Uses and Limitations of Stress Testing in the Evaluation of Ischemic Heart Disease

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SUMMARY

The results of stress testing in patients being assessed for coronary artery disease have led to conflicting claims and conclusions. It seems reasonably clear that stress testing is of considerable predictive value in epidemiologic studies; i.e., patients manifesting or developing a positive exercise test have a much higher probability of subsequently experiencing coronary events (angina pectoris, myocardial infarction, or coronary death) than those individuals with normal stress tests. Moreover, the risk seems to be related to the degree of S-T segment depression. In contrast, despite earlier claims regarding the diagnostic accuracy with which single-load stress tests could predict the presence or absence of ischemic heart disease in individual patients, studies correlating the results of testing with the degree and extent of angiographically demonstrated coronary artery disease have not consistently shown either acceptable sensitivity or specificity. Although on theoretic grounds it would be anticipated that multistage stress tests would be superior to single-stage protocols, this has not been borne out in the few published studies in which the results are correlated with angiography. Thus, the available evidence suggests that there remain appreciable numbers of patients with documented coronary artery disease in whom no ECG abnormalities are detected despite relatively intense levels of exercise, and an appreciable number of patients with abnormal ECG responses but normal coronary arteries. Stresses other than exercise have been and are being utilized in the evaluation of patients with chest pain; however, no single test as yet offers the desired specificity and sensitivity.

We conclude that, in patients with typical angina pectoris or with chest pain which clearly does not resemble angina pectoris, stress testing appears to be superfluous since it provides little additional information beyond that which may be obtained from the patient's history. It is in those patients presenting with atypical anginal syndromes that a reliable noninvasive test would be of great value. Currently available technics are neither sufficiently sensitive nor specific to satisfactorily aid in solving this problem.

It has long been recognized that acute changes in the resting ECG occur during spontaneous attacks of angina pectoris and that similar reversible changes can be precipitated during attacks of angina pectoris induced by exercise. The suspicion that such changes may in part reflect or be caused by myocardial ischemia is supported by the observation that the onset of S-T segment depression occurring during exercise or atrial pacing in patients with coronary artery disease is associated with the production of lactate, a biochemical index of ischemia. Since myocardial ischemia occurs when myocardial oxygen consumption (MV02) exceeds the capacity of the coronary arteries to deliver oxygen, it is apparent that interventions causing an increase in MV02 may be employed to uncover a reduction in coronary reserve capacity.

While the electrocardiographic response to stress testing has received broad acceptance as an approach that can be employed to detect occult ischemic heart disease, a closer inspection of the published studies suggests that the applicability of these tests may be more limited than has been generally appreciated. The purpose of this review is to critically appraise the various stress tests currently used and to propose criteria for the selection of appropriate patients.
being used in patients with suspected ischemic heart disease and to define more carefully the limitations and usefulness of such testing procedures.

Exercise Tests and Electrocardiographic Indices of Ischemia

A great deal of interest and many investigations relating to the diagnosis of ischemic heart disease predated the development of sophisticated recording and diagnostic technics. It is therefore not surprising that exercise, a simple and straightforward form of stress, was employed in virtually all the earlier studies in which stress testing was used as an aid in the diagnosis of ischemic heart disease. For similar reasons, changes in the electrocardiogram were evaluated for potential indices of ischemia. Although other technics have developed in recent years, the basic appeal of these initial relatively simple approaches is supported by the fact that much of the current research relating to stress testing in coronary artery disease is oriented toward the refinement and assessment of the validity of these earlier methods.

The formal beginning of the era in which analysis of the ECG is used to judge whether chest pain is cardiac or noncardiac in origin stems from the studies of Bousfield and Pardee, which showed that the ECG may change during spontaneous attacks of myocardial ischemia. In 1928, Feil and Siegel demonstrated that similar alterations in the ECG appeared when angina was precipitated by exercise, and in 1932 Goldhammer and Scherf, who demonstrated exercise-induced electrocardiographic changes in over half of their patients with angina, recommended exercise stress testing as a useful diagnostic aid in the evaluation of patients with chest pain.

Two-Step Exercise Test

An important impetus leading to the popularization of exercise stress testing came from Master, who in 1929 published the first of many studies that eventually led to his new well-known “two-step” stress test. Although many of Master’s original criteria of “ischemic” ECG changes and the diagnostic reliability he subsequently ascribed to the procedure have been refuted, his lasting contribution to the field is based on his efforts to quantitate and compare the exercise-induced ECG changes occurring in subjects believed to be normal with those believed to have coronary artery disease.

The two-step exercise test, as described by Master, involves the performance of 10 to 37 trips up and down two measured steps over 1 min; the number of trips is determined by the age, weight, and sex of the subject. A “double two-step” involves twice the number of trips over 3 min. Master’s original criteria for an abnormal electrocardiographic response evolved considerably as his experience with the test increased; the criterion most commonly accepted at the present time as indicative of a positive test is depression of the RS-T segment below the isoelectric line. The amount and type of depression that is most reliable in diagnosing ischemic heart disease is, however, still not agreed upon.

