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EXERCISE TESTING IN ARTERIOSCLEROTIC HEART DISEASE

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INTRODUCTION

Clinical exercise testing was in the past performed primarily to provoke ischemic electrocardiographic abnormalities. Increased knowledge of the circulatory response to various forms of physical exercise in normal subjects and in patients with different cardiac lesions has provided a basis for a much wider usage. It has become evident that exercise constitutes a most convenient means of imposing a graded load on the circulatory system. Furthermore, the nature of the load may be varied by altering the pattern of activity. The range of techniques utilized to characterize the response has been broadened to include a wide variety of invasive and non-invasive methods.

Exercise tests are now frequently performed in patients with non-arteriosclerotic heart disease. Quantitation of physical performance capacity has also become more important. The standard functional classification system does not satisfy the need for accurate, objective data. Multiple-level graded exercise tests carried to the intensity at which the patient demonstrates limiting symptoms or signs add significant information that frequently influences the choice between different medical and surgical therapeutic alternatives.

The present review deals with methodological aspects and uses of exercise tests in patients with latent or overt coronary heart disease. A brief discussion of physiological data is included to furnish background information relevant to the techniques and to the interpretation of the results.

A comprehensive review of technical aspects of exercise testing and pertinent physiological concepts is available as a monograph (H. Blackburn, Ed: Measurement in exercise electrocardiography, The Ernst Simonson Conference; Charles C. Thomas, Springfield 1969). More general information on exercise and heart disease, including some guidlines for the practicing physician, may be found in The Proceedings of the National Workshop on Exercise in the Prevention, in the Evaluation, and in the Treatment of Heart Disease, Suppl. 1 to Vol. 65 of J. South Carol. Med. Assn, 1969. Recent reviews of exercise testing include R. A. Bruce and T. R. Hornsten: Exercise testing in evaluation of patients with ischemic heart disease, Progr. Cardiovasc. Dis. 11:371-390, 1969 and Simonson, E: Electrocardiographic Stress Tolerance Tests, Progr. Cardiovasc. Dis. 13:269-292, 1970.

The Textbook of Work Physiology by P. O. Åstrand and K. Rodal, McGraw-Hill, New York 1970, is an excellent source of physiological data relating to all aspects of human physical performance.

Table I.

Factors determining myocardial oxygen demand

1. Intramyocardial tension
   Ventricular pressure
   Intraventricular volume
   Myocardial mass

2. Heart rate

3. Contractile state

4. Basal metabolism of the myocardium

5. External work of the heart

I. PHYSIOLOGICAL CONSIDERATIONS

Determinants of myocardial oxygen demand.

Table I (quoted from Sonnenblick et al, 1968) summarizes the determinants of myocardial oxygen demand. Factors (1) intramyocardial tension, determined by ventricular pressure, intraventricular volume, and myocardial mass, and (3) the contractile state are primary factors. 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 pressure. The effect of an 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 an increased energy utilization 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 demands. Arterial or left ventricular pressure is taken as an indication of wall tension. Tension-time index (TTI), the integral of the ventricular pressure pulse, has been widely used since Sarnoff et al (1958) demonstrated in a controlled animal preparation that the heart rate-peak systolic blood pressure product (Katz and Feinberg, 1958) under some conditions correlated poorly with myocardial oxygen uptake.

Recent clinical studies in patients with coronary disease suggest that the less complicated heart rate x blood pressure product is a more accurate index in the intact human subject (O'Brien et al, 1969 and Kitamura et al, 1970). Use of the triple product heart rate x systolic blood pressure x left ventricular ejection time may increase the accuracy of predicted myocardial oxygen demand, but the evidence is equivocal. (Robinson 1967, Holmsberg 1967, Kitamura et al, 1970)

Table II.

Classification of occupational activities

Class	Peak caloric expenditure	Peak heart rate
Sedentary	2.5	90
Light	5	110
Medium Heavy	7.5	130
Heavy	10.0	150

Circulatory response to various activities

Standard classifications of various jobs and activities primarily reflect levels of energy expenditure. Table II illustrates a classification based on peak loads. Changing the base to loads that may be maintained for prolonged periods, i.e., for more than 1/2 to 1 hour, would reduce the values by 50%. The classification closely corresponds to that used by U. S. Department of Labor in the Dictionary of Occupational Titles, the most comprehensive source available on the requirements of different occupations. Supplement 2 to the dictionary contains a listing of 4,000 jobs classified with respect to energy demands and other characteristics.

