Use of Exercise Testing for Diagnostic and Functional Evaluation of Patients with Arteriosclerotic Heart Disease

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SUMMARY
Myocardial oxygen demand generally increases with increasing levels of energy expenditure, but several factors which modify this relation must be considered, both in the design of the test methods and in interpretation of results of exercise tests in patients with arteriosclerotic heart disease (ASHD).

A wide variety of exercise test methods are currently used. Master's test is simple to perform and requires no elaborate equipment. It has been more widely employed than any other test and much clinicopathologic and correlative data are available. However, Master's test provides little information on the patient's physical work capacity. Multistage tests, carried to a symptom-limited or maximal/near-maximal workload level, provide quantitative data on physical performance capacity and also result in fewer false-negative ECG responses among patients with ASHD.

Follow-up studies of asymptomatic subjects have demonstrated that a horizontal S-T depression during or after exercise is associated with a high risk of developing clinical ASHD. The prognostic significance of the exercise test appears to be independent of other known risk factors.

Studies correlating the ECG response to exercise with findings at coronary angiography have demonstrated an abnormal ECG response in 0–30% of patients with no demonstrable arterial disease. The number of patients with significant coronary artery disease and negative ECG response tends to be higher.

Evaluation of physical performance capacity is the primary indication for exercise testing in patients with known ASHD. The results of the test form a basis for recommendations on occupational and recreational physical activity. Serial tests may be used to evaluate objectively the effect of medical and surgical therapy.

Additional Indexing Words:
Myocardial oxygen demand Occupational activities Energy expenditures
Exercise methods and end points Exercise risks Electrocardiography
Latent coronary disease Chest pain Isometric exercise

Clinical exercise testing in the past was performed primarily to provoke electrocardiographic abnormalities. The results were interpreted in purely qualitative terms: presence or absence of signs of myocardial ischemia. Modern graded exercise tests serve the dual purpose of provoking ECG abnormal-

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EXERCISE TESTING

... or other diagnostic symptoms and signs and providing a basis for quantitative evaluation of the physical performance capacity or the degree of physical impairment. Progressive increases of work loads are used, and the test is carried to the intensity at which the patient develops limiting symptoms and signs, including ECG signs of ischemia, or approaches his maximal rate of energy expenditure. Peak levels of exercise are characterized with respect to work load, oxygen uptake, or indices of myocardial oxygen demand. This information can be utilized in many different ways, e.g., to supplement the standard classification of function in patients who are candidates for surgery, to evaluate objectively the results of various medical or surgical therapeutic interventions, and to serve as a basis for advice on physical activity. The application is not limited to arteriosclerotic heart disease (ASHD). Exercise tests are now frequently performed on patients with chronic heart disease of any etiology.

Physiologic Considerations

Determinants of Myocardial Oxygen Demand

Intramyocardial tension (determined by intraventricular pressure, ventricular volume, and myocardial mass), heart rate and the contractile state are the major determinants of myocardial oxygen demand. External work, the product of load and fiber shortening, requires relatively little energy above that utilized in the development of wall tension. Raising external work by increasing stroke volume is much less costly than increasing cardiac work to the same extent by elevating ventricular pressure. The effect of increased contractility on myocardial oxygen demand is important but not always apparent in a clinical situation. An increase in the velocity of fiber shortening is associated with increased utilization of energy, but the demand for increased oxygen supply may be offset by a simultaneous decrease in ventricular volume and a decrease in wall tension.

Various indices derived from hemodynamic measurements have been used to estimate myocardial oxygen demand. Arterial or left ventricular pressure is taken as an indication of wall tension. Tension-time index (TTI), the integral of the ventricular pressure curve, has been widely used since Sarnoff and associates demonstrated in a controlled animal preparation that the product of heart rate and peak systolic blood pressure under certain conditions correlated poorly with myocardial oxygen uptake.

Recent studies on patients with coronary disease and in normal subjects suggest that the less complicated heart rate times blood pressure product is a more accurate index for the intact human subject than TTI, and the results of several clinical studies support its validity. Use of the triple product, heart rate x systolic blood pressure x left ventricular ejection time, may improve the accuracy of predicted myocardial oxygen demand, but the evidence is equivocal. Even the simple measurement of heart rate during exercise gives a fair estimate of myocardial oxygen demand.

Circulatory Response to Various Activities

The maximal energy expenditure that an individual can attain may be defined clinically by measurement of maximal oxygen uptake. Various methods are used. All are based on exercise engaging large muscle groups, and oxygen uptake is measured during exercise at increasing work loads. Maximum is reached when an increase in work load no longer is associated with an increase in oxygen uptake, that is, when the oxygen uptake at a given work load falls significantly below the expected value.

Maximal oxygen uptake is frequently used as an index of physical work capacity or physical performance capacity for clinical purposes since oxygen transport is the limiting function in most patients with cardiovascular disease.

