Diagnosis of Obstructive Coronary Disease by Maximal Exercise and Atrial Pacing

By Michael H. Kelemen, M.D., Ronald E. Gillilan, M.D., Richard J. Bouchard, M.D., Richard L. Heppneb, M.D., and J. Richard Warbasse, M.D.

SUMMARY
The reliability of graded maximal exercise treadmill testing and right atrial pacing in diagnosing significant obstructive coronary artery disease was evaluated in 74 consecutive patients referred to a cardiac unit with chest pain consistent with angina pectoris. The results of maximal exercise testing and right atrial pacing, with regard to the presence or absence of the patient's characteristic chest pain or discomfort and ischemic ST segment depression, were compared with the findings determined by selective coronary arteriography. Ischemic ST segment depression was defined as a downward displacement of one full mm or more of a horizontal or downward sagging ST segment.

Forty-nine of the 74 patients studied were found to have significant coronary arteriographic obstruction, i.e., greater than 75% obstruction of one major coronary artery. The occurrence of the patient's characteristic chest pain or discomfort during maximal exercise testing or right atrial pacing is an excellent indicator of the presence of obstructive coronary artery disease, since all of the 41 patients developing their characteristic pain on maximal exercise testing had coronary arteriograms positive for obstructive coronary disease (no false positives), and 46 of 47 patients with characteristic chest pain on right atrial pacing had selective coronary arteriograms positive for obstructive coronary disease. When present, one mm ST depression during maximal exercise treadmill testing also reliably indicates arteriographic obstructive coronary disease (26 of 27 patients). However, the presence or absence of ischemic ST depression during right atrial pacing is a particularly unreliable indication of the presence or absence of arteriographic obstructive coronary disease: 15 of 25 false positive tests, and 13 of 49 false negative tests.

Additional Indexing Words:
Coronary arteriography Chest pain Stress tests Ischemic ST depression

The ability to distinguish chest pain due to obstructive coronary artery disease from chest pain from other causes is of obvious clinical importance. Two methods of stressing the heart that have been used extensively, and that appear to be most useful in making this differentiation, are maximal exercise testing\(^1\)-\(^5\) and right atrial pacing\(^6\)-\(^11\).

The present investigation evaluates maximal exercise treadmill testing and right atrial pacing in relation to the presence and degree of coronary artery obstruction determined by selective coronary arteriography. The purpose of this report is to assess the usefulness of maximal exercise testing and atrial pacing in the clinical evaluation of patients referred to a cardiac unit with chest pain. The importance of the careful evaluation of symptoms experienced during and immediately after maximal exercise and atrial pacing, as well as the electrocardiographic changes that occur, will be emphasized. Assuming that there is a significant positive correlation between the results of these two stress tests and the findings at selective coronary arteriography, then the results of the two stress tests can be utilized in future cases to help select those patients who have the best clinical indications for coronary arteriography, with its attendant risks.

Methods
Selection of Patients
Seventy-four patients referred to this Cardiac Unit with chest pain consistent with angina pectoris are...
reported. All of the 74 patients consecutively included were considered by a group of cardiologists to have refractory and limiting angina pectoris and/or clinical indications making the definitive diagnosis of obstructive coronary artery disease particularly important, thus clinically justifying selective coronary arteriography. Fifty-eight men, mean age 49 years (range 28–68), and 16 women, mean age 47 (range 23–61), are included. Those patients with coexisting heart disease, including hypertensive cardiovascular disease, were excluded from this study. Digitalis preparations were discontinued at least two weeks prior to testing, and propranolol was discontinued at least 24 hours prior to evaluation. Nitrates were not administered prior to exercise testing and pacing testing.

