A Multivariate Approach for Interpreting Treadmill Exercise Tests in Coronary Artery Disease

JULIAN L. BERMAN, M.D., JOSHUA WYNNE, M.D., AND PETER F. COHN, M.D.

SUMMARY To determine the value of a multivariate approach for the analysis of the treadmill exercise tolerance test (ETT), 237 patients referred for evaluation of chest pain who underwent a standard Bruce protocol ETT and coronary arteriography were studied. Predictive value of a positive ETT was 0.78 (43/55) using 1.0–1.9 mm ST segment depression criterion, 0.97 (59/61) using ≥ 2.0 mm ST segment depression. When the 1.0–1.9 mm ST criterion was combined with peak systolic blood pressure-heart rate product (double product) ≤ 23,000, exercise duration less than 6 minutes, and ST depression for greater than 3 minutes into recovery, predictive value improved to 0.89 in 18 patients with any two of the above. Predictive value for multivessel disease was also improved using non-ST criteria. Predictive value of a negative ETT for absence of coronary artery disease was 0.60 (29/48), and was 0.86 (12/14) if double product was ≥ 30,000. Presence of chest pain during ETT did not improve predictive value of any type of test. Digitalis ingestion in 33 patients was not associated with decreased predictive value of a positive test. These data suggest that the predictive value of both positive and negative ETT in a symptomatic population can be improved with a multivariate approach.

THE DEFINITIVE DIAGNOSTIC TEST for evaluation of chest pain syndromes is the coronary arteriogram. Because this is an in-hospital procedure with a small but definite morbidity and mortality, many investigators have attempted to identify factors in the history and noninvasive evaluation of patients with chest pain that would identify those patients with a high likelihood of having coronary artery disease.1 The exercise test is the most widely used of the available noninvasive procedures for identifying patients with probable coronary artery disease. It is safe, not difficult to perform, and relatively inexpensive. Evaluation of ECG changes, specifically ST segment depression during or after exercise, has been the traditional criterion for evaluating the exercise tolerance test. However, problems with false positive and negative tests, especially in patients with atypical or no angina pectoris,4–6 have stimulated efforts to examine other aspects of the exercise response besides the presence or absence of exercise-induced ST segment depression in order to increase the diagnostic utility of the test.7–10 In this study, we have attempted to supplement the traditional ST segment criterion by analyzing the importance of the following additional variables in the interpretation of the exercise tolerance test: 1) anginal chest pain induced by exercise; 2) heart rate-blood pressure product (double product) at peak exercise; 3) persistence of ST segment depression during recovery from exercise; and 4) depth of ST depression.

Materials and Methods

The records of all patients undergoing cardiac catheterization at the Peter Bent Brigham Hospital, Boston, Massachusetts, from January 1, 1975 to July 1, 1977 were retrospectively reviewed. Patients undergoing catheterization for chest pain syndromes who had maximal, symptom-limited Bruce protocol11 exercise tolerance tests performed at the Peter Bent Brigham Hospital or its outpatient facility were selected for a further evaluation. Electrocardiograms with bundle branch block in the resting tracing were not included in this series. The exercise protocol involved recording the supine, upright and post-hyperventilation (60 sec) 12-lead ECG at rest. All ECGs at rest and during and after exercise were taken using the Mason-Likar modification of the standard ECG lead placements.12 No patients had orthostatic or post-hyperventilation ECG changes. ECGs were then taken, along with cuff blood pressures, every 3 minutes during exercise. Supine ECGs and cuff blood pressures were taken at 0, 1, 3, 5, and 8 minutes after exercise, or until ECG returned to baseline. A positive test was defined as one showing 1 mm of ST segment elevation or depression (of any morphology and in any lead except aVR) 80 msec after the end of the QRS complex any time after exercise was begun. If there was resting ST segment depression or elevation, a 1 mm increase was required for a positive test. A negative test was one without this degree of ST segment change and in which the patient achieved 85% of the maximum predicted heart rate for his age. All other tests were considered nondiagnostic.