Standard classifications of various jobs and activities primarily reflect levels of energy expenditure. A classification based on peak loads is shown in table 1. Changing the base to loads that may be maintained for prolonged periods, i.e., for more than ½ to 1 hour, would reduce caloric expenditure by 50%. The
Table 1

Classification of Occupational Activities

<table>
<thead>
<tr>
<th>Class</th>
<th>Peak caloric expenditure* (cal/min)</th>
<th>Typical peak heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>2.5</td>
<td>90</td>
</tr>
<tr>
<td>Light</td>
<td>5</td>
<td>110</td>
</tr>
<tr>
<td>Medium heavy</td>
<td>7.5</td>
<td>130</td>
</tr>
<tr>
<td>Heavy</td>
<td>10.0</td>
<td>150</td>
</tr>
</tbody>
</table>

*The caloric equivalent of an oxygen uptake of 1 liter/min varies between 4.8 and 5 depending on the relative rate of carbohydrate and fat metabolism.

classification closely corresponds to that used by U.S. Department of Labor.

Most professional activities, domestic work, and most tasks in light industry, laboratory and hospital work, retail, and distribution are classified as sedentary or light. Jobs in building and construction, agriculture, steel industry, and armed services fall in the medium and heavy range. The highest energy expenditures, occasionally exceeding 10 cal/min, are found in commercial fishing, forestry, mining, and dock labor.

Duration of Work

There is a close correlation between energy expenditure and myocardial oxygen demand during steady-state work that involves large muscle groups. Heart rate and systolic blood pressure are linearly related to oxygen uptake.

The relation between energy expenditure and the load imposed on the circulatory system becomes more tenuous with shorter duration of the activity. Cardiac output and oxygen uptake do not reach a steady state until at about 2 min after the beginning of work at a fixed submaximal rate, and the blood pressure response is also gradual. Most occupational work except in the sedentary category tends to be intermittent in nature. Relatively short periods of strenuous activity alternate with low intensities. Persons with a low physical work capacity and a low maximal oxygen uptake are likely to tolerate surprisingly high work loads provided that the peaks are of short duration and that adequate rest periods are interspersed. On the other hand, peak loads of short duration that contribute little to the average level of energy expenditure will sometimes rule out a given job for a patient with angina pectoris who would have no difficulties at a work-load level equal to the 8-hour average for the job.

Endurance athletes (long-distance runners, cross-country skiers) are able to sustain high levels of effort over prolonged periods. Untrained persons cannot ordinarily utilize more than 50% of their capacity for more than 1 hour. Studies have been made of construction workers in jobs demanding heavy labor, motivated by a piece-work pay system but with freedom to regulate the pace within reasonable limits. They tended to select an average work intensity during actual working hours corresponding to 40% of maximal capacity. An average level of 30% of capacity as calculated for a full 8-hour period has also been generally advocated as the upper limit for safe employment.

Type of Work: Isometric Exercise

A series of conditions other than the duration of the effort is known to affect the relationship between energy expenditure and the determinants of myocardial oxygen demand. Much attention has recently been focused on isometric exercise.

Isometric exercise may be defined as a sustained muscular contraction against a fixed resistance. Isometric effort is part of many daily life activities, e.g., lifting, carrying, and pushing various objects. It seems likely that the word "isometric" should not be interpreted too strictly and that the characteristic circulatory response is caused by sustained development of tension in the muscle as opposed to the very brief tension development alternating with relaxation during dynamic exercise of such types as walking and running. Lind and co-workers demonstrated that a sustained isometric forearm contraction caused a marked increase in blood pressure, proportional to the tension, probably mediated by stimulation of sensory nerves and a reflex increase in heart rate and cardiac output. The amount of muscle mass involved seems to have little effect on the response.

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Angina pectoris is less frequently provoked by an isolated isometric contraction than by dynamic exercise despite the large increase in blood pressure. Only one of 20 patients studied by both methods in our laboratory had angina during a handgrip test (unpublished observations). The heart rate increase is relatively small, and the heart rate-blood pressure product is almost always below the threshold level reached during bicycle exercise. On the other hand, ventricular arrhythmias are more readily provoked by handgrip stress than by dynamic exercise, particularly in patients with coronary disease.15

Many activities include a combination of dynamic and isometric exercise. The blood pressure response to isometric exercise tends to be an increase of the same magnitude whether the basal condition is rest or dynamic exercise.14 The additive effects are apparent during arm work, e.g., hand cranking. Both systolic and diastolic blood pressures are significantly higher during arm work than during leg work at any given level of oxygen uptake.16, 17

Temperature
That cold temperatures lower the threshold for angina pectoris is well known. The mechanisms seem to be an exaggerated heart rate and blood pressure response to a given work load, and also a small increase in oxygen uptake.17, 18 Angina pectoris tends to occur earlier, and S-T depressions are more prominent than under standard laboratory conditions. Corresponding data on the effects of exercise in hot environments on angina patients are not available.

Emotional Stress
Many activities represent a combination of emotional and physical stresses. It is well known that anxiety can modify the circulatory response to exercise.19 The circulatory changes associated with alterations of effect, however, are usually of relatively small magnitude. Recorded increases in heart rate and blood pressure during stressful interviews and other situations have generally been modest, usually less than 25 beats/min and 25 mm Hg.20, 21 Many activities represent a combination of emotional and physical stresses. There are several studies (recently reviewed by Simonson and co-workers22) on the cardiovascular response to automobile driving under various conditions. Heart rate increases of more than 30 beats/min are seen only in a minority of drivers even in heavy urban traffic. Blood pressure increases of more than 20 to 30 mm Hg are also unusual. Nonspecific ECG changes have been observed in as many as one third of the normal subjects and one half of the patients with angina pectoris, but ischemic changes are less frequent; a 10% incidence of ischemic S-T depression during driving has been reported in one series of 48 patients with coronary disease. Extremely high heart rates have been observed in professional drivers monitored during car races, in test pilots, and in downhill skiers immediately before the race. Sinus tachycardia with rates of 180 to 200 beats/min is not unusual under these conditions.

