. The predictive value of the presence of either abnormality was 66.7%; similarly, their absence predicted lesser degrees of coronary artery involvement in 70.4% of patients.

Reproducibility

The reproducibility of abnormal blood pressure and marked ischemic ST depression was examined by performing stress tests within 6 months after the first study. All patients with a significant event that might affect the results of stress testing, such as myocardial infarction or saphenous vein coronary bypass surgery, were excluded. Forty-one pairs of tests were available for analysis. Of 23 patients who had an abnormal blood pressure response on the initial test, 16 (69%) had similar abnormalities on repeat testing. On repeat testing, six patients had a blood pressure response that was clearly not normal but did not meet our criteria. One had a normal blood pressure response. Of the 27 patients with ST abnormalities, 24 (89%) had reproducible ST changes of 0.3 mV or more, two had 0.2 mV and one patient had 0.1 mV on subsequent stress tests.

Discussion

This study indicates that an abnormal blood pressure response or a marked ST-segment abnormality during exercise testing are reliable predictors of severe coronary artery disease. Other studies have shown that marked ST depression is generally a sign of advanced disease.11-14 Our data support these observations and reveal another significant feature: Blood pressure abnormalities are also highly specific in predicting severe disease and therefore should be considered a critical parameter in the evaluation of stress testing. In fact, 70% of patients with an abnormal blood pressure response had three-vessel disease or left main stenosis. The sensitivity of an abnormal blood pressure response for disease of this severity (38.6%) was identical to that of a marked ST-segment change; the use of either parameter as the criterion for abnormality increased the sensitivity to 56.4%. Less stringent criteria would obviously include a much higher percentage of patients with such severe disease. The increased sensitivity would be obtained at the cost of decreased specificity, which is 87% for an abnormal blood pressure and 90% for a marked ischemic blood pressure.

### Table 4. Resting Ejection Fraction in Patients with and Without Marked Ischemic ST Abnormality

<table>
<thead>
<tr>
<th>Number of vessels with ≥70% stenosis</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.3 mV ST depression</td>
<td>0.66 ± 0.07</td>
<td>0.55 ± 0.13</td>
<td>0.54 ± 0.12</td>
<td>0.50 ± 0.15</td>
<td>0.49 ± 0.19</td>
</tr>
<tr>
<td>≥0.3 mV ST depression</td>
<td>0.55</td>
<td>0.62 ± 9.10</td>
<td>0.55 ± 0.12</td>
<td>0.53 ± 0.13</td>
<td>0.56 ± 0.14</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are mean ± sd.*

Abbreviation: LM = left main stenosis.

### Table 5. Exercise Duration (Minutes) in Patients with and Without Marked Ischemic ST Abnormality

<table>
<thead>
<tr>
<th>Number of vessels with ≥70% stenosis</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.3 mV ST depression</td>
<td>6.5 ± 2.2</td>
<td>6.7 ± 2.1</td>
<td>6.3 ± 2.1</td>
<td>5.8 ± 2.3</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>≥0.3 mV ST depression</td>
<td>9.0</td>
<td>6.4 ± 1.0</td>
<td>7.1 ± 2.1</td>
<td>6.3 ± 2.2</td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are mean ± sd.*

Abbreviation: LM = left main stenosis.

### Table 6. Sensitivity, Specificity and Predictive Value of Abnormal Blood Pressure and Marked Ischemic ST Depression for Three-vessel and Left Main Disease

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Abnormal BP</td>
<td>38.6</td>
<td>87.4</td>
<td>70.0</td>
</tr>
<tr>
<td>MIST</td>
<td>38.6</td>
<td>89.8</td>
<td>74.1</td>
</tr>
<tr>
<td>Abnormal BP or MIST</td>
<td>56.4</td>
<td>78.6</td>
<td>66.7</td>
</tr>
<tr>
<td>Abnormal BP and MIST</td>
<td>20.8</td>
<td>98.6</td>
<td>91.8</td>
</tr>
<tr>
<td>Abnormal BP and angina</td>
<td>21.5</td>
<td>95.4</td>
<td>77.8</td>
</tr>
<tr>
<td>BP drop below resting</td>
<td>4.3</td>
<td>99.5</td>
<td>87.5</td>
</tr>
<tr>
<td>BP drop before stage III</td>
<td>16.7</td>
<td>95.4</td>
<td>73.0</td>
</tr>
</tbody>
</table>

*Abbreviations: BP = blood pressure; MIST = marked ischemic ST depression.*
response. The population defined by these abnormalities is unique and at a considerably higher risk than one with less severe coronary artery disease. Significant obstruction of the left main coronary artery exemplifies the type of coronary disease in which early recognition is sought. Twenty-nine patients in our study group (7.7% of the patient population) had left main disease; 28 had additional significant obstruction in all other major coronary arteries. All patients had a positive treadmill test; 62% were identified by an abnormal blood pressure response and 59% by marked ischemic ST depression. Twenty-five of the 29 patients (86%) had one or the other of these responses. Such discrimination should greatly influence the clinician in evaluating the patient for catheterization and alert the angiographer to take extraordinary care. Significant ST depression in left main disease has been previously reported.11, 12

Exercise blood pressure abnormalities appear to carry a poor prognosis because of their frequent association with severe coronary disease. In a study by Irving and co-workers18 the incidence of sudden cardiac death was 4.6 times greater in patients with exercise systolic blood pressure less than 140 mm Hg than those with higher pressures. Furthermore, maximal systolic blood pressure was a better predictor of mortality than ST-segment depression or arrhythmias.