Although Master and his co-workers claimed that a negative double two-step test essentially excluded the existence of coronary artery disease, this conclusion was challenged by other investigators in the field who reported that false-negative responses were elicited in from 12 to 49% of patients believed on clinical grounds to have unequivocal evidence of coronary artery disease. The high specificity claimed by Master and co-workers was also challenged, with false-positive responses reported to occur in from 18 to 39% of supposedly normal individuals.

Although these latter studies cast considerable doubt on the reliability of using the Master’s two-step test to diagnose the presence or absence of coronary artery disease in a given subject, the prevalence of false-positive and false-negative exercise responses was
### Table 1

Studies in which the Results of Exercise Electrocardiography have been Correlated with the Findings of Coronary Arteriography

<table>
<thead>
<tr>
<th>Study</th>
<th>No. pt</th>
<th>Selective cine criteria for CAD (% luminal narrowing)</th>
<th>Exercise protocol</th>
<th>S-T criteria for positive test (mm depression)</th>
<th>Sensitivity (true positive)</th>
<th>Specificity (true negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.(^1)</td>
<td>34</td>
<td>Not defined</td>
<td>2 step; HR &gt; 120/min or exercise for &gt;3 min; 12-lead ECG after exercise</td>
<td>≥ 0.5</td>
<td>27/34 (63%)</td>
<td>—</td>
</tr>
<tr>
<td>Likoff et al.(^2)</td>
<td>74</td>
<td>≥ 50</td>
<td>Supine bicycle 50–150 W; leads I, II, III, aVF; V&lt;sub&gt;3&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt; recorded during and after exercise</td>
<td>≥ 1.0</td>
<td>14/24 (58%)</td>
<td>34/50 (68%)</td>
</tr>
<tr>
<td>Demany et al.(^3)</td>
<td>75</td>
<td>≥ 50</td>
<td>Double Master’s; leads II, V&lt;sub&gt;3&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt; after exercise</td>
<td>≥ 1.0</td>
<td>18/42 (43%)</td>
<td>23/33 (69%)</td>
</tr>
<tr>
<td>Hultgren et al.(^4)</td>
<td>65</td>
<td>≥ 50</td>
<td>“Usually” double Master’s; leads II, V&lt;sub&gt;3&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt; after exercise</td>
<td>≥ 1.0</td>
<td>20/32 (60%)</td>
<td>23/23 (103%)</td>
</tr>
<tr>
<td>Mason et al.(^5)</td>
<td>84</td>
<td>≥ 50</td>
<td>Graded exercise (escalator or treadmill) 90% predicted max HR; modified 12-lead ECG during and after exercise</td>
<td>≥ 0.5</td>
<td>43/49 (88%)</td>
<td>24/35 (69%)</td>
</tr>
<tr>
<td>Kassebaum et al.(^6)</td>
<td>67</td>
<td>≥ 50</td>
<td>Supine bicycle 85% predicted max HR; 12-lead ECG during and after exercise</td>
<td>≥ 0.5</td>
<td>25/34 (73%)</td>
<td>32/33 (97%)</td>
</tr>
<tr>
<td>Most et al.(^7)</td>
<td>65</td>
<td>≥ 50</td>
<td>Master’s; 12-lead ECG after exercise</td>
<td>≥ 0.5</td>
<td>43/65 (66%)</td>
<td>—</td>
</tr>
<tr>
<td>Roitman et al.(^8)</td>
<td>46</td>
<td>≥ 50</td>
<td>Multistage treadmill; 90% predicted max HR; Frank and V&lt;sub&gt;3&lt;/sub&gt; leads during and after exercise</td>
<td>≥ 1.0</td>
<td>38/65 (58%)</td>
<td>—</td>
</tr>
<tr>
<td>Fitzgibbon et al.(^9)</td>
<td>132</td>
<td>“Cor obstr index” approx 50</td>
<td>Double Master’s; leads II, aVF, V&lt;sub&gt;3&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt; after exercise</td>
<td>≥ 0.5</td>
<td>44/92 (48%)</td>
<td>32/40 (80%)</td>
</tr>
<tr>
<td>McConahay et al.(^10)</td>
<td>100</td>
<td>≥ 50</td>
<td>Double Master’s; 12-lead ECG (except V&lt;sub&gt;3&lt;/sub&gt;, V&lt;sub&gt;4&lt;/sub&gt;) after exercise</td>
<td>≥ 0.5</td>
<td>41/65 (63%)</td>
<td>29/35 (83%)</td>
</tr>
<tr>
<td>Cohn et al.(^11)</td>
<td>110</td>
<td>≥ 75</td>
<td>Double Master’s; 12-lead ECG or II, V&lt;sub&gt;3&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt; after exercise</td>
<td>≥ 0.5</td>
<td>65/77 (84%)</td>
<td>24/33 (73%)</td>
</tr>
</tbody>
</table>