Hellerstein and Friedman23 found in a series of middle-aged, middle-class men with ASHD that conjugal sexual activity imposed only a relatively low load on the cardiovascular system. Peak heart rates during intercourse varied between 90 and 144 beats/min, mean 117. The heart rate increase and electrocardiographic changes were usually comparable to or less prominent than those during peak loads at work.

Exercise Test Methods
Master's Test
The test is simple to perform and requires no elaborate equipment. More important, the amount of clinicopathologic correlative data and follow-up data available on the ECG response to Master's test is much larger than that for any other exercise procedure. However, it is not a satisfactory procedure for quantitation of the degree of disability. It may be used as a screening test since any patient who is able to complete a double Master's test with no or only slight symptoms also is likely to meet the physical demands of any job classified as sedentary or light.
The energy expenditure irrespective of body size is approximately 8.5 cal/min which corresponds to an oxygen uptake of 1.7 liters/min.\textsuperscript{25, 26} A subject with low body weight is penalized since maximal oxygen uptake in terms of liters per minute is closely correlated to lean body mass. He will as a rule perform exercise at levels closer to his maximal capacity than a heavier subject. Single-stage treadmill tests or step tests requiring the same number of trips and equal duration of exercise for all subjects share two major disadvantages with the Master test:

1. Large interindividual variability exists with respect to the myocardial oxygen demand imposed by the test as judged from the heart rate response. Peak heart rates during exercise ranging from approximately 90 to 180 beats/min have been reported\textsuperscript{27, 28} for a double Master's test and a treadmill test of comparable intensity (speed 3 mph; 5% grade).

2. Physical performance capacity can only be characterized as being above or below a certain level of energy expenditure.

The level of energy expenditure during a Master's test may be characterized as moderately heavy for the average healthy adult man, but the work load is sometimes too light to precipitate symptoms and signs in patients with ASHD and high physical work capacity. On the other hand, the work load is supramaximal for many patients with angina pectoris. These patients are forced to discontinue exercise before a steady state is reached, i.e., in a phase during which heart rate and blood pressure are increasing rapidly.

The interval between the beginning of exercise and the onset of angina pectoris during a Master's test has been used as a measure of physical performance capacity. However, angina will usually occur during the initial, nonsteady phase of exercise when the steady-state requirements grossly exceed the patient's myocardial oxygen supply. Significant improvement in performance capacity may be induced by antianginal drugs. Changes are readily demonstrated when the patient undergoes serial multilevel exercise tests, including levels well below the threshold of angina. If the load is supramaximal, significant changes may be completely obscured or reflected only as insignificant changes in the time required to produce angina pectoris.\textsuperscript{9}

**Multistage Tests**

Modern tests are designed to satisfy the dual requirements (1) of provoking electrocardiographic abnormalities and other diagnostic symptoms and signs and (2) of providing a basis for quantitative evaluation of physical performance capacity. Taylor's group\textsuperscript{28} have recently reviewed current procedures. Three basic forms of exercise are used: step climbing, treadmill, and bicycle ergometer exercise. All involve dynamic leg exercise. Any of the three methods may be used for determination of maximal oxygen uptake. The oxygen uptake achieved during exercise involving smaller muscle groups, e.g., during dynamic arm or during isometric exercise, is significantly below that seen during leg work at maximal intensity. Maximal oxygen uptake measured during bicycle exercise tends to be slightly lower than during treadmill exercise. However, the difference is small, usually about 10%, and unlikely to be of clinical significance. Hemodynamic data from normal subjects indicate that maximal heart rate and total arteriovenous oxygen difference are similar during maximal treadmill and bicycle exercise. The lower maximal oxygen uptake during bicycle exercise is associated with a lower maximal stroke volume and cardiac output than during treadmill exercise. Arterial blood pressure tends to be somewhat higher at any given level of oxygen uptake during bicycle exercise.\textsuperscript{29, 30} Small differences with respect to ventilation and lactate levels have also been reported.

Use of leg exercise tends to minimize interindividual variations in mechanical efficiency. This is important from a practical point of view since it obviates the need for direct determination of oxygen uptake in routine applications. Oxygen uptake during a step test and during treadmill or bicycle ergometer exercise at submaximal levels may be predicted with fair accuracy (± 10%) from parameters defining the work load.\textsuperscript{31} All three
methods are compatible with ECG monitoring during exercise. Selection may be based on criteria such as cost and bulkiness of the equipment, the relative ease with which cardiographic recordings can be made, and acceptability to the patient.

A large number of different test protocols are now in use. A majority may be classified as belonging to one of three basic types: (1) continuous test with stepwise load increment with duration of exercise at each level of 1 to 3 min; (2) continuous test with an initial rapid increase in work load and subsequent adjustment of the work-load level to reach a predetermined heart rate which then is maintained for 2 to 3 min; (3) exercise for 5 to 6 min at each level in a series of progressively heavier work loads, interspersed with rest periods.