The peak blood pressure was usually measured just before termination of exercise, before the patient returned to the supine position. Presence or absence of exercise-induced angina (defined as either typical anginal distress or the patient’s usual anginal equivalent) was recorded, as were peak blood pressure, heart rate and depth and duration of ST segment change during recovery. No systematic attempt was made to measure ST segment changes during exercise,
Two or All three of Two or All three of Two or All three of Two or All three of Two or All three of Two or All three of All tests (n = 116)  
Peak double product* (n = 74)  
Duration of exercise ≤ 6 min. (Stage I-II) (n = 52)  
ST\[^1\] persisting ≥ 3 minutes into recovery (n = 78)  
Peak double product* and duration of exercise ≤ 6 min (Stage I-II) (n = 41)  
Peak double product* and ST\[^1\] persisting ≥ 3 minutes into recovery (n = 51)  
Duration of exercise ≤ 6 min (Stage I-II) and ST\[^1\] persisting ≥ 3 minutes into recovery (n = 31)  
Two of above criteria (n = 61)  
All three of above criteria (n = 28)  
One or more of above criteria (n = 102)  
Two or three of above criteria (n = 23)  

Predictive Value for CAD  
All ST\[^1\] < 2mm ST\[^1\] ≥ 2mm All ST\[^1\] < 2mm ST\[^1\] ≥ 2mm  
0.88 (102)  
0.78 (43)  
0.97 (59)  
0.71 (83)  
0.56 (31)  
0.85 (52)  
0.75 (63)  
0.71 (20)  
0.93 (43)  
0.84 (43)  
0.71 (56)  
0.48 (13)  
0.84 (43)  
0.93 (27)  
0.88 (14)  
0.64 (9)  
1.0 (27)  
0.90 (46)  
0.67 (10)  
1.0 (36)  
0.90 (28)  
0.62 (5)  
1.0 (23)  
0.97 (59)  
0.89 (16)  
1.0 (43)  
0.90 (55)  
0.78 (14)  
0.95 (41)  
0.88 (24)  
0.33 (2)  
1.0 (22)  
0.82 (84)  
0.66 (29)  
0.95 (55)  
0.74 (54)  
0.50 (14)  
0.89 (40)  

Predictive Value for MVD  
All ST\[^1\] < 2mm ST\[^1\] ≥ 2mm All ST\[^1\] < 2mm ST\[^1\] ≥ 2mm  
0.89 (116)  
0.55 (61)  
0.81 (55)  
1.0 (61)  

*The eight patients with ST segment elevation were also considered to have markedly positive tests, and are included in this subgroup from this point on.

due to the frequency of baseline wandering and muscle artifact.

Coronary arteriograms were interpreted by three staff cardiologists and cardiovascular radiologists, and the consensus of their findings as recorded on the final catheterization report was used to determine the number of obstructed coronary arteries. Seventy percent luminal diameter narrowing was considered obstructive. Involvement of four possible vessels was considered: 1) the main left coronary artery, considered equivalent to two vessels if obstructed; 2) the left anterior descending and/or any of its diagonals or ramus medianus branch; 3) the left circumflex and/or any of its obtuse marginal branches; and 4) the right coronary, posterior descending, and/or any of its acute marginal branches. Coronary arteriograms were usually performed within 48 hours, but never more than several weeks, of the exercise test.

The presence and number of obstructed coronary arteries was compared with the exercise data. The predictive value of a positive exercise tolerance test is defined as the percentage of the positive tests associated with at least one significantly obstructed coronary artery (true positive/all positive), and that of a negative exercise tolerance test is defined as the percentage without at least one significantly obstructed artery (true negative/all negative). The predictive value for multivessel coronary artery disease is defined in a similar manner, with the requirement of at least two significantly obstructed coronary arteries for positive tests and no or one significantly obstructed artery for negative tests.