Abbreviations: CAD = coronary artery disease; W = work load in watts; HR = heart rate; ECG = electrocardiogram.
estimated by comparing the results of exercise testing with a diagnosis of coronary artery disease based only on clinical assessment; i.e., coronary arteriography was not performed. Nevertheless, more recent studies in which the electrocardiographic response to exercise has been correlated with coronary angiographic findings have confirmed the earlier reports indicating that the specificity and sensitivity of the two-step test leave much to be desired.21-27

Table 1 summarizes the results of those studies in which selective coronary angiography was performed to determine whether or not coronary artery disease was present in a given individual.21-31 All the studies defined an abnormal electrocardiographic response to exercise as a horizontal or downsloping S-T segment, i.e., one that extends horizontally for at least 0.08 sec or sags below the junction of the S wave and S-T segment before returning to the isoelectric line. If an abnormal response was defined as a depression of the S-T segment equal to or greater than 0.5 mm, false-negative responses ranged from 12 to 52%, and false-positive responses from 3 to 31%. If the S-T segment criteria for ischemia were made more stringent so that an abnormal response was defined as a depression diminish with an increase in the number of false-negative responses. This tendency was most pronounced when an S-T segment depression of 2 mm was used to define an abnormal response. With this criterion the equal to or greater than 1 mm below the isoelectric line, there seemed to be in some studies a tendency for less false-positive diagnoses; i.e., the specificity improved (table 1, fig. 1). However, the sensitivity tended to specificity was excellent.24,27 However, there was a considerable decrease in the sensitivity of the test as the criterion for an ischemic response was made more rigid. Thus, despite the widespread enthusiasm for use of the two-step tests as an aid in the diagnosis of ischemic heart disease, the results of rather carefully performed studies would indicate a relatively low sensitivity and rather poor specificity, with sensitivity and specificity tending to vary inversely as ischemic criteria are made more or less stringent.

Limitations of the Single-Load Exercise Stress Test

There are several basic physiologic and conceptual objections to any form of single-load stress test used to elicit evidence of myocardial ischemia.22-36 Myocardial ischemia occurs when there is an imbalance between myocardial oxygen requirements and the ability of the diseased coronary arteries to deliver oxygen to the myocardium. Although the critical level of MVO₂ at which myocardial ischemia occurs is relatively constant in each patient on repeated testing, there is marked patient-to-patient variation.33 Thus many patients may have a reasonably good coronary
reserve and develop angina pectoris only when MVO₂ is rather high (fig. 2). In these individuals the amount of exercise performed during any single-load exercise test may be insufficient to provoke ischemia despite the existence of underlying coronary artery disease. Moreover, the single-load stress test does not take into account the fact that the heart rate and arterial pressure response to a given level of exercise may vary considerably among patients. Since heart rate and arterial pressure are important determinants of MVO₂, it follows that there also must be considerable variability in MVO₂ resulting from a given exercise level. This variability in the response to exercise is illustrated by the results of Sheffield, who reported in a study of 216 men that heart rates ranged from 90 to 190 beats/min in response to the standard Master's double two-step test. Similarly, Keys found rates in the range of 80-172 beats/min in 1040 railroad employees walking on a treadmill at 3 mph and 5% grade for 3 min. These rather marked differences in the circulatory response to exercise are probably based in part on innate differences in exercise capacity among patients, and in part on whether the patient is in good or poor physical condition.

The latter is attested to by the observation that the heart rate and arterial pressure responses to exercise can be altered appreciably by physical training (fig. 3). It would appear, therefore, that there are two major reasons why a single-level exercise stress test may result in an excessive number of false-negative responses: (1) some patients have less severe disease than others and will therefore be able to exercise to a higher level of MVO₂ before ischemia results (fig. 2); (2) the circulatory response (and therefore MVO₂) to a single standard level of exercise will be less in some patients than in others and may also be altered by training in a given patient such that the resulting level of MVO₂ may not exceed that necessary to precipitate ischemia (fig. 3).

**Graded Exercise Stress Tests**

The above considerations led to the hypothesis that a more sensitive method for the detection of underlying coronary artery disease would be to increase the intensity of stress until evidence of ischemia appeared, or until the level of stress was considered to be relatively high. As indicated previously, the circulatory response of individual patients to a

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**Figure 2**

The responses to graded exercise in two patients with angina pectoris due to coronary artery disease. The triple product of heart rate, systolic arterial pressure, and ejection time is on the vertical scale, and the work load in watts (3 min at each level) is on the horizontal scale. The circulatory response to exercise was similar in both patients but the level of the triple product attained at angina differed markedly.

**Figure 3**

The effect of physical training on the response to graded exercise in a patient with angina pectoris. The triple product is on the vertical scale, and the duration of exercise and work load in watts are on the horizontal scale. The data points to the left depict the results obtained at the initial pretraining study. After 3 weeks there was a marked alteration in the circulatory response to exercise as shown by the data points in the center. This effect was even more marked following 6 weeks of training (data points to the right).
given level of exercise varies considerably so that a standard "maximal" level of exercise cannot be defined. Since the maximal heart rate that can be achieved during exercise falls into narrow limits for a given age and sex, one method of ensuring that a given exercise load produces a sufficient stress in an individual patient is to increase the intensity of exercise until signs or symptoms of ischemia occur, or until the maximal predicted heart rate or a given percentage of maximal heart rate is achieved.