Type 1 was originally designed by Balke and Ware32 to be used as a physical fitness test and for rapid determination of maximal oxygen uptake. It has been adapted for clinical use by Bruce and associates33 and employed on a large series of normal subjects and patients. Type 2 was described by Sheffield and co-workers.34 It is the most rapid of the methods but has an inherent disadvantage of providing a less accurate basis for estimation of oxygen uptake than the other two types. The target heart rate is usually 85 or 90% of the average age-specific maximal rate. Type 335 is time-consuming, but most subjects approach a steady state at submaximal loads. Multiple measurements may thus be obtained at each level. Initial work load and magnitude of the increment usually correspond to oxygen uptakes of 0.6 to 0.9 liter/min but may be reduced for patients with a history suggesting low physical performance capacity.

The physical work load during a treadmill test or a step test will define oxygen uptake in terms of “ml/kg × min” while the bicycle ergometer load determines oxygen uptake in absolute units or as liters per minute. Results can easily be compared by using body weight as a conversion factor. The work load during treadmill exercise may be varied by changing speed or grade or both. The load during bicycle exercise or the power developed while pedaling may be measured as watts or kilogram-meters per minute (kg-m/min). One watt equals 6 kg-m/min. The load is sometimes given as kilopond-meters per minute (kp-m/min). The pond is the force by a mass of 1 kg at normal acceleration of gravity, i.e., kg-m/min and kp-m/min are identical under normal laboratory conditions but not in outer space.

More work has to be done to establish to what extent findings during exercise tests performed according to different protocols are truly comparable. It may prove feasible to base comparisons of results obtained by different methods on common standards of reference, e.g., oxygen uptake for physical performance capacity, and heart rate or heart rate × systolic blood pressure for myocardial oxygen demand. Table 2 lists bicycle and treadmill loads equivalent to a Master's test.

**ECG Technic**

Technical aspects of exercise electrocardiography have recently been reviewed in detail by Blackburn.36 Current standards call for ECG monitoring and recording during exercise to increase both patient safety and diagnostic yield. Careful attention to the methodology is a requirement for the production of records of acceptable quality. Several sources contribute to a lower signal-to-noise ratio during exercise than at rest. The electrical activity of skeletal muscle immediately underlying the electrodes will inevitably be recorded and can only be avoided by proper selection of electrode sites. Variations in skin-electrode contact associated with motion are another important source but may be minimized by the use of any of several light-weight well-type or liquid contact electrode systems. Special low-noise electrode cables in which the standard braided shield has been replaced by metallic dust have also reduced the magnitude of various motion artifacts. Careful skin preparation to reduce the skin resistance is important. Dermal abrasion with a sterile needle or light application of a dental burr has been found useful by some investigators. Improvements in the electrode-cable

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Table 2

Equivalent Work Loads

| 1. | Master’s double-step test |
| 2. | Treadmill exercise at 3 mph, 10% grade |
| 3. | Bicycle exercise at 600 kg-m/min = 100 watts |

Oxygen uptake approximately 1.5 liters/min or 20 ml/kg X min for body weight of 75 kg.

assembly have largely eliminated the need for telemetric monitoring of the ECG in the laboratory setting.

Lead Systems

Three different classes of ECG lead systems are being used: (1) simple bipolar chest leads, (2) conventional or modified 12-lead systems, and (3) orthogonal or vector three-lead systems. Each lead and each system has specific advantages and disadvantages with respect to ease of application, sensitivity, specificity, and relative freedom from noise during exercise.

S-T depressions of the type generally recognized as ischemic tend to be oriented spatially in a direction opposite to that of the mean QRS vector. A lead with an electrical axis corresponding to that of precordial lead V7 or V8 should theoretically provide an optimal display of S-T abnormalities, but the amplitude is usually low in these leads. Furthermore, the normal S-T vector is frequently oriented anteriorly and therefore will be displayed as an S-T depression in leads V7 and V8 which are oriented posteriorly. Electrode positions corresponding to precordial leads V5 and V6 should offer the best compromise between sensitivity and specificity if a single lead is to be used. Clinical studies are in agreement with this conclusion. Blackburn studied a group of 100 patients with ASHD and significant S-T depressions. Ninety percent had S-T changes in one or more of the lateral leads (I, aV5, or V4, 5, 6) and 30% had S-T depressions in the vertical leads (II, III, and aVF). However, in only 10% of the patients was the S-T depression seen exclusively in a vertical lead. Blackburn also found corresponding distributions when using a vector lead system. Similar figures have also been reported by others. Most bipolar leads designed specifically for exercise testing in patients with ASHD also use a positive-electrode site corresponding to lead V5. The location of the negative electrode is variable. A high anterior chest or high back position (right subclavicular area, manubrium, or right inferior scapular border) includes a vertical component and performs better than a strictly horizontal lead.

A modified conventional system with left and right arm electrodes relocated to the subclavicular area and the left leg electrode to the left midclavicular line halfway between the left costal margin and the iliac spine has been designed by Mason and associates. This system, unlike the standard 12-lead system, performs well during exercise. The modifications introduce only minor changes in amplitude relative to the standard leads.

Orthogonal lead systems represent theoretical advantages over other systems in terms of information content per lead.

Available data suggest that the use of multiple rather than single leads is associated with a small but significant increase in sensitivity, probably of the order of magnitude of 10%. This gain has to be weighed against the obvious advantages of the simple bipolar leads with respect to recording and data analysis.