Maximal Exercise Test

The maximal treadmill multistage exercise test was performed as described by Bruce and Hornsten and Doan et al.1 Within one week of the time of coronary arteriography patients were exercised in the fasting state. After a 12 lead resting electrocardiogram was obtained, the patients were exercised in the upright position in three minute stages, progressively increasing both speed and grade. Exercise was continued until the onset of the patient’s characteristic chest pain or discomfort, or until other limiting symptoms such as fatigue, dyspnea, or claudication appeared. Characteristic chest pain or discomfort in this study is defined as the patient’s usual, or presenting symptom of pain; while this pain or discomfort was consistent with angina pectoris it was not necessarily typical of angina pectoris. During and immediately after the exercise test (and pacing test, below) the physicians performing the test carefully established whether or not the pain or discomfort noted during the test was that characteristically experienced by the patient. If so, the test was considered positive for chest pain or discomfort. ST abnormalities were not used as a criterion to terminate the test. No arrhythmia requiring termination of the test was observed. A single bipolar chest lead, with the positive electrode in the normal V5 position, and the negative electrode over the right scapula, was used.1 Cuff blood pressure and electrocardiogram were recorded during each stage of exercise, at zero recovery time, and at one and three minute recovery. The electrocardiogram was then recorded at 2 min intervals until it returned to baseline. The intraexercise and postexercise electrocardiograms were assessed for ischemic ST abnormalities, considered to be horizontal or downward sloping ST segment depression of one mm (0.1mv) or more for 0.08 sec or longer, using the P-R segment as the baseline.1, 12 Electrocardiograms, including ST depression, were interpreted independently and in a blinded fashion by two of the authors (R.G. and M.K.).

Right Atrial Pacing Test

Right atrial pacing was also always performed within one week of coronary arteriography. Under mild oral pentobarbital sedation (Nembutal 100 mg) and local lidocaine (Xylocaine) anesthesia, an arm vein was isolated and a standard bipolar pacing catheter was inserted and positioned in the right atrium. The bipolar chest lead, described above, and standard leads I, II, III, aVR, V5, V6, and V4 were recorded on a photographic (Electronics for Medicine DR8) recorder. After all electrical equipment was carefully grounded, heart rate was increased with a battery powered (Cordis) pacemaker. Pacing was initiated at a heart rate of 90 beats/min for three minutes, and was increased by increments of 10 (and maintained at each heart rate for 3 min periods) until the patient either developed his characteristic chest discomfort or attained his maximal predicted heart rate. An electrocardiogram was recorded at each heart rate and also for 5 sec immediately after the pacemaker was turned off. Thus, the electrocardiogram could be interpreted without interference from the pacing artifact (fig. 1) and with the longer ST segment due to the slower heart rate. Intravenous atropine, one mg, was administered to permit pacing with 1:1 atrial ventricular conduction at higher rates. The electrocardiographic and chest pain criteria for evaluating the pacing test were the same as those described for the exercise test.

Selective Coronary Arteriography

Coronary cine arteriography was performed by the standard percutaneous femoral approach of Judkins.13 Multiple projections of each coronary artery were filmed, giving adequate visualization of the entire coronary circulation of each patient. Using a scale similar to that of Bailer and MacLeod,14 an index of severity of coronary artery disease in the particular major arteries present was arbitrarily graded as follows: zero = no disease, 1 = 50–75% obstruction, 2 = 75–90% obstruction, 3 = 90–99% obstruction, 4 = total occlusion. The right coronary artery, the main left coronary artery, the left anterior descending artery, the diagonal branch, the circumflex artery, and the obtuse marginal branch were graded individually. The extent of coronary artery obstruction was considered to be the sum of the individual graded lesions. Patients were classified as having significant coronary obstructive disease ("positive" coronary arteriogram) if there was greater than 75% obstruction of at least one of the major arteries.

Results

Positive coronary arteriograms, as defined above, were found in 44 men and 5 women. Negative coronary arteriograms, defined as less than 50% obstruction in all major coronary arteries, were present in 14 men and 11 women. There were no patients found to have 50–75% occlusion of one or more coronary arteries who did not have greater than 75% occlusive disease in at least one other major coronary artery. There are two more patients included in the pacing test group than in the exercise test group because two patients were not exercised due to increase in the frequency of chest pains in the several weeks prior to study. One of these patients had positive coronary arteriograms, and one had negative coronary arteriograms. Thus
there are two patients less in table 1 than in table 2. The only complication suffered by any patient from any procedure described in this report was a single right femoral artery thrombosis secondary to coronary arteriography. This thrombus was removed by a Fogarty balloon catheter with immediate return of all the right leg pulses to normal.