Although on theoretic grounds it would appear that a multistage exercise stress test would be superior to single-stage protocols, sufficient numbers of studies in which angiographic data are correlated with the results of multistage testing have not as yet been performed. As is evident from the results listed in table 1, there are an appreciable number of individuals who have angiographically demonstrated coronary artery disease but in whom no abnormalities can be elicited despite relatively intense levels of exercise. Moreover, it is not as yet clear whether false-positive responses will be even more of a problem than with two-step tests, since it is quite possible that stress tests in general lose specificity as they gain sensitivity.

Additional studies have been performed which, although lacking angiographic confirmation of the presence or absence of coronary artery disease, do compare the results of the Master's protocol with those obtained in the same patients using a protocol of graded exercise. Thus, Mason and Likar compared the double Master's test with a protocol in which patients exercised on a bicycle ergometer at successively increasing levels until the heart rate reached 90% of the predicted maximal, or until chest pain, fatigue, or a 1-mm depression of the S-T segment occurred. It was found that 80% of 30 patients with typical angina pectoris had a positive result with the multistage exercise test as compared with 57% using Master's protocol. Sheffield and co-workers compared the results of the single and double Master's test with a graded exercise test that was continued until the heart rate reached 85% of the predicted maximal for the patient's age. Master's two-step test resulted in 65% positive responses, and the graded exercise test increased this yield by 14% in a group of patients with typical angina pectoris. Bellet and Roman have published similar results. Although these findings could be interpreted as supporting the conclusion that graded stress tests are more sensitive than single-stage tests, it must be emphasized that coronary angiography was not carried out in these studies, and it is therefore unknown whether the greater yield of positive responses represents an increased sensitivity (true positives) or a decreased specificity (false positives).

While graded exercise tests may eventually be shown to be superior to single-stage exercise tests in the detection of patients with coronary artery disease, the greater physical stress could conceivably be associated with a higher risk to the patient. From published reports it would appear that only isolated instances of cardiac arrest or myocardial infarction have been associated with exercise testing. Moreover, these have occurred after both the Master's and the multistage stress tests. However, there is insufficient data available from which to draw definite conclusions regarding the relative risk factors of the single and multistage protocols.

Measurements Made during Exercise

Until recently, electrocardiographic changes had been measured immediately after the cessation of exercise. However, several studies have been performed indicating that changes may occur during exercise and disappear immediately upon the completion of exercise. Thus, Mason has shown that, in six of 56 patients (11%) with abnormal ECG responses to multistage exercise testing, the changes were confined to recordings taken during exercise. Again, whether the increased yield of "ischemic" ECG changes occurring when recordings taken during exercise are added to the testing procedure means that sensitivity is enhanced or specificity diminished remains to be determined.

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Hypoxemia in the Detection of Ischemic Heart Disease

In 1941, Levy and co-workers introduced the "anoxemia test" as a method of stress in the diagnosis of coronary insufficiency. This method of stress has not enjoyed great popularity since special equipment has to be used and the test may take longer to complete than exercise stress tests. In addition, it is more difficult to standardize than the exercise tests. Nevertheless, hypoxemia (a more appropriate title than anoxemia), has the advantage that muscle artifact is eliminated from the ECG, and the difficulties associated with interpretation of S-T segment changes during exercise-induced tachycardias are largely avoided since the increase in heart rate is only modest.

Recently Kassebaum and co-workers have reassessed the current status of hypoxemia and have compared the results of the test with graded supine bicycle exercise in patients in whom the presence or absence of coronary disease was documented by selective angiography. The maximum duration of hypoxemia was 20 min but was terminated if chest pain occurred, if significant (≥1.0 mm) S-T depression appeared, or if the arterial oxygen saturation fell below 70%. Exercise was continued until chest pain or significant S-T segment change occurred, or until the heart rate reached 85% of the predicted maximal heart rate for the patient's age. Using S-T depression of ≥1.0 mm as the criterion for a positive stress test, the sensitivity with hypoxemia was 48% (16 of 33 patients with documented coronary artery disease) and with exercise, 73% (25 of 34 patients with documented coronary artery disease). The specificity was 92% (23 of 25 with normal coronary arteries by angiography) with hypoxemia and 88% (22 of 25 with normal coronary arteries) with exercise. By using ≥0.5-mm S-T depression as the criterion for ischemic change, the sensitivity could be increased to 68% (23 of 34 patients with coronary artery disease) with the hypoxemia test while the specificity remained high at 88% (22 of 25 patients with angiographically normal coronary arteries).