**Results**

Sixty-eight patients (31 men, 37 women) had no evidence of obstructive coronary artery disease, 45 (32 men, 13 women) had one vessel obstruction, 59 (51 men, eight women) had two vessel obstruction, 65 (57 men, eight women) had three vessel obstruction, and seven (five men, two women) had left main coronary artery obstruction. Of a total of 204 exercise tolerance tests in patients not on digitalis glycosides, 116 (89 men, 27 women) were positive, 48 (31 men, 17 women) were negative, and 40 (25 men, 15 women) were nondiagnostic. Unless otherwise stated, none of the analyses included patients taking digitalis.

**Predictive Value of Positive Exercise Tolerance Tests for Coronary Artery Disease and Multivessel Coronary Disease (Table 1)**

The predictive value of a positive exercise tolerance test for coronary disease was 0.88 (102/116) overall, 0.78 (43/55) if ST depression was less than 2 mm (less positive exercise tolerance test), 0.97 (59/61) if it was greater than or equal to 2 mm (markedly positive exercise tolerance test). For multivessel disease, the

TABLE 1. Predictive Value of Positive Exercise Tolerance Tests for Coronary Artery Disease and Multivessel Disease

<table>
<thead>
<tr>
<th>Predictive Value for CAD</th>
<th>Predictive Value for MVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ST[^1] &lt; 2mm</td>
<td>ST[^1] ≥ 2mm</td>
</tr>
<tr>
<td>0.88 (102)</td>
<td>0.78 (43)</td>
</tr>
</tbody>
</table>

*The eight patients with ST segment elevation were also considered to have markedly positive tests, and are included in this subgroup from this point on.*

Abbreviations: ETT = exercise tolerance test; CAD = coronary artery disease; MVD = multivessel disease.
Influence of Exercise Induced Anginal Chest Pain on Predictive Value of Positive Exercise Tolerance Test

<table>
<thead>
<tr>
<th></th>
<th>Predictive value for CAD</th>
<th>Predictive value for MVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST $\downarrow &lt; 2$mm</td>
<td>ST $\downarrow \geq 2$mm</td>
</tr>
<tr>
<td>All tests</td>
<td>Pain</td>
<td>0.8 (22/27)</td>
</tr>
<tr>
<td></td>
<td>No pain</td>
<td>0.64 (18/28)</td>
</tr>
<tr>
<td>Peak double product</td>
<td>Pain</td>
<td>0.75 (12/16)</td>
</tr>
<tr>
<td>$\geq 23,000$</td>
<td>No pain</td>
<td>0.75 (9/12)</td>
</tr>
<tr>
<td>Duration of exercise</td>
<td>Pain</td>
<td>0.67 (6/9)</td>
</tr>
<tr>
<td>$\leq 6$min. (Stage I-II)</td>
<td>No pain</td>
<td>0.70 (7/10)</td>
</tr>
<tr>
<td>ST$\downarrow$</td>
<td>Pain</td>
<td>0.77 (10/13)</td>
</tr>
<tr>
<td>persisting $\geq 3$</td>
<td>No pain</td>
<td>0.92 (11/12)</td>
</tr>
<tr>
<td>minutes into recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more of above</td>
<td>Pain</td>
<td>0.86 (22/26)</td>
</tr>
<tr>
<td></td>
<td>No pain</td>
<td>0.78 (14/18)</td>
</tr>
<tr>
<td>Two or three of above</td>
<td>Pain</td>
<td>0.71 (10/14)</td>
</tr>
<tr>
<td></td>
<td>No pain</td>
<td>0.93 (13/14)</td>
</tr>
<tr>
<td>All three of above</td>
<td>Pain</td>
<td>0.50 (2/4)</td>
</tr>
<tr>
<td></td>
<td>No pain</td>
<td>1.0 (2/2)</td>
</tr>
</tbody>
</table>

Abbreviations: ETT = exercise tolerance test; CAD = coronary artery disease; MVD = multivessel disease.