Sedentary work primarily involves sitting with occasional walking and standing and lifting or carrying objects weighing up to 10 pounds. Light work involves lifting 20 pounds maximum with frequent lifting and carrying of objects up to 10 pounds. A job in this category requires walking or standing to a significant degree or sitting with a degree of pushing or pulling of arm and/or foot controls. Medium work requires lifting 50 pounds maximum with frequent lifting and carrying of objects weighing up to 25 pounds. Heavy and very heavy work are defined by weight limits of up to and over 100/50 pounds.

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 the 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.

Data on occupational activities are customarily given in terms of calories per minute. The caloric equivalent of oxygen varies between 4.8 and 5.0 depending on the relative rate of carbohydrate and fat metabolism. Calories per minute may simply be converted to oxygen uptake in liters per minute by dividing by 5. An energy expenditure of 5 cal/min corresponds to an oxygen uptake of 1 liter/min.

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 meet the demands until at about 2 minutes after the beginning of a steady state task, 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 (Hellerstein and Ford, 1959; I. Åstrand, 1967).

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. Mechanization of the forestry industry provided a striking illustration to the relation between load and duration of effort. Peak loads were greatly reduced by the introduction of power equipment. The level of energy expenditure averaged over a work day was essentially unchanged. This change forced retirement of many workers with minor disabilities. They were able to cope with short heavy loads so long as they could regulate their own pace and provide rest periods for recovery but were unable to tolerate a sustained effort at a level that was much lower than the old peak loads (I. Åstrand, personal communication).

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.

The relation between the time for which a sustained effort can be tolerated and relative load (expressed as a fraction of maximal work capacity) is exponential. 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 (I. Åstrand, 1967). An average level of 30% of capacity as calculated for a full 8-hour period has also generally been advocated as the upper limit for safe employment (Falls, 1969).

Type of work: Isometric Exercise

A series of conditions other than duration of efforts are 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 isometric should not be interpreted too strictly and that the characteristic circulatory response is caused by a sustained development of tension in the muscle as opposed to the alternating tension development and relaxation during dynamic exercise of type walking and running. Lind et al (1966) demonstrated that a sustained isometric forearm contraction caused a marked blood pressure increase 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.

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, arrhythmias are more readily provoked by handgrip stress than by dynamic exercise, particularly in patients with coronary disease. Twelve of twentyfour patients with coronary disease developed significant arrhythmias during a handgrip test versus only 4 during dynamic exercise. Six of the arrhythmias in the coronary group during handgrip were ventricular tachycardias, versus 1 during bicycle exercise (Matthews et al, 1971).

Many activities include a combination of dynamic and isometric exercise. The blood pressure rise in response to isometric exercise tends to be of the magnitude whether the basal condition is rest or dynamic exercise (Lind et al, 1966). The additive effects are apparent during arm work, e.g. hand cranking. Both systolic and diastolic blood pressures are significantly higher during arm work at any given level of oxygen uptake (Åstrand et al, 1965). Similar differences between arm work and leg work have been reported in patients with angina pectoris (Blomqvist, 1965).

Environmental factors

Environmental factors modify the circulatory response to exercise. The effect of cold temperatures on the threshold of angina 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 (Blomqvist, 1965). Angina pectoris tends to occur earlier and ST changes are more prominent than under standard laboratory conditions. Similar findings have been reported by Epstein et al, 1969. Corresponding data on the effects during exercise in hot environments in angina patients are not available.

EMOTIONAL STRESS

Emotional stress is a classical precipitating factor in angina pectoris. Most, but by no means all, patients who frequently experience angina during emotional strain also tend to get angina at low work load levels during exercise. Several studies on the circulatory effects of experimentally induced alterations of affect are consistent with that impression. Recorded increases in heart and blood pressure during stressful interviews etc., have generally been modest, usually less than +25 beats/min. and +25 mm Hg. (Bogdonoff et al, 1959, Shapiro 1961, Adsett 1962).

There are several studies (recently reviewed by Simonson, 1968) 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 20-30 mm Hg. are also unusual. Non-specific ECG changes have been observed in as many as 1/3 of normal subjects and 1/2 of patients with angina pectoris, most ischemic changes are less frequent; a 10 per cent incidence of ischemic ST 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. are not unusual under these conditions.