Atrial Pacing in the Detection of Ischemic Heart Disease

Atrial pacing provides another method by which heart rate (and thereby M\(\overline{V}O_2\)) can be increased until S-T segment changes occur or chest pain is produced.\(^{50, 51}\) An inherent advantage of this technic over exercise is that ECG signals are not affected by muscle artifact or baseline shifts. Moreover, multiple leads may be monitored during the course of pacing, a facility not easily accomplished during exercise. In addition the increased heart rate can be reversed immediately after the onset of angina, resulting in rapid relief of symptoms.

Lau and co-workers\(^{52}\) compared the results of atrial pacing and Master's single or double exercise tests in a group of 34 patients with typical or atypical chest pain. An S-T segment response was considered positive when depression of ≥0.5 mm occurred in any of the recorded leads (I, II, \(V_1\), or \(V_4\) and \(V_6\)). Twenty-seven of 34 patients (79%) had a positive atrial-pacing test compared with 25 of 34 patients (74%) with a positive Master's test. Since coronary angiography was not performed, the relative specificity of the stress tests could not be ascertained. Thus it would appear that the sensitivity of atrial pacing as a diagnostic method for ischemic heart disease is comparable to a Master's two-step test; however, atrial pacing is an invasive procedure and does require special equipment and facilities, factors which would limit its wider application.

Factors Leading to Interpretive Difficulties

Regardless of which stress protocol is employed in the detection of myocardial ischemia, there are several factors responsible for difficulties in interpretation of the electrocardiographic changes.

Definition of ECG Criteria of Ischemia

As previously suggested, selection of the optimal criteria for judging whether an S-T segment response is normal or abnormal is
complicated by the fact that rigorous criteria result in a high percentage of false-negative responses, while less rigorous criteria result in an increase in the frequency of false-positive responses.

Another recurrent problem of assessing the meaning of ECG changes induced by exercise relates to the significance of junctional (J-point) depression. While Master and Rosenfeld believed that 30% of patients they studied who manifested a "J" type of depression had organic heart disease, Robb and Marks found that persons having junctional depression had the same coronary mortality rates as those with no such changes on exercise. However, these latter authors did not distinguish between degrees of junctional depression. Other observers consider that junctional depression greater than or equal to 1-1.5 mm constitutes an abnormal response, and it has been shown that such changes may precede the onset of exercise-induced "ischemic" S-T segment depression. Several attempts have been made to develop more reliable criteria for "normal" and "abnormal" junctional depression. Lepeschkin and Surawicz employed the QX/QT ratio to facilitate measurement of junctional changes. The numerator QX represents the duration from the onset of the Q wave to X, the point at which the S-T segment returns to the isoelectric line. QT is the duration of electrical systole. Other investigators have measured the area bounded by the S-T segment and the isopotential line and the area that represents the first half of the interval between the QRS and the end of the T wave. In addition, the S-T segment slope (mv/sec) has been plotted against the magnitude of S-T depression. It must be concluded, however, that the relationships between ECG changes other than horizontal or downsloping S-T segment depression and the findings on selective coronary arteriography are not known, and no definitive conclusions concerning the reliability of these additional criteria can be made at present.

**Exercise Protocols**

A major problem impeding a definitive assessment of the reliability of exercise testing is the lack of uniformity of exercise protocols used in different laboratories, so that results of one investigation cannot be meaningfully compared to those of others. Mason and Likar, using a constant-load bicycle ergometer, exercise patients for 5 min at each load level with 5-min intervening rest periods until an end point is reached— ischemic ST-T depression, chest pain, fatigue, or a heart rate of 90% of the predicted maximal for the patient's age. Other laboratories also utilize the bicycle ergometer for exercise testing, but a standard interlaboratory protocol has not been adopted. In the hope of eventual standardization, it should be pointed out that myocardial oxygen consumption, as approximated by the triple product of heart rate, systolic pressure, and ejection time, tends in most instances to reach a steady state by about the fourth minute of exercise at a single work load. It would therefore appear unnecessary to continue exercise at each work load for longer periods.

Similar nonuniformity of exercise protocols is found in laboratories utilizing the treadmill. The initial level of the treadmill protocol devised by Bruce et al. is 1.7 mph at a 10% grade (expressed as vertical lift in percent of horizontal travel) with increments every 3 min of 0.8 mph and 2% grade. In contrast, Kattus keeps grade constant (10%) and increases speed by 0.5 mph every 3 min. Naughton and co-workers' initial level is 2.0 mph at zero grade with increments of 3.5% every 3 min while speed remains constant.