Maximal Exercise Test

Table 1 summarizes the results of the maximal exercise tolerance test. Forty-one of 48 or 85% of patients with positive selective coronary arteriograms developed their characteristic or usual chest pain during maximal exercise testing. Of the seven patients who did not develop chest pain or discomfort, four stopped exercise because of generalized fatigue, two because of dyspnea, and one because of claudication in both lower extremities. However, all of the 41 patients who did develop characteristic chest pain or discomfort with maximal exercise had positive coronary arteriograms, i.e., no false positive tests. Conversely, among the 24 patients with negative coronary arteriograms, none experienced characteristic chest pain or discomfort.

Ischemic ST segment depression developed in 26 of 48 or 54% of those with positive coronary arteriograms (table 1). Twenty-two of the 48 patients did not develop ischemic ST depression, and thus constituted false negative results. There was a slight, statistically insignificant, difference in coronary artery disease index between these 22 false negative patients and the 26 true positive patients. The mean index of the former was 10.8 ± 3.6, and the latter 12.5 ± 4.3. There was also an insignificant difference in maximal heart rate attained during exercise between the two groups, with the false negative group attaining a more rapid average heart rate (135 compared with 130 beats/min). However, all but one of the 27 patients who did develop ischemic ST depression with maximal exercise had positive coronary arteriograms, i.e., only one false positive result.

Other criteria for ischemic ST abnormalities were evaluated. Only one patient in the study group had 0.5–0.9 mm of horizontal or downward sloping ST segment depression, and this one patient did not have coronary artery disease. The criterion recommended for maximal exercise testing by McDonough and Bruce10 of 1 mm of ST depression 60 msec beyond the J point regardless of slope was evaluated. Eight additional patients with obstructive coronary artery disease were found to have a positive exercise test by this criterion, raising the total to 34 of 48 or 71%. However, four patients with negative selective coronary arteriography (17% of the total) also had positive tests by this criterion. Thus, although sensitivity (true positive results) was increased, specificity (true negative results) of the test was significantly decreased using this criterion.

Of the six patients found to have 75% or greater occlusion of the main left coronary artery, five had at least 2 mm ST segment depression16 on the maximal exercise test. However, eight additional patients also had 2 mm or greater ST segment depression on exercise, but did not have main left coronary artery occlusion. These latter eight patients did not have significantly more widespread or more severe coronary disease12, 17 (index 11.8) than did all other coronary disease patients (index 10.6).

Right Atrial Pacing Test

Table 2 summarizes the right atrial pacing results. Forty-six of 49 or 94% of patients with positive selective coronary arteriograms developed their characteristic chest pain or discomfort during right atrial pacing. One of the three patients with a false negative response (no pacing chest pain and positive coronary arteriograms) developed incomplete atrioventricular block despite atropine, and could not be paced above a heart rate of 120. Of the 47 patients who developed chest pain or discomfort during right atrial pacing, only one had a negative coronary arteriogram, i.e., one false positive result.

Table 1

<table>
<thead>
<tr>
<th>Selective coronary arteriogram</th>
<th>Maximal exercise characteristic chest pain</th>
<th>Maximal exercise ischemic ST depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>41 (85%)</td>
<td>26 (54%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Selective coronary arteriogram</th>
<th>Atrial pacing characteristic chest pain</th>
<th>Atrial pacing ischemic ST depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>46 (94%)</td>
<td>36 (73%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>15 (60%)</td>
</tr>
</tbody>
</table>
Thirty-six of 49 or 73% of patients with positive coronary arteriograms developed ischemic ST segment depression during pacing, but 13 of the 49 did not, i.e., 27% false negative results (table 2). In addition, 15 of 25 patients with negative coronary arteriograms developed ischemic ST depression, i.e., a 60% false positive result. Figure 1 is an example of such ischemic ST depression during and immediately after pacing in a patient with normal arteriograms. It is noteworthy that no patient developed 1 mm or greater ST segment elevation with either pacing or exercise testing.