Hellerstein and Friedman (1970) 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.

II. EXERCISE TEST METHODS

Master's test.

Master's test (for an historical account and for references, see Master, 1969) has been more widely used than any other test. Exercise is performed on a two-step staircase with 9" steps. The number of trips to be completed over 1-1/2 minutes (single test) or 3 minutes (double test) is determined by taking into account the patient's age, sex, and body weight. The test was originally designed to provide an equivalent physiological work load for all subjects by correcting variations in physical work capacity related to age, sex, and body weight. However, studies by Rowell et al (1965) have demonstrated that the correction procedure tends to equalize external rather than relative load. The energy expenditure (Hellerstein et al, 1966) is approximately 8.5 cal/min. which corresponds to an oxygen uptake of 1.7 l/min. A subject with low body weight is penalized and will as a rule perform exercise at levels closer to his maximal capacity than a heavier subject. The variability with respect to relative work load that results from the fixed external load is reflected in the heart rate during the final minute of the test. Sheffield and Reeves (1965) reported a range from 95 to 180 beats per minute (bpm), mean 128 in a normal subject during a single test. Corresponding figures for a double test were 108 to 192 and a mean of 143 bpm. The large variability is a common feature of all single stage tests employing a fixed load for all subjects. Taylor and associates (1967) reported a heart rate range from 80 to 172 bpm in a series of 1,040 middle-aged railroad employees who performed a treadmill walk for 3 minutes at 3 mph and 5% grade.

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 frequently 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 in 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. Small variations in the duration of exercise may then represent significant differences in performance capacity that will become apparent when the patient undergoes a multilevel exercise test including levels well below the threshold of angina (Redwood et al, 1970). Failure to recognize this mechanism has resulted in publications stating that Isordil and propranolol have no objectively demonstrable effects in angina pectoris.

It is evident that Master's test is not an optimal procedure for quantitation of physical performance capacity. 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. Furthermore, the test is simple to perform and requires no elaborate equipment. More important, the amount of clinico-pathological correlative data and follow-up data available on the ECG response to the Master's test is much larger than that for any other exercise test procedure.

Multi-stage tests.

Modern protocols are designed to satisfy the dual requirements of provoking electrocardiographic abnormalities and other diagnostic symptoms and signs and providing a basis for quantitative evaluation of physical performance capacity. Taylor et al (1969) have recently reviewed current procedures. Three basic forms of exercise are used: step climbing, treadmill and bicycle ergometer exercise. All involve dynamic leg exercise and 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 5 to 10 per cent, and unlikely to be of clinical significance. Small differences with respect to ventilation and lactate levels have also been reported. More important, the relation between heart rate and oxygen uptake is similar for all three methods. Observations on intraarterial pressures and cardiac output in the same individuals studied during treadmill and bicycle exercise are scarce but suggest that no major differences exist (Saltin and Åstrand, personal communication). Use of leg exercise also 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 or routine applications. Oxygen uptake during a step test and during treadmill or bicycle ergometer exercise may be predicted with fair accuracy (± 10 per cent) from parameters defining the work load (Åstrand, 1960). 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 groups:

(1) Continuous test with stepwise load increment, duration of exercise at each level usually 2 to 3 minutes.

(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 and to maintain it for 2 to 3 minutes.

(3) Exercise for 5 to 6 minutes at each level in a series of progressively heavier work loads, interspersed rest periods.

Type (1) was originally designed by Balke and Ware (1959) 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 associates and employed in large series of normal subjects and patients (Bruce and Hornsten, 1969). Method (2) was described by Sheffield et al (1965). It is the most rapid of the methods but has an inherent disadvantage of providing a less accurate basis for estimation of oxygen uptake. The target heart rate is usually 85 or 90 per cent of the average age-specific maximal rate. Method (3) (Wahlund, 1948) is time-consuming but most subjects approach a steady state at submaximal loads and thereby provide the investigator with the opportunity to obtain multiple measurements at each level. Initial work load level and magnitude of the increment usually correspond to oxygen uptake of 0.9 and 0.6 l/min. but may be reduced for patients with a history suggesting low physical performance capacity.

The physical work load level during a treadmill test or a step test will define oxygen uptake in terms of ml/kg x min. while the bicycle ergometer load determines oxygen uptake in absolute units or as l/min. Results can easily be compared using body weight as a conversion factor.