Exercise End Points: Criteria and Significance

Criteria

Modern procedures call for individual adjustment of work loads. Peak work load and the point at which the test is discontinued are always determined by criteria referring to the patient’s response. The target load for asymptomatic patients and normal subjects may be either maximal oxygen uptake or heart rate during exercise corresponding to 85 to 100% of the mean age-specific maximal heart rate. Most physicians discontinue the test at lower work levels if any of the following events is encountered:

1. Chest pain unless minor and clearly of extracardiac origin
2. Symptoms or signs suggesting cerebral ischemia

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3. Undue or unusual dyspnea, weakness, fatigue, pallor, or cyanosis
4. Fall in blood pressure or heart rate with increasing workload
5. Leg pain suggesting claudication
6. Significant electrocardiographic abnormalities if not present at rest
   a. Progressive horizontal S-T depression ≥1 mm (0.1 mv), progressive S-T elevation
   b. Serious dysrhythmias: increasing number of premature ventricular contractions (≥1/5), multifocal PVCs, runs of two or more PVCs, any sustained atrial tachyarrhythmia, and atrioventricular block
   c. Complete bundle-branch block or major atypical intraventricular conduction defect.

Symptoms and signs listed under 1 to 5 are all compatible with a restricted cardiac output or with deficient regional perfusion. Chest pain is included as an end point since angina pectoris may occur without ECG signs of ischemia.

Lack of motivation, inability to cooperate, and muscle and joint pain are the most common noncardiovascular reasons for interruption of the test before a target level has been reached. Clinical observation of the patient supplemented with measurements of heart rate and respiratory rate usually form a sufficient basis for deciding whether the patient has been limited by abnormal cardiopulmonary function or failed to exert himself. Measurements of oxygen uptake and lactate levels may be used to verify that a maximal or near-maximal work load has been achieved.31 A lower oxygen uptake than predicted indicates accumulation of an oxygen debt and anaerobic metabolism which are also reflected in high blood lactate levels. These data are particularly helpful in patients with cardiovascular or pulmonary disease since heart rates and respiratory rates frequently deviate from expected values.

**Significance**

Exercise tests provide information with respect to physical performance capacity and mechanisms limiting physical performance. Physical performance capacity is defined as the measured or estimated oxygen uptake at the point at which the patient experiences limiting symptoms. Other indices have been used, e.g., work load at a given heart rate, but are frequently misleading. Peak oxygen uptake may be related to age- and sex-specific normal standards49 (table 3) and to the known energy requirements of various occupational and recreational physical activities.

A detailed interpretation of the various symptoms and signs that may be observed during exercise is beyond the scope of this review. It should be emphasized that none of the end points listed above is specific for arteriosclerotic heart disease. Quantitative data on the significance are available only for electrocardiographic abnormalities.

The significance of horizontal or downsloping S-T depression was firmly established during the 1950's. Wood and associates40 separated horizontal or "ischemic" depression from physiologic depression of the QRS-ST junction. A series of population studies, including long-term follow-up studies, documented the validity of criteria requiring 0.5-mm or 0.05-mv horizontal or downsloping S-T depression below the level of the P-R segment at the onset of QRS for a diagnosis of borderline and of 1.0 mm or more for definite abnormality but failed to establish any definite correlation between ASHD and other ECG abnormalities, e.g., isolated T-wave changes.41 It has been clearly demonstrated that despite its predictive value in populations the 0.5-mm limit results in a large number of

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### Table 3

<table>
<thead>
<tr>
<th>Age</th>
<th>Oxygen uptake (ml/kg × min)</th>
<th>Mean</th>
<th>Lower limit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>41</td>
<td>31</td>
<td>28</td>
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<tr>
<td>45-49</td>
<td>38</td>
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<td>50-54</td>
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<td>55-59</td>
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</tr>
<tr>
<td>60-64</td>
<td>33</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>

*Lower limits represent mean — 2 sd.
false-positive diagnoses when it is applied to individual patients.42

Use of graded exercise test up to a maximal or near-maximal level has supported the conclusion of Wood's group40 that an isolated junctional S-T depression is a physiologic response. It has also been shown that in normal subjects the magnitude of junctional depression is proportional to heart rate.17, 38, 43 A physiologic junctional depression is sometimes superimposed on an abnormal segmental depression during exercise at high work loads and high heart rates. Punsar and associates44 and Sheffield45 have presented evidence to suggest that a slowly ascending (rate of change less than 1 mv/sec) S-T segment under these conditions is the equivalent of a strictly horizontal depression during less intensive exercise. It seems likely that further experience with graded tests eventually will result in the definition of multiple sets of criteria to be applied to specific heart rate levels and conditions, e.g., during exercise and at various intervals after exercise.