Heart rate at the time of development of the pacing-induced ischemic ST depression was evaluated in an attempt to differentiate the 36 true positive patients from the 15 false positive patients just described. Nine of the 15 or 60% of the false positive tests occurred at a heart rate of 160 or greater, whereas only 5 of 37 or 14% of the true positive tests first occurred at or above this rate. However, there was marked overlap of the two groups at a heart rate of 140–160. When the ischemic ST depression in pacing tests to a maximal heart rate of 140 beats/min is examined, specificity improves in that only two patients with negative coronary arteriography exhibited ischemic ST changes at this heart rate. However, the sensitivity of the test decreases because only 25 of 49 or 51% of the group with positive coronary arteriography exhibited ischemic ST depression at this rate.

Combined Results of Maximal Exercise Testing and Right Atrial Pacing

Combining the results of maximal exercise testing and right atrial pacing with reference to chest pain or discomfort (table 3), 48 of the 49 patients with positive coronary arteriography experienced their characteristic chest symptoms with either exercise testing or atrial pacing, a 98% true positive result. Twenty-four of the 25 patients with negative selective coronary arteriograms were without chest pain or discomfort on either exercise testing or atrial pacing, a 96% true negative result. Thus, the presence or absence of significant obstructive coronary artery disease was correctly predicted in 72 of the 74 patients or 97% by evaluating the occurrence of the patient's characteristic chest pain or discomfort during the stress tests performed.

Electrocardiographic Lead System

The electrocardiographic leads selected for use in exercise testing are one factor in the percentage of positive tests obtained.\textsuperscript{18, 12} The frequency with which a particular electrocardiographic lead disclosed ischemic ST depression was evaluated during right atrial pacing by comparing the single bipolar chest lead\textsuperscript{3} (previously described) with the multiple lead electrocardiogram, (I, II, III, aVF, V\textsubscript{2}, V\textsubscript{4}, V\textsubscript{6}). With regard to the sub-group of 37 patients with ischemic ST changes on right atrial pacing and positive selective coronary arteriography, 35 or 95% had ischemic changes in the bipolar chest lead (table 4). Thus, this lead was a diagnostically reliable lead. With respect to the 15 false positive atrial pacing tests, the bipolar chest lead was positive in all 15, while lead V\textsubscript{4} was positive in 14 cases. Thus, table 4 illustrates that with atrial pacing none of the eight ECG leads which were examined reliably indicated both the presence and absence of arteriographic obstructive coronary disease.

Table 3

<table>
<thead>
<tr>
<th>Selective coronary arteriograms</th>
<th>Characteristic chest pain with maximal exercise or pacing tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>49 positive</td>
<td>1</td>
</tr>
<tr>
<td>25 negative</td>
<td>24 (96%)</td>
</tr>
</tbody>
</table>

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Table 4

<table>
<thead>
<tr>
<th>ECG Leads</th>
<th>True (+) Test</th>
<th>False (+) Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4/37 (11%)</td>
<td>1/15 (7%)</td>
</tr>
<tr>
<td>II</td>
<td>8/37 (22%)</td>
<td>7/15 (47%)</td>
</tr>
<tr>
<td>III</td>
<td>4/37 (11%)</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>aVF</td>
<td>4/37 (11%)</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td>V2</td>
<td>4/37 (11%)</td>
<td>7/15 (47%)</td>
</tr>
<tr>
<td>V3</td>
<td>27/37 (73%)</td>
<td>14/15 (90%)</td>
</tr>
<tr>
<td>V4</td>
<td>33/37 (95%)</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>V5</td>
<td>11/37 (30%)</td>
<td>6/15 (40%)</td>
</tr>
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</table>

History of Chest Pain and Obstructive Coronary Artery Disease

Patients in the present series were classified as having typical angina pectoris by history if they had pain in the chest conforming to the classical Heberden description, i.e., chest pain clearly precipitated by physical exertion and relieved by rest, lasting continuously for one to 20 minutes, and described as squeezing, crushing, pressing or equivalent. Relief with nitroglycerine was not used as a criteria, and pain that was sticking, knife-like, rhythmic, momentary was not considered to be typical angina. Forty-three of 49 of the patients with positive selective coronary arteriography had typical angina pectoris by history, 88% true positive results. The remaining six patients were considered to have atypical angina pectoris. Nineteen of 25 patients with negative selective coronary arteriography were considered to have atypical chest pain, 76% true negative results. Combining the true positive and true negative groups, the clinical history of chest pain or discomfort on exercise was concordant with the findings on selective coronary arteriography in 62 of 74 or 84% of patients.