Influences of Chest Pain on Positive Exercise Tolerance Tests (Table 2)

Exercise-induced angina did not appear to be useful in increasing the overall predictive value of less positive exercise tolerance tests, nor of markedly positive exercise tolerance tests. The combination of chest pain with the exercise parameters (double product, exercise duration, or the persistence of ST segment change) did not enhance the improved predictive value seen with combinations of these parameters alone, either for coronary artery disease or for multivessel coronary artery disease.

Hypotension with Exercise

Eleven patients had a decrease of blood pressure at peak exercise (mean 10 mm Hg, range 5–22 mm Hg). None of these patients exercised for more than 6 minutes. Ten had coronary artery disease, seven had electrocardiographically positive tests, and nine had two vessel, three vessel or left main coronary artery obstruction.

Predictive Value of Negative Exercise Tolerance Test for Absence of Coronary and Multivessel Disease

Tables 3 and 4 summarize the predictive value of negative exercise tolerance tests for the absence of significant coronary artery disease and for the absence of multivessel coronary artery disease, respectively.
Predictive value for the absence of overall coronary artery disease increased from its overall value of 0.60 (29/48) to 0.86 (12/14) if a double product of greater than 30,000 was achieved, and for multivessel coronary artery disease from 0.81 (39/48) to 1.0 (14/14). No notable increase in predictive value was associated with increased exercise duration, and increased exercise duration did not appear to enhance the improved predictive power of exercise tolerance tests with higher double product (tables 5 and 6).

Anginal chest pain occurred in only seven negative exercise tolerance tests — too few to assess its value in diagnosis. The increased predictive value with greater double product was essentially unchanged in the group without angina during exercise, as was the lack of additional predictive influence of the exercise duration.

Nondiagnostic Exercise Tolerance Tests

In the patients with inadequate heart rate response, predictive value for coronary artery disease was 0.52 (21/40). No combination of exercise parameters and chest pain improved this lack of separation of normal patients from those with significant coronary artery disease.

Correlation of Exercise Parameters with the Extent of Coronary Disease

Table 7 shows the mean ± SEM for double product and exercise duration for all patients whose exercise was not limited by extracardiac problems. Patients with coronary disease and multivessel disease who had positive exercise tolerance tests had significantly lower double products at peak exercise than those with no coronary disease ($P < 0.02$, unpaired $t$ test). Patients with multivessel disease and positive exercise tolerance tests also had significantly lower peak double product than those with one vessel disease ($P < 0.01$, unpaired $t$ test), who did not differ significantly in this parameter from normals.

For exercise duration, the identical trends were noted, but failed to reach statistical significance ($0.1 > P > 0.05$, unpaired $t$ test for all similar comparisons).

Male vs Female Patients

For the positive exercise tolerance test, predictive value of the markedly positive exercise tolerance test for coronary disease was high for both sexes: 0.95 (53/55) for males, 1.0 (6/6) for females. For multivessel disease, the equivalent figures are 0.84 (46/55) and 1.0 (6/6), respectively. However, the less positive exercise tolerance test was significantly more predictive of coronary disease and multivessel disease in males. The values are 0.91 (30/33) vs 0.46 (9/19) and 0.55 (18/33) vs 0.21 (4/19) (both $P < 0.01$, chi square test). When the values of exercise duration, double product, and duration of ST segment change (and various combinations thereof) (table 1) for the small group of females were tested, no tendency toward increased predictive value was noted, but the numbers in any subgroup were quite small.

For the negative exercise tolerance test, there was a tendency toward increased predictive value in females, both for absence of coronary artery disease and for the absence of multivessel coronary artery disease. The values for no coronary disease are 0.71 (12/17) vs 0.55 (17/31), and for no multivessel disease 0.88 (15/17)

### Table 3. Predictive Values of Negative Exercise Tolerance Tests for the Absence of Significant Coronary Obstructive Lesions