The significance of ECG changes during and after exercise in patients who have an abnormal ECG at rest has not been fully established. Progressive S-T-segment elevations in lateral or vertical leads are never seen in normal subjects but occur in patients with a healed myocardial infarction and residual QRS changes. S-T elevation during or after exercise is probably as specific as S-T depression.46

Horizontal or downsloping S-T depression is frequently seen in patients without coronary artery disease, but with other conditions it is likely to be associated with a discrepancy between myocardial oxygen supply and demand, e.g., left ventricular overload and hypertrophy from any cause, anemia, and arterial desaturation.47, 48

Dysfunction of the autonomic nervous system, with and without hyperventilation, may produce significant S-T depression during exercise on occasion.49 Abnormal sympathetic stimulation may produce ECG abnormalities in neurocirculatory asthenia. Characteristically, S-T depressions of this type are precipitated by prolonged standing as well as by exercise. They are rarely progressive, i.e., they tend to be as prominent or more prominent at low work loads than during heavy work and may be abolished by beta-adrenergic blockade.50

Digitalis may cause a segmental S-T depression during exercise even in the absence of significant S-T depression in the resting ECG.51 The effect of hypokalemia is disputed.52–54 The Wolff-Parkinson-White syndrome is frequently associated with a positive exercise test in the absence of ASHD.55 This may be true also for variant forms.56 Finally, meals, glucose administration, temperature-humidity extremes, smoking, and physical exertion preceding the test rarely by themselves cause segmental depression but are apt to exaggerate the degree of abnormality.41

Data based on studies of patients with verified ASHD demonstrate a highly significant increase in sensitivity (at least 33%) over the exercise ECG when a maximal or near-maximal load is used rather than a Master's test.27, 37, 57

The magnitude of the increase in sensitivity associated with ECG recording during, as well as after, exercise is not firmly established. A representative figure, 10%, was reported by Mason's group.37

There is evidence that an ischemic S-T depression is a highly reproducible finding.33, 54 and that transient arrhythmias and conduction defects provoked by exercise are highly variable.59

Observer Variation

Blackburn's group60 have demonstrated that diagnostic interpretation of the exercise ECG carries considerable interobserver variation. In this study a panel of electrocardiographers interpreted a selected series of postexercise ECGs according to their personal criteria. The rate of responses judged positive varied between 5 and 50%. The range decreased significantly to 27 to 37% when the participants were asked to adhere rigidly to specified criteria.

There are several reasons why computer technics are likely to prove helpful in exercise electrocardiography, e.g., by providing means
of eliminating noise and eliminating intraobserver variation.36

Risks and Safety Procedures
Mortality and morbidity attributable to exercise testing have recently been examined by Rochmis and Blackburn.38 They used questionnaires to obtain data from 73 physicians and physiologists. A majority of the respondents were associated with cardiology departments of teaching medical centers, or with work-evaluation units. The combined experience represented 170,000 tests with a predominance of multistage progressive tests (73%). A total of 16 deaths, giving a mortality of 1/10,000 tests, were attributed to the test and occurred within 1 week of the test. Eight deaths were immediate. Forty subjects were hospitalized for nonfatal events, usually chest pain or arrhythmias, i.e., a rate of 2.4/10,000 tests.

A large percentage of the participants required at least an abbreviated medical history and a resting ECG prior to testing. Common contraindications were (1) evidence of active or recent myocardial disease, (2) recent change in angina pectoris pattern, (3) acute noncardiac illness, and (4) serious arrhythmia.

Only a minority considered an abnormal resting ECG a contraindication to testing unless it was suggestive of recent myocardial infarction.

This is in variance with standard Master's test methodology and may reflect the fact that many of the patients included in the study by Rochmis and Blackburn had known ASHD and ECG abnormalities at rest. A Master's test is rarely used for patients of this type. Direct supervision by physician and ECG monitoring during exercise were required by a majority of participants in the Rochmis and Blackburn group. All but three respondents had available both a DC defibrillator and a staff trained in arrhythmia recognition and resuscitation.

Uses of Exercise Testing in Various Groups of Patients with Arteriosclerotic Heart Disease

Patients with Latent Coronary Disease
The value of the electrocardiographic exercise test in predicting future development of clinical arteriosclerotic heart disease in subjects who are asymptomatic at the time of the test was first demonstrated by Robb and associates,61, 62, Brody,63 and Mattingly.64

The material studied by Robb's group included 1,659 life-insurance applicants who underwent a double Master's test and who were followed for 2 to 11 years. Isolated junctional S-T depressions did not affect mortality. Ischemic or horizontal S-T depression was associated with a 4.4-fold increase in mortality. The ratio of actual to expected deaths increased progressively with the degree of S-T abnormality from 1.9 for horizontal depressions of 0.1 to 0.9 mm to 19.1 for S-T depressions of 2.0 mm or more. Approximately half of the men in this series had atypical chest pain.

Mattingly61 reported similar figures or a 4.8-fold increase in mortality in a series of military men with ischemic S-T depression.

Brody63 presented the first systematic study of 756 unselected asymptomatic subjects. Twenty-three of these subjects had ischemic S-T depression of 0.5 mm or more at the initial examination, and sixteen of the 23 men (70%) developed classical angina or had a myocardial infarction during a 3-year follow-up period. Corresponding figures for the 733 with a negative exercise test were 55 (0.75%). Ischemic S-T depression was associated with a nearly 100-fold increase in coronary morbidity.

A larger population study has recently been published by Doyle and Kinch.65 They subjected 2,003 men, most of them New York State employees, to an exercise test consisting of a treadmill walk for 10 min at 3 mph against a grade of 5%. The level of energy expenditure approximated that of a double Master's test. The group was followed for as long as 13 years. Twenty-eight men had an abnormal exercise ECG upon entry in the study, and 61% of these 28 subjects developed additional evidence of ASHD during the follow-up period. Seventy-five men developed an abnormal exercise ECG response during follow-up, and 45% of these 75 men also developed clinical ASHD.
The 5-year probability of developing clinical ASHD after the occurrence of a positive exercise ECG in an asymptomatic subject, calculated by using life-table technics, equaled 85%. Corresponding ASHD risk for a subject with normal exercise ECG was 2.5%, i.e., a positive exercise response was associated with a more than 30-fold increase in risk of ASHD.