More work has to be done to establish to what extent findings during exercise tests performed according to different protocols are truly comparable. Available data suggest that heart rate or oxygen uptake during exercise could be used as a common denominator. Table III lists bicycle and treadmill loads equivalent to a Master's test.

Table III.

Equivalent Work Loads.

1. Master's double step test

2. Treadmill exercise at 3 mph, 10 per cent grade

3. Bicycle exercise at 600 kpm./min.

Oxygen uptake approximately 1.5 l/min. or 20 ml/kg x min.

ECG technique.

Technical aspects of exercise electrocardiography have recently been reviewed in detail by Blackburn (1969). 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 is 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 assembly have largely eliminated the need for telemetry 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
3. Orthogonal or vector 3-lead systems

Each lead and each system has specific advantages and disadvantages with respect to ease of application, sensitivity and specificity, and relative freedom from noise during exercise.

ST depressions of the type generally recognized as ischemic tend to be oriented spatially in a direction opposite that of the mean QRS vector (Blomqvist 1965, Blackburn 1969). A lead with an electrical axis corresponding to that of precordial lead V_7 or V_8 should theoretically provide an optimal display of ST abnormalities but the amplitude is usually low in these leads. Furthermore, the normal ST vector is frequently oriented anteriorly and will therefore be displayed as a ST depression in leads V_7 and V_8 which are oriented posteriorly. Electrode positions corresponding to precordial leads V_5 and V_6 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 (1969) studied a group of 100 patients with ASHD and significant ST depressions. Ninety per cent had ST changes in one or more of the lateral leads (I, aVL, $V_{4,5,6}$) and 30 per cent had ST depression in the vertical leads (II, III, avF). However, only in 10 per cent of the patients was the ST depression seen exclusively in a vertical lead. Blackburn (1969) also found corresponding distributions using a vector lead system. Similar figures have also been reported by others (Mason et al 1967). Most bipolar leads designed specifically for exercise testing in patients with ASHD also use a positive electrode site corresponding to V_5. The location of the negative electrode is variable. A high anterior chest or high back position (right subclavicular area, manubrium, right inferior scapular border) includes a vertical component and improves performance relative to 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 contal margin and the iliac spine has been designed by Mason and Likar (1966). The system performs well during exercise unlike the standard 12-lead system. 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 10 per cent. 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, significance

Criteria

Modern procedures call for individual adjustment of work load levels. 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 in asymptomatic patients and normal subjects may be either a maximal oxygen uptake or a heart rate during exercise corresponding to 85 to 100 per cent of mean age specific maximal heart rate. Most physicians discontinue the test at lower work levels if any of the following events is encountered (Rochmis and Blackburn, to be published):

1) Chest pain unless minor and clearly of extra-cardiac origin

2) Symptoms or signs suggesting cerebral ischemia

3) Undue or unusual dyspnea, weakness, fatigue, pallor or cyanosis

4) Fall in blood pressure or heart rate with increasing work load

5) Leg pain suggesting claudication

6) Significant electrocardiographic abnormalities if not present at rest
    a) Progressive horizontal ST depression ≥1mm (0.1 mV), progressive ST elevation

    b) Serious dysrhythmias: increasing number of ventricular premature contractions (≥1/5), multifocal PVC's, runs of 2 or more PVC's, any sustained atrial tachyarrhythmia, any atrioventricular block

    c) Complete bundle branch block or major atypical intraventricular conduction defect.

Symptoms and signs listed under 1 - 5 are all compatible with a restricted cardiac output or with deficient regional perfusion. Chest pain is included as an endpoint since angina pectoris may occur without ECG signs of ischemia (see below).

Lack of motivation, inability to cooperate, and muscle and joint pain are the most common non-cardiovascular reasons for interruption of the test before a target level has been reached. Clinical observation of the patient complemented with measurements of heart rate and respiratory rate usually form a sufficient basis for deciding whether the patient has been limited by abnormal cardio-pulmonary 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 (I. Astrand, 1960). 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 test findings provide information with respect to physical performance capacity and mechanisms limiting physical performance. Physical performance capacity is defined as measured or estimated peak oxygen uptake. Other indices have been used, e.g. work load at a given heart rate, but frequently misleading. Peak oxygen uptake may be related to age and sex specific normal standards, see Table IV, and to the known energy requirements of various occupational and recreational physical activities.