<table>
<thead>
<tr>
<th>Exercise duration</th>
<th>All</th>
<th>&gt; 24,000</th>
<th>&gt; 26,000</th>
<th>&gt; 28,000</th>
<th>&gt; 30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.60 (29/48)</td>
<td>0.71 (27/38)</td>
<td>0.74 (26/35)</td>
<td>0.70 (19/27)</td>
<td>0.85 (12/14)</td>
</tr>
<tr>
<td>&gt; 6 min</td>
<td>0.57 (24/42)</td>
<td>0.58 (21/36)</td>
<td>0.61 (20/33)</td>
<td>0.63 (17/27)</td>
<td>0.86 (12/14)</td>
</tr>
<tr>
<td>&gt; 8 min</td>
<td>0.56 (15/27)</td>
<td>0.59 (14/24)</td>
<td>0.59 (14/24)</td>
<td>0.65 (13/23)</td>
<td>0.73 (8/11)</td>
</tr>
<tr>
<td>&gt; 10 min</td>
<td>0.69 (11/16)</td>
<td>0.67 (10/15)</td>
<td>0.67 (10/15)</td>
<td>0.73 (8/11)</td>
<td>1.00 (6/6)</td>
</tr>
</tbody>
</table>

### Table 4. Predictive Value of Negative Exercise Tolerance Tests of Multivessel Disease

<table>
<thead>
<tr>
<th>Exercise duration</th>
<th>All</th>
<th>&gt; 24,000</th>
<th>&gt; 26,000</th>
<th>&gt; 28,000</th>
<th>&gt; 30,000</th>
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<tr>
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</tr>
<tr>
<td>All</td>
<td>0.81 (39/48)</td>
<td>0.87 (33/38)</td>
<td>0.91 (32/35)</td>
<td>0.93 (25/27)</td>
<td>1.0 (14/14)</td>
</tr>
<tr>
<td>&gt; 6 min</td>
<td>0.86 (36/42)</td>
<td>0.89 (32/36)</td>
<td>0.90 (30/33)</td>
<td>0.93 (25/27)</td>
<td>1.0 (14/14)</td>
</tr>
<tr>
<td>&gt; 8 min</td>
<td>0.85 (23/27)</td>
<td>0.93 (27/29)</td>
<td>0.97 (28/29)</td>
<td>0.94 (26/27)</td>
<td>1.0 (11/11)</td>
</tr>
<tr>
<td>&gt; 10 min</td>
<td>0.88 (14/16)</td>
<td>0.87 (13/15)</td>
<td>0.93 (14/15)</td>
<td>0.91 (10/11)</td>
<td>1.0 (6/6)</td>
</tr>
</tbody>
</table>
versus 0.77 (25/31). In those patients with inadequate heart rate response, males were much more likely to have coronary disease. The predictive value for coronary artery disease in males is 0.64 (16/25), and in females 0.2 (3/15) (P < 0.01, chi square test).

Digitalis Group

Of the 33 patients taking digitalis, 26 men and seven women aged 42–66, 22 had at least 1 mm increase in resting ST depression (with one false positive test), giving a predictive value for coronary artery disease of 0.95. (The false positive result occurred in a patient with an increase of 2.5 mm over the resting ST segment depression.)

There were four negative exercise tolerance tests (three were false negative) and seven nondiagnostic tests, four in patients with coronary artery disease. Two patients with multivessel disease had hypotension. This percentage (6%) is similar to the percentage of hypotension in the non-digitalis patient group (11/204, 5.4%). The virtual absence of false positive exercise tolerance tests and the small number of negative and nondiagnostic exercise tolerance tests precluded further analysis.

Discussion

Positive Exercise Tests

The positive treadmill exercise test is highly predictive of coronary artery disease in a symptomatic population where the disease is prevalent. In a number of studies using both maximal and submaximal types of exercise, the predictive value of a positive test was 0.88 to 0.96,8, 12–25 while in another it was 0.73. Our overall predictive value is 0.88. As the frequency of the disease in the population falls, the false positive test becomes more of a problem.26 In most studies, a greater likelihood of a false positive result is seen in the population with a less positive (< 2 mm ST depression) exercise test.2 However, the parameters of exercise we evaluated (double product, exercise duration and duration of ST segment change in recovery), appeared individually and in combination to enhance the predictive value of this subset of positive tests, both for overall coronary artery disease and for multivessel disease. Although overall predictive values are high, some combinations of parameters did achieve statistically significant improvement in predictive value for multivessel disease.