The predictive power of the exercise ECG thus appears to be very high. It must be emphasized, however, that the incidence of positive tests in an asymptomatic middle-aged population is fairly low, or about 4% in both Brody's series and in the population studied by Doyle and Kinch.

The rate of abnormal responses increases significantly if higher work loads are used. Doan and co-workers reported segmental S-T depression in 24% of ostensibly healthy men between 50 and 59 years old. Similarly high rates have been found by others when using maximal tests. Sufficient follow-up data are not yet available to permit an evaluation of the effect of high work loads on specificity.

A positive exercise test is frequently associated with other risk factors, but Blackburn and associates have been able to show that a positive exercise test (step test, oxygen uptake of 1.5 liters/min) has a prognostic significance that is independent of age, blood pressure, serum cholesterol, obesity, smoking, and physical activity. A positive ECG implies a threefold increase in the risk of future clinical ASHD when all other risk factors are held constant.

Exercise Tests in the Differential Diagnosis of Chest Pain

Chest pain suggesting angina pectoris is the classical indication for exercise testing. Coronary angiography has been used as a standard in most recent attempts to evaluate quantitatively the diagnostic contribution of the exercise ECG.

A perfect correlation between angiographic and electrocardiographic findings should not be expected. James has recently discussed the sensitivity of coronary angiography. He expressed the opinion that most patients with classical angina pectoris and normal coronary arteries according to the interpretation of the angiogram do in fact have changes in their large coronary vessels. He pointed out that complete occlusion of a major branch near its origin may easily be overlooked. The diagonal branches of the left coronary artery are particularly difficult to evaluate. Complete occlusion of a vessel may not be associated with any regional imbalance between oxygen supply and demand, e.g., if the area previously supplied by the now-occluded artery has been completely transformed into a fibrous scar or if it consists of normal muscle with an adequate blood supply through collaterals.

Coronary arteriography, nevertheless, remains the method by which the diagnostic performance of the exercise ECG must be judged. Salient findings in six different series comparing angiographic and electrocardiographic findings appear in Table 4. An overwhelming majority of the patients were studied with angiography because of chest pain.

The results of the last four series are similar. The poor performance of the exercise ECG in the series published by Demany and associates is striking. There is no apparent reason for the large number of false positives. Twenty-three patients in a total series of 75 had a positive exercise electrocardiogram but negative coronary angiogram. The low rate of positive ECG responses, 18 of 42, among patients with positive coronary angiograms may be at least partly related to the use of a Master's test rather than a graded exercise test.

The paper published by Roitman and associates contains a detailed clinical analysis. The material was analyzed both (A) in toto (100 patients) and (B) after elimination of patients with conditions known to preclude proper interpretation of S-T changes (46 patients). Reasons for exclusion were arterial hypertension, aortic valve disease, mitral valve incompetence, left ventricular hypertrophy, and QRS prolongation or S-T depression at rest. Sensitivity and specificity were as expected higher in the selected series.

Circulation, Volume XLIV, December 1971
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Table 4

Correlation between Segmental S-T Depression during and after Exercise and Results of Coronary Angiography

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Total</th>
<th>C+</th>
<th>C-</th>
<th>C+</th>
<th>C-</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demany et al.⁴⁸</td>
<td></td>
<td>75</td>
<td>18</td>
<td>24</td>
<td>10</td>
<td>23</td>
<td>43</td>
<td>70</td>
<td>Double Master</td>
</tr>
<tr>
<td>Hultgren et al.⁴⁹</td>
<td>44</td>
<td>20</td>
<td>6</td>
<td>0</td>
<td>18</td>
<td>77</td>
<td>100</td>
<td></td>
<td>Double Master, treadmill</td>
</tr>
<tr>
<td>Mason et al.⁵⁷</td>
<td>84</td>
<td>36</td>
<td>11</td>
<td>4</td>
<td>33</td>
<td>77</td>
<td>89</td>
<td></td>
<td>GXT 90; normal resting ECG</td>
</tr>
<tr>
<td>Kassebaum et al.⁵⁰</td>
<td></td>
<td>66</td>
<td>21</td>
<td>17</td>
<td>0</td>
<td>29</td>
<td>57</td>
<td>100</td>
<td>GXT 85; normal resting ECG</td>
</tr>
<tr>
<td>Roitman et al.⁷¹</td>
<td>(A) 100</td>
<td>45</td>
<td>17</td>
<td>7</td>
<td>31</td>
<td>73</td>
<td>82</td>
<td></td>
<td>GXT 85</td>
</tr>
<tr>
<td></td>
<td>(B) 46</td>
<td>24</td>
<td>6</td>
<td>2</td>
<td>14</td>
<td>50</td>
<td>87</td>
<td></td>
<td>GXT 85</td>
</tr>
</tbody>
</table>

*Sensitivity (%) = no. of true positives ÷ (no. of true positives + no. of negatives) × 100.

Specificity (%) = no. of true negatives ÷ (no. of true negatives + no. of false positives) × 100.