Resting Electrocardiogram, Prior Infarction

Eighteen of 49 or 37% of patients with positive selective coronary arteriography had electrocardiographic evidence of a remote transmural myocardial infarction, 0.03–0.04 sec Q wave. None of the 25 patients with negative selective coronary arteriography had evidence of a transmural infarction. Table 5 summarizes the findings of transmural myocardial infarction on the resting electrocardiogram in relation to the results of maximal exercise testing and pacing in the 49 patients with positive coronary arteriograms. There was no significant difference in the incidence of chest pain or discomfort with either exercise testing or right atrial pacing between the 18 patients with myocardial infarction, and the 31 patients without myocardial infarction. There was, however, a difference in occurrence of ischemic ST depression. Nineteen of 31 patients or 61% without evidence of myocardial infarction had ischemic ST depression during maximal exercise treadmill testing, while 7 of 18 or 39% of the group with myocardial infarction had ischemic ST depression. In the case of right atrial pacing this difference was more marked: 27 of 31 or 87% of non-myocardial infarction patients developed ischemic ST depression, while only 10 of 18 or 56% with myocardial infarction developed such changes, P < 0.025.

The group of 18 patients with electrocardiographic evidence of myocardial infarction was then divided by location of the infarction. Of the eight patients with isolated anterior wall infarction or combined anterior and inferior wall infarction, one developed ischemic ST changes during exercise, and two did so during right atrial pacing. Although the numbers in the groups are small, differences in relation to the other ten myocardial infarction patients (nine with inferior infarction, and one with true posterior infarction) were significant at the P < 0.01 level. Of these ten patients, ischemic ST depression was present in six on maximal exercise and in nine on atrial pacing.

Discussion

Since the coronary arteriogram reveals only the presence or absence of anatomic obstructive lesions

Table 5

<table>
<thead>
<tr>
<th>Electrocardiogram</th>
<th>Maximal exercise test</th>
<th>Atrial pacing test</th>
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<tbody>
<tr>
<td></td>
<td>Characteristic chest pain</td>
<td>Ischemic ST depression</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18</td>
<td>15 (83%)</td>
</tr>
<tr>
<td>No myocardial infarction</td>
<td>31</td>
<td>26 (84%)</td>
</tr>
</tbody>
</table>

*Difference significant at the P < .025 level.

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in the arteries, and the chest pain and ST depression produced by exercise and pacing stress tests provide only a functional measure of myocardial ischemia, the close correlation between the findings of arteriography and stress testing is surprising. The results of the present investigation are consistent with recent reports that ischemic ST depression produced by strenuous exercise yields true positive results as determined by coronary arteriography in approximately 60% of tested patients.\(^5,19\) It is emphasized that this figure of about 60% sensitivity critically depends on using one mm (0.1 mv) ST segment depression\(^5,19\) as previously discussed, to defined the ischemic ST segment. Had the exercise test not been stopped with the onset of chest pain or discomfort, it is expected that greater than 54% sensitivity would have been attained, i.e., more patients would have developed abnormal ST segment depression. However, it is also particularly noteworthy that in the present study the careful observation of the occurrence of characteristic chest pain or discomfort on maximal exercise test increased the test from 54% (ST segment depression) to 68% (pain or discomfort). This increase in sensitivity was accomplished without any decrease in specificity, since there were no false positive tests for these chest symptoms associated with the maximal exercise test. Related to these results is the demonstration by Ascoop et al.\(^19\) and by Van Herpen, Bruschke and Hansen\(^29\) of the importance of the physician's careful evaluation of the patient's clinical history of angina pectoris in assessing the findings at coronary arteriography.