**Recording Technics**

Differences in recording technics also influence the results of exercise testing. It has been shown that virtually all the S-T segment information contained in the conventional 12-lead exercise ECG is contained in leads II, aVF, and V5-V6. Moreover, Blackburn and co-workers found that 89% of that information is contained in lead V5. In a series of 100 middle-aged males having ischemic S-T segment changes of ≥0.5 mm in one or more leads of a 12-lead ECG after the double Master's
two-step test, the ratio of positive findings in the left lateral leads (I, aV_L, and V_4–V_6) to the vertical leads (II, III, and aV) was 10:1. Similar results have been obtained using the Frank lead system. Thus it was found that 65% of patients had changes confined to the X lead, 25% to both X and Y, and 10% to Y. Because of these results, attempts have been made to simplify the lead system used for recording purposes. Investigations in which the relative lead strengths and discriminative power of several bipolar leads have been studied have shown that the greatest R-wave height and greatest S-T depression are found in leads CM_5 and CS_5 (CM_5 = reference electrode over manubrium sterni, exploring electrode at V_5; CS_5 = reference electrode over right lateral subclavicular area, exploring electrode at V_5). Although the sensitivity-specificity relationships to ischemic heart disease of bipolar-lead systems is not known, Blackburn’s study of the relative discriminative power of the 12-lead ECG, bipolar leads, and XYZ leads suggests that the bipolar leads are at least as sensitive as the 12-lead ECG, while the XYZ leads are less sensitive. We are currently using the CM_5 bipolar lead with a third electrode placed on the sacrum for recording a vertical lead in order to detect inferior-wall changes which may not be visible on transverse leads.

Skin-Electrode Contact

Improvement in the quality of the signal at source clearly facilitates processing of the data and more accurate analysis. An important factor is removal of the superficial layers of the epidermis which cannot be consistently accomplished by use of electrode paste. Dermal abrasion with a needle or dental burr is now generally accepted as giving optimal results. Low-mass silver-silver chloride electrodes constructed in such a way that the electrode is separated from the skin by 1–2 mm give better signals than other types of plate electrodes. Wire mesh is also a satisfactory material to use for the skin electrode, and this is probably due to close contact made between the mesh and the paste in its interstices. Sources of motion artifact and baseline drift which derive from change in contact resistance between the skin and the electrode are thereby minimized. Placing electrodes on the trunk at bony sites also has the advantage that considerable noise reduction can be achieved compared to the conventionally placed limb lead sites. McHenry has found that for optimal recording purposes the resistance across the electrodes, wires, and skin-contact points should be less than 1000 ohms.

Sensitivity and Specificity of Coronary Angiography

Finally, it is generally assumed that the absence of coronary artery disease as ascertained by coronary angiography indicates an absence of ischemic heart disease, and, conversely, the presence of angiographically demonstrable significant anatomic disease indicates the presence of ischemic heart disease. However, coronary arteriography is not a foolproof method of diagnosing either coronary artery disease (an anatomic abnormality) or ischemic heart disease (a physiologic abnormality), and it is quite possible that a certain percentage of patients judged to have false-positive responses to stress testing do indeed have coronary artery disease undetected by arteriography. Similarly, patients with minor degrees of angiographically documented coronary artery disease, interpreted as indicating ischemic heart disease, may not in fact be experiencing ischemic symptoms. In our experience, however, it is uncommon for a patient with classical angina pectoris to have normal coronary arteries. Conversely, it is very uncommon for patients with chest pain syndromes that historically do not sound ischemic in origin to have major narrowing of a coronary vessel. On this basis we believe that any errors made in estimating the frequency with which false-positive or false-negative responses to exercise stress tests occur are small when the diagnostic touchstone is coronary arteriography.

Computerization of ECG Data

Considerable interpretive variation has been
shown to occur when the exercise electrocardiogram is processed manually.\textsuperscript{72} For this reason increasing attention has been paid to computer technics for eliminating subjective error in measurement. Pertinent to these technics is the importance of obtaining an optimal ECG signal from which to compute the S-T segment changes. Even with adequate skin preparation and electrode design and placement, there is frequently noise artifact that will further be accentuated by exercise. For this reason, methods have been devised to further reduce the signal artifacts.\textsuperscript{71, 73} Such technics rely on the fact that a large percentage of signal noise in a typical exercise record occurs at random and can therefore be eliminated by appropriate averaging technics. In addition, AC noise can effectively be eliminated by 60-Hz notched filters or low-pass filters (30–40 Hz), although ECG signal distortion will occur especially with cutoff frequencies as low as 30 Hz.\textsuperscript{73} Baseline shift presents special problems, and although it can be reduced or eliminated by low-frequency filtering (1–2 Hz), Berson and Pipberger\textsuperscript{74} have shown that this frequently produces significant distortion of the ECG signal. A cutoff frequency of less than 0.1 Hz and preferably 0.5 Hz has been recommended to avoid these errors;\textsuperscript{74, 75} these criteria do not appear to influence the S-T segment and will distort the T wave by less than 0.1 mv.

Prognostic Implications of Exercise Stress Tests

Most of the preceding discussion has related to use of exercise stress testing as an aid in the diagnosis of ischemic heart disease in the individual patient. A different application of this technic is to be found in epidemiologic studies in which exercise stress testing has been evaluated as it relates to prognosis. Robb and Marks\textsuperscript{56} analyzed the results of the Master’s double two-step stress test in insurance applicants. The death rate from coronary artery disease was found to be eight times higher among those subjects with a positive exercise test than among those with a negative test. In addition, mortality was found to increase as the amount of S-T segment depression induced by the stress test increased (fig. 4). Similarly, Mattingly\textsuperscript{76} has shown in a 10-year follow-up that of 145 patients with positive double Master’s tests there was a cumulative incidence of myocardial infarction of 38%, with a 55% fatality rate. However, in both these studies many of the patients had overt clinical evidence of possible coronary artery disease. The question can therefore be raised as to whether results similar to those obtained with exercise stress testing would have been obtained by simply following those patients who had symptomatic or resting electrocardiographic evidence of coronary artery disease.