Abbreviations: C+ and C− denote positive and negative coronary arteriogram; E+ and E−, the presence and absence of segmental S-T depression of 1 mm or more during or after exercise or at both times; GXT 85 and GXT 90 = graded exercise test to 85 and 90% of estimated age-specific maximal heart rate; (A) = unselected series; (B) = excluding patients on digitalis, with LVH or S-T abnormalities at rest, or both.⁷¹

(B). The overall agreement between ECG response and angiography was 83% in series (B) and 76% in series (A).

It is conceivable that metabolic abnormalities would correlate better with the exercise ECG than with coronary angiography, but available data on lactate production are equivocal.⁷²–⁷⁴

A special group with apparent dissociation between clinical findings, arteriogram, and exercise electrocardiogram deserves comment. A syndrome found in young and middle-aged women and consisting of typical angina pectoris, abnormal exercise ECG, and normal coronary arteries according to the angiogram has been described by Likoff and co-workers⁷⁵ and Kemp and co-workers.⁷⁶ Eliot and Bratt⁷⁷ have implicated an abnormal hemoglobin-dissociation curve, possibly related to cigarette smoking. They described 15 women with the syndrome. Three patients subsequently died and were found to have normal coronary arteries but subendocardial infarctions. A recent study by Kimbiris and associates⁷⁸ nevertheless, suggests that angina pectoris in women without angiographic abnormalities is a benign and frequently transient syndrome.

Follow-up over a period of 6 months to 2½ years of 86 patients revealed no sudden deaths or myocardial infarctions. The chest pain had disappeared in half of the patients.

The specificity and sensitivity of the exercise electrocardiogram have not been adequately studied in any female group. Most studies, both clinical and epidemiologic, have been limited to men or include only small numbers of women. There is some evidence to suggest that a segmental S-T depression is a less specific sign in a woman. There are reports demonstrating a frequent occurrence of segmental S-T depression in young and middle-aged women who have a lower incidence of overt ASHD.⁴⁹, ⁷⁹

Patients with Documented Arteriosclerotic Heart Disease

Determination of physical work capacity is the most important indication for exercise testing in patients with documented ASHD.

Several follow-up studies of patients who have sustained a myocardial infarction suggest that one half to two thirds of those who were employed at the time of the infarct are able to return to gainful employment. As many as one fourth of the remaining patients are able also
to go back to work but to a less demanding position than they held before their infarct. The importance of extracardiac factors has been pointed out repeatedly in studies of patients referred to work-evaluation units. A stable work background before the infarct, quality education, occupational training, and employment in jobs classified as sedentary or light all favor return to work.88

Data on the distribution in functional classes according to the New York Heart Association criteria are in agreement with the relatively high employment figures. In a representative series of 200 patients, studied at an average interval of 7 years after their infarct, 45% were in class I and less than 10% in class IV. Fifty percent had angina and less than 10% congestive failure.81

Clinical data provide a reasonable basis for advice on occupational activity in many patients, e.g., men in sedentary occupations who have a mild infarct with no residual symptoms or signs or patients in overt heart failure. However, an objective evaluation of physical performance capacity is helpful in a majority of patients with ASHD. Questions relating to nonoccupational physical activity frequently require attention. Exercise testing also provides an objective method for evaluation of the effect of various therapeutic interventions, medical and surgical.

Laboratory measurements show that the average patient with documented ASHD is likely to have moderate reduction of his physical work capacity. Mean values one third below normal capacity have been reported with a range from total disability to a work capacity above average.82-86 Patients with angina pectoris tend to have lower physical work capacity than patients with uncomplicated, healed myocardial infarction.86 The variability in work capacity within groups of patients with ASHD is considerable. Our own data (unpublished) indicate that patients with angina pectoris and significant arterial lesions according to coronary angiography may start experiencing chest pain and show S-T changes at work loads requiring oxygen uptake anywhere between 0.4 and 3 liters/min or at peak heart rates during exercise varying between 80 and 170 beats/min. Data such as these further emphasize the need for individualized work loads.

Physical work capacity in angina pectoris correlates poorly with the degree of left ventricular dysfunction present at rest (as judged from end-diastolic pressure, ventricular volumes, and wall motion (table 5). The lack of correlation is consistent with a limitation of physical work capacity due to myocardial ischemia rather than due to left ventricular dysfunction with restricted cardiac output.

A correlation between extent of arterial disease according to angiography and physical work capacity is present but weak.87 Possible reasons for the discrepancy between angiographic and electrocardiographic changes have been discussed above. One might speculate that the product of heart rate and systolic blood pressure during exercise at the level producing angina would show a better correlation, but data are not yet available.

The difficulties associated with evaluation of the effectiveness of any treatment of angina pectoris have been discussed and vividly illustrated by Diamond and associates88 in a study comparing the effects of internal mammary artery ligation and a sham operation.

<table>
<thead>
<tr>
<th>Maximal work load (kp-m/min)</th>
<th>End-systolic volume</th>
<th>Wall dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal, Increased</td>
<td>Markedly increased</td>
</tr>
<tr>
<td>&lt;250</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>250-499</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>500-749</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>750+</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 5

Correlation between Physical Work Capacity and Left Ventricular Angiography87

_Circulation, Volume XLIV, December 1971_
Serial exercise testing, with a properly designed test protocol and angina associated with typical ischemic S-T changes as the end point, provides a method that overcomes most pitfalls. No appreciable placebo effect can be demonstrated.89

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C. GUNNAR BLOMQVIST

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