Previous studies have also shown a tendency for the proportion of false positive tests to rise with increasing maximum heart rate and double product achieved,8, 14, 22, 26 at least in male patients.10 Low heart rates achieved for a given duration of exercise have been related to increased prevalence of coronary disease and to subsequent coronary events independent of ST segment changes.27, 28 Hypotensive responses to low level of exercise clearly point to ischemic left ventricular dysfunction.29, 30 In the analysis of the postoperative coronary bypass graft patient, increased heart rate and double product with maximal exercise have been correlated with the adequacy of revascularization,31, 32 but have also been seen in patients showing clinical improvement despite closure of all grafts.33 Maximum heart rate and double

| Table 5. Influence of Exercise Induced Chest Pain on Predictive Value of Negative Exercise Tolerance Tests (ETT) of Significant Coronary Artery Disease. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | All                              | Double product                  |                                |                                |
|                                | > 24,000                         | > 26,000                        | > 28,000                        | > 30,000                        |
| Negative ETT with angina       | 0.43 (3)                         | 0.50 (3)                        | 0.50 (3)                        | 0.67 (2)                        |
|                                | 7                                | 6                               | 6                               | 3                               |
| Negative ETT without angina    | 0.63 (26)                        | 0.75 (24)                       | 0.69 (20)                       | 0.74 (17)                       |
|                                | 41                               | 32                              | 29                              | 23                              |

| Table 6. Predictive Value of Angina in Negative Exercise Tolerance Tests for Absence of Multivessel Disease |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | All                              | Double product                  |                                |                                |
|                                | > 24,000                         | > 26,000                        | > 28,000                        | > 30,000                        |
| Angina                         | 0.71 (5)                         | 0.67 (4)                        | 0.67 (4)                        | 0.75 (3)                        |
|                                | 7                                | 6                               | 6                               | 4                               |
| No angina                      | 0.83 (34)                        | 0.91 (29)                       | 0.97 (28)                       | 0.96 (22)                       |
|                                | 41                               | 32                              | 29                              | 23                              |

| Table 7. Mean Values for Exercise Duration and Double Product for Exercise Tolerance Test Subgroups |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Double product                  | Exercise duration               |
|                                | (mm Hg-min•10⁻³)                | (min)                           |
| CAD +Test                      | 20.6 ± 0.7*                      | Mean ± SEM                      |
|                                | 6.4 ± 0.3                        |                                |
| CAD -Test                      | 21.8 ± 1.1                       |                                |
| No CAD +Test                   | 23.8 ± 2.2*                      |                                |
|                                | 8.1 ± 1.3                        |                                |
| No CAD -Test                   | 23.1 ± 1.1                       |                                |
|                                | 7.6 ± 0.4                        |                                |
| One vessel +Test               | 24.0 ± 1.6†                      |                                |
|                                | 7.5 ± 0.6                        |                                |
| One vessel -Test               | 23.2 ± 1.6                       |                                |
|                                | 8.7 ± 0.6                        |                                |
| MVD +Test                      | 20.0 ± 0.7†                      |                                |
|                                | 6.2 ± 0.3                        |                                |
| MVD -Test                      | 20.7 ± 1.3                       |                                |
|                                | 7.0 ± 0.6                        |                                |

*P < 0.02.
†P < 0.01.
Abbreviations: CAD = coronary artery disease; MVD = multivessel disease.
product of normal individuals, as well as in those with coronary artery disease, correlate with maximum myocardial oxygen uptake. When the blood flow to the left ventricle is limited, as it is in ischemic heart disease, myocardial ischemia is likely to occur at lower levels of myocardial oxygen consumption.

For the Bruce protocol, exercise duration also relates to ventricular function and in most studies, the prevalence of coronary disease in an ECG positive test group decreases as exercise duration increases. In one study, which examined false positive exercise tests by multivariate analysis, exercise duration was not found to be a useful predictor of false positivity.