In contrast to the above investigations, Doyle and Kinch\textsuperscript{77} studied the frequency with which ischemic heart disease can be inferred from S-T segment changes occurring in totally asymptomatic subjects after submaximal exercise, using either the Master’s double two-step test or a standard treadmill test. The study group comprised 2003 subjects without overt evidence of existing coronary artery disease, e.g. those without antecedent myocardial infarction or angina pectoris and who had a normal exercise test at entry into the study.

Table 1

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{ Coronary Death Rates} & \textbf{ Per 1,000 Person Years of Observation} \\
\hline
\textbf{ Non-ischemic} & 3 & 12 & 25 & 101 \\
0.1–0.9 mm & & & & \\
10–19 mm & & & & \\
\geq 20 mm & & & & \\
\hline
\end{tabular}
\end{center}

\textbf{Figure 4}

Mortality rates in relation to the degree of S-T segment depression obtained during Master’s stress tests. (Reprinted from JAMA, by permission.)\textsuperscript{56}
Figure 5 shows the yearly cumulative probability of not developing an overt manifestation of ischemic heart disease (angina pectoris, myocardial infarction, or coronary death). Of the 75 men who developed abnormal exercise tests during the course of the study, 85% developed overt disease over the next 5 years. This contrasts markedly to the follow-up of the subjects who continued to have normal exercise tests; these individuals had only a 1.5% probability of developing overt manifestations of ischemic heart disease over 5 years. Another longitudinal study of 756 asymptomatic men showed that, of 23 with an abnormal electrocardiographic response to stress, there was a 70% probability of developing further ischemic symptoms or signs in the next 3-10 years. Similarly, Bellet et al. followed 795 asymptomatic men, aged 30-65 years, for 3 years and found a tenfold increase in coronary episodes in the group with positive exercise tests compared with the group with negative tests. Moreover, Doyle and Kinch also found that, of the 264 asymptomatic men with normal exercise stress tests on admission to the study who eventually died coronary deaths or who developed angina or myocardial infarction, 30% developed an abnormal stress test as the first manifestation of coronary artery disease. There is thus ample evidence to suggest that an abnormal stress test has high predictive value for coronary artery disease.

It should be pointed out, however, that predictions of percentage risk for a given subject or group of subjects is undoubtedly not only dependent on the type of exercise protocol, ECG criteria, and recording technics employed, but also on the subject population selected for study. For example, the results of studies in which the patient population is selected because of the presence of some type of chest pain probably cannot be extended to persons with similar degrees of exercise-induced S-T segment depression but with no overt clinical suspicion of coronary artery disease. In addition, Doyle and Kinch found that in asymptomatic subjects the probability of developing an overt manifestation of ischemic heart disease is markedly different in the individual who develops an abnormal exercise test during follow-up as compared to the individual who at initial evaluation is found to have an abnormal stress test. Thus, the cumulative probability of developing another manifestation of ischemic heart disease was considerably lower in the subjects with an abnormal initial exercise stress test than that found in subjects with a normal initial stress test that became abnormal after entering the study (fig. 5). As the authors indicate, the subjects presenting with an initially abnormal test are highly selected as compared to those with an initially normal one, since they represent the survivors of a group of undetermined size whose exposure to risk of ischemic heart disease is not known.

**Indices other than Electrocardiographic for Detection of Ischemic Heart Disease**

**Ventricular Gallops**

Several studies have been carried out to determine the prevalence with which third and fourth heart sounds occur in patients with ischemic heart disease and whether the frequency with which these sounds can be elicited during stress tests can be utilized as an additional criterion in the diagnosis and prognosis of ischemic heart disease. McGinn
and associates compared the phonocardiographic findings at rest in 30 patients with fluoroscopically evident ventricular aneurysms following myocardial infarction with a second group of 30 patients without evidence of aneurysm following infarction. Although an S4 was more frequent in patients with an aneurysm (83%) it was recorded in a significant percentage of patients with no aneurysm (23%). More recently, Aronow et al. compared the effects of exercise (double Master’s) on the prevalence of recorded fourth heart sounds in patients with angina pectoris with its effects in a group of subjects who on clinical grounds were judged to be normal. At rest, 43% of patients and 14% of normal subjects had a fourth sound while after exercise this was recorded in 94% of patients and 29% of normal subjects. In addition, 15% of patients had a third sound at rest compared with 1% of normal subjects. After exercise a third sound was recorded in 60% of the angina patients and 11% of normal subjects. The presence of an S4 in the normal subjects was not associated with hypertension, valvular disease, or known myocardial disease. It was noted, however, that 18% of the subjects with an exercise-induced S4 also had an abnormal exercise electrocardiogram (S-T depression \( \geq 0.5 \) mm). Quite obviously, however, the frequency with which this sound occurs in subjects with angiographically documented normal coronary arteries must be determined before the appearance of an S4 during stress testing can be used as an indicator of underlying coronary artery disease.