In the present report, the occurrence of the patient's characteristic chest pain or discomfort induced by atrial pacing correctly predicted 94% of those with arteriographic obstructive coronary artery disease, with only 4% false positive response. Bahler and MacLeod reported pacing-induced angina in 22 of 23 patients (96%) with relatively severe angina and arteriographic coronary disease.\(^14\) Helfant et al. reported pacing-induced angina in 20 of 41 patients (49%) with arteriographic coronary disease.\(^10\) Linhart reported pacing-induced angina in 38 of 67 patients (57%) with arteriographic coronary disease, and also ischemic ST depression in 33 of 67 patients (49%), but virtually all of these patients were paced to a rate no greater than 140/min.\(^11\) All of the above cited reports were hemodynamic studies of the effect of atrial pacing\(^4,10,11\) very little diagnostic information or information on patient selection more than that summarized above was presented. The present investigation, in contrast, is a diagnostic evaluation of the results of maximal exercise and pacing tests in a consecutive series of 74 patients having clinical indications of coronary arteriography.

Maximal exercise electrocardiography with suitable precautions may be readily performed in a physician's office. Although atrial pacing testing is quite simple to perform, it is an invasive procedure and is probably best performed in a hospital. In the case of most patients, it is possible to perform both exercise testing and atrial pacing tests. Thus, in the present investigation, the presence or absence of significant arteriographic coronary artery obstruction was correctly predicted in 97% of patients by the presence or absence of the patient's characteristic chest pain or discomfort at either the maximal exercise or the atrial pacing test. However, the high degree of sensitivity of these test results is based mainly on right atrial pacing, since 94% of patients with positive coronary arteriograms developed chest pain during right atrial pacing. The chance of obtaining results from maximal exercise or atrial pacing testing that do not correlate with the presence or absence of significant arteriographic coronary obstruction are clearly delineated in tables 1 and 2, and serve to emphasize the limitations of maximal exercise and of atrial pacing testing. Except for the absence of false positive results for chest pain or discomfort on maximal exercise testing, both exercise and atrial pacing tests produced at least some false positive and some false negative results in regard to both chest pain or discomfort and ischemic ST depression.

In a preliminary report, Jelinek et al.\(^21\) noted that all of 30 patients with both one mm ST segment depression or elevation and angina pectoris on exercise test had arteriographic coronary artery disease. Thus, despite differences of opinion regarding the value of stress testing\(^22\) selected stress tests, or a combination of such tests, can provide very significant evidence as to the presence or absence of obstructive coronary disease as determined by arteriography.

In contrast to the positive correlations described above, ischemic ST depression induced by atrial pacing was found to be very unreliable in indicating the presence or absence of arteriographic obstructive coronary disease. This is of considerable clinical significance, since 26% false negative results and more importantly, 60% false positive results were obtained. There is relatively little published information concerning this matter. Helfant et al.\(^10\)
noted 21 of 28 or 75% of patients with arteriographic coronary disease had pacing-induced ST segment depression, as did Bahler and MacLeod14 in 11 of 23 or 48% of patients. However, the results of pacing-induced ST depression in patients without obstructive coronary disease were not included in either of the latter two investigations.

Ischemic ST segment depression present in any one of seven additional ECG leads during right atrial pacing yielded only a 5% increase in sensitivity beyond that provided by the single bipolar chest lead. Blackburn and Katigbak16 reported that in the case of the exercise test multiple ECG leads yield only 11% more positive results than did lead V5. In the present investigation there was a slight but statistically insignificant difference in the extent of arteriographic coronary disease in those with ischemic ST depression on exercise (true positives), as compared to those without such ST depression (false negatives). The heart rate attained by the two groups was similar. Other electrocardiographic criteria for interpreting exercise testing were evaluated, and resulted in increased sensitivity but decreased specificity.12,18 The only identified factor that resulted in a statistically significant decreased incidence of ischemic ST depression on maximal exercise test was the presence of a remote anterior wall myocardial infarction on the resting electrocardiogram. It can be hypothesized that anterior infarction results in less myocardium being rendered ischemic by exercise as determined by an anterior (Bruce bipolar V3) lead.

Acknowledgment

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