Table IV

Maximal Oxygen Uptake in Sedentary Men and Women
(Bruce et al, 1970, unpublished data)

Age	Sedentary men Mean	Sedentary men Lower limit	Sedentary women Mean	Sedentary women Lower limit
	ml/kg x min.		ml/kg x min.	
20-29	44	35	39	31
30-39	40	32	37	30
40-49	37	30	33	27
50-59	35	28	31	25
60-69	32	26	29	23
70-79	29	23	25	20

Lower limits represent -2 standard deviations. Values for active subjects approximately 10 ml/kg x min. higher.

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 ASHD. Quantitative data on the significance are available only for electrocardiographic abnormalities.

The significance of a segmental, i.e. horizontal or downsloping ST depression was firmly established during the 1950's. Wood et al (1950) separated segmental or "ischemic" depression from physiological 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 segmental ST 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 (for a review see Simonson, 1969).

Further data relating to the significance of a horizontal ST depression will be presented in the section on applications.

Use of graded exercise test up to a maximal or near-maximal level has supported Wood's et al (1950) conclusion that an isolated junctional ST depression is a physiological response. It has been clearly demonstrated that the magnitude of junctional depression is proportional to heart rate (Sjostrand 1950, Blomqvist 1965, Bruce and Hornsten 1969). A physiological junctional depression and an abnormal segmental depression are sometimes superimposed during exercise at high work load levels and high heart rates. Punsar et al (1968) and Lester et al (1967) have presented evidence to suggest that a slowly ascending (rate of change less than 1 mV/sec.) ST segment under these conditions is the equivalent of a strictly segmental depression during less intensive exercise.

The significance of ECG changes during andafter exercise in patients who have an abnormal ECT at rest has not been fully established. Progressive ST segment elevations in lateral or vertical leads are never seen in normal subjects but occur in patients with a history of a myocardial infarction and residual QRS changes. ST elevation during or after exercise is probably as specific as ST depression (Fortuin and Friesinger, 1970).

Segmental ST depression is frequently seen in patients without coronary artery disease but with other conditions 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 (Hellerstein et al 1961, Datey and Misra, 1968).

Autonomic nervous system dysfunction with and without hyperventilation may on occasion produce significant ST depression during exercise (for a review see Lepeschkin 1969). Abnormal sympathetic stimulation may produce ECG abnormalities in neurocirculatory asthenia. Characteristically, ST 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 load levels as during heavy work, and may be abolished by beta-adrenergic blockade (Furberg 1967).

Digitalis may cause a segmental ST depression during exercise even in the absence of significant ST depression in the resting ECG (Nordstrom 1964).

The effect of hypokalemia is disputed (Gubner 1961, Georgopoulos et al, 1961, Soloff and Fewell 1961).

The Wolff-Parkinson-White syndrome is frequently associated with a positive exercise test in the absence of ASHD (Gazes 1969). This may be true also for variant forms (Åstrand et al, 1969).

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 (Simonson 1969).

Data based on studies of patients with verified ASHD demonstrate a highly significant increase in sensitivity (at least +1/3) of the exercise ECG when a maximal or near-maximal load is used rather than a Master's test (Doan et al 1965, Sheffield and Reeves 1965, Mason et al, 1967).

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 per cent, was reported by Mason et al (1967).

There is evidence that a segmental ST depression is a highly reproducible finding (Areskog and Hallen 1964, Bruce and Hornsten 1969), and that transient arrhythmias and conduction defects provoked by exercise are highly variable (Gooch and McConell 1970).

Observer variation

Blackburn et al (1968) has demonstrated that diagnostic interpretation of the exercise ECG carries considerable interobserver variation. In his study a panel of electrocardiographers interpreted a selected series of post-exercise ECG's according to their personal criteria. The rate of responses judged positive varied between 5 and 50 per cent. The variation decreased significantly or to 27-37 per cent when the participants were asked to adhere rigidly to specified criteria.

Computer techniques

There are several reasons why a computer techniques are likely to prove helpful in exercise electrocardiography, e.g. by providing means of eliminating noise and eliminating intraobserver variation. Several centers are working in this area. A detailed survey of the present state of the art is available in the proceedings of the Ernst Simonson Conference, edited by Blackburn (1969).

Risks and safety procedures.