**Intensity of S4**

Based on the assumption that an increase in the intensity of S4 during exercise reflects, among other things, an exercise-induced increase in dP/dt, Bergman and co-workers have reported preliminary evidence to suggest that the degree of increase in the intensity of S4 during exercise may prove useful in documenting ventricular dysfunction due to coronary artery disease. Thus, during bicycle exercise in normal subjects there was a 3.2-fold increase in the intensity of S4 for a heart-rate increment of 30 beats/min compared with a 1.8-fold increase in patients with angina pectoris. Moreover, the intensity of S1 decreased at the work load which precipitated angina compared with its intensity during the preceding work load, despite further increase in heart rate. Additional studies by these investigators suggest, however, that there may be considerable overlap between the patient and normal groups depending on the degree to which ventricular function is impaired.

**Systolic Time Intervals**

Determination of the phases of left ventricular systole by means of external recordings has provided a noninvasive method of detecting alterations in myocardial performance. Pouget and co-workers have shown that systolic time intervals in patients with angiographically documented coronary artery disease differ from those in clinically normal individuals both at rest and after a standard exercise load. At rest, the preejection period (PEP) was longer and the corrected left ventricular ejection time (LVET) shorter in patients with angina pectoris than in the control group of normal subjects. After exercise, the shortening of the PEP in the angina group exceeded that of the normal group while LVET increased in patients with angina pectoris and remained unchanged in normal subjects.

It has been shown that the systolic time intervals at rest in normal subjects and in patients with ventricular failure or myocardial ischemia show considerable overlap. Although the response to exercise may effect a clearer separation of normal subjects and patients with myocardial disease, further studies are necessary to define the sensitivity-specificity relationships of systolic time intervals in the diagnosis of ischemic heart disease.

**Conclusions**

When the relative usefulness of stress testing is evaluated, two general applications of such testing procedures must be considered: epidemiologic and diagnostic. On the
basis of the material presented in this review, it seems clear that exercise stress testing is of value in epidemiologic studies of ischemic heart disease. This use of stress testing is of particular interest when applied to studies in which asymptomatic subjects are being assessed since (1) an abnormal exercise stress test occurs in about 30% of patients as the first manifestation of ischemic heart disease, and (2) the appearance of an abnormal exercise stress test in an asymptomatic patient during the course of follow-up examinations suggests that the patient is in a group at high risk of developing an overt clinical manifestation of ischemic heart disease within the next several years.

Before summarizing our conclusions regarding the usefulness of stress testing as a diagnostic procedure, i.e., its ability to detect the presence or absence of ischemic heart disease in the individual patient, it would be helpful to consider the comparable accuracy of the history in determining whether chest pain is ischemic or nonischemic in origin. Ross and Friesinger, examining the frequency with which coronary artery disease was correctly diagnosed on the basis of a careful history, found that when an individual had typical angina pectoris and the clinical diagnosis of coronary artery disease was made, the frequency of a false-positive diagnosis, as judged by coronary angiography, was only 4%. That is, the correct diagnosis was made in 96% of cases. On the other hand, when all physicians agreed that the patient's chest-pain syndrome was not that of angina pectoris, the frequency with which patients with angiographically documented coronary artery disease were diagnosed as not having coronary artery disease was only 12%. That is, the correct diagnosis was made in 88% of cases. The most difficult group of patients to diagnose were those having chest pain designated as "atypical angina pectoris" (pain which had some but not all the characteristics of typical angina pectoris). Ten of 25 such patients had normal coronary arteries (fig. 6). Similar results were obtained by McConahay and co-workers who more recently correlat-ed the relative diagnostic accuracy of the history and exercise stress testing in patients with chest pain.

Thus, the specificity and sensitivity of a careful history in the diagnosis of coronary artery disease seems to be equal or superior to that of stress testing in both patients with typical angina pectoris and patients with a chest-pain pattern that by history does not resemble that of angina pectoris. Therefore, in these two groups of patients, exercise stress testing would appear to be superfluous since it provides no additional information beyond that which can be obtained from the patient's history. The patients with chest-pain syndromes who present the greatest diagnostic problem are those with "atypical angina," and it is in these patients that a reliable noninvasive test for distinguishing ischemic from nonischemic pain would be of great value. Unfortunately, an overall assessment of the results of virtually all published studies indicates that presently employed stress tests are not sufficiently sensitive or specific to aid
satisfactorily in solving this problem. Whether greater reliability of diagnostic stress testing will result when the results of such studies are used in conjunction with other noninvasive procedures or laboratory tests remains to be determined.

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