Persistence of ST changes into recovery has also been correlated with increasing prevalence and severity of coronary lesions. In our study, the data suggest that part of this association may be due to the tendency for the less positive exercise ECGs to normalize more quickly and to be associated more often with normal vessels or less severe coronary artery disease.

**Negative Exercise Tests**

There is a wider variation of predictive values for the absence of significant coronary disease. In the studies alluded to previously, the range is 0.36–0.92. However, most of the values clustered around 0.60, the predictive value found in this study. A higher achieved double product correlated with increasing predictive value for a negative test, both for absence of coronary disease and multivessel disease. Predictive value was not further improved with increased exercise duration, in contrast to improvement found by other workers. We found a decreased frequency of negative tests in patients with multivessel disease (also noted by others), but not any particular association of old myocardial infarction and false negative tests. This association has led to the suggestion that the false negative test is often true negative, infarction having "cured" the patient's ischemia, so that coronary disease exists without active ischemia.

In both positive and negative exercise tests, the lower peak double product achieved with multivessel coronary disease suggests that diffuse cardiac ischemia limits exercise capacity (in the absence of limiting leg ischemia or other extracardiac causes of exercise limitation). This presumably occurs either by development of ischemic ST changes with or without chest pain, by limitation of cardiac output leading to fatigue, or by increase in left ventricular filling pressure leading to pulmonary congestion and dyspnea. It may be hypothesized that such limitations in cardiac function may prevent sufficient local ischemia to cause ST changes and/or chest pain in some patients.

Contrary to several other studies, we were unable to show enhancement of the predictive value for coronary disease of positive tests, nor a decrease of that for absence of coronary disease of negative tests if there was exercise-induced chest pain. However, the numbers were small in most of the subgroups in this analysis.

**Nondiagnostic Exercise Tolerance Tests**

Little has been written about the exercise test which is nondiagnostic because of low peak heart rate and absence of ST segment change. It has been suggested that, because left ventricular dysfunction may prevent sufficient exercise stress to bring out ischemia on the ECG, most nondiagnostic tests would occur in patients with coronary disease. We found that the nondiagnostic exercise tolerance test predicted neither presence nor absence of coronary disease with or without the use of non-ST segment exercise parameters.

**Male vs Female Patients**

Most of the studies which have dealt with the value of exercise testing in females as opposed to males, whether of symptomatic or asymptomatic, presumably normal females, have shown decreased predictive value of the positive exercise test in females and some increased predictive value of the negative test. One study came to different conclusions, but our data agrees with the other studies cited. Interestingly, in the analysis of the nondiagnostic exercise test, most of the women had normal coronary arteries and most of the men had coronary disease. This statistically significant finding suggests that the mechanism for poor exercise performance in the two sexes is often different — usually cardiac in men and usually extracardiac in women.

**Digitalis Therapy**

We hypothesized that the digitalized patient would offer a clear opportunity to demonstrate the usefulness of exercise parameters as the predictive value of the positive test in this group is said to be diminished. However, we found that the predictive value of a positive test in this group was 0.95, using a 1 mm increase in ST depression as a criterion for positivity. A previous preliminary report also showed no increase in false positivity with digoxin therapy. The use of a greater increase in ST depression than 1 mm has been suggested as a way to improve predictive value. The lack of uniformity in findings suggests a place for further analysis of ECG changes and exercise parameters in the digitalized patient.

**Conclusions**

It appears that the use of the simple, conveniently measured exercise cuff blood pressure, in addition to the duration of exercise and ST segment change after exercise, can enhance the predictive value of positive and negative exercise tests in a population with chest pain. An exception is the ≥ 2 mm ST segment criterion. This criterion alone has been highly predictive of coronary artery disease in the present study as well as others, using the treadmill, confirming work...
reported earlier from our laboratory using the two-step test. As the non-ST segment parameters of exercise relate to limitations of overall cardiac function (in the absence of extracardiac symptoms) they should also be useful in asymptomatic and atypically symptomatic populations where the lesser frequency of coronary disease leads to decreased predictive value for ECG changes alone. In addition, the findings that predictive values for multivessel disease are consistently higher using non-ST segment exercise parameters should help identify patients with such disease in these populations. In order to enhance noninvasive diagnosis of coronary artery disease, studies involving larger patient groups are needed to determine the most useful values for double-product, exercise duration and other exercise parameters.