The studies of Morris et al.7 and Thomson and Kelemen8 show that after successful myocardial revascularization abnormal blood pressure responses usually return to normal. This suggests that exercise-induced hypotension is related to ischemic left ventricular dysfunction. The fact that patients with multiple-vessel disease, especially left main, primarily manifest this abnormal response strongly supports this hypothesis, as does the fact that 41% of patients with abnormal blood pressure had greater than 0.3 mV ST depression. Our results are consistent with those of Morris et al.7 in that systolic blood pressure does not have to drop below resting levels to have predictive significance. In our patients a drop in blood pressure below resting levels showed a higher specificity (99%) for three-vessel or left main disease but a very poor sensitivity (4%). Similarly only 45 patients had angina simultaneously with the onset of hypotension. Using both criteria increased the specificity to 95% but decreased the sensitivity to 21%.

Our findings do not confirm the results of Levites et al.8 In our patient population, which was predominantly male, exertional hypotension was highly specific for severe coronary disease. Furthermore, hypotension was not very frequent in females. Among the 57 women in our study 10 had an abnormal blood pressure response; five of them had three-vessel or left main disease, four had two-vessel and one had one-vessel disease. We did not observe exertional hypotension in any of the 23 women with normal coronary arteriograms.

The significance of a decline in blood pressure during exercise must be interpreted considering other clinical factors that may cause hypotension:

1) Normal subjects may experience hypotension at maximal exhaustive exercise, usually after 12–15 minutes on the Bruce protocol and at near-maximal heart rates. The average duration of exercise in patients with an abnormal blood pressure was 5.7 ± 2.2 minutes; it is doubtful that a fall in blood pressure was caused by this physiologic mechanism. Furthermore, the exercise duration did not differ from the group with normal blood pressure response.

2) Apprehensive patients with labile blood pressure elevations before or in the initial stages of the exercise test may show a drop in blood pressure as the test progresses and the patients' anxiety abates. This mechanism may have caused the inappropriate blood pressure response in the 11 patients with mild coronary disease or normal coronary arteriograms.

3) A vasovagal discharge may result in hypotension, which is generally associated with bradycardia. This is unlikely to have been the cause in our study group because all patients had progressive increases in heart rate while their blood pressure was decreasing.

4) Abnormal blood pressure responses should be interpreted with caution in patients taking propranolol or other antihypertensive medications. However, we found no increased prevalence of blood pressure abnormalities in such patients. Furthermore, their inclusion or exclusion from the study group did not alter the results of the statistical analysis.

5) Patients with a fixed stroke volume, such as patients with aortic or mitral stenosis or congestive cardiomyopathy, may have little increase in systolic blood pressure with exercise. Such patients were not included in our study.

6) The accuracy of clinical sphygmomanometry is questionable. In our laboratory blood pressure is obtained during each minute of exercise by highly trained personnel with extensive experience in exercise testing. In such a setting it is unlikely that blood pressure variations greater than 20 mm Hg are caused by measurement error. Blood pressure measurements in stage 4 or 5 of the Bruce protocol may be more difficult to obtain with accuracy, as the subject is usually running. This was not a problem because all but two of the patients in this study had a blood pressure drop before stage 4 of the Bruce protocol. Furthermore, when patients with an abnormal blood pressure response had repeat exercise testing, a high percentage again met this criterion.

Finally, the predictive value of a test is greatly influenced by the prevalence of disease in the tested population. Most of our patients were middle-aged men with known coronary artery disease. The prevalence of three-vessel or left main disease was 43%; the predictive value of the presence or absence of an abnormal blood pressure or a marked ischemic response was 67% and 70%, respectively. These results would be different if the population to be tested were young, asymptomatic subjects without risk factors. Table 7 illustrates the theoretical predictive values of a test in relation to disease prevalence using the sensitivity (56.4%) and specificity (78.6%) of an abnormal blood pressure or a marked ischemic ST response.

The overall prevalence and distribution of coronary
artery disease in our study population is probably similar to that of other referral centers. In this setting, exercise-induced blood pressure abnormalities or marked ischemic ST depression are highly predictive of advanced coronary disease. Noninvasive identification of a cohort of potentially high-risk patients is of considerable value because these patients could benefit the most from more intensive diagnostic and therapeutic interventions.

Acknowledgment

We acknowledge the technical assistance of Will Findlater, R.C.P.T. for his help in the statistical analysis, Randolph Ice, R.C.P.T., Raymond Blessey, R.C.P.T. and Linda Carroll, R.C.P.T. for performing the exercise studies, and the Professional Staff Association for its assistance with manuscript preparation.

References


<table>
<thead>
<tr>
<th>Disease prevalence (%)</th>
<th>Predictive value of a positive test (%)</th>
<th>Predictive value of a negative test (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>12.5</td>
<td>97.2</td>
<td>77.5</td>
</tr>
<tr>
<td>10</td>
<td>22.7</td>
<td>94.1</td>
<td>76.3</td>
</tr>
<tr>
<td>20</td>
<td>40.0</td>
<td>87.8</td>
<td>74.2</td>
</tr>
<tr>
<td>30</td>
<td>53.0</td>
<td>80.9</td>
<td>72</td>
</tr>
<tr>
<td>40</td>
<td>63.7</td>
<td>73.0</td>
<td>69.7</td>
</tr>
<tr>
<td>50</td>
<td>72.5</td>
<td>64.3</td>
<td>67.5</td>
</tr>
</tbody>
</table>
*Based on sensitivity = 56.4% and specificity = 78.6%.
Abnormal blood pressure response and marked ischemic ST-segment depression as predictors of severe coronary artery disease.
M E Sanmarco, S Pontius and R H Selvester

Circulation. 1980;61:572-578
doi: 10.1161/01.CIR.61.3.572

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/61/3/572

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/