Mortality and morbidity attributable to exercise testing has recently been examined by Rochmis and Blackburn (to be published). They used questionaires 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 multi-stage progressive tests (73%). A total of 16 deaths were attributed to the test and occurred within 1 week giving a mortality of 1 per 10,000 tests. Eight deaths were immediate. Forty subjects were hospitalized for non-fatal events, usually chest pain or arrhythmias, i.e. a rate of 2.4 per 10,000 tests.

A large majority 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 non-cardiac illness, (4) serious arrhythmia.

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

Standard safety precautions included direct supervision by physician and ECG monitoring during exercise. All but three respondents had a D. C. defibrillator available, and staff trained in arrhythmia recognition and resucitation.

III. USES OF EXERCISE TESTING IN VARIOUS GROUPS OF PATIENTS WITH ASHD

1. Patients with latent coronary disease.

The power of the electrocardiographic exercise test to predict future development of clinical ASHD in subjects who are asymptomatic at the time of the test was first demonstrated by Robb et al (Robb et al 1956, Robb and Marks 1967), Brody (1957) and Mattingly (1962).

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

Mattingly (1962) reported similar figures or a 4.8 fold increase in mortality in a series of military men with ischemic ST depression.

Brody (1957) presented the first systematic study of unselected asymptomatic subjects. Twentythree of 756 subjects had an ischemic ST depression of 0.5 mm or more at the initial examination. Sixteen men, or 70 per cent, developed classical angina or had a myocardial infarction during a three-year follow-up period. Corresponding figures for the group with a negative exercise test were 55/733 or 0.75 per cent. Ischemic ST depression was associated with a nearly 100-fold increase in coronary morbidity.

A larger population study has recently been published by Doyle and Kinch (1970). They subjected 2,003 men, most of them New York State employees, to an exercise test consisting of a treadmill walk for 10 minutes at 3 mph against a grade of 5%. The level of energy expenditure approximates that of a double Master's test. The group was followed for up to 13 years. Twentyeight men had an abnormal exercise ECG upon entry in the study, and 61% of the subjects in this group developed additional evidence of ASHD during the follow-up period. Seventyfive men developed an abnormal exercise ECG response during follow-up, and 45% of these 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 was calculated using life-table techniques and equalled 85 per cent. Corresponding ASHD risk for a subject with normal exercise ECG was 2.5 per cent, i.e. a positive exercise response was associated with a more than 30-fold increase in ASHD risk.

The predictive power of the exercise ECG thus appears to be very high. However, it must be emphasized that the incidence of positive tests in an asymptomatic middle-aged population is fairly low, or about 4 per cent 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 et al.(1965) reported segmental ST depression in 24 per cent of ostensibly healthy men between 50 and 59 years old. Similarly high rates have been found by others using maximal tests (Blomqvist 1965). 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 the presence of other risk factors. Blackburn et al (1970) have been able to show that a positive exercise test (step test, oxygen uptake 1.5 l/min.) has a prognostic significance that is independent of age, blood pressure, cholesterol, obesity, smoking, and physical activity. A positive ECG implies a 3-fold increase in the risk of future clinical ASHD when all other risk factors are held constant.

2. Exercise tests in the differential diagnosis of chest pain.

Chest pain suggesting angina 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 (1970) 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 a complete occlusion of a major branch near its origin may easily be overlooked. The diagonal branches of the left artery are particularly difficult to evaluate. A 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 against 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 V. An overwhelming majority of the patients were studied with angiography because of chest pain.

Table V

Correlation between segmental ST depression during and after exercise and results of coronary angiography.

Author	No. of patients	C+ E+	C+ E-	C- E+	C- E-	Sensitivity	Specificity	Comments
Demany et al. (1967)	75	18	24	10	23	43	70	Double Master
Hultgren et al. (1967)	44	20	6	0	18	77	100	Double Master, treadmill
Mason et al. (1967)	84	36	11	4	33	77	89	GXT 90 Normal resting ECG
Kassebaum et al. (1968)	66	21	17	0	29	57	100	GXT 85 Normal resting ECG
Roitman et al. (1970)	(A)100	45	17	7	31	73	82	GXT 85
	(B) 46	24	6	2	14	80	87	GXT 85

C+ and C- denote positive and negative coronary arteriogram, E+ and E- presence and absence of segmental ST depression of 1 mm or more during and/or after exercise. GXT 85 and GXT 90 = graded exercise test to 85 and 90 per cent of estimated age-specific maximal heart rate. Roitman et al. (A) - unselected series, (B) - excluding patients on digitalis, with LVH and/or ST abnormalities at rest.