References
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Alterations in Calcium Levels of Coronary Sinus Blood During Coronary Arteriography in the Dog

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SUMMARY Intracoronary administration of contrast materials causes myocardial depression which is related to several physiochemical properties of the contrast solution. The role of variations in ambient calcium ions (Ca$^{2+}$) in mediating this effect was evaluated in 19 anesthetized dogs. Sodium metrizoate diatrizoate caused decreases in left ventricular peak systolic pressure (LVPSP), $-12.6 \pm 3.2\%$, and dp/dt at a left ventricular pressure (LVP) of 40 mm Hg. $-14.3 \pm 4.1\%$. The total calcium (Ca) decreased from 10.2 to 0.2 to 6.5 to 0.2 mg%, while Ca$^{2+}$ decreased from 4.6 to 0.1 mg% to 2.3 to 0.7 mg%. In the presence of systemic hypocalcemia the myocardial depressant actions of this contrast material were accentuated. Intracoronary administration of contrast material with added Ca$^{2+}$, calcium sodium meglumine metrizoate, caused no myocardial depression. Total calcium decreased only slightly (10.2 to 0.2 to 9.1 to 0.2 mg%), while Ca$^{2+}$ increased (4.8 to 0.1 to 5.1 to 0.2 mg%). During systemic hypocalcemia, the calcium metrizoate compound induced increases in LVPSP and dp/dt/LVP. Thus, contrast materials caused myocardial depression which, at least in part, was related to reductions of ambient calcium through a dilutional and binding action. The addition of Ca$^{2+}$ to monomeric contrast materials reversed the myocardial depressant action and produced a transient rise in ambient Ca$^{2+}$.

ACUTE LEFT VENTRICULAR power failure and electromechanical dissociation are rare but disastrous complications of coronary arteriography. Currently utilized ionic contrast materials have a direct depressor action on the ventricular myocardium which is related at least in part to the hyperosmolarity$^{1,2}$ and high sodium ion content$^{3,4}$ of the solution. This solution, which displaces blood during coronary arteriography, is also deficient in calcium ions (Ca$^{2+}$), which have a critical role in contractions of the sarcomere.$^5$ Moreover, it has been suggested that the material most frequently used for coronary arteriography contains chelating properties which might further reduce ambient Ca$^{2+}$ in the myocardium.$^{11}$ It is well-established from early investigations$^{8,9}$ that excitation-contraction coupling depends on the presence of free Ca$^{2+}$, and electromechanical dissociation ensues upon lowering ambient Ca$^{2+}$ in perfusate of isolated heart preparations. Recently, contrast material has been implicated as a causative factor in electromechanical dissociation occurring during coronary arteriography.$^{11}$ The purpose of this study was: 1) to determine the extent of and the mechanism by which calcium is lowered in the coronary circulation during coronary arteriography; 2) to compare the severity and time sequence of depression in calcium levels in a “control state” and an induced acute heart failure state; 3) to assess the influence of preexisting systemic hypocalcemia on the myocardial depression induced by contrast materials; and 4) to compare the effects on calcium levels and myocardial contractility of a contrast material containing calcium ions with currently used non-calcium-containing contrast materials.

Methods

Nineteen mongrel dogs weighing 23–32 kg were anesthetized with pentobarbital sodium, 25 mg/kg, mechanically ventilated at 12 cycles/min, and right thoracotomies were performed. Teflon catheters were inserted into the left ventricle through an apical incision and positioned with the single end hole just below the aortic valve. The position was confirmed by fluoroscopic observation during the hand injection of a
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