Sensitivity (per cent) = No. of true positives/ (No. of true positives +No. of negatives) x 100.

Specificity (per cent) = No. of true negatives/ (No. of true negatives +No. of false positives) x 100.

The results of the last four series are similar. The poor performance of the exercise ECG in the series published by Demany et al. (1967) is striking. There is no apparent reason for the large number of false positives. The low sensitivity 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 et al. (1970) contains a detailed clinical analysis. The material was analyzed both in toto (A), 100 patients, and after elimination of patients with conditions known to preclude proper interpretation of ST changes, (B), 46 patients. Reasons for exclusion were arterial hypertension, aortic valve disease, mitral valve incompetence, left ventricular hypertrophy, and QRS prolongation or ST depression at rest. Sensitivity and specificity were as expected higher in the selected series (B). The over-all 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 coronary angiography, but available data (on lactate production) are equivocal (Cohen et al. 1966, Herman et al. 1967, Parker et al. 1969).

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 and abnormal exercise ECT and normal coronary arteries according to the angiogram has been described by Likoff et al. (1967) and Kemp et al. (1967). Eliot and Bratt (1969) have implicated an abnormal hemoglobin dissociation curve, possibly related to cigarette smoking. They described 15 women with the symdrome. Three patients subsequently died and were found to have normal coronary arteries but subendocardial infarctions. A recent study by Kimbiris et al. (1970) nevertheless suggests that angina pectoris in women without angiographic abnormalities is a benign and frequently transient syndrome.

Follow-up over 6 months to 2-1/2 years of 86 patients revealed no sudden deaths or nyocardial infarctions. The chest pain had disappeared in 1/2 of the patients.

The specificity and sensitivity of the exercise electrocardiogram has not been adequately studied in any female group. Most studies, both clinical and epidemiological, have been limited to men or include only small numbers of women. There is some evidence to suggest that a segmental ST depression is a less specific sign in a women, primarily the discrepancy between the frequent occurrence of segmental ST depression and the rarity of ASHD in young and middleaged women (I. Åstrand 1965, Lepeschkin 1969).

3. Patients with documented ASHD

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 1/2 to 2/3 of those who were employed at the time of the infarct are able to return to gainful employment. As many as 1/4 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 and occupational training, and employment in jobs classified as sedentary or light all favor return to work (Rosenbaum and Belknap (Part IV), 1959).

Data on the distribution on functional class according to NYHA 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 per cent had angina and less than 10% congestive failure (Sievers, 1963).

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 therapeutical interventions, medical and surgical.

Laboratory measurements show that the average patient with documented ASHD is likely to have a moderate reduction of his physical work capacity. Mean values 1/3 below normal capacity have been reported with a range from total disability to a work capacity above average (Bolt et al, 1957; Malmborg, 1965; Benestad, 1967; Bjork et al, 1967; Kasser and Bruce, 1969). Patients with angina pectoris tend to have a lower physical work capacity than patients with an uncomplicated, healed myocardial infarction (Kasser and Bruce, 1969).

Physical work capacity in angina correlates poorly with the degree of left ventricular dysfunction present at rest (as judged from end-diastolic pressure, ventricular volumes, and wall motion).

TABLE VI

CORRELATION BETWEEN PHYSICAL WORK CAPACITY AND LV ANGIOGRAPHY

Wmax	End-Systolic Volume			Wall Dysfunction	
(kpm/min)	Normal	+	++	0	+
<250	8	7	3	8	10
250-499	8	7	5	10	10
500-749	5	7	-	5	7
750+	2	-	-	2	-

The lack of correlation between angiographic data on left ventricular performance and physical work capacity is illustrated in Table VI. The results are 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 (Areskog et al, 1967). Possible reasons for the discrepancy between angiographic and electrocardiographic changes have been discussed above. One might speculate that the heart rate-systolic blood pressure product 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 Dimond et al (1960) in a study comparing the effects of internal mammary artery ligation and a sham operation. Serial exercise testing using a properly designed test protocol (Redwood et al, 1970) and as end-point angina associated with typical ischemic ST changes provides a method that overcomes most pitfalls. No appreciable placebo effect can be demonstrated (Atkins et al, 